A STANDARD INTRAVENOUS GLUCOSE TOLERANCE TEST

BY

THEODORE CRAWFORD, B.Sc., M.B., Ch.B.

(From the Department of Paediatrics, University of Glasgow, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow.)

Since the introduction of micro-methods for the estimation of the blood-sugar the oral glucose tolerance test has been the accepted means of differentiating between the various forms of glycosuria. For this purpose it has proved both convenient and reliable. As a research weapon, however, it is less satisfactory,

FIG. 1.—Two oral glucose tolerance tests performed at an interval of one week in a child of 12 yr. 8 mth. under standard conditions.

first because of the wide normal range and secondly because wide variations may occur from time to time in the same individual even when the tests are performed without alteration in the controllable conditions. This variability has been studied especially by Svensgaard (1931).

Adults and older children subjected to the oral glucose tolerance test on two

occasions usually give fairly similar curves ; but in a proportion of cases wide variations within normal limits are found (fig. 1). In young children such variations are more frequent, and in infants they appear to be the rule rather than the exception. In these children and infants the variations may be considerable, two curves on the same subject sometimes differing in the three important features of maximum level, time of maximum level and duration of hyperglycaemia (fig. 2). It would therefore appear that even with standardized external conditions the state of the alimentary canal itself cannot be so regulated as to produce a consistent rate of absorption.

In view of these facts, it is evident that any conclusions based on slight variations in the blood-sugar curve following oral glucose must be guarded. In

FIG. 2.—Successive oral curves showing variation in maximum level, time of maximum level and duration of hyperglycaemia.

order to exclude the variable factor of absorption, certain workers have recently studied the blood-sugar curve following intravenous injection of a glucose solution. In these circumstances absorption plays no part, so that the factors tested are the rates of utilization, storage and excretion. Unfortunately different investigators have employed widely varying dosages of glucose and modes of administration, rendering the interpretation of results, and more especially the comparison of one worker's results with those of another, matters of considerable difficulty.

The present paper is a preliminary report of a more extensive investigation of intermediary carbohydrate metabolism with special reference to children ; it presents an attempt to devise a standard intravenous glucose tolerance test applicable at all ages, and to determine the normal range and constancy of the curves obtained and what constitutes a significant variation in any particular case.

Technique of the test

Various doses and methods of administration have been employed, but the following technique has been found most generally satisfactory :

The patient has no food for eight hours prior to the test, but may be allowed water to drink. If a series of curves is to be performed on the same subject the test should be made at the same time of day on each occasion. A fasting specimen of capillary blood is removed from the lobe of the ear, or from the heel in the case of infants, and then the injection is given. The dose of glucose used is half a gramme per kgm. of body weight, and it is injected intravenously as a 20 per cent. solution in 0.9 per cent. sodium chloride. The injection is made into a vein using a 20 c.c. syringe fitted with a two-way stop-cock and

H.S. ENLARGED TONSILS. $7\frac{1}{2}$ YEARS WT. 20 KGM
(10 gm. GLUCOSE INTRAVENOUSLY)

FIG. 3.—Example of typical intravenous curve in a normal subject.

rubber tubing leading to the glucose reservoir. The rate of injection can be accurately measured and the time allowed is 45 seconds for each 20 c.c. Specimens of capillary blood are removed for sugar estimation 2 minutes after the end of the injection and again at 15, 30, 45, 60, 75 and 90 minutes. The bladder should be emptied before the injection is given and again when the last specimen of blood has been taken. Blood-sugar has been estimated by a modification of the method of Hagedorn and Jensen (1923) and urinary sugar by Benedict's method (1911).

Characteristics of the normal curve

The features of a typical curve in a normal subject are illustrated in fig. 3. The blood-sugar level attains its maximum at the end of the injection and immediately begins to fall rapidly. Even when frequent samples of blood have been examined during the first thirty minutes (fig. 4) no interruption of the

steep descent of the curve in this period has been found. Ross (1936a), on the other hand, reports several double-peaked curves with minor rises during this phase, but does not advance any explanation of this rather unexpected finding. Fasting levels are regained in from forty-five to seventy-five minutes, and later specimens frequently show subnormal values (below 75 mgm. per 100 c.c.).

Constancy of the curve in the individual.—The concentration of the blood-sugar in the two-minute sample is of little importance. At this stage the blood-sugar is falling rapidly, so that slight variations in rate of injection, time of

FIG. 4.—Intravenous blood-sugar curve with frequent readings during half-hour after injection of $13\frac{1}{2}$ gm. glucose.

collection of the sample, and rate of flow of blood from the skin puncture may produce wide variations in this reading. In ten subjects the test has been performed on two occasions at an interval of one week. The results are given in table 1. In this table column (a) represents the findings on the first occasion and column (b) those on the second occasion. Column (c) gives the difference between corresponding readings in the two experiments. In five of these cases the difference between the two-minute readings on the two occasions was more than 20 mgm. per 100 c.c. ; but usually by the fifteen-minute reading and always at thirty minutes the curves were within 10 mgm. per 100 c.c. of one another—a much closer proximation of the curves than is found after successive oral

TABLE 1
THE RESULTS OF TWO INTRAVENOUS TESTS ON EACH OF TEN CASES

Case	..	I		2		3		4		5		6		7		8		9		10		Average difference										
		a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b		c									
Fasting	..	86	86	0	98	82	16	92	92	0	90	88	2	91	81	10	62	61	1	90	89	1	81	77	4	87	89	2	93	95	2	3.8
2 minutes		298	282	16	390	364	26	306	340	34	335	321	14	408	460	52	428	500	72	368	394	26	296	308	12	408	400	8	390	388	2	26.2
15	"	232	228	4	251	238	13	202	216	14	238	231	7	244	255	11	274	282	8	253	245	8	206	212	6	282	277	5	219	221	2	7.8
30	"	168	163	5	199	190	9	139	148	9	200	192	8	165	169	4	202	205	3	188	182	6	175	173	2	194	202	8	139	146	7	6.1
45	"	125	122	3	154	149	5	111	119	8	166	160	6	119	126	7	158	167	9	154	150	4	122	126	4	114	123	9	95	94	1	5.6
60	"	101	102	1	115	111	4	77	81	4	127	124	3	83	90	7	109	110	1	104	106	2	95	97	2	97	99	2	86	89	3	2.9
75	"	88	79	9	98	97	1	61	76	15	92	90	2	66	79	13	78	81	3	91	88	3	92	94	2	75	90	15	92	87	5	6.8
90	"	88	83	5	84	87	3	59	72	13	74	79	5	76	69	7	66	70	4	77	71	6	81	84	3	68	83	15	81	83	2	6.3

a = First test. Blood-sugar levels in mgm. per 100 c.c.
b = Second test. " " " " " "
c = Difference between corresponding readings in mgm. per 100 c.c.

glucose tests. Occasionally subnormal blood-sugar values were found seventy-five and ninety minutes after the injection. When this occurred there was sometimes a relatively wide separation between the two readings at these times (table 1, cases 3 and 9).

The normal range : variation with age.—A considerable degree of constancy of the curve at different times in the same individual has thus been demonstrated, and it remains to consider the amount of variation between normal subjects. For this purpose fifty-three normal or convalescent individuals in whom no abnormality of carbohydrate metabolism was suspected were submitted to the test. On comparison of the results obtained the most constant feature was found to be the time at which normal fasting levels were regained. The upper limit of the fasting level in the present normal series was found to be 100 mgm. per 100 c.c. and the times at which the first readings at or below this level were obtained are summarized according to age groups in table 2. Although the number of cases in some of the age groups is small, these figures show that the power of the infant, relative to body weight, to utilize and store carbohydrate is high ; and that this so-called high carbohydrate tolerance falls off progressively during childhood until the adult level is reached in the ten to thirteen year age group.

TABLE 2

SUMMARY OF TIMES AT WHICH FIRST BLOOD-SUGAR READING AT OR BELOW 100 MGM. PER 100 C.C. WAS OBTAINED

Age groups . .	0-2	2-4	4-7	7-10	10-13	Adults.
No. of cases	4	6	18	11	8	6
Fall in 15 min.	—	—	—	—	—	—
„ 30 „	75 per cent.	—	—	—	—	—
„ 45 „	25 „	50 per cent.	33 per cent.	18 per cent.	—	—
„ 60 „	—	50 „	50 „	46 „	35 per cent.	50 per cent.
„ 75 „	—	—	17 „	36 „	63 „	50 „
„ 90 „	—	—	—	—	—	—
Average of injected glucose excreted in urine.	4 „	5.1 „	8 „	5 „	7.8 „	8.5 „

Discussion

As indicated above, the test described has been devised for research purposes rather than for use as a diagnostic procedure. Jorgensen and Plum (1922) used an intravenous test for the differentiation of malignant and benign glycosurias, claiming that their test gave a smaller proportion of doubtful results than are obtained with an oral glucose tolerance test. They employed a con-

stant dosage of 20 gm. glucose in 50 c.c. of water, and for the assessment of the results Jorgensen (1926) introduced the 'loading figure'—the sum of the area of the curve above the fasting level in sq. cm. and the time in minutes for the fasting level to be restored. This technique was not adopted in the present experiment for the following reasons :

1. The projected work was to be conducted on children, so that variation of dosage with body weight was considered essential. An infant weighing 5 kgm. and having a blood volume in the region of 400 c.c. could hardly be subjected to the same injection as a child of twelve years of age with a blood volume between three and four litres if the resulting curves were to be comparable.

2. In comparing the effects of glucose injections using water and physiological saline as solvents it was found that not only were nausea and pyrexia more frequent after the water injections but also that the blood-sugar level behaved in a more erratic manner than when the injection was made with saline. For this reason all the injections in the present series have been made with the glucose dissolved in 0.9 per cent. sodium chloride solution. Ross (1936*a*, 1936*b*) employed water as the solvent, and it is possible that the upset of osmotic equilibrium produced accounts for the double-peaked and irregular curves which he reports ; but Jorgensen also employed a watery medium and he reports no such findings.

3. The introduction of such a mixed and artificial factor as Jorgensen's 'loading figure' was considered undesirable, especially when it was found that the type of the curve could be accurately defined by reference to the time at which the first blood-sugar reading at or below 100 mgm. per 100 c.c. was obtained.

The choice of this point—the time of restoration of the blood-sugar to 100 mgm. per 100 c.c.—possibly requires some explanation, the usual point taken by other workers being the time at which the original fasting value has been regained. In children to a greater degree than in adults the fasting value fluctuates from time to time, and after eight hours' fasting it tends in many cases to be about the lower limit of normal (table 1, cases 5, 6 and 8). In these circumstances it seems fairer to judge the intermediary mechanism by its ability to restore a normal fasting blood-sugar level rather than the actual level present when the test commenced.

The technique of Jorgensen and Plum has been widely followed by other Scandinavian workers, including Torning (1932), Thaysen (1932) and Morgensen (1927). These latter workers employed the test in an attempt to explain the 'low blood-sugar curve' (Thaysen, 1932) of non-tropical sprue. Ross (1936*a*) employed an intravenous test, using 10 gm. glucose in 50 c.c. of water in an investigation of carbohydrate absorption in coeliac disease and abdominal tuberculosis ; and an intravenous glucose tolerance test was also used by Fikri and Ghalioungui (1937) to elucidate abnormal oral glucose curves found by them in ankylostomiasis. They employed a dosage of $\frac{1}{3}$ gramme glucose per kgm. of body weight, but they do not state in what concentration the glucose was injected.

G.S. 4 ¹⁰/₁₂ YEARS CYCLICAL VOMITING

FIG. 5.—Intravenous glucose curve during attack.

J.D. 2 ¹/₂ YEARS WT. 13 K.G.M.

FIG. 6.—Intravenous glucose curve twelve hours after a convulsion.

Conclusions

The test which has been described presents clearly defined normal limits : it can be stated that if the fall to 100 mgm. per 100 c.c. occurs in less than forty-five minutes in children between two and ten years of age, or in less than sixty minutes in children over ten years of age, then increased tolerance is present. If, on the other hand, the fall to 100 mgm. per 100 c.c. is delayed beyond sixty minutes in children under four years of age, or beyond seventy-five minutes above that age then there is some degree of impairment of the carbohydrate tolerance. These statements for the lower age groups are made with some reservation owing to the small numbers of the younger children examined.

The constancy of the curve in the individual (table 1) is such that a change in the time at which the first reading of 100 mgm. per 100 c.c. or less is obtained may be accepted as evidence that a change of tolerance has occurred—a diminution in tolerance if the time has increased and a rise of tolerance if the time has diminished.

From this work it would seem that the intravenous glucose tolerance test gives a more reliable estimate of the intermediary carbohydrate metabolism than does the oral test. The question whether significant variations occur in pathological conditions is at present under investigation. Examples of abnormally slow and abnormally rapid fall are illustrated in figs. 5 and 6 respectively. The former is from a case of cyclical vomiting, the latter obtained during the upset of carbohydrate metabolism which frequently follows a convulsion (McLean, 1936).

Summary

An intravenous glucose tolerance test is described, applicable to children at all ages, as well as to adults. The dosage employed is half a gramme of glucose per kgm. body weight, injected as a 20 per cent. solution in 0.9 per cent. sodium chloride. Carbohydrate tolerance is gauged by the time taken for a normal fasting level to be attained. The test shows a high degree of constancy for the individual ; and the limits of normality are well defined. The blood-sugar curve descends more rapidly in young children than in adults.

Thanks are due to Professor G. B. Fleming and Dr. Noah Morris for valuable criticism and advice. This work was carried out during the tenure of a Hall Tutorial Fellowship.

REFERENCES

- Benedict, S. R. (1911). *J. Amer. med. Assoc.*, **57**, 1,193.
Fikri, M. M., and Ghalioungui, P. (1937). *Lancet*, **1**, 800.
Hagedorn, H. C., and Jensen, B. N. (1923). *Biochem. Ztschr.*, **135**, 46.
Jorgensen, S., and Plum, T. (1922). *Acta med. scand.*, **58**, 161.
— (1936). *Ibid.*, **65**, 116.
MacLean, M. B. (1936). *Arch. Dis. Childh.*, **11**, 247.
Morgensen, E. (1927). *Quart. J. Med.*, **6**, 119.
Ross, C. W. (1936a). *Trans. Roy. Soc. Trop. Med. Hyg.*, **30**, 33.
— (1936b). *Arch. Dis. Childh.*, **11**, 215.
Svensgaard, E. (1931). *Acta paediatr. Stockh.*, **12**, Supp. 4, 10.
Thaysen, T. E. H. (1932). *Non-Tropical Sprue*, Copenhagen.
Torning, K. (1932). *Acta paediatr. Stockh.*, **12**, 219.

CORRECTION

A STANDARD INTRAVENOUS GLUCOSE TOLERANCE TEST

In the paper entitled A Standard Intravenous Glucose Tolerance Test by Dr. T. Crawford, published in the last number of the Archives, the work of Dr. C. Wallace Ross was incorrectly quoted.

It was stated that he had used a watery solution of glucose for an intravenous glucose tolerance test, and the suggestion was made that the watery medium was responsible for some irregular and double-peaked curves which he had reported. Actually Dr. Ross used a solution of glucose in normal saline for the tests, so that the suggestion made cannot be supported.

The author of the paper regrets having allowed this error to arise.