Glycosuria in Pregnancy.

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I. Introduction.

The occurrence of excess of sugar in the urine during pregnancy is sufficient to excite interest, if not alarm. Fortunately, like many other slight abnormalities of metabolism, it rarely gives rise to any serious consequences. There is, however, the possibility that glycosuria may be the herald of that dread disease, diabetes mellitus, and the exclusion of this type is therefore warranted. The object in bringing this subject forward is to emphasize the progress that has been made in our knowledge of glycosuria, and the factors concerned in its production. This knowledge has been applied to the study of the particular forms of glycosuria which are of special interest to obstetricians. We propose to divide the cases of glycosuria in pregnancy into two groups, viz.:—

(1) Transient or intermittent glycosuria.
(2) Severe glycosuria, and diabetes mellitus.

The greater bulk of the work has been concentrated upon the first group, since it presents features of peculiar interest, apart from the fact that it is the commoner type.

With regard to glycosuria in pregnancy, we require information as to the possibilities of diagnosis of the particular type, and in certain cases the prognosis. The introduction of newer methods of urine and blood analysis has provided means of investigating such cases, and from the accumulated data available, much valuable information can be obtained. This investigation therefore comprises the detection and estimation of normal and abnormal amounts of sugar in the urine, the variations in the blood sugar in normal non-pregnant women and pregnant women, and the application of the glucose tolerance test as a means of diagnosis.

II. Methods of Diagnosis.

(*a*) Chemical analysis of the blood with special reference to the sugar content.

The estimation of sugar in the blood has attracted attention for many years, and numbers of different methods have been applied. One method may prove to be quite reliable in the hands of a worker provided with a well-equipped laboratory, whilst others may fail to get the desired results. There are several well known methods which when submitted to trial and comparison, yield equally satisfactory results. These methods are the Bang,[1] MacLean,[2] Folin and Wu,[3] and the micro-chemical method of Mackenzie Wallis and Gallagher.[4] These different methods when compared on the same samples of blood yield almost identical results. Their uniformity is seen by the constant figures obtained for the normal "fasting" blood sugar, viz., 0.08—0.110 gram per cent. It therefore becomes a question which method to adopt. One of us (R.L.M.W.) used the Bang method, and found it gave reliable results. It suffered from the disadvantage that the reagents did not keep well and had to be renewed constantly, further, it required a well equipped laboratory and a good gas pressure. The same objection applies, though not so forcibly, to the MacLean method, but this being a titration method has much to commend it. The new micro-chemical method which is given in detail in this paper represents a combination of the Bang and Folin and Wu methods with the elimination of most of the pitfalls peculiar to these methods. The ease and rapidity with which a blood sugar estimation can be made is an additional advantage. The method is simple and easily followed, and consistent results are obtained by most workers after a few preliminary trials. One of us (Dr. Bose) has acquired the technique in a very short time, and his results compared with those of R.L.M.W. show variations in the third place of decimals. As a result of nearly two years' extensive practice with this method we have no hesitation in recommending its use.

The Micro-chemical method of estimation of Sugar in the Blood.

The principle of the method is that an estimation of the sugar content of the blood is made upon a few drops of blood obtained by a small prick of the finger. The hæmoglobin and proteins are precipitated from a known weight of blood by means of tungstic acid, and a crystal clear watery filtrate obtained. This filtrate when heated in a water bath with an alkaline solution of copper tartrate produces a reduction of the copper according to the amount of sugar present. The addition of a solution of phosphomolybdic acid of such a strength that equal quantities will cause the copper

solution to lose its blue colour, results in the production of a deep blue coloured solution. This blue colour is compared in a colorimeter with the colour obtained by treating a known standard sugar solution in the same way.

Reagents and Apparatus required.[1]

(1) A sharp needle for pricking the finger.

(2) Starch free absorbing papers of sufficient size to absorb 120 to 130 milligrams of blood. The usual size supplied for this purpose is 16 × 28 mm., and the paper is specially prepared.

(3) Steel wire clips to hold the papers, and suspend them on the hook of the torsion balance.

(4) A good torsion balance capable of weighing from 1 to 500 milligrams. This torsion balance if well constructed will give constant weights irrespective of temperature or humidity.

(5) Small test tubes of such a size that the special absorbing papers slip in, and can be completely submerged in the extracting medium.

(6) Starch free filter papers (No. 1 Whatman).

(7) Two burettes of 2 cc. capacity graduated in one-fiftieths with double bore stopcocks and mechanical fillers, to hold the two precipitating solutions, viz. :—

(*a*) A 10 per cent. solution of sodium tungstate (pure crystals).

(*b*) A two-thirds normal solution of sulphuric acid.

(8) A burette of 10 cc. capacity for distilled water.

(9) A boiling water bath with holes of a suitable size to hold the special boiling tubes in an upright position.

(10) Boiling tubes of resistance glass graduated to hold at least 40 cc. with graduation marks at 12.5 cc., and 25 cc. The lower end of the boiling tube is provided with a bulb of 4 cc. capacity, and a narrow neck above, 2 cm. in length and not more than 8 m.m. in diameter. The bulb is designed to hold the mixture of blood filtrate, and copper solution, and the constricted neck serves to prevent re-oxidation of the copper oxide by reducing the volume of liquid exposed to the air in the tube above.

(11) Oswald pipettes of 1 cc. and 2 cc. capacity.

(12) Alkaline copper solution made up as follows :—

Anhydrous sodium carbonate 40 grammes
Tartaric acid, 7.5 grammes.
Crystalline copper sulphate (pure), 4.5 grammes.

The sodium carbonate is dissolved in about 400 cc. of distilled water contained in a litre flask, warming of the mixture on a water

1. All the apparatus mentioned in this paper can be obtained from Messrs. A. Gallenkamp & Co., 19-21, Sun Street, Finsbury Square, E.C.

bath being necessary. The copper sulphate is dissolved separately, and then added to the carbonate solution, and finally the tartaric acid is added to the mixture. The solution is made up to 1 litre volume with distilled water, and then filtered.

(13) Phosphomolybdic acid solution. This is prepared by dissolving 35 grammes of pure molybdic acid (free from ammonia) in 200 cc. of 10 per cent. sodium hydroxide. To this add 200 cc. of distilled water, and heat until all traces of ammonia are expelled. Cool, and then add 125 cc. of phosphoric acid (85 per cent. strength), and finally make up in a 500 cc. flask to the mark with distilled water. This solution should be of such a strength that 2 cc. will completely discharge the blue colour from 2 cc. of the copper solution. It is advisable to test these reagents from time to time, and to do blank estimations with the reagents occasionally.

(14) Standard solution of glucose. One gram of pure glucose is dissolved in 100 cc. of distilled water, and preserved with toluol. Its strength is determined by the polarimeter and quantitative analysis. In this strength it can be kept in a refrigerator for a month or more and used as a stock solution. To make up the standard solution from this, 1 c.c. of the stock solution is placed in a 50 cc. flask, and diluted to the mark with distilled water. Each cc. of this standard solution contains 2 milligrams of glucose.

(15) A good colorimeter, preferably the Kober type. The plungers in this instrument are fixed, and the cups are movable. The sides of the plungers are of black glass as also the sides of the cups, and thus there is no space between the fluid and the prisms to allow of extraneous sources of light, which introduces errors into instruments like the Duboscq colorimeter. Another advantage of the Kober instrument is that the standard solution can be fixed at any point, and moved in relation to the unknown solution thus enabling both strong and weak-coloured solutions to be compared with ease and accuracy. To ensure readings of the colorimeter it is advisable to use the same volume of reagents in each case, and the same dilutions. Working with the standard solution and the usual weights of blood absorbed on the special papers it is possible to obtain colours which match very well, and give readings close together on the colorimeter scale. The depth of colour is proportional to the amount of sugar present, and if the amount of sugar in one cup is known then the amount of sugar in the unknown can easily be calculated.

Method of Estimation.

The finger of the patient is cleansed carefully with alcohol or ether, and the flow of blood assisted by pressure of a piece of soft rubber tubing. The portion of finger just below the bed of the nail

is selected, and a sterile needle inserted. The paper and hook having been weighed, is now soaked with blood as evenly as possible, and rapidly weighed. With a good flow of blood from the prick and careful absorption of blood about 120 milligrams of blood can be obtained on each paper, and this is quite sufficient for a single estimation. To ensure good results with the torsion balance it is necessary to acquire speed in absorbing the blood and also weighing, and not to touch either the paper or hook with the fingers. All the manipulations of the paper and hook are done with a pair of fine-pointed forceps, preferably ivory-tipped. Using good absorbing paper, and quick weighing on the torsion balance the loss of weight by evaporation is almost negligible. This method of collecting and weighing the blood has much to recommend it, as it is rapid, accurate, cleanly, and impressive. The patient suffers just the slight inconvenience of the prick of the finger, and thus the estimation can be carried out on persons of any age, sex or temperament, without any danger of emotional disturbance. Sufficient blood for an estimation has been obtained from a patient during sleep, and the manipulations have been so slight that the sleep remained undisturbed.

The paper soaked with blood is now inserted into a small test tube and 3.6 cc.s of distilled water added. This amount of fluid is sufficient to cover the paper, and extract the blood from it, the extraction being allowed to proceed for exactly half an hour at ordinary room temperature. At such temperatures, and with this interval of time, extraction is complete, and there is no danger of glycolysis occurring with consequent disappearance of the sugar.[1] The extraction must not be allowed to proceed beyond one hour. The proteins, etc., are now removed by means of the tungstic acid precipitation method of Folin and Wu,[3] 0.2 cc. of the 10 per cent. sodium tungstate solution being first added, then 0.2 cc. of two-thirds normal sulphuric acid. This makes a total volume of 4 cc.s. The mixture shows a reddish precipitate which rapidly turns brown with

1. Dennis and Martha Aldrick (*Journ. Biol. Chem.*, 1920, xiv, 203) have found that glycolysis can be inhibited for 96 hours by the addition of 2-3 drops of formalin (40 per cent.) to each 5 cc. of blood. This amount of formalin does not interfere with the subsequent procedures, since it does not exert a reducing action on the copper solution, the low alkalinity of the latter reagent being the explanation of this. The use of formalin as a preservative of blood is advantageous especially where it may be necessary to send oxalated blood from a distance. In this case 2 cc. of blood are run into a small tube containing not more than ten milligrams of finely powdered potassium oxalate, and one drop of strong formalin is added. For estimation of the sugar the blood can be absorbed on the paper, and weighed on the torsion balance, or 0.2 cc. of blood taken up with a pipette, and added to 3.6 cc. of distilled water.

the formation of a thick viscous precipitate. The precipitation is complete when a note like shaking mercury in a glass vessel is emitted. The mixture is now ready for filtration through a starch-free filter paper into a small clean tube, and if precipitation has been complete a clear watery filtrate is obtained. It is important to note that all the materials and reagents used are standardized to precipitate a given amount of blood. Care should, therefore, be taken to ensure that at least 100 milligrams and not more than 140 milligrams of blood are taken for each estimation. The sodium tungstate solution and sulphuric acid solution should be so balanced that after precipitating a given weight of blood the filtrate is neutral or only slightly acid in reaction.

For an estimation 2 cc. of the clear filtrate are measured by means of an Oswald pipette, and placed in one of the special boiling tubes and 2 cc. of the alkaline copper solution added. In another boiling tube place 1 cc. of the standard glucose solution and 2 cc. of copper solution, and make up to the neck with distilled water.* The two tubes are now inserted in a boiling water bath and allowed to remain exactly six minutes. They are then removed from the bath and 2 cc. of the phosphomolybdic acid solution added to each. A brisk effervescence occurs, and in the presence of sugar a deep blue colour results, the depth of colour depending on the amount of sugar present. The contents of both the standard and the unknown are now diluted to the 12.5 cc. mark and thoroughly mixed. The two solutions are now placed in the two black cups, and compared in the colorimeter. The standard sugar solution may be set at any position in the colorimeter, but it is advisable to obtain readings of the unknown as near as possible to that of the standard solution. The colour is of such a distinct blue that after a little practice it can be matched with ease and remarkable accuracy.

The calculation is made as follows:

Weight of paper and hook = 250 mgms.

Weight of paper, hook and blood = 360 mgms.

Weight of blood taken = 360 − 250 = 110 mgms.

With the standard sugar solution set at 20 mm. on the colorimeter scale the reading of the unknown solution is 25 mm. 1 cc. of the standard sugar solution contains 0.2 milligrams of glucose. The amount of sugar present in 2 cc. of the tungstic acid filtrate =

$$\frac{\text{Reading of standard} = 20}{\text{Reading of unknown} = 25} \times 0.2 = 0.056$$

* N.B.—to ensure complete mixing it is advisable to tap the bulb against the palm of the hand a few times, but to avoid vigorous shaking.

The amount of blood taken = 110 milligrams, and the amount of extracting fluid used = 4 cc.

The amount of blood in the 2 cc. of filtrate = $\frac{110 \times 2}{4}$ = 55 mgms.

Percentage of sugar in the blood = $\frac{0.056 \times 100}{55}$ = 0.101.

This result indicates a normal blood sugar content, the normal average figures ranging from 0.08 to 0.110 gram per cent.

II. (*b*) *The detection and estimation of sugar in the urine in normal and abnormal amounts.*

When glucose is present in the urine in abnormal amounts its detection by any of the well-known tests is a simple matter. Some observers are satisfied with a negative result to Fehling's test as an indication of the absence of glycosuria. This test, however, may often give an indefinite result, and it is advisable to apply other tests for confirmation. It has been our custom to use Benedict's test, the Nylander test, Osazone test, Polarimeter, and actual estimation of the reducing power of the urine. On the findings of all these tests we have in many cases been able to decide whether sugar is present or not. There are, however, instances by no means infrequent when a urine is found to give an indefinite reaction with both Fehling's test and Benedict's test, but definite osazone crystals. The rotation with the polarimeter is so slight as to render this method of little value. Further, quantitative estimation of the reducing power of the urine by the ordinary method shows anything from 0.1 to 0.3 gram per cent. The question arises as to whether this is true glycosuria or not, and this is often of the greatest importance not only for diagnostic purposes, but for use with the glucose tolerance test, and also for following the effects of treatment. We also require to know what is the line of demarcation, if any, between the normal sugar content of the urine ("glycuresis" of Benedict) and clinical glycosuria. This subject has attracted the attention of several observers for many years, but has been beset by many difficulties. The chief disturbing factor in all methods which have been tried has been the presence of creatinine. In the method which we have now devised, practically all the difficulties and obstacles encountered have been overcome. The precipitating agent which we finally selected precipitates all the creatinine from the urine, all the pigments, the greater part of the uric acid, and urea, and other interfering substances. The clear watery filtrate contains practically no nitrogenous constituents, but all the sugar. The estimation of sugar is carried out exactly as described above for blood sugar determination.

New method of estimation of normal sugar in urine.

In addition to the apparatus and reagents described above for blood sugar estimation the precipitating reagent is required. This is made up as follows :—

Five grammes of pure phosphotungstic acid are placed in a 250 cc. flask and dissolved in hot distilled water, about 100 cc. being used for this purpose. To this solution add drop by drop 12 cc. of concentrated sulphuric acid (98 per cent.) with constant shaking. Great care should be taken in adding the acid in order to avoid a violent reaction due to overheating. Cool to room temperature, and then make up to the 250 cc. mark with distilled water inverting several times to ensure complete mixing. Filter through a starch free filter paper into a clear, dry, amber-coloured bottle. This reagent should be kept in a cool dark place, and made up at intervals. On standing exposed to light the solution assumes a lavender tint, and loses its properties to some extent.

The estimation is carried out as follows :—Into a test tube measure out 1 cc. of the urine by means of an Oswald pipette, and then add 2 cc. of the sulphuric phosphotungstic-acid mixture. A dense precipitate appears of a reddish violet colour. This precipitate contains the creatinine, uric acid, urochrome, and other pigments. Shake the test tube and then add 7 cc. of distilled water to make up the volume to 10 cc. Filter through a starch free filter paper into a clean dry test tube. The estimation of the sugar in the clear filtrate is carried out in the same way as the blood sugar estimation described above. One cc. of the filtrate is used for this purpose and the same standard solution of sugar, viz., 0.02 per cent. The alkaline copper solution and filtrate are boiled in the special test tubes for six minutes in a boiling water bath and the blue colour obtained with phosphomolybdic acid compared in the colorimeter against the standard glucose solution.

Calculation.—Amount of normal urine taken = 0.1 cc. (*i.e.*, 1 cc. of original urine + 2 cc. of precipitating reagent + 7 cc. of water = 10 cc., of which 1 cc. is taken for estimation). Amount of glucose present in the standard solution = 0.2, *i.e.*, 1 cc. of 0.02 gram glucose per cent.

$$\frac{\text{Reading of Standard}}{\text{Reading of unknown.}} \times \frac{.2 \times 100}{.1} = x \text{ per cent.}$$

Example :—

Reading of Standard ... ... = 22 mm.
„ „ Unknown ... ... = 50 mm

$$\text{Percentage of sugar in urine} = \frac{22}{50} \times \frac{.2 \times 100}{.1} = 88,$$

or 0.088 gram per cent.

Should the urine contain more than a trace of reduction with Benedict's test it is advisable to use less urine, viz., 0.5 cc. and 1 cc. of the phosphotungstic mixture and make up as before to a volume of 10 cc. Where there is clinical glycosuria this method may be used for an estimation of the sugar provided the original urine is diluted previously.

The above method has been given an extensive trial, and found to yield reliable results. In many ways it has proved invaluable, as it is of undoubted advantage to have comparative records of both the blood and urinary sugar content. Further, we would emphasize the fact that the methods of estimation are quite comparable, and the same apparatus and reagents are used for both estimations. We find that by this method every normal urine examined contains sugar varying in amount between 0.06 and 0.09 gram per cent., and amounting in the twenty-four hours to a total of 0.8 to 1 gram. These results show that the percentage sugar content of normal urine is slightly lower than that of the blood.

II. (*c*) *The Glucose Tolerance Test.*

A normal healthy individual is capable of absorbing 100 grammes of glucose without the appearance of abnormal amounts of sugar in the urine. If the amount is increased to 200 grammes, there is nearly always a temporary glycosuria. By giving glucose by the mouth, and examining the urine for evidence of glycosuria it has been found that the normal glucose tolerance is about 150 grammes. This test has been used for many years, but suffers from many disadvantages, rendering the results inconclusive. There are so many factors concerned in the mechanism of production of so-called alimentary glycosuria besides such factors as rate of absorption, renal permeability, individual variations of tolerance to glucose, and other sugars, as to render this test of historical value only.

The introduction of micro-chemical methods of blood analysis has rendered possible the repeated estimation of the blood sugar content at frequent intervals after the ingestion of glucose, and the glucose tolerance test has consequently developed along newer and more scientific lines. Many of the errors associated with the older test have been eliminated, and consequently more reliable results obtained. In the glucose tolerance test, we attempt to study the response of a given individual to the passage of sugar into the blood-stream. The procedure as used by one of us for several years is as follows :—

The patient is given a light meal in the early morning, consisting of one egg and tea or coffee with no sugar. Three hours after, the urine is collected, measured, and the amount of normal urinary sugar estimated. At the same time the blood is taken from the

finger by means of a simple prick, and the sugar content is estimated by the method described above.

The patient now consumes 50 grammes of glucose dissolved in 150—200cc. of water. This amount of glucose has been found to be quite sufficient, since it is the type of response we are gauging, and not the actual amount of sugar in the blood at any given moment. Further, for every given individual the type of curve obtained is identical in form, whether 25, 50, 100 or 150 grammes of sugar are given. Exactly 15 minutes after the last drop of sugar solution has been consumed, the blood is taken again, and the sugar content estimated. This blood sugar estimation is repeated at the half hour, 1 hour, 1½ hours and 2 hours intervals, after the sugar has been consumed. At the end of the hour and 2 hours intervals the urine is collected, measured, and the amount of sugar present determined. In this way we have figures of the blood sugar before the test, ¼ hour after, ½ hour after, 1 hour after and 1½ hours after, and also 2 hours after. After collecting a large number of results of tolerance tests carried out in this way, we plotted the curves on a large sheet of graph paper and proceeded to pick out all the curves which showed the same type of response. There were the normal controls, of course, and in addition four distinct groups. Reference to the curves and clinical notes of the patients revealed the fact that there was a marked correspondence between the curve of blood sugar and the nature of the disease causing the glycosuria. The four groups were :—

(1) Thyroid pancreatic group (No. 4 on Chart I).
(2) Severe glycosuria (No. 2 on Chart I).
(3) Glycosuria without hyperglycæmia (No. 5 on Chart I).
(4) Hyper-pituitarism (No. 3 on Chart I).

The four types are illustrated in the accompanying chart. (Chart I.)

The only group showing blood sugar figures below the normal (Chart II) is the third group. The pituitary cases, in contrast with the normal, show a long drawn out type of curve, with flattened top, and, instead of the blood sugar falling to the previous level at the 1 hour interval, it is often still raised at the 2 hours interval. The most striking feature, however, and one which intimately concerns us, was the placing of the curves obtained from tolerance tests upon cases of glycosuria in pregnancy. All these cases fall into the same group as the pituitary cases. Needless to say, the cases selected for tolerance tests in the first instance were typical cases, where there was little, if any, doubt as to the nature of the disease. Subsequent investigations upon a larger series have more than ever confirmed our opinion that these four groups constitute definite entities.

The cases of glycosuria in pregnancy are given in separate charts, and the type of curve is identical in all the cases examined. In the glucose tolerance test we feel convinced we have the best, and, at present, the only means of detecting degrees of hyper-function of the pituitary body. This explanation of transitory

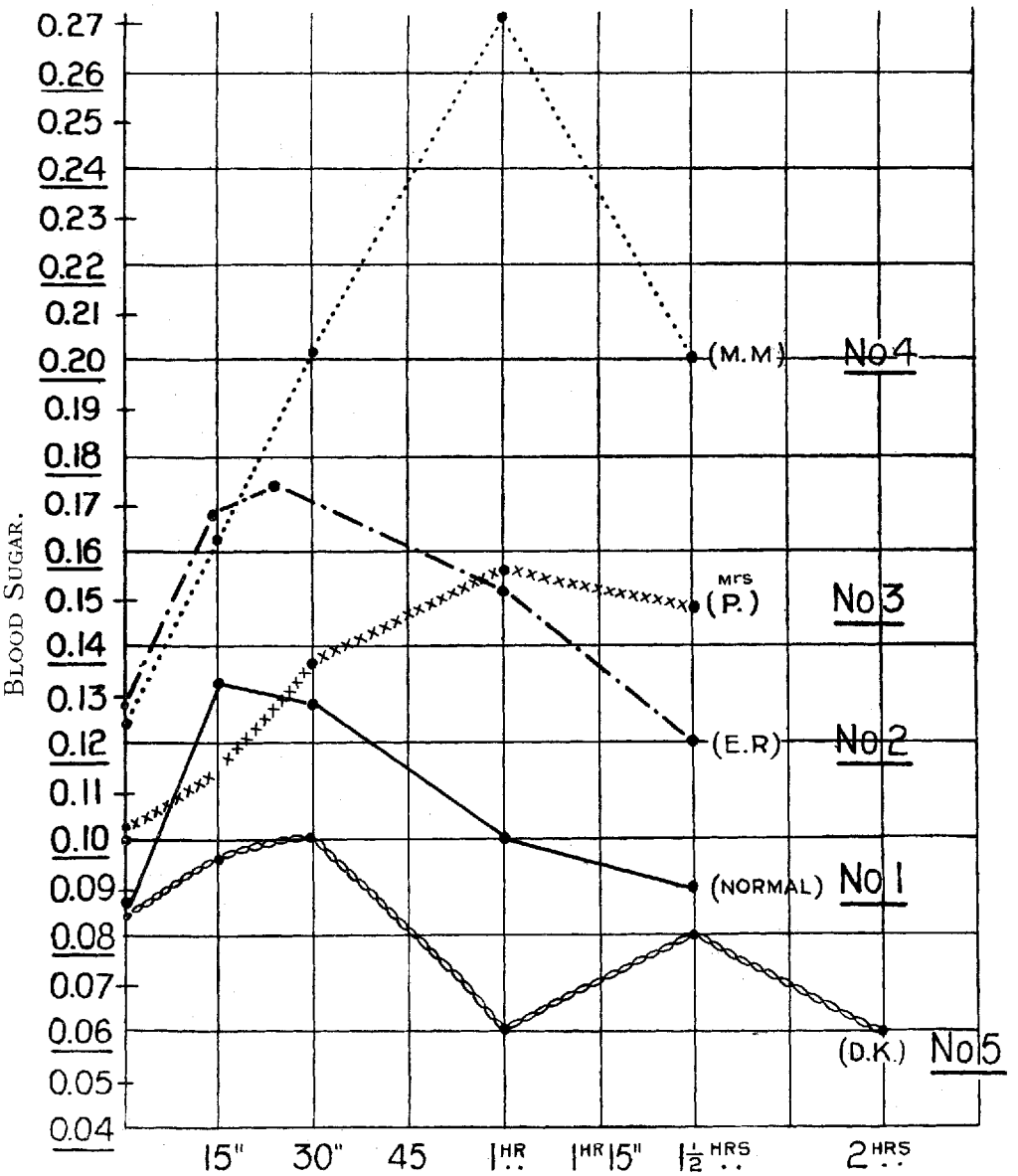

Chart I. This chart illustrates the four types of curve obtained by means of the Glucose Tolerance Test in different conditions as compared with the normal curve No. 1.

glycosuria in pregnancy would appear to be the most reasonable, and the results are certainly suggestive. The greater number of cases of glycosuria in pregnancy in our experience, fall into this group, and this investigation adds a further link in the chain of evidence associating intermittent glycosuria with hyperpituitarism. A simple blood sugar examination may be of value, since with glycosuria and a normal blood sugar, the possibility of the case falling into this group may be considered.

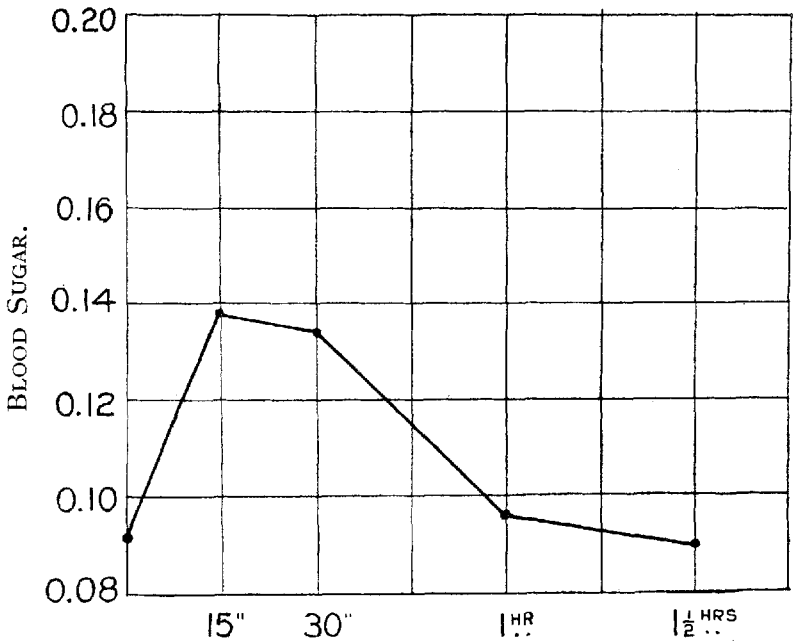

Chart II. Normal non-pregnant woman. Glucose Tolerance Test. This chart illustrates the normal response to the ingestion of 50 grammes of glucose. It will be noted that the blood sugar rarely rises above 0.15 gramme per cent., and in one hour the blood sugar has fallen to its previous normal level.

III. INTERMITTENT, OR TRANSIENT, GLYCOSURIA OF PREGNANCY.

In 1912 Mackenzie Wallis and Roper[5] described a case of intermittent glycosuria. This patient had polyuria, intermittent glycosuria, and all the symptoms pointing to an excessive functional activity of the pituitary gland. As far as we have been able to review the literature, this case was the first recorded of true intermittent glycosuria. In 1921, Geoffrey Evans and Mackenzie Wallis described two cases of diabetes insipidus with intermittent glycosuria, and both these cases showed many of the characteristic signs and symptoms of hyperpituitarism. Our knowledge of the effects of hyperpituitarism are based upon studies of cases of acromegaly, a disease in which all the characters of hyper-function

of this gland are strikingly portrayed. There has naturally developed from this the idea that hyper-function of the gland is only of pathological import when the classical signs and symptoms of acromegaly are apparent. It is a matter of very little difficulty to diagnose hyper-function of the pituitary in such typical cases, but in cases of hyperpituitarism without ancral changes the diagnosis is often in doubt.

In our opinion the only method of diagnosis so far devised is the glucose tolerance test. Acromegaly is often accompanied by intermittent or permanent glycosuria, particularly in the early stages of the disease. Borchard in summarising 176 cases recorded in the literature, found that spontaneous glycosuria was present in 63, and so-called "alimentary glycosuria" in 8. The point of chief interest is that the glycosuria when present is transient in character, and frequently occurs without any relation to diet. One feature which is frequently exhibited by such cases is polyuria, and an almost classical symptom of the associated glycosuria is extreme lassitude.

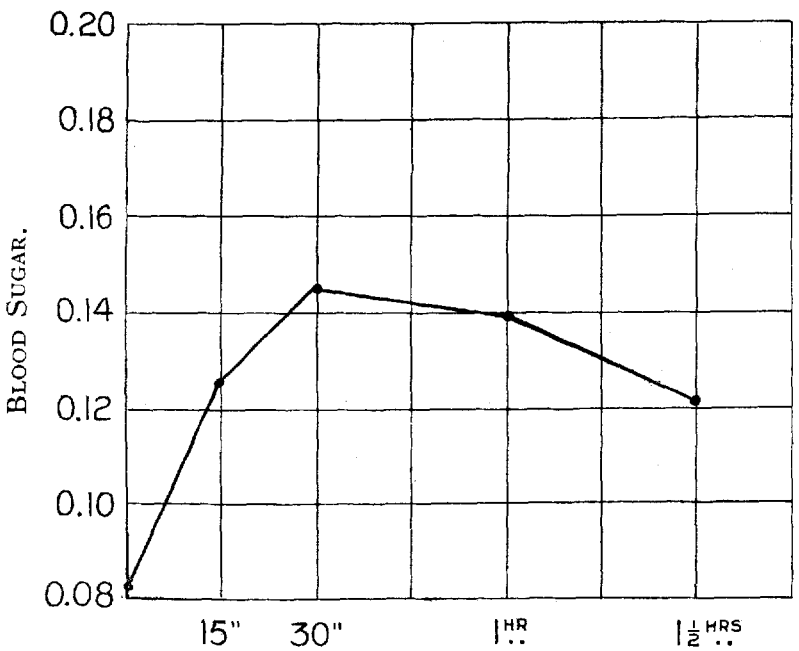

Chart III. Glycosuria in Pregnancy. Typical curve obtained with the glucose tolerance test.

These characters are nearly always present in cases of intermittent glycosuria, where there is no evidence of bony changes, no enlargement of the sella turcica, nor hyperplastic changes in the soft parts. There are a number of cases of glycosuria in pregnant women, where sugar is found in the urine, and the amount of sugar

present is unaffected by diet. The sugar may be detected on one day and examination on the following day shows that it is quite absent. The blood sugar content is usually normal or only slightly raised. This intermittent glycosuria may occur throughout the pregnancy, but directly the pregnancy is over, the sugar disappears and does not recur. We know that the pituitary gland undergoes changes during pregnancy, frequently exhibiting definite hypertrophy. Cases have been recorded of true acromegaly appearing in pregnancy with complete recovery afterwards. There are also several signs and symptoms observed during pregnancy, which it is tempting to ascribe to hyper-function of the pituitary body, particularly polyuria, symptoms of increased intra-cranial pressure, and hyper-excitability of the sympathetic nervous system. We unfortunately know very little of the physiology and pathology of the pituitary gland, but all are agreed that the gland is essential to

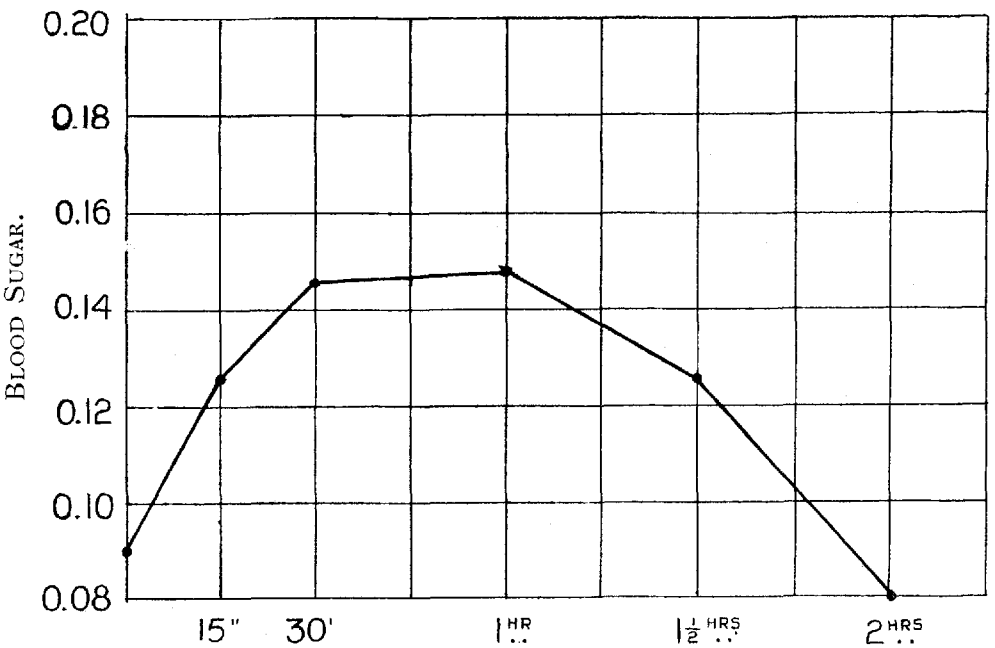

Chart IV. Glycosuria in Pregnancy. Glucose Tolerance Test.

life. The secretion of the posterior lobe is probably concerned with the regulation of metabolism, especially of carbohydrates, and to a certain extent with fats, whilst the anterior lobe controls the processes of metabolism concerned with growth. Although the explanation of transitory glycosuria in pregnancy seems to be obtained by ascribing it to hyper-function of the pituitary, the question arises as to whether we have any proofs. Our object is to try and demonstrate, by means of the results obtained with the glucose tolerance test, that this test yields data upon which to base

conclusions as to the part played by the pituitary in this condition. A number of cases of glycosuria in pregnancy have been examined, and curves of glucose tolerance obtained. (See Charts III, IV, V,

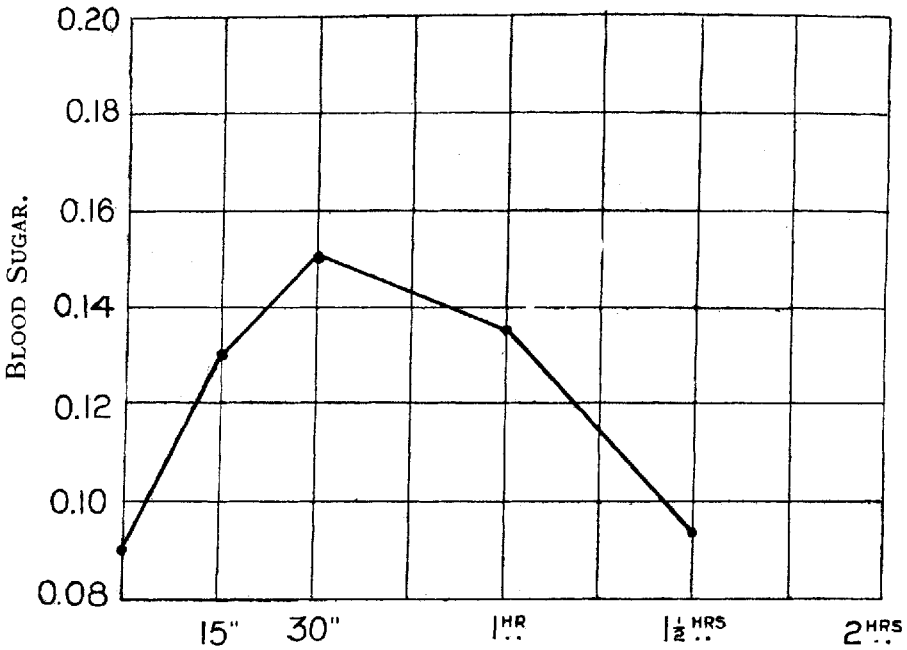

Chart V. Glycosuria in Pregnancy. Glucose Tolerance Test.

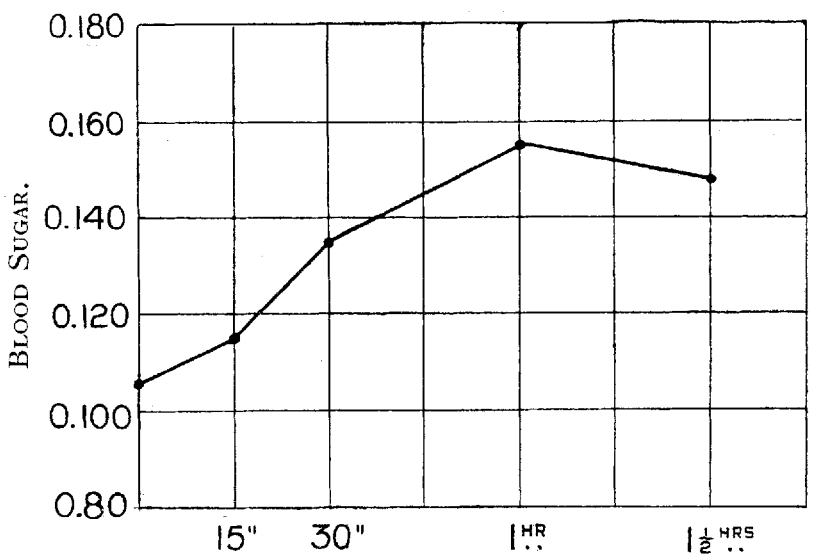

Chart VI. Glycosuria in Pregnancy. Glucose Tolerance Test.

VI.) When plotted in conjunction with others, it was found that in every case they correspond with those obtained with cases known to be suffering from disease of the pituitary body. In this group we find cases of true acromegaly, adiposus dolorosa (see Chart VII), extreme adiposity, and cases of intermittent glycosuria with clinical signs and symptoms of hyper-pituitarism. The curves shown all illustrate the same general characters. The blood sugar after 50 grammes of glucose shows a steady rise, and the maximum response is generally found at the 1 hour and 1½ hour intervals, after which the blood sugar as slowly falls. This, in our opinion, is very characteristic of hyper-pituitarism, and we are inclined to conclude that the transitory glycosuria of pregnancy is intimately related to over-activity of the pituitary gland. The outcome of this investigation is that cases who present this type of curve are best left alone. They are able to tolerate 50 grammes of glucose without the passage of sugar in the urine in abnormal amounts. Restriction of carbohydrates is therefore unnecessary in this type of case, and may, on the other hand, be harmful. This course of procedure has been adopted in such cases with no untoward results.

IV. Severe Glycosuria in Pregnancy.

In contrast to the cases of intermittent glycosuria in pregnancy, we find cases with severe glycosuria where any information of the state of carbohydrate metabolism is of value not only for diagnosis, but for prognosis. It is a wise plan to regard every case of glycosuria in pregnancy as a potential case of diabetes mellitus until proved otherwise. The first step appears to be to determine whether the sugar present in the urine is glucose, and the method described above is found to be extremely useful for this purpose. The presence of lactose and other sugars is always considered and excluded. A blood sugar determination is also made, and if the fasting blood sugar shows a value above 0.2 gramme per cent. there is, of course, evidence of gross disturbances of carbohydrate metabolism. The single blood sugar examination is of value in such a case, especially if the observations are repeated during the progress of treatment. In this way, with examination of the 24 hours collection of the urine, the effects of dietetic treatment may be studied. A single blood sugar examination may also pick out a case of so-called "renal diabetes," since in such cases we find glycosuria without an excess of sugar in the blood, *i.e.*, hypoglycæmia, and not hyperglycæmia. Thus by means of a combined urine and blood analysis we may be able to differentiate certain forms of glycosuria. Further, if the blood sugar is normal, or only slightly raised, a glucose tolerance test can then be performed with safety, and much more valuable information obtained thereby. (See

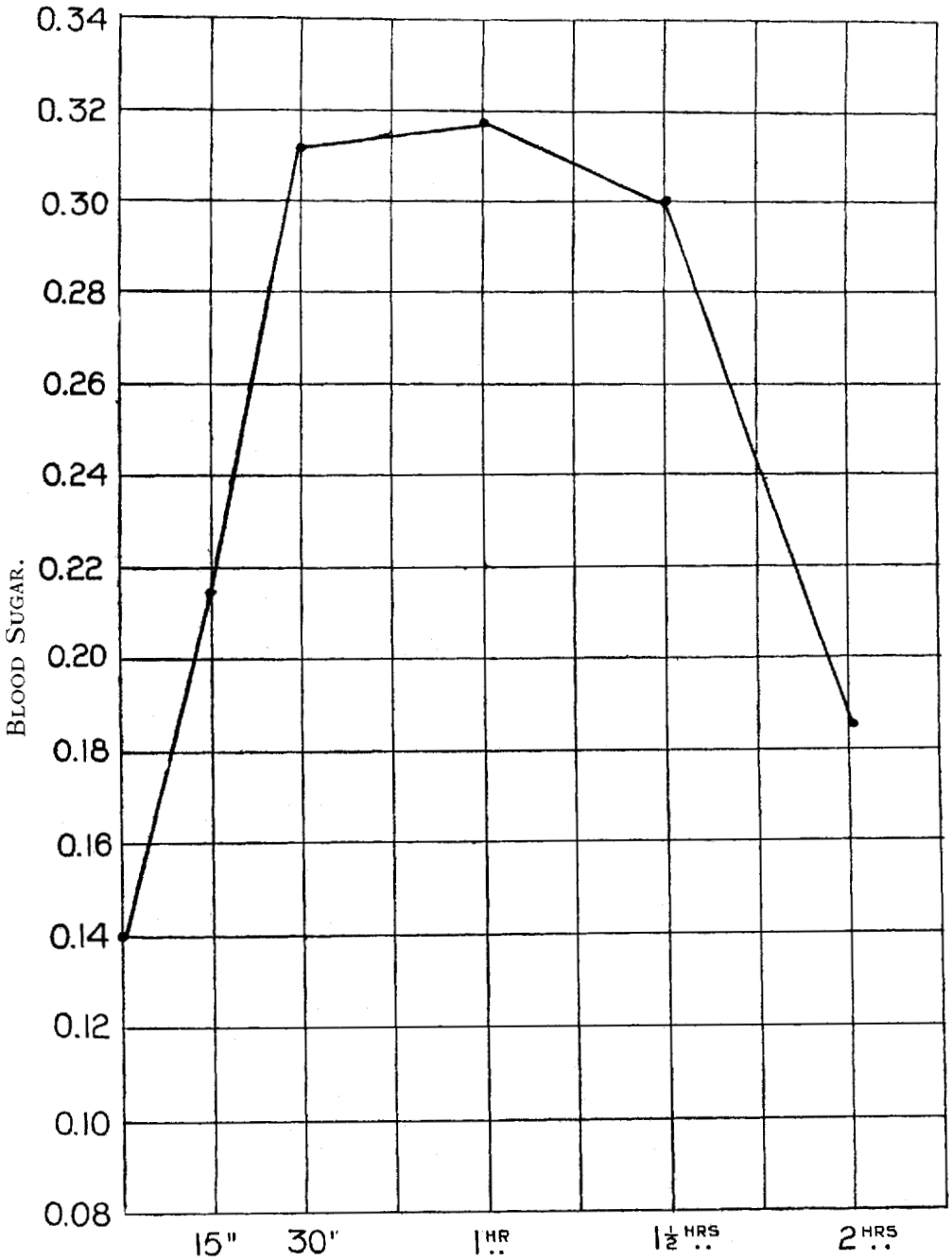

Chart VII. Adiposus Dolorosa. Glucose Tolerance Test.

Chart VIII.) To illustrate the value of blood sugar determination in cases of severe glycosuria in pregnancy, I would refer to the case described by Dr. Herbert Williamson in the *Clinical Journal* for 20th Nov., 1912. This case was carefully investigated, and was thought to be a case of transient glycosuria. Subsequently, at a second pregnancy, the glycosuria returned, but at this time our

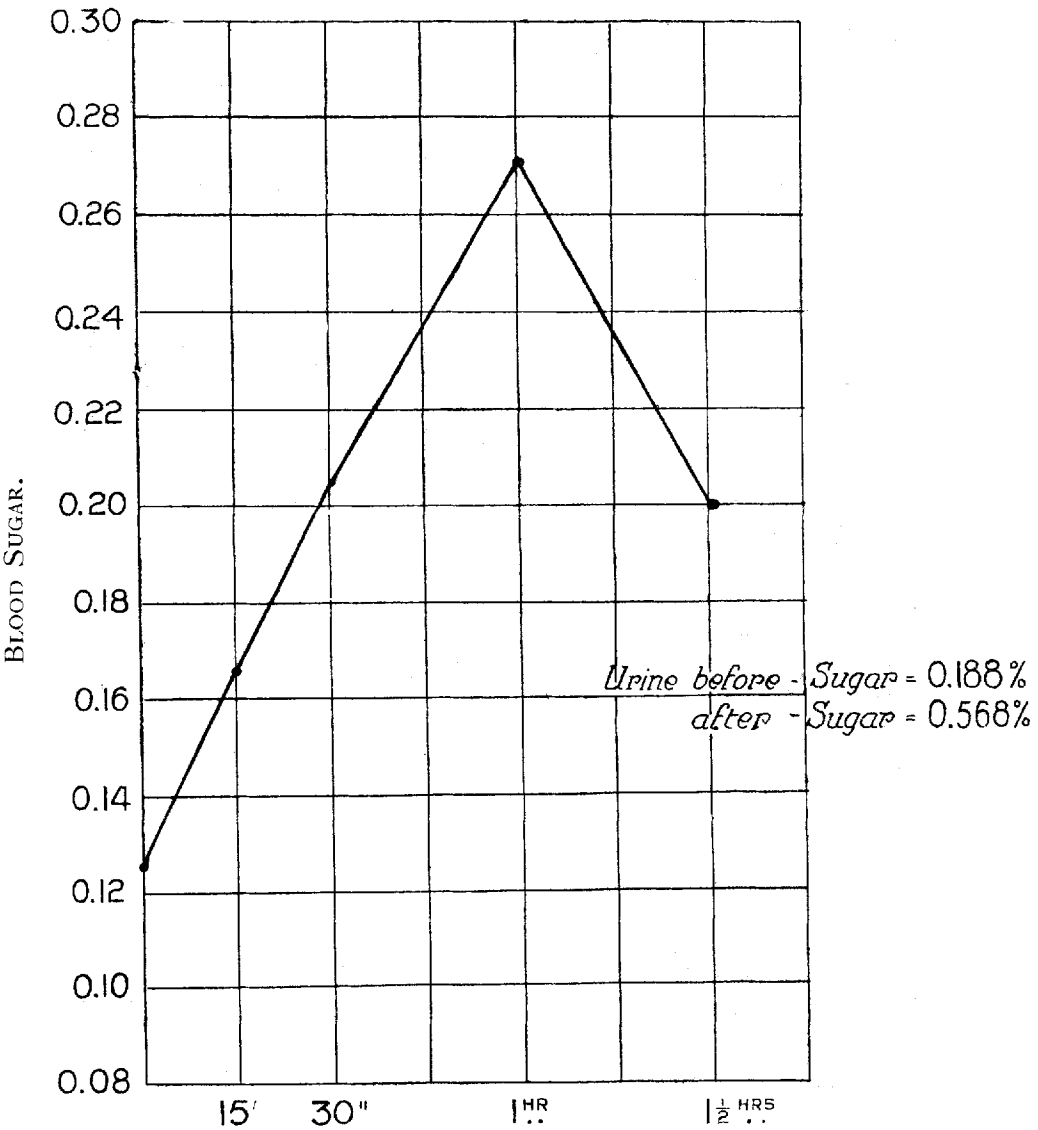

Chart VIII. Exophthalmic Goitre Glucose Tolerance Test, showing the maximum response in one hour for comparison with the curves obtained in cases of glycosuria in pregnancy.

methods of estimating sugar in the blood were not perfected, and so no blood sugar determinations were made in this case. The fact that the glycosuria was reduced and even disappeared on a strict diet, rather suggested that the case was one of true diabetes mellitus. The blood sugar determination is therefore of value if it is possible to watch the progress of the case, and the effects of treatment. When the patient has been dieted and is found to be sugar free, it is quite possible to submit this patient to a glucose tolerance test, especially if only 25 grammes are given. The results of such a tolerance test show that the extra sugar presented to the blood is followed by a sharp rapid rise, and just as sudden fall, and a large portion of the 25 grammes of sugar administered appears in the urine. With regard to the use of the sugar tolerance test in prognosis data are as yet incomplete, and so no definite conclusions can be drawn. Many of the patients with severe glycosuria who give the type No. 2 curve (see Chart No. I) have died in diabetic coma, or at present are suffering from severe and intractable glycosuria. The presence of a high blood sugar content in pregnancy, and glycosuria which yields to dietetic treatment is to be regarded as unfavourable. If, in addition, a tolerance test shows that even 25 grammes of sugar cannot be tolerated, the unfavourable prognosis is confirmed.

V. Cases of Intermittent or Transitory Glycosuria.

Case I. Six months pregnant. Glycosuria averaging about 1.0 gramme per cent., or 15—16 grammes in the 24 hours. Regarded as a case of severe diabetes and, on a restriction of diet as regards carbohydrates, lost weight, acetone bodies appeared in the urine, and the glycosuria increased. Blood sugar content showed 0.128 grammes per cent. On this result the patient was placed on a fairly liberal diet, the only restriction being the removal of sugar as such. Normal labour, and the glycosuria disappeared immediately afterwards and has not reappeared.

Case II. Seven months pregnant. Glucose discovered in urine. Estimation showed 0.4 gramme per cent. No levulose or lactose could be isolated, and no acetone bodies found. Blood sugar estimation showed 0.099 gramme per cent. No signs and symptoms of severe glycosuria.

Case III. Aged 21. Primipara. Became pregnant in August and sugar discovered in urine 6 months later. There was no polyuria, unusual thirst, or hunger. No pruritis, sores, ulcers or boils. An estimation of the sugar content of the urine showed 0.32 gramme per cent. She was then dieted very strictly but in spite of this the sugar content of the urine increased to 3.0 per cent. Five days later the patient was given a normal diet without actual sugar, and the sugar in the urine estimated. The percentage was now 0.703 per cent., or 8.7 grammes per diem. There was no polyuria and no acetone bodies could be detected. The blood sugar showed 0.123 grammes per cent. A few days later the total output of sugar had been reduced to 6 grammes per diem, on a diet containing abundance of carbohydrates,

Case IV. Aged 30. Six months pregnant. Primipara. In November sugar was discovered in urine, and proved to be glucose. Three months later a small amount of glucose was found, and estimation by the new method showed 0.182 grammes per cent. The blood sugar content estimated at the same time was 0.104 gramme per cent. Whilst in hospital a month later there was still slight glycosuria. Abortion occurred. The liquor amnii showed a normal sugar content, viz., 0.054 gramme per cent., and sugar was absent from the urine.

Case V. Aged 30. Primipara. Glycosuria without hyperglycæmia known to exist in patient, and also in other members of the same family (so-called " renal diabetes "). (See curve No. 5. Chart 1.) The urine showed glucose to the extent of 1.2 per cent., or 16.7 grammes per diem. The blood sugar content was 0.109 gramme per cent. The glycosuria was not influenced by diet, and there were no signs and symptoms of diabetes mellitus. As far as could be ascertained pregnancy had no influence on the glycosuria.

Case VI. Primipara. Aged 29. Glycosuria discovered at sixth month. The sugar in the urine proved to be glucose, and was present to the extent of 0.8 gramme per cent. The blood sugar content was found to be 0.128 gramme per cent. No restriction of diet was advised except withdrawal of sweets and chocolates. Labour normal, and glycosuria disappeared immediately afterwards.

Case VII. Primipara. Glucose discovered in urine at sixth month. Examination of the blood sugar content showed 0.113 gramme per cent. Whilst in hospital on a diet free from actual sugar there was only slight glycosuria, which disappeared after labour.

Case VIII. Aged 39. Glycosuria discovered at sixth month. No signs and symptoms of true diabetes mellitus. The blood sugar content was 0.146 gramme per cent., and the urinary sugar content averaged 1.0 gramme per cent., and 12—16 grammes per diem. With the reduction of the carbohydrates in the diet the blood sugar remained practically the same, viz., 0.143 grammes per cent., and the glycosuria persisted. She was then given a more liberal diet with the restriction of actual sugar in the diet, and again the blood sugar remained unaltered, with slightly less glycosuria. Labour was normal, and the glycosuria disappeared, with no return after six years.

In all about forty cases of this type of glycosuria in pregnancy have been investigated, both from analysis of the blood and urine. In several the glucose tolerance test has been applied, with results described above. All cases of lactosuria have of course been excluded from this series. Summarizing the results, we find the following points are of value in the diagnosis of this type :—

(1) The condition is usually discovered about the sixth month of pregnancy.

(2) The glycosuria is of a mild type, often intermittent, and there is only a very slight hyperglycæmia.

(3) Restriction of carbohydrates in the diet produces little, if any, alteration in the blood sugar content, but may, on the other hand, increase the glycosuria.

(4) There are no signs and symptoms of true diabetes mellitus.

(5) The condition is non-progressive, and rapidly disappears after labour. Further, there is no recurrence even in the course of years, unless the patient again becomes pregnant.

VI. Summary and Conclusions.

The results recorded above show that much valuable information can be obtained by the application of newer methods of blood and urine analysis. This appears to be true, particularly when one type of glycosuria is subjected to a thorough investigation, as, for example, the glycosuria met with in pregnancy. The subject of intermittent or transient glycosuria is one of particular interest, and so far little, if any, attention has been paid to it. This may be due to the fact that, owing to its fleeting character, cases of this type are often overlooked. With the establishment of ante-natal clinics, the urines of patients attending such clinics are examined much more frequently, and, in consequence, glycosuria appears to be of fairly common occurrence. The results of our work demonstrate that when a reducing substance is present it is necessary to determine whether this is due to the presence of sugar or sugars. By means of the new method we describe above, this is now rendered possible, and, further, we are able to decide their nature and amount. Having ascertained this, we require to know whether there is an excess of sugar in the blood sufficient to account for the glycosuria. In cases of transient glycosuria one or two single blood sugar estimations may suffice for this purpose. The glucose tolerance test has been applied to a number of cases of intermittent glycosuria with interesting results. The close correspondence between the curves and those obtained in cases of pituitary lesions with evidence of hyperpituitarism are very striking. We would emphasize this similarity and suggest that it represents even more than mere coincidence. There would thus appear to be sufficient evidence to show that the increased activity of the pituitary body is sufficient to produce changes in carbohydrate metabolism leading to intermittent glycosuria. That this type of glycosuria does not usually appear until the sixth month, and rapidly disappears after labour is worthy of note. This period corresponds with the increased period of activity of the pituitary and the appearance of other signs and symptoms of hyperpituitarism. The condition represents a definite abnormality of pregnancy, and as such demands attention. The prognosis is of course favourable, yet one has always to be on guard and to make certain that the condition is not one of true diabetes mellitus. Fortunately, the latter condition is rarely met with in pregnancy, possibly due to the fact that women with true diabetes mellitus rarely become pregnant. This condition has always to be

excluded, and this is only possible by the application of the methods described above. The observations recorded above are of interest from many aspects, and, apart from any practical consideration, add a further link in the chain of evidence of the part played by the pituitary body in pregnancy.

We would, in conclusion, express our indebtedness to Sir Frederick Andrewes, F.R.S., in whose department we have had the opportunity to carry out these investigations. Most of the cases have been under the care of the staff of the Maternity Department, St. Bartholomew's Hospital, and to them we offer our most cordial thanks for permission to publish the records.

Conclusions.

(1) There are two types of glycosuria met with in pregnancy, viz., (*a*) intermittent or transitory glycosuria; (*b*) severe glycosuria and true diabetes mellitus.

(2) The intermittent or transitory glycosuria shows certain characteristic features, and may be diagnosed by means of blood and urinary analysis, and the glucose tolerance test.

(3) A new method of estimation of sugar in the urine in normal and abnormal amounts is described, and the value of this method in cases of glycosuria in pregnancy emphasized.

(4) By means of the glucose tolerance test it is possible to correlate the occurrence of intermittent glycosuria of pregnancy with hyper-activity of the pituitary body.

(5) The application of blood and urinary analysis to cases of glycosuria in pregnancy renders it possible to differentiate between the two types.

(6) The importance of differential diagnosis is emphasized by the fact that the treatment of the two conditions is totally different, the intermittent or transitory type requiring little, if any, dietetic treatment.

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