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PHYSIOPATHOLOGY OF GLUCOSE EXCRETION BY THE HUMAN KIDNEY*

BY

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Renal physiology, after being based on hypotheses and inferences for many years, was given a factual basis when Richards (1929), Wearn, Walker, and others succeeded in obtaining samples of glomerular and tubular fluid from amphibia for chemical analysis. These authors proved by direct observation how glucose is excreted by the amphibian kidney. (1) Glucose enters the nephron exclusively by glomerular filtration; this is why it is not excreted by aglomerular kidneys. (2) The concentration of glucose in the glomerular filtrate is the same as in the plasma. (3) Since the capsular fluid contains glucose when the bladder urine is free of that substance, glucose must be reabsorbed by the tubules. (4) Phlorizin, when injected in high doses, is capable of completely blocking the reabsorption of glucose. These basic facts being duly proved by direct observation in amphibia, it is essential to know whether the same facts are true for the mammalian kidney.

Starling and Verney (1925) suppressed the function of the tubules in a heart–lung–kidney preparation by poisoning them with cyanide. The urine was similar to an ultrafiltrate of the plasma, and its glucose content was the same as that of the plasma. This suggests that in mammals, as in amphibians, glucose is present in the glomerular filtrate in the same concentration as in the plasma.

Theory of Clearance Tests

Rehberg (1926) showed that it was possible to measure glomerular filtration by the renal excretion of substances having definite characteristics: (1) they must enter the nephron only by way of glomerular filtration; (2) their concentration must be identical in plasma and in glomerular filtrate; and (3) they must not be reabsorbed by the tubules. When these conditions are present the volume of glomerular filtrate may be easily computed.

Let us call D the amount of that substance excreted in 1 minute, b the amount of that substance in 1 ml. of plasma; b is also the concentration of that substance in 1 ml. of glomerular filtrate. Therefore, to deliver D in the bladder urine $\frac{D}{b}$ ml. must have been ultrafiltered. The general formula is: Volume of glomerular filtration $=\frac{UV}{B}$, where V is urine volume per minute and U and B are concentrations of the same substance in urine and blood.

Rehberg considered that creatinine was a suitable substance to measure the glomerular filtration in man and dog. This opinion is still true so far as the dog is concerned (Fig. 1); in man, the measure of glomerular filtration by exogenous creatinine is now generally regarded as inaccurate, and therefore inulin, mannitol, or sodium thiosulphate is commonly used. As in the dog it is possible to measure the glomerular filtrate by creatinine one can calculate the amount of glucose filtered per minute, assuming that the glucose concentration in the glomerular filtrate is the same as in the plasma.

$$\text{Filtered glucose} = \frac{\text{U. creat. V}}{\text{B creat.}} \times \text{glucose concentr. in 1 ml. plasma}$$

Supposing, for example, that a normal dog excretes 0.6 mg. of creatinine a minute, when 0.01 mg. of creatinine is present in 1 ml. of plasma, then we may say that the volume of glomerular filtrate is $0.6/0.01 = 60$ ml. a minute. The glucose concentration being at the same time 1 mg. per ml., the 60 ml. of ultrafiltrate must contain 60 mg. of glucose. As we find no glucose in the urine of that normal dog we must assume that the 60 mg. filtered is completely reabsorbed.

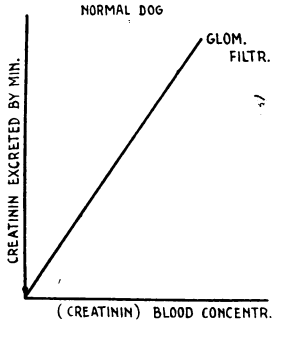

FIG. 1

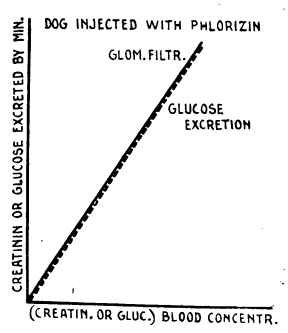

FIG. 2

Now, if phlorizin is capable of completely blocking the reabsorption of glucose, we must, when the dog has been injected with a sufficient dose of that drug, recover in the bladder urine all the filtered glucose, which in the aforesaid conditions is 60 mg. This experiment was first made by Poulsson (1930), and its results were those predicted. It was later repeatedly verified (Fig. 2).

So we get an indirect but very consistent proof that the mechanism of glucose excretion by the dog's kidney is identical with that of the amphibian kidney: (1) glucose enters the nephron exclusively by glomerular filtration; (2) its concentration is the same in plasma and glomerular filtrate; and (3) the reabsorption of glucose can be totally suppressed by phlorizin.

*Lecture delivered at the University of London on January 31.

The law of glucose excretion in the dog under the action of phlorizin is thus perfectly defined and formulated by:

Excreted glucose = plasma glucose × glomerular filtration

Glucose Excretion by Dog when Blood Level of Glucose is High

Now we must consider how glucose is excreted in the dog, under normal circumstances, when there is no hindrance to the reabsorptive function of the tubules.

Shannon and Fisher (1938) have described the law of glucose excretion in the dog in the following way: When the blood concentration of glucose is progressively increased the urine remains free of sugar until a certain level of blood glucose is reached, when glucose just appears in the urine (Fig. 3). That critical value of the blood sugar (A) is called the threshold. When glycaemia is increased to much higher values (for instance, between 350 and 1,000 mg. per 100 ml.) the ratio glucose excreted/blood glucose is a straight line parallel to the line OC, the slope of which corresponds to the volume of glomerular filtration. For each point on the abscissa corresponding to a stated concentration of blood glucose the amount of filtered glucose is the ordinate from that point to the line OD. So long as the blood concentration is lower than A, the whole of the filtered glucose is reabsorbed, as there is no glycosuria. The distance DA corresponds to the glucose reabsorbed when the threshold is just reached: this is the maximal amount of glucose which the kidney can reabsorb per unit time. It is what H. Smith calls "maximal tubular reabsorption" or "TmG." When the blood glucose is increased to E the amount of glucose filtered is: blood glucose OE × filtration.

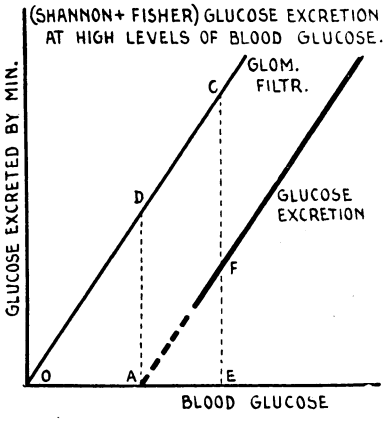

FIG. 3

In Fig. 3 it can be seen that OE × filtration = EC. From that amount the kidney reabsorbs TmG, which is equal to CF, and excretes EF, which equals AE × filtration. Therefore the law of glucose excretion which can be deduced from the observations of Shannon and Fisher at very high levels of glycaemia is:

Filtered glucose = blood glucose × filtration
Excreted glucose = filtered glucose − TmG
TmG = threshold × filtration
Excreted glucose = (blood glucose − threshold) × filtration

The law formulated by Shannon and Fisher is correct only when the blood glucose is kept very high. We were able to verify it in 1939 by studying glucose and creatinine excretion in pancreatectomized dogs (Govaerts and Muller, 1939).

It may be interesting to point out that the mechanism of glucose excretion is fundamentally similar in the phlorizinized dog and in the dog with a high glycaemia. In the phlorizinized dog the reabsorptive power of the tubules is completely blocked by the drug: the whole of the filtered glucose is excreted and the output is:

Excreted glucose = blood glucose × filtration

In the normal dog whose glycaemia has been raised to a high level it is glucose itself which blocks the reabsorption. Such a process of saturating the tubules needs a constant quantity of glucose (TmG), which is subtracted from the total amount of glucose filtered by the glomeruli of the whole kidney. As shown above, TmG = threshold × filtration

$$\therefore \text{Threshold} = \frac{\text{TmG}}{\text{Filtration}}$$

Thus the threshold may be regarded either as a portion of the concentration of glucose in the blood or as a portion of the concentration of glucose in the glomerular filtrate.

In the ultrafiltrate the threshold is the maximal amount of glucose which for a stated filtration rate is subtracted from each millilitre of glomerular filtrate in order to saturate reabsorption. In the blood the threshold is the amount of glucose which is of no account in glucose excretion, since when the blood yields to the glomerular filtrate the glucose content of 1 ml. of plasma it gets back an amount of glucose equal to the quantity called the threshold. Therefore it is equivalent to write

either

Excreted glucose = (blood glucose − threshold) × filtration

or

Excreted glucose = (glucose concentr. of ultrafiltrate − glucose reabsorbed from 1 ml. ultrafiltrate) × filtration

Measure of Glomerular Filtration in Man

If the aforesaid considerations be correct, it must be possible to measure the rate of glomerular filtration from the ratio glucose excreted/blood glucose when the blood sugar is raised to very high levels. This is what we did, by the following procedure (Govaerts *et al.*, 1948; Govaerts, 1949a):

The blood glucose is raised to a very high level (about 800 mg. per 100 ml.) by an intravenous injection of glucose. Thereafter the blood-sugar level is allowed to fall and four separate specimens of urine are taken in succession. Each of these is collected during a strictly measured period of about eight minutes. A sample of blood is taken before and after each urine collection, and so the mean concentration of blood glucose during each period of urine excretion is computed. When glucose excreted per unit time is plotted against blood glucose one gets four points which fall on a straight line.

The slope of this line corresponds to the glomerular filtration. Extrapolation of the line to its point of intersection with the abscissa yields the value of the "threshold" of Shannon and Fisher. The ordinate DA is equal to TmG of Smith.

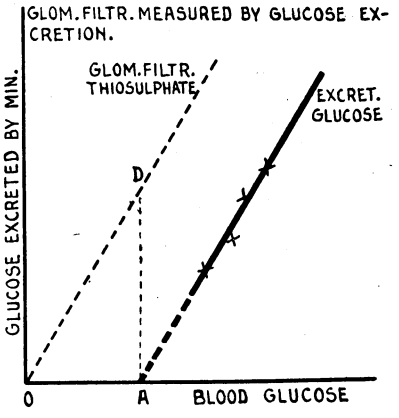

FIG. 4

We have measured by this method the filtration rate in 17 patients. The figures obtained agree fairly well with the simultaneous thiosulphate clearance. So did the figures for the value of TmG and of the threshold calculated by both methods. The mean values of our results for the group of 17 patients are:

	Filtration	Threshold	TmG
Computed from thiosulphate excretion	107·3 ml.	236 mg./100 ml.	252 mg.
Computed from glucose excretion	105·6 ,,	230 ,,	245 ,,

The measure of glomerular filtration by intravenous injection of glucose could be used in clinical work. It has the advantage that the substance injected is not foreign to the organism.

This method assumes that glomerular filtration remains identical during the successive collections of urine. This does not seem to be an objection. As a matter of fact, the filtration was very constant in our patients during the period of high blood glucose concentration : this was shown by the successive measurements by the thiosulphate method. This stability of filtration rate is the reason why the two methods (glucose and thiosulphate) gave identical results.

Glucose Excretion in Man when Blood Glucose Level is Progressively Raised

From the theoretical point of view, the procedure using glucose is of interest. It proves: (1) that in man, as in the dog or in the frog, glucose enters the nephron exclusively by glomerular filtration ; and (2) that its concentration is the same in the ultrafiltrate as in the plasma.

Thus, by using objective measurements and experimental data, we have got an insight into the mechanism of glucose

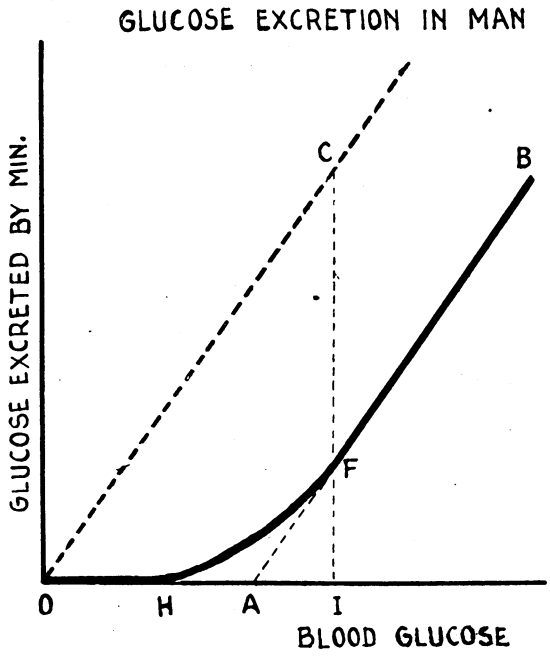

FIG. 5

excretion by the human kidney. Unfortunately, this description is correct only when the blood sugar is higher than about 350 mg. per 100 ml. Now, in diabetes mellitus, which causes the most common variety of glycosuria, the level of blood sugar fluctuates as a rule between 150 and 350 mg. per 100 ml. These are the levels of blood sugar at which the law of glucose excretion would thus be most interesting for the clinician.

When, in a normal man, glucose output per unit time is measured while the concentration of the blood sugar is progressively raised, the relation plotted with respect to the ordinates (excreted glucose) and the abscissa (blood glucose) is shown by a line which may be divided into three parts, each of which has quite different features (Fig. 5). The first part, coincident with the abscissa, indicates the absence of excretion. The second part is a curve with a hyperbolic shape. The third part is the straight line described by Shannon and Fisher and corresponding to glucose excretion at very high concentrations of blood sugar.

The blood concentration OH is the lowest level of blood glucose at which sugar is found in the urine when the glycaemia is rising. It may be called the *minimal threshold.* At that level of blood sugar, although there is a slight glycosuria, the power of the kidney to reabsorb glucose is far from being saturated. In Fig. 5, where the filtration is supposed to be uniform and set to 120 ml. a minute, the amount of glucose reabsorbed at any concentration of blood sugar is shown by the ordinates between the line OC (filtered glucose) and the line HFB (excreted glucose). It is easy to see that when the glucose concentration rises from H to F the amount of reabsorbed glucose steadily increases until it reaches a maximum equal to FC, which is the TmG of Smith. From then on, the reabsorption is constant (and equal to TmG) for any further increase of blood sugar.

The curvilinear aspect of HF means that the reabsorptive capacity of the kidney is saturated in a slowly progressive way, when the amount of filtered glucose is steadily increased. This observation has been explained by supposing that the glucose reabsorptive power varies considerably among different individual nephrons. This would not be surprising, as among the nephrons there are obviously wide differences in shape, length, and in proportions between glomerulus and tubule. Therefore, considering their glucose reabsorptive capacity, some nephrons may be called " weak " and some " strong."

According to such a view, the minimal threshold OH (sometimes called " threshold of appearance ") is the concentration of blood sugar at which the glucose reabsorptive capacity of the " weakest " nephrons is just saturated. The concentration of blood glucose OI might be called the *maximal threshold,* being the glycaemia at which the reabsorptive capacity of the " strongest " nephron is saturated.

Finally, the point A, where the extrapolation of the straight line BF intersects with the abscissa, is the threshold of Shannon and might be called the *mean threshold.* This is the level of blood glucose at which the reabsorptive power of all the nephrons would be saturated if this power were the same in each of them and were equal to the *mean* of the actual reabsorptive power of all the individual nephrons.

The mean threshold is the value which ought to be subtracted from the blood sugar to calculate glucose excretion by Shannon and Fisher's formula :

Excreted glucose = (blood sugar − mean threshold) × filtration.

It is also the amount of glucose which is reabsorbed from each millilitre of glomerular filtrate when the capacity of the nephrons for reabsorbing glucose is completely saturated.

It is of interest to point out that a relation similar to that of glucose excreted/blood glucose would be found between the level of water uphill and the flow of water downhill, supposing that in a water-duct with a rectangular section the flow of water were hindered by a transverse wall, sloping from side to side (Figs. 6 and 7) (Govaerts, 1949b, 1950).

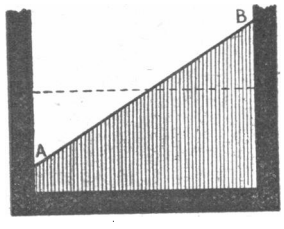

FIG. 6

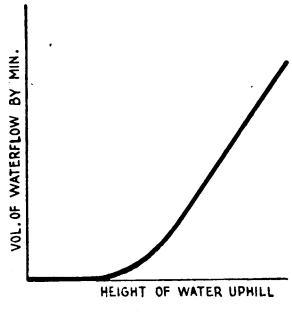

FIG. 7

The relation would first be a horizontal line coincident with the abscissa, then a curve with a hyperbolic shape, and then a straight line with a definite slope. When the water completely overflowed the dam the hindrance to the flow would be constant and equal to that of a horizontal wall with a height equal to the mean of A + B.

This comparison helps one to understand the effect of inequality of the nephrons on the excretion of glucose.

Titration of Saturation Capacity of Individual Nephrons

Let us consider the hyperbolic curve in Fig. 8. If we suppose that every nephron gets an equal part of the total

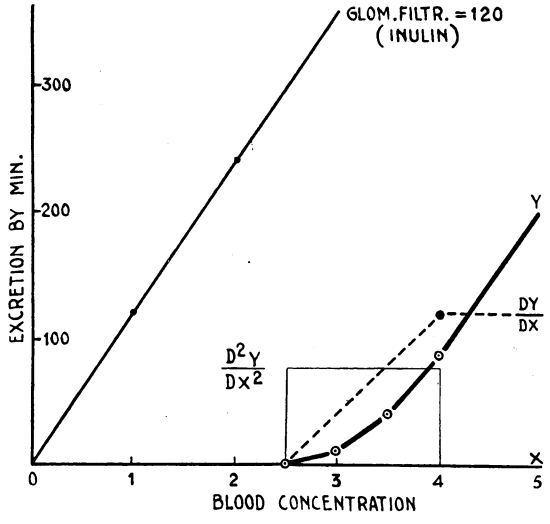

FIG. 8

volume of filtration, and that the individual nephrons differ only in their glucose-reabsorption capacity, it can be easily proved that the differential coefficient $\frac{dy}{dx}$ divided by the filtration would indicate for any point on the curve—that is, for any value of blood glucose—the percentage of completely saturated nephrons.

Moreover, the second differential coefficient $\frac{d^2y}{dx^2}$ divided by the filtration would indicate (in percentage of the total number of nephrons) how many more nephrons get saturated for any increment of blood glucose.

Another method of calculation has been employed by Smith (1951), who uses much more complicated premises. He stresses the necessity for caution in applying these formulae to the study of the frequency distribution curve of the reabsorptive power of the nephrons in a human patient. Such a method of calculation could not give results representing actual facts unless one has gathered, by repeating measurements on the same patient, sufficient data from which a curve with a very precise shape can be drawn. It is essential that the collection of urine be complete and accurately timed, that the analyses be made in duplicate, and that, during the whole experiment, the filtration rate be constant. Despite our present technical achievements such conditions are rarely met.

The most urgent task is thus to multiply correct observations, which are still infrequent. One ought to find out what would be the change in glucose excretion when only one of the three variables—glycaemia, filtration, reabsorption—is systematically modified.

It has been repeatedly claimed that several hormones are able to change the TmG or the threshold. Such an opinion is based on the fact that glycosuria has been repeatedly observed in pregnancy, hyperthyroidism, and acromegaly. But in such conditions both glycaemia and filtration are often abnormal.

Hormonal Factors which Might Change the Threshold

Insulin has been said to raise the threshold, but the observations are contradictory and therefore a conclusion cannot be reached at present.

More recently, adrenocortical or pituitary hormones were also considered as capable of changing either the threshold or the TmG. Rusznyák *et al.* (1947) stated that a deoxycortone glucoside ("hydrosoluble percorten") would raise the threshold of glucose in the dog. Lambert *et al.* (1948) could not confirm these findings; they even got, in man, entirely different results. The deoxycortone glucoside decreased the TmG by about 30%. It did not change the glomerular filtration rate. Its action was similar to that of a very small dose of phlorizin (which is also a glucoside). On the other hand, deoxycortone acetate had no action on TmG. Therefore, Lambert *et al.* (1949) were inclined to link these properties of deoxycortone glucoside with the glucoside radical rather than with the corticosterone itself.

Conn *et al.* (1949) have claimed that A.C.T.H. could lower the tubular reabsorptive capacity for glucose (TmG). This also was not confirmed by the work of Lambert *et al.* (1951a, 1951b), who did not observe any change in the TmG of patients who were injected with A.C.T.H. a few hours previously or treated with A.C.T.H. for several days.

In conclusion, the investigations concerning the possibilities of altering either TmG or the mean threshold show the remarkable stability of these characteristics of kidney function. They indicate that hormonal influences are less active in this respect than had been previously assumed.

However, one may observe, in a certain number of human beings, congenital or acquired abnormalities in glucose reabsorption which bring about glycosuria, although the blood sugar is normal. We shall now devote the final chapter of this lecture to the analysis of such conditions.

Renal Diabetes

In the human species the level of blood glucose at which glycosuria just begins is not the same for different individuals, and its frequency might be illustrated by a normal distribution curve. The most frequent value of the minimal threshold (also called the threshold of appearance) is probably about 170 mg. per 100 ml. Since, in the normal, the blood glucose does not rise to such a figure even after a meal rich in carbohydrates, there is in the great majority of human beings no glycosuria in physiological conditions. On the other hand, in a few patients the threshold is low enough to be overflowed during the rise in blood sugar (to 130–140 mg. per 100 ml.) which normally occurs after a meal or after ingestion of glucose. Such a condition is called "innocent glycosuria" or "orthoglycaemic glycosuria."

Finally, one may observe in a few human beings such a low renal threshold that glycosuria is permanent even when the concentration of blood glucose is lowered to hypoglycaemic levels. These several types of glycosuria due to a low renal threshold and differing only by their intensity may all be called "renal diabetes." This abnormality of the threshold is obviously a constitutional and hereditary character. Its relationship with diabetes mellitus is open to question.

Many authors, especially Hjärne (1927), deny any connexion between renal diabetes and diabetes mellitus. Others accept that patients with renal diabetes might occasionally become true diabetics. What is certain is that when such an association occurs the renal abnormality persists.

This is well shown by observation of a female patient whom I have known for more than 25 years. She was first seen when she was 30 years old, with a normal carbohydrate metabolism and such a marked degree of renal diabetes that she still had glycosuria when the blood-sugar was lowered to 40 mg. per 100 ml. A few years later she became diabetic, with fairly high blood glucose and a very large glucose excretion. She is still diabetic, but, as ever, when her blood glucose is brought down by insulin, the glycosuria does not cease even at hypoglycaemic levels.

This example shows that renal diabetes manifests itself in two ways: (1) these patients excrete much more glucose than the common diabetics when both have the same level of hyperglycaemia; and (2) they keep excreting glucose even when the blood sugar is brought to normal or even lower.

These two characteristics, which were stressed by Cambier (1933, 1934) and by me in studying renal diabetes, imply both a low minimal threshold and an abnormally small global reabsorptive capacity (TmG). These two characteristics were found again in some cases recently studied by Dr. Lambert and me, using thiosulphate to measure glomerular filtration (Govaerts and Lambert, 1949). This view was also confirmed by Nielsen (1948).

"Pseudo-renal Diabetes"

On the other hand, Friedman *et al.* (1942) describe, under the name of "renal diabetes," a condition observed in several patients whose renal minimal threshold was low, and nevertheless the reabsorptive capacity TmG and the mean threshold were normal. Similar observations were reported by Reubi (1951). This author confirms our opinion that constitutional renal diabetes is characterized both by a low minimal threshold and by a small TmG. He proposes that the name of "pseudo-renal diabetes" be given to the condition described by Friedman *et al.* and characterized by a low minimal threshold and a normal TmG. He thinks that the "pseudo-renal diabetes" is not a congenital defect, but rather the consequence of renal disease. These several conditions may be illustrated as in Fig. 9.

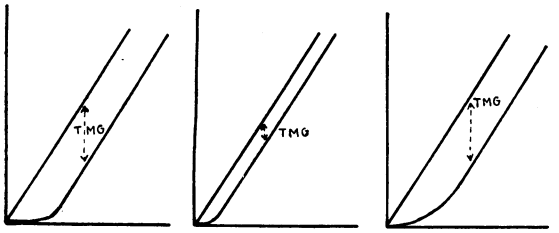

FIG. 9

Dr. Lambert and I have elsewhere discussed the meaning of the abnormal function of the kidney in constitutional renal diabetes (Govaerts and Lambert, 1949). One might suppose that the basis of renal diabetes was an anatomical defect—for instance, the proximal part being absent or too short. According to that hypothesis one would expect to find some disturbance in the phosphate reabsorption, which is known to be effected by the same proximal part of the tubules as that which reabsorbs glucose.

In two cases of renal diabetes in which Dr. Lambert studied the phosphate excretion at very different levels of blood phosphates, the characteristics of phosphate excretion were completely normal. Therefore the congenital abnormality which is called renal diabetes is not likely to be a structural defect in the tubules. It is more probably due to a disturbance in those enzymatic processes that make possible the transfer of glucose through the tubular cells.

As yet we have had no opportunity of studying patients with "pseudo-renal diabetes." This condition might be due to an increased dispersion of the frequency distribution curve of the nephrons in respect of their reabsorptive capacity.

It is interesting to note that a condition similar to "pseudo-renal diabetes" was temporarily observed in man, in cyanide poisoning. Lambert *et al.* (1950) studied two patients who, when recovering from an acute cyanide poisoning, excreted glucose in their urine, although the blood sugar was not increased. While their minimal threshold was low, their tubular maximal reabsorptive capacity (TmG) was normal, and therefore at high levels of blood sugar the glucose excretion was not greater than in normal individuals.

It may be of interest to compare these observations in man with some recent experiments by Nicholson (1949), who found that, in the dog, cyanide poisoning of one kidney produced a slight glycosuria without affecting the glucose-reabsorption capacity. Any interpretation concerning the mechanism of that remarkable effect of cyanide poisoning would be at present entirely hypothetical.

Conclusion

I have given a short account of the mechanism of glucose excretion by the human kidney.

We may conclude that in man the fundamental mechanisms of that excretion are identical to those which Richards, Wearn, and Walker found out in the kidney of amphibians. Furthermore, we have seen that several mathematical expressions can be formulated concerning the relation between blood sugar and glucose excretion in man. Some of these formulae are reasonably simple, but they are applicable only when the blood sugar is extremely high. Other formulae concern moderate levels of hyperglycaemia, as are often found in diabetic patients. Unfortunately they are much more complicated and more insecure in their applications.

Nevertheless, taking into due account their limitations, these mathematical developments have allowed the glomerular filtration to be measured by glucose excretion and the significance of renal diabetes to be appreciated.

There remains a wide field to be explored. Among the questions of present interest we might cite: (1) the precise measurement of the minimal threshold at stated rates of filtration; (2) the influence of the several hormones on the threshold and on TmG; and (3) the mechanism by which cyanide and other toxic substances disturb glucose excretion.

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Participants from 30 European and other countries met at Chichester on July 19 for a seminar on Mental Health and Infant Development, sponsored by the World Federation for Mental Health, whose headquarters are in London. The seminar was opened by Sir Weldon Dalrymple-Champneys, Deputy Chief Medical Officer of the Ministry of Health, and continues until August 10. The World Health Organization, Unesco, the International Children's Centre of Paris, the U.S. National Advisory Mental Health Council, and the Grant Foundation of New York are all contributing to the conduct of the seminar, which is for medical officers of health, paediatricians, psychiatrists, psychologists, social workers, district nurses, and others. Most of these hold senior or responsible positions in the public health service of their own countries, or in training institutions connected with public health. The 15 teachers, drawn from the United Kingdom, France, and the U.S.A., include Miss Anna Freud, of the Child Study Centre, London; Dr. Margaret Mead, anthropologist, of the American Museum of Natural History: and Professor Boutonier, psychologist, of the University of Strasbourg. The director of the seminar is Dr. Kenneth Soddy, assistant director of the World Federation for Mental Health.