THE DIAGNOSIS OF RENAL GLYCOSURIA*

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THIS paper was prompted by the fact that within the last twelve months three diabetics were admitted to this hospital with the disease fairly well advanced and, in each case, a diagnosis of renal glycosuria had been made less than two years previously. One of these patients now requires forty units of insulin a day in order to keep the disease under ideal control. This patient will be referred to again, as the diagnosis in his case was based upon the results of a blood sugar time curve and, incidentally, was made in a hospital.

Since renal glycosuria in no way, except for the glycosuria, resembles diabetes, it is rather difficult, on the basis of probabilities, to assume that all these individuals developed diabetes only recently. However, one of the essentials for the diagnosis of renal glycosuria is that the individual so affected must not subsequently develop diabetes. The purpose of this paper is, therefore, to outline the essentials for the diagnosis of this condition and demonstrate its main features by the report of a case met with recently. From this outline, it will appear that the diagnosis is rather complicated, demands hospital management, a knowledge of elaborate laboratory technique, and can hardly be made in office practice. This is exactly the idea the writer intends to convey. In office practice, the safest procedure is to assume that glycosuria indicates diabetes until proved otherwise. Since, when compared with diabetes, the incidence of renal glycosuria is extremely low, it is suggested that it is a much safer plan to underfeed a normal individual temporarily than to overfeed a diabetic.

In a previous study of renal glycosuria in this hospital[1], a striking feature noted was the small number of authentic cases recorded in the literature. Since then, the literature has increased. In the experience of our diabetic clinic, the incidence still continues to be very low. This may be due to the operation of the laws of chance, and it is not suggested here that the diagnoses in the great majority of cases recorded were not correct. It may, however, be observed that on the basis of the available evidence only, that is, the recorded data, the diagnosis of renal glycosuria in a large number of these cases is not proved.

Renal glycosuria may be defined as a condition in which there is undue permeability of the kidneys to sugar, the concentration of sugar in the blood remaining within the normal limits. The quantity of sugar excreted is usually small, being unaffected, or not much increased, by carbohydrate-containing foods. There is a marked contrast between renal and true diabetes in that in the former the functions of mobilization, storage, and utilization of sugar are unimpaired. Unlike true diabetes, insulin does not influence the rate of the urinary excretion of sugar in the absence of marked hypoglycæmia. The condition is compatible with good health and long life, as symptoms of diabetes do not develop. Insurance companies, whose medical departments keep up with the advances of medicine, do not regard these individuals as "sub-standard" and accept them as policyholders at ordinary rates. The features of importance will now be dealt with separately:—

1.—THERE MUST BE NO SIGNS NOR SYMPTOMS OF DIABETES

This hardly requires further comment.

2.—THERE SHOULD, IDEALLY, BE NO FAMILY HISTORY OF DIABETES

Interpretation of this part of the history is, at times, difficult, since the incidence of a family history tends to be large, both in diabetes and renal glycosuria. As a matter of fact, the familial character of renal glycosuria is sufficiently marked to constitute a cardinal feature of the condition.

3.—THE FIGURE FOR BLOOD SUGAR OBTAINED IN THE FASTING STATE MUST ALWAYS BE NORMAL

It might here be pointed out that a normal blood sugar obtained in the fasting state, even

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when found repeatedly, and when no alterations whatever have been made in the dietary habits of the individual, does not exclude diabetes. Mild diabetics, particularly of the chronic progressive type, when the glycosuria is still of a post-prandial character, may, over a period of months and even years, have normal blood sugars and urines free of sugar in the fasting state. It is only, as a rule, when the glycosuria is found persistently throughout the twenty-four hours that hyperglycæmia is found in the fasting state. With regard to blood sugar studies, a blood sugar time curve obtained following the ingestion of glucose may be the only indication of diabetes. Here, again, there are pitfalls in the interpretation of data. A few observations may be made at this point.

It is the exception rather than the rule, at least in the experience of the writer, when patients apply for such tests that they have not had their diet altered with regard to its sugar content for a number of days at least. The usual history is that glycosuria was discovered during a routine examination for insurance, etc. The individual then consulted his own physician who suggested a blood sugar time curve, but advised the patient to restrict carbohydrates, for purposes of safety, until the diagnosis was certain. Wise practice as this may be from a therapeutic point of view, the fact remains that it may mask true diabetes when the latter is in its very early stages. In very mild, though definite, diabetes, it is possible under these conditions to obtain a perfectly normal blood sugar curve. For this method of diagnosis, one must, therefore, make certain that the individual has not in any way altered his dietary habits for some days prior to the test.

Another, and not uncommon, error in the interpretation of blood sugar time curves is the assumption that if, during the period of observation, sugar is excreted when the blood sugar is below the usually accepted threshold level, namely, 0.18 per cent, the individual has renal glycosuria. As a matter of fact, the diagnosis in one of the three patients referred to, that is, in the one who now requires insulin (Hosp. No. 6037-29), appears to have been made chiefly on this basis. It is important to recognize that once hyperglycæmia and glycosuria are produced by the ingestion of glucose, sugar may continue to be excreted for some time in spite of the fact that the blood sugar is falling. Thus:—

	Blood sugar	*Urine sugar*
	Per cent	
Fasting Period.....	0.100	0
Given 100 grams of glucose:		
30 minutes after ingestion.....	0.250	+
60 " " "	0.153	+
120 " " "	0.111	trace
150 " " "	0.085	0

Note the presence of sugar in the urine when the blood sugar was falling and was only 0.153 per cent. Incomplete emptying of the bladder is excluded.

Another point to consider with regard to blood sugar time curves is that there is still disagreement as to the significance of certain results, though all workers are in agreement as to the constitution of a perfectly normal curve. The above curve is cited as an example. Here, we note a normal blood sugar before and after the test, but a marked hyperglycæmic response at the end of one-half hour. Some regard this curve as normal. As a matter of fact, some insurance companies request blood sugars before and two hours after glucose only. From the experience of this hospital, this curve is regarded as abnormal. We now have about three thousand blood sugar time curves correlated with the clinical conditions, and only in very few instances have we been unable to find some condition which may lead to disturbance of carbohydrate metabolism associated with it.

Assuming the above type of curve to be abnormal, another fact to consider is that it is possible to have marked and undetected hyperglycæmia. The usual practice is to obtain the blood sugar one-half hour after glucose ingestion. The blood sugar may, however, rise to a much higher level sometime before this period. This may then lead to sugar excretion and the conclusion from the *curve alone* would be that sugar is excreted without hyperglycæmia, or below the threshold level. On this basis, a diagnosis of renal glycosuria might be made. It is interesting, in this connection, to note that glucose is very rapidly absorbed from the gastro-intestinal tract. As a matter of fact, its oxidation may be detected as early as seven minutes after its ingestion[2].

There are a number of other factors which may influence blood sugar curves and it is suggested that one making use of this test for diagnosis should be familiar with them. They may be found in all standard works of physiology.

4.—THERE MUST BE LITTLE OR NO RELATIONSHIP BETWEEN THE INTAKE AND EXCRETION OF SUGAR

This may be detected in two ways, namely, (a) by daily urinalysis over long periods of time while the individual is following his ordinary dietary habits, or (b) increasing the sugar content of the diet over a short period of time, while the patient is under hospital care. The results of such observations will be shown in the accompanying case report.

5.—THE RATE OF UTILIZATION OF SUGAR SHOULD BE NORMAL

This is determined by studying the respiratory metabolism. Again, as with blood sugar time curves, there are a number of variables to be considered in the interpretation of data. These have been repeatedly emphasized in standard works. The technical details of this test and the interpretation of the results are not only more difficult but more numerous than with blood sugar time curves. When, however, properly performed and properly interpreted, this method is a most valuable index of carbohydrate metabolism. It was, so far as the writer can ascertain, first employed in the study of renal glycosuria in this hospital. The results obtained have been corroborated by the use of a much more elaborate technique by Ladd and Richardson[3].

6.—THE INDIVIDUAL MUST NOT SUBSEQUENTLY DEVELOP DIABETES

Time is, therefore, an important factor in the diagnosis of this condition.

REPORT OF CASE

(No. 207/30.) A male, 48 years of age, was admitted to the surgical service of Dr. A. T. Bazin, on January 9th, 1930, with a fracture of the lower third of the tibia and fibula, due to a fall on the same day. During a routine examination, sugar was found in his urine and, according to the practice in this hospital, his case was immediately referred to the Metabolism Department for observation.

Family History irrelevant. There was no history of diabetes nor of glycosuria.

Personal History in regard to past illnesses also irrelevant, and in regard to the glycosuria the following is of interest:—

At eighteen years of age, the patient applied for and received a life assurance policy. He applied again at the age of twenty and twenty-two years and was accepted on both occasions. At twenty-seven years of age, he again applied and, for the first time, sugar was discovered in his urine. He was then given a diet by his physician and, though adhering to it strictly, sugar was repeatedly found in the urine. As he did not feel ill, in spite of the persistent glycosuria, he broke diet and during the last twenty years has not restricted his diet in any way and, except for his recent accident, has always felt well.

Except for the local condition, the physical findings were entirely negative. There were no signs, subjective or objective, except for the sugar in his urine, to suggest diabetes. The maximum, average, and present weights are about the same. The laboratory findings, except those of the study of his carbohydrate metabolism, were as follows:—

Urine:

Clear; specific gravity 1012; no albumin; sugar, present; no acetone nor diacetic acid; microscopically, negative.

Blood:

Red cells	4,800,000 per c.mm.
White cells	8,200
Hæmoglobin	83 per cent (van Slyke)
Wassermann Test	negative
Sugar	0.111 per cent
van den Bergh Test	negative

Kidney Function:

Urea nitrogen	0.18 mgm. per 100 c.c.
Creatinine	1.43 mgm. per 100 c.c.
Uric acid	2.66 mgm. per 100 c.c.
Plasma chlorides	0.590 per cent

Urine urea concentration following the ingestion of 15 grams of urea,

1st hour	2.64 per cent
2nd hour	2.61 per cent

	Urea	
	Given	*Not given*
Urea concentration factor	39	69
Urea secretion constant (van Slyke)	6.4	11.0
Blood urea clearance (van Slyke)	42.9	78.0

X-Ray (routine in all of our diabetics):—

Feet	No evidence of arteriosclerosis
Chest	No evidence of tuberculosis

Since, the blood sugar was normal, in the fasting state, a blood sugar time curve was obtained on the following day with these results:—

Period	*Blood sugar*	*Urine*
	Per cent	
Fasting	0.111	+
Given 100 grams of glucose:		
30 minutes after ingestion	0.166	+
60 " " "	0.137	+
120 " " "	0.114	+
150 " " "	0.087	+

The points to be noted are (a) glycosuria, in the fasting state, in spite of the normal blood sugar; (b) a maximum sugar of 0.166 per cent; (c) a return of the blood sugar to the normal level at the end of two hours; and (d) persistent glycosuria throughout the test, regardless of the blood sugars.

In view of the above findings, it was desired to make certain of good storage of carbohydrates before attempting further studies, particularly with regard to the respiratory metabolism. Incidentally, by increasing the amounts of carbohydrate, one could observe the relationship between the intake and excretion of sugar. The following were the results:—

Date	COH.	Fat	Prot.	Total available glucose	Urine Volume	Specific gravity	Blood sugar
15	250	117	63	300	600	6.0	0.098
16	347	117	68	400	850	10.2	0.100
17	448	121	65	500	1200	18.0	0.131
18	550	93	64	600	650	10.4	0.122
19	550	93	64	600	900	9.0	0.120
20	550	93	64	600	500	6.0	0.113
21	550	93	64	600	450	3.3	0.116

The following are to be noted:—

(a) absence of polyuria;

(b) the daily amounts of sugar excreted were small and not influenced by sugar intake;

(c) an intake of as much as 600 grams of available glucose. The patient felt uncomfortable with this amount of sugar since, as he stated, it was much greater than he was ordinarily accustomed to;

(d) normal blood sugars daily, except for a slight disturbance on one day, at which time there was a slight fever. However, it will again be noted that it was not related to the maximum food intake and was not found again.

As the patient by now had been on a heavy carbohydrate diet for four days, respiratory studies were made. The combined data are shown in the following table. The technique employed was the same as that employed previously[1], except that the protein metabolism was not assumed to be fifteen per cent of the total heat production. He voided urine before and three hours after the test.

The following are to be noted:—

1. A rise in the respiratory quotient almost to unity and maintained at a high level.

2. A normal increase in the heat production above the basal level, *i.e.*, a normal specific dynamic response.

3. A normal rate of oxidation of sugar.

4. A low rate of excretion of sugar; during the entire period of observation there was only 2.83 grams.

5. Again, it will be noted there was no polyuria.

SUMMARY

To summarize, we have here an individual in whom:

1. Sugar was accidentally discovered in the urine.

2. There were no signs nor symptoms to suggest diabetes at the time of the discovery of the sugar.

3. There was no family history of diabetes.

4. The daily blood sugars were normal, in the fasting state, though sugar was persistently found in the urine during these periods.

5. The blood sugar time curve obtained after glucose ingestion was normal, except for the glycosuria.

6. Daily observation with increasing quantities of carbohydrate food showed that there was no relationship between the amount of sugar ingested and excreted. The amount excreted was small.

7. There was no polyuria.

8. The respiratory metabolism was normal and, lastly,

9. After twenty years of glycosuria, with no alteration whatever in his dietary habits, the patient did not develop any signs nor symptoms of diabetes. The diagnosis of renal glycosuria is, therefore, made in this case. This, it may be

RESPIRATORY METABOLISM

Period	Per hour			Resp. Quotient		Calories per hour		Calories per hour from			Grams food oxidized per hour			URINE		
	Litres	Litres	Urine-N grm.	Total	Non-protein	Total	Increase above basal %	COH.	Fat	Prot.	COH.	Fat	Prot.	Volume c.c.	Sugar Per cent	Sugar grm.
Before glucose	13.140	9.581	0.344	0.727	0.720	61.34		2.51	49.72	9.12	0.63	5.47	2.22	40		
30 min. later	14.330	11.156	0.430*	0.778	0.778	67.70	10.3	14.19	42.12	11.40	3.55	4.63	2.78			
60 min. later	13.370	12.440	0.430*	0.930	0.959	65.51	6.7	46.67	7.35	11.40	11.67	0.81	2.78			
120 min. later	13.870	12.480	0.430*	0.901	0.920	67.46	10.1	40.83	15.25	11.37	10.21	1.68	2.77			
180 min. later	13.360	11.140	0.430*	0.834	0.834	63.87	4.1	23.94	28.56	11.37	5.98	3.14	2.77	156	1.80	2.83†

*Average per hour obtained from 3 hour sample.
†Total excretion during 3 hours following glucose.

stated, is our routine in every case before such diagnosis is made. It is obvious that this procedure is hardly possible in office practice. The purpose of recording all of the data in detail is to emphasize that it is unwise to make a diagnosis of renal glycosuria in office practice. As stated above, the condition is very uncommon. It is, therefore, safer to underfeed a normal individual than to overfeed a diabetic. The patient referred to above who now requires insulin emphasizes the fact that an individual with glycosuria should be regarded as a diabetic until proved otherwise.

The writer is indebted to Dr. A. T. Bazin for his kind co-operation in allowing the patient to overstay the time necessary for the relief of his surgical condition, and, thus, to occupy a bed which could have been used to greater advantage in a surgical service.

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THE RELATIONSHIP BETWEEN THE CLINICAL AND PATHOLOGICAL FINDINGS IN PRIMARY PULMONARY MALIGNANCY*

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MEDICAL text books dealing with the subject of primary malignancy of the lung give as the typical symptoms, pain, cough, hæmoptysis, certain typical sputa, dyspnœa, and loss of weight, but no account is given as to how and in what order these arise and progress. Now this symptom complex is rather that of disease of the lungs than of any particular disease and is not very enlightening. Brunn[1], in an excellent analysis of the published records of six hundred and twenty-nine cases, analyses the incidence of the main symptoms reported, as follows:—

	Per Cent
Cough	65
Sputum	75
Bloody Sputum	40
Pain	60
Dyspnœa	50
Loss of Weight	35
Fever	45
Effusion, early	15
Effusion, late	45
Metastases	85

He does not, however, attempt to correlate the times of onset with any particular stage of the disease.

Standard literature on the subject of the x-ray diagnosis gives descriptions of several types of malignancy—infiltrating, hilar, nodular, lobar, and the varied appearances produced by these are discussed. But, again, one cannot gather a very clear impression as to the pathognomonic or characteristic appearances differentiating this disease, especially in its early stages, from other pulmonary diseases.

It is my desire in this paper to point out that the symptoms arise in a definite sequence, depending on the actual underlying pathological condition, that this is demonstrable in the living by x-ray, and that the symptoms or symptom-complex of any stage are more or less constant for that stage. A conception such as this, while not infallible, gives one a much clearer picture of the disease.

Some of the indefiniteness arises from the fact that sarcoma of the mediastinum, which early involves the lungs, and metastatic malignancy, which is considerably more common than primary growths, are apt to be confused, although they are distinctly separate entities with different clinical pictures. Confusion occurs, too, from the prejudice that malignancy of the lung is a chronic disease, producing only one of several varied clinical conditions and roentgenographic appearances. This mistaken idea has given the more trouble because the most rapidly growing of all lung carcinomata, the so-called "oat-celled" carcinoma has not been considered, but has been frequently inaccurately classified as a sarcoma[2]. Actually, however, carcinoma of the lung is a rapidly progressive disease. According to Hunt[3], the average duration of the disease is six and one half months, while death occurs often within a few months of the first consultation with a physician. During this brief period the pathological processes show a number of changes

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