GLYCOSURIA: MECHANISM AND EVALUATION

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GLYCOSURIA has, until recently, been thought of in terms of a "renal threshold" by which glucose is retained or excreted according to its concentration in blood. Useful as it has been, this explanation is physiologically unsound (Govaerts and Muller,[1] Mirsky and Nelson).[2] Furthermore it does not resolve clinical problems to which newer concepts of glycosuria apply directly. Hence, the clinician has often had to lead his glycosuric patient through a maze of glucose tolerance tests, measurements of arterial (capillary) and venous blood sugar, and even changes of diet, only to emerge with an insecure conclusion.

The purpose of this paper is to describe the mechanism of glycosuria as it applies to clinical problems, and to suggest a procedure which may aid in establishing the nature of glycosuria in doubtful cases.

Mechanism of Glycosuria

Formation of urine begins with the outpouring through glomerular capillaries of an ultrafiltrate of plasma. About 1200 cc. of blood, containing 650 cc. of plasma, pass through the kidneys and over the glomerular capillary bed per minute. The hydrostatic pressure furnished by the heart squeezes out from the 650 cc. of plasma about 130 cc. of filtrate. This filtrate consists of plasma water and of the substances dissolved in it. Among these is glucose. Consequently (fig. 1) at a plasma glucose concentration of 100 mg. per 100 cc., the rate of glucose filtration is 130 mg. per minute.

The next step in urine formation is selective reabsorption. This consists in a transfer from the tubule back into the blood of most of the substances present in the filtrate; substances which are not reabsorbed are excreted in urine. Some substances, such as creatinine and inulin are not reabsorbed at all and others only partially. The reabsorption of urea, for example, is passive and partial. It depends on the movement of this highly diffusible substance back into the blood together with the 129 cc. of water reabsorbed from the filtrate. Some of the amino acids, vitamin C, phosphate and sulfate, are actively reabsorbed up to a certain maximum capacity. Thus, the amounts of these substances present in urine remain small until the capacity for active reabsorption is exceeded by an increase in the rate at which they are filtered from blood.

In the case of glucose, reabsorption is active and, normally, virtually complete. The enzymes in cells of the upper part of the proximal convoluted tubules couple glucose with phosphate at the luminal surface of the cell and uncouple the hexosephosphate at the basement membrane, (Marsh and Drabkin).[3] This discharges the glucose into the renal interstitial fluid from which it is carried off in the peritubular blood capillaries. The process can be schematized as a system of carrier belts (fig. 1).

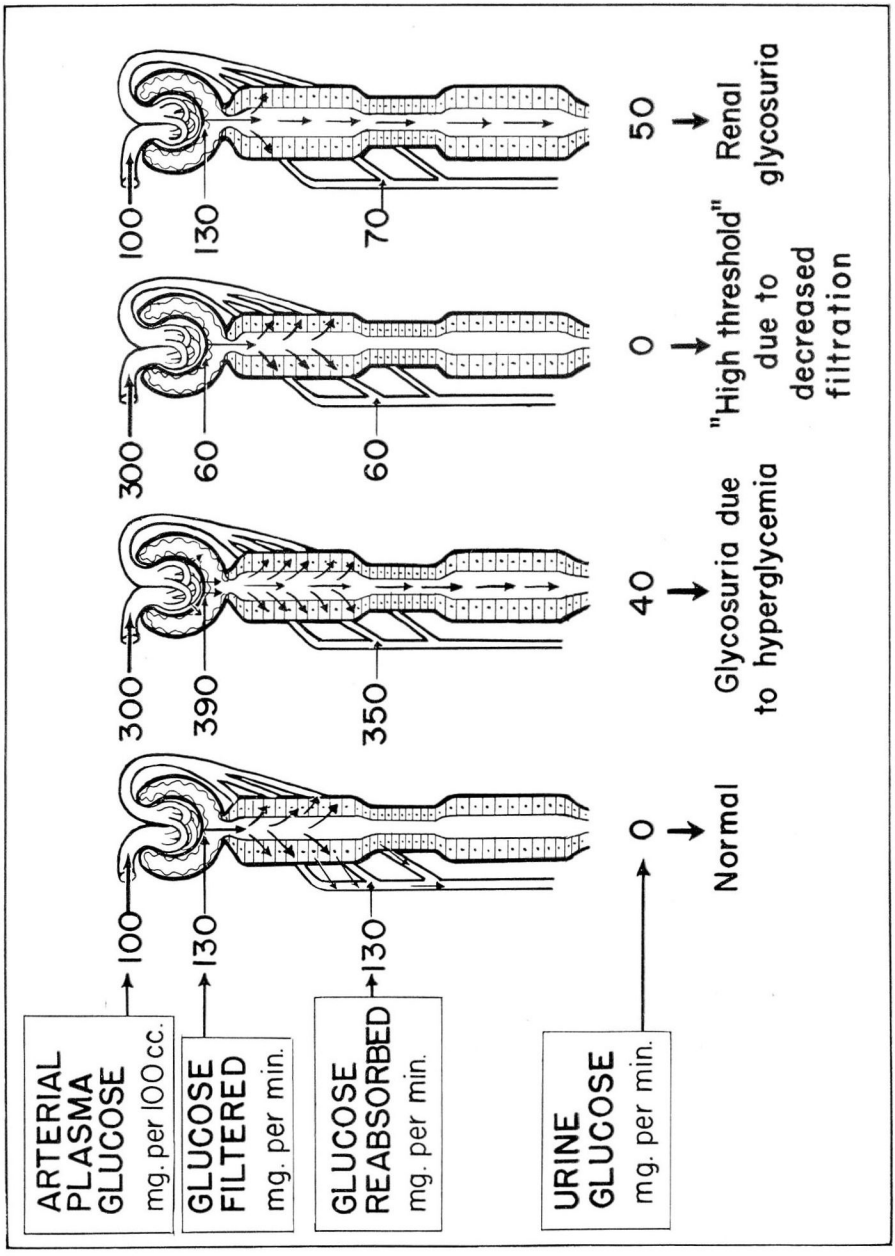

FIG. 1

When, for example, the plasma arterial concentration of glucose is tripled and the filtration rate remains unchanged, the amount of glucose presented for filtration becomes 390 mg. per minute. This load of glucose is more than the tubule cells can transfer through the carrier system, which picks up as much as it can and allows the remainder to pass on down the tubule. Here a small fraction may enter into the cells of distal part of the convoluted tubule and be deposited as glycogen. But the bulk of it passes on into the urine. The normal person would, in this circumstance, reabsorb from 300 to 350 mg. per minute and excrete from 40 to 90 mg. per minute. A further increase of blood sugar to 400 mg. per 100 cc. will raise the amount filtered to 520 mg. per minute. The amount excreted in the urine will then increase to from 160 to 220 mg. per minute, while the amount reabsorbed remains constant at 300 to 350 mg. per minute. The amount reabsorbed per minute is therefore at a peak level as Tm_G, where T = tubule, m = maximum and G indicates glucose. The normal average of this function in women is 300 and in men 350 mg. per minute.

Onset of glycosuria is normally dependent on an excess of glucose load (amount of glucose filtered per minute) over the glucose reabsorptive capacity. The latter is a function of the enzymatic activity of tubule cells. But the glucose load depends on arterial plasma glucose concentration and on the rate of glomerular filtration. Hence, there are three factors to be considered in the evaluation of glycosuria. These are (a) plasma glucose content (b) rate of glomerular filtration and (c) reabsorptive capacity of the tubules.

Glycosuria and Hyperglycemia

Glycosuria during hyperglycemia is the result of an excess of renal glucose load (plasma glucose concentration times rate of glomerular filtration) over glucose reabsorptive capacity. As such, it occurs in a wide variety of conditions associated with hyperglycemia. The chief of these is diabetes mellitus, but transitory emotional glycosurias, transient glycosuria after head injury, meningitis and other conditions must be included. The diagnosis of these is not germane to the present topic. However, in considering them, it is important to remember that venous blood sugar content is usually lower than arterial and that arterial content determines the presence or absence of glycosuria. Arteriovenous blood sugar differences can be minimized by heating the forearm for thirty minutes in a water bath at 40° C. before sampling the venous blood which is thus arterialized. Finger-puncture (capillary) blood can be taken as equal to arterial.

So-called "high threshold" diabetes is a problem of serious concern. An increase in apparent threshold may result from (a) decrease in the rate of glomerular filtration, so that the glucose load is not increased beyond reabsorptive capacity as the result of hyperglycemia or (b) from an actual increase in reabsorptive capacity beyond the normal maximum.

Experimentally, reabsorptive capacity for glucose is increased in dogs by administration of thyroxin (Eiler, Althausen, and Stockholm),[4] but human kidneys are apparently less responsive to this sort of stimulation than those of dogs (Corcoran, Taylor, and Page).[5] Indeed, hyperglycemia in hyperthyroid-

ism is not infrequently associated with glycosuria. A recent preliminary report (Farber, Berger, and Earle)[6] demonstrates unusually high glucose reabsorptive capacities (401-460 mg. per minute) in a group of middle aged women with diabetes (normal 300 mg. per minute). This work implies that prolonged hyperglycemia may stimulate reabsorption by a sort of work hypertrophy. This view is in line with clinical experience and accords with one of the observations (Case 4) presented in Table 1.

Unfortunately, the "high renal threshold" of patients suffering from diabetes is often not the result of an increased reabsorptive capacity, but rather due to degenerative vascular disease which decreases the rate of glomerular filtration more than it damages tubules. This vascular disease may consist in renal arteriolar and arterial sclerosis, which decreases renal blood flow, filtration pressure and filtration rate and, consequently, tubular glucose load during hyperglycemia. Or the same may result from deposition of hyaline between the glomerular capillaries (intercapillary glomerulosclerosis). An example of this sort is shown in Table 2, Case 5, in which the estimation of glomerular filtration rate and glucose reabsorption is made during hyperglycemia in a diabetic with decreased renal function. An extreme form of this type of "high threshold" is sometimes seen in patients who are aglycosuric during diabetic coma because glomerular filtration has been sharply decreased by dehydration and hypotension.

TABLE 1

	Arterial Glucose mg. per 100	Glomerular Filtration Rate cc/min.	Glucose Filtered mg. per min.	Glucose Excreted mg. per min.	Glucose Reabsorbed mg./min.	Tm_{D-l} mg./min.	Tm_{PAH} mg./min.
Normal	100	130	130	0	130		
Male	300	130	390	40	350	52	80
Female	300	120	360	60	300	40	60
Case 1	62	100	62	0.1	61.9		
Renal Glycosuria	110	101	112	3	109		
Glomerulonephritis	285	107	305	65	240		
(male)	495	94	466	230	236	35.8	
Case 2	87	110	95	50	45		
Renal Glycosuria	144	117	170	90	80		
(female)	231	134	310	215	95		
	338	112	380	285	95	66	
Case 3	70	145	102	14	88		
Renal Glycosuria	125	122	153	50	103		
(male)	240	123	295	130	165		
	254	143	364	158	206		103
Case 4	495	126	623	165	458		81
Diabetes Mellitus							
(female)							

Mean normal values in 3 patients with renal glycosuria and in 1 with "high threshold" diabetes. The methods used have been described elsewhere (Corcoran, Taylor, and Page).[7]

TABLE 2

	Blood Sugar mg. per 100 cc.	Urea Clearance C_m. cc. per min.	Estimated Glomerular Filtration cc. per min.	Estimated Glucose Load mg. per min.	Glucose Excreted mg. per min.	Glucose Reabsorbed mg. per min.
Normal	100	75	125	125	0	125
Case 3 (Table 1)	60	90	150	90	5	85
Case 5						
Diabetes	300	20	33	99	0	99
Glomerulosclerosis	500	20	33	166	15	151

Examples of estimation of glucose reabsorption from urea clearance and arterialized blood sugar content in a normal subject, in a case of renal glycosuria (Case 3) and in a patient with intercapillary glomerulosclerosis incident to diabetes mellitus.

Renal Glycosuria

Theoretically, renal glycosuria might sometimes result from an untoward increase in glucose load due to increased glomerular filtration. Practically, this does not occur, because of the relative stability of glomerular filtration rate. Rather, renal glycosuria is an expression of decreased reabsorptive capacity, which may be focal and due to relative failure of the enzyme system n some tubules, while it is relatively intact in others, or to a diffuse failure in all the nephrons.

Glycosuria due to diffuse renal tubular damage occurs in nephroses due to heavy metals (lead, uranium, dichromate) in which the initial injury is tubular rather than glomerular. The coincidence of normal glucose load with decreased reabsorptive capacity results in glycosuria which tends to diminish as renal damage increases and glomerular rate falls. Phloridzin glycosuria is apparently due to a fixation of the glucoside on the enzyme system which blocks the transfer of glucose, but does not destroy the cell. Clinically, minor glycosuria due to focally inadequate tubules appear during chronic glomerulonephritis, or sometimes during recovery from acute glomerulonephritis. Its presence indicates that here and there is a nephron the tubule of which has not recovered its function as rapidly as has the attached glomerulus. Observations in one such patient are summarized in Table 1, Case 1. In this patient, who has a history of glomerulonephritis in remission, the levels of renal blood flow and glomerular filtration were normal. There was minor renal glycosuria at normal blood sugar levels and definite, and approximately equal impairment of the discrete tubular functions of glucose reabsorptive and diodrast secretion. A similar type of "renal glycosuria," not identified as nephritic, has been reported previously (Castex, Biasotti, and Patalano).[8] However, significant renal glycosuria is only rarely the result of renal disease. This is because glomerular and tubular functions are usually concurrently damaged so that glucose load decreases at about the same rate as reabsorptive capacity.

The more severe forms of renal glycosuria are apparently caused by a specific familial defect of the function of glucose reabsorption in the renal

tubules. The condition is uncommon. Observations on 2 such patients are summarized in Table 1.

In the one patient (Case 2) reabsorption of glucose is about 60 per cent complete at normal glucose loads. The maximum reabsorptive capacity as measured during hyperglycemia at high glucose loads is less than one-third normal. In contrast, other measures of renal function (renal plasma diodrast, inulin, xylose and urea clearances) are within normal limits and tubular secretory capacity for diodrast is greater than normal. In another patient (Case 3) glucose reabsorption is about 90 per cent complete at normal loads and reaches an apparent maximum at about two-thirds normal during hyperglycemia. The defect is not as severe as in Case 2. For this reason the patient (Case 3) did not have hypoglycemia during periods of exertion and food-deprivation as did Case 2. Tubular secretion of p-aminohippurate (which measures the same function as diodrast) was beyond, and other renal function tests within normal limits in this patient. Thus, in both these patients the only demonstrable defect in renal function is a selective impairment of the function of glucose reabsorption. They contrast with Case 1 in whom renal glycosuria was a sequal to glomerulonephritis because they do not exhibit depression of tubular secretory function for diodrast or p-aminohippurate.

Others, Friedman, et al.[9] have observed patients with renal glycosuria in whom the *maximum* reabsorptive capacities for glucose were within or above normal limits, although glycosuria was present at even low renal glucose loads. The mechanism of glycosuria in such cases is not as readily explained as in 2 cases here reported. One might suppose that a maximum glucose load sometimes acts as a stimulus to a sluggish reabsorptive mechanism.

Renal glycosuria due to a specific renal defect does not alter health or well-being except as it may predispose to hypoglycemia. Rather, its importance lies in its consequences on employability and insurability. Here, unless it is recognized and proved as such, renal glycosuria can work greatly to the patient's economic disadvantage.

Estimation of Glucose Reabsorption

Proof of renal glycosuria is better achieved by measuring the patient's reabsorptive capacity for glucose than by estimations of intermediary glucose metabolism. Indeed, since renal glycosuria may be present in a patient suffering from diabetes mellitus, estimations of glucose tolerance, may cloud the issue without solving the problem. Ideally, estimation of reabsorption demands concurrent measurements of arterial blood sugar, of glomerular filtration rate and of the urinary excretion of glucose. The first two of these are not readily performed. An expedient which uses means available to most physicians is therefore suggested.

The estimation depends on the fact that the rate of glomerular filtration is, under most circumstances, equal to 1.6 times maximum urea clearance expressed in cc. per minute or 1.2 times urea clearance expressed as per cent of normal.

The patient is prepared for the test by frequent administration of water, in order to maintain urine flows close to 2 cc. or more per minute. Heating the forearm in water at 40° C. for thirty minutes before the test and during arterializes the venous blood. Samples of blood are taken at the beginning of the urea clearance and sixty and one hundred and twenty minutes later. Sugar is measured in each sample and urea in the sixty minute sample. The mean blood sugar level is found for each one hour period of the two hour test. The glucose load for each period is calculated as mg. glucose per cc. of blood multiplied by the glomerular filtration rate as estimated from urea clearance. The urine specimens are analyzed for both glucose and urea. The rate of glucose excretion is expressed in mg. per minute and the difference between this rate and the glucose load is taken as the rate of glucose reabsorption. It is important that nothing be done during the procedure to cause sharp change of blood sugar concentration. The procedure applies to the measurement of glucose reabsorption in renal glycosuria at normal blood sugar levels and in patients with hyperglycemia.

Examples of its application are shown in Table 2. In interpretation, it is important to remember that the demonstration of renal glycosuria raises the question of its possible origin in renal damage. As in Case 1, Table 1, this question is not necessarily answered by a clearance test. A thorough review of the history and examination of other renal functions is therefore necessary before the glycosuria can be dismissed as an unimportant defect.

The approximate level of blood sugar at which glycosuria will *begin* can be calculated from maximum glucose reabsorptive capacity (Tm_G). To do so, Tm_G is divided by the rate of glomerular filtration and multiplied by 100. This gives the concentration of plasma glucose at which the reabsorptive capacity of every nephron is fully engaged. This, in a normal male, is, for example $350/130 \times 100 = 269$ mg. per 100 cc. An allowance of 10 per cent is made for the difference between the sugar contents of plasma and whole blood, thus, $269 \times 90/100 = 242$ mg. per 100 cc. of blood. Finally, an allowance of 25 per cent is made for the concentration at which glycosuria will *begin* because the reabsorptive capacities of the shorter nephrons have been exceeded. In the example, we would have $242 \times 75/100 = 181$ mg. per 100 cc. as the estimated concentration of venous blood sugar at which glycosuria will begin (Nielsen).[10] Since whole blood is used in the clinical test here described, correction for plasma and blood sugar difference is omitted. The calculation, in case 5 (Table 2) becomes $151/33 \times 100 = 458$ mg. per 100 cc. and the probable concentration at the onset of glycosuria is $458 \times 75/100 = 343$ mg. per 100 cc. It should be recognized that such estimates are only approximate.

Summary

Glycosuria is the result of excess of glucose load (plasma glucose content times rate of glomerular filtration) over renal tubular reabsorptive capacity. Glycosuria may be caused by an increase of glucose load during hyperglycemia with normal filtration rate; it may fail to appear in spite of hyperglycemia when glomerular filtration is depressed. The latter mechanism is the

more common cause of so-called "high renal thresholds" in diabetes, although glucose reabsorptive capacity is increased in some patients.

Renal glycosuria is due to a focal or diffuse failure of the enzymatic process of glucose reabsorption. This failure may arise from renal tubular damage, such as occurs in toxic nephrosis or glomerulonephritis, or it may be an isolated specific defect, usually familial.

A method is described for the approximate determination of glucose reabsorptive capacity from urea clearance and concurrent blood and urine sugar.

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