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Research Article

BENIGN GLYCOSURIA DUE TO DISTURBANCES IN THE BLOOD SUGAR REGULATING MECHANISM[1]

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Chr. Bohr, the Danish physiologist, always emphasized the importance of making an exact study of the adjustments exhibited by the organism to adapt the functions of the various organs to each other, and thereby to ensure the equilibrium of the organism necessary for maintaining a healthy, undisturbed life.

Among these adjustments that of the blood sugar is one of the most interesting, both on account of its great significance in ensuring an undisturbed metabolism and also because quite minor disturbances in its regulation manifest themselves by abnormal phenomena in the individual.

Besides the liver, acting as a reservoir between the intestine and the blood, one of the best known means possessed by the organism for the maintenance of a certain concentration of glucose in the blood is the sugar threshold. Since Claude Bernard's experiment in the middle of the last century, it has been known that glucose is not excreted in the urine until it exceeds a certain concentration. Ambard and after him Cushny thoroughly examined the "problem of threshold" in detail. After Bang had introduced the micro-method for the determination of blood sugar, Jacobsen (15) in our clinic found the value of the threshold in normal persons to be about 0.16 to 0.18 per cent of blood sugar. A number of investigators have subsequently confirmed this, in so far as they have demonstrated that this is the usual threshold value in normal individuals but on the other hand, higher or lower values are by no means rarely observed. Subsequently it was proved that the blood sugar level is not

[1] Herter Lecture given in Baltimore, February 18, 1926.

constant. On the contrary the blood sugar rises after every meal containing carbohydrates and follows in the course of the

TABLE 1

Normal female, 21 years, weight 60 kgm. Blood sugar, mgm. per 100 cc.

Time	Ear	Vein
9:05	85	85
15	103	
25		124
25	156	
45		111
55	149	
10:05		91
15	119	
30	80	
35	85	
45		67
55	93	
11:05		65
15	76	
28		58
35	64	

At 9:08, 60 grams of glucose in 600 cc. of water.

TABLE 2

Diabetic female, 65 years, weight, 98 kgm. Blood sugar, mgm. per 100 cc.

Time	Ear	Vein
11:30	128	128
50	193	
12:00	212	
10	237	
17	237	
20	236	236
22	235	
30	229	
40	225	
1:30	173	

At 11:30, 42 grams glucose in 250 grams water.

day a curve with several peaks, which are dependent upon the time and number of meals. Jacobsen (14) was the first to demonstrate that in human beings this variation occurs not only

after the ingestion of glucose but also after ordinary meals containing carbohydrates. The greater the quantity of carbohydrates ingested the higher the blood sugar rises, both after the ingestion of sugar and of starch. When the alimentary hyperglycemia rises above the threshold for blood sugar, glycosuria sets in. The rise in the alimentary hyperglycemia, however, is not proportional to the quantity of the carbohydrates ingested.

Important investigations in this field have been conducted in Denmark by Hagedorn (7) and Karen Marie Hansen. Hagedorn (8) has demonstrated that when a person is fasting the percentage of blood sugar is equally high in arterial and venous blood, but after ingestion of carbohydrates the rise in blood sugar is considerably higher in arterial than in venous blood. During the circulation through the capillaries a removal of the blood sugar in the peripheral tissues takes place. This is not seen in true diabetes where there is no difference, or much less, between the blood sugar in the arteries and the veins. Hansen (10) has furthermore shown that the organism possesses the capacity to accelerate the removal of blood sugar when the blood sugar otherwise would rise abnormally high. As a result of this regulating capacity the blood sugar in normal individuals never exceeds a certain maximum which Hansen terms the optimum concentration. In normal individuals this does not, as a rule, exceed 0.18 per cent. The blood sugar after ingestion, for instance, of 50 grams of glucose, rises to 0.18 per cent and it does not rise any higher after ingestion of 100 grams; or even after ingestion of 200 or 400 grams of sugar. This is beautifully illustrated by the four curves shown in figure 1. They are all taken from the same individual. In five normal individuals Hansen found the highest value to which the blood sugar rose after the ingestion of 200 to 400 grams of glucose to be 0.16 to 0.18 per cent. In other words no assimilating limit as regards glucose is to be found in normal persons.

Hansen terms this regulating mechanism the acceleration capacity of the organism; i.e., a capacity to accelerate the removal of the sugar from the blood. Justifiably she calls attention to the interesting fact that the maximum value to which the blood sugar rises has nearly the same value as that of the usual blood sugar threshold. This explains why in the majority of normal individuals we cannot

produce glycosuria by administration of carbohydrates. In the morning when the patient is fasting the blood sugar is about 0.09 to

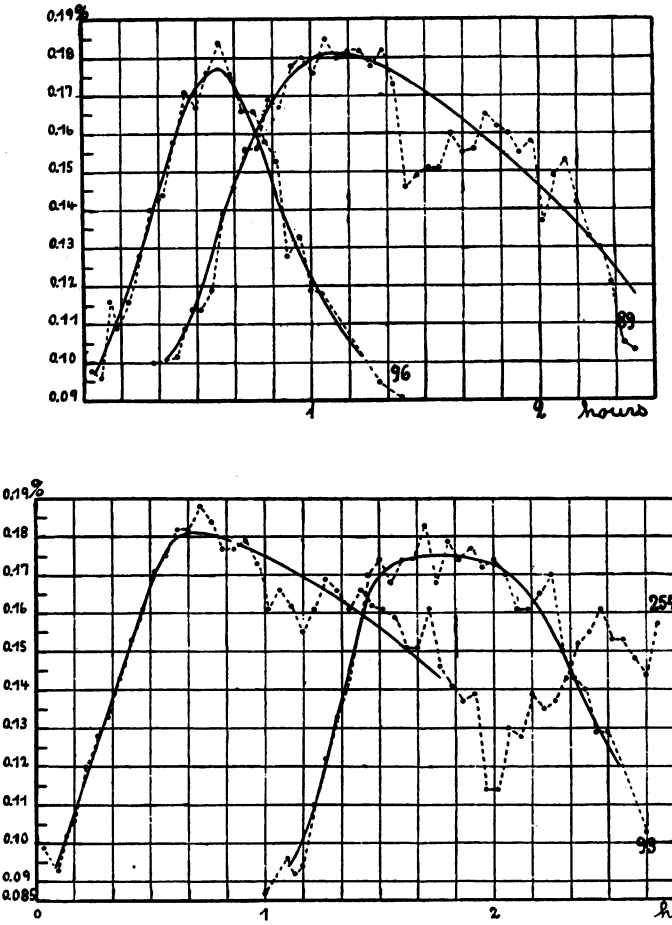

FIG. 1. FOUR BLOOD SUGAR CURVES FROM A NORMAL INDIVIDUAL

Curve 89. 100 grams of glucose in 200 cc. of tea.
Curve 96. 20 grams of glucose in 160 cc. of tea.
Curve 93. 50 grams of glucose in 160 cc. of tea.
Curve 254. 200 grams of glucose in 250 cc. of tea.

0.11 per cent and after meals containing carbohydrates it rises to about 0.18 per cent, but not higher and does not exceed the threshold.

Thus we see how the blood sugar regulation keeps the blood sugar value at a suitable level by means of two different mechanisms; (*a*) the blood sugar threshold, (*b*) the acceleration of blood sugar removal into the tissues.

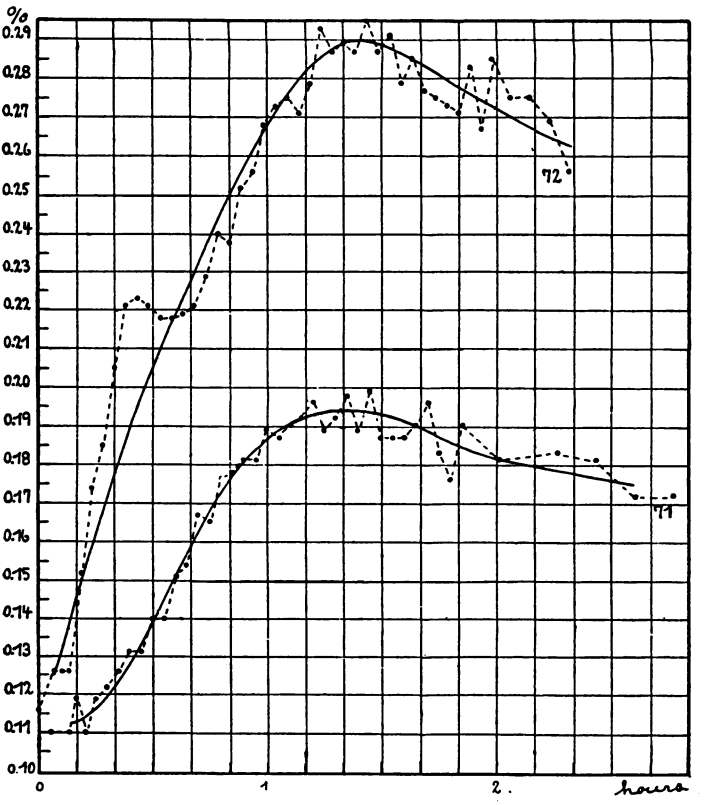

FIG. 2. BLOOD SUGAR CURVES FROM A PATIENT WITH DIABETES MELLITUS
Curve 71. 35 grams of glucose in 160 cc. of coffee.
Curve 72. 58 grams of glucose in 160 cc. of coffee.

When a disturbance in the blood sugar regulation occurs, glycosuria sets in. The classical example of this is seen in ordinary diabetes due to pancreatic insufficiency. Here hyperglycemia occurs, the organism having lost its power to remove the sugar from the blood when it exceeds the usual value. In the curves in figure 2 is seen

the blood sugar rise following the administration of glucose in a case of diabetes. The deficiency of insulin not only prevents the combustion and the hepatic storage but also the peripheral removal of glucose. Arterial and venous blood contain, as a rule, about the same quantity of sugar and hyperglycemia develops.

Glycosuria may occur, however, following the ingestion of glucose without the presence of diabetes. This may occur in two different ways. Either the threshold is lower than the normal, or the blood sugar after ingestion of carbohydrates may rise above the normal level. Both these possibilities deserve special study.

We have previously stated that the threshold is usually at 0.16 to 0.18 per cent. It lies, however, not infrequently higher, above 0.20 per cent or even higher still. It will readily be seen that a higher position of the threshold does not give rise to glycosuria and is consequently of little practical significance in normal individuals. It is a different matter when the threshold is subnormal. When the alimentary blood sugar rise is normal, the blood sugar may exceed the threshold and a glycosuria will result. In a certain number of patients the threshold is so low that the blood sugar always or almost always is above the threshold; we have then a case of true renal glycosuria. In such the threshold is found to be as low as from 0.05 to 0.12 per cent.

Should the threshold lie between 0.12 and 0.15 per cent we may encounter a renal alimentary glycosuria. Clinically this will manifest itself in what we have termed cyclic glycosuria. In the morning the urine is free from sugar, but after a meal containing carbohydrates the blood sugar rises during the day above the threshold, a glycosuria appears that again disappears in the evening or during the night.

It is significant to note that the position of the threshold may vary greatly in different individuals, but in the same individual the position is constant during his or her whole lifetime. This view as to the constancy of the threshold was first advanced by Faber and Norgaard (4) in 1919 at the Northern Congress for Internal Medicine at Copenhagen. This view was later confirmed as to normal individuals by Hagedorn. In respect to patients with constant or cyclic renal glycosuria, the continually recurring glycosuria alone shows that the

threshold is constantly low. We have also been able to demonstrate this fact time after time by means of examinations.

In this connection it is of importance to emphasize that very frequently renal glycosuria is a familial or hereditary weakness. We find a number of cases in the same family, who during their whole lifetime, suffer from renal glycosuria or a constantly recurring cyclic glycosuria. The low threshold is thus an individual characteristic, a constitutional abnormality and the glycosuria is not a sign of any metabolic disturbance. It is not the result of disease but is, as a rule, a congenital abnormality.

Whereas most students of this subject have come to agree with these views, opinions differ regarding the question of the position of the threshold in true diabetics. Here the opinion has been constantly advanced that the threshold is very mobile and is especially displaced under the influence of glycosuria and under the influence of a treatment causing the glycosuria to subside.

In 1915, the Swede, Engstrand maintained this and was of the opinion that when a decrease in the glycosuria was brought about by dieting, the blood sugar threshold rose in value and the carbohydrate tolerance in diabetics was also improved. From this point of view it will be observed that the question of the constancy of the threshold in diabetics is of great practical significance. Hamman and Hirschman (9), in 1917, likewise came to the conclusion that they could demonstrate that glycosuria caused a displacement of the threshold and Williams and Humphreys (16) obtained a similar result. In Scandinavia, too, similar views have been repeatedly advanced.

In contrast to these ideas, we have been led by our investigations carried out with Norgaard (4) and Hansen, (3) to conclude that in diabetics also the blood sugar threshold is constant in every individual and that it is influenced neither by glycosuria nor by the duration or degree of the affection. Just as in non-diabetics the threshold is in some diabetics at the normal level, but, as we have found in a number of cases, it may be either higher or lower. In any given case however it is always found at the same level.

The reason that this view has not been generally accepted must be attributed to the fact that the difficulties inherent in an accurate

determination of the threshold, and the means of surmounting these difficulties, have not been realized.

The method frequently employed has been to determine the value of the blood sugar in the morning while the patient is still fasting and to compare this value with an examination of the urine passed later. If the whole of the urine passed during the following day is used for this purpose it will readily be seen that this will lead to considerable error, as the blood sugar in the course of the day rises after every carbohydrate-containing meal. I am of the opinion that Williams and Humphreys and later Petrén were lead to erroneous conclusions by such a procedure. The determination of the threshold by this means will give a value that is too low. The same error occurs also if the morning blood sugar is compared with the urine passed immediately after the blood sample is withdrawn. This urine actually corresponds to the blood sugar values of a considerably earlier point of time than when the urine was passed. As the blood sugar has further diminished in the morning, too low a blood sugar value is compared with the urine examined. Thus by this means too low a value for the threshold is obtained, and a varying and unknown error is produced.

A better method is to determine the blood sugar curve after an alimentary ingestion and to observe at what blood sugar level the glycosuria sets in and ceases. Here, too, however, there are important factors to take into consideration. In order to ascertain the highest peak of the blood sugar curve it is necessary to make very frequent blood sugar determinations, best every five minutes. Then again venous blood must not be used, but cutaneous blood; that is to say, arterial blood. It is, as a matter of fact, the blood sugar percentage in the renal arteries that must be presumed to be a decisive factor in the occurrence of the glycosuria. For such serial determinations, Hagedorn and Normann Jensen's (8) method for micro-determinations is more suitable than any other. The whole of the blood is here used in the analysis. It would perhaps be more correct to determine the content of the plasma, but with the small quantities of blood one is obliged to use for serial determinations at very short intervals of time, this cannot be done.

When the blood sugar curve is determined in this manner, it is

observed that the glycosuria sets in late during the rise in blood sugar, usually not until the threshold is overstepped, whereas it lasts during the fall of the blood sugar for a long time after the glycemia has passed its maximum and after the threshold value has been passed during the fall of the blood sugar to normal values (fig. 3). Hamman and Hirschman (9) in 1917 were the first to call attention to this phenomenon, and they therefore came to the conclusion that glycosuria depressed the threshold. We found, however, that it depends upon a measurable time elapsing from the moment the threshold is overstepped until the glycosuria is established. The time varies some-

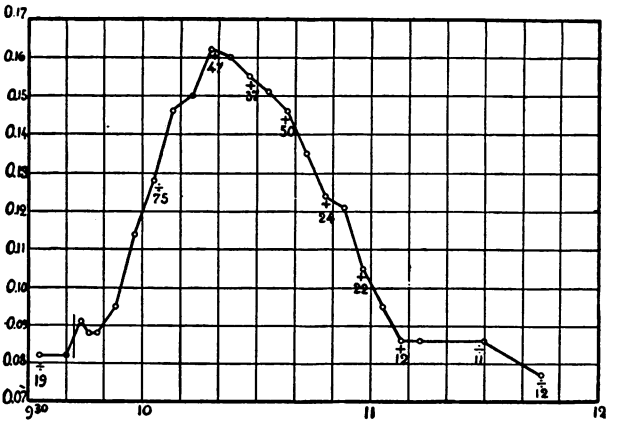

FIG. 3. GLYCOSURIA. 50 GRAMS OF GLUCOSE AT 9:42 A.M., FEBRUARY 26, 1923
+ = glycosuria; ÷ = no glycosuria. The figures indicate the amount of urine

what in the different experiments and can by no means be explained by the passage of the urine through urethra and bladder. Consequently, to determine the threshold we must have two blood sugar curves, determined by serial examinations after administration of carbohydrates. If the one administration does not cause glycosuria, whereas it sets in after a larger administration, it is evident that the position of the threshold is between the peaks of the two curves. The two curves in figure 4 from a diabetic serve as an example. After 25 grams of glucose were administered the blood sugar curve rose to 214 mgm. per cent without glycosuria. After 35 grams of glucose to 236 with glycosuria. Thus between these two values lay the

glycosuria threshold, although during the last test glycosuria was still present at a blood sugar value of 205. This curve (fig. 5) demonstrates the necessity for very frequent measurements. Every five minutes a test is taken. There is a high peak between two tests.

By a series of experiments carried out with this accurate method we found the threshold to be constant in diabetics. By repeated

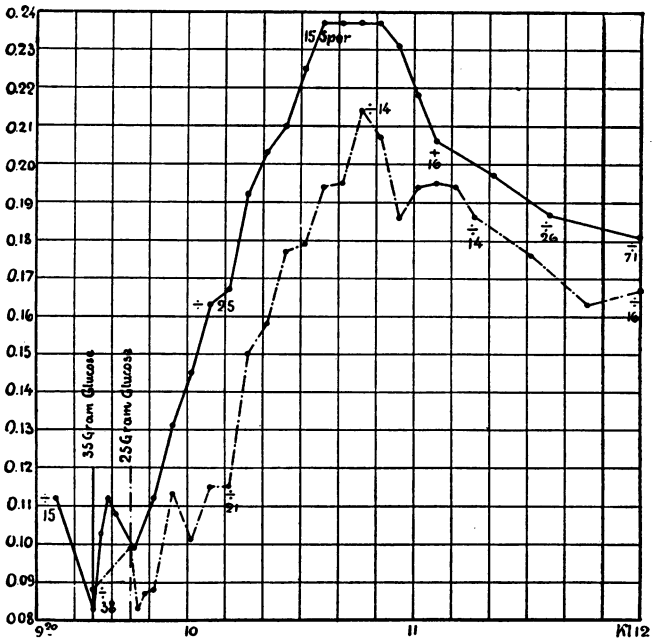

FIG. 4. DIABETES MELLITUS

Broken line, blood sugar curve after 25 grams of glucose on December 13, 1922. Solid line, blood sugar curve after 35 grams of glucose on December 18, 1922.

examinations during the course of treatment we found similar values, even if the patient by dieting was kept free from glycosuria during the whole time, and under conditions which according to earlier views would cause a rise in the threshold.

To elucidate this the examples in table 3 are given.

In each of these cases the threshold is determined by using two blood sugar curves. Between the lower and the higher value is the

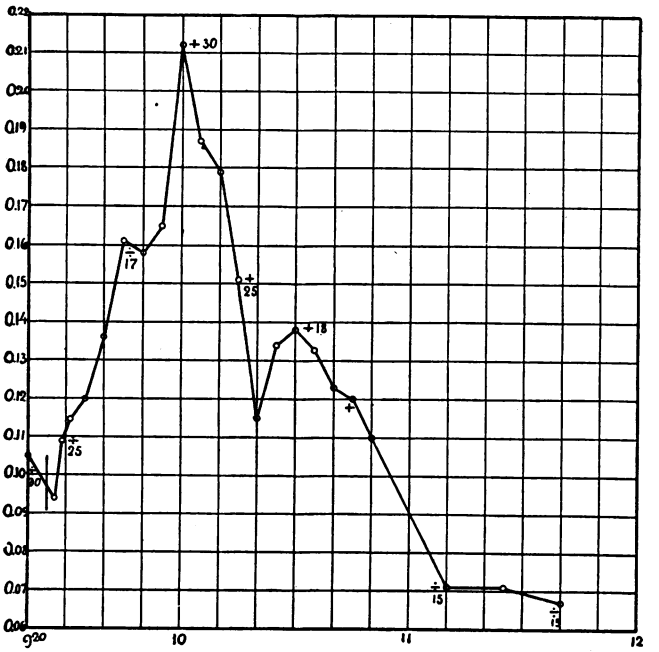

FIG. 5. GLYCOSURIA. BLOOD SUGAR CURVE AFTER 50 GRAMS OF GLUCOSE MARCH 10, 1923

TABLE 3

	Age	Duration of diabetes	Situation of threshold (mgm. per cent)	Interval
A. H.	24	1½ years	August 30–31, 1921, over 169, below 192 September 14–15, 1921, over 171, below 179	2 weeks
H. M.	22	8 days	November 15–16, 1921, over 191, below 205 December 5– 6, 1921, over 195, below 214	3 "
N. P. M.	35	4 months	December 13–14, 1921, over 160, below 182 January 20–21, 1922, over 162, below 169	5 "
M. H.	16	9 months	May 14–21, 1921, over 169, below 190 October 15–16, 1923, over 160, below 171	2½ years

position of the threshold. The determination is repeated after a certain time and after the patient has been kept free from glycosuria for two to five weeks by regulation of the diet. In the last case the

patient was investigated two and a half years later and the threshold was found to be still at about 170 mgm.

We believe therefore that it may be maintained that the glycosuric-threshold in diabetics, just as in non-diabetics, has a constant value in one and the same individual, whereas in different individuals it may vary somewhat. The value is independent of the duration of the disease or the age of the patient.

As a general rule we must conceive the glycosuric threshold as an inherent quality in the individual, a constitutional quality that is constant as regards every single individual, but may vary considerably from individual to individual in diabetics as in normal persons. By this we do not infer that the sugar threshold of an individual does not change under varying conditions. Thus we know that experimentally, glycosuria without hyperglycemia may be produced by administration of phloridzin and some few other substances. A change of threshold may also cause the frequent glycosuria of pregnancy.

Since the investigations of Maase, Novak, Porges and Strisower, Frank and Jacobsen we know that glycosuria frequently occurs in pregnancy with normal blood sugar, and the question of glycosuria of pregnancy subsequently has been the object of a series of researches, especially by Frank (5) (6) and his collaborators, by Holst, Fr. Jensen and many others. The diagnostic value of alimentary glycosuria has been studied especially in early pregnancy (Frank). It would appear that the diagnostic value is rather insignificant, as an alimentary glycosuria may so often be observed in non-pregnant women. The phenomenon itself, however, is of great significance in studying the threshold problem.

In order to ascertain whether the glycosuria of pregnancy is exclusively due to a fall in the threshold, and whether such a fall is purely a transient disturbance, I have made accurate threshold determinations during pregnancy and after parturition in two women, with the following results.

1. A 20-year-old primipara had a normal delivery on January 10, 1924. Before parturition, on December 20 and 27, 1923, the threshold was over 121 and under 132 mgm. while after parturition, on January 18, 1924, the threshold was under 156 mgm. and on August 12, 1924, the threshold was over 197.

2. A 19-year-old primipara had a normal delivery on February 9, 1924. Before

parturition on February 6 and 8, 1924, the threshold was over 95 and under 131 while after parturition, on February 15, 1925, it was under 142 mgm. and on April 9, 1925, it was over 150 mgm.

In both patients during pregnancy glycosuria was demonstrated on ordinary diet, but their urine was free from sugar in the mornings. In

TABLE 4

Before parturition

December 20, 1925. Kl. 9, 10 Indg.; 25 grams glucose				December 27. Kl. 9, 20; 15 grams glucose			
Time	Blood sugar	Urine		Time	Blood sugar	Urine	
		Diuresis	Sugar			Diuresis	Sugar
	mgm. per cent	*cc.*			*mgm. per cent*	*cc.*	
9:02	54	23	−	9:12	64	50	−
10	54			19	64		
13	61			22	79		
15	70			24	77		
17	81			26	80		
22	104	27	−	31	107	60	−
27	114			36	109		
32	114	37	−	41	121	85	−
37	121			46	117		
42	132	30	+	51	100	44	−
47	121			56	95		
52	111	14	+	10:01	73	42	−
59	93			06	61		
10:02	77	12	+	11	55	33	−
07	72			16	53		
12	61			21	55	28	−
17	59			26	55		
22	52	13	+	31	53		
27	52			35	55	44	−
32	46	8	−				
37	43						
42	48	20	+				

both cases the threshold before parturition lay below 132 and some months after in case 1 above 197; in case 2 above 150 mgm. The normal value of the sugar threshold was thus again reached and the glycosuria had disappeared. It will be observed that the normal threshold was not reached immediately after parturition, for during the first weeks the threshold was still abnormally low. Here we have

therefore a striking example of the fact that the threshold, under certain abnormal conditions may be temporarily changed.

In order to give further details of these determinations of threshold, the blood sugar analyses for the 4 leading tests made in case 1 will be given. (See tables 4 and 5 and figs. 6 and 7.)

TABLE 5

After parturition

January 18, 1924. Kl. 9, 10; 25 grams glucose				August 12, 1924. Kl. 9, 35; 100 grams glucose			
Time	Blood sugar	Urine		Time	Blood sugar	Urine	
		Diuresis	Sugar			Diuresis	Sugar
	mgm. per cent	*cc.*			*mgm. per cent*	*cc.*	
9:00	81	22	−	9:25	94	19	−
10	78			34	108		
13	78			37	96		
15	83			39	108		
17	83			41	120		
22	103			46	140		
27	125	10	−	51	169		
32	156			56	190		
37	144			10:01	197		
42	154	12	−	06	192		
47	127			11	187	40	−
52	131			16	174		
57	110	14	Trace	21	174		
10:02	110			26	183		
07	88			31	165	55	−
12	94	14	+	36	165		
17	85			41	156		
22	88			46	174		
27	85	16	Trace	51	103		
32	70	14	−	56	156		
37	74			11:01	152		
37	74			06	152		
				15	140	50	−

Having discussed the disturbances in the blood sugar regulation produced by abnormal conditions of the blood sugar threshold, we shall now consider the results of disturbances in the second regulating mechanism, namely the removal of the blood sugar in alimentary hyperglycemia. We have mentioned disturbance of this function found in true diabetics. But disturbance in this regulating mech-

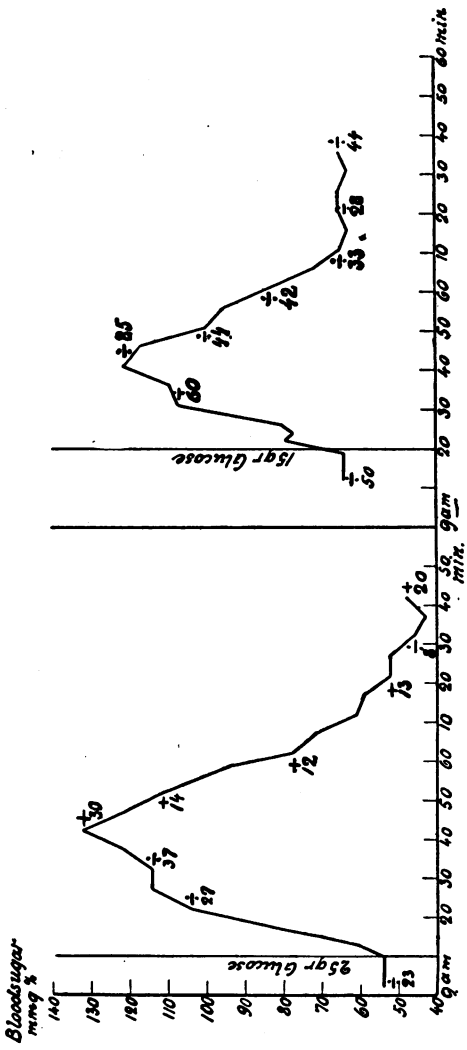

FIG. 6. BLOOD SUGAR CURVES BEFORE PARTURITION

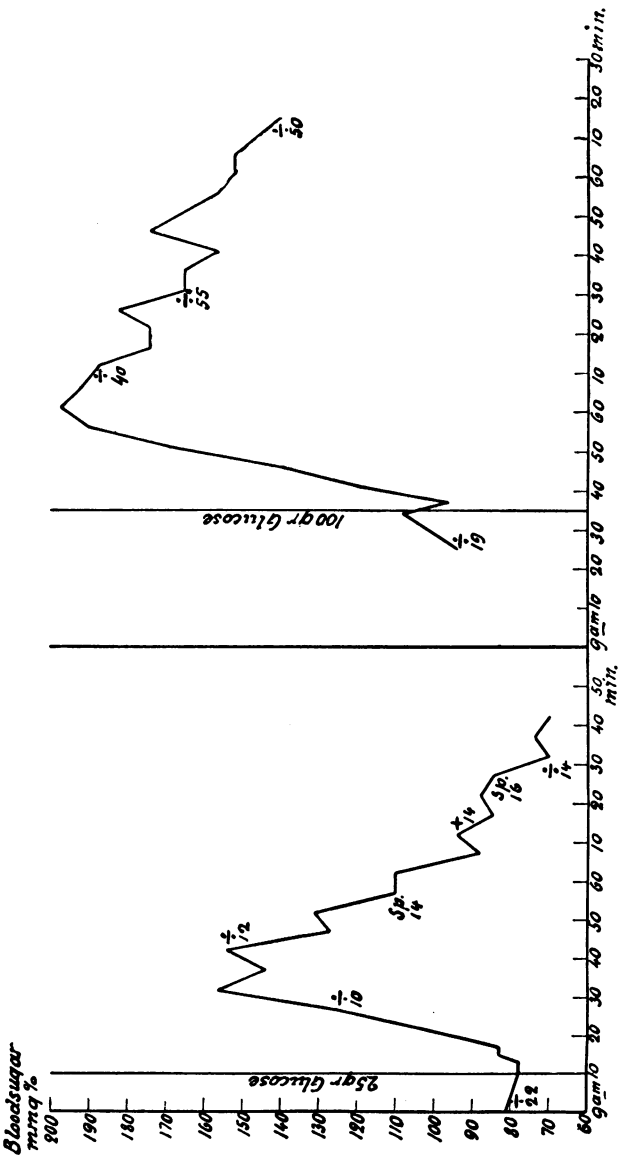

FIG. 7. BLOOD SUGAR CURVES AFTER PARTURITION

anism may be observed without there being any question of diabetes and without there appearing to be a deficiency of insulin production.

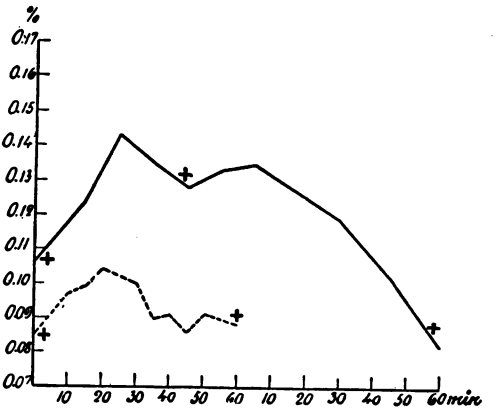

FIG. 8. TRUE RENAL DIABETES—CONSTANT GLYCOSURIA
Blood sugar threshold below 90 mgm.

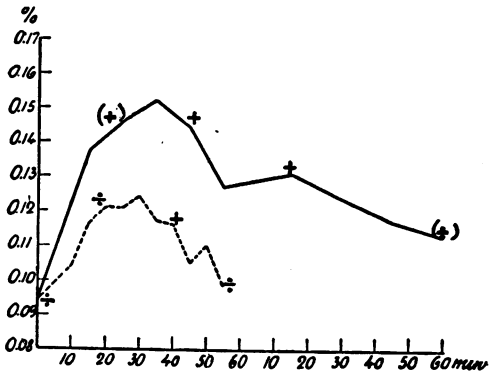

FIG. 9. CYCLIC GLYCOSURIA, THRESHOLD BELOW 120 MGM.

This disturbance manifests itself by an abnormal rise of the blood sugar after an alimentary ingestion. Instead of stopping at about 180 mgm. as is the case in normal individuals, the blood sugar level

rises up to between 200 or 300 mgm. and if the blood sugar threshold is at its usual position it is exceeded and glycosuria sets in.

The curves in figures 8 to 12 will demonstrate these different cases.

It will be readily understood that if an unusual rise in blood sugar occurring after alimentary ingestion is the only abnormality, a cyclic glycosuria will appear clinically in quite the same manner as the cyclic glycosuria that occurs with a low blood sugar threshold. In the morning the blood sugar is normal and the urine free from glucose. After

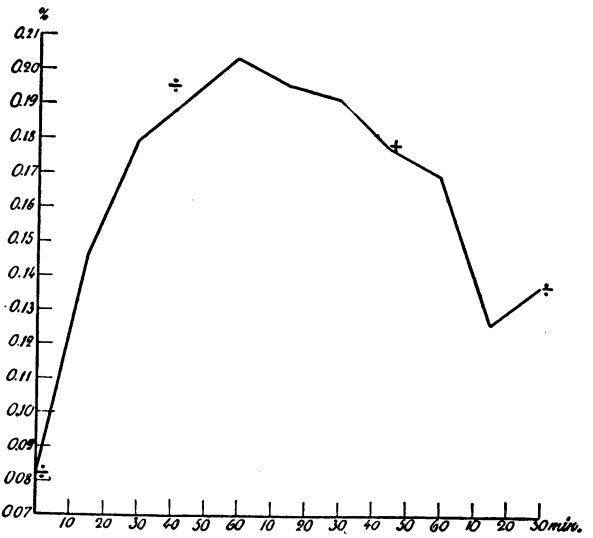

FIG. 10. CYCLIC GLYCOSURIA AFTER THE INGESTION OF GLUCOSE, THE CURVE RISING ABNORMALLY HIGH TO 200 MGM. AND ABOVE THE THRESHOLD

meals the blood sugar rises abnormally high, exceeding the threshold. We then get glycosuria that again disappears during the evening and night. The same can be observed in incipient, mild diabetes, but doubtless such a cyclic glycosuria, which is due entirely to an excessive alimentary rise may be observed fairly frequently and may be present for years, perhaps forever, without the development of true diabetes.

In the examination of 163 patients who formerly had been declared by life insurance companies to be diabetics on account of a glycosuria, Holst (12) was able to demonstrate the frequency of this benign form

of glycosuria. Such a demonstration is obviously of great practical significance to the patient.

He found 27 cases of this type of glycosuria which have been observed for from 1 to 25 years without any other sign of diabetes having manifested itself, although the majority of them have ceased restricting their diet. By repeated examinations of the same patient he has demonstrated that year by year the same abnormally high rise in

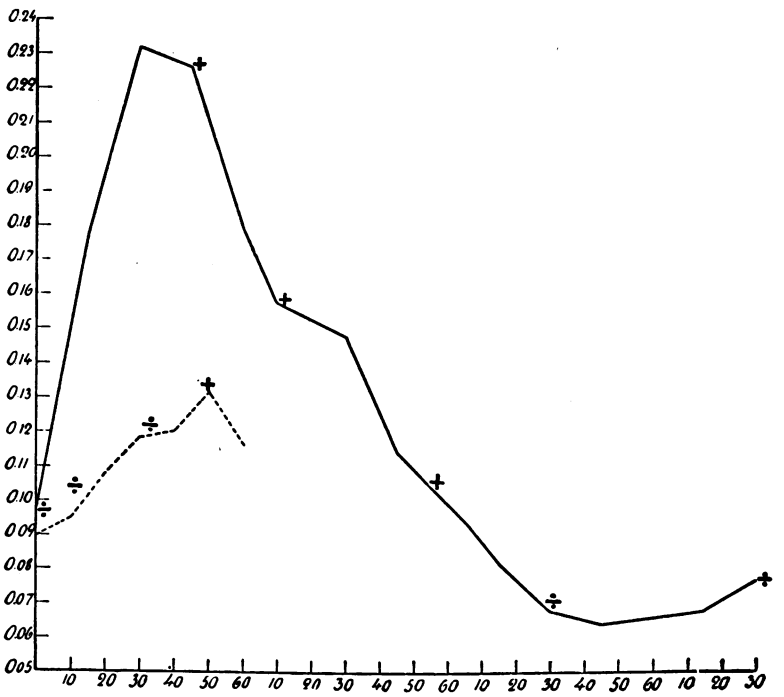

FIG. 11. A COMBINATION OF A HIGH ALIMENTARY RISE AND A LOW THRESHOLD, BELOW 130 MGM.

blood sugar to about 200 mgm. occurred after administration of 50 grams of glucose. In one patient he found that the blood sugar rose in 1916 to 205, in 1920 to 205 and in 1921 to 215 mgm. per cent. The patient showed therefore a constant, harmless cyclic glycosuria.

This disturbance in the blood sugar mechanism does not, however, always remain as constant as an abnormal value of the threshold. In

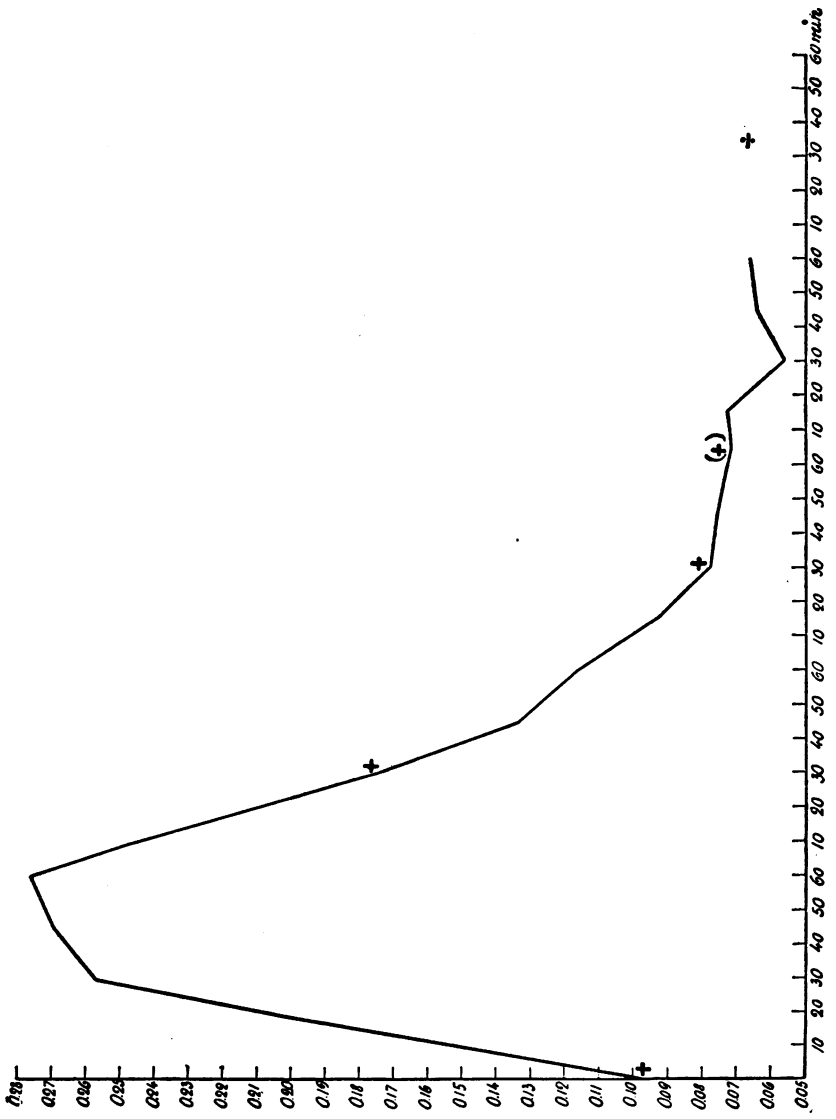

FIG. 12. A COMBINATION OF A HIGH ALIMENTARY RISE AND A LOW THRESHOLD

In this case the threshold is so low that there is a nearly constant renal glycosuria. The threshold must be below 100 mgm.

several cases Holst found that the high alimentary rise later disappeared.

It is readily seen that this form of cyclic benign glycosuria is more difficult to distinguish from a beginning diabetes than a glycosuria due only to a low threshold. A mild diabetes would manifest itself in the same way as a cyclic glycosuria if the diet is restricted.

The question is whether it is generally possible for us to distinguish between these cases and a mild true diabetes when faced with a cyclic glycosuria that is not due to low threshold.

In this respect Holst (13) has called attention to the fact that when a patient lives on a full normal diet without carbohydrate restriction, an absolutely normal fasting blood sugar will almost certainly preclude true diabetes. Should a cyclic glycosuria set in during the course of the day an abnormally low threshold or an excessive alimentary rise is indicated, neither of which denote an abnormal metabolism which has any serious influence on the future of the individual.

This conception cannot as yet be considered so sufficiently established that it can be carried into practice but the conception deserves to be carefully tested.

As a result of the consideration we have given to the question of glycosuria we wish to emphasize the point that two essentially different forms of glycosuria exist. The first is due to a disease of the islands of Langerhans. This is true diabetes. The second form of glycosuria is due to a deficient blood sugar regulation which is dependent either on an habitual abnormally low threshold or on an habitually high alimentary blood sugar rise. In some cases both may be observed, the patient presenting both an abnormally low threshold and an abnormally high alimentary blood sugar rise. In 75 such cases observed for from 1 to 25 years Holst (11) found the cause to be an abnormally low threshold in 22, an excessively high alimentary rise in blood sugar in 15 and in 11 a combination of low threshold and high alimentary rise. In 27 the type was not determined. In all these cases the glycosuria is the result of an individual constitutional abnormality rather than of disease. This form of glycosuria is harmless to the individual and deserves to be estimated as such by doctors and insurance companies.

The practical significance of knowledge of these benign glycosurias

cannot be overestimated. The more extensive and the more careful the examination of urine for glucose becomes among medical men the more frequently will a glycosuria be discovered and the more frequently will individuals be regarded as diabetics in spite of the fact that they are only suffering from an insignificant passing glycosuria. This very often occurs. At the aforementioned examination of 163 applicants for life insurance conducted by Holst, only 30 per cent were true diabetics, the remainder suffering from benign glycosuria.

When all the samples of urine from patients are examined in a routine manner after they have partaken of a meal containing much sugar, as in Denmark, for instance after sweet soup, one is surprised to note that glucose may be demonstrated in one or more samples of urine in 20 to 30 per cent of the patients. After ingestion of larger quantities of glucose considerable glycosuria is found in about 33 per cent, and even after the ingestion of starch it may be seen in about 20 per cent. A daily recurring cyclic glycosuria on ordinary diet is of course less frequent.

The correct interpretation of a glycosuria is of the very greatest importance to the patient. In making the *diagnosis* there is a possibility of error in two directions. A harmless excretion of sugar may be regarded as an incipient diabetes mellitus, an error which may have economic, social, and of not least import, psychic consequences of a grave nature for the patient. It will be just as unfortunate if early diabetes is regarded as benign glycosuria, for the mistake in such cases is often not discovered until the disease has progressed and is perhaps already so far advanced that the most appropriate time to attack and arrest its development has passed.

The difficulty arises when we detect a glycosuria without other symptoms of diabetes. The subjective symptoms may be entirely absent in true diabetes. Among the applicants for life insurance, Holst found that of 43 diabetes cases fortuitously detected at the first observation by glycosuria only 6 presented typical symptoms of diabetes, while 33 or 77 per cent showed complete absence of any subjective sign of the disease. It is therefore necessary to make blood sugar examinations in every case of glycosuria which is not of a purely transitory nature. What we want to know is if there is any hyperglycemia when the patient is fasting.

Most of the cases of glycosuria are discovered by the general practitioner, who, at present is not in a position to make the necessary blood examination. Some time will usually elapse therefore from the time the glycosuria is discovered until it comes to be investigated. It is of great importance for this investigation that no dietetic treatment is begun in the interval, otherwise there is a strong possibility of erroneous conclusions, because an existing hyperglycemia may disappear.

If the patient is examined without previous treatment the diagnosis will depend upon the fasting blood sugar. If this is abnormally high the diagnosis of true diabetes should be made. If it is normal, the examination ought to be repeated several times at intervals of a few weeks. In the intervening period the patient should be allowed to eat food with carbohydrates.

If the patient has shown for a long time a normal fasting blood sugar, that is below 0.11 per cent, although the food is rich in carbohydrate, it can be taken as highly probable that the glycosuria is of benign nature and is not indicative of diabetes.

As a supplementary investigation the determination of the type of glycosuria may be carried out. This is done by obtaining several blood sugar curves after administration of carbohydrates. It is of most interest when it can be demonstrated that a low threshold is the *only* cause of the glycosuria. Then the case must be considered as certainly benign.

If there is an alimentary rise to abnormal height more caution is necessary. We see this in diabetes but, as mentioned above, a cyclic glycosuria due to excessive alimentary rise may be present for years without the development of diabetes.

Regarding these observations the question may be raised as to whether an individual who shows a benign glycosuria is more apt than other people to develop later a true diabetes. This is said by several authors to occur and it is difficult to deny. I can only say that I do not know of any case where a benign glycosuria has turned out to be true diabetes after it was definitely determined to be a benign glycosuria.

If we glance back at the development of the doctrine of benign glycosuria during the last decennium it will be seen that it is due to the careful study of the glucose content of the blood and that

these researches have been especially aided by the micro method introduced by the Norwegian, Ivar Bang, by which the sugar content of blood can be determined from a few drops of blood. Elaborated in the micro method of Hagedorn and Norman Jensen, it gives us a means of making accurate blood sugar curves after alimentary ingestion. The whole development is a fine example of the advantage of exact laboratory analyses, and in addition it demonstrates the fact that a full understanding of the conditions can only be obtained by the use of analyses on a large number of patients, and that only by accurately studying the patients over a considerable period of time is the significance of deviations from the normal to be seen.

BIBLIOGRAPHY

1. Faber, K.: Wien. klin. Woch., 1923, lxxiii, 1190. Bestimmung der Blutzuckerschwelle bei der Glykosurie.
2. Faber, K.: Hospitalstid, 1925, lxviii, 1039. Glycosuric Blood Sugar Threshold in Diabetics and in Pregnants.
3. Faber, K., and Hansen, K. M.: Acta Med. Scandinav., 1923, lviii, 372. Threshold of Glycosuria and Errors Involved.
4. Faber, K., and Norgaard: Acta Med. Scandinav., 1921, liii, 670. The Relations Between Glycosuria and Glycaemia.
   Faber, K., and Norgaard: Acta Med. Scandinav., 1921, liv, 289. Studies on the Threshold of Glycosuria.
5. Frank, E.: Arch. f. exp. Path. u. Pharm., 1913, lxxii, 387. Über experimentalle und klinische Glykosurien renalen Ursprungs.
6. Frank, E., and Nothmann, M.: Münch. Med. Woch., 1920, lxvii, 1433. Ueber die Verwertbarkeit der Renalen Schwangerschaftsglykosurie zur Frühdiagnose der Schwangerschaft.
7. Hagedorn, H. C.: Blodsukkerregulationen hos Mennesket. Copenhagen, 1921. Also Physiological Papers dedicated to Prof. Aug. Krogh. Copenhagen, 1926, 80.
8. Hagedorn, H. C., and Jensen, N.: Ugesk. f. Laeger, 1918, lxxx, 1217. Test for Sugar.
9. Hamman, L., and Hirschmann, I. I.: Arch. Int. Med., 20, 761. Studies on Blood Sugar. I. Alimentary Hyperglycemia and Glycosuria as a Test of Sugar Tolerance.
10. Hansen, K. M.: Investigations on the Blood Sugar in Man. Copenhagen, 1923.
11. Holst, J. E.: Zeit. f. klin. Med., 1922, xcv, 394. Studien über die Alimentaire Glykosurie.

12. Holst, J. E.: Acta Med. Scandinav., 1922, lvii, 188. Untersuchungen über leichte Glykosurien.
13. Holst, J. E.: Acta Med. Scandinav., 1925, lxiii, 47. Investigations into Benign Glykosuria and Diabetes Mellitus.
14. Jacobsen, A. T.: Biochem. Zeitschr., 1913, lvii, 446.
15. Jacobsen, A. T.: Blodsukkerindholdet hos Normale og ved Diabetes Mellitus. Copenhagen, 1917.
16. Williams, J. R., and Humphreys, E. M.: Arch. Int. Med., 1919, xxiii, 537. Clinical Significance of Blood Sugar in Nephritis and Other Diseases.