ALIMENTARY RENAL GLYCOSURIA *

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INTRODUCTION

The glucose content of normal human urine is under 0.1 per cent., usually merely a trace. The kidneys normally excrete urine containing a lower concentration of glucose than is found in the blood. When the kidneys show a higher permeability for glucose, sugar should appear in the urine while the tissues still retain the normal power of utilizing dextrose. So-called "renal glycosuria" occurs on account of an abnormal permeability of the kidneys, without any disturbance of intermediary carbohydrate metabolism. In such a condition there are no diabetic symptoms and the blood sugar is normal.

The existence of this condition was first declared by Klemperer¹ at the Congress of Internal Medicine, in Berlin, 1896, and the conditions for its diagnosis were given as follows:

1. The glycosuria has almost no relation to the quantity of carbohydrate in the diet.
2. Not only is there no hyperglycemia, but sometimes even hypoglycemia.
3. When nephritis occurs the sugar in the urine diminishes or disappears.

Vo Noorden,² in his book, "Zuckerkrankheit," refused to recognize the cases of renal diabetes previously reported, and held that the condition had not been demonstrated. Allen,³ who recognizes renal glycosuria, in his book, "Glycosuria and Diabetes," says that "the name diabetes is unjustifiable, diabetic symptoms are absent, but those of nephritis, neurasthenia and malnutrition are frequent;" and again, "almost always the glycosuria is very slight, a mere fraction of 1 per cent." Joslin⁴ recognized renal glycosuria and declared that an observation of several years was necessary for its diagnosis, clinical diagnosis without long observation of the patient being dangerous.

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1. Klemperer, G.: Cong. Int. Med., Berlin, 1896. Ueber Regulatorische Glykosuria u. renalen Diabetes, Berl. klin. Wchnschr., 1896, **33**, 571.

2. Von Noorden, C.: Die Zuckerkrankheit und ihre Behandlung, Ed. 6, Berlin, 1912, p. 37.

3. Allen, F. M.: Glycosuria and Diabetes. 1913.

4. Joslin, E. P.: Treatment of Diabetes Mellitus. 1917.

Since the initial report of Klemperer, a few reports of cases have been made in Germany by Lüthje,⁵ Bönninger,⁶ Weiland,⁷ Tachau,⁸ Frank,⁹ de Langen,¹⁰ and Galambos;¹¹ and in America recently by Lewis and Mosenthal,¹² Murlin and Niles¹³ and Strouse.¹⁴ The details of these reports will be included in the chapter of discussion.

REPORT OF CASE

As renal glycosuria is considered rare, observations on one case are here reported as follows:

History.—Man, aged 33, Japanese physician. No diabetic or neuropathic heredity; healthy childhood; at the age of 22 the patient had typhoid fever in the course of which albumin and casts were found in the urine for about two weeks. After university graduation in 1909, he was assistant at the university hospital. He was healthy; no complaint; of good nutrition; body weight, 50 kg.; height, 161 cm. Since 1911, his weight gradually increased to 54 kg.; there was increasing appetite, particularly for sweets; besides regular diet, cakes containing about 50 to 70 gm. of sugar were eaten once and sometimes twice in the afternoon. In April, 1913, after a meal consisting of 200 gm. rice, 150 gm. meat, vegetables cooked with sugar, after Japanese fashion, and much candy, an examination of the urine passed within two hours revealed 0.75 per cent. sugar. The determination of sugar in the urine was made qualitatively by the Almen-Nylander method, and quantitatively by Kumagawa and Suto's modification of Pavy's method. On the following day, after a lunch of 50 gm. bread and tea, the urine showed a slight sugar reaction. On the third day, after keeping in the meantime to carbohydrate-free diet, the urine showed no sugar reaction after a meal of 30 gm. bread; but after a lunch of 60 gm. bread, the glycosuria was present. He considered himself diabetic and treated himself accordingly. After eating 60 gm. bread at one time, sugar regularly appeared in the urine passed within two hours. The percentage of sugar was always below 0.7.

From June to November, 1913, a diabetic diet was followed. Sugar was excluded, but about 30 gm. carbohydrate in the form of bread and rice were taken with each meal, or from 90 to 100 gm. daily. The urine, examined

5. Lüthje, H.: Beitrag zur Frage des renalen Diabetes, München. med. Wchnschr., 1901, **38**, 1471.

6. Bönninger, M.: Beitrag zur. Frage des Nierendiabetes, Deutsch. med. Wchnschr., 1908, **34**, 780.

7. Weiland, W.: Ueber einige ätiologisch bemerkenswerte Diabetesformen, Deutsch. Arch. f. klin. Med., 1911, **102**, 167.

8. Tachau, H.: Beitrag zum Studium des Nierendiabetes, Deutsch. Arch. f. klin. Med., 1911, **104**, 448.

9. Frank, E.: Ueber experimentelle u. klinische Glycosurien renalen Ursprungs, Arch. f. exper. Path. u. Pharmacol., 1913, **72**, 387 and 443.

10. de Langen, C. D.: Beitrag zur Kasuistik des renalen Diabetes, Berl. klin. Wchnschr., 1914, **51**, 1792.

11. Galambos, A.: Ueber den renalen Diabetes, Deutsch. med. Wchnschr., 1914, **40**, 1301.

12. Lewis, D. S., and Mosenthal, H. O.: Renal Diabetes, Bull. Johns Hopkins Hosp., 1916, **27**, 133.

13. Murlin, J. R., and Niles, W. L.: Renal Glycosuria, Am. Jour. Med. Sc., 1917, **153**, 79.

14. Strouse, S.: Renal Diabetes, Med. Clinics of Chicago, 1916, **2**, No. 2, p. 239.

from time to time showed an occasional sugar reaction. From January, 1914, the strict diabetic diet was remitted, but no sugar was taken; the diet included from 150 to 200 gm. carbohydrate daily, in the form of rice and vegetables. For a period of two years, the urine was not examined. Beginning April, 1916, after coming to America, sugar was added to the diet according to inclination, in the form of candy and ice cream. During this time the subject felt well and experienced no weakness. Sept. 17, 1917, examination of the urine after the ordinary lunch showed almost 0.2 per cent. sugar. The determination of sugar in the urine was made qualitatively and quantitatively by Benedict's method.¹⁵ From September 20 to October 15, the diet consisted approximately of 100 gm. fat, 150 gm. carbohydrate, and from 150 to 200 gm. protein per day. Sugar was excluded; the urine showed no sugar reaction. But on a free diet containing sugar the urine two hours after meals occasionally showed a slight sugar reaction, not more than 0.2 per cent. The urine volume was not increased, and no sugar reaction was seen with mixed twenty-four-hour urine.

Experimental.—October 20, blood was taken at 9 a. m., before breakfast, after fasting over night, and determination of sugar in the blood made by the method of Lewis and Benedict;¹⁶ cholesterol in whole blood by Bloor's method,¹⁷ and carbon dioxide in the plasma by Van Slyke's method.¹⁸ All showed normal. The blood pressure was also normal.

TABLE 1.—FINDINGS IN PLASMA AND WHOLE BLOOD
OCT. 20, 1917, AT 9 P. M., BEFORE BREAKFAST,
AFTER FASTING OVER NIGHT

Sugar in Plasma, Per Cent.	Cholesterol in Whole Blood, Gm. per 100 C.c.	CO ₂ Capacity of Plasma, Vol. Per Cent.
0.11	0.22	74

From November 29, every morning a certain amount of carbohydrate was ingested after the night's fast, with results as follows: After 33 gm. starch and 25 gm. fat, no sugar appeared in the urine, but with increase of starch to 39 gm., sugar appeared one or two hours after meals, but in quantities so slight that it was hard to estimate its percentage by Benedict's quantitative method. Blood sugar was examined for every thirty minutes after meals, but no hyperglycemia appeared. After ingestion of 150 gm. banana (34 gm. carbohydrate), the urine showed sugar, presumably because of the sugar content of

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

16. Lewis, R. C., and Benedict, S. R.: A Method for the Estimation of Sugar in Small Quantities of Blood, *Jour. Biol. Chem.*, 1915, **20**, 61.

17. Bloor, W. R.: The Determination of Cholesterol in Blood, *Jour. Biol. Chem.*, 1916, **24**, 227. The Distribution of the Lipoids (Fat) in Human Blood, *Jour. Biol. Chem.*, 1916, **25**, 577.

18. Van Slyke, D. D., Stillman, E., Cullen, G. E., and Fitz, R.: Studies of Acidosis, *Jour. Biol. Chem.*, 1917, **30**, No. 2, p. 289.

the banana. After 50 gm. oatmeal (34 gm. carbohydrate), the urine showed sugar in two hours, but the blood sugar was normal. After 150 gm. potato (36 gm. carbohydrate), there was glycosuria in one hour, but no hyperglycemia. Therefore, after the ingestion of more than 34 gm. carbohydrate, the urine showed sugar after meals, without regard to the kind of starch taken, while the blood sugar was always normal.

In the third experiment (Table 3), large quantities of carbohydrate were ingested to determine the rise of blood sugar.

After the ingestion of 130 gm. rice (carbohydrate about 100 gm.), the urine showed from 0.16 to 0.29 per cent. sugar, which lasted to the fourth hour after meals. The total sugar excreted amounted to 0.25 gm. Blood sugar, which reached its maximum in the first hour, amounted only to 0.115 per cent. No hyperglycemia was seen. After ingestion of 200 gm. starch, the urine showed from 0.2 to 0.3 per cent. sugar which lasted for 2.5 hours. The total amount of sugar excreted was 0.17 gm. Blood sugar reaching its maximum in 2.5 hours was 0.145 per cent. Sugar appeared in the urine after thirty minutes, when the blood sugar showed only 0.139 per cent.

In the fourth experiment (Table 4), glucose was taken in various quantities, in the morning as in the former experiments.

After 50 gm. glucose, sugar appeared in the urine in 30 minutes to 1.5 hours, the total amount being 0.07 gm. The maximum of blood sugar was 0.128 per cent., with return to normal at the end of the first hour. After 100 gm. glucose, sugar appeared in the urine at 30 minutes to 1.5 hours with a total amount of 0.9 gm.; blood sugar reached its maximum at 0.164 per cent. with return to normal within 3 hours. After 200 gm. glucose, sugar appeared after 30 minutes and lasted 4.5 hours, with a total excretion of 0.6 gm.; the maximum of blood sugar was 0.175 per cent. with return to normal at the third hour. Examination of the urine by polarimeter showed dextrorotation and agreed with the results obtained by Benedict's method. A fermentation test with yeast gave positive results, showing that the reducing substance in urine is glucose, not pentose. After the ingestion of 100 gm. levulose, the urine showed sugar after 30 minutes and continuing for 3 hours, with a total excretion of 0.09 gm. The polarimeter showed left rotation, blood sugar, a maximum of 0.143 per cent., with return to normal in the second hour.

Summary.—After the ingestion of more than 34 gm. starch, the urine showed sugar without any hyperglycemia; after 100 gm. starch the urine contained 0.25 gm. sugar, while after 200 gm. starch the urine showed only 0.17 gm. sugar; the maximum of blood sugar was 0.115 per cent. after ingestion of 100 gm. starch and 0.145 per cent.

TABLE 2.—DETERMINATION OF CARBOHYDRATE TOLERANCE.—

Date, 1917	Diet (Test meals at 9 a. m. after fasting over night)							Urine			
	Foodstuffs, Gm.					Carbo- hydrate, Gm.	Fat, Gm.	Volume, C.c.			
	Bread	Butter	Coffee	Cream	Salt			1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.
Nov. 29	45	30	2 cups	...	...	27	25	53	40	24	31
Nov. 30	55	30	2 cups	...	1	33	25	45	39	21	20
Dec. 1	65	30	2 cups	...	1	39	25	46	28	25	30
Dec. 2	Banana 150	...	2 cups	...	...	33	...	44	40	23	28
Dec. 3	Oatmeal 50	30	2 cups	30	1	34	31	50	33	40	30
Dec. 4	Potato 150	30	2 cups	30	1	36	31	51	42	36	21

* Sugar test by Benedict's method, shows very slight reduction, qualitatively not measurable.

TABLE 3.—STARCH TEST. TEST MEALS—

Date, 1917	Diet (Test meals at 9 a. m. after fasting over night)							Urine									
	Foodstuffs, Gm.					Carbo- hydrate, Gm.	Fat, Gm.	Volume, C.c. Dextrose									
		But- ter	Cof- fee	Cream	Salt			30 Min.,	1 Hr.,	1.5 Hr.,	2 Hrs.,	2.5 Hrs.,	3 Hrs.,	3.5 Hrs.,	4 Hrs.,	4.5 Hrs.,	
Dec. 5	Rice, 130 gm. (dry weight), boiled with 100 gm. water	30	2 cups	30	4	100	31		42 +		27 +		23 +		20 +	16 —	
Dec. 14	Starch (Merck), 200 gm. Paste made with 100 gm. water	..	2 cups	...	..	200	..	45 +	8 +	15 +	6 ±	9 +	11 —	10 —	8 —	7 —	

TABLE 4.—SUGAR TEST. SUGAR AT—

Date, 1917	Glu- cose, Gm.	Water, C.c.	Urine										Sugar in Hours, Per Cent. Total Quantities Sugar, Gm.			
			Volume, C.c. Dextrose										1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.
			30 Min.	1 Hr.	1.5 Hrs.	2 Hrs.	2.5 Hrs.	3 Hrs.	3.5 Hrs.	4 Hrs.	4.5 Hrs.					
Dec. 19	50	300	30 +	15 +	16 ±	30 —	32 —	.. —	.. —	.. —	.. —	0.14 0.063				
Nov. 1	100	500	182 +	100 +	42 +	76 —	50 —	.. —	.. —	.. —	.. —	0.32 0.68	0.16 0.16			
Dec. 26	200	300	11 +	8 +		17 +	6 +	6 +	5 +	4 +	8 ±	1.26 0.24	1.08 0.19	0.99 0.12	0.39 0.04	
Dec. 8	Levu- lose 100	300	35 +	12 +	4 +	11 +	6 +	21 +	23 —							

—TEST MEALS AT 9 A. M., AFTER FASTING OVER NIGHT

Urine				Blood								Remarks
Dextrose				Sugar in Whole Blood, Per Cent.								
1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	Before Test	30 Min.	1 Hr.	1.5 Hrs.	2 Hrs.	2.5 Hrs.	3 Hrs.	3.5 Hrs.	
—	—	—	—									Sugar in plasma in 1.5 hr., 0.102 per cent.
—	—	—	—									
—	Trace*	—	—	0.081	0.085	0.087	0.082	0.085	0.086		0.071	
Trace	—	—	—									
—	Trace	—	—				0.071					
Trace	Trace	—	—				0.081					

—AT 9 A. M., AFTER FASTING OVER NIGHT

Urine					Blood									
Sugar in Hours, Per Cent. Total Quantities Sugar, Gm.				Excreted Sugar in Toto	Sugar in Whole Blood, Per Cent. Sugar in Plasma, Per Cent.									
1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.		Before Test	30 Min.	1 Hr.	1.5 Hrs.	2 Hrs.	2.5 Hrs.	3 Hrs.	3.5 Hrs.	4 Hrs.	5 Hrs.
0.16 0.067	0.26 0.07	0.29 0.067	0.18 0.04	= 0.25 gm. Polarimetric 0.19 per cent.	0.076 0.103		0.069 0.115		0.058 0.111		0.057 0.083			0.055 0.085
0.20 0.106	0.3 0.06				0.08 0.105	0.122 0.139		0.105 0.133		0.118 0.145		0.093 0.102		

—9 A. M., AFTER FASTING OVER NIGHT

Total Sugar Excreted	Blood									
	Sugar in Whole Blood, Per Cent. Sugar in Plasma, Per Cent.									
	Before Test	30 Min.	1 Hr.	1.5 Hrs.	2 Hrs.	2.5 Hrs.	3 Hrs.	3.5 Hrs.	4 Hrs.	
= 0.07 gm.	0.082 0.097	0.085 0.128	0.095 0.116		0.088 0.094					
	Plasma 0.09	 0.164	 0.135	 0.123	 0.131		 0.095			
= 0.9 gm.	0.081 0.091	0.112 0.175	0.099 0.133		0.098 0.121		0.082 0.105		0.097 0.133	
	0.09 gm. 0.105 per cent.	0.072 0.101	0.071 0.143	0.061 0.128		0.094 0.106		0.061 0.114		
Polarimetric left rotation 0.098 per cent.										

after 200 gm. starch. Furthermore, after the ingestion of 100 gm. glucose, more sugar was excreted in the urine than when 200 gm. were taken, while the blood sugar was higher and remained higher for a longer period after 200 gm. glucose was ingested than after 100 gm. When levulose was given it was excreted as levulose itself, not as glucose.

The Renal Threshold for Glucose.—There are many reports concerning the renal threshold for glucose of the normal person. It is generally accepted that the kidney is permeable for sugar when the blood sugar reaches 0.16 to 0.17 per cent. Hamman and Hirschman¹⁹ say that in a normal individual the renal threshold is not a constant factor, but is usually between 0.17 and 0.18 per cent. of blood sugar, although some otherwise normal individuals have a low renal threshold, below 0.14 per cent. (0.12 to 0.14 per cent., or 0.13 to 0.14 per cent.). Foster²⁰ found the renal threshold between 0.149 and 0.164 per cent. in a patient who had undergone ether narcosis. Jacobsen²¹ gives the blood concentration as 0.16 to 0.17 per cent. In the person reported on here, the renal threshold is as follows: whole blood, 0.069 to 0.071 to 0.081 to 0.085 per cent.; plasma, 0.115 per cent.

Hyperglycemia After the Intake of Carbohydrate and Glucose.—Much has been written on this subject, but very little that is trustworthy. For this the apparent reason is that prior to the introduction of Bang's method in 1914 and the present more accurate method of Lewis and Benedict a determination involved the use of much more blood than is now required, with consequently but one or two tests in each case, whereas an examination is requisite every thirty minutes. Consequently the conclusions drawn from former experiments involve confusion.

Frank,²² in 1911, asserted that in eight persons hyperglycemia of from 0.12 to 0.18 per cent. was found in the blood plasma after the intake of 100 gm. glucose in one hour's time, and that three persons showed a little sugar in the urine. Tachau²³ (1911), reported that no hyperglycemia was seen in one hour's time after a dose of 100 gm. sugar. Bing and B. Jakobsen²⁴ (Bang's micromethod) found hyperglycemia of 0.098 to 0.17 per cent. Among ten persons, after intake of glucose, two showed 50 per cent. and one showed 70 per cent. rise of blood sugar. The average rise after one hour was 36 per cent.,

19. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar, *THE ARCHIVES INT. MED.*, 1917, **20**, 761.

20. Foster: *Am. Soc. Adv. Chem. Invest.*, 1917. Cited by Joslin (Footnote 4).

21. Jacobsen, Th. B.: Untersuchungen über den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, Zuckerkranken u. graviden Personen, *Biochem. Ztschr.*, 1913, **56**, 471.

22. Frank, E.: Weitere Beiträge zur physiologie des Bluzuckers, *Ztschr. f. physiol. Chem.*, 1911, **70**, 291.

23. Tachau, H.: Ueber alimentäre Hyperglykämie, *Deutsch. Arch. f. klin. Med.*, 1911, **104**, 432.

24. Bing, H. J., and Jakobsen, B.: Blutuntersuchungen unter normalen u. einiger pathologirn Verhältnissen, *Deutsch. Arch. f. klin. Med.*, 1914, **113**, 571.

and after two hours, only 11 per cent. These authors believe that a rise of more than 50 per cent. at the end of the first hour must be considered as pathologic.

Th. B. Jacobsen²¹ (Bang's micromethod) found that 100 gm. glucose produces a rapid hyperglycemia which usually reaches its maximum in from fifteen to thirty minutes after the intake, keeps up one to three hours, and then falls to normal or even below. His experiments included fourteen persons whom he held to be normal. Among them six persons showed no urinary sugar, with blood sugar reaching from 0.12 to 0.16 per cent. Another group of eight persons showed sugar in the urine, with blood sugar of 0.17 to 0.227 per cent. However, the greatest amount excreted was only 1.38 gm. In the first group of six persons showing sugar, the hyperglycemia lasted about 1.75 hours; in the second group, about 2.5 hours. After 167 gm. bread (100 gm. carbohydrate), all fourteen persons reacted with a hyperglycemia (0.138 to 0.206 per cent.) which lasted from two to four hours, and six cases showed glycosuria (0.06 to 0.92 gm.). The only difference between the effect of dextrose and of starch was in the rapidity of the rise and fall of the blood sugar curve; that is, only a quantitative difference due to the difference in the rate of absorption. Jacobsen's results seem to be somewhat higher than normal, according to our present conception. There is a possibility that the use of the method was not accurate, with consequent high results, or that the experiments included persons of carbohydrate tolerance lower than normal.

Hopkins²⁵ (Bang's micromethod), in experiments with eight persons, found that the blood sugar reached its maximum (0.14 to 0.156 per cent.) in 30 minutes and lasted 2 hours. No urine examinations are reported. Graham²⁶ (Bang's micromethod), with three persons, noted that after 100 gm. glucose, the greatest rise of blood sugar was from 0.09 to 0.18 per cent., and the smallest was from 0.095 to 0.14 per cent. The maximum was usually reached in 20 minutes with return to the original level in from 1 to 1.5 hours. Cummings and Piness²⁷ after the intake of 100 gm. glucose, found about a 50 per cent. rise during the first hour, with a drop of about one half of this during the second hour. In subjects having a low tolerance for sugar, the rise following the ingestion of 100 gm. glucose is distinctly higher than normal and the high level is well sustained up to the end of the second hour.

Hamman and Hirschman¹⁹ (Lewis and Benedict's method) say that in the normal person, after the ingestion of 100 gm. glucose the blood sugar rises promptly to a level not exceeding 0.15 per cent., the high point is usually reached in about 30 minutes, and the whole reaction lasts from 1 to 2 hours, occasionally longer. They noted in many instances that where there is a considerable glycosuria, the excretion of sugar continues long after the blood sugar has fallen below the level at which it first appeared.

This latter fact—the continued excretion of sugar after the fall of blood sugar—may also be remarked in my case. Here, the maximum

25. Hopkins, A. R.: Studies in the Concentration of Blood Sugar in Health and Disease as Determined by Bang's Micromethod, *Am. Jour. Med. Sc.*, 1915, **149**, 254.

26. Graham, G.: Variations in the Blood Sugar in Health, *Jour. Physiol.*, 1915-1916, **1**, 285.

27. Cummings, R., and Piness, G.: A Study of Blood Sugar. Comparison of Tolerance for Glucose in Diabetic and Normal Subjects, *THE ARCHIVES INT. MED.*, 1917, **19**, 777.

height and duration of the hyperglycemia after starch and glucose remain within the normal limit; the excreted sugar is below 1 gm., and there is no proportion between the glucose intake and the excreted sugar. Therefore, it is difficult to consider this case as a diabetes mellitus, but there is almost no doubt that it is a renal glycosuria, since the sugar excretion is due to the abnormally lowered threshold of the kidney, not to a pathologic hyperglycemia.

The Blood Sugar and the Renal Threshold of Diabetes.—The blood sugar of the diabetic is in higher concentration than normal. It is only in the mild form of the disease or under strict treatment that the blood sugar is normal. Following the administration of 100 gm. of glucose the rise in the blood sugar is greater than normal, and the rise is sustained longer than in normal men. Jacobsen²¹ found in two cases of diabetes that an appreciable amount of sugar appeared in the urine, with sugar-freedom at the beginning of the experiment, and blood sugar below 0.15 per cent. He explained these facts on the ground that the diabetic excretes more sugar than normal at a certain level of blood sugar. It is also known that there is frequently a higher threshold for sugar in diabetics without evident renal lesions; some are free from glycosuria even when the blood sugar reaches 0.5 per cent.

According to Cummings and Piness,²⁷ in the mild form of diabetes, following the administration of 100 gm. glucose, the rise of blood sugar is longer sustained than normal, even to the end of the second hour. In a really or moderately severe case the blood sugar is higher two hours after intake of 100 gm. glucose than one hour after. Hamman and Hirschman¹⁹ confirmed the finding that the hyperglycemia in mild diabetes is abnormal in definite respects: the blood sugar rose more slowly and reached its highest point later than normal; it also rose to a much higher level, all their three cases exceeding 0.2 per cent. Likewise, the fall of the blood sugar occurred much more slowly than in the normal, the whole reaction occupying from three to four hours. These authors believe that the *duration* of the hyperglycemia is a more important index of the severity of the alteration of carbohydrate metabolism than is the height of the hyperglycemia. Concerning the renal threshold in diabetes, they found that mild cases show a normal level, while moderately severe cases sometimes show a threshold below 0.15 per cent., but usually higher.

Graham,²⁸ in 1916, reported lower and higher thresholds for diabetes. His patient of lower threshold—a man of 32—in whom glycosuria had been detected five years previously, followed an unrestricted diet most of the time, with a sugar output of about 10 to 30 gm. daily. The blood sugar before a meal and

28. Graham, G.: Variations in the "Leak Point" in Diabetes Mellitus. I. A Low Level, Jour. Physiol., 1915, **49**, Proc. Physiol. Soc., p. 47.

after semi-starvation for twenty-four hours varied from 0.1 to 0.13 per cent., and sugar was always present in the urine. After 100 gm. dextrose the blood sugar rose 0.22 per cent. in one hour and had not quite fallen to its original level three hours later. The results in this case seem to indicate that the escape of sugar was due in some degree to permeability of the kidneys, or in other words, this case might represent a combination of renal glycosuria and true diabetes.

The Test of the Renal Function.—As it was clear that my case showed a lowered threshold for sugar, examinations of the renal function were made. McLean's²⁹ adaptation of the Ambard constant was employed for the determination of the excretion of urea and sodium chlorid.

TABLE 5.—THE RELATION OF THE RATE OF UREA EXCRETION TO CONCENTRATION IN THE BLOOD

Dec. 21, 1917 (10:20 a. m. to 11:32 a. m.); bleeding at 10:50; total urine, 168 c.c.

Weight, Kg.	Urea				NH ₃	Acidity (Folin)
	Per Liter of Blood, Gm.	Per Liter of Urine, Gm.	Per 24 Hours, Gm.	Index	Per Liter of Urine, Gm.	N — Acid per Liter 10 of Urine C.c.
51	0.244	9.05	30.41	270	0.229	55.8

Breakfast at 8 a. m.; bread, 40 gm.; butter, 20 gm.; 2 eggs; half grape fruit; 1 cup of tea.

TABLE 6.—THE RELATION OF THE RATE OF CHLORID EXCRETION (CALCULATED AS SODIUM CHLORID) TO CONCENTRATION IN PLASMA

Same morning.

Weight, Kg.	Sodium Chlorid					
	Per Liter of Urine, Gm.	Per 24 Hours, Gm.	Per Liter of Plasma			Threshold
			Calculated, Gm.	Actual, Gm.	Difference, Gm.	
51	7.8	26.2	6.21	6.25	+0.04	5.66

McLean has shown that the urea excretion index as an indicator of renal function is preferable to determinations of blood urea interpreted without reference to urea excretion. The tests were conducted as follows: breakfast at 8 a. m.; at 9:50, 200 gm. water drunk; at 10:20, urine passed; at 10:50, blood taken; at 11:32, that is, seventy-two minutes after the bladder was first emptied, the urine was collected, measured, and used for analysis. McLean's 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 lies above 80, with an average 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. An index above 300 may occur in healthy young persons 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" (Schlayer).

29. McLean, F. C.: The Numerical Laws Governing the Rate of Excretion of Urea and Chlorids in Man, Jour. Exper. Med., 1915, **22**, Nos. 2 and 3, pp. 212 and 366.

The urea index of my case is 270. This is due to the high fluid output, the rate of water excretion for twenty-four hours being 3,300 c.c. by calculation, while the daily volume of urine is always from 1,200 to 1,800 c.c. actually.

McLean has confirmed Ambard and Weill as to the law of chlorid excretion in relation to its blood concentration, and has found that normally the plasma chlorid varies from 5.62 to 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 constant and that actually found.

The actual plasma sodium chlorid content in my case is 6.25, and the difference between the actual content and the calculated result is 0.04. Consequently, in this case the renal test shows no disturbance of kidney function according to the urea and chlorid excretion.

The Relation Between Diabetes and Nephritis.—It is well known clinically that when chronic nephritis occurs as a complication in diabetes, the kidney excretes less sugar than before and the sugar content in the urine is diminished. It is also known that hyperglycemia (without glycosuria) often occurs in cases of nephritis.

Myers and Bailey³⁰ lately reported hyperglycemia in nephritis and discussed the elevating influence of the nephritis generally accompanying advanced diabetes on the threshold of sugar excretion. According to Hopkins,²⁵ nephritic cases all furnish very high figures of blood sugar after feeding glucose, the duration of hyperglycemia lying between that of normal and of diabetic patients. Bing and B. Jakobsen,²⁴ in some cases of nephritis, after ingestion of glucose found an abnormal hyperglycemia but no alimentary glycosuria. Hamman and Hirschman¹⁹ say that the renal threshold in nephritis is often above 0.2 per cent. In spite of the fact of the frequently high renal threshold in nephritis, however, there is sometimes a normal threshold in nephritis, and these authors found also a nephritis with a low threshold for glucose, in the neighborhood of 0.15 per cent.

As regards the kidney function in diabetes, Fitz³¹ found that the urea index in the majority of the cases tended to be normal or abnormally high. In diabetes the plasma chlorid is usually lower than would be calculated from the chlorid excretion according to the formula of Ambard and Weill. McLean²⁹ found a lowering of the plasma chlorid in the majority of his observations in twenty-four cases of diabetes.

30. Myers, V. C., and Bailey, C. V.: The Lewis and Benedict Methods for the Estimation of Blood Sugar, with Some Observations Obtained in Disease, *Jour. Biol. Chem.*, 1916, **24**, 147.

31. Fitz, R.: Observations on Kidney Function in Diabetes Mellitus, *THE ARCHIVES INT. MED.*, 1917, **20**, 809.

REVIEW OF THE HITHERTO REPORTED CASES OF RENAL GLYCOSURIA

A search of the literature of renal glycosuria gives the following data:

1. Klemperer¹ (1896, Congress of Internal Medicine, Berlin) reported a case of old nephritis which showed 0.35 per cent. sugar in the urine with the normal figure for blood sugar; the intake of bread and 150 gm. glucose exerted no influence on the sugar content either of urine or blood; sugar in the whole blood was 0.175 per cent., which, according to our modern conception, must be considered as hyperglycemia. At the Congress of Internal Medicine in Wiesbaden in 1913, where the problem of renal glycosuria was again discussed, Klemperer's case was no longer recognized as a renal glycosuria.

2. Lühje² reported a patient, aged 22, a merchant, with gonorrhea, cystitis, and probably ascending pyelonephritis. In the urine were found albumin and sugar below 1 per cent., reaching at the utmost 15 gm. a day. There was a constant excretion of sugar showing but very slight variation in the quantity despite great difference of carbohydrate intake per day. The single determination of sugar in the blood showed sugar as 0.055 per cent. in the whole blood. No mention was made, however, of the time or the relation to the diet, so that a conclusion concerning this case is consequently impossible. Lühje claimed a relation between glycosuria and the nephritis because his case was apparently free from sugar *before* the nephritis, while sugar appeared in the urine shortly *after* the nephritis.

3. Bönninger³ describes a patient, a man, aged 37, an alcoholic, who said that he had once shown urinary sugar of 2 per cent. After admission to the hospital he excreted sugar to the extent 0.2 per cent. on normal diet. During thirty-three days' observation in hospital, the percentage of sugar in the urine was remarkably constant in spite of great differences in carbohydrate intake, varying only between 0.1 and 0.5 per cent. The sugar content of the serum was 0.097 per cent.; of whole blood, 0.078 per cent. Occasionally when the urine contained 0.5 per cent. sugar, the blood sugar was 0.062 per cent. This patient, who was observed for six years, is in perfect health and still excretes a small amount of sugar. His son is also affected with renal glycosuria.

4. Weiland⁴ makes a report of three cases which are not all, however, renal glycosuria.

5. Tachau⁵ reports a patient, 21 years of age, a merchant, who developed gastro-enteritis after an excessive indulgence in fruit. The urine showed albumin, erythrocytes and casts (transient acute nephritis). The following schedule shows the results of experiments.

Diet	Days Observed	Urinary Glucose in 24 Hours, Gm.
Carbohydrate-free	4	0
Mixed (158 to 192 gm. C. H.).....	6	0
Mixed (124 to 412 gm. C. H.).....	15	1.1 to 6.0
Mixed plus 100 gm. dextrose.....	3	0.6 to 4.2

The percentage of sugar in the whole blood after fasting was from 0.085 to 0.086; one hour after 100 gm. glucose it was 0.07 to 0.109.

5. E. Frank⁶ reports two cases: (a) a patient aged 51, who for four years had suffered from severe diarrhea of four weeks' duration, four or five times a year, without apparent cause. After the attacks glycosuria lasting about ten days was observed. Dextrose in the urine ranged from 0.05 to 0.5 per

cent.; sugar in the whole blood equaled 0.09 per cent.; in the plasma, 0.106 per cent.; (b) this patient suffered from a nervous complaint. Sugar in the urine was from 0.4 to 0.65 per cent.; in the whole blood, 0.08 per cent.; in the plasma, 0.08 per cent. In both cases, however, the time of the blood sugar determination and its relation to the diet were not shown, consequently, this report is incomplete. Frank's paper is valuable rather as a report of the literature and of his own experiments of renal glycosuria in animals under heavy-metal intoxication, as mercury, uranium and chrome. In these experiments he proved a true renal glycosuria. His exposition of increased renal permeability after poisoning with heavy metals, and also during pregnancy, suggests the existence of a clinically permanent renal glycosuria. Frank further emphasized the importance of estimating sugar in the plasma instead of in the whole blood.

7. In de Langen's¹⁰ case, a patient of 22 years, sugar was always present in the urine, the quantity of excreted sugar varying between 4 and 19 gm. in twenty-four hours, and showing no proportional relations to the quantity of carbohydrate intake. After a carbohydrate-free diet there was a high content of sugar in the urine, while the smallest excretion of sugar was seen after a high carbohydrate intake. Intake of theobromin sodium salicylate (diuretin), which, according to some authors, influences sugar excretion, had no influence in this case. Blood sugar was determined in whole blood by Bang's method; there was hypoglycemia (0.054 to 0.073 per cent.); these results are, however, not decisive because the determination was not made until three hours after the meals instead of one or two hours, but they probably serve to rule out diabetes.

8. Galambos¹¹ reported a patient 50 years of age. During observation over a period of twenty-one days, while the carbohydrate content of the diet was between 50 and 354 gm. per day, the glycosuria varied between 66 and 198 gm. and the concentration of urinary dextrose between 2.6 and 7.4 per cent. Blood sugar during fasting showed 0.089 and 0.052 per cent.; one and a half hours after taking 100 gm. dextrose it was 0.17 per cent. After caffeine, the urinary sugar was increased with the increase of urine volume. This case shows polyuria, polydipsia and acidosis, with much urinary sugar. The respiratory quotient was said to be 0.709 in fasting.

9. Lewis and Mosenthal¹² report the case of a man aged 29, who for the previous two or three years had had a tendency to increased frequency of urination during the day, but not at night. This condition had evidently been a pollakiuria rather than a polyuria, as the quantities voided apparently had not exceeded the normal. There were no diabetic symptoms. The patient excreted from 11 to 13 gm. sugar in twenty-four hours on "ward light diet." After the ingestion of 100 gm. glucose a hyperglycemia of 0.15 per cent. was evident within thirty-five minutes. Two hours and five minutes after the experiment was begun the blood sugar level returned to normal and subsequently became depressed below the normal level. The phenolsulphonephthalein test showed an excretion of 42 per cent. in two hours. Ambard's constant, determined at various times, was from 0.07 to 0.11 per cent. The kidneys were intact as far as physical and urinary signs were concerned; functional tests, however, revealed some impairment, as shown by a slightly diminished phenol-sulphonephthalein excretion and an Ambard's constant barely within the upper normal figure.

10. Murlin and Niles¹³ report a case of a man aged 20, with no diabetic heredity, who two years previously had furuncles, polyuria and thirst with loss of 10 pounds in one month. After admission to the hospital, sugar in the urine was between 19 and 34 gm. when the carbohydrate in the diet was between 15 and 100 gm. Examination for blood sugar at 11 a. m., five hours after break-

fast, revealed a normal percentage on several days. As this case was accompanied by diabetic symptoms, however, and as the blood sugar was not tested at the proper time, it is hard to classify it as renal glycosuria.

11. Strouse¹⁴ had a patient aged 13 who felt perfectly well. With noncarbohydrate diet the urine showed a trace of sugar, not quantitatively measurable. After prolonged ingestion of carbohydrate, the urine showed the same trace of sugar, apparently no more and no less than was present when the patient was on a carbohydrate-free diet. Blood sugar was 0.04 per cent. one hour after a meal rich in carbohydrate.

DISCUSSION

There has been a gradual change from the former to our present conception of renal glycosuria. Klemperer¹ regarded this condition as a sort of anomaly of metabolism characterized by normal content of blood sugar with independence of sugar excretion from carbohydrate intake. Lüthje⁵ and Naunyn³² believed that a relation existed between renal glycosuria and nephritis. Naunyn³² remarked a renal glycosuria occurring with granular nephritis; he reported three cases, but the lack of blood sugar determination leaves us uncertain whether there was hyperglycemia or hypoglycemia. Naunyn believes that nephritis influences the epithelia of the kidney to facilitate the excretion of sugar. This same author also reported glycosuria occurring after renal hemorrhage which had no apparent relation to the diet and which disappeared without any restriction of diet.

It is believed that glycosuria in pregnancy and in the puerperium is probably a renal process. Furthermore, Frank's⁹ experiments confirm the work of many investigators concerning experimental renal glycosuria due to an increased permeability for sugar after poisoning with mercury, uranium, and chromate. Among the clinical cases of renal glycosuria already cited, the ones showing a previous affection of the kidney are those of Klemperer, Lüthje and Tachau. My patient also has a record of febrile albuminuria during typhoid fever ten years previously. But the general conception now is that the existence of kidney affection, that is, anatomic change of the kidney (morbus brightii and contracted kidney) is not necessary for the occurrence of renal glycosuria. The reasons for the permeability of the kidney to sugar are not yet known.

It has been shown that the blood sugar rises after meals (Bing and B. Jakobsen,²⁴ Th. B. Jakobsen,²¹ Strouse³³), and Joslin⁴ says that the percentage of sugar in the blood of normal individuals rises promptly after meals and may reach 0.17 per cent. Accordingly, if the sugar threshold of the kidney is below the normal level, 0.17 to 0.18 per cent.,

32. Naunyn, B.: *Der Diabetes mellitus*, Wien, 1906, p. 136.

33. Strouse, S., Stein, I. F., and Wiseley, A.: *The Accurate Clinical Study of Blood Sugar*, Bull. Johns Hopkins Hosp., 1915, **26**, 211.

there must occur regularly after meals a glycosuria which lasts for a certain time and disappears spontaneously. It is pointed out by Hamman and Hirschman¹⁹ that the lowered renal threshold may occur in otherwise normal individuals. They believe that a relation between the lowered renal threshold and renal glycosuria is obvious.

The intensity of the renal glycosuria will vary with the degree of the affection of the kidney, that is, its permeability to dextrose: (1) If the permeability is severely affected, with marked depression, urinary sugar will constantly appear even when the blood sugar content is very low. (2) When the renal permeability is but mildly affected, sugar will appear only at the high level of hyperglycemia of physiologic limit, and there will be no sugar in the urine with carbohydrate-free diet, because with that diet there occurs no high physiologic hyperglycemia. Under a diet rich in carbohydrate, the blood sugar will rise to the high level of physiologic hyperglycemia and sugar will appear in the urine. This high level of physiologic hyperglycemia is, in the normal subject with normal permeability of the kidney, a preglycosuric level.

Since we know that the blood sugar undergoes marked and rapid fluctuation after the ingestion of carbohydrate, and that urinary sugar has some relationship to hyperglycemia after meals, it is hardly possible to deny, to a certain extent, at least, the existence of a relationship of urinary sugar in renal glycosuria to the carbohydrate content of the diet. In the case under consideration there was no urinary sugar when the carbohydrate in the diet was below 34 gm., because the alimentary hyperglycemia occurring with that diet is under the threshold of the kidney for sugar. Blood sugar was highest after 200 gm. glucose, but the urinary glucose in that case was less than after 100 gm. glucose.

From the foregoing facts it is apparent that renal glycosuria may depend to a certain extent on the carbohydrate content of the diet. Therefore, a classification of this condition is necessary: (1) When the renal permeability is but slightly affected, glycosuria may not appear after a carbohydrate-poor diet; but, when it is severely affected, glycosuria will not disappear even after the entire withholding of carbohydrate from the diet. (2) Urinary sugar is not excreted proportionately to the increase and decrease of carbohydrate in the diet.

Von Noorden² remarks that in mild diabetes the urinary sugar is often independent of the carbohydrate intake. Therefore, too much attention must not be paid to the fact of the independence of urinary sugar to the carbohydrate in the diet.

The most important factor in the diagnosis of renal glycosuria is the presence of the normal level of the blood sugar when sugar appears in the urine.

Von Noorden² also says that renal glycosuria must be observed not a few weeks or months, but over a long period of time, since its progress is different from that of ordinary diabetes. Joslin⁴ remarks the same thing. The author's case has been observed for five years, and the tolerance for carbohydrate is still the same and the subject is in good health.

Suggestions as to the Nature of Renal Glycosuria.—In the foregoing discussion I have tried to show that renal glycosuria may be defined according to the following characteristics:

1. Glycosuria occurs without *abnormal* hyperglycemia. Abnormal hyperglycemia, as previously stated, is entirely different from alimentary hyperglycemia of from 0.16 to 0.17 per cent., which is physiologic. Glycosuria occurs although the blood sugar is within this physiologic limit.

2. There is no disturbance of carbohydrate metabolism; the nature of renal glycosuria is entirely different from that of true diabetes mellitus, and consequently, there are clinically no diabetic symptoms.

3. Urinary glucose may or may not have some relationship to the carbohydrate in the diet, according to the degree of permeability of the kidney. In a mild case, sugar will disappear from the urine during a carbohydrate-free diet; glucose usually appears after rich carbohydrate intake.

4. During a long period of time no progressive increase of the abnormality occurs.

It is obvious that the term "renal diabetes" is not fitting for the characteristics just described, since the condition is not diabetes, but is "alimentary renal glycosuria."

Diagnosis of Renal Glycosuria.—Notwithstanding the fact that it is perfectly simple to observe that the lowering of the renal threshold results in the appearance of glucose in the urine without disturbance of intermediary carbohydrate metabolism, nevertheless, the question of renal glycosuria was left for a long time unsolved. The recent improved methods of blood sugar analysis have afforded the first opportunity of settling the question of blood sugar and especially of alimentary hyperglycemia. Now we know that when an individual shows sugar in the urine we must determine the blood sugar before we can make the diagnosis "diabetes," and furthermore, that in case of doubt, sugar must be determined in the plasma, because the renal threshold pertains most strictly to it. Examination of blood sugar is required not only once after fasting, but also at least twice every hour after a certain carbohydrate diet with resultant glycosuria. The elevation of the blood sugar and the renal threshold of the individual must

also be studied. Comparison of single blood sugar determinations is without value. By these means, just stated, we can learn whether the glycosuria is due to disturbance of carbohydrate metabolism or to the increased permeability of the kidney for sugar, according as the hyperglycemia present is within the physiologic limit or not. We learn at the same time the level of the renal threshold in the patient.

The glucose test, which must next be considered, consists in the study of the blood and urine of the patient beginning thirty minutes and continuing two or three hours following the intake of 100 gm. glucose with from 250 to 300 gm. water, after an over-night fast. This test shows the condition of carbohydrate assimilation of the individual. If the hyperglycemia still remains within the physiologic limit after the test, we may exclude diabetes mellitus and consider that the urinary sugar is due to the increased permeability of the kidney to sugar.

The one more important point is the observation of the case over a period of years, because, as remarked by von Noorden, there is a form of mild diabetes which shows a high tolerance for sugar in the early period of the disease. To differentiate renal glycosuria from this mild form of diabetes mellitus one must determine the course and watch the outcome.

Since renal glycosuria brings about no injury to the health or annoyance to the individual, it is possible that persons with a lowered sugar threshold may unconsciously for a long period excrete sugar in the urine after meals. The absence of symptoms may quite possibly conceal many cases of renal glycosuria which are not at present credited. It is also possible that some of the cases of the so-called mild diabetes in practice may belong to this form of glycosuria because the majority of them are diagnosed only by the examination of sugar in the urine, or, at most, by a single determination of blood sugar without relation to the preceding meal. An imperfect examination might easily diagnose as mild diabetes cases which in reality are renal glycosuria with a lowered threshold of the kidney for sugar and perfect carbohydrate metabolism.

Prognosis of Renal Glycosuria.—The present conception of renal glycosuria is that this condition is stationary; the glycosuria has no tendency to increase and the subject remains in good health. My case shows, during five years, only the same slightly depressed threshold and consequently only intermittent glycosuria after a meal rich in carbohydrate. Whether this condition will continue for a long period of time, say 10 or 20 years, or whether sooner or later a marked depression with constant excretion of sugar in the urine will occur, only the future can reveal.

Therapy of Renal Glycosuria.—It is believed at present that it is useless to keep to a strict diet in renal glycosuria. However, with the cases hitherto reported so few and the time of their observation so short, there is no surety that it is harmless to give carbohydrate and glucose in large amounts to persons with lowered kidney thresholds, since there is a chance that the depression might be thereby increased. The question is still open.

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