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John P. Peters, … , Anna J. Eisenman, Carter Lee

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TOTAL ACID-BASE EQUILIBRIUM OF PLASMA IN HEALTH AND DISEASE

VI. Studies of Diabetes

By JOHN P. PETERS, HAROLD A. BULGER, ANNA J. EISENMAN and CARTER LEE

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

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INTRODUCTION

In the first article of this series (1) a method for the determination of the total acid-base equilibrium of serum was presented together with certain studies of the electrolyte equilibria of healthy persons under various circumstances and of hospital patients who presented miscellaneous conditions that disturbed the electrolyte equilibrium of the blood. The most important point established by these studies was the fact that the organism responds to the production of abnormal amounts of acids of various kinds or the reduction of bicarbonate by a transfer of water, chloride or base from the tissues to the blood or vice versa. Reduction of the plasma chloride by this means liberates base for combination with other acids and, therefore, tends to reduce acidosis, while an increase of chloride has the opposite effect. A transfer of chloride in one direction is equivalent to a movement of base in the opposite direction. The whole mechanism confers on the blood a greater ability to resist the disturbing effects of conditions that alter electrolyte equilibrium by rendering the acid and base stores of the tissues available where and when they are most needed. The reactions involved must be quite comparable to those which have long been known to occur between the cells and the plasma in response to similar chemical disturbances. They may occur with such rapidity as to produce recognizable differences in the composition of arterial and venous blood and their ability to absorb, transport and dissociate carbon dioxide and oxygen.

The present paper deals with the application of this method to the study of the electrolyte changes that occur in diabetes. The procedure has been described in detail in the preceding paper (1). It consists, in brief, of the simultaneous determination of the total base and the acids, protein, bicarbonate, chloride and phosphate of plasma or serum. The difference between the total base and the base combining powers of these acids, expressed in millimols of monovalent base, represents the base combined with organic acid and sulfate. As the latter is usually negligibly small and as any acid in serum must be entirely neutralized by base, the difference becomes, for all practical purposes a measure of the organic acid of serum in terms of the base which it binds.

EXPERIMENTAL PROCEDURE

Table 2 gives the data of all the blood examinations made. Protocols of the cases are presented at the end of the paper. The first column of the table shows the oxygen capacity of the whole blood, determined by a modification (1) of the procedure of Van Slyke and Stadie (2). In the second column is the cell volume determined by means of an ordinary hematocrit. Column 3 shows the ratio *oxygen capacity : cell volume;*[1] column 4 the plasma or serum protein determined by the Kjeldahl technique. In those experiments in which serum was used the protein value is followed by an *s.* - The base combining value of protein has been calculated by the equation of Van Slyke, Wu and McLean (3). CO_2, which appears in column 5 was determined by the technique of Van Slyke and Stadie (2). Blood was either withdrawn and treated throughout without contact with air or else it was brought into equilibrium with a mixture of air and carbon dioxide of known composition at 38°C. before the serum was separated, by methods previously described (4, 5, 1). Sometimes arterial and sometimes venous blood was employed. Column 13 indicates the nature of the blood and the treatment to which it was subjected. *A* and *V* stand for arterial and venous blood respectively. *Cont.* means that the blood was examined as drawn, without contact with the air; *cap.* that it was brought into equilibrium with 40 mm. of CO_2 in air at 38°C. Cl, column 6, was determined at first by the method of Austin and Van Slyke (6); after September 1923, the more recent procedure of Van Slyke (7) was used. The latter gives somewhat lower and more reliable results. Inorganic phosphorus, column 7, was estimated by the technique of Briggs (8) at first, later the modifications suggested by Benedict and Theis (9) were adopted. Total acid, column 8, represents the sum of the base combined with protein, bicarbonate, chloride and inorganic phosphorus, expressed in millimols of monovalent base. Total base, in

[1] The average value of this ratio in oxalated blood of normal individuals is about 46.0. The corresponding ratio for defibrinated blood is only about 42.0.

column 9, was determined by a modification of Fiske's urine method (10) devised by Cullen and Robinson[2] and is expressed in the same terms. *Organic acid* represents the difference, *total base — total acid.* In the *cont.* experiments pH was determined by the colorimetric method of Cullen (11). In the *cap.* experiments it was calculated from the CO_2 tension and the CO_2 content of the serum by the equation of Henderson and Hasselbalch. Whole blood was analyzed for non-protein nitrogen by micro-digestion, distillation and titration of a Folin and Wu tungstic acid filtrate; for sugar, by the regular Folin and Wu procedure (12).

When analyses for certain constituents were omitted, average values were assumed; for protein 7.00 per cent, for inorganic phosphorus 3.5 mg. per cent, for pH 7.35 and for non-protein nitrogen 30 mg. per cent.

For urine sugar Benedict's qualitative or Shaffer and Hartmann's (13) quantitative method was used; acetone has been estimated by Legal's qualitative test.

The limits of variation of total base and the different acids in the serum or plasma of normal individuals are given in table 1.

TABLE 1

Protein	6–7.8 per cent	10– 13.5 millimols
CO_2	52– 73 vols. per cent	22– 31 millimols
Chloride	355–390 mg. per cent	100–110 millimols
Inorganic phosphorus	2.5– 5 mg. per cent	1.5– 3 millimols
"Organic acid"		<20 millimols
"Total acid"		135–155 millimols
Total base		147–167 millimols

DISCUSSION OF RESULTS

In table 2, are presented 25 observations from 21 patients (cases 1 to 21) with diabetes of an essentially mild grade or satisfactorily controlled by diet and insulin. In no case did the urines collected at the time the blood was examined give a definite qualitative test for acetone, and in the majority of instances glycosuria was also absent. In all but 3 of the 15 determinations more than 160 mM. of base was found. This brings the average level of base distinctly above that usually observed in normal individuals. It has been suggested frequently that the low level of plasma chlorides so frequently observed in diabetes might represent a mechanism for the compensation of the disturbance of osmotic pressure produced by the increased blood sugar concentration. Herrick (14) has recently presented studies of plasma

[2] Personal communication.

TA

Case number	Hospital number	Date	1 Oxygen capacity	2 Cell volume	3 Ratio of column 1 to column 2	4 Proteins	5 CO_2	C
			vols. per cent	*vols. per cent*		*per cent*	*vols. per cent*	*mg. 100*
1	5105.	November 23, 1922	21.3	45.6	46.7	6.91	54.5	39
2	15533	January 30, 1923	21.1	43.9	48.0	7.66	51.5	38
3	Alf.	June 4, 1924						
4	39423	January 4, 1925				6.76	66.6	35
5	10888	November 22, 1922	17.8	38.3	46.6	6.47	74.2	36
6	12562	November 7, 1922	20.0	43.0	46.5	7.41	48.9	43
7	18582							
8	16727	February 16, 1923	20.5	44.6	46.0	7.36	57.5	38
9	29843	April 5, 1924						
10	22718	June 2, 1924						
11	33528	June 11, 1924						
12	20387	January 17, 1924	18.1	38.2	47.4	5.39	57.2	35
13	33331	May 25, 1924						
		May 31, 1924						
14	33222	May 11, 1924						
		May 31, 1924						
15	33229	May 13, 1924						
16	10801	November 17, 1922	19.5	41.7	46.9	6.60	45.1	38
17	29771	April 1, 1924						
		May 23, 1924						
18	26315	November 9, 1923					61.4	33
19	15733	February 20, 1923	17.8	38.5	46.1	5.98	63.8	36
20	34490	September 5, 1924						
21	33333	May 23, 1924						
		June 2, 1924						
22	34618	September 19, 1924	17.7	34.2	51.8	6.40	58.9	35
23	34156	July 31, 1924						
24	19838	June 16, 1923	20.1	41.5	48.4		53.3	33
25	18867	June 11, 1923	18.3	39.7	46.1		41.2	33
26	15267	January 3, 1923	19.2	37.4	51.4	6.28	52.8	32
27	15924	May 9, 1923	14.3	32.3	44.3	6.25	43.5	30
28	15175	November 29, 1924	20.9	41.9	49.9	7.25	53.4	34
29	10572	October 24, 1923	17.5	41.4	42.2	7.68	45.1	34
30	18467	November 7, 1923	15.3			6.72	59.2	32
		November 7, 1923	16.6			6.26	55.4	32
31	29754	March 28, 1924	20.1	44.0	46.0	7.93	43.9	31
		March 30, 1924	17.7	40.7	43.3	6.66	85.0	28
32	36016	February 21, 1925		40.6		6.07s	78.0	30
33	10629	October 26, 1922	18.7	41.5	45.1	7.48	47.8	37
		October 30, 1922					46.1	38

7	8	9	10	11	12	Blood sugar	Nature and treatment of blood	Urine sugar	Urine acetone
anic P	Total acid	Total base	Organic acid	pH	Blood non-protein nitrogen				
g. cent	*mM.*	*mM.*	*mM.*		*mg. per 100 cc.*	*mg. per 100 cc.*			
	146.8			7.36		231	V. cap.	0	0
	143.9			7.33	29	119	V. cap.	+	+
.7		161.7			37	172	V. cont.	0	0
	142.9					138	V. cont.	0	0
	147.2			7.50	33	311	V. cap.	0	0
	157.9			7.31	30	139	V. cap.	0	0
		178.8			27	271	V. cont.	0	0
	147.3			7.38		147	V. cap.	0	0
		165.0			30	163	V. cont.	0	0
.6		162.2				126	V. cont.	0	0
.8		165.5				185	V. cont.	0	0
	136.6			7.38	33	263	V. cap.	+	0
.6		153.3				251	V. cont.	0	0
.9		166.0				111	V. cont.	0	0
		160.1			32	230	V. cont.	2+	0
.1		160.3				169	V. cont.	0	0
		162.1			29	231	V. cont.	4+	0
	140.5			7.27	31	411	V. cap.	3+	0
		161.1			28	266	V. cont.	4+	0
.4		173.0				160	V. cont.	0	0
	135.2			7.47		316	V. cont.	4+	0
	142.4			7.43	30	319	V. cap.	4+	±
.7		137.4				217	V. cont.	2+	0
		166.6				188	V. cont.	2+	0
.9		151.9				185	V. cont.	0	0
	138.6					309	V. cont.	4+	4+
.3		147.6			28	155	V. cont.	4+	4+
	131.3			7.39		220	A. cont.	4+	+
	126.0			7.39		326	V. cont.	2+	+
	126.6			7.34		811	V. cap.	4+	3+
	118.2				65	112	V. cont.	0	0
	134.4			7.35	37	244	V. cap.	0	0
	131.6			7.27		271	V. cap.	4+	4+
.1	136.9			7.51		322	A. cont.	4+	0
.6	135.1			7.42		133	A. cont.	0	0
.6	130.0					234	V. cont.	4+	4+
.4	135.4			7.44		113	V. cont.	0	+
.0	131.9	141.3	9.4		33	226	V. cont.	2+	+
	139.4			7.30		291	V. cap.	4+	3+
	142.8			7.28		366	V. cap.	4+	3+

TAI

Case number	Hospital number	Date	1 Oxygen capacity	2 Cell volume	3 Ratio of column 1 to column 2	4 Proteins	5 CO_2	6 Cl
			vols. per cent	*vols. per cent*		*per cent*	*vols. per cent*	*mg. 100*
34	29127	February 22, 1923	18.4	42.6	43.2	6.72	57.4	289
35	35283	November 29, 1924	25.2	59.8	42.1		59.9	379
36	34704	September 25, 1924					19.5	350
37	15120	December 13, 1922	20.1	46.2	43.4	7.14	50.6	335
		December 14, 1922	22.3	46.8	47.6	7.43	52.1	306
38	33964	July 12, 1924	16.1	39.6	40.7	6.64	54.2	376
39	18067	March 21, 1923	23.3	44.7	52.0	5.45	16.5	342
40	34878	October 16, 1924	17.6	36.7	47.9	5.69s	40.3	341
41	34513	October 25, 1925	19.7			6.03	51.3	330
		October 27, 1925				4.57	57.6	322
42	35857	February 8, 1925	20.4	49.6	41.1	6.24s	66.6	349
43	34611	September 17, 1924				6.13s	41.4	
		September 22, 1924	19.6	42.7	45.9	5.45s	63.0	336
44	16670	February 12, 1923	13.8	27.8	49.8	5.36	30.9	370
		February 22, 1923	15.2	30.9	49.0	5.03	62.1	372
		August 25, 1923					26.6	337
		November 3, 1924						
45	10572	November 14, 1922	17.2	36.2	47.6	5.75	63.3	365
46	34295	August 23, 1924	18.0	41.5	43.4	6.22	70.3	358
		August 30, 1924	16.7			6.64	68.0	358
47	36140	March 4, 1925	19.9			6.39s	22.0	
		March 6, 1925	18.3	43.4		5.22s	50.6	351
		March 14, 1925	16.2			4.95s	64.7	378
		March 23, 1925	14.8			4.98s	61.8	389
	36140	March 31, 1925	17.4			6.17s	67.6	375
48	15096	December 11, 1922	22.4	47.2	47.4	7.29	51.1	279
		December 13, 1922	21.3	45.1	49.3	5.77	76.5	277
		January 11, 1923	18.4	40.1	45.9	6.30	54.1	388
49	22513	August 16, 1923, a.m.					36.8	350
		August 16, 1923, p.m.					36.6	361
		August 17, 1924					41.2	354
		August 18, 1923					39.5	353
		August 19, 1923					41.3	321
		August 20, 1923					45.6	352
		August 21, 1923					52.3	337
50	29061	January 28, 1924	22.5	45.8	49.3	8.37	16.8	337
		January 29, 1924	21.0	42.4	49.6	8.07	41.6	
		January 30, 1924	19.0	40.6	46.8	6.20	49.3	393
		February 6, 1924	18.4	38.2	48.2	5.85	60.9	355

Continued

7	8	9	10	11	12				
ganic P	Total acid	Total base	Organic acid	pH	Blood non-protein nitrogen	Blood sugar	Nature and treatment of blood	Urine sugar	Urine acetone
mg. per cent	*mM.*	*mM.*	*mM.*		*mg. per 100 cc.*	*mg. per 100 cc.*			
	121.3			7.61	33	167	V. cont.	4+	0
2.3	145.4	178.2	32.8		53	88	V. cont.	4+	2+
race	112.8	132.3	13.5			469	V. cont.	4+	4+
	129.9			7.32	39	449	V. cap.	4+	2+
	123.1			7.34		274	V. cap.	0	0
3.8	142.6	168.2	25.6		54	255	V. cont.	4+	+
	111.8			6.78	38	1,000	V. cap.	2.5%	4+
2.3	124.4	156.3	31.9		25	206	V. cont.	2+	4+
1.5	126.1	161.9	35.8		43	197	V. cont.	4+	2+
	124.8					176	V. cont.	+	0
3.8	139.4	181.8	42.4		55		V. cont.	2+	+
						315	V. cont.	4+	3+
3.5	133.6	149.1	15.5	7.48		341	V. cont.	0	0
	127.4			7.09		441	V. cap.	4+	4+
	142.1			7.42		313	V. cap.	+	+
	118.0			7.02		435	V. cap.	4+	4+
4.2		162.7					V. cont.	0	0
	142.2			7.43		290	V. cap.	0	+
3.5	143.9	144.6	0.7			200	V. cont.	2+	+
3.7	143.3	144.7	1.44	7.39		152	V. cont.	0	0
2.4	146.6	146.6			37	341	V. cont.	4+	3+
1.8	130.3	153.4	23.1		24	179	V. cont.	+	+
3.4	144.1	163.0	18.9			127	V. cont.	0	0
2.9	144.4	156.3	11.9			155	V. cont.	+	0
3.9	147.0	155.4	8.4		23	206	V. cont.	0	0
	114.5			7.33	67	742	V. cap.	4+	4+
	123.5			7.51	39	216	V. cap.	0	0
	145.0			7.35	22	297	V. cap.	0	+
	127.2			7.18	44	497	V. cap.	4+	4+
	129.9			7.17		400	V. cap.	4+	4+
	130.4			7.23		278	V. cap.	4+	4+
	129.2			7.21		294	V. cap.	4+	4+
	121.3			7.23		251	V. cap.	4+	4+
	131.9			7.28	37	233	V. cap.	4+	4+
	131.1			7.34		200	V. cap.	3+	3+
4.4	118.5			7.28	37	308	V. cont.	4+	4+
2.4				7.37		142	V. cont.	4+	+
2.0	144.7			7.52		229	V. cont.	+	0
2.9	138.8			7.54		241	V. cont.	+	0

TAB

Case number	Hospital number	Date	1 Oxygen capacity	2 Cell volume	3 Ratio of column 1 to column 2	4 Proteins	5 CO_2	6 Cl
			vols. per cent	*vols. per cent*		*per cent*	*vols. per cent*	*mg. pe 100 c*
51	22350	November 19, 1923	20.1			8.02	13.5	372
		November 20, 1923	20.1			7.45	33.7	345
		November 21, 1923	17.0			5.94	47.8	348
		November 27, 1923	16.9			6.24	73.8	311
		December 17, 1923	16.7			6.73	67.4	335
		September 6, 1924					19.0	
		September 7, 1924				5.06s	26.7	358
		September 8, 1924				3.22s	47.0	367
		September 10, 1924				4.75s	28.0	310
		September 16, 1924				6.70s	59.8	366
		September 24, 1924	16.5	37.6	43.9	6.14s	57.7	353
		October 7, 1924	16.5	40.9	40.4	6.98s	65.1	369
52	29176	February 9, 1924	18.9	40.6	46.6	6.95	20.8	336
		February 10, 1924	16.7	36.8	45.1	6.37	38.3	343
		March 5, 1924	14.8	34.2	43.3	6.23	66.2	375
		November 10, 1924, 2 p.m.	20.8	58.2	35.7	7.74s	14.5	322
		November 10, 1924, 10 p.m.	20.5	51.2	40.0	7.60s	19.5	305
		November 11, 1924	20.3	48.4	41.8	6.90s	43.1	360
		November 13, 1924	16.9	43.8	38.6	6.55s	55.6	345
53	26416	March 26, 1924	20.4	44.3	46.1	6.37	56.9	347
		March 31, 1924	19.2	42.5	45.2	6.20	64.0	337
		March 22, 1925	20.0	48.5	41.2	7.43s	7.6	356
		March 24, 1925	20.1	46.2	43.5	7.40s	43.0	365
		March 27, 1924	15.4	37.7	40.9	6.03s	51.7	365

chloride after the administration of glucose that support such a theory. One of the authors[3] several years ago attempted to establish a similar relation between blood sugar and plasma chlorides unsuccessfully. In certain experiments reciprocal variations of the two elements were observed, but this effect could not be produced consistently. The

[3] Peters, J. P.: Unpublished experiments.

Continued

7	8	9	10	11	12				
rganic P	Total acid	Total base	Organic acid	pH	Blood non-protein nitrogen	Blood sugar	Nature and treatment of blood	Urine sugar	Urine acetone
mg. er cent	*mM.*	*mM.*	*mM.*		*mg. per 100 cc.*	*mg. per 100 cc.*			
				7.07	37	616	V. cont.	0.8%	4+
5.8	127.2			7.31		344	V. cont.	2.0%	3+
2.9	131.5			7.30		349	V. cont.	0.3%	0
1.6	134.8			7.45		249	V. cont.	+	0
2.7	137.0			7.52		242	V. cont.	0	0
3.0	143.1								
		143.1			31	462	V. cont.	2.1%	3+
		152.5	28.9		37	370	V. cont.	2.5%	4+
4.5	123.6	150.7	20.8		37	233	V. cont.	2.3%	4+
2.2	129.9	152.6	45.3		35	257	V. cont.	2.5%	4+
	106.8	140.5	−3.5		29	270	V. cont.	1.1%	+
4.0	144.0	145.8	7.0	7.49		462	V. cont.	0	0
5.7	138.8	154.7	9.2		22	130	V. cont.	0	0
	145.5								
				7.29		300	V. cont.	4+	4+
3.7	117.2					121	V. cont.	0	2+
5.5	127.0			7.34		150	V. cont.	0	0
4.4	147.3								
		150.5	37.8	6.95		317	V. cont.	3.5%	4+
8.9	112.7	143.7	32.8			429	V. cont.	3.5%	4+
6.0	110.9	143.6	10.3	7.29		278	V. cont.	5.5%	
3.7	133.3	140.8	5.7			246	V. cont.	2.8%	0
5.3	135.1								
				7.19		263	V. cont.	4+	4+
3.4	133.6			7.29		199	V. cont.	+	2+
2.9	134.0								
		154.2	34.7		46	450	V. cont.	4+	4+
5.3	119.5	146.5	11.8		37	174	V. cont.	2+	+
1.7	134.7	140.6	3.1		29	283	V. cont.	3+	0
4.2	137.5								

administration of large amounts of glucose causes such a variety of changes in the metabolism and the composition of blood that a study of something more than the chlorides is necessary before one can discuss osmotic equilibrium. Although total base is not in any sense a measure of the osmotic pressure of the blood, it does offer an estimate of the fraction of the total osmotic pressure contributed by the electro-

lytes. If the electrolytes compensate for the accumulation of non-electrolytic osmotically active substances such as glucose, one would expect to find some evidence of such a mechanism in diabetic patients with high blood sugar. On the contrary, in the cases of our series with hyperglycemia, but without ketosis, the level of base is high rather than low. In some cases, to be sure, such as 13 and 17 base and glucose change in opposite directions. On the other hand, in 14 base remains unchanged as the blood sugar falls and in 21 base falls to a surprising extent while the level of glycemia remains entirely unaltered.

Examination of the different acids in the 10 cases in which they were studied shows, with two exceptions, a rather high total acid level, which is due usually to an elevation of chloride (the high CO_2 of 5 followed the administration of salicylates and sodium bicarbonate).

Although the general trend of both acid and base figures is towards high rather than low values, there are several exceptions to the rule so striking that generalizations concerning the character of the electrolyte picture of diabetes seem hardly warranted. If one examines the protocols of these patients which are presented in brief below, one can hardly be surprised that such variations are encountered. The average diabetic patient who enters a general hospital does so not because he has diabetes, but because of some concomitant condition which has usually aggravated the diabetes. The effect of these conditions must be taken into account in any analysis of blood chemistry. Further than this the manifestations of uncomplicated diabetes are variable. Diuresis or polyuria and other symptoms do not always bear a constant relation to the disorder of carbohydrate metabolism. This is well illustrated by the findings in 12. Proteins and chloride were both low in this case although there was nothing peculiar in the clinical picture. Careful study of the clinical notes revealed the fact that on the day the blood was taken she developed a striking diuresis that continued for 3 days.

Cases 22 to 26 represent 5 observations on patients with uncomplicated diabetes of a severe type with marked ketosis, but without any dyspnea and without any considerable reduction of plasma CO_2. To these may be added the first two observations of 54, the last case in the table. The dissociation of acidosis and ketosis has long been

recognized. Ketonuria without reduction of the alkaline reserve is not uncommon in patients with moderately severe, uncomplicated diabetes. Y. Henderson (15) indeed uses this as an argument against the current theory of diabetic acidosis which presumes that the base which neutralizes ketone acids in the blood is derived from bicarbonate. He says "if lactic acid or any other strong acid is added to blood, most of the alkali which neutralizes it is drawn from the hemoglobin alkali reserve; and it causes, therefore, only a very slight decrease in the plasma bicarbonates." It has already been shown (1) that in the case of the lactic acid of exercise, to which Henderson is especially referring in this sentence, most of the alkali which neutralizes the foreign acid is derived not from the hemoglobin, but from the tissues. In this case, however, the body is dealing with an acid that can be and usually is oxidized. The provision of alkali from the tissues does not, therefore, ultimately lead to any appreciable depletion of the base stores of the organism. The acidosis of diabetes, on the other hand, is due to the accumulation of acids which the body can not destroy and which can only be disposed of through the kidneys in combination with a certain amount of base. From the diminution of the chlorides exhibited by these patients it would appear that in conditions of more or less chronic ketosis these acids were able to spare bicarbonate, robbing chloride of its base instead. This not only preserves the bicarbonate, but also prevents a change of blood pH.

On the other hand it may be that the chloride recession is only a means of maintaining a fixed level of base and a constant electrolytic concentration. From these experiments alone it is impossible to decide between these alternative possibilities because there are no simultaneous determinations of acid and base. In the case in which base was determined it proved to be quite low. In this instance, certainly, the electrolytic fraction of the osmotic pressure was low. Whatever may be the mechanism which determines the depression of chloride, the base which neutralized the bicarbonate was certainly not derived, as Henderson suggests, from the hemoglobin. The base combined with hemoglobin is, as Van Slyke, Wu and McLean (3) have shown, determined by the pH and the concentration of hemoglobin in the cells. The pH of the cells bears a definite relation to that of the plasma. The latter, in these cases is normal as is the height

of the carbon dioxide absorption curve. The amount of base combined with hemoglobin was also, then, presumably normal because it is inconceivable on theoretical grounds that the carbon dioxide and pH of the cells could have been reduced without affecting the plasma. That there may be no possible doubt about the matter, however, it may be mentioned that the whole bloods of 24, 25 and 26 were also analyzed for CO_2. The relation between the CO_2 of cells and plasma was in each case quite normal.

The majority of the cases in the table from 27 on demonstrate quite conclusively the point made above, that in estimating the cause of changes in the metabolic or chemical picture of diabetic patients due attention must be given to the associated pathologic conditions. Clinical knowledge of diabetes would be measurably advanced if case reports and studies contained more details regarding the clinical condition of patients, even at the expense of metabolism data. This series of cases gives a fairly representative idea of the type of conditions which the severe diabetics in a general hospital present. There has been much discussion of Bock, Field and Adair's (16) discovery of organic acids other than ketone acids in diabetic patients. There is no reason to consider this as extraordinary unless it can be proved that these acids were produced as the result of the metabolic disorder of diabetes itself. This they did not prove. Case 4 of their series presented symptoms not usually encountered in uncomplicated diabetes and a well marked elevation of temperature. In our experience diabetic acidosis and coma may be taken as presumptive evidences of some infection or other pathologic condition and are seldom, if ever, as is generally taught, entirely the result of mismanagement or dietary indiscretions. The latter bring their own uncomfortable rewards of a different kind and may, to be sure, greatly intensify the harmful effects of any accident or infection. Often enough the infection is so slight that it is overlooked or neglected. Case 44 shows what even a slight cold may do to a diabetic patient who observed dietary regulations at all times with meticulous care. On two occasions a mild coryza precipitated severe ketosis and acidosis and brought him to the hospital on the verge of coma.

Cases 27 to 32 demonstrate that low chlorides are often observed in diabetic patients without ketosis and in the presence of a normal

alkaline reserve. This does not mean that the reductions noted in the previous group may not have been, at least in part, due to ketosis. Some light is thrown on this question by the contrast between 30 and 31. On both two observations were made: one at the time of admission when there was an extreme hyperglycemia and glycosuria, the second when both hyperglycemia and glycosuria had been reduced by treatment. Case 31 also had severe ketosis at the time of his first examination, while 30 showed no ketonuria. The total acid concentration of the latter remained unaltered after treatment, while that of 31 increased, presumably to satisfy the base freed by the combustion of organic acid.

The mechanism of the acid increase is interesting. As chloride had been largely responsible for the original low acid level, one would naturally have expected chloride to play the major part in the restoration of equilibrium. On the contrary, chloride instead of going up fell further, while bicarbonate rose to an excessively high point. This tendency for bicarbonate to overshoot the mark in the recovery from acidosis was first pointed out by one of the authors (17) in 1917 and has since been confirmed by Stillman, Van Slyke, Cullen and Fitz (18), Cullen and Jonas (27) and Bock, Field and Adair (16). The latter have, furthermore, found that this rise of bicarbonate results in shifting the pH somewhat to the alkaline side of normal. It had already been shown by Peters (17) and by Stillman et al. (18) that the alveolar CO_2 under these conditions remained relatively low, which in itself was an indication that such a shift of pH must occur.

A possible explanation of this phenomenon is offered by these experiments. The low base of cases 23 and 32 and the general low level of total acid and chlorides even when there is no ketosis and, therefore, in all probability, no great excess of organic acid, intimates that the blood, at least, is deficient in both chloride and base. It is, perhaps, advancing too far to suggest that this deficiency in the blood may reflect a similar depletion of the tissues. If such a depletion does exist, however, it is not impossible that it has its origin in an excessive excretion of chloride. From the standpoint of the blood alone, in any case, chloride does not appear to be available to replace the base released by the combustion of the ketone acids. Carbon dioxide has, therefore, to bear the whole load. CO_2 is, however, rendered

available only as it is produced in the metabolism and excretion usually follows production *pari passu*. The rapid seizure of carbon dioxide by the newly liberated base reduces the tension of free carbon dioxide and consequently the pulmonary carbon dioxide excretion, and causes the pH of the blood to rise.

If there is a depletion of the chloride and base stores of the body this depletion is not a direct result of ketosis because it is encountered when ketonuria is absent. Furthermore, there is no reason to suppose that the excretion of ketone acids, which in themselves abstract base from the tissues, would provoke a chloride diuresis which could only withdraw further base at a time when it is most urgently required. Diabetic polyuria may lead to the excretion of excessive chloride. Unfortunately no opportunity to study the inorganic metabolism of these patients during the development of the acute condition is afforded, especially since in insulin such an efficient weapon has been provided against all the misfortunes of diabetes. Serious diuresis seldom survives efficient insulin therapy long. The comparatively low chloride, protein and total acid of 12, mentioned above, which coincided with the institution of a secondary polyuria would be readily explained if diabetic polyuria is associated with chloride diuresis.

On the whole, it is evident, that the majority of patients with uncontrolled diabetes of a type inherently severe or rendered serious by some concurrent condition, whether they develop ketosis or not, generally exhibit a reduction of plasma chlorides and probably of total base. Case 33 is an exception, but it is hard to estimate in this case the relalative effects of diabetes, fractured skull and therapeutic measures.

Cases 34 to 38 had pneumonia. Cases 34, 36 and 37, with typical lobar pneumonia, presented extremely low chlorides and total acid, even in the absence of ketonuria. If diabetes and pneumonia both tend to reduce chloride, such a result might reasonably be expected. The pneumonia of 35 certainly began as a pulmonary infarction. This, the presence of severe cardiac decompensation and the previous subcutaneous administration of saline may together account for the high base, acid and chloride.

This experiment is the first in which ketonuria occurs and in which both total base and acid were determined. It affords, then, the first opportunity for the estimation of the value of the procedure as a

means of detecting and evaluating the accumulation of ketone acids in the blood. The value of organic acid is, as it should be, far above normal. By the same criteria, however, the method fails completely in the next case, 36, in whose serum only 13.5 millimols of organic acid were found, although she was in diabetic coma and had marked ketonuria. This stands as the only observation in which ketonuria was discovered without a concomitant increase of the organic acid of the serum. The accuracy of the procedure must not be lightly condemned on this account. In the first place the proteins were not determined and the value ascribed to them was probably excessive because it is fair to assume in the light of experience that pH and protein concentration were both reduced.

Case 38 had high base, normal acids and plasma organic acid high in proportion to the degree of ketosis indicated by urine examination. She had, however, advanced cardiac decompensation, edema and almost complete anuria. Severe ketonemia with minimal ketonuria as a terminal event in diabetes has been encountered not infrequently. On the other hand it is quite as possible that the organic acidemia was caused by other acids, the product not of diabetes but of the associated diseases.

Case 39 had been vomiting for about 36 hours before she was admitted to the hospital. Vomiting, with acute abdominal pain as the precipitating cause of diabetic toxemia appears several times in this series of patients. In this case and in that of 53 the picture was so strongly suggestive of an acute abdominal condition that the advisability of immediate exploratory operation was seriously considered. In most instances rest, proscription of fluids by mouth, the administration of large amounts of fluid containing salt and glucose by other routes together with large doses of insulin has resulted in the rapid elimination of symptoms. The improvement is so rapid in these cases that it is hard to believe that the syndrome is referable to organic disease of the pancreas or any other abdominal organ. Case 52 both times that she was admitted presented a similar syndrome. In her case it seemed quite possible that the attacks were initiated by some disorder of the action of the heart.

The electrolyte disturbance produced in the diabetic by vomiting is quite different from that which develops in the normal individual.

Plasma chloride does, to be sure, diminish and base may, as will appear subsequently, also fall. Bicarbonate decreases, however, with extraordinary rapidity and serious acidosis may eventuate within a few hours. Either the vomiting or the underlying cause of the vomiting has a profound effect on carbohydrate metabolism, practically deleting the power of the individual to utilize glucose. This is evidenced by the maximum blood sugar values encountered in vomiting cases. The inevitable consequence of this loss of carbohydrate tolerance is the rapid accumulation of ketone acids in the blood. This may be furthered by the failure of the excretory powers of the kidney to which the authors have called attention in another connection (25). The case is comparable to the acidosis which develops in vomiting infants. Shaw, Moriarty and Talbot (20) have shown that this acidosis is due to a starvation ketosis and may be rapidly relieved by the administration of carbohydrate. They believe that ketosis can be produced more easily in infants than in adults because the former possess a smaller reserve supply of carbohydrate. To this must be added another factor. As vomiting reduces the chloride and base of blood the usual defenses of the body against organic acid is diminished. Bicarbonate must, as it were, bear the whole acid burden alone. This leads to earlier alteration of pH in the acid direction.

The effects of intestinal obstruction and peritonitis attended by vomiting were briefly presented in the preceding paper of this series (1). Chloride and base proved to be reduced. Case 40 presented constipation of such severity that it amounted to complete intestinal obstruction. For three days preceding the examination her bowels had not moved. She had not vomited, but had taken little food. The diabetes had been so aggravated that there was considerable ketonuria, but total base had not diminished. Chloride is, indeed, reduced and bicarbonate has also suffered some loss, but only because they have been displaced by organic acid. Case 41, with cholelithiasis presents a very similar picture; she had vomited only once during the course of the abdominal condition.

The next case, 42, does not properly belong among true diabetics. With an intestinal obstruction following resection of the cecum he developed glycosuria, hyperglycemia and ketonuria. The metabolic disturbances disappeared completely shortly after the operation. At

the time of the blood examination he had received insulin and glucose, but glycosuria and ketonuria had not yet cleared up. This explains the high organic acid concentration of the serum. The excessive amount of base may be the result of large hypodermic saline injections which he had received. If this is the case the low chloride must be looked upon not as a true salt deficiency, but as a displacement of chloride, probably into the tissues, to free base to the ketone acids.

Case 43 illustrates the electrolyte picture during the latter stages of the recovery from severe acidosis provoked by an attack of vomiting. Base is still somewhat depressed, although bicarbonate has returned to the normal level; chloride is quite low. The pH is near the upper limit of normal.

The occurrence of edema in diabetic patients has long been recognized, but has never been explained in a satisfactory manner. Because it can be delivered rapidly by the administration of acidifying diuretics (21, 22) and because it seldom, if ever, appears in association with acidosis it is generally believed to be in part due to an alkalosis. The six patients, 44 to 49 inclusive, all presented subcutaneous edema at some stage in the course of their illnesses. All attempts to connect the edema with a characteristic electrolyte picture fail. It is quite true that edema never occurred during acidosis; but the level of bicarbonate during edema was frequently well below the upper normal limit. That acidosis causes dehydration and recovery from acidosis is attended with the retention of water is well established (23). During the recovery from severe diabetic acidosis body weight increases at a surprising rate and to a remarkable extent even if edema does not develop. There is less certain evidence that the administration of excessive amounts of alkali will produce an abnormal retention of fluid. In a healthy individual it has not proved possible to provoke a true edema by means of alkali. In certain pathologic conditions, however, edema has been produced by the administration of sodium bicarbonate, as if the disease had increased the sensitivity of the organism to the hydrating effect of alkali. Thus Binger, Hastings and Neill (24) have reported the occurrence of edema after bicarbonate therapy in a case of pneumonia.

Under certain circumstances diabetes seems to confer such a sensitivity to alkali. Case 49 developed a moderate edema, in spite of

the presence of severe ketosis, after she had received sufficient bicarbonate to restore the carbon dioxide absorption curve of the blood to the normal level. In another connection (19) it was pointed out that this edema did not affect the blood which was highly inspissated as is indicated by the high hemoglobin, cell volume and plasma protein. It did succeed in displacing chloride, which was probably already low because of the combination of ketosis and vomiting, to an extreme degree. By the administration of insulin ketosis was entirely eliminated in the course of 36 hours and the base released by the ketone acids was taken up by bicarbonate. As the latter had been high at the outset it rose far above the normal limit. The total acid, however, remained low and vomiting persisted. With the impression that the chlorides and base of the body were depleted the patient was given sodium chloride on the third day. This was followed almost immediately by alleviation of symptoms. With a clear recognition of the dangers of *post hoc* reasoning the results of sodium chloride therapy in this and other similar cases has seemed to the authors to be of distinct benefit, a further intimation that the low chlorides and base indicate salt depletion.

Comparison of the other four cases during and subsequent to edema shows that the latter may occur when base is high or low, when chloride is high, low or normal, when protein is at any level. Finally, from 46 it appears that it may come and go without any significant change of the acids or base. The ultimate cause of the predisposition to the hydrating effect of alkali which these diabetic patients exhibit the authors are inclined to ascribe to malnutrition. In their experience edema is encountered only in patients who have undergone tissue wastage as a result of severe or improperly treated diabetes. In all the cases they have encountered edema has disappeared spontaneously when an adequate diet had been maintained for a sufficient period. If this is the case diabetic edema, for which no cause can be found in complicating pathologic conditions may be accepted as evidence that the patient has received an inadequate diet. At the same time it is a presumptive indication that he is not suffering from acidosis.

The next case, 50, illustrates again the manner in which chloride comes to the aid of bicarbonate in compensating chronic ketosis.

The same is true of 51. In this case feeding was difficult because of the mental condition of the patient. Whether it was failure to administer sufficient salt or the development of pneumonia that caused the reduction of chloride of the last observation only analysis for base, which was not carried out, could have determined.

Case 52 has already been mentioned. She was admitted to the hospital three times: first for the usual diabetic symptoms, on both subsequent occasions because vomiting and abdominal pain had precipitated severe acidosis. In spite of the fact that she was almost comatose and the CO_2 was extremely reduced chloride had not suffered any loss. As ketosis cleared up, although she was given saline by hypodermoclysis, chloride fell as bicarbonate rose. Again the failure to determine base prevents any deductions concerning the general electrolyte level. Vomitus was not, in this case, analyzed for acid and chloride. It is, therefore, impossible to say whether vomiting had resulted in loss of chloride or not. It may have been that the vomitus contained little or no chloride. The urine at the time of admission and until the diabetic toxemia had been relieved was almost free from chloride. The concentration as well as the total amount of chloride was diminished. This, as we have shown (25) is quite characteristic of the condition. At the same time the patient was extremely dehydrated. This dehydration must be brought about by several factors. Dyspnea must lead to excessive loss of fluid by evaporation. Vomiting prevents restoration of this loss and promotes further fluid depletion. The water lost by respiration carries with it no salt. The urine, as the toxemia advances contains relatively more and more water and less chloride. Unless the vomitus contains large amounts of acid or salt there must be a tendency to concentrate chloride in the body. Such a concentration may occur if the total chloride in the body remain constant or even if it diminish. This will depend entirely on the relative amounts of chloride and water excreted. Between the first two blood examinations 52 received about 7 gm. of NaCl and excreted only 0.3 gm. in the urine. During the same period she was given 1300 cc. of fluid, while only 200 cc. of urine and 200 cc. of vomitus were recovered. Between the second and third examinations she received 21 gm. of salt and 4000 cc. of fluid and excreted 2200 cc. of urine containing 6 gm. of sodium chloride and vomited only

50 cc. of fluid. There was, then a large retention of both fluid and salt. (The patient was afebrile and the respiratory ventilation diminished rapidly, so that presumably the loss of water by means of the lungs was comparatively normal.) It is impossible to estimate the relative amounts of fluid and salt retained in the body because the amount of water lost by other routes and the amount of salt in the vomitus were not measured.

The proportion of water and salt retained in the plasma can be calculated. From the plasma protein figures it appears that the volume of the plasma at the time of the second observation was to that at the time of the first observation as $\frac{8.02}{7.45}$ or 1.08. The ratio of the chlorides from the same plasmas was $\frac{372}{345}$ which also equals 1.08. If plasma protein may be considered a criterion of plasma volume, the actual amount of chloride in the plasma has not changed. The reduction of chloride concentration is due entirely to dilution of the plasma. Between the second and third examinations the proteins fell another 27 per cent, while chloride remained practically unchanged. This can only mean that the actual amount of chloride in the plasma increased, but that the plasma water increased at the same rate.

It appears then that blood chlorides, and probably tissue chlorides, were actually depleted at the time of admission, but that this depletion was masked by inspissation of the plasma. This theory is supported by the avidity with which chloride and water were taken up by the blood and tissues during recovery.

The last time this patient entered the hospital she was in even worse condition and recovery was proportionately delayed. This time more studies were made although the first blood analysis, which was done in haste late at night was quite incomplete. There can be no doubt this time that base was low, so low that chloride concentration must have been reduced. Vomiting continued for some time. This vomitus was found to contain only the most minute amounts of chloride. For example the patient lost by emesis during the first 24 hours about 2200 cc. of fluid, which contained altogether only about a gram of sodium chloride. The sodium chloride in the urine of the same period amounted to less than 2 gm. The patient had,

however, received 2000 cc. of normal saline subcutaneously and a considerable, but uncertain amount by rectum. Because the vomitus analyzed in the hospital was chloride free one can not argue that earlier emesis had not played a part in the reduction of the plasma salt. The relation of blood chloride to the excretion of hydrochloric acid by the stomach is still obscure. The latter may diminish as the chloride stores of the body become impoverished.

Ketosis in this case diminished but slowly in spite of the administration of large doses of insulin. Therefore, although total base returned to its normal level rapidly after the administration of large doses of salt, chloride and bicarbonate rose only gradually, yielding to the load of organic acid. On September 10, when the condition of the patient seemed to be progressing favorably a new attack of vomiting was precipitated. Within 4 hours acidosis had again developed and both bicarbonate and chloride had fallen to extremely low levels, chloride bearing the brunt of the load. Respiratory ventilation had increased to such an extent that the power of eliminating carbon dioxide must have been taxed to the utmost and chloride was forced to come to the rescue. In this instance certainly vomiting can have had little direct influence because only 0.2 gm. of chloride was found in the vomitus which was recovered, more than half of the total. This may be the reason that the effect of the upset on the total base was minimal. The fact that the total base concentration was relatively unimpaired enabled the blood to assume the extraordinary acid load with greater ease.

The reduction of base and chloride at the next examination may have been due to the fact that during the recovery period little attention was given to the administration of salt, while glycosuria and diuresis continued. As general improvement continued and diet and insulin were regulated all the electrolytic elements gradually returned to the normal level.

The next patient, 53, was also admitted twice. The first time he had vomited but once and from his story acidosis seemed to have developed slowly. Base figures are not available but in view of the height of total acid it can hardly have been greatly reduced. Both chloride and bicarbonate were low. With diet and insulin alone he recovered rapidly, all the acids resuming their normal values.

The second admission followed an acute attack of vomiting and abdominal pain. This had lasted only a few hours before he entered the hospital, but he was already seriously dehydrated and in a critical condition. Again base is little reduced, but the ketones have displaced both chloride and bicarbonate. There is an evident anhydremia. This time he was given immediately a hypodermoclysis of glucose and 1000 cc. of normal salt. Almost no further salt was given, however, for the next two or three days. Under these circumstances, although the acidosis was overcome base and chloride remained relatively low. In this case vomiting persisted for some time after he entered the hospital, the vomitus containing small, but appreciable amounts of chloride.

The first admission of case 54 has already been mentioned. On this occasion he came in suffering from diabetic symptoms only: polyuria, dehydration, loss of weight and weakness. He had ketosis with normal bicarbonate and low chloride.

The second time he was driven to the hospital by an acute respiratory infection and an active tuberculosis, in deep diabetic coma. CO_2 had fallen to an almost unprecedented point while chloride had suffered little reduction. He was given 2000 cc. of saline and 600 of glucose solution subcutaneously within the next twenty-four hours and as much fluid containing carbohydrate as possible by mouth. Because of his mental state the amount given by mouth was comparatively small. After this he again received little salt for the next few days. Again base fell, although chloride remained constant. In this case and the last there was apparently a certain amount of chloride reserve in the tissues that could be called upon to neutralize part of the base liberated by ketones and to maintain a constant concentration of bicarbonate in spite of the fact that the serum was diluted, but this was not enough to keep up the total salt concentraion of the serum.

In contrast to these cases it may be well to turn again to case 48. This patient had a severe acidosis, but it had apparently developed gradually. At the time of admission he had moderately severe ketosis and reduction of both base and CO_2 (serum chloride was not determined). He was entirely rational and able to take a regular diet. He was given 50 gm. of protein, 150 of fat and 100 of carbohydrate with

large doses of insulin at once. This insured him an adequate supply of salt. This may be the reason that during the recovery period both salt and base rose rapidly to the normal level. In fact for a while they surpassed this level.

GENERAL DISCUSSION

The general effect of ketosis on the total electrolytes of the blood is evidently somewhat variable, depending upon the severity and duration of the ketosis, and the nature of associated symptoms or pathologic conditions. If ketosis develops comparatively slowly over a long period it may attain a considerable degree of severity without producing an appreciable reduction in the concentration of bicarbonate in the blood. In these cases bicarbonate is spared at the expense of chloride, which is proportionately reduced. Occasionally the total base may increase, but this is rather unusual. More often base is diminished. In cases of severe acidosis, especially if it has developed rapidly, with symptoms of grave diabetic toxemia bicarbonate has invariably been reduced. Even in these conditions, however, chloride is usually also affected. Base may be normal, but is often low and rarely, if ever, high. The ability of the organism to utilize for the neutralization of organic acid the base usually combined with chloride in addition to that derived from bicarbonate permits it to sustain a given acid load with less disturbance of the pH and a less serious demand on the respiratory mechanism.

The delivery of base by chloride may occur with extreme rapidity. In case 52 on September 10 the chloride content of serum studied only four hours after the onset of a vomiting attack which had precipitated a recurrence of ketosis and acidosis was extremely low. It is hard to escape the conclusion that in this case, at least, chloride had merely been transferred to the tissues. Certainly it was not excreted in the vomitus, and the urine of that day contained less chloride than did the urines of the preceding and following days. Unless an excessive amount was lost in the stools, which is hardly probable, the only possible inference is that the base of chloride can be rendered available for the neutralization of excess organic acids without the intervention of the kidneys, the chloride merely passing into the tissues. Once in the tissues, the chloride ions must again find base

with which to unite. This may seem like robbing Peter to pay Paul. In order to prevent changes in the reaction of the blood the organism immobilizes the base stores of the tissues. If these stores are as limited as those of the blood such a process could only result in the impairment of the ability of the tissues to neutralize other acids. It is, however, quite possible that the tissues possess reserve supplies of base in a more fixed form, in the bones, for instance, that may be mobilized to meet just such emergencies.

In most of the cases with severe diabetic toxemia in this series the base of the serum was seriously diminished. Often enough this depletion exhibited itself in a reduction of the concentration of base. In other instances, although the concentration of base was normal, the volume of the serum had been reduced by dehydration. The natural inference is that the total amount of base in circulation was diminished. This inference is supported by the alterations in the electrolytes observed during recovery from toxemia. In the majority of instances total base, total acid and chloride diminished during the stage of water retention that accompanied the recovery process.

Although reduction of serum chloride can be effected without the intervention of excretory organs and does not necessarily imply any deficiency in the chloride content of the body as a whole one can not escape the impression that in most of these patients with severe ketosis and diabetic toxemia there is an actual depletion of the body salts and especially of chloride. The process of transfer to the tissues may be only a temporary expedient for the mobilization of base to meet a sudden emergency. The same forces may determine the transfer of chloride ions through the kidney into the urine in excess as the process continues and thus prevent the excessive accumulation of chloride in the tissues which would otherwise occur. Loss in the feces may be increased in the same manner. The fact that vomitus has been found, in a few instances, poor in chloride at a time when the serum chlorides were already low is no evidence that at an earlier period vomiting did not play an important rôle in the production of those same low serum chlorides. However the chloride depletion may have been effected, circumstantial evidence of its existence is found in the persistent depression of the chloride level during recovery from ketosis. If the chloride has actually escaped from the body and

is not merely segregated in the tissues it has presumably been excreted without the loss of an equivalent amount of base, the latter having been retained for the neutralization of the continuously renewed ketone acids. By only one means can the body effect such a differential excretion of as strong an acid ion as Cl, that is by the substitution of ammonia for an equivalent of fixed base.

It is not difficult to appreciate why diabetic acidosis should produce base deficiency. Every molecule of organic acid excreted must carry with it from the body into the urine a certain amount of alkali. The amount of fixed alkali thus removed is reduced to a minimum by two factors: the ability of the kidney to excrete an acid urine and to substitute ammonia for the alkaline metals. These safeguards are not, however, sufficient to spare base entirely under the strain of continued acid production. A certain amount of base is inevitably lost. Gamble, Ross and Tisdall (26) have shown in the analogous condition of starvation acidosis, that the body excretes sufficient water to maintain the concentration of base in the body at a constant level. If this explanation be accepted acidosis is the primary cause of dehydration and of salt or base depletion. J. B. S. Haldane (23) has shown that a great variety of acidifying measures lead to diuresis and water depletion.

Although the theory of Gamble and his associates explains in a satisfactory manner the phenomena of starvation acidosis, it does not entirely cover the phenomena of diabetes. The most severe stages of dehydration are undoubtedly encountered in conjunction with acidosis; but minor grades of dehydration occur at times in the absence of all evidences of acidosis and ketosis. This dehydration is presumably referable to polyuria which has in turn been ascribed to the effect of glycosuria. Unless the water loss in these cases were attended by an equivalent loss of base the concentration of salts in the body would become increased. Retention of water during recovery seems to take place even if an inadequate amount of salt is given, with the result that in many cases the concentration of base in the plasma falls as the patient first begins to improve.

Without denying that acidosis is an important agent in the production of dehydration in diabetics and with complete deference to the cogent arguments of Gamble concerning the mechanism by which acidosis produces this effect, in diabetes other forces, possibly glyco-

suria itself, may aid in provoking an excessive elimination of water. A primary loss of salt will, as Gamble has shown lead to a secondary discharge of water; it seems likely also that a primary loss of water, if it lead to true dehydration of the tissues, will be attended by an equivalent loss of salt. When the two forces are both active, as in diabetic toxemia, therefore, the body will suffer a maximum loss of both water and salts.

These observations have a certain bearing on therapy. It has already been demonstrated by Cullen and Jonas (27), Bock, Field and Adair (16) and others that insulin itself is the most efficient weapon with which to combat the acidosis of diabetes. Foster (28) has called attention to the necessity of providing with the insulin an adequate supply of carbohydrate. In this the authors heartily concur. Such carbohydrate does not only protect against the possible contingency of hyploglycemic shock. These patients have exhausted their glycogen stores. The only source from which they are able to derive the necessary antiketogenic material is the body protein. As Shaffer has shown the excess of antiketogenic over ketogenic equivalents in protein is very small. If the organism is forced to rely entirely on protein for the provision of antiketogenic materials it has no margin of safety. The failure to save 39 may have been partly due to the failure to recognize the necessity of administering glucose with insulin. On more than one occasion she recovered consciousness and her hyperpnea diminished, but the effect was only momentary. A further reason for giving carbohydrate is to diminish the destruction of protein which characterizes diabetic toxemia. It has become our custom to disregard the presence or degree of glycosuria until ketonuria and acidosis have been overcome.

The chief contraindication to the administration of carbohydrate is the fear that the persistence of glycosuria will tend to maintain diuresis and dehydration. On just this ground Bock, Field and Adair, although they employed carbohydrate freely in the treatment of diabetic acidosis, express some doubt as to the advisability of such therapy. In actual practice the persistence of glycosuria does not seem to prevent the body from retaining water. This is demonstrated by the results obtained with cases 52, 53 and 54 especially. In all these cases dilution of the blood and relief from excessive polyuria resulted long

before glucose had been eliminated from the urine. Apparently the dehydrating effect of acidosis is more powerful than that of glycosuria.

If acidosis is entirely due to the overproduction of ketone acids it can be rapidly and completely eliminated by the proper use of insulin and carbohydrate. The use of bicarbonate is not only entirely unnecessary, but even inadvisable. The combustion of ketones under the influence of insulin may in itself release so much base to combine with CO_2 as to produce an alkalosis. The administration of additional bicarbonate only heightens this effect and may precipitate edema. Whether bicarbonate is beneficial in the treatment of acidosis due to other acids or not, is a point on which no one can afford to be dogmatic. Its effect is to displace from the serum an equivalent amount of chloride. It usually does, to be sure, at the same time raise the pH of the blood and quiet respirations. If the non-ketogenetic organic acidosis is, as we are inclined to surmise, referable not to diabetes, but to some associated disease, its treatment can be adequately discussed only when the nature of that disease has been ascertained.

Finally, if, as we have inferred, chloride can aid in the maintenance of the blood reaction by yielding base for the neutralization of the ketone acids and can, by this means, spare bicarbonate and relieve the respiratory mechanism, the administration of sodium chloride in conditions of acidosis would seem to be a rational procedure. If, furthermore, the base stores of the body are actually or relatively depleted in states of diabetic toxemia such treatment is the more imperatively indicated and should be continued during the recovery process.

The authors are quite aware that these conclusions are supported more by inference than fact. They represent the first attempt to evaluate and interpret the general electrolytic disturbances of diabetes and diabetic toxemia. Further and more extensive studies to test these hypotheses are contemplated and will be carried out as material presents itself.

SUMMARY

By a procedure outlined in a previous communication the total acid-base equilibrium of the serum or plasma in diabetes has been studied. The procedure has proved capable of detecting any considerable accumulation of ketone acids in the serum.

Ketosis of considerable severity may develop without appreciably affecting the bicarbonate of the plasma. In these cases chloride is usually found reduced and the base required for the neutralization of the organic acid is evidently derived from chloride.

In severe diabetic acidosis base for the neutralization of ketone acids may be ceded by both bicarbonate and chloride. The reduction of chloride may occur with extreme rapidity and without any appreciable augmentation of chloride excretion, indicating that the chloride ion is merely transferred to the tissues.

In profound diabetic toxemia the salt content of the blood and probably that of the tissues is seriously depleted.

The bearing of these phenomena on the treatment of diabetic toxemia, ketosis and acidosis has been discussed.

BIBLIOGRAPHY

1. Peters, J. P., Bulger, H. A., Eisenman, A. J., and Lee, Carter: Total Acid-base Equilibrium of Plasma in Health and Disease. I. General Method of Study and Application to Problems of Physiology. (To appear.)
2. Van Slyke, D. D., and Stadie, W. C.: Jour. Biol. Chem., 1921, xlix, 1. The Determination of the Gases of the Blood.
3. Van Slyke, D. D., Wu, Hsien, and McLean, F. C.: Jour. Biol. Chem., 1923, lvi, 765. Studies of Gas and Electrolyte Equilibria in the Blood. V. Factors Controlling the Electrolyte and Water Distribution in the Blood.
4. Austin, J. H., Cullen G. E., Hastings, A. B., Peters, J. P., and Van Slyke, D. D.: Jour. Biol. Chem., 1922, liv, 121. Studies of Gas and Electrolyte Equilibria in Blood. I. Technique for Collection and Analysis of Blood, and for Its Saturation with Gas Mixtures of Known Composition.
5. Peters, J. P., Bulger, H. A., and Eisenman, A. J.: Jour. Biol. Chem., 1923, lv, 687. Studies of the Carbon Dioxide Absorption Curve of Human Blood. I. The Apparent Variations of pK_1 in the Henderson-Hasselbalch Equation.
6. Austin, J. H., and Van Slyke, D. D.: Jour. Biol. Chem., 1920, xli, 345. Determination of Chlorides in Whole Blood.
7. Van Slyke, D. D.: Jour. Biol Chem., 1923, lviii, 523. The determination of Chlorides in Blood and Tissues.
8. Briggs, A. P.: Jour. Biol. Chem., 1922, liii, 13. A Modification of the Bell-Doisy Phosphate Method.
9. Benedict, S. R., and Theis, R. C.: Jour. Biol. Chem., 1924, lxi, 63. A Modification of the Molybdic Method for the Determination of Inorganic Phosphorus in Serum.
10. Fiske, C. H.: Jour. Biol. Chem., 1922, li, 55. A Method for the Estimation of Total Base in Urine.
11. Cullen, G. E.: Jour. Biol. Chem., 1922, lii, 501. Studies of Acidosis. XIX.

The Colorimetric Determination of the Hydrogen-ion Concentration of Blood Plasma.

12. Folin, Otto, and Wu, Hsien: Jour. Biol. Chem., 1920, lxi, 367. A System of Blood Analysis. Supplement I. A Simplified and Improved Method for the Determination of Sugar.
13. Shaffer, P. A., and Hartmann, A. F.: Jour. Biol. Chem., 1920, xlv, 365. The Iodometric Determination of Copper and Its Use in Sugar Determination. II. Methods for the Determination of Reducing Sugars in Blood, Urine, Milk and Other Solutions
14. Herrick., W. W.: Jour. Lab. Clin. Med., 1924, ix, 458. Reciprocal Relationship of Chlorides and Glucose in Blood.
15. Henderson, Yandell: Physiol. Rev., 1925, v, 131. Physiological Regulation of the Acid-base Balance of the Blood and Some Related Functions.
16. Bock, A. V.; Field, H., Jr., and Adair, G. S.: Jour. Metab. Res., 1923, iv, 27. The Acid-base Equilibrium in Diabetic Coma, Being a Study of Five Cases Treated with Insulin.
17. Peters, John P.: Amer. Jour. Physiol., 1917, xliv, 84. The Response of the Respiratory Mechanism to Rapid Changes in the Reaction of the Blood.
18. Stillman, Edgar, Van Slyke, D. D., Cullen, G. E., and Fitz, Reginald: Jour. Biol. Chem., 1917, xxx, 405. Studies of Acidosis. VI. The Blood, Urine, and Alveolar Air in Diabetic Acidosis.
19. Peters, John P., Bulger, H. A., and Eisenman, A. J.: Jour. Clin. Invest., 1925, i, 451. The Plasma Proteins in Relation to Blood Hydration. II. In Diabetes Mellitus.
20. Shaw, E. B., and Moriarty, M. E.: Amer. Jour. Dis. Child., 1924, xxviii, 553. Hypoglycemia and Acidosis in Fasting Children with Idiopathic Epilepsy. Talbot, F. B., Shaw, E. B., and Moriarty, M. E.: Jour. Amer. Med. Ass., 1924, lxxxiii, 91. Hypoglycemia and Acidosis.
21. Atchley, D. W., Loeb, R., and Benedict, E. M : Physicochemical Studies of Calcium Chlorid Diuresis. Jour. Amer. Med. Ass., 1923, lxxx, 1923.
22. Rockwood, Reed, and Barrier, C. W.: Arch. Int. Med., 1924, xxxiii, 643. Calcium Treatment for Edema.
23. Haldane, J. B. S.: Lancet, 1924, i, 537. Experimental and Therapeutic Alterations of Human Tissue Alkalinity.
24. Binger, C. A. L., Hastings, A. B., and Neill, J. M.: Arch. Int. Med., 1923, xxxi, 145. Edema Associated with Moderate Bicarbonate Administration during Convalescence from Pneumonia.
25. Bulger, H. A., and Peters, J. P.: The Concentration of the Blood and Urine in Diabetic Toxemia. (To appear.)
26. Gamble, J. L., Ross, G. S., and Tisdall, F. F.: Jour. Biol. Chem., 1923, lvii, 633. The Metabolism of Fixed Base during Fasting.
27. Cullen, G. E., and Jonas, L.: Jour. Biol. Chem., 1923, lvii, 541. The Effect of Insulin Treatment on the Hydrogen Ion Concentration and Alkali Reserve of the Blood in Diabetic Acidosis.
28. Foster, N. B.: Jour. Amer. Med. Ass., 1924, lxxxiv, 719. Diabetic Coma.

PROTOCOLS

Case 1. A male, aged 38, laborer, entered the hospital November 22, 1922, recovering from a cold which had aggravated a mild diabetes. Venous puncture with moderate stasis.

Case 2. A male, aged 18, entered the hospital January 30, 1923, with a mild upper respiratory infection and glycosuria of only 2 weeks' standing. (Urine had been examined at frequent intervals for 2 years because of an earlier nephritis from which he had recovered completely.) His cold was subsiding and temperature normal at the time of the venipuncture.

Case 3. An obese female, aged 28, who had had glycosuria without any diabetic symptoms for 2 months.

Case 4. A male, aged 36, with uncomplicated diabetes of moderate severity. Venipuncture at about 11 a.m. At this time he was receiving an adequate diet, and his urine was kept free from sugar and acetone with a single morning dose of insulin.

Case 5. A stout female, aged 53, admitted to the hospital November 20, 1922, with an acute attack of recurrent arthritis with fever. At the time of the venipuncture her temperature was only 99.6°F. and her general condition greatly improved. She had received large amounts of salicylate and bicarbonate. Although sugar was found only in the first urine examination, her fasting blood sugar remained consistently elevated and she presented an excessive alimentary hyperglycemic reaction.

Case 6. A moderately obese female, aged 45, admitted to the hospital November 1, 1922, for glycosuria of 4 years' duration and distinct enlargement of the liver. The glycosuria responded readily to mild dietetic treatment.

Case 7. A somewhat obese female, aged 56, admitted to the hospital for steadily increasing glycosuria. On a liberal diet glycosuria and acetonuria disappeared rapidly.

Case 8. An obese male, aged 55, admitted to the hospital February 2, 1923, with glycosuria and chronic hypertrophic spondylitis. The glycosuria responded readily to mild dietetic treatment

Case 9. A moderately obese male, aged 64, admitted to the hospital April 4, 1924, with progressive dementia and mild glycosuria. The latter disappeared rapidly with mild dietetic treatment. Spinal fluid examination and Wassermann tests proved negative.

Case 10. An obese female, aged 73, admitted to the hospital May 30, 1924, with glycosuria and severe, generalized senile eczema. She presented moderate evidences of arteriosclerosis and hypertension but no signs of cardiac or renal insufficiency. Her diabetes was controlled by the mildest dietary restriction.

Case 11. A female, aged 27, admitted to the hospital June 10, 1924, for an uncomplicated diabetes of moderate severity which was easily controlled by dietary regulation and small doses of insulin.

Case 12. A somewhat obese female, aged 43, with diabetes of 8 years' duration,

admitted to the hospital January 14, 1924, because of a recurrence of diabetic symptoms, which had set in 6 weeks earlier. No complicating condition was discovered. On the day of the blood examination glycosuria, which had proved amenable to mild dietetic treatment, suddenly recurred attended by a profuse diuresis that persisted for three days.

Case 13. A male, aged 51, admitted to the hospital May 21, 1924, with phimosis, mild balanitis, slight evidences of arteriosclerosis and mild hypertension, but no evidences of circulatory or renal failure. Glycosuria had been discovered during a routine insurance examination a few days earlier and was not attended with diabetic symptoms. At the time of the second bleeding the balanitis was cured and the diabetic condition controlled with an adequate diet without insulin.

Case 14. A female, aged 53, admitted to the hospital May 10, 1924, complaining of nervous attacks, weakness and glycosuria and recurrent attacks of gallstone colic. X-ray revealed a large calculus in the gall bladder, and advanced chronic hypertrophic spondylitis. Her diabetes was moderately severe, but responded to diet and moderate doses of insulin.

Case 15. A female, aged 56, admitted to the hospital May 12, 1924, for attacks of weakness, associated with dyspnea, orthopnea and throbbing epigastric pain; occasional edema of the ankles; and glycosuria. Five years earlier an apoplectic stroke had resulted in temporary left sided hemiplegia, and in 1920 cardiac decompensation brought her to the hospital, where glycosuria was discovered. At the time of the venipuncture she had slight hyperpnea and orthopnea, and a few râles at the bases of both lungs, a little pitting edema of both ankles, and slight tachycardia, moderate hypertension and phenolsulfonephthalein excretion of 40 per cent.

Case 16. An obese female, aged 66, admitted to the hospital November 14, 1924, for a burning sensation and weakness of her left hand, nervousness, severe headaches, dyspnea and cardiac palpitation. Her arteries were thickened, her heart enlarged, and her blood pressure somewhat increased. At the time of the venipuncture her general condition was greatly improved.

Case 17. An obese female, aged 60, admitted to the hospital March 30, 1924, for an ulcer on the dorsum of her left foot. Glycosuria had been discovered 5 years earlier. Her heart was moderately enlarged, her systolic blood pressure 236; she had slight dyspnea, orthopnea and tachycardia and a phenolsulfonephthalein excretion of 48 per cent. There was a small superficial ulcer with little inflammatory reaction on the dorsum of the left foot. At the time of the second bleeding her general condition was greatly improved: systolic blood pressure 176, pulse and respirations normal, ulcer healed, diet adequate, no insulin and urine free from sugar.

Case 16. An obese male, aged 66, admitted to the hospital November 8, 1923, for typical diabetic symptoms of four months' duration, with the remains of a subsiding cold. The diabetes was eventually easily controlled by diet without insulin.

Case 19. A female, aged 64, admitted to the hospital February 19, 1923, because of slight cerebral hemorrhage the preceding day, with a mild diabetes discovered 14 years earlier. Her heart was moderately enlarged, her systolic blood pressure 170, her mind somewhat confused.

Case 20. A female, aged 60, admitted to the hospital September 4, 1924, for glycosuria with mild diabetic symptoms of 10 years' duration. In 1923 she had an apoplectic stroke that left her with some disability and sensory disturbances of the left hand. Her heart was moderately enlarged, her systolic blood pressure 190, but no evidences of cardiac or renal insufficiency. The glycosuria disappeared rapidly under dietetic treatment and a single small dose of insulin daily.

Case 21. A male, aged 62, admitted to the hospital May 22, 1924, with a diabetes of 4 years' standing, recently aggravated by a coryza, and jaundice which had recurred at intervals for 30 years, increasing in frequency, duration and intensity, which proved to be hemolytic in type. The diabetes was readily controlled by dietetic treatment alone. The Wassermann was negative. At the time of the second examination the patient was receiving an adequate diet and no insulin.

Case 22. A thin, but not emaciated female, aged 33, admitted to the hospital September 18, 1924, for the treatment of glycosuria and diabetic symptoms, which had developed acutely about 5 weeks earlier, shortly after the removal of an infected tooth. The glycosuria disappeared rapidly under insulin therapy and dietetic regulation.

Case 23. A thin female, aged 65, admitted to the hospital July 20, 1924, with a diabetes of 4 years' duration. Her heart was slightly enlarged, her systolic blood pressure 168 without evidences of cardiac or renal insufficiency. With insulin and dietary regulation the glycosuria soon disappeared.

Case 24. An emaciated male, aged 25, entered the hospital June 15, 1923, with diabetes discovered 14 months earlier and recently aggravated by the appearance of furunculosis. At the time of admission and venipuncture the furuncles were practically healed; he appeared somewhat dehydrated, but did not display any hyperpnea. The glycosuria proved amenable to insulin therapy.

Case 25. A poorly nourished male, aged 16, admitted to the hospital, June 9, 1923. Diabetic symptoms had come on acutely about 3 months earlier, his weight had fallen from 49.5 to 39.5 kilos. There was no evidences of any organic disease other than diabetes. Between the time of admission and the bleeding polyuria had continued and his weight had fallen another kilo.

Case 26. An emaciated male, aged 21, admitted to the hospital, January 3, 1923. He had suddenly developed acute diabetic symptoms a few weeks earlier. He appeared emaciated and dehydrated, his respirations somewhat increased in rate and depth, his urine loaded with sugar and acetone, but no complicating conditions could be discovered. Blood was withdrawn from an arm vein, with moderate stasis, at once. Glycosuria and ketonuria subsided rapidly under treatment by diet and insulin. In the course of treatment acute catarrhal jaundice, lobar pneumonia and pleurisy with effusion appeared and resulted fatally.

Case 27. A female, aged 65, admitted to the hospital March 8, 1923, with gangrene of her foot which had developed 4 or 5 weeks earlier and had aggravated a diabetes of 10 years standing which had, till then, been easily controlled by dietetic treatment. For a month she refused operation and then consented only to amputation below the knee. The flaps broke down immediately. Dietetic regulation controlled the diabetes successfully except for a day after the operation when she had transient glycosuria. Her appetite failed rapidly, however, and she became stuporous. About May 5th edema appeared and, by the time of the blood examination on May 9th had become quite marked. The edema and stupor increased continuously until her death on May 18th.

Case 28. An obese female, aged 60, admitted to the hospital November 28, 1924, with lacerations of the scalp and a fractured patella received in an automobile accident and a diabetes of at least 8 years' standing, which had proved amenable to moderate dietary restriction. Glycosuria disappeared rapidly with little dietary regulation as she recovered from the nervous shock and the acute trauma of the accident.

Case 29 and 45. A small, emaciated, male, aged 46, admitted to the hospital for the first time in November, 1922, with a mild acidosis. With dietetic treatment alone he was rendered aglycosuric on a diet containing only 25 gm. of carbohydrate, 50 gm. of protein and 125 of fat. Under these circumstances he developed slight, persistent, subcutaneous edema of the ankles and legs which was present at the time of the first bleeding. He remained well until a severe cold with fever and acute pain in the chest aggravated by breathing and coughing resulted in the recurrence of glycosuria and diabetic symptoms despite treatment and forced him to enter the hospital October 23. At this time he had signs of a subsiding coryza and acute fibrinous pleurisy with some evidences of acidosis. At the time of the venipuncture, the next morning before breakfast, his general condition had improved greatly.

Case 30. A male, aged 50, with moderately severe diabetes of about 3 years' duration, which had been adequately controlled by diet until aggravated by an acute upper respiratory infection, admitted to the hospital November 6, 1923, with a coryza and reddened throat, breathing quietly and apparently not much dehydrated. The first blood examination was made at once; the second the same evening after he had received 40 units of insulin.

Case 31. A small emaciated male, aged 37, admitted to the hospital March 27, 1924. For 3 years he had suffered from polyuria, polydypsia, and increasing weakness. Two weeks before admission he had developed a coryza, a week later his right ear began to discharge pus and on March 26 the left ear followed suit. At the time of the first bleeding he appeared emaciated and somewhat dehydrated, weighing only 37.7 kilos; respirations slightly exaggerated, temperature 98°F. pulse 110. Both ears were discharging pus, his tonsils were inflamed. The second examination was made two days later when the patient had received adequate food, fluids and insulin and had gained 2 kilos. As the infections cleared up tolerance improved and he was discharged from the hospital, aglycosuric, with an adequate diet and a single large daily dose of insulin.

Case 32. A male, aged 57, admitted to the hospital February 20, 1925, with a long standing, mild diabetes which had been recently aggravated by an intercurrent infection. At the time of the blood examination he appeared acutely ill, his temperature 100.5°F., pulse rapid, respirations rapid and shallow, tongue dry and coated, evidences of infection of lungs, kidneys, and urinary tract and a blood culture containing pure Staphylococcus aureus. For the preceding 24 hours he had received little fluid.

Case 33. A female, admitted to the hospital October 25, 1922, with a fracture of the base of the skull and of the achromial end of the right clavicle, the results of a fall, unconscious. At the time of the second bleeding she had signs of consolidation of the lower lobe of the right lung, and a temperature of 104°F. It was impossible to administer adequate amounts of fluid.

Case 34. An obese female, aged 50, admitted to the hospital February 21, 1923, on the sixth day of a lobar pneumonia which had aggravated a mild diabetes of some years' duration. At the time of the first bleeding she was quite cyanotic and dyspneic, with rapid pulse, high temperature, and signs of consolidation of the whole right lung. She did not appear dehydrated and took fluids well, receiving insulin and frequent feedings of milk and cream with lactose. After the pneumonia subsided the glycosuria rapidly disappeared and she was discharged aglycosuric without insulin.

Case 35. A male, aged 65, admitted to the hospital November 28, 1924. One week earlier he was seized with pain in his left chest, bloody expectoration, and irregularity of the heart. For 2 days before admission he had become increasingly stuporous.

The night he entered the hospital he was semi-stuporous, cyanotic, with deep, rapid respirations, a totally irregular pulse, extreme cardiac enlargement, signs of consolidation over the lower lobe of the right lung, temperature of 102°F. and urine containing considerable sugar and a moderate amount of acetone. He was given frequent doses of insulin, orange juice and water during the night without benefit. All specimens of urine gave heavy reactions for sugar and moderate reactions for acetone. The blood examination was made at 9 a.m. the next morning when he was almost moribund, temperature 106°F., pulse almost imperceptible. In spite of saline, glucose and insulin he died within two hours.

Case 36. A female, aged 58, with diabetes which had been well controlled for 8 or 9 years, first with diet alone and later with insulin. On September 22 anorexia and general malaise led her to omit insulin. Glycosuria increased rapidly even when insulin, without carbohydrate was resumed. She entered the hospital at 9 p.m. on September 26, emaciated, dehydrated, in deep coma, with deep accelerated, sighing respirations, a rapid, weak pulse, and profuse showers of râles over the lower lobes of both lungs, especially marked on the left side, where the breath sounds were tubular in character, and a temperature of 102°F. No urine could be obtained by catheter. Venipuncture, which was done immediately required considerable stasis. In spite of insulin, saline and glucose solutions subcutaneously she died within 4 hours.

Case 37. An obese female, aged 57. Mild glycosuria had been discovered in 1919 when she had a cerebral hemorrhage. On December 6, 1922, she developed a severe cough. Five days later she expectorated bloody sputum and became drowsy and mentally confused.

When she entered the hospital, December 13, she was semicomatose, somewhat delirious, extremely cyanotic, sitting propped up in bed, breathing rapidly and with difficulty, with a rattle in her throat; temperature 101°F., pulse 120, systolic blood pressure 170. Over the left upper lobe and both lower lobes were dulness and tubular breathing, and coarse, bubbling râles were heard over the whole chest. Blood was examined at once, and insulin administered.

The second blood examination was made the next morning. Cyanosis was less intense, tracheal râles less marked, and mental condition clearer although the whole left lung was frankly consolidated. She died suddenly a few hours later.

Case 38. An emaciated colored female, aged 70, admitted to the hospital July 11, 1924. Glycosuria with senile dementia had developed a year earlier, and symptoms of cardiac decompensation had recently appeared. She was entirely disoriented and confused, involuntary of urine and feces, breathing rapidly and noisily. Her heart was enlarged and systolic and diastolic murmurs were audible over the whole precordium. Systolic blood pressure was 180. Sibilant and sonorous râles were heard over the chest. There was well marked pitting edema of the lower extremities. A little later frank signs of pneumonia appeared and she made a rapid exodus.

Case 39. An emaciated female, aged 37, admitted to the hospital March 21, 1923. Thirty-six hours earlier she suddenly developed acute abdominal pain, nausea and vomiting. By the next morning she was weak and stuporous and within 24 hours had sunk into deep coma.

She was admitted in deep coma, breathing rapidly and extremely deeply, emaciated and dehydrated, with systolic blood pressure only 88. Blood was examined at once. After insulin and a hypodermoclysis of saline she recovered consciousness, only to relapse rapidly in spite of further treatment. Vomiting continued. The urine output was scanty and further injections of saline resulted only in the production of subcutaneous edema. No carbohydrate was injected. She died within two days without the appearance of further symptoms to explain the origin of the acute illness. No history of diabetes preceding the present illness could be obtained.

Case 40. An emaciated female, aged 64, admitted to the hospital October 16, 1924. Mild diabetes had been recognized for a year previous. For 4 days before admission she was unable to move her bowels in spite of numerous cathartics and had taken almost no food nor fluids, but had not vomited.

On admission, when the blood examination was made, she appeared weak, emaciated and dehydrated, her abdomen distended with gas, her rectum filled with impacted feces. Cleaning out the rectum thoroughly with enemata, regulation of diet, small doses of insulin and treatment of hemorrhoids resulted in alleviation of all symptoms.

Case 41. An obese female, aged 61, admitted to the hospital September 6, 1924, for treatment of a gangrenous toe which had aggravated a mild diabetes of 10 years' standing. The diabetes was readily controlled by diet and insulin and the toe healed without surgical interference. While she was in the hospital she had an attack of biliary colic and jaundice which subsided spontaneously and for which she refused operation. She also had an enormous ovarian cyst and moderate hypertension with some evidences of beginning heart failure.

October 22 she developed dull pain in the abdomen, nausea, and vomiting, and jaundice. When the blood was examined, October 25, she was deeply jaundiced, acutely ill and dehydrated with rapid, irregular pulse, but normal respirations, and enlarged liver and tenderness in the right upper quadrant. October 28 the gall bladder was drained. The second blood examination was made just after the operation. Intractable distention developed and she died October 31.

Case 42. A male, aged 46, admitted to the hospital February 4, 1925, with an acute appendicitis with abscess. Extensive necrosis of the cecum necessitated resection and end to side anastomosis of the ileum and cecum. Three days later persistent vomiting and abdominal distention appeared. February 8 urine contained no sugar, but considerable acetone. His blood sugar at 11 a.m. was 366 mg. per cent. He was given 1500 cc. saline subcutaneously at noon and at 5:30 p.m. 500 cc. of 5 per cent glucose and 400 cc. of saline with 20 units of insulin. Cecostomy was performed about 2 hours later. The blood was examined about 2 hours after the operation, when his temperature was 102°F. He recovered after a protracted illness without further recurrence of glycosuria or hyperglycemia.

Case 43. An emaciated male, aged 18, admitted to the hospital September 17, 1924. For 3 years he had had a diabetes, controlled with difficulty by diet and insulin. On September 14 he became soaked and fatigued, exhausted his supply of insulin, and took one or two large meals. The next day nausea and vomiting set in and he continued without insulin. By night he was almost comatose, overventilating and excreting large amounts of glucose and acetone. He received only broth and 60 units of insulin in the next 24 hours, at the end of which time he was brought to the hospital. On admission, when the first venipuncture was made he seemed tired and drowsy, but mentally clear, extremely dehydrated, breathing quietly, with rapid pulse. Vomiting had ceased. During the course of the night he was given 50 units of insulin and large amounts of fluid containing carbohydrate. The next morning he was able to resume his former diet. The second blood examination was made before breakfast 5 days later. Meanwhile he had gained more than 3 kilos of weight and his urine had been free from sugar and acetone for 24 hours.

Case 44. An undernourished male, aged 26, admitted to the hospital February 12, 1923, for treatment of diabetes which had developed acutely 3 years before and recently been aggravated by a coryza. At the time of admission when the first blood was taken he appeared dehydrated and presented definite hyperpnea He weighed only 47.7 kilos. At the time of the second examination, 10 days later his weight had increased to 64.3 kilos although he was receiving only 1340 calo-

ries a day and he had marked, generalized, subcutaneous edema, ascites and double hydrothorax. When his diet was increased to 1450 calories daily his edema rapidly disappeared without other treatment. With dietary regulation and insulin regained weight and strength and was able to resume his normal occupation.

On August 25, 1923, he was again admitted with all the evidences of acidosis and dehydration, precipitated by a coryza. The third blood was taken as soon as he entered the hospital. He recovered rapidly and his carbohydrate tolerance returned to its former level.

The last blood was examined when he called to report progress. He had been continually aglycosuric, had regained his normal weight, and his carbohydrate tolerance had not diminished.

Case 45. (See no. 29.)

Case 46. A male, aged 23, admitted to the hospital August 12, 1924. Diabetic symptoms had begun suddenly 8 months earlier. He first came to the outpatient department January 6, 1924, weighing 78.7 kilos, large and well-developed, not obese, without evidences of organic disease other than diabetes. With moderate dietary restriction glycosuria and diabetic symptoms disappeared, but again recurred in May.

When he entered the hospital August 12 he weighed only 63.2 kilos and appeared weak and somewhat dehydrated. His blood sugar before breakfast was 210 mg. per cent and his urine contained large amounts of sugar and acetone. On a diet of 65 gm. of protein, 150 of fat and 100 carbohydrate and 55 units of insulin, as glycosuria and ketonuria diminished his weight increased rapidly. On August 22 he presented well marked edema of the ankles and the next day, when the first blood was taken, weighed 67.3 kilos. Without change in treatment, but with a spontaneous increase of carbohydrate tolerance the weight began to fall the next day. He was discharged September 2, weighing 64.1 kilos, aglycosuric, free from edema, on a diet containing protein 65 gm., fat 200, carbohydrate 100, 2537 calories, taking only a single dose of 15 units of insulin daily. The second blood was taken August 31, when the edema had disappeared.

Case 47. A very small, emaciated male, aged 27, admitted to the hospital March 4, 1925. Severe diabetic symptoms had suddenly developed 4 months before this after a severe cold, and were again aggravated 2 months later by an acute otitis media. When he entered the hospital he weighed only 30.6 kilos, 20 kilos less than he had weighed before the onset of the diabetic symptoms, and had extreme polyuria. He appeared emaciated and dehydrated, his respirations were somewhat increased, purulent discharge issued from his left ear and his tonsils were slightly inflamed. The first blood was taken at once.

On a diet of 50 gm. of protein, 150 of fat and 100 of carbohydrate and increasing doses of insulin glycosuria, acetonuria and polyuria rapidly disappeared and his weight increased, reaching a maximum of 37.2 kilos on March 17. From this point on it again diminished rapidly, the edema disappearing as his general condition and tolerance improved. At the time of the second blood study the acidosis had disappeared; at the time of the third edema was quite evident (weight 36

kilos); at the time of the fourth edema was no longer evident (weight 34 kilos). At the time of the last bleeding he was aglycosuric on a diet containing 60 gm. of protein, 150 of fat and 110 of carbohydrate with 30 units of insulin daily and weighed 34.5 kilos.

Case 48. A female, aged 47, admitted to the hospital December 11, 1922. One year earlier, when she had furunculosis, otitis media and pyuria, glycosuria had been discovered, which cleared up when the furunculosis disappeared. Two weeks before admission she developed a cold and cough, which increased in severity. December 7th persistent, distressing hiccough and vomiting appeared, followed by increasing drowsiness and dyspnea, for which large amounts of sodium bicarbonate and fruit juices were given.

When she entered the hospital and the first blood was drawn she was quite stuporous, but restless; slightly cyanotic, breathing slowly and superficially. Her heart was enlarged, pulse 101, systolic blood pressure 180. Harsh breathing and scattered râles were heard over both sides of the chest. There was slight subcutaneous edema of the ankles and shins. The urine contained large amounts of pus, and considerable sugar and acetone.

Thirty units of insulin were given in the course of the night and, by the next morning, her urine contained neither sugar nor acetone, she was mentally clearer, and the râles in the chest were less profuse. Hiccough and vomiting persisted and interfered seriously with the administration of fluid.

The following day, when the second blood was taken improvement was more marked, but the edema had increased and vomiting continued. The vomitus contained no free HCl and almost no combined acid. In the course of the day she received 1000 cc. of normal saline solution by hypodermoclysis. Vomiting and edema disappeared rapidly and she improved steadily from this time on.

The third blood was taken January 11, when she was receiving a diet containing 50 gm. of protein, 100 of fat and 75 of carbohydrate, without insulin. Her urine still contained pus and a faint trace of acetone, her lungs were clear and there were no signs of edema.

Case 49. A female, aged 57, admitted to the hospital August 16, 1923 with gangrene of the foot which had aggravated a mild diabetes of 7 years standing.

When she entered the hospital she was semi-stuporous, breathing rapidly and rather deeply, and appeared somewhat dehydrated. The right little toe and the adjacent portion of the dorsum of the foot were black and gangrenous and there were evidences of spreading cellulitis extending from the gangrenous area. Operation was refused by the family. In spite of increasing doses of insulin and large amounts of fluid containing carbohydrate it was impossible to control the diabetes continuously in the face of an advancing infection and constantly increasing temperature and toxemia, as is evidenced by the result of the first six blood examinations, the first of which was made as soon as she entered the hospital and the other five before breakfast on the days indicated in the table.

The leg was amputated above the knee August 20, shortly after the sixth examination, and the seventh was made before breakfast the next morning. She

improved for the first few days after the operation, but the flaps then broke down and she sank gradually. In spite of the fact that the diabetes was adequately controlled by diet and insulin, she died about a month later.

Case 50. A female, aged 56, admitted to the hospital January 28, 1924. Five years earlier she had a sudden attack of unconsciousness lasting several days during which glycosuria was discovered. After that she remained free from symptoms with moderate dietary regulation although she showed a slight, persistent glycosuria. Forty-eight hours before she entered the hospital she seemed confused when she awoke in the morning. She became unconscious in a few hours and shortly after this hyperpnea and acetonuria appeared.

The first specimen of blood was taken just after she entered the hospital, when she was in deep coma, breathing very deeply, 26 to the minute, and markedly dehydrated. Her temperature was 101°F., pulse 108, systolic blood pressure 140. Over the base of the right lung there was dulness, with diminished breath sounds and râles. Her blood count showed 6.3 million red blood cells and 27,000 leucocytes with 91 per cent of polymorphonuclear neutrophiles. Urine, obtained by catheter, contained a very faint trace of albumin, many hyaline and granular casts, and large amounts of sugar and acetone.

She was at once given hypodermoclysis containing 500 cc. of 5 per cent glucose solution and 1000 cc. of normal saline and 12 hours later another of 500 cc. of glucose and 300 cc. of saline. She also received orange juice sweetened with sugar, by mouth, and 70 units of insulin in frequent divided doses. The next morning, when the second examination of the blood was made her respirations were quiet, her pulse rate was normal and her urine contained considerable sugar, but only a trace of acetone. Her temperature was still 100°F. and she was still in deep coma.

In the next 24 hours she received 5600 cc. of fluid and large amounts of sugar. This included a hypodermoclysis of 500 cc. of 5 per cent glucose solution and 1000 cc. of normal saline. When the third blood was taken on the 30th, her mental state was somewhat clearer; but she remained quite stuporous, unable to respond to questions and her right hand seemed distinctly weak. Her urine contained little sugar, but no acetone.

After this she improved rapidly. On February 1 she had roused from her stupor, but presented a definite motor aphasia, slight dysphagia, and weakness of the right arm and the right side of her face.

At the time the fourth blood was taken she was receiving a diet containing 50 gm. of protein, 100 of fat and 100 of carbohydrate, and 60 units of insulin daily, the aphasia persisted, per pulse was quite irregular, with frequent extrasystoles, and the electrocardiograph subsequently revealed evidences of coronary disease. The signs in the lungs remained unchanged; temperature 100.8°F.

The patient was discharged from the hospital some weeks later, without glycosuria, receiving an adequate diet and only 15 units of insulin daily. The asphasia did not clear up.

Case 51. A poorly nourished female, aged 50 first admitted to the hospital

in July, 1923, with a moderately severe diabetes which was controlled by a diet containing 50 gm. of protein, 175 of fat and 75 of carbohydrate, with 15 units of insulin daily. She did not adhere strictly to this diet, glycosuria recurred and increased in spite of increasing doses of insulin. In September polyuria, polydypsia and weakness developed and one day, while shopping, she fainted. On November 15 she had a sudden attack of abdominal pain and vomited. The pain and vomiting persisted and she became increasingly drowsy. She was brought to the hospital November 19, mentally clear, but extremely drowsy and exhausted, markedly dehydrated, respirations deep and somewhat rapid, pulse rapid, but regular. There was some pain and tenderness in the epigastrium, but no other signs of organic disease. The blood count showed 6,100,000 red blood cells and 13,200 leucocytes with 76 per cent polymorphonuclear neutrophiles. Her urine contained 7.6 gm. per liter of sugar, large amounts of acetone and diacetic acid, a trace of albumin and a few hyaline casts. The first blood was taken at once.

The patient was immediately given insulin and a hypodermoclysis of 1000 cc. of normal saline solution. At the same time dilute sugar solution was administered by mouth with frequent doses of insulin. By the next morning, when the second sample of blood was examined, her mental condition was clearer and she was breathing more quietly. Her urine contained about 20 gm. of glucose per liter, but considerably less acetone.

The administration of large amounts of fluid, carbohydrate and insulin was continued and by the morning of November 21, when the third blood was taken, respirations were normal and the urine free from acetone, although it still contained 4 per cent of sugar. She still vomited small amounts occasionally.

After this she improved steadily. Vomiting and other symptoms disappeared and she was able to resume a mixed solid diet. When the fourth blood was taken, November 27, she was receiving a diet containing 55 gm. of protein, 200 of fat and 70 of carbohydrate, with 120 units of insulin daily, and her urine showed no acetone nor diacetic acid and only an occasional trace of sugar. At this time she weighed 56.7 kilos.

When the fifth blood was taken she was receiving the same diet; but only 70 units of insulin.

After she left the hospital she was forced to increase her insulin to 130 units daily, but on this régime and in spite of frequent dietary lapses she remained aglycosuric and free from symptoms. In July she tried to reduce the insulin but glycosuria and weakness at once developed. About the same time she developed a furuncle on her leg which temporarily reduced her tolerance further. In the middle of August she again cut down her dosage of insulin against advice. Two weeks later she began to suffer from weakness and increasingly frequent attacks of dizziness, cardiac palpitation and breathlessness, occasionally resulting in syncope. On September 5, after one of these attacks she was suddenly seized by abdominal pain and a little later vomited. From that time until she entered the hospital at 10 p.m. the next day, September 6, she vomited continuously.

Blood was taken as soon as she entered the hospital. She was drowsy and complained of continuous nausea, extreme thirst and slight abdominal pain. She was extremely dehydrated; her respirations were somewhat rapid, very deep, and interrupted at frequent intervals by retching and vomiting. Her pulse was rapid and quite irregular, apparently because of the occurrence of frequent extrasystoles, her heart sounds weak, distant and extremely irregular. Her lungs were clear, the abdomen everywhere tender, but not resistant. Her urine contained 2.1 per cent of sugar only 0.02 per cent of sodium chloride, and gave a heavy reaction for acetone. She received at once 1000 cc. of normal saline and 500 cc. of 5 per cent glucose solution subcutaneously, together with 40 units of insulin, and was allowed water and sweetened orange juice by mouth.

At 1 a.m. September 7, her condition was little improved, so another 40 units of insulin was given, followed by two 20 unit doses at 3 and at 7 a.m. The second blood was taken at 9 a.m. By this time nausea and abdominal pain were less severe, her pulse was slower and more regular, the respirations somewhat quieter. She complained of severe headache and vomited at intervals. Her urine contained 2.5 per cent of sugar, 0.02 per cent of NaCl and much acetone. During the day, as vomiting continued, another hypodermoclysis of 1000 cc. of saline and 500 cc. of 5 per cent glucose was given and peroral fluids were limited to 50 cc. of water every half hour. This checked the vomiting and by midnight she seemed greatly improved.

The third blood was taken at 9 a.m., September 8. At this time, although her urine still contained 2.3 per cent of sugar and gave a heavy reaction for acetone, her respirations were normal, pulse regular, and vomiting had ceased. Improvement continued throughout the day and it proved possible to increase the diet somewhat. In spite of large doses of insulin sugar disappeared from the urine at intervals only.

Early in the morning of September 10, she got out of bed without permission and at once became dizzy and vomited. Cardiac palpitation and abdominal cramps soon developed, she vomited once or twice more, and within an hour presented air hunger and all the other evidences of severe acidosis. By 10 a.m., 5 hours after the onset of the attack, when the fourth blood was taken, she was again overventilating, her pulse was rapid and weak, she appeared dehydrated and complained of extreme thirst. Diet was stopped, she was given an enema and allowed only small doses of orange juice and water by mouth. Vomiting ceased rapidly and by the next morning she was greatly improved and able to resume her diet in frequent, small feedings.

On the night of September 11, she had an attack of cardiac palpitation and dyspnea. At 5 a.m. the next day, September 12, she was awakened by severe abdominal cramps and a little later vomited a large amount of yellowish fluid. The symptoms this time subsided rapidly. By 9 a.m., the pain had subsided. Although she had not vomited again she exhibited evident hyperpnea. Improvement now proceeded rapidly. On September 13 the urine finally became free from sugar and acetone. During the night she had a slight attack of palpitation

which caused the appearance of considerable sugar and acetone in the next specimen of urine voided. Otherwise recovery was uninterrupted.

The three last examinations of blood were made before breakfast on the days indicated in table 2 and mark the progress of convalescence. She was finally discharged from the hospital October 7, aglycosuric, receiving a diet containing 60 gm. of protein, 200 of fat and 100 of carbohydrate and 90 units of insulin daily.

An attempt is made in table 3 to present the metabolism data in abstract form.

Case 52. An emaciated male, aged 36, first admitted to the hospital February 8, 1924. Three months earlier he had been suddenly seized with sharp, cramp-like pains in the upper part of the abdomen, which lasted about 24 hours. Immediately after this he developed extreme thirst and polyuria, which lasted about a week, gradually diminishing in intensity, attended by rapid loss of weight and strength. (On February 5 he vomited again once and had a recurrence of diabetic symptoms.) During the first week of his illness he lost 14 kilos and subsequently had lost another 10.

When he entered the hospital he complained especially of anorexia and extreme weakness. He appeared seriously ill, emaciated and dehydrated, with moderate hyperpnea. Except for the presence of pyorrhea and several bad teeth, examination revealed no evidences of any organic disease other than diabetes. His urine contained large amounts of sugar and acetone. The first blood was taken the next morning when his condition was practically unchanged and he had received nothing but non-nutritive fluids. He was given orange juice and water with large doses of insulin at frequent intervals throughout the day and, by the next morning, February 10, when the second blood was taken, his condition was greatly improved, his urine was free from sugar and gave only a moderate reaction for acetone and he felt able to take a regular diet. He was accordingly ordered 50 gm. of protein, 150 of fat and 100 of carbohydrate daily and insulin was adjusted as rapidly as possible. Under these circumstances his weight increased at the rate of a pound a day for two weeks, at the end of which time he presented slight edema of the ankles. The diet was subsequently increased and insulin dosage reduced as he improved and he was finally discharged from the hospital on March 7, aglycosuric, receiving a diet which contained 50 gm. of protein, 200 of fat and 100 of carbohydrate, without insulin. The third blood was taken when he was in excellent condition, free from edema and glycosuria.

After he left the hospital he was careless about his diet and habits. He also had a few minor disorders of digestion. His carbohydrate tolerance diminished and he was forced to first resume and then to increase insulin therapy until he was taking 40 units a day.

November 9 he did not feel well and was unable to eat any supper. At 3 a.m. the next morning he awoke nauseated and vomited. Almost immediately he developed severe epigastric pain. From that time until he entered the hospital, at 2 p.m. the pain persisted and he vomited every time he tried to take anything by mouth. For 3 days preceding this attack he had been eating and drinking carelessly and had been without insulin.

TABLE 3

Case 22350

Date	Intake					Urine			Vomitus				Treatment
	Protein	Fat	Carbohydrate	Fluids	Cl as NaCl	Volume	Sugar	Cl as NaCl	Volume	Sugar	Cl as NaCl	Insulin	
	gm.	*gm.*	*gm.*	*cc.*	*gm.*	*cc.*	*gm.*	*gm.*	*cc.*	*gm.*	*gm.*	*units*	
September 6*.....	0	0	25+	1,500+	9.0	440	12	0.1	710	6.2	0.4	90	1000 cc. of saline and 500 cc. 5 per cent glucose were given subcutaneously. An uncertain amount of water and sweetened-orange juice were taken by mouth
September 7.....	0	0	70+	6,500	6.3	1,750	45	3.5	1,310	2.8	0.6	140	700 cc. of saline and 500 cc. 5 per cent glucose subcutaneously and 45 grams of sugar as orange juice by mouth. Glucose was also given by rectum, but only a small and uncertain amount was retained
September 8.....	30	90	100	2,500	?†	2,370	83	9.6	0	0	0	90	Diet of orange juice, milk-cream-lactose and tea and toast
September 9.....	48	100	100	4,200	?†	4,060	131	7.4	0	0	0	100	Diet of same character, but more liberal
September 10.....	0	0	62	2,500	0	2,250	57	4.5	1,000‡	6‡	0.4‡	120	Only sweetened orange juice and water given
September 11.....	35	100	75	2,400	?†	2,220	71	5.0	0	0	0	110	Diet similar to those of September 8 and 9
September 12.....	22	78	49	1,900	?†	1,540	18	3.8	180	0	0.2	130	Similar diet, somewhat reduced in amount because patient vomited once
September 13.....	45	100	75	3,300	?†	2,910	54	2.9	0	0	0	90	Diet was gradually altered in quality to conform more nearly to the normal character by the introduction of small amounts of meat and cereal
September 14.....	45	100	75	3,800	?†	1,950	21	2.2	0	0	0	110	
September 15.....	45	100	75	3,000	?†	1,400	32	1.7	0	0	0	110	
September 16.....	45	100	75	4,300	?†	1,500	17	3.9	0	0	0	80	

* From time of admission, 10 p.m. September 6, to 7 a.m. the next morning.

† Only about one-half the vomitus, 510 cc., was actually recovered and analyzed. This contained 0.2 grams NaCl and 3 grams of sugar.

‡The chloride content of these diets was uncertain. From the nature of the food stuffs employed they must have been comparatively low in chloride.

When he entered the hospital and the first blood was taken he appeared desperately ill, semi-stuporous, emaciated and dehydrated, with extreme hyperpnea, rapid, weak pulse, a temperature of 99°F., systolic blood pressure 112. The abdomen was everywhere rigid, and there was an area of marked tenderness just to the left of the naval. His blood count showed 5.6 million red blood cells and 30,000 leucocytes with 86 per cent polymorphonuclear neutrophiles. The urine contained a moderate amount of albumin, many granular casts, 3.5 per cent of sugar and considerable acetone.

He was given immediately 1000 cc. of normal saline and 500 cc. of 5 per cent glucose solution by hypodermoclysis with 40 units of insulin. Urine was collected as frequently as possible, and, as glycosuria persisted, 2 additional 20 unit doses of insulin were given in the course of the afternoon. By 6 p.m. the abdominal pain and tenderness had disappeared, but he was still partially stuporous and his respirations were still greatly exaggerated. He had vomited coffee-ground material twice. From this time on until the next morning he received 20 units of insulin every two hours and 5 gm. of carbohydrate in the form of sweetened orange juice and water every half hour. The second blood examination was made at 10 p.m. that night and the third at 8:30 a.m. the next morning. Urinary sugar had not diminished, but ketonuria had practically disappeared by this time.

From this time on his condition improved steadily. Vomiting did not recur. He was able to resume his diet and glycosuria disappeared. He was finally discharged from the hospital on December 4, aglycosuric, receiving a diet containing protein 60 gm., fat 200 gm., and carbohydrate 100 gm. with 60 units of insulin daily.

Up to the time of the third examination, before breakfast on November 13, he had received only sweetened orange juice, two slices of bread, a small amount of milk and cream and one cup of soup. The total salt content of the diet must, therefore, have been minimal.

Case 53. A male, aged 33, was admitted to the hospital March 26, 1924, for the treatment of glycosuria and diabetic symptoms which had developed quite suddenly a few weeks earlier. (The patient had a bilateral herniotomy performed in this hospital in November, 1923. At that time urine both before and after operation was free from sugar.) He appeared comparatively well nourished, but somewhat dehydrated, and complained of continuous thirst and polyuria. Examinations, including x-ray of the chest and examination of the sputum, revealed no evidences of any organic disease other than diabetes. His urine contained large amounts of sugar and acetone. The first blood was taken the next morning, when his condition was practically unchanged. The second was taken two days later. By this time, with insulin and dietetic treatment, his general condition had improved greatly, he had gained 5 pounds in weight and his urine contained only a trace of sugar and a moderate amount of acetone. Improvement continued uninterrupted and he was discharged on April 18, aglycosuric, receiving a diet containing 70 gm. of protein, 200 of fat and 100 of carbohydrate, with 10 units of insulin daily.

After he left the hospital he continued his treatment with excellent results for some time. About the first of January, 1925, he stopped taking insulin. Polyuria and polydypsia returned and began to increase steadily in intensity. In a few weeks he lost 2.7 kilos of weight. In spite of this he became more and more careless of his diet and continued without insulin. About the middle of February he developed a productive cough which grew continuously more severe. March 18 weakness and chilly sensations appeared and two days later substernal pain. The next day he had a distinct chill, vomited several times, and gradually sank into a stupor. He was brought to the hospital in deep coma March 22, extremely dehydrated, with maximal respirations, cold and somewhat cyanotic, with subnormal temperature, rapid, weak pulse, a systolic blood pressure of only 80, his throat inflamed and edematous, and dulness, suppressed breath sounds and showers of râles over the whole right chest below the third rib. His blood count showed 5.2 million red blood cells and 11,700 leucocytes with 83 per cent polymorphonuclear leucocytes; tubercle bacilli were found in his sputum and subsequent x-ray examination revealed an extensive lesion of the right lung. His urine contained large amounts of sugar and acetone, a trace of albumin and many granular casts.

The first blood examination was made at once and he was immediately given 30 units of insulin and 200 cc. of orange juice followed shortly by a hypodermoclysis of 1000 cc. of normal saline and 500 cc. of 5 per cent glucose solution and another 30 units of insulin. During the remainder of the night he received 80 units of insulin in addition and 120 gm. of carbohydrate in the form of sweetened orange juice.

The next morning he was given another hypodermoclysis of 1000 cc. of saline and 500 of glucose solution and in the afternoon an additional 1000 cc. of 5 per cent glucose. By 2 p.m. he began to respond to questions. This day, March 23, besides the fluids administered subcutaneously, he received about 200 gm. of carbohydrate and a minimal amount of protein and fat in the form of orange juice, lactose, milk and cream. He was given 70 units of insulin in the 24 hours.

The next morning, March 24, when the second blood was taken he had improved greatly. His urine contained only a moderate amount of sugar and no acetone. His respirations were quiet and normal and he was more rational. His diet was varied somewhat by the addition of eggs and he was given less insulin. By the following morning he was quite rational and able to take a diet containing 60 gm. of protein, 150 of fat and 100 of carbohydrate.

The morning of the 27th when the last blood was examined, he was receiving this diet. His urine at the time of the venipuncture contained considerable sugar but no acetone.

His temperature, which had been subnormal when he entered the hospital, rose to 100°F., on the second day and remained somewhat elevated for about a week, when it fell to normal. The general condition of the patient and his tolerance for carbohydrate improved so much that he was able at one time on a diet containing protein 75 gm., fat 250 gm. and carbohydrate 125 to reduce insulin to 10 units a day without the appearance of glycosuria.