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The Intravenous Glucose Tolerance Equation

By G. D. GREVILLE, *Biochemical Department, Runwell Hospital, near Wickford, Essex*

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The intravenous glucose-tolerance test in which the blood-sugar is measured at intervals for an hour or two following a single intravenous injection of glucose has received steady but not intensive attention during the last 20 years. Recent important contributions include those of Crawford [1938], Ross [1938], Lozner, Peters, Taylor & Winkler [1941], Hamilton & Stein [1942], McKean, Myers & von der Heide [1935] and Tunbridge & Allibone [1940]. The two last-named papers contain reviews of the literature up to 1935 and 1938 respectively.

The lack of agreement among the various workers regarding procedure is remarkable. This applies not only to the dose of glucose given, but also to the assessment of the results. As the latter involves interpretation of the curve obtained for each test when the blood-sugar is plotted against the time after injection, a study of such curves seems most desirable. This paper concerns curves obtained in a series of glucose tolerance tests performed in this Hospital in 1940 in collaboration with Dr Derek Russell Davis; I undertook recently an examination of them. The following data are important for an appreciation of what follows; fuller practical details are given later in the paper.

In all, 35 tests were carried out on 13 adult psychotic patients. In 26 tests the dose of glucose was 15 g. per sq. m. body surface, in 8 it was 0.5 g. per kg. body weight, and in 1 test it was 27.6 g. [cf.

Tunbridge & Allibone, 1940]. The glucose was injected in 33½ % solution in water over a period of 2 min., and the time at which the blood specimens were taken was measured from the mid-time of the injection. 14 specimens were taken at intervals from 5 to 90 min. (both inclusive) after, and 4 specimens before the administration of glucose. The blood-sugar (in mg./100 ml.) will be denoted by y , the time (in min.) by t , and the graph obtained by plotting y against t will be called 'the curve'. Two of the curves obtained are shown in Figs. 1 and 3 (points represented by circles).

AN EQUATION FOR THE INTRAVENOUS GLUCOSE TOLERANCE CURVE

A simple relationship which might hold approximately is that the rate of fall of blood-sugar at any instant after the injection of glucose is proportional to the value of the blood-sugar at that time, i.e.

$$\frac{dy}{dt} = -Ky, \quad (i)$$

where K is a constant. This gives on integration

$$\log y = -Kt + \text{const.} \quad (ii)$$

Such a relationship has been found to hold approximately for the disappearance of foreign sugars from the blood [Fishberg, 1930], and also for the disappearance of calcium ion from the blood following

the intravenous injection of calcium salts [Greville, 1931], although in the latter case y represents not the blood-calcium but its excess above the initial value. If equation (ii) holds for the intravenous glucose-tolerance curve, then when $\log y$ is plotted against t a straight line should be obtained. In their recent paper Hamilton & Stein [1942] have shown that this is true to a limited degree. The points in the middle part of the plot of $\log y$ against t (corresponding to blood-sugars between 100 and 200–250) fall approximately on a straight line; at both ends the points usually deviate, in the direction of increasing y . Now

a positive value of y which will be denoted by y_0 . The equation which applies is therefore

$$y = -\frac{1}{k} \frac{dy}{dt} + y_0,$$

so that on rearrangement we have instead of equation (i)

$$\frac{dy}{dt} = -k(y - y_0), \quad (\text{iii})$$

where k , the slope of the line, is given in Fig. 1 by LY/Yy_0 . Thus at any instant, the rate

Fig. 1. Intravenous glucose tolerance test. Circles ($\bullet$), blood-sugar (y) plotted against time (t) (curve fitted by hand). Crosses ($\times$), dy/dt (slope of y, t curve) against y . P = pre-injection blood-sugar. For other symbols see text.

if equation (ii) holds, equation (i) should also apply, in which case dy/dt plotted against y should give a straight line which passes through the origin. In Fig. 1, dy/dt , which is the slope of the y, t curve, has been measured for several values of y , and then plotted against y (crosses). The points fall approximately on a straight line, which, however, does not pass through the origin, but intersects the y -axis at

of fall of blood-sugar is proportional not to the blood-sugar, but rather to the excess of the blood-sugar above some value y_0 , which is a constant for the particular test. In that of Fig. 1 y_0 equals 70.

Integrating (iii) we have

$$\log(y - y_0) = C - kt, \quad (\text{iv})$$

where C is a constant, and expressing equation (iv) in the exponential form,

$$y = e^{C-kt} + y_0. \quad (v)$$

Equation (iv) shows that when $\log (y - y_0)$ is plotted against t a straight line should result. This actually occurs, as will be seen from the graph marked ' $y_0 = 70$ ' in Fig. 2. This was obtained by plotting $\log (y - y_0)$ against t , using the data of Fig. 1 and the value of y_0 (70) derived above. The points fall close to a straight line over the whole range of the measured blood-sugar values. A still closer fit is shown in Fig. 3 (graph III) for another test ($y_0 = 52$). With all 35 tests of this series it was found that when $\log (y - y_0)$ is plotted against t the points lie about a straight line for the whole, or nearly the whole, of

plotted against t , and the smooth curve drawn which seems best to fit the points. Then the slope of the curve is measured graphically for several values of y , usually chosen at intervals of 20 mg./100 ml., more frequently where the curve has greatest curvature. It is best to take the mean of two measurements of the slope for each value of y . The values thus obtained for the slope (dy/dt) are plotted against the corresponding values of y , as in Fig. 1. The straight line which best seems to fit the points is drawn; it intersects the y -axis at y_0 . y_0 is read off, $\log (y - y_0)$ calculated for each blood specimen, and plotted against t , as in Fig. 2. The points are fitted by eye with a straight line; k is given by the slope of the line, and C by the point at which it intersects the $\log (y - y_0)$ axis.

Fig. 2. Same test as Fig. 1. ' $y_0 = 70$ ', $\log (y - 70)$ against t (straight line fitted using constants of regression equation). ' $y_0 = 0$ ', $\log y$ against t . lp : value of $\log (y - 70)$ corresponding to pre-injection blood-sugar.

the range 5-90 min. We may therefore state that, for the series of tests under consideration, equation (iv) represents the data of any test with considerable accuracy; and equation (v) is an intravenous glucose-tolerance equation in the exponential form.

Estimation of the constants of the equation

Method 1: graphical. This, the method of choice, follows the principles already outlined. y is first

Method 2: trial and error. $\log (y - y_0)$ is plotted against t several times, using different arbitrary values of y_0 each time, until that value of y_0 is found which brings the points most nearly in a straight line. k and C are then measured from this line as in method 1. Method 2 is somewhat laborious and not very sound, but is occasionally useful.

Method 3: calculation. Let (y_1, t_1) , (y_2, t_2) , (y_3, t_3) be three points on the curve separated by equal time

intervals, so that $t_2 - t_1 = t_3 - t_2$. Then it can be shown that if equation (iv) holds,

$$y_0 = (y_2^2 - y_1 y_3) / (2y_2 - y_1 - y_3). \quad (\text{vi})$$

I am indebted to Dr Tudor Jones for pointing out this relationship. The method is to read off from the

Fig. 3. A different test from that of Fig. 1. Circles (●), observed values of y plotted against t . I (solid curve) represents the equation $y = e^{C-kt} + y_0$, where $C = 5.638$, $k = 0.02310$, $y_0 = 52$. II (broken curve) represents the same equation with k increased to 0.04 and y_0 increased to 72. III, $\log(y - 52)$ against t (straight line fitted using constants of regression equation).

smooth y, t curve the values of y at (say) 10, 35 and 60 min. y_0 is then calculated by equation (vi). At the same time k can be calculated by the equation

$$k = \frac{1}{t_2 - t_1} \log \frac{y_1 - y_2}{y_2 - y_3}. \quad (\text{vii})$$

Equations (vi) and (vii) have, in general, not yielded very accurate results, but once again the method has proved useful on occasion.

Notes on method 1

(a) The logarithms in the above equations and figures are of course natural logarithms, to the base e . One can if necessary plot logarithms to the base 10, and multiply the values of C and k found from the graph by $\log_e 10 = 2.30$.

(b) Fitting a straight line to the $(dy/dt, y)$ points is sometimes a little difficult. There is often a systematic departure from the straight line with the first one or two points where y is large, which is much

more marked in this graph than in the $\log(y - y_0), t$ plot. These deviating points are best neglected and the line fitted to the remainder. Again, small deflexions of the y, t curve may produce considerable changes in the slope, and the $dy/dt, y$ plot may be slightly sigmoid as in Fig. 1.

In order to get some idea of the error involved in the drawing of the y, t curve and the measurement of slope, the y, t curve was drawn twice for each of 34 tests. Each curve was used to construct a $dy/dt, y$ curve, so that for each test there were two evaluations of y_0 . Statistical examination showed that in 95 tests out of 100 the difference between the two evaluations would not be expected to exceed 15 (standard error = 4.89).^{*} Experience showed that when y_0 was used to construct a $\log(y - y_0), t$ curve and hence to estimate k , alteration of y_0 by 15 caused an error of about 13.5% in the estimate of k . This is not great, considering that the range of k in the series is from 0.016 to 0.039.

Another check on the suitability of the graphical method arises from the circumstance that the $dy/dt, y$ graph should have the same slope k as the $\log(y - y_0), t$ graph. For each of the 34 tests, the mean of the two estimates of y_0 , derived from two drawings of the y, t curve as above, was used to construct the $\log(y - y_0), t$ graph and hence obtain an estimate of k . The slopes of the two $dy/dt, y$ graphs also gave two estimates of k , of which the mean was taken. The arithmetic mean of k from the whole series of $\log(y - y_0), t$ graphs was 0.0268, and from the whole series of $dy/dt, y$ graphs 0.0270. In any individual case a series of approximations should strictly be made until the two values of k agree satisfactorily, but the first approximation was generally found to give good enough agreement for all practical purposes, and the closeness of the means of the two sets supports the decision to neglect the small differences.

Goodness of fit: statistical examination

In an attempt to assess the goodness of fit, the linear regression equation relating Z to t was calculated, namely,

$$Z = C - kt,$$

where $Z = \log(y - y_0)$, and C and k are constants, $-k$ being the regression coefficient of Z on t . r^2 , the square of the correlation coefficient between Z and t , was then found. r^2 is a measure of the fraction of the variability of Z which is attributable to the linear relationship.

The regression equations have been computed for six tests only, as it would be laborious and of no great worth to calculate them for all; the constants can be

^{*} It should be recognized that the standard error used here is not a measure of the accuracy with which y_0 is determined, but a measure of the consistency of results obtained by the graphical method.

estimated satisfactorily by the graphical method. In order to obtain representative figures the tests were divided into three groups, 'best', 'medium' and 'worst', having regard to the amount of scattering of the points round the y, t curve. They were thus probably assessed according to the amount of

some of the tests there seem to be systematic deviations which need consideration.

It is difficult to fix any standard with which to decide whether a point deviates from the line. It is best to examine the graphs with a sense of proportion. I have judged as fairly as I could for each

Table 1. *Intravenous glucose-tolerance test protocols, showing simultaneous values of blood-sugar y (mg./100 ml.) and time t (min.), together with the values of the constants y_0 , C and k in the equation $\log(y - y_0) = C - kt$ calculated for each test*

No.	...	...	1	2	3	4	5	6
Sex, age	...	...	F, 47	F, 46	F, 36	M, 38	M, 54	M, 44
Diagnosis*	...	...	Mel.	C.Ps.	Mel.	Mel.	Par.	Mel.
Weight (kg.)	...	...	44.5	52.6	47.2	51.3	64.9	49.4
Surface area (m. ²)	...	...	1.43	1.53	1.45	1.59	1.66	1.61
Glucose injected (g.)	...	...	21.3	26.3	21.6	24.0	25.0	24.0
y_0	...	...	63	73	50	78	61	64
C	...	...	5.68	5.64	5.55	5.24	5.56	5.38
10^4k	...	...	304	385	239	208	259	289

	t	y	t	y	t	y	t	y	t	y	t	y
Initial value	...	94	...	85	...	85	...	87	...	99	...	88
	5	323	5	309	5	314	5	259	5	299	5	256
	10	264	10	262	10	261	10	231	10	257	10	223
	21	220	20	201	20	205	20	197	20	209	20	185
	26	195	30	167	30	178	30	181	30	182	30	151
	37	182	35	149	35	164	35	170	35	168	35	144
	41	142	40	137	40	148	40	159	40	156	40	136
	46	144	45	123	45	140	45	152	45	154	45	125
	51	130	50	110	50	127	50	145	50	129	50	116
	56	115	55	107	60	112	55	139	55	120	55	104
	60	106	60	98	65	104	60	132	60	115	60	97
	65	103	65	97	70	100	65	128	65	110	65	96
	70	98	71	90	80	87	70	120	70	104	70	92
	80	89	80	84	90	82	80	115	80	93	80	86
	85	84	90	84	—	—	90	108	90	88	90	80

* C.Ps. confusional psychosis; Mel. melancholia; Par. paraphrenia.

experimental error. The two most representative tests of each group were then selected. The results are given in Table 2. The calculations were done for the whole of the range 5–90 min., except that in no. 1 the last specimen was at 85 min. Test no. 7 is that represented in Fig. 3; r^2 is here as high as 0.9989.

Table 2. *Constants of the regression equation $Z = C - kt$, where $Z = \log(y - y_0)$*

Group	No. of test	y_0	C	10^4k	r^2
Best	7	52	5.638	231.0	0.9989
	4	78	5.245	207.6	0.9973
Medium	1	63	5.690	306.9	0.9957
	2	73	5.637	384.9	0.9906
Worst	8	63	5.510	335.8	0.9594
	9	55	5.280	217.8	0.9592

Goodness of fit: range

Above we have assessed the goodness of fit of the straight line given by equation (iv) to the data over the whole experimental range. In Figs. 2 and 3 (III) the points lie close to the line throughout, but in

test, the first and last points which lie close to the line.

In 10 tests out of 31 the 5 min. point was judged to deviate, in each case above the line, so that the blood-sugar was falling more rapidly than equation (iii) allows. The 10 min. point deviated in only 2 out of 35 tests. The blood-sugar corresponding to the first point lying near the line was noted for each of 35 tests; the average was 275 mg./100 ml. (range 187–332).

In 13 tests the 90 min. point deviated above or below the line; in 19 it did not. The average of the 35 blood-sugar values corresponding to the last point near the line was 90 (range 75–137). In 16 tests out of 30, equation (iv) continued to be obeyed after the blood-sugar had fallen below the pre-injection value, in one case as far as 24 mg./100 ml. below.

Goodness of fit: exponential curve

A demonstration of the goodness of fit consists in reconstruction of the y, t curve. Thus, the constants of equation (iv) for test no. 7 (Fig. 3) having been accurately determined (Table 2), they are inserted

in equation (v) so that y can be calculated for any t . For the blood specimens we have

t	5	10	20	30	35	40	45
y calc.	302.5	275	229	193	177	163.5	152
y obs.	306	273	225	193	179	165	152

t	50	55	60	65	70	80	90
y calc.	140.5	131	122	114.5	108	96.5	87
y obs.	141	130	121	115	107	96	88

In Fig. 3 the solid curve (I) represents equation (v) with the appropriate values of the constants, i.e.

$$y = e^{5.638 - 0.02310t} + 52,$$

and the circles represent the experimental values of y .

These results speak for themselves.

The constants

y_0 , which might be called the 'limiting value of y ', is the level which the curve would approach asymptotically were equation (v) to be obeyed when t becomes large. What happens when y actually approaches y_0 cannot be stated; none of the tests were continued after 90 min., and all the 90 min. values of y were greater than y_0 . In Fig. 1 the curve seems to be approaching y_0 with precision. In two curves y reached a minimum (approx. 75 and 68) and then rose again. The values of y_0 in these tests were low (25 and 32 respectively), so that y rose long before y_0 was reached, otherwise hypoglycaemic signs might have appeared. y_0 does not appear to be correlated with the pre-injection blood-sugar, but in all tests it was smaller than the latter. y_0 ranged from 25 to 91.

of $(y - y_0)$ be denoted by B , and that of y by η , then $\eta = B + y_0$ and equation (iv) becomes

$$y - y_0 = Be^{-kt}. \quad (\text{viii})$$

C ranged from 5.12 to 5.82, B from 167 to 337, and η from 234 to 369.

Non-psychotic subjects

As many psychotics show abnormal oral glucose-tolerance curves, the above findings should be controlled by observations on non-psychotic subjects. I have taken data from the literature, thus covering different experimental conditions, and found C , k and y_0 for a considerable number of tolerance tests. The results with a few of these are shown in Table 3. Except with nos. 2, 8 and 9, it was necessary to measure the published graphs to obtain y and t .^{*} Some of the values of y_0 and k in these tests fall outside the range found with the psychotics. The columns headed 'Range of t ' and 'Range of y_0 ' show the range over which equation (iv) was judged to apply. This was wide, especially with nos. 6 and 9.

EXPERIMENTAL DETAILS

In view of Himsworth's well-known work, the patients were kept on a constant carbohydrate intake of 282–299 g. daily. Absence of infection was checked by determinations of the erythrocyte sedimentation rate. The tolerance tests were performed in the morning, after a fast of about 15 hr. The glucose was injected with the aid of a three-way tap fitted to the syringe nozzle, and 0.1 ml. blood specimens were taken from the ear-lobe [see Harrison, 1937].

Table 3. Constants of the intravenous tolerance equation in non-psychotic subjects

Reference	Glucose injected	y_0	10^4k	C	Range of t	Range of y	Description
(1)	?	96	1068	5.58	2–30	296–106	Normal curve
(2)	0.5 g./kg.	65	334	5.61	2–75	298–88	? children
(3)	0.5 g./kg.	150	686	5.17	3–30	270–171	Child, 11 yr., rheumatism
(4)	30 g.	85	453	5.48	$3\frac{1}{2}$ – $51\frac{1}{2}$	291–110	Normal man, aged 32 yr.
(5)	15 g.	80	555	5.06	$1\frac{1}{2}$ – $44\frac{1}{2}$	226–94	Same subject as no. 4
(6)	27.6 g.	62	375	5.56	$2\frac{1}{2}$ – $64\frac{1}{2}$	305–85	Normal medical student aged 21 yr.
(7)	27.6 g.	105	263	5.61	10–78	319–142	Fractured femur, man, aged 68 yr.
(8)	25 g.	59	289	5.42	5–120	254–67	Normal male, aged 52 yr.
(9)	20 g.	56	334	5.55	4–112	280–62	Heart disease, female aged 15 yr.

(1) Ross [1938], Fig. 17. (2) Crawford [1938], Table 1, case 1, test α . (3) Ibid. Fig. 4. (4) Tunbridge & Allibone [1940], Fig. 4, curve I. (5) Ibid. Fig. 4, curve II. (6) Ibid. Fig. 10, curve II. (7) Ibid. Fig. 11, curve I. (8) Lozner *et al.* [1941], Table 1, no. 5. (9) Jørgensen [1926–7], no. Axxv.

k , as is seen from equation (iii), gives the rate of fall of blood-sugar per unit excess of blood-sugar above the limiting value y_0 . The unit is min.^{-1} . Throughout the tests there was a slight tendency for k to increase with y_0 . k ranged from 0.0176 to 0.0386.

C . If equation (iv) were to hold for values of t approaching zero, then C would be the value of $\log (y - y_0)$ when $t = 0$. If the corresponding value

Blood-sugar was determined by the cerimetric direct titration method of Miller & Van Slyke [1936], which gives values very close to the 'true' blood-

^{*} Since many workers present their results in the form of diagrams only, it is difficult to use their work for comparison. Protocols of six tests in the present series are given in Table 1, in case any reader would care to use them for checking the assertions made here.

sugar, and about 7 mg./100 ml. lower than the Hagedorn-Jensen values. Methyl violet 5 B was found to be an excellent indicator [cf. Vanossi & Ferramola, 1936].

DISCUSSION

Blood-sugar dynamics. The remarkable thing which has emerged is that the rate of disappearance of glucose from the blood, although presumably the resultant of a number of simultaneous processes, conforms with considerable accuracy to a simple equation.

In the first few minutes the blood-sugar is clearly higher than is to be expected from equation (v). In several tests even the 5 min. value of y is greater than η , the value of y at $t=0$ given by equation (v). On the other hand, Table 3 shows that the 1½ and 2 min. points can on occasion lie approximately on the calculated curve. There is, however, an extremely rapid disappearance of glucose from the blood during a short period after the injection.

Thus, with test no. 7 (Fig. 3), 21.4 g. of glucose were injected into a 44.0 kg. woman. The average blood volume of women, according to Harington, Pochin & Squire [1940], is 72.3 ml./kg., so here it would be 3.18 l. The blood-sugar should therefore rise immediately by 673 mg./100 ml.; hence from the pre-injection level of 89 it should rise to 762. For this test, however, η was calculated to be 333, and the 5 min. value of y was 306. Even if the blood volume were as high as 5 l., y would be expected to rise to 517. Several authors have made a somewhat similar calculation (cf. also Greville [1931] on the injection of calcium salts).

A working hypothesis, unsupported by direct evidence, for the events following the injection of glucose is as follows. The blood-sugar reaches a maximum quickly,* and then falls extremely rapidly, partly due to osmotic entry of water into the blood, but mostly to rapid diffusion of glucose from the blood into the tissue fluids. The glucose is rapidly spread over the 'active volume of the tissue fluids' [Burn & Dale, 1924; Orr-Ewing, 1931]. After a time the blood-glucose will come into dynamic equilibrium with the tissue fluid-glucose. It is now suggested that when this occurs, the rate of fall of the blood-sugar conforms to equation (iii). The disappearance of glucose from the blood at this stage mirrors, as it were, the net metabolic removal of glucose in the tissues. Finally, at a low blood-sugar level, processes tending to raise the blood-sugar achieve predominance, the curve rises, and equation (v) no longer holds.

* Although McKean *et al.* [1935] and Fairley [1936] found that the maximum occurs some minutes after the injection, probably owing to slow mixing of the glucose solution with the blood, the curves of Tunbridge & Allibone [1940] and Crawford [1938] show that the maximum usually occurs before the end of the first minute.

Equation (iii) shows that the rate of fall of blood-sugar bears a straight-line relationship to the blood-sugar level. In experiments in which the rate of glucose utilization was estimated at various maintained blood-sugar levels, it has been found that the former bears an approximate straight-line relationship to the latter, both in the eviscerated, hepatectomized dog [Soskin & Levine, 1937] and in the perfused hind-limb of the cat [Lundsgaard, Nielsen & Ørskov, 1938]. Thus the present findings with a rapidly-falling blood-sugar, and the interpretation of these findings, are in conformity with the observations with steady glycaemic levels.

Properties of the curve. It is seen from equation (v) that when y_0 is altered the curve shifts bodily upwards or downwards. k largely determines the shape of the curve. Thus in Fig. 3, the broken curve (II) was obtained by increasing k to 0.04 from 0.0231, the value applying to the solid curve; increasing k has caused the curve to bend more sharply. (y_0 was also increased, to facilitate comparison by raising the curve.) Similarly, decreasing k would straighten the curve somewhat. When C (or B) is altered, the values of $(y - y_0)$ are all changed in the same ratio (equation viii).

Assessment of tolerance tests. The methods which have been used to characterize the results of intravenous glucose-tolerance tests should now be examined in the light of the findings of this paper.

The time taken for the blood-sugar to return to the pre-injection level [Tunbridge & Allibone, 1940], or to 100 mg./100 ml. [Crawford, 1938], or the value of the blood-sugar at a certain time after the injection [Lozner *et al.* 1941] are criteria which do not seem at first to give any information about the shape of the curve, which depends on k . Nevertheless, any or all of these may possibly be correlated with k ; indeed, in the series of tests on psychotics there appears to be a rough relationship between k and the time taken for the blood-sugar to return to 95, one tending to increase as the other decreases.

Ross [1938] has used as a criterion the area under the curve bounded by certain arbitrary limits. Despite the criticisms of this by Tunbridge & Allibone [1940], one should not dismiss it before satisfying oneself that the area is not correlated with any of the characteristics of the curve.

The procedure of Hamilton & Stein [1942] needs more detailed comment. These workers plotted $\log y$ against t , and found that equation (ii) is approximately obeyed in the middle part of the graph. In Fig. 2, $\log y$ has been plotted against t using the data of Fig. 1. The graph is labelled ' $y_0 = 0$ ', since equation (iv) becomes identical with equation (ii) when y_0 is put equal to zero. It is clearly curved, in contrast to the plot for the same data of $\log (y - y_0)$ against t when $y_0 = 70$. It is true that in several of the other tests the graph of $\log y$ against t is much straighter

in the middle part than that in Fig. 2; but an examination of all the tests leaves no doubt that equation (iv) gives a very much better representation of the data than does equation (ii). The constant K of equation (ii) multiplied by 100 was proposed as a measure of the test. Since it then gives the rate of fall of blood-sugar at any instant as a percentage of the blood-sugar at that instant (equation (i)), it would be very convenient. Unfortunately, as we have seen, equation (ii) does not represent the data well, and it is not easy to determine K by drawing a straight line through points lying on a curve.

When the test is used in the diagnosis of disease, any criterion may be taken which proves adequate in practice. For example, Lozner *et al.* [1941] showed that the blood-sugar 2 hr. after the injection of 25 g. of glucose is a reliable guide for distinguishing between benign glycosuria and diabetes mellitus. They established a mean normal value for the 2 hr. blood-sugar, and also found the standard deviation. Any value differing from the mean by more than three times the standard deviation was considered abnormal. Of course in any test the blood-sugar may have passed through a minimum during the first 2 hr., but this does not matter: the criterion is justified by experience.

We have seen that the curve is characterized by three constants, k , y_0 and C . It is unfortunate from the practical point of view that one is not enough. However, the intravenous glucose tolerance test is regarded as a 'delicate instrument' [Ross, 1938], which 'deserves a somewhat more accurate method of measuring' than is obtained by noting the time at which the blood-sugar returns to normal levels [Hamilton & Stein, 1942]. These views suggest that it may prove necessary in the future to characterize experimental curves by the constants of the tolerance equation, though experience may establish a connexion between any one or any combination of the

constants and any of the factors, normal and pathological, on which the outcome of the test depends.

SUMMARY

1. In the intravenous glucose-tolerance test, following a single injection of glucose, the value of the blood-sugar (y) is related to the time (t) after the injection by the equation

$$\log (y - y_0) = C - kt,$$

where y_0 , C and k are constants, the values of which vary from test to test.

2. This relationship is obeyed with considerable accuracy over all, or nearly all, of the time period 5–90 min. after the injection. It was found to apply in a series of tests on psychotics, and also in numerous tests on normal subjects taken from the literature.

3. The intravenous glucose-tolerance curve thus approximates to an exponential curve of the form

$$y = Be^{-kt} + y_0,$$

where $\log B = C$; and at any instant the rate of fall of blood-sugar is proportional to the excess of the blood-sugar above the 'limiting value' y_0 .

4. Methods for determining the constants of the equation are described, and an attempt is made to estimate the goodness of fit.

5. The assessment of the results of intravenous glucose-tolerance tests is discussed in the light of these findings.

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