

OBSERVATIONS ON KIDNEY FUNCTION IN DIABETES MELLITUS *

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In the history of diabetes numerous theories as to the cause of the disease have been proposed, although no single one has had an anatomic basis definite enough to establish the underlying pathologic process. At present, while the etiology of diabetes is believed by most observers to be due to insufficiency of the internal secretion of the pancreas, yet pathologic anatomists have demonstrated that the kidneys of diabetic patients usually show certain well defined and characteristic lesions.

Armanni¹ was the first to point out that in diabetes there was an almost specific injury to the epithelium of the straight tubules by which they lost their cytoplasm and were transformed into hyaline-like vesicles without definite structure. Ebstein² confirmed this finding and described in coma a typical massing together of necrotic cells. Finally, Ehrlich³ proved that the peculiar hyaline degeneration described by Armanni was due to the deposition of glycogen in the cells and that the so-called "glycogenic degeneration" could be found in the majority of cases.

Albertoni and Pisenti⁴ fed rabbits and dogs with acetone, producing first albuminuria and eventually hyaline changes analogous to those already described, without, however, causing glycogenic degeneration. Trambusti and Nesti⁵ were able to produce similar lesions in phlorizinized dogs when the animals excreted appreciable amounts of acetone in the urine. Thus it has been shown by both clinical and experimental material that the diabetic kidney has a more or less definite anatomic appearance which is comparable to that obtained in animals associated with the passage of acetone bodies from the blood into the urine. In view of these findings it is interesting that no systematic studies as to the relation of the kidney function to diabetes have been recorded. Work already reported and abundantly confirmed, however, has brought out four interesting features in this respect.

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1. Armanni: Quoted by Cantani, *Le diabète sucré et son traitement diététique*, 1876.

2. Ebstein: *Deutsch. Arch. f. klin. Med.*, 1881, **28**, 143; 1882, **31**.

3. Ehrlich: *Ztschr. f. klin. Med.*, 1883, **6**, 33.

4. Albertoni and Pisenti: *Arch. f. exper. Path. u. Pharmakol.*, 1887, **23**, 393.

5. Trambusti and Nesti: *Ziegler's Beitr. z. path. Anat.*, 1893, **14**, 337.

First, the diabetic kidney is at times under the influence of a diuretic. This has been shown most simply by the characteristic symptoms of polyuria and polydipsia, and somewhat more systematically by the relation between the day and night urine. Laspeyres⁶ found a nocturnal polyuria in two out of five cases of diabetes studied, and Carles⁷ in six cases. Lépine mentions that in diabetes the normal difference between day and night urine is less marked, an observation confirmed by Péhu⁹ and Külz.¹⁰

Secondly, albuminuria either constant, intermittent or terminal, is found in many cases. Thus Aldehoff¹¹ found albuminuria in 79 per cent. of 680 observations, von Noorden¹² in 21 per cent. of 650 observations, and various other writers in from 10 to 68 per cent. of their cases. While the discrepancy in figures is wide, possibly owing to the different methods of analysis employed, yet the fact remains that the diabetic kidney is abnormally prone to albuminuria.

Thirdly, edema may occur. Naunyn¹³ says that edema is not a rare occurrence in cachetic patients with severe diabetes. Williamson¹⁴ has observed anasarca in more than 5 per cent. of his patients, Frerichs¹⁵ in twenty-five out of 400 cases, and Joslin and Goodall¹⁶ in seven cases at a time when the patients presented slight, if any, other evidence of heart or kidney disease.

Finally, the urine of patients on the verge of coma has been found repeatedly to contain masses of hyaline and granular casts, the so-called "Komazylinder" of Aldehoff.

The present paper reports studies on renal function in diabetes under varying conditions of glycosuria, hyperglycemia and acidosis. It seemed of greatest interest to study the effect on the kidney of sugar and acetone bodies because they are usually not a feature in nephritis. Moreover, it is generally believed that an increasing concentration of sugar in the blood without concomitant glycosuria is due to a specific holding back of sugar on the part of the diabetic kidney, a fact which in itself is evidence of abnormal kidney function. Under normal conditions, too, the organism depends on the kidney to regulate the acid-base equilibrium. Unless the rate of elimination of acids keeps up

6. Laspeyres: *Deutsch. Arch. f. klin. Med.*, 1900, **68**, 192.

7. Carles: *Province méd.*, 1906.

8. Lépine: *Le diabète sucré*, 1909.

9. Péhu: *Revue de méd.*, 1903, p. 279.

10. Külz: *Klinische Erfahrungen über Diabetes mellitus*, 1899.

11. Aldehoff: Quoted from Külz, Footnote 10.

12. Von Noorden: *Die Zuckerkrankheit und ihre Behandlung*, 1912.

13. Naunyn: *Diabetes Mellitus*, 1906.

14. Williamson: *Diabetes Mellitus and Its Treatment*, 1898, p. 227.

15. Frerichs: *Ueber den Diabetes*, 1884.

16. Joslin and Goodall: Experiments on an Ash-Free Diet and Salt Metabolism, *Jour. Am. Med. Assn.*, 1908, **51**, 727.

with their rate of production, true "acidosis" results. Thus the permeability of the kidney for both sugar and acid may well be an important factor in helping to establish the symptoms due to glycosuria and acidosis.

At present, the common tests for renal function used in heart and kidney diseases in addition to urinalysis are the phenolsulphonephthalein test of Rowntree and Geraghty,¹⁷ some form of "test renal meal" as advocated by von Monakow,¹⁸ Hedinger and Schlayer,¹⁹ O'Hare²⁰ and Mosenthal,²¹ estimation of nonprotein nitrogen or urea of the blood alone as advocated by Ascoli,²² Strauss,²³ and Folin,²⁴ or in relation to the simultaneous excretion of urea in the urine according to the method of Ambard²⁵ and McLean,²⁶ and estimation of the blood chlorid in relation to its excretion in the urine according to Ambard's laws. Comparative studies with those tests in nephritis have shown that as the renal function becomes impaired, the excretion of phenol-sulphonephthalein diminishes, the nonprotein nitrogen and urea of the blood increase, the kidney is less able to excrete nitrogen and in certain instances water and sodium chlorid, and the ratio between urea in the blood and that in the urine changes so that Ambard's constant for urea becomes higher as McLean's index becomes proportionally lowered. Interesting information in regard to renal physiology has been obtained by such tests and two significant conclusions have been drawn: (1) Ambard and McLean have demonstrated that the excretion of certain substances from the blood through the kidney into the urine is carried on according to laws capable of numerical expression. (2) The kidney has selective and independent powers of excretion for several of the different urinary constituents.

For the studies reported here a series of cases of diabetes of differing severity was selected. Renal function in relation to the excretion of urea and sodium chlorid was tested by McLean's adaptation of the Ambard constant. These tests seemed sufficiently comprehensive

17. Rowntree and Geraghty: *Jour. Pharm. and Exper. Therap.*, 1909, **1**, 579.

18. Von Monakow: *Deutsch. Arch. f. klin. Med.*, 1911, **102**, 248.

19. Hedinger and Schlayer: *Deutsch. Arch. f. klin. Med.*, 1914, **114**, 120.

20. O'Hare: *A Study of Salt, Nitrogen and Water Excretion in Nephritis*, *THE ARCHIVES INT. MED.*, 1916, **17**, 711.

21. Mosenthal: *Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine*, *THE ARCHIVES INT. MED.*, 1915, **16**, 733.

22. Ascoli: *Arch. f. d. ges. Physiol.*, 1901, **87**, 103.

23. Strauss: *Die Chronische Nierentzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung*, 1902.

24. Folin and Denis: *Jour. Biol. Chem.*, 1912, **11**, 527.

25. Ambard: *Physiologie Normale et Pathologique des Reins*, 1914.

26. McLean: *Clinical Determination of Renal Function by an Index of Urea Excretion*, *Jour. Exper. Med.*, 1915, **22**, 212, 336; *Jour. Am. Med. Assn.*, 1916, **66**, 415.

because McLean has shown that the urea index is a good indicator of total renal function, gives practically the same information as the phenolsulphonephthalein test, and is preferable to those tests which rely on blood analysis alone, since they can be interpreted only when the intake of the substance studied is known. The chlorid excretion was determined in addition, to study renal function in more than one way. "Test meal" studies were not made because the cases differed so widely in severity as to make a common diet for all impossible. The blood and urine sugar, as well as the carbon dioxid tension of the alveolar air,²⁷ were estimated to disclose any relation between abnormal renal function, as illustrated by ordinary tests, and glycosuria or abnormal amounts of sugar or acetone bodies in the blood. Obviously, the carbon dioxid tension of the alveolar air gave an indirect measure of the blood acetone bodies. Winterstein²⁸ and Hasselbalch,²⁹ however, have established that variations in the carbon dioxid content of the blood, and consequently of the alveolar air, are inverse to the production of nonvolatile acids. Observations to be published in another paper show that in diabetes the fall in the alveolar carbon dioxid which occurs in acidosis is more or less parallel to the increase of acetone bodies in the blood; thus the information so obtained was significant.

The tests were all made in the same fashion according to McLean's adaptation of Ambard's methods. The patients were taken for observation in the morning before breakfast to avoid the effect of feeding. One-half hour before the period began the subjects were given 150 or 200 c.c. of water and took no more fluid or food until the observation period was ended. At the beginning of the period the bladder was emptied. Thirty minutes later about 25 c.c. of blood was taken from an arm vein into a dry tube containing about 100 mg. of powdered potassium oxalate to prevent clotting. At the same time samples of alveolar air were obtained. At the end of 72 minutes³⁰ after the bladder was first emptied, the specimen of urine secreted during the 72-minute period was collected, carefully measured and used for analysis.

27. The carbon dioxid tension of the alveolar air was determined in the Peter Bent Brigham Hospital cases. In the others it was calculated from the capacity of the blood plasma to combine with carbon dioxid (Van Slyke: *Jour. Biol. Chem.*, 1917, **30**, 289), the volume per cent. of carbon dioxid bound by the plasma being multiplied by 0.69 in order to make the results numerically comparable to alveolar carbon dioxid tensions expressed in millimeters of mercury. The results from the two methods are usually alike, as has been shown by Van Slyke and by Frothingham and Walker (*THE ARCHIVES INT. MED.*, 1916, **18**, 304), although in diabetes the alveolar air sometimes indicates acidosis when the blood alkali is really normal (Stillman, Van Slyke, Cullen and Fitz: *Jour. Biol. Chem.*, 1917, **31**, 405).

28. Winterstein: *Arch. f. d. ges. Physiol.*, 1911, **138**, 167.

29. Hasselbach: *Biochem. Ztschr.*, 1912, **46**, 403.

30. In a few cases the length of time was one or two hours. In such instances the blood was drawn in the middle of the time selected.

A 72-minute period was ordinarily taken, since it is one-twentieth of 24 hours, and the calculation of the rate of excretion for 24 hours was made simple.

A portion of the blood was analyzed for urea by the method of Van Slyke and Cullen,³¹ and for sugar by the Benedict-Lewis³² method, except in a few cases when Bang's³³ micromethod was used. The remainder of the blood was centrifugalized and the plasma pipetted off. A portion of the plasma was analyzed for sodium chlorid by the McLean and Van Slyke³⁴ method, and for the combining power for carbon dioxid according to Van Slyke's³⁵ method. Alveolar air samples were collected according to the Plesch³⁶ method and were analyzed in a Haldane³⁷ gas analysis instrument. Since the blood or air was taken in about the middle of the period, it was assumed to represent the concentration in the blood for the substances whose simultaneous excretion in the urine was studied. The urine was analyzed for sugar by Benedict's³⁸ method or polarization in a few instances; for chlorids by a modified Volhard titration; and for urea and ammonia by Van Slyke and Cullen's method. The results are divided into two groups dealing with (1) the urea index, and (2) the relation of plasma chlorid to the excretion of chlorid in the urine.

In Table 1 are recorded observations on the urea index. In considering the results it is necessary to compare them with similar observations on normal individuals. McLean has published 107 such tests made according to the same methods, which serve as a good control. His tables show that the normal concentration of urea in the blood varies from 0.2 to 0.5 gm. per liter. The normal urea index varies between 80 and 200, with an average reading of 120 based on 100 tests. Any index below 80 is considered abnormal, and the degree of impairment of functional ability or damage to the kidneys becomes greater as the index gets lower. Any index above 200 is abnormal, although its significance is less certain. A high index may occur in healthy young individuals with low blood urea; it may result from the washing out of urea with a high fluid output; or it may occur with "vascular hypersensitiveness," according to the conception of Schlayer. Repeated indexes made on the same normal individual at different times may

31. Van Slyke and Cullen: *Jour. Biol. Chem.*, 1914, **19**, 211.

32. Benedict and Lewis: *Jour. Biol. Chem.*, 1915, **20**, 61.

33. Bang: *Der Blutzucker*, 1913.

34. McLean and Van Slyke: *Jour. Biol. Chem.*, 1915, **21**, 361.

35. Van Slyke: *Jour. Biol. Chem.*, 1917, **30**, 289.

36. Plesch: *Ztschr. f. exper. Path. u. Therap.*, 1909, **3**, 380.

37. Haldane: *Methods of Gas Analysis*, 1912.

38. Benedict: *The Detection and Estimation of Glucose in Urine*, *Jour. Am. Med. Assn.*, 1911, **57**, 1193.

TABLE 1.—THE RELATION OF THE RATE OF UREA EXCRETION TO CONCENTRATION IN BLOOD ARRANGED ACCORDING TO THE UREA INDEX

$$\text{Index (I)} = \frac{\text{Gm. per 24 hrs.} \sqrt{\text{Gm. per liter} \times 8.96}}{\text{Wt. in Kg.} \times (\text{Blood Urea})^2}$$

Number	Subject	Weight, Kg.	24 Hour Urine, C.c.	Urea			Index I
				Gm. per Liter of Blood Ur	Gm. per Liter of Urine C	Gm. per 24 Hrs. D	
1	P. B. B. H. 6353	30.0	3,600	0.726	6.99	25.20	37
2	P. B. B. H. 6493	70.6	3,072	0.458	9.09	27.92	50
3	R. I. H. 2341	54.0	1,694	0.167	3.72	6.30	72
4	Fl.	45.0	6,000	0.360	4.16	25.00	79
5	R. I. H. 2234	50.0	2,000	0.410	12.35	24.70	93
6	R. I. H. 2480	47.0	1,680	0.273	8.11	13.62	100
7	P. B. B. H. 5921	61.7	2,880	0.267	6.76	19.47	104
8	R. I. H. 2128	40.2	1,500	0.314	10.05	15.10	108
9	P. B. B. H. 5938	40.0	4,800	0.280	3.94	18.91	108
10	P. B. B. H. 6328	68.3	1,200	0.494	30.77	36.92	110
11	P. B. B. H. 5975	64.0	1,080	0.377	25.66	27.71	138
12	P. B. B. H. 6364	64.2	1,560	0.265	12.60	19.66	139
13	R. I. H. 2280	28.5	800	0.232	9.64	7.70	140
14	P. B. B. H. 6032	48.0	1,440	0.257	10.75	15.48	144
15	R. I. H. 2680	48.0	2,000	0.262	8.88	17.76	144
16	R. I. H. 2525	47.8	4,080	0.190	3.60	14.70	145
17	L. T.	50.0	2,540	0.260	8.09	20.58	156
18	R. I. H. 2111	49.2	5,400	0.225	4.07	22.00	160
19	R. I. H. 2684	31.7	6,740	0.169	1.81	12.20	162
20	P. B. B. H., 6483	61.9	1,200	0.272	17.61	21.13	174
21	C. R.	37.3	3,460	0.162	3.11	10.75	175
22	R. I. H. 2382	46.5	1,740	0.220	9.16	15.94	192
23	P. B. B. H. 6205	62.0	780	0.212	18.23	14.22	198
24	R. I. H. 2516	87.2	2,997	0.307	15.40	46.13	198
25	R. I. H. 2414	39.8	1,280	0.165	7.11	9.09	200
26	M. L.	64.0	3,840	0.218	6.98	26.40	205
27	R. I. H. 2394	42.0	2,800	0.215	6.37	17.70	206
28	P. B. B. H. 5564	52.0	3,360	0.135	3.51	11.79	210
29	Fl.	95.4	6,000	0.230	7.44	44.64	217
30	Di.	48.7	2,200	0.192	7.38	16.24	220
31	R. I. H. 2487	50.2	1,800	0.092	3.26	5.86	223
32	R. I. H. 2469	50.4	5,000	0.160	4.17	20.85	296
33	C. A.	60.0	2,900	0.222	10.60	30.74	305
34	R. I. H. 2686	25.8	2,700	0.109	2.52	6.80	315
35	P. B. B. H. 5593	65.6	1,500	0.210	16.71	25.06	320
36	R. I. H. 2457	52.2	3,500	0.152	7.62	26.67	550
37	R. I. H. 2679	41.2	3,400	0.115	5.06	17.20	635
38*	P. B. B. H. 6482	71.3	7,320	0.240	20.65	151.16	1498

* Excluded from table of averages.

show such marked differences as from 87 to 196. The meaning of such variation is not defined.

Table 1 shows that twenty-one cases of diabetes, or 56 per cent. of those studied, have a urea index within normal limits. Thirteen cases, or 34 per cent., have an index above 200; four cases, or 10 per cent., have an index below 80, and must therefore be considered to have an impaired renal function. It is of interest that such a large number of cases should have a high index, especially when it is realized that the average index of those cases within normal limits is 146, which is significantly higher than McLean's normal average of 120. One reason for such findings may be the low blood urea found in several cases. Thus Case 31, with an index of 223, had a blood urea of 0.092 gm. per liter, Case 25 an index of 200, with 0.165 gm. of urea per liter of blood, and Case 28 an index of 210, with 0.135 gm. of urea per liter of blood. A more probable explanation lies in the high fluid output which occurred frequently. For instance, in the thirteen cases with an index above 200, the rate of water excretion for twenty-four hours was never below 1,500 c.c., in one case it reached 7,320 c.c., and averaged 3,770 c.c., while in the entire series the lowest output was 780 c.c. per twenty-four hours, and the average was 3,034 c.c. In McLean's normals, on the other hand, the highest fluid output encountered was 5,400 c.c., the lowest was 462 c.c., while the average was 1,738 c.c.

The patients, both normal and diabetic, had taken the same amount of fluid to drink at the same time before the period was begun. It therefore seemed that the diabetic kidney often had a rate of water elimination more rapid than normal. Since acids or sugar might possibly produce such a diuretic effect, the rate of water excretion per twenty-four hours was compared with the height of blood sugar, with the glycosuria, and with the degree of acidosis in those cases with a normal or high urea index. The results of this study are shown in Table 2.

The results studied from this point of view are inconclusive. Of the thirty-four observations, twenty-three had a fluid output above the average normal rate of 1,740 c.c. in twenty-four hours. In this group acidosis could not be assumed to produce the polyuria, as cases with a low alveolar air showed no tendency to excrete more fluid than did those with high alveolar air. Twelve cases showed an appreciable excretion of sugar. The fluid output in these cases bore relation neither to the total excretion in twenty-four hours nor to the concentration of sugar per liter of urine. The sugar-free cases appeared to excrete water with as much ease as those with glycosuria. It is of possible significance that only four of the twenty-three cases had a blood sugar below 0.17 per cent. This observation alone might suggest that hyper-

TABLE 2.—THE RELATION OF THE RATE OF WATER EXCRETION IN TWENTY-FOUR HOURS TO SUGAR EXCRETION, AND TO CONCENTRATION IN THE BLOOD OF SUGAR OR ACIDS (AS ESTIMATED BY THE CARBON DIOXID TENSION OF THE ALVEOLAR AIR) IN THOSE CASES OF DIABETES WITH A UREA INDEX ABOVE 80. TABULATED ACCORDING TO THE FLUID OUTPUT

Number	Subject	Weight, Kg.	24-Hour Urine, C.c.	Sugar			Alveolar CO ₂ , Mm.
				Gm. per Liter of Blood S	Gm. per Liter of Urine C	Gm. per 24 Hrs. D	
1	P. B. B. H. 6482	71.3	7,326	3.40	18.50	135.42	39.9
2	R. I. H. 2684	31.7	6,740	1.37	Negative	42.6
3	Fl.	95.4	6,000	2.26	7.50	45.00	35.0
4	R. I. H. 2111	49.2	5,400	2.00	Traces	37.8
5	R. I. H. 2469	50.4	5,000	1.33	Negative	38.9
6	P. B. B. H. 5038	40.0	4,800	3.18	12.50	60.00	12.8
7	R. I. H. 2525	47.8	4,080	1.56	Negative	40.2
8	P. B. B. H.	64.0	3,840	1.49	Negative	40.8
9	R. I. H. 2457	52.2	3,500	2.94	18.52	64.62	23.2
10	C. R.	37.3	3,460	2.63	32.30	111.50	15.5
11	R. I. H. 2679	41.2	3,400	2.66	Negative	43.2
12	P. B. B. H. 5564	52.0	3,360	2.30	Negative	37.3
13	R. I. H. 2516	87.2	2,997	2.63	16.40	49.14	38.8
14	P. B. B. H. 5921	61.7	2,880	2.16	Traces	31.6
15	R. I. H. 2394	42.0	2,800	2.33	22.20	62.00	20.2
16	C. A.	60.0	2,900	2.50	23.80	69.02	35.0
17	R. I. H. 2686	25.8	2,700	2.00	Negative	41.3
18	L. T.	50.0	2,540	2.56	41.60	106.00	29.6
19	DI.	48.7	2,200	4.35	34.48	75.85	36.8
20	R. I. H. 2030	48.0	2,000	3.00	16.00	32.00	20.1
21	R. I. H. 2234	50.0	2,000	2.08	Negative	38.2
22	R. I. H. 2487	50.2	1,800	2.38	Negative	42.2
23	R. I. H. 2382	46.5	1,740	3.12	23.20	40.37	35.3
24	R. I. H. 2480	47.0	1,680	4.16	Traces	33.0
25	P. B. B. H. 6364	64.2	1,560	1.37	Negative	38.2
26	P. B. B. H. 5593	65.6	1,500	1.72	Negative	42.5
27	R. I. H. 2123	40.2	1,500	2.08	Negative	36.2
28	P. B. B. H. 6032	48.0	1,440	1.03	Negative	39.1
29	R. I. H. 2414	39.8	1,280	1.67	Negative	47.6
30	P. B. B. H. 6483	61.9	1,200	2.92	31.00	37.20	33.9
31	P. B. B. H. 6328	68.3	1,200	2.56	22.00	26.40	35.1
32	P. B. B. H. 5975	64.0	1,080	1.43	Negative	38.7
33	R. I. H. 2280	28.5	800	3.12	Negative	36.9
34	P. B. B. H. 6005	62.0	780	2.82	Negative	32.5

glycemia was an important factor in diuresis. But against this are the eleven cases with a more nearly normal fluid output, five of which had a hyperglycemia well above 0.17 per cent.

On the whole, it appears from this series of cases that many diabetics have an abnormally high urea index. This is probably due in part to a washing out of urea through an increased output of fluid. Such polyuria does not depend on acidosis or glycosuria, but is apt to be coincident with a pronounced hyperglycemia. These findings suggest that the diabetic kidney is ordinarily hyperfunctional and hypersensitive to such a diuretic as an increased amount of sugar in the blood. They may explain in a measure the observations of earlier workers who commented on the frequency of nocturnal polyuria in the disease.

Of much greater interest both from the point of view of kidney function and diabetes are those cases with a urea index below 80, or, in other words, those cases with a definitely impaired renal function. These cases will be discussed in detail and will include certain other cases which should be placed in the same group for comparison. The cases fall into two divisions, the first consisting of one case in which the abnormal renal function was probably due to a coexistent chronic nephritis, and the second including seven cases of impending or true diabetic coma.

REPORT OF CASES

The first case, R. I. H. 2341, was a Russian woman aged 51. During a pregnancy twenty-eight years previously, the patient apparently had an attack of acute nephritis which recurred a year before entry to the hospital. Her diabetic symptoms were of two and one-half years' duration. Her physical examination was essentially negative except for an enlarged heart with an apical systolic murmur, and a blood pressure which on repeated examinations was above 190 systolic. The urine had a large trace of albumin and was without casts in the sediment. In view of the patient's history and physical examination it seemed probable that the urea index of 72 was due to a chronic nephritis, and was independent of her diabetes, which was relatively mild.

Of the coma cases, the first, C. R., was a young woman 30 years old. Her diabetes was of three years' duration, had shown a progressive, downward tendency and was accompanied by great emaciation and weakness. When seen, her physical examination was negative. Mentally she was bright and said that she was no more uncomfortable than she had been for a year. Her breathing, however, was abnormally deep, and her pulse was small and rapid. The carbon dioxide tension of her alveolar air was 15.5 mm. The urine contained acetone, diacetic acid and much sugar. There was a large trace of albumin and the sediment contained many hyaline and granular casts. Renal function tests showed a urea index of 280. The patient was treated by her own physician who reported her death about ten days later.

Three cases were seen at shorter intervals before death.

F1. was a Russian aged 60 years, with diabetes of several years' duration. A month previously he developed a carbuncle on his neck, which was still draining, though apparently in good condition. Two days before being seen he became alarmingly sleepy and short of breath. When seen, he still could be

roused, though he was evidently in a serious condition. His physical examination was negative except for his carbuncle and a diffuse bronchitis. His pulse was rapid and weak. His breathing showed marked air hunger. The urine contained much acetone, diacetic acid and sugar, had a heavy trace of albumin, and was loaded with hyaline and granular casts. Here again the carbon dioxid tension of the alveolar air was low (23.2 mm.). The urea index was 79. The patient continued to grow worse and died in a few days. No further studies on renal function could be made.

The third case, P. B. B. H. 6353, was that of a boy aged 13 years, with symptoms of diabetes of a few months' duration. The day before entry he suddenly became dyspneic and went into deep coma. His urine in addition to acetone, diacetic acid and sugar, contained a large trace of albumin and had showers of hyaline and granular casts in the sediment. The renal function tests showed a urea index of 36.5, pointing to a severe injury to his kidneys. Associated with this was a carbon dioxid tension in the alveolar air of 12.8 mm. The patient died in a few hours.

The fourth case, R. I. H. 2787, was a girl aged 12 years. Her diabetes was of a year's duration. She first entered the hospital Nov. 16, 1916, with considerable acidosis and glycosuria which cleared up under treatment. At the time of entry her urine contained albumin and casts, her urea index was 510, her glycosuria was 27 gm. to the liter or 89 gm. in twenty-four hours, and her blood sugar was 0.31 per cent. Her alveolar carbon dioxid tension was 23.3 mm. She was discharged Dec. 23, 1916, in good condition.

She reentered March 10, 1917, in coma. According to the history she had been well until the day before, when she began to feel "short of breath" and subsequently had grown stuporous. She died in a few hours after reaching the hospital. Her urine on this admission contained more albumin than on the time before, but fewer casts. Her urea index was 34, her glycosuria was 9.52 gm. to the liter or 33.74 gm. in twenty-four hours, and her blood sugar was 0.46 per cent. Her alveolar carbon dioxid tension was 10 mm.

If these four cases are grouped together as one, it is seen that as coma developed the renal function grew worse. This was best shown by the rapidly falling urea index. It so happened, moreover, that in each case the concentration and total output of sugar were comparable, yet the blood sugar increased as the urea index fell, an observation suggesting that the kidney was becoming impermeable to sugar as well as urea.

Opportunity to inquire more specifically into kidney function in diabetic coma was afforded by three other cases which were studied for several successive days.

P. B. B. H. 6493, was a woman aged 60 years. Her history was unimportant except for a characteristic diabetic history of ten years' duration. Until a week before entry into the hospital she had been reasonably comfortable. Then for no apparent reason she had become worse and on the day of entry was nearly comatose.

She was a very plethoric, obese woman. Her physical examination was negative except as to urine and blood analyses. She lived five days. By way of treatment she was fasted and was given fluids, soup, whisky and sodium bicarbonate in large doses. The progress of her illness and its effect on renal function is shown in Table 3.

At entry the urine contained albumin and casts in addition to sugar, acetone and diacetic acid. It was evident from these signs, as well as on account of such a low carbon dioxid tension of the alveolar air (23.7 mm. tension) that she had a marked acidosis. Clinically, during the three days following admis-

sion she appeared to improve. Her kidney function, however, grew worse despite the fact that enough alkali must have been absorbed to neutralize her acidosis in part and to cause a definite rise in the carbon dioxid tension of her alveolar air. On the morning of the fifth day the urea index was only 6. Her condition was so bad that it was impossible to obtain a specimen of alveolar air for analysis. She died within a few hours.

TABLE 3.—CASE P. B. B. H., 6493

Date	Wt., Kg.	24 Hr. Urine	Urea			Index	Sugar			Alveo- lar CO ₂ , Mm.
			Gm. per Liter Blood Ur	Gm. per Liter Urine C	Gm. per 24 Hrs. D		Gm. per Liter Urine C	Gm. per 24 Hrs. D	Gm. per Liter Blood B	
8/29/15	70.6	3,072	0.458	9.09	27.92	50	51.5	158.2	5.65	23.7
8/30/15	71.5	2,960	0.458	7.88	23.32	39	17.0	50.3	5.60	17.1
8/31/15	71.5	3,840	0.304	4.22	16.21	45	9.20	35.0	5.60	24.7
9/ 1/15	69.8	2,880	0.314	3.97	11.43	30	7.00	20.0	4.55	38.6
9/ 2/15	69.8	2,240	0.466	2.74	6.22	6	10.00	22.4	6.80	Not ob- tained

The excretion of sugar in this case is noteworthy. At entry the blood sugar was high and was accompanied by a relatively high sugar output. Under fasting the blood sugar showed a slight diminution, with a sudden rise taking place just before death. The sugar excretion on the other hand showed a persistent decrease.

P. B. B. H. 5938 is a similar case. The patient was a young woman aged 30 with an unimportant history except for diabetes. This was of two years' duration and had caused marked loss of weight and emaciation. The day before entry to the hospital she had become dyspneic and stupid. At entry she could still be roused but had pronounced air hunger. Her physical examination was negative except for her blood and urine. She died three days after

TABLE 4.—CASE P. B. B. H., 5938

Date	Wt., Kg.	24 Hr. Urine	Urea			Index	Sugar			Alveo- lar CO ₂ , Mm.
			Gm. per Liter Blood Ur	Gm. per Liter Urine C	Gm. per 24 Hrs. D		Gm. per Liter Urine C	Gm. per 24 Hrs. D	Gm. per Liter Blood S	
6/30/15	40.0	4,800	0.280	3.94	18.91	108	12.50	60.00	3.18	17.9
7/ 1/15	40.0	4,380	0.855	4.00	17.52	62	13.00	57.00	3.72	19.5
7/ 2/15	40.0	4,016	0.374	2.50	10.00	25	23.00	92.00	5.35	12.8

entry. Her treatment in the hospital consisted in whisky and fluids by mouth. In addition she was given infusions of sodium bicarbonate and glucose. Tests for renal function gave results shown in Table 4.

In this case, as well, the urea index showed a rapidly progressing drop, which may have been hastened by the fact that the acidosis was not appreciably influenced by the alkali. The blood sugar rose but interpretation of the findings in respect to it are obscured because the patient had received glucose.

R. I. H. No. 2770, was a boy aged 9 years. His diabetes was of two years' duration. On Oct. 28, 1916, he was in fairly good condition though the urine showed some sugar and a moderate ferric chlorid reaction. He entered the hospital two days later on the verge of coma. He lived for eight days, during which time he was practically comatose. At first he was fasted and given sodium bicarbonate by mouth. On the seventh day he was given two eggs and 5 gm. of carbohydrate in vegetables. Tests for renal function are given in Table 5.

TABLE 5.—TESTS FOR—

Date	Weight, Kg.	Urine per 24 Hrs., C.c.	Urea			Index I	Sugar		
			Gm. per Liter of Blood Ur	Gm. per Liter of Urine C	Gm. per 24 Hrs. D		Gm. per Liter of Blood S	Gm. per Liter of Urine C	Gm. per 24 Hrs. D
10/31/16	14.6	535	0.392	4.20	2.25	26.0	4.55	4.00	2.14
11/ 1/16	14.4	1,200	0.763	2.79	3.35	4.3	2.64	1.85	2.22
11/ 2/16	14.0	1,200	1.01	5.13	6.16	3.3	4.20	4.55	5.47
11/ 3/16	13.8	1,000	0.715	5.00	5.00	14.4	4.11	5.89	5.89
11/ 4/16	13.3	1,500	0.630	4.61	7.91	29.0	5.56	6.25	9.39
11/ 6/16	13.1	1,400	0.487	3.22	4.50	29.0	5.56	3.65	5.11
11/ 7/16	12.7	800	0.730	4.34	3.46	9.6	5.00	9.09	7.26

* Acetone bodies in blood and urine determined by Van Slyke's method.

In this case the urea index fell at first from 26 to 3 and then rose slightly. On the day before death it fell again. The blood sugar remained high with a comparatively small excretion of sugar in the urine. The alveolar carbon dioxide tension was low at first but rose, probably as the result of sodium bicarbonate. When the sodium bicarbonate was omitted it fell again, but returned toward normal with food. The day before death it was 33.4 mm., which would justify the conclusion that acidosis alone was not sufficient to be fatal.

Unfortunately acetone determinations were not made in the other cases. In this, however, the findings are noteworthy. The blood acetone rose to tremendously high figures while sodium bicarbonate was being given, and diminished in the blood when the drug was omitted and food was taken. On the other hand, the urinary excretion of acetone in no way kept pace with the blood concentration.

It is interesting to contrast these results with two severe cases which improved immediately under treatment and on which repeated tests were made.

R. I. H. 2680 was a woman aged 28 years with a history of diabetes developing four months before entry to the hospital. A week before, she had noticed increasing polyuria and polydipsia accompanied by dyspnea on slight exertion. Her physical examination was negative except for slight air hunger. Her urine at entry contained a trace of albumin, without casts in the sediment. There was much sugar, and a heavy diacetic acid reaction. While under observation she was fasted until she became sugar-free and was then given a diet sufficiently low in protein carbohydrate and fat to keep her urine free from sugar.

R. I. H. 2475 was a boy aged 26 months. He had been a healthy child until three weeks before entry. Then there had been a gradual onset of polyuria, polydipsia, and polyphagia. At entry the child was drowsy and extremely irritable. His physical examination was essentially negative. He was treated by fasting, after feeding for one day, and was then given carbohydrates in green vegetables to his point of tolerance. The renal function tests on the two cases are grouped together.

—RENAL FUNCTION

Acetone Bodies (including Beta-hydroxybutyric Acid)*			Alveolar CO ₂ , Mm.	Urinary Findings	Remarks
Mg. per 100 C.c. of Blood A	Gm. per Liter of Urine C	Gm. per per 24 Hrs. D			
150.0	8.00	4.26	15.3	Albumin and casts	259 sodium bicarbonate
240.0	7.91	9.50	20.2	Albumin and casts	69 sodium bicarbonate
260.0	7.76	9.32	30.3	Albumin and casts	159 sodium bicarbonate
270.0	7.20	7.20	34.7	Albumin and casts	29 sodium bicarbonate
368.0	4.54	6.80	26.8	Albumin and casts	
212.0	3.84	5.38	26.9	Albumin and casts	Fast broken
192.0	2.18	1.74	33.4	Albumin and casts	Fast broken

In both cases the urea index showed considerable variation from day to day without any progressive downward tendency. Other non-fatal cases which have been followed in similar fashion have shown variation in the urea index which, however, has usually remained well above normal. Occasional cases have been encountered which have shown temporary impairment of function. Some of these have been complicated by edema and one will be described in detail later.

These cases as a whole demonstrate two significant facts: Judged by the urea index, kidney function in diabetes is usually normal. In diabetic coma, on the other hand, pronounced renal insufficiency occurs. This is shown by a falling index which tends to become progressively lower as the severity of the condition increases. Such functional derangement may be accompanied by an increase in the blood sugar, with a lessened output, suggesting that other functions beside that of urea excretion are involved. At present the underlying cause of this complication is uncertain.

McLean has confirmed Ambard and Weill as to the laws of chlorid excretion in relation to its blood concentration and has tabulated seventy-two observations on normal individuals made according to the methods used in the present paper. McLean has found that normally the plasma chlorid varies between 5.62 and 6.25 gm. per liter according to the amount of salt ingested. There is a close agreement between

the chlorid calculated in the plasma by Ambard and Weill's constants and that actually found. The maximum differences in normal individuals were, with one exception, between 0.22 above the calculated value and 0.16 below. In one case the actual chlorid was 0.38 lower than the theoretical. Under pathologic conditions relatively increased concentration of chlorid occurs in certain types of cardiac and renal disease and usually accompanies edema. Relatively low concentration of chlorid occurs in fevers and under the influence of diuretics. There is no connection between urea and chlorid functions.

As can be seen from the table, in the twenty-eight cases of this series which were studied, the plasma chlorid varied between 5.05 and 6.31 gm. per liter. In eight cases the actual plasma chlorid was higher

TABLE 6.—CASE R. I. H., 2680

Date	Weight, Kg.	24 Hr. Urine	Urea, Gm. per Liter Blood Ur	Index of Ex- cretion I	Sugar			Alveo- lar CO ₂ , Mm.
					Gm. per Liter Blood S	Gm. per Liter Urine C	Gm. per 24 Hrs. D	
10/16/15	48.0	2,000	0.262	144	3.00	16.00	32.00	20.1
10/17/15	48.4	2,000	0.190	230	2.70	14.30	28.60	28.7
10/18/15	49.5	6,800	0.150	142	2.62	3.00	20.40	41.4
10/20/15	49.4	2,680	0.162	210	2.33	3.77	10.10	39.5
11/3/15	11.8	1,020	0.336	414	5.70	43.48	44.35	21.8
11/4/15	11.8	1,680	0.408	256	4.65	32.26	54.20	23.6
11/5/15	11.7	600	0.186	227	2.00	3.70	2.22	27.8
11/6/15	12.2	2,300	0.228	310	1.44	Traces	Traces	23.6
11/8/15	12.2	800	0.262	230	1.54	Negative	Negative	29.4

than the calculated, while in the remaining twenty it was lower. This confirms McLean, who found a similar lowering of the plasma chlorid in the majority of his observations on twenty-eight other cases of diabetes. By comparing the rate of chlorid excretion with the degree of acidosis, the urea index and the blood sugar, no interrelationship could be found. It would seem that in diabetes as well as nephritis the modes of excretion of urea and chlorid are independent.

Studies were made in three cases which may throw light on edema in diabetes.

R. I. H. 2394, was a man aged 31 years. He entered the hospital in March, 1915, with diabetes of short duration. His glycosuria responded to fasting and he was discharged sugar-free on a fairly liberal mixed diet. During his first stay in the hospital his urine was albumin-free and did not contain casts. For six months after discharge he did well. Then he grew careless, ate a

TABLE 7.—THE RELATION OF THE RATE OF CHLORID EXCRETION (CALCULATED AS SODIUM CHLORID) TO CONCENTRATION IN PLASMA, ARRANGED ACCORDING TO RATE OF EXCRETION AS MODIFIED BY CONCENTRATION IN URINE AND EXPRESSED AS

$$\text{Calculated plasma NaCl} = 5.62 + \sqrt{\frac{\text{Gm. per 24 hrs.}}{\text{Wt. in Kg.} \times 4.23}} \times \frac{\text{Gm. per Liter of Urine}}{\text{Gm. per Liter of Plasma}}$$

Number	Subject	Weight, Kg.	24 Hrs. Urine, C.c.	Blood Urea per Liter	Index of Urea Excretion I	Blood Sugar per Liter	Alveolar CO ₂ , Mm.	Sodium Chlorid		
								Gm. per Liter of Urine C	Gm. per 24 Hrs. D	Gm. per Liter of Plasma Actual Difference
1	P. B. B. H.	40.0	4,870	0.290	108	3.18	17.9	0.20	0.96	5.56
2	P. B. B. H.	70.6	3,072	0.458	50	5.65	23.7	0.60	1.85	5.69
3	P. B. B. H.	63.6	1,500	0.210	320	1.72	42.5	1.70	2.55	5.73
4	P. B. B. H.	39.0	3,600	0.736	36	4.35	12.8	0.60	2.15	6.25
5	P. B. B. H.	48.0	2,000	0.262	144	3.00	20.1	1.70	3.40	5.77
6	P. B. B. H.	61.7	2,880	0.267	104	2.16	31.6	2.20	5.81	6.01
7	P. B. B. H.	64.0	1,080	0.377	138	1.43	38.7	5.10	5.51	6.22
8	P. B. B. H.	62.4	1,440	0.212	242	2.08	41.9	4.70	6.77	6.31
9	P. B. B. H.	54.0	1,604	0.167	172	1.25	41.0	4.40	7.45	5.86
10	P. B. B. H.	64.2	1,560	0.265	130	1.37	38.2	5.10	7.98	5.87
11	P. B. B. H.	53.3	3,360	0.135	210	2.30	37.3	2.70	9.07	5.88
12	P. B. B. H.	42.0	2,800	0.215	206	2.33	30.2	2.75	7.70	5.89
13	P. B. B. H.	52.2	3,500	0.182	500	2.14	29.2	2.90	10.15	5.92
14	P. B. B. H.	39.8	1,280	0.163	200	1.67	47.6	5.10	6.52	5.93
15	P. B. B. H.	60.0	2,240	0.222	303	2.50	33.0	4.30	12.82	5.93
16	G. A.	70.0	2,400	84	1.10	38.1	2.80	7.55	6.03
17	R. I. H.	25.8	2,700	0.109	315	9.00	33.3	2.80	11.56	5.98
18	R. I. H.	50.0	2,000	0.410	93	2.08	38.2	5.60	14.20	5.98
19	R. I. H.	50.0	2,540	0.260	156	2.56	33.6	7.80	23.37	6.02
20	J. T.	87.2	2,987	0.307	108	2.03	38.8	6.80	14.56	6.05
21	R. I. H.	48.7	2,200	0.162	220	4.35	36.3	2.45	16.50	6.06
22	D.	31.7	6,740	0.169	162	1.37	42.6	2.45	22.06	6.07
23	R. I. H.	64.0	3,840	0.218	205	1.49	40.8	5.90	22.06	6.08
24	M.	46.5	1,740	0.220	192	3.12	35.3	8.30	14.44	6.10
25	R. I. H.	49.2	5,400	0.225	160	2.00	37.8	4.30	23.20	6.13
26	R. I. H.	41.2	3,400	0.115	635	2.86	43.2	5.60	19.03	6.19
27	P. B. B. H.	48.0	1,440	0.257	144	1.03	39.1	12.80	18.43	5.81
28	R. I. H.	50.4	5,000	0.160	296	1.33	38.9	6.30	31.50	6.23

diet beyond his tolerance, so that he showed sugar constantly and was on the decline. He reentered the hospital June 9, 1916, in poor condition. His physical examination was negative. His urine contained sugar and diacetic acid. There was a trace of albumin but no casts. The carbon dioxid tension of his alveolar air was 21 mm. His blood was strikingly lipemic. He was fasted for nine days with benefit to his acidosis and lipemia, although his glycosuria persisted. It seemed wise to interrupt his fast for four days by allowing a protein-fat diet of 1,000 calories. During this period he developed a tremendous edema so that he looked like a case of chronic nephritis. His color grew pasty, there was edema of his eyelids and genitals, as well as of his entire body.

A second fast for three days cleared his glycosuria. He was then given carbohydrates in the form of green vegetables to the point of tolerance, and finally a mixed diet of 1,700 calories containing 85 gm. of protein and 15 gm. of carbohydrate. He was discharged on this diet, sugar-free and acid-free. Repeated renal function studies were made up to and during the edema formation. They are shown in Table 8.

TABLE 8.—

Date	Weight, Kg.	Diet	Chlorid Intake	24 Hr. Urine	Blood Urea	Urea Index	Sugar		
							Gm. per Liter C	Gm. per 24 Hrs. D	Blood Sugar S
6/10/16	42.0	Mixed observa- tion diet	10.00	2,800	0.215	205	22.20	62.00	2.33
6/12/16	42.0	Fasting	10.00	2,400	0.204	91	6.20	14.90	2.63
6/13/16	42.0	Fasting	10.00	1,600	0.195	78	9.40	15.09	2.56
6/14/16	42.0	Fasting	10.00	1,900	0.180	71	6.90	13.10	3.85
6/16/16	41.6	Fasting	10.00	1,600	0.215	83	12.50	20.00	3.23
6/26/16	50.0	Fasting	10.00	4,000	0.170	62	*	*	2.32
10/ 4/16	47.8	Mixed diet	—	4,900	0.262	210	Negative	Negative	1.22

* Heavy reaction not quantitated.

At the first observation the urea index was high and the patient was excreting chlorid with a plasma chlorid lower than the theoretical. As soon as fasting began the renal function became abnormal. This was shown by a falling urea index, a rising blood sugar with a lowering output, and by a marked chlorid retention and edema. Acidosis as estimated by both the alveolar carbon dioxid and actual amount of acetone in the blood diminished. It was only after the chlorid intake was restricted that the condition improved. Finally normal function returned. The effect of withdrawal of salt on the edema is shown graphically by the accompanying chart.

Two possible explanations of the condition come to mind. One is that the acetone bodies exert a specific effect on the kidneys. In support of this, there was presumably a considerable accumulation of acetone bodies in the tissues when the edema was at its height. Although the plasma bicarbonate was normal, the plasma acetone increased, which, according to Marriott³⁹ and Sassa,⁴⁰ shows that the

39. Marriott: Jour. Biol. Chem., 1914, **18**, 507.

40. Sassa: Biochem. Ztschr., 1914, **59**, 362.

acetone content of the organs was increased as well. Another explanation is that the patient had a true nephritis which cleared up under treatment. In either event the case illustrates the importance of following the chlorid balance in cases with edema.

Another factor of importance in the development of edema in diabetes is the manner in which the body reacts to sodium bicarbonate. It has been recognized that healthy individuals as well as diabetics will develop edema after they have taken continued large doses of the drug. Widal, Lemierre and Cotoni⁴¹ followed the output of sodium chlorid in a patient who was given a known diet, and at the same time the body weight, the development of edema, and its connection with the intake

—CASE R. I. H., 2394

Chlorid					Alveolar CO ₂ , Min.	Total Blood Acetone Bodies† (Gm. Ace- tone per Liter)	Urinary Findings
Gm. per Liter C	Gm. per 24 Hrs. D	Plasma Chlorid Cl	Calculated Plasma Chlorid	Difference			
2.75	7.70	5.67	5.89	—0.21	20.2	0.842	Albumin trace; no casts
1.74	4.17	5.40	5.80	—0.40	23.0	0.842	Albumin trace; few casts
1.35	2.16	5.35	5.74	—0.39	26.3	0.854	Albumin trace; few casts
1.15	2.18	5.48	5.73	—0.25	30.8	0.627	Albumin trace; no casts
1.30	2.08	5.27	5.73	—0.46	36.2	0.590	Albumin trace; no casts
0.50	2.00	5.58	5.70	—0.12	43.9	0.270	Albumin negative; no casts
—	—	6.25	—	45.6	0.060	Albumin negative; no casts

† Blood acetone bodies determinations were made on plasma by Marriott's nephelometric method.

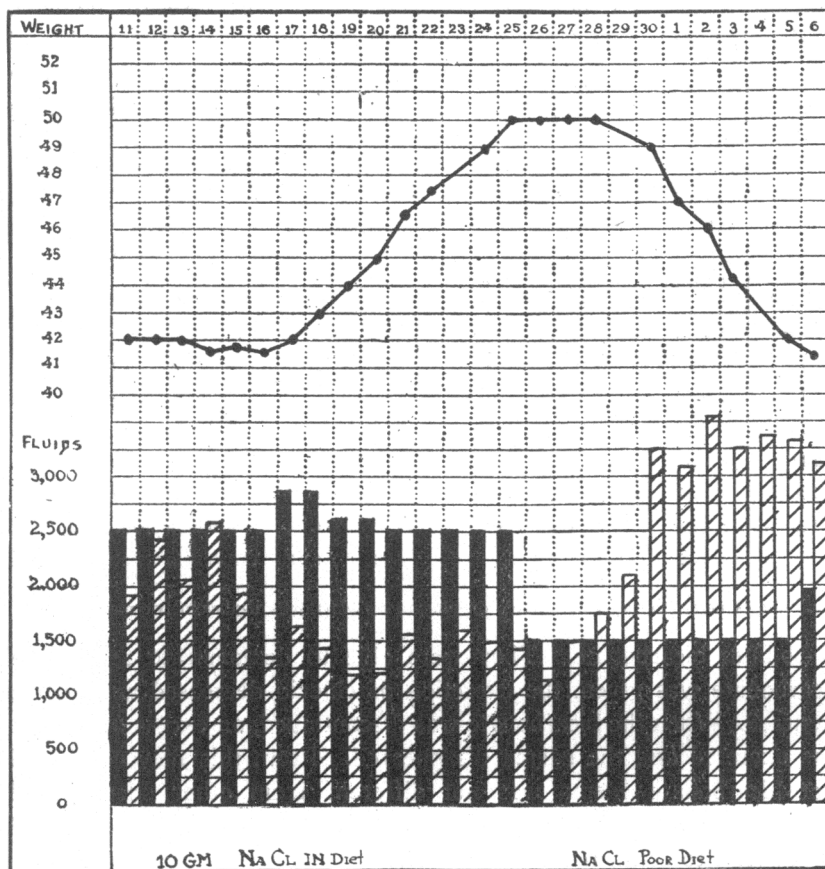
of sodium bicarbonate. They were able to demonstrate that when bicarbonate was given, the excretion of chlorid decreased and edema occurred. When the bicarbonate was discontinued, an excess of chlorid was excreted and the edema disappeared. From this they concluded that bicarbonate edema was not different from other edemas and depended on chlorid retention. The two cases reported in Table 9 would tend to confirm these observers.

In each case the plasma chlorid was lowered after the ingestion of an alkali, and, coincidentally, the rate of chlorid excretion in the urine. Since normal chlorid excretion bears a definite relationship to the plasma chlorid content, any agent lowering the latter would tend to suppress the output of the former. If large amounts of sodium chlorid were taken, and were not excreted on account of a plasma chlorid lowered by alkali, edema would naturally result.

41. Widal, Lemierre and Cotoni: *Semaine méd.*, 1911, **31**, 325.

SUMMARY

Observations on renal function were made in a series of cases of diabetes mellitus. Urea excretion was studied by the urea index of McLean. Chlorid excretion in relation to its concentration in the blood plasma was studied by Ambard and Weill's constants. In addition, observations were made on the effect on renal function of varying degrees of acidosis, hyperglycemia and glycosuria.



Graphic representation of the effect of the withdrawal of salt from the diet on the edema in Case R. I. H. 2394.

The urea index in the majority of cases tended to be normal or abnormally high. This was in part due to the rapid rate of water elimination which characterized many of the cases. Such diuretic effect was not dependent on acidosis or glycosuria, but seemed to be more or less associated with hyperglycemia.

The urea index in six cases of fatal diabetic coma was abnormally low. Renal function appeared to become progressively worse as the

TABLE 9.—THE EFFECT OF SODIUM BICARBONATE ON THE ALVEOLAR AIR,
PLASMA CHLORID AND CHLORID EXCRETION, CASE R. I. H., 2680
CALCULATED SODIUM CHLORID IN PLASMA

Date	24 Hr. Urine Rate of Excretion	Sodium Chlorid Output Rate of Excretion in 24 Hrs.	Plasma Chlorid	Alveolar CO ₂ , Mm.	Remarks
10/16/15	2,000	3.40	6.01	20.1	
10/16/15	4,272	2.56	5.68	33.6	30 gm. sodium bicarbonate
10/17/15	2,000	0.80	5.85	28.7	
10/18/15	6,800	0.68	5.37	41.4	20 gm. sodium bicarbonate
10/19/15	2,200	1.32	5.58	30.1	
10/20/15	2,680	1.34	5.26	39.5	15 gm. sodium bicarbonate
10/21/15	5,000	Traces	5.23	44.1	10 gm. sodium bicarbonate
10/25/15	4,900	2.45	5.82	39.9	
Case R. I. H., 2128					
3/20/16	5,690	14.20	5.93	23.2	
3/21/16	5,000	8.40	5.99	23.0	
3/21/16	3,000	2.22	5.35	38.6	30 gm. sodium bicarbonate
3/22/16	4,400	6.50	5.89	39.0	
3/24/16	3,635	4.82	5.97	33.2	

coma persisted. One patient had a pronounced accumulation of acetone in the blood plasma without a corresponding increase in excretion, and five patients showed a glycemia which seemed proportionally higher than the corresponding glycosuria. These cases suggest that fatal diabetic coma is accompanied by impaired renal function in which more than one of the kidney's functions are involved. The cause of the complication is not known.

In diabetes the blood plasma chlorid is usually lower than would be calculated from the chlorid excretion according to the formula of Ambard and Weill. This abnormality of excretion is not necessarily associated with acidosis, an abnormal urea index, the degree of glycemia or glycosuria.

Edema due to sodium chlorid retention may be encountered in diabetes. In one case it was accompanied by a falling urea index and by an increase of acetone in the blood without acidosis, as evidenced by an abnormally low alveolar carbon dioxid tension. The edema cleared up promptly when the sodium chlorid intake was restricted.

Edema following the administration of sodium bicarbonate is probably due to sodium chlorid retention, as the plasma chlorid diminishes and at the same time the excretion of sodium chlorid in the urine is lessened when the drug is given.