

d-GLUCOSE TOLERANCE IN HEALTH AND DISEASE *

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In previous communications¹ from this laboratory descriptions have been given of apparatus devised for the purpose of making continuous intravenous injections at accurately controlled rates. The present paper deals with the application of this apparatus and the principles of timed intravenous injection to a clinical study of glucose tolerance in normal human individuals and in a series of pathologic conditions. In order that the work may appear in its proper relationship to that of previous writers the more important contributions to the subject may be reviewed.

It has long been known that sugars administered by mouth in sufficient amounts cause melituria, but an attempt to learn the size of the dose which would accomplish this was first made by Worm Müller² in 1884. Two healthy men on a diet free from carbohydrate received weighed quantities of glucose, lactose and saccharose and it was found that 50 gm. of glucose, 50 gm. of saccharose or 100 gm. of lactose produced just a trace of reducing substance in the urine, while larger doses caused severe melituria.

Hofmeister³ in 1889 conducted a more elaborate investigation with dogs. The sugar was fed by mouth and it was found that the maximum dose that could be given and just fail to cause sugar to appear in the urine was very constant for the individual dog, although widely different for different dogs. This dose he called the "assimilation limit," a term that has since been widely employed. Hofmeister is also the author of the term "tolerance," as applied to sugars, which he used in the following connection:⁴

The diabetic of the milder type on a strictly regulated meat diet has a certain tolerance for sugars and starches, inasmuch as he only passes a saccharine urine when such substances are administered in excess of a definite limit.

* Submitted for publication Aug. 11, 1916.

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1. Woodyatt, Sansum and Wilder: *Jour. Am. Med. Assn.*, 1915, **65**, 2067.

2. Müller, Worm: *Arch. f. d. ges. Physiol.*, 1884, **34**, 576.

3. Hofmeister: *Arch. f. exper. Path. u. Pharmakol.*, 1889, **25**, 240.

4. *Der Diabetiker, leichter Form zeigt, bei streng gehandhabter Fleischkost, eine gewisse Toleranz für Zucker und für Amylaciën, insofern er nur bei Zufuhr derselben über eine gewisse Grenze hinaus Zuckerhaltigen Harn liefert.*

It does not appear that he drew a distinction between tolerance and assimilation limits, and since this time assimilation limits, as measured by Hofmeister's method, have been interpreted as tolerance limits.

In 1895 Linossier and Roque⁵ confirmed the observations of Worm Müller and Hofmeister, but proposed, as a truer measure of the assimilability (Nutzwert) of a sugar, the coefficient obtained by dividing the quantity of sugar excreted by the quantity given. The constants as found by these authors were variable, even for the same sugar; but in 1898 Gilbert and Carnot⁶ obtained a fairly constant ratio of excretion to administration by giving the sugar intravenously. Inconstant proportions occurred when the injected amounts were small, but with doses between 2.5 and 10 gm. per kilogram of body weight, the ratio of grams excreted and grams injected was always about 40 to 100.

The intravenous injection of sugar is an old procedure and it has frequently been observed when different sugars were given in this way that some were excreted more freely than others. On the basis of such observations conclusions have been drawn regarding the relative utilizabilities of the various sugars. But whether these conclusions are justified on the basis of the experiments made is open to question because of the excessive variations that occur in the results of different writers and even in those of the same observer. Pavy,⁷ for example, after injecting the same sugar (glucose) in doses of 0.25 gm. per kilogram of body weight in a series of rabbits, recovered in the urine of one as little as 3.1 per cent. and from another as much as 39.6 per cent. More consistent results with intravenous injections were obtained by McGuigan and Mathews,⁸ who gave dilute, 0.5 per cent., sugar solution in such a manner that 5 c.c. entered every five minutes. In some cases these injections were continued for as long as seventy-seven minutes and conclusions concerning the relative ease of oxidation of the sugars were drawn from their time of appearance in the urine. Previous to this Doyon and Dufourt⁹ had discovered that the *rate* of intravenous administration influenced the amount of sugar excreted and it would appear that the variation in the results obtained by the earlier writers was due to their failure to appreciate the importance of controlling the rate of injection. Doyon and Dufourt used dogs and gave to each 2 gm. of glucose per kilogram of body weight, "en un temps variable mais avec une vitesse toujours uniforme." They do not explain how they maintained such constant injection rates and simply report the

5. Linossier and Roque: Arch. de méd. expér. et d'anat. path., 1895, **7**, 228.

6. Gilbert and Carnot: Compt. rend. Soc. de biol., 1898, **50**, 330.

7. Pavy: Jour. Physiol., 1899, **24**, 479.

8. McGuigan and Mathews: Am. Jour. Physiol., 1907, **19**, 175.

9. Doyon and Dufourt: Jour. de physiol. expér., 1901, **3**, 703.

result of one typical experiment which disclosed that 98.64 per cent. of the sugar was retained if the duration of the injection was made eighty minutes, while only 85.62 per cent. remained in the body when the same quantity was injected in fifteen minutes.

In 1905 Blumenthal¹⁰ pointed out that the utilization of sugar by the tissues is expressible only in terms that apply to velocities, for example, as unit weight of sugar, per unit weight of tissue, per unit weight of time. The rate at which sugar is brought to the tissues must therefore be controlled if it is desired to measure its rate of utilization. This necessitates precise knowledge of the rate at which it enters the blood; but when a sugar is given by any method entailing absorption as a preliminary to its entrance into the blood, the latter rate is subject to uncontrollable variations. The most nearly exact method of determining sugar tolerance must therefore consist in direct intravenous injection. These principles he applied in a series of experiments and found (1) that glucose could be rapidly injected into rabbits in doses of about 0.85 gm. per kilogram of body weight without causing melituria, but if this dose was only slightly exceeded or if within a short time after the first dose a second injection was made, intense melituria would result; (2) that a dose of sugar could be selected which could be repeatedly injected at fifteen minute intervals for indefinite periods and always just fail to appear in the urine. From these observations Blumenthal concluded that the tissues are able to remove sugar from the blood at a rapid rate up to a certain limit, that is, until they have become "saturated," but no inference concerning utilization can be drawn from the size of the dose necessary to cause saturation or the rate at which this dose is absorbed. Such a dose represents simply a saturation limit (*Sättigungsgrenze*). On the other hand, that dose whose repeated injection at fifteen minute intervals just fails to produce melituria gives a measure of utilization, a utilization limit (*Ausnutzungsgrenze*). For glucose in rabbits this was found to be between 0.15 and 0.325 gm. per kilogram of body weight per fifteen minutes, that is, from 0.6 to 1.2 gm. per kilogram per hour.

In 1906 Comessatti¹¹ used the Blumenthal method and demonstrated that sugar assimilation was increased by exercise. During rest, doses of 0.2 gm. per kilogram per fifteen minutes led to melituria in two rabbits, while after exercise in a treadmill doses of 0.25 gm. given in the same manner caused no glycosuria. In 1909 Loeb and Staddler,¹² with the same method, obtained figures in resting rabbits which were lower than those reported by Blumenthal (0.09 and 0.16

10. Blumenthal: Beitr. z. chem. Phys. u. Path., 1905, **6**, 329.

11. Comessatti: Beitr. z. chem. Physiol. u. Path., 1906, **9**, 67.

12. Loeb and Staddler: Arch. f. exper. Path. u. Pharmakol., 1914, **77**, 326.

gm. per kilogram of body weight per fifteen minutes, that is 0.36 and 0.64 gm. per kilogram per hour).

There can be no doubt of the correctness of the principle stated by Blumenthal or of the insuperable difficulties which lie in the way of accurate measurement of the power of the tissues to utilize sugar when methods are used in which it is impossible to control the rate of entry of sugar into the blood. If the sugar is given by mouth, as in the Hofmeister procedure, the rate of absorption will depend on variable factors entirely beyond control, and when the subcutaneous or intraperitoneal routes are chosen the same difficulty is encountered. A tolerance limit obtained by such methods is at best only the resultant of absorption and utilization, and yet since the appearance of Blumenthal's article writers other than those quoted above have failed to appreciate the soundness of his views and continue in their adherence to absorption methods.

In clinical studies it is a common practice to give by mouth 100 gm. of d-glucose dissolved in 200 c.c. of water or lemonade and to speak of a low tolerance if this amount of sugar leads to melituria. If no melituria results when 150 or 200 gm. are fed, tolerance is considered high, but the test is by no means reliable, as many normal persons can tolerate any quantity of glucose which they can be made to take and retain, a fact which has been confirmed strikingly by the experiments of Taylor and Hutton.¹³ Nevertheless, such tests have been applied in a wide variety of clinical conditions, especially in diseases of the "glands of internal secretion," and have formed the basis of extensive theory. Other methods for measuring tolerance have received little attention from clinicians. Subcutaneous injections of sugar have been made (Voit,¹⁴ Achard¹⁵ and others), but the pain and danger of infections which they involve have limited their general use. Intravenous sugar injections, while employed for therapeutic purposes (Kausch¹⁶ and others) have not been used in clinical tolerance studies and the attention of clinicians seems not to have been directed to the contribution of Blumenthal.

But while Blumenthal's statement of the principles governing accurate measurement of sugar tolerance is sound and demands recognition, his technical application of these principles is capable of improvement. This is particularly true if the method is to be applied in clinical investigation. Blumenthal's method involves repeated injections at fifteen minute intervals, and the technical difficulties of performing these on time, and with assurance that no leakage occurs, are

13. Taylor and Hutton: *Jour. Biol. Chem.*, 1916, **25**, 173.

14. Voit, F.: *Deutsch. Arch. f. klin. Med.*, 1897, **58**, 523.

15. Achard, cited by Lepine: *Le diabète sucré*, Paris, 1909, p. 234.

16. Kausch: *Deutsch. med. Wchnschr.*, 1911, **37**, 8.

very material, particularly in patients with small superficial veins. The Blumenthal procedure is furthermore insufficient to accomplish that which Blumenthal's principles demand, namely, a perfect control of the rate of administration. His injections, repeated every fifteen minutes, are not continued at a uniform rate over the fifteen minutes, but are given rapidly at the beginning of each period. Under these conditions it is clear that in the first part of each fifteen minute period, that is, during the time actually occupied by the injection, the concentration of sugar in the blood must rise as a wave and in the interval between the injections the concentration must fall. If now the injection is made more rapidly in one case than another, the crest of the wave produced will be higher, and such a wave may overflow the kidney threshold and result in melituria, even though the tolerance for the fifteen minute period is by no means exceeded. Under these conditions it is incorrect to assume that a melituria indicates that the rate of utilization for the period has been overstepped. That this objection to Blumenthal's procedure is sound is shown by figures for the tolerance of rabbits published by Blumenthal,¹⁰ by Comessatti¹¹ and by Loeb and Staddler,¹² all of whom used the same method. One rabbit of Blumenthal's showed a tolerance of 0.325 gm. per kilogram of body weight per fifteen minute period, while one of Loeb and Staddler's was as low as 0.09 gm. per kilogram per fifteen minutes; and Blumenthal's own results ranged, as stated above, from 0.15 to 0.325 gm. per kilogram per fifteen minutes, a variation of over 100 per cent. It is probable that the higher figures obtained by these authors were more nearly correct than the lower ones and that the latter occurred when the injections were made too rapidly.

In order to avoid periodic waves of sugar concentration and to give no opportunity for melituria to occur until the rate of administration at all times surpasses that of utilization, it is clearly advisable to discard intermittent or discontinuous injections in favor of continuous administration at constant rates. The latter procedure was adopted in the present study, and for the purpose of giving continuous injections use was made of the apparatus referred to above. This apparatus consists of a small pump which is driven by an electric motor. The stroke of the pump may be made very short and the number of strokes per minute raised to forty or sixty, so that the stream pumped is practically continuous. Such pulsations as occur are furthermore almost obliterated by the elasticity of the rubber tubing that connects the pump with the needle in the patient's vein. The rates of injection are easily controlled and accurately regulated by means of a rheostat.

By the use of this instrument it is a simple matter to find that rate of injection which just equals the rate of utilization or the tolerance limit.

The limits for d-glucose of different dogs and rabbits tested in this way were nearly constant and approximated Blumenthal's higher figures, as might be anticipated. Reports of these animal experiments will appear in other communications, as the present paper is limited to the results obtained in human subjects.

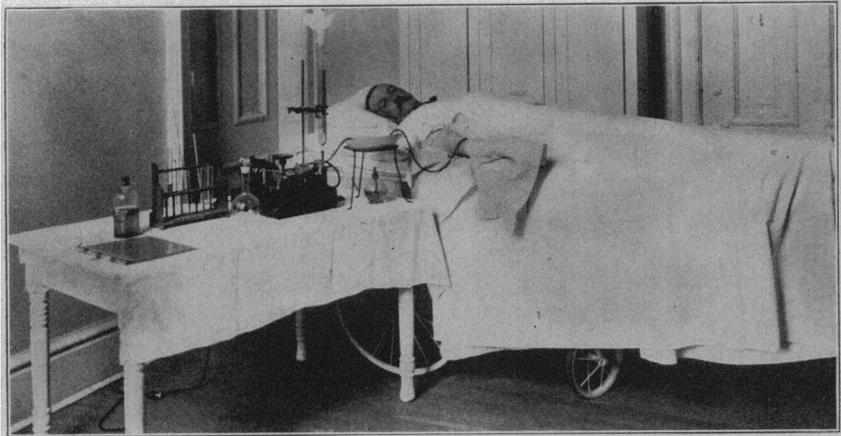
PROCEDURE IN TESTING THE d-GLUCOSE TOLERANCE OF MAN

It is to be anticipated that the intravenous tolerance limits for glucose will vary with a number of physiologic factors capable of influencing the basal metabolism. If the tolerance is expressed as grams of glucose per unit of body weight per unit of time, then sex, age, the proportion of the different types of tissue entering the body structure, the relative proportion of fat, glycogen and protein in the respective tissues, the ratio of surface to mass, the state of the activity of the muscles, etc., all require due consideration. In the present study it was found that in health both men and women showed the same tolerance. The influence of age was minimized by confining the work to adults between the ages of 20 and 45. (One child of 14 is reported.) The subjects chosen were with one exception in an average state of nutrition. All had been on a general mixed diet for several days before examination and none had partaken excessively of carbohydrates. On the day of the test no food was given by mouth and the sugar injection was commenced in the afternoon between 2 and 4 p. m. Uniform conditions of rest were secured by keeping the subjects in bed on the day of the test, and finally, in order to minimize possible delays in the excretion of glucose, once the tolerance limit had been exceeded, as well as to study the effects of different rates of glucose injection on the diuresis, water was given by mouth in amounts equivalent to the amount of fluid necessary to administer during the injection, in such a way that the subject would receive during each hour of the foreperiod an amount of water equivalent to the quantity which he was to receive by vein in each hour of the test.

Material.—The d-glucose employed in earlier experiments was a preparation of Merck labeled "purissimum." Later a high grade granular commercial dextrose (Argo corn sugar) was purified in the laboratory by decoloration with animal charcoal and repeated recrystallization from alcohol. The final product was dissolved in freshly distilled water (prepared with such precautions as are employed for salvarsan administration) to make from 16 to 20 per cent. solutions. (The molecular weight of glucose being 180, the gram molecular solution is 18 per cent.) Such a solution is sufficiently hypertonic to avoid hemolysis and has been found for other reasons to be the best standard solution to employ for the present purposes. In earlier experiments

solutions of greater strength were employed, with a view to keeping the volume injected small, but the opportunity for slight variations in the injection rate was thereby correspondingly increased and on this account the 18 per cent. solutions were adopted. The solutions showed only pale straw color when observed in flasks of two liter volume, smaller volumes appearing colorless. The solutions were divided in one and two liter flasks which were sterilized in the autoclave. The titer of each was determined by a polariscope directly before injection.

In the entire course of this work, in which the solutions were injected at rates slightly above and below the tolerance limit, no chills, shock or other general reactions were encountered. In two cases thrombosis of the vein used for the injection resulted. In one of these



Illustrating apparatus and method of making the glucose injection.

the thrombus was limited to an inch of the vein, in the other it extended to the axilla, but in neither did it result in a bad effect. It is probable that the thrombus formation in the most extensive of these cases was favored by trauma, as the subject of the test refereed a football game on the day after his injection.

Technic of Injection.—As previously stated, use is made of the injecting machine developed in this laboratory and described elsewhere. A buret to serve as a reservoir, together with the necessary rubber tubing, are sterilized by autoclave. The parts of the pump which come into contact with the fluid are removed and boiled. The apparatus is then assembled in the manner illustrated, the glucose solution is poured into the buret and all air expelled from the tube and pump.

The initial rate for injection is purposely chosen below what is thought to be the velocity of assimilation; for example, if the subject is apparently normal, it is assumed that a rate of 0.7 gm. per kilogram of body weight per hour will be tolerated, and this rate is given. If the patient weighs 75 kg. and the glucose solution, as determined by polariscope, is 20 per cent., this would mean an injection of $0.7 \times 75 \times 5$, or 262.5 c.c. of a 20 per cent. solution per hour, or 4.37 c.c. per minute. The machine is set to deliver the solution at this rate, the needle is introduced into a suitable vein and the injection begins.

This initial injection rate must be maintained long enough to permit a thorough saturation of the tissues before the urine is collected and tested for sugar. This requires from twenty to thirty minutes, as has been found by experiment. If the injection rate only slightly exceeds the rate of utilization, glycosuria will occur within this time; if it does not, no glycosuria will occur even after several hours of continuous injection. This latter statement is based on experiments with dogs. For this reason the first collection of urine is made about thirty minutes after the beginning of the experiment. One cubic centimeter of urine is added to 5 c.c. of heated Haines' solution, the mixture boiled for ten seconds and cooled and the absence of reduction is taken to indicate that the tolerance of the patient lies above the rate of injection. The injection is then accelerated and continued for thirty minutes at this higher rate, for example, at 0.8 gm. per kilogram per hour in the case under consideration. The urine is then tested again and by gradually stepping up the rate of injection, 0.1 gm. per kilogram per hour at a time, that rate can be found which first causes glycosuria and the rate just preceding this is accepted as the tolerance limit.

RESULTS

d-Glucose Tolerance in Health.—Four young adults, two men and two women, were chosen for the tests of normal glucose tolerance. All of them had been working in the medical college or the hospital and were known to be in good health. On the day preceding the test they were put to bed and subjected to the experimental conditions outlined above. The results in all these cases were the same. Glucose injected at the rate of 0.8 gm. per kilogram of body weight per hour caused no glycosuria, but in each case sugar appeared in the urine when the injection rate was 0.9 gm. per kilogram per hour. From this it would appear that the tolerance limit for d-glucose of normal men and women is practically constant and that it equals a rate of approximately 0.85 gm. per kilogram of body weight per hour of time. For a 75 kg. man such an injection would represent the administration of 63.75 gm. per hour.

Tolerance in Diseases of the Pancreas.—Three patients, one with organic disease of the pancreas and the other two with suspected mild diabetes mellitus, were tested for their glucose tolerance. In both a low limit was demonstrable. The first suffered from a chronic interstitial pancreatitis, a diagnosis which was confirmed by subsequent operation. His tolerance limit lay below 0.7 gm. per kilogram of body weight per hour. The second patient had recently shown a trace of sugar in the urine at a life insurance examination, but had been sugar free since then. His tolerance lay below 0.5 gm. per kilogram per hour. The third was similar to the second, with a tolerance of 0.4 gm. per kilogram per hour; but since the state of his nutrition and other factors besides the pancreatic disease were not strictly comparable with the controls, some reserve is expressed as to the significance of this result.

Tolerance in Diseases of the Thyroid.—Five patients with exophthalmic goiter, two men and three women, have been tested for their glucose assimilation and in all the tolerance limits were reduced. Two of these patients had severe general symptoms and these cases showed glycosuria when glucose was administered at the rate of 0.5 gm. per kilogram per hour. Two milder cases gave a limit exceeded by the administration of 0.6 gm. per kilogram per hour, and the fifth, a still milder case, had a tolerance between 0.6 and 0.7 gm. per kilogram per hour. It would appear, therefore, that a depressed glucose tolerance is a fairly constant accompaniment of exophthalmic goiter. Such results are in harmony with the observation of alimentary glycosuria in exophthalmic goiter made by Kraus and Ludwig,¹⁷ Chvostek,¹⁸ Falta¹⁹ and many others and with the glycosurias which may be produced in animals and normal persons by feeding thyroid tablets (Ewald,²⁰ Dale,²¹ Denning,²² von Noorden²³ and others). On the other hand, a typical case of myxedema was found to have a normal tolerance, by the intravenous method, a result which is not in agreement with the observations of those who use the alimentary tests and find high assimilation limits in this disease, suggesting that a delay in the rate of absorption is accountable for their findings.

Tolerance in Disease of the Hypophysis.—Two cases of acromegaly have been studied, one case of suspected gigantism and two with dys-

17. Kraus and Ludwig: Wien. klin. Wchnschr., 1891, **4**, 898.

18. Chvostek: Wien. klin. Wchnschr., 1892, **5**, 17.

19. Falta: Die Erkrankungen der Blutdrüsen, Berlin, 1913, p. 65.

20. Ewald: Die Erkrankungen der Schilddrüsen, Myxödem und Kretinismus, Ed. 2, Leipzig, 1909.

21. Dale: Brit. Jour. Dermat., 1894, **6**, 177.

22. Denning: München. med. Wchnschr., 1895, **42**, 389.

23. Von Noorden: Ueber den Einfluss der Schilddrüsenbehandlung auf den Kohlehydratstoffwechsel, Berl. klin. Wchnschr., 1897, **34**, 518.

pituitarism, showing the Fröhlich syndrome. The glucose tolerance of all these cases was found to lie close to the normal limits. Three showed a bare trace of sugar in the urine after the injection of 0.8 gm. per kilogram per hour and all gave a definite glycosuria after receiving 0.9 gm. per kilogram per hour. These results are in disagreement with those obtained when the oral administration is used (Cushing,²⁴ Bondi,²⁵ Falta¹⁹) and suggest, as in the case of myxedema, that the increased tolerance of such patients for sugar given by mouth is due rather to a retarded absorption from the bowel than to any anomaly of the intermediate metabolism, as certain writers have assumed.

Tolerance in Cirrhosis of the Liver.—A normal d-glucose tolerance limit was found in a case of alcoholic cirrhosis.

SUMMARY

Adopting the premise previously suggested by Doyon and Dufourt, and notably Blumenthal, that glucose tolerance must be dealt with as a velocity, that is, in terms of the number of grams of glucose which may be brought into the tissue per unit of body weight per unit of time without causing an abnormal overflow of glucose into the urine, we injected from 16 to 20 per cent. solutions of pure d-glucose intravenously at different uniform rates by means of the motor driven quantitative injection pump, which has been described in other reports from this laboratory. Observations have been made on rabbits, dogs, and normal resting men and women of average size, weight and nutrition. These experiments indicate that glycosuria appears when the rate of injection lies above 0.8 gm. and below 0.9 gm. per kilogram of body weight per hour.

It is realized that variations from these limits may be ascribed, *a priori*, to any one of several factors, namely, (1) variation in the ability of the colloids of the body at large, including those of the kidney, to hold glucose in a state of adsorption or its equivalent (variations in the threshold for glucose); (2) the variation in the rate at which glucose may be entering the cells from endogenous sources, notably glycogen and protein, but especially the former, since endogenous supplies of glucose to the cells must be regarded as superadding themselves to the glucose supplied by injection; (3) to variation in the rate at which glucose can be utilized within the cell, the utilization in this instance being taken to imply the sum of those processes by which glucose may undergo a chemical change into some substance other than glucose.

The purpose of the present report is to record objectively experi-

24. Cushing: The Pituitary Body and Its Disorders, Philadelphia, 1911.

25. Bondi: Arch. f. exper. Path. u. Pharmakol., 1910, **63**, 347.

mental findings without entering into detailed considerations of the physiologic factors which have been concerned.

Observations have been made of the intravenous glucose tolerance limit in the following clinical conditions: chronic interstitial pancreatitis, one case; very mild diabetes, two cases; thyroid disease, six cases, five representing different grades of symptoms of hyperthyroidism and one a typical instance of myxedema; hypophysis disease, five cases giving clinical pictures which would be designated as such; gigantism (?), one case; Frölich syndrome, two cases (one with diabetes insipidus and one without); acromegaly two cases; and cirrhosis of the liver, one case.

Many questions which arise as to the variations of the intravenous glucose tolerance as the result of variations in the state of nutrition, the amount of stored glycogen, the character of the previous diet, the water and salt balance of the body, etc., will be further discussed in other reports from this laboratory.

CONCLUSIONS

The following conclusions would appear to be justified:

1. Normal resting adult men and women of average size, weight and nutrition begin to excrete abnormal quantities of glucose in the urine when the injection rate into the vein is above 0.8 gm. and below 0.9 gm. per kilogram of body weight per hour.

2. Cases of nondiabetic pancreas disease may evince a lowered tolerance for glucose when measured by this method even when administration of glucose by the alimentary route gives no definite evidence of such diminution. The same is true of very mild cases of diabetes mellitus. In these cases it may be fancied that the lowered tolerance arises from a diminished utilization.

3. Cases with increased thyroid function show a uniformly diminished intravenous glucose tolerance. In such cases it is suspected that this effect may be ascribed to an increased glycogenolysis, which is tantamount to an endogenous glucose supply to the cells superimposed on the intravenous injection, or, what amounts virtually to the same thing, a decreased ability on the part of the body to build up glycogen, since increased glycogenolysis implies the disbalance between the synthesis and catalysis of glycogen in favor of the latter. On the other hand, a case with decreased thyroid function (myxedema) showed no increased glucose tolerance, but appeared to have a normal tolerance, excreting sugar promptly when this was injected at a rate faster than 0.9 gm. per kilogram of body weight per hour.

4. In none of the cases of hypophysis disease has there been any increase of the glucose tolerance above the normal limits, but on the

contrary, a tendency toward decrease, which would seem to imply that increases of glucose tolerance in such cases, following alimentary administration of glucose, are due to delays in absorption rate rather than to changes in the intermediate metabolism.

5. The d-glucose tolerance of an advanced case of alcoholic cirrhosis of the liver was found to be normal.

6. The determination of glucose tolerance by the method described is a practical clinical procedure, more accurate than those methods which depend on absorption from a local site as a preliminary to the entrance of glucose into the blood and giving more constant results than have been obtained by any other technic involving intravenous injections.

PROTOCOLS AND CASE HISTORIES

The protocols of these experiments, the case records and a composite chart of the results (Fig. 2) are appended.

CASE 1.—B. T., a healthy woman, aged 25, weight 42.7 kg., rested in bed on the day of the test.

TABLE 1.—GLUCOSE SOLUTION, 18 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	3.16	30	0		
0.9	3.56	30	++	0.4	0.96
Subsequent loss.....					0.75+
Total glycosuria.....					1.71+

Tolerance lies between 0.8 and 0.9 gm. per kilogram per hour.

CASE 2.—P. G., a healthy woman, aged 21, weight 60 kg., rested in bed on the day of the test.

TABLE 2.—GLUCOSE SOLUTION, 18 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	4.45	38	Trace*	0.16	0.77
0.9	5	20	+	0.33	1.45
Subsequent loss.....					?
Total glycosuria.....					2.22+

* During the last three minutes of injection at the 0.8 gm. rate the pump accidentally accelerated. This accounts for the trace of sugar found in the urine. The tolerance, therefore, probably lies above 0.8 but below 0.9 gm. per kilogram per hour.

CASE 3.—W. S., a healthy man, aged 35, weight 73.2 kg., rested on the day of the test.

TABLE 3.—GLUCOSE SOLUTION, 40.91 PER CENT.

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscopes	Total Gm.
0.85	2.38	32	Trace	0.23	0.15
0.9	2.68	30	+	0.86	1.12
Subsequent loss.....					0.76
Total glycosuria.....					2.03

Tolerance lies very close to 0.85 gm. per kilogram per hour.

CASE 4.—J. V., a healthy man, aged 25, weight 75.45 kg., rested in bed on the day of the test.

TABLE 4.—GLUCOSE SOLUTION, 19.75 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscopes	Total Gm.
0.8	5.1	30	0		
0.9	5.73	30	+	0.64	1.66
Subsequent loss.....					1.02
Total glycosuria.....					2.68

Tolerance lies between 0.8 and 0.9 gm. per kilogram of body weight per hour.

CASE 5.—Diagnosis, chronic pancreatitis. J. W., aged 45, was admitted to the service of Dr. J. B. Herrick at the Presbyterian Hospital on Nov. 6, 1915, with complaints of jaundice and intense itching. He gave a history of syphilis in 1888, for which he received treatment, herpes zoster in 1911, and in 1912 jaundice without pain, fever or chills, which lasted two weeks. In August, 1915, he again became jaundiced, this time with cold sweats, a chill and fever. There was no pain and the fever disappeared, but the jaundice continued. The patient lost in weight from 138 to 124 pounds.

Examination disclosed an intense icterus. The gallbladder was barely palpable, but not tender. The temperature was recorded as 100.6 on the day of admission, but remained normal for the next two weeks. The urine showed a large amount of bile, but no albumin or sugar. The stools were mushy, clay colored, gave a strongly positive Weber test for blood, and contained fat in abundance and some starch. The stomach contents after Ewald's test breakfasts showed no blood and were of normal acidities. Duodenal contents, aspirated by means of an Einhorn tube, contained blood and ferments, but no bile.

A diagnosis of organic disease of the head of the pancreas was made, which was confirmed by operation on Dec. 6, 1915. The patient showed marked

improvement following operation, gaining 12 pounds in weight. A second operation was made on Jan. 22, 1916, and the mass in the head of the pancreas was found to be smaller. Probable diagnosis was made of ulcer of the duodenum with secondary chronic pancreatitis and obstructive jaundice.

An intravenous glucose tolerance test on this patient made Nov. 22, 1915, gave the results shown in Table 5. The weight of patient was 54.3 kg.

TABLE 5.—GLUCOSE SOLUTION, 20.25 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.2	0.89	30	0		
0.5	2.24	70	0		
0.7	3.13	32	Trace	0.1	0.25
0.9	4.02	35	++	0.66	2.00

The threshold of tolerance lies at or very close to 0.7 gm. per kilogram of bodyweight per hour, which is slightly below normal.

CASE 6.—Diagnosis, mild diabetes. R. D., a physician, aged 33, showed a trace of sugar in the urine in a recent examination. In one twenty-four hour specimen this had amounted to 0.2 per cent. He had suffered from an attack of appendicitis and underwent an operation in 1911. Two sisters had died of tuberculosis and one brother was obese, weighing 225 pounds.

The patient was a tall, muscular man. The tonsils were small and cryptic. There were a few fillings in the teeth and the gums were retracted at the roots of the left upper molars. The thyroid was not enlarged. A urinalysis was negative.

An intravenous glucose tolerance test was made and resulted as shown in Table 6. The weight of the patient was 83.2 kg.

TABLE 6.—GLUCOSE SOLUTION, 21.94 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	3.16	30	++	0.69	0.53
Subsequent loss.....					1.19+
Total glycosuria.....					1.72+

The threshold of tolerance lies well below 0.5 gm. per kilogram of bodyweight per hour. The urine was only collected for one hour after the injection stopped.

CASE 7.—Diagnosis, mild diabetes. W. K., aged 49, was admitted to the service of Dr. Billings at the Presbyterian Hospital on June 23, 1916. His complaints were aching pains in the right thigh and the suspicion of diabetes.

He gave a history of excellent health up to 1910, when sugar was found in his urine. At that time he was losing weight, had excessive thirst and hunger and polyuria. He was placed on a restricted diet and was soon apparently normal. During the last year he has had rather frequent urination and for the

last three months has suffered from pains in the right thigh and a feeling of weakness in the legs on ascending stairs.

Examination showed a well-nourished man of average height. The teeth were badly discolored and decayed and the Roentgen ray revealed a chronic abscess at the root of one molar. The gums were retracted. A slight systolic murmur was audible at the apex. In all other respects the examination was negative.

Urinalysis of twenty-four-hour specimens showed 1,500 to 1,800 c.c., with specific gravities of 1.010 and 1.013. No reduction of Haines' solution was obtained and there was no evidence of diacetic acid or acetone.

An intravenous d-glucose tolerance test was made on June 26 with results as shown in Table 7. The weight of the patient was 75.4 kg.

TABLE 7.—GLUCOSE SOLUTION, 16.4 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.3	2.29	80	0		
0.5	3.06	80	+	0.5	2.225

The threshold of tolerance lies between 0.3 and 0.5 gm. per kilogram of body weight per hour.

CASE 8.—Diagnosis, hyperthyroidism. M. R., a girl, aged 19, complained on admission of goiter, nervousness, dyspnea, palpitation, and edema of the feet. The trouble began as nervousness eighteen months ago. Six months later the thyroid enlarged and the eyes became prominent, and before admission the right lower jaw had often been swollen and painful. Menstruation had been normal.

On examination the patient presented a marked exophthalmos, a fairly large goiter of uniform, firm consistence over which a double murmur could be auscultated, a fine tremor of the tongue and fingers and a pulse ranging from 120 to 140. Adenoids and tonsils were hypertrophic. In the tonsils were deep crypts which contained pus. There were several broken-down teeth at the roots of which abscesses were demonstrable.

Blood counts revealed a moderate anemia and a mononucleosis of from 40 to 46 per cent. Urinary examinations showed an albuminuria of less than 0.1 per cent., a few casts, but no erythrocytes and no sugar.

An intravenous glucose tolerance test was made on this patient with results as shown in Table 8. The weight of the patient was 70 kg.

TABLE 8.—GLUCOSE SOLUTION, 21.8 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.6	3.21	69	+	0.267	1.92
Subsequent loss.....					2.12
Total glycosuria.....					4.04

The threshold of tolerance lies below 0.6 gm. per kilogram of body weight per hour.

CASE 9.—Diagnosis, hyperthyroidism. E. L., a woman, aged 32, was admitted to the service of Dr. B. W. Sippy at the Presbyterian Hospital on Jan. 16, 1916, with complaints of goiter, bulging eyes, palpitating heart, nervousness and weakness. The family history was remarkable in that all the female members of the mother's side, including the grandmother, had large goiters. None had suffered from symptoms of exophthalmic goiter.

The patient had no goiter until the onset of the present trouble, but was always nervous. She had measles at 9, and had suffered from catarrh of the nose and throat from her eighteenth year. At 25 came an acute attack of tonsillitis. Her present illness commenced two months before admission with painful swelling of the thyroid. The pain disappeared in a week, but the swelling persisted; exophthalmos, palpitation and tremors appeared; she grew very nervous and lost weight rapidly.

Examination revealed a young woman in a fair state of nutrition. Exophthalmos was extreme and von Graefe, Möbius and Stellwag signs were present. The goiter was of medium size and of a uniformly firm consistence. A systolic bruit was heard over it. Submanubrial dulness was 7 cm. wide (thymus?). The heart was normal in size, the pulse 112 and regular. The leukocyte count was 8,500 with 45 per cent. mononuclears. The urine was normal on repeated examination.

An intravenous sugar tolerance test was made with results as shown in Table 9. The weight of the patient was 62.3 kg.

TABLE 9.—GLUCOSE SOLUTION, 17.6 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	2.95	45	0		
0.6	3.54	46	+	0.5	3.23
Subsequent loss.....					3.41
Total glycosuria.....					6.64

Tolerance lies between 0.5 and 0.6 gm. per kilogram per hour.

CASE 10.—Diagnosis, hyperthyroidism. A. S., a man, aged 41, was admitted to the service of Dr. C. B. Davis of the Presbyterian Hospital on Aug. 16, 1915, with complaints of goiter, prominence of the eyes, palpitation, nervousness and loss of weight. His disease began in 1903 with thyroid swelling and nervousness. Exophthalmos occurred in 1904 and until 1905 he was very ill. Then followed a period of improvement, lasting until 1913, but after 1913 he suffered from extreme nervousness and palpitation and has lost twenty-five pounds in weight. Sugar has been found in the urine on several occasions.

When examined the patient presented the typical appearance of exophthalmic goiter. He was very thin, very weak and highly nervous. Exophthalmos was extreme, and von Graefe, Möbius and Stellwag signs were positive. The tumor of the neck was large and of a uniformly hard consistence. Over it was heard a systolic, diastolic bruit. The veins of the neck were distended. The heart was enlarged to the left, the apex lying in the fourth space, 11 cm. to the left of the midsternal line. A soft systolic murmur occurred over the apex; a louder systolic murmur was heard at the base and this was transmitted to the neck. The pulse rate was 104. A blood count on the day of admission gave 6,150 whites, with a mononuclear percentage of 29. The urine was normal.

An alimentary test for tolerance, 50 gm. of glucose, was made on Aug. 17, 1915, and 1.6 per cent. glycosuria obtained. Seventeen gm. of sugar were excreted and traces of sugar appeared in the urine for several days.

On Aug. 24, 1915, the upper poles of the thyroid were ligated.

The intravenous tolerance test was made on Feb. 3, 1916, with results as shown in Table 10. The weight of the patient was 53.2 kg.

TABLE 10.—GLUCOSE SOLUTION, 17.67 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	2.51	31	0		
0.6	3.01	33	++	0.48	1.78
Subsequent loss.....					13.39
Total glycosuria.....					15.12

Tolerance lies between 0.5 and 0.6 gm. per kilogram per hour.

CASE 11.—Diagnosis, hyperthyroidism, myositis. J. S., aged 52, was admitted to the Presbyterian Hospital on the service of Dr. Frank Billings with complaints of soreness and weakness of the muscles. The trouble started acutely in May, 1915, with a fever of 104, headache, great muscle soreness and severe weakness. He lost 50 pounds in weight.

Examination revealed extensive muscular atrophies and contractures and tenderness of many tendons. There were no deformities of the joints. In addition, the thyroid was moderately enlarged and there was a fine tremor of the hands and tongue. Ocular symptoms were absent. There was also a diffuse dilatation of the heart and a loud mitral systolic murmur could be heard at the apex. Both great toe nails were ingrown and infected, the tonsils appeared diseased and the teeth were in bad condition. Blood counts gave 3,700,000 erythrocytes, 65 per cent. hemoglobin and 6,300 leukocytes, of which 42 per cent. were mononuclears. Urinalyses were normal. The pulse was fast, ranging from 90 to 120. The temperature proved irregular, occasionally mounting to 101 or 102 F.

TABLE 11.—GLUCOSE SOLUTION, 22.36 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	1.75	44	0		
0.6	2.1	41	0		
0.7	2.45	46	+	0.21	0.34
Subsequent loss.....					1.94
Total glycosuria.....					1.97

The threshold of tolerance lies below 0.7 gm. per kilogram of body weight per hour.

From October 6 to October 12 the patient received 9 gm. of thyroid extract daily and within forty-eight hours the thyroid became more prominent and the nervousness and tremors increased. The thyroid extract was discontinued. The tonsils were removed and the teeth attended to.

An oral sugar tolerance test was made on October 22. One hundred gm. of glucose given on the fasting stomach produced no glycosuria.

An intravenous glucose tolerance test was made on November 29, and resulted as shown in Table 11. The weight of the patient was 47 kg.

CASE 12.—Diagnosis, hyperthyroidism. A. W., a woman, aged 30, suffered from goiter, dyspnea, and palpitation for four years. An attack of tonsillitis with fever immediately preceded the first appearance of these symptoms. Another severe attack of tonsillitis three years later was followed at once by nervousness, tachycardia and loss of weight.

The patient presented a moderate enlargement of the isthmus of the thyroid and a von Graefe. The pulse ranged from 90 to 110. Exophthalmos and tremor were absent. The tonsils were atrophic, but showed in their scarred fibrous surfaces and adhesion to the pillars definite evidence of infection. A moderate anemia was found. The leukocyte count was 8,000 and the mononucleosis 45 per cent. The urine was normal.

An intravenous tolerance test resulted as shown in Table 13. The weight of the patient was 49.54 kg.

TABLE 12.—GLUCOSE SOLUTION, 40.59 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	1.02	60	0		
0.7	1.42	30	++	0.43	0.75
Subsequent loss.....					0.95
Total glycosuria.....					1.70

The threshold of tolerance lies well below 0.7 gm., but above 0.5 gm. per kilogram of body weight per hour.

CASE 13.—Diagnosis, myxedema. Mrs. A. L., aged 64, was admitted to the Presbyterian Hospital on Aug. 15, 1916, with complaints of thickened skin, stiffness of the hands and feet and mental dulness. The family history was negative except for one daughter, who developed an exophthalmic goiter when 40 years of age. The patient has had twelve healthy children, and gives no history of syphilis. She was always well up to her 61st year, when symptoms of the present trouble appeared.

The diagnosis of myxedema was made at the Central Free Dispensary in 1913, and for several months the patient received thyroid extract, but for the last two years she has been away and has had no treatment.

Examination showed the patient to be an elderly Jewish woman who appeared uninterested in her surroundings and mentally dull. The skin was dry and stretched tight over the arms and legs. It had a board-like or bacony feel, especially over the face and arms. There were no axillary hairs, the eyebrows were scanty, and the hair of the scalp was thin and very dry. The pulse was slow, 60 to 70, and the respiration was shallow. The thyroid was not palpable. The lungs had normal resonance, and the breath sounds were clear, except for occasional moist râles at the base. The abdomen was negative.

The temperature was normal. The blood count gave 3,780,000 red cells, 8,100 white and a hemoglobin percentage of 75. The urine was normal in amount and free from albumin or sugar.

The intravenous tolerance test gave results as shown in Table 12. The weight of the patient was 70 kg.

TABLE 13.—GLUCOSE SOLUTION, 18.21 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	5.13	48	0		
1	6.41	25	++	0.97	2.14

Subsequent loss not determined.

The second injection rate is well above the patient's tolerance, which undoubtedly lies between 0.8 and 0.9, the normal limits.

CASE 14.—Diagnosis, acromegaly. W. F., aged 40, was admitted to the service of Dr. Dean Lewis of the Presbyterian Hospital in 1913, with complaints of blindness and an increase in the growth of the hands, feet and head. His attention was first attracted to his condition in 1905, when he found that his hats were small. A year later his feet outgrew his shoes. In 1907 he was troubled with blurred vision and photophobia. His color sense was lost and finally in 1909 he became totally blind. His weight remained nearly stationary, about 225 pounds, during the entire course of the disease.

Examination revealed conditions typical of acromegaly, hypertrophied bones of the calvarium and jaw, huge hands and enormous feet. The skin was thick and the hair coarse and dry. An examination of the eyes revealed a complete amblyopia, due to a bilateral optic atrophy. There was also a marked horizontal nystagmus to the left. A Roentgen-ray plate of the skull showed an enormous sella.

The patient remained in the hospital until May, 1915. During this interval the temperature was practically normal and the pulse varied between 80 and 100. Twenty-four-hour urinary volumes were rather high, at times over 3,000 c.c. The urine often contained small amounts of albumin and a few casts, but never any sugar.

TABLE 14.—GLUCOSE SOLUTION, 19.43 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	6.91	35	Trace	0.16	0.03
1	8.64	30	++	0.8	0.29
Subsequent loss.....					2.01
Total glycosuria.....					2.33

The threshold of tolerance lies very close to 0.8 gm. per kilogram of body weight per hour.

An oral glucose tolerance test was made on March 15, 1915. On giving 125 c.c. of glucose at 7 a. m., no glycosuria resulted.

The patient returned to the hospital in November. His condition had remained practically stationary. An intravenous tolerance test was made and resulted as shown in Table 14. The weight of the patient was 103.6 kg.

CASE 15.—Diagnosis, acromegaly. C. H., man aged 38 was admitted to the service of Dr. Dean Lewis of the Presbyterian Hospital on Jan. 4, 1916, with complaints of diminishing vision, increasing size, headache, weakness and loss of sexual desire. The patient was an adopted child and could tell nothing about his parents. At 7 years of age he had a severe illness the nature of which he ignores, and in 1906 suffered from a light attack of malaria. He was married in 1915 and had no children. The present illness seems to have begun in 1913, when he began to increase in size and weight. He is now 6 feet 1 inch tall and weighs 210 pounds. His former weight was 185. His feet and hands are bigger and he is obliged to buy $7\frac{1}{4}$ inch size of hats instead of his former size $6\frac{7}{8}$. Visual disturbance first occurred in February, 1915.

On examination the findings were those typical of acromegaly and roentgenograms of the hypophysial region revealed a sella very much enlarged. The leukocyte count was 7,600, with 58 per cent. mononuclears. The urine was normal on repeated examination. Two hundred gm. of glucose were given by mouth without producing glycosuria.

An intravenous tolerance test resulted as shown in Table 15. The weight of the patient was 95.5 kg.

TABLE 15.—GLUCOSE SOLUTION, 19.01 PER CENT.

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscopes	Total Gm.
0.7	5.85	30	0		
0.9	7.52	30	++	3.18	2.7
Subsequent loss.....					7.98
Total glycosuria.....					10.68

Tolerance lies below 0.9 gm., but above 0.7 gm. per kilogram per hour.

CASE 16.—Diagnosis, hypophysial disease (Frölich syndrome). H. C., a girl, aged 14, complained of obesity, delayed sexual development and frontal headache. The headaches began when she was about 10 years old. At 12 obesity was noticeable. At 13 she became uncertain of her balance and would sometimes fall to the ground, without, however, losing consciousness. She has never menstruated.

Examination revealed a corpulent child of small stature, mentally very bright. The head was larger than normal. The vision was good and the color fields were unaltered. The pupils, however, reacted sluggishly and both optic disks were abnormally pale, so that an early optic atrophy was diagnosed. Secondary sexual characteristics were lacking.

Urine examinations were completely negative and the twenty-four-hour urinary amounts were normal. The spinal fluid contained only 5 cells per c.mm. and gave negative Wassermann, Nonne and Lange tests. Roentgen-ray plates of the head showed a sella much increased in size. A subsequent decompression operation revealed marked intracranial pressure.

An intravenous glucose tolerance test was made on this patient before the decompression operation was performed and resulted as shown in Table 16. The weight of the patient was 47 kg.

TABLE 16.—GLUCOSE SOLUTION, 19.43 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	3.23	42	+	0.31	0.372
Subsequent loss.....					0.405
Total glycosuria.....					0.777

The threshold of tolerance lies a little below 0.8 gm. per kilogram of body weight per hour. There is certainly no increase over normal.

CASE 17.—Diagnosis, hypophysial disease (gigantism?). T. W., a man, aged 26, was admitted to the service of Dr. D. P. Abbott at the Presbyterian Hospital on Jan. 10, 1916, with complaints of temporal headaches, weakness and nervousness. The headaches were of only a few days' duration. The weakness was not great. The nervousness had been present since childhood. The patient had no severe illnesses other than a chronic infection of the right ear which began early in childhood and only healed in 1912. He was, however, slow in learning to walk (2 years), was always big for his age and had always been backward in school. His family history was negative and venereal infection was denied.

Examination revealed a man 6 feet 1 inch tall, and big in proportion. The sexual development, pubic hair, etc., appeared normal. There was an old perforation in the right ear drum. A roentgenogram of the hypophysial region showed an unusually small sella and it was thought probable that a correlation existed between this and the rather peculiar development.

An intravenous glucose tolerance test resulted as shown in Table 17. The weight of the patient was 80.7 kg.

TABLE 17.—GLUCOSE SOLUTION, 19.2 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.2	1.4	30	0		
0.7	4.9	30	0		
0.8	5.6	30	++	Not determined

Tolerance lies between 0.7 and 0.8 gm. per kilogram per hour. It may be subnormal, but is certainly not increased.

Blood sugar determinations were made before and after the injections by Dr. G. Pearce and showed a percentage of 0.115 and 0.212, respectively.

CASE 18.—Diagnosis, hypophysial disease, diabetes insipidus. M. L., a man, aged 40, was admitted on the service of Dr. Joseph Miller at the Cook County Hospital in August, 1915. His complaints were polyuria and sexual impotence.

The first symptoms of disease occurred in 1907 and consisted of severe headache, occasional vomiting and excessive thirst. He would drink from 10 to 12 gallons of water a day. Sexual power was lost in 1911. Since 1913 he has been free from headaches and the thirst has been somewhat less. The appetite has always been moderate. He had four or five gonorrhoeal infections, and in 1901 a genital chancre. He was treated for this and no secondary symptoms of syphilis followed.

Examination revealed a moderately corpulent man of medium height and with small bones. The pubic hairs were found scanty and had a feminine distribution. The beard was very thin. Penis and testicles were small. In the right eye was a cataract, in the left the vision was good, but the red and green color fields showed some interlacing of their margins. The urine was found to be large in amount, the twenty-four-hour specimens containing from 3,000 to 6,000 c.c. The specific gravity was low and sugar was absent. Roentgenograms of the head revealed a slight enlargement of the sella and destruction of the posterior clinoid processes.

The intravenous glucose tolerance test resulted as shown in Table 18. The weight of the patient was 63.6 kg.

TABLE 18.—GLUCOSE SOLUTION, 20.11 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	2.64	43	0		
0.6	3.16	56	0		
0.8	4.22	60	0		
0.9	4.76	97	+	0.29	0.59
Subsequent loss.....					0.86
Total glycosuria.....					1.45

The threshold of tolerance lies between 0.8 and 0.9 gm. per kilogram of body weight per hour.

CASE 19.—Diagnosis, cirrhosis of the liver. G. R., a man, aged 47, was admitted to the service of Dr. Billings at the Presbyterian Hospital on June 29, 1916. His complaints were loss of weight, weakness and pigmentation of the skin.

The history contained a record of scarlet fever at the age of 11 and malaria at 25, but excepting these illnesses, good health up to the spring of 1916.

Since April he has felt weak, has decreased in weight from 202 to 162 pounds, and has observed a pigmentation of the skin of the entire body. There has never been any icterus of the sclera and the color of the skin is more brown than yellow. In May he visited the dispensary, and from there was sent to the hospital. His family and venereal records are negative, but for years he has been drinking daily very considerable quantities of beer and whisky.

Examination revealed a poorly nourished man of average height. The pigmentation of the skin was unequally distributed, the nipples, pubic region and axillae were very dark; there were no spots in the mouth and the sclera were clear. There was a moderate pyorrhea and the teeth were discolored. The chest was normal in shape, the lungs slightly emphysematous, the heart borders somewhat wider than normal. A slight systolic blow was heard at the apex. The abdomen was somewhat pendulous, but contained no fluid. The spleen was palpable during inspiration, very firm, smooth and not tender.

The upper border of the liver was found at the fourth rib; the lower border extended 6 cm. below the costal arch in the mammary line. The edge was firm and regular and the surface was smooth.

The blood pressure, systolic, was 140, diastolic 70. Wassermann tests were negative. A blood count gave 3,500,000 erythrocytes, 4,000 leukocytes and 70 per cent. hemoglobin.

The urine was examined repeatedly without finding sugar or bile pigments. The stools contained bile in normal amount.

On July 2, 50 gm. of glucose were given on the empty stomach without leading to melituria. Levulose and galactose tolerance tests were omitted, owing to the impossibility of obtaining these sugars.

An intravenous d-glucose tolerance estimation, made on July 5, 1916, resulted as shown in Table 19. The weight of the patient was 74 kg.

TABLE 19.—GLUCOSE SOLUTION, 17.48 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose	
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope
0.4	2.82	40	0	
0.6	4.23	20	0	
0.8	5.64	15	0	0

Tolerance is above 0.8 gm. per kilogram of body weight per hour and is apparently normal.