STIMULATION OF THE SUGAR-REGULATING MECHANISM AS SHOWN BY DUPLICATE BLOOD SUGAR CURVES.*

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After the oral administration of glucose, when the concentration of the sugar in the blood is falling, ingestion of a second dose of glucose may result in little or no increase in blood sugar. This occurred in nine out of thirteen experiments conducted by Foster (1). Maclean and de Wesselow (2) had previously reported a single case in which a second dose of glucose produced a curve which was nearly as high as the first. Foster used 100 gm. and Maclean only 50. As we shall show later, this difference in the amounts of glucose used may account for the discrepancy in the results of the two observers. One or two observations have been reported also by Staub (3), Traugott (4), and du Vigneaud and Karr (5). As an explanation of this lack of hyperglycemia after a second dose of glucose, Foster accepts the suggestion proposed by Frank (6) and others for the hypoglycemia following the administration of glucose; viz., that the glucose overstimulates the formation of glycogen. Foster's observations disprove the explanation of Folin and Berglund (7), that such hypoglycemia is due to decreased need for transport of glucose to the tissues.

In a study of the blood sugar curves of a group of 170 non-diabetic individuals, we encountered many bizarre results. It occurred to us that additional information concerning the carbohydrate metabolism of some of these subjects might be obtained.

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by comparing their response to duplicate doses of glucose when administered both by mouth and intravenously. We wished to observe the response to various amounts of glucose and to determine whether ingested or intravenously injected glucose had the greater effect in stimulating the process which causes reduction in the concentration of sugar in the blood.

Material and Methods.

Most of our subjects had had previous repeated blood sugar curve tests. They were therefore accustomed to the procedure, and we were familiar with their type of response. Twenty-four subjects were used for these experiments. Two were healthy persons, the others were patients subject to recurring convulsions. For the ingestion experiments, we used 1.5, 0.75, and 0.33 gm. of glucose per kilo of body weight in 33 per cent solution. For the injection experiments, we used 1.5 and 0.33 gm. of glucose per kilo of body weight in 20 per cent watery solution. In all experiments the duplicate dose of glucose was of the same amount as the first. The interval between doses varied from 20 minutes to 2 hours. Venous blood was drawn at frequent intervals, as noted in the accompanying charts. Blood sugar was measured by the method of Folin and Wu (8), using the sugar tubes suggested by Rothberg and Evans (9). Further details concerning material and methods are given in other publications (10-12). For the sake of brevity we shall speak of curves following ingestion and intravenous injection of glucose as ingestion and injection curves respectively. The terms first and second curves refer to blood sugar curves following the initial and the duplicate administration of glucose in the same experiment.

Results.

Of the twenty-four subjects used, twenty had tests performed both by ingestion and intravenous injection. In all, 56 duplicate curves were made, of which thirty were double ingestion and twenty-six were double injection curves. The blood sugar curves obtained in these experiments were so variable that it is difficult to display results by means of illustrative cases. We have, however, presented data of twenty-two of the 56 experiments in Figs.
1 to 5 which follow. In each of the first four charts the upper
dotted lines represent injection and the lower solid lines ingestion
curves. The solid squares and rectangles indicate time when
glucose was given and the approximate relative amounts. In the
injection experiments shown in the first four figures 0.33 gm. per
kilo of glucose was used.

Fig. 1. Blood sugar curves of Subjects 133 and 164. The latter was a
patient with diabetes insipidus. Double injection and ingestion curves
were made before institution of treatment. Ingestion curve marked
"after pit." was begun 10 minutes after intramuscular injection of 1 cc.
of pituitrin. Curve marked "pituitrin" was made following injection of
1 cc. of pituitrin. In this experiment no glucose was administered. The
abscissa represents minutes and the ordinate measures mg. of sugar per
100 cc. of whole blood. In this and the three subsequent figures the broken
lines indicate intravenous blood sugar curves and solid lines ingestion
curves. Solid squares and rectangles indicate time when glucose was
administered and the approximate relative amounts. The amounts of
glucose used were as follows: for ingestion, 1.5, 0.75, and 0.33 gm. per kilo
of body weight, and for injection, 1.5 and 0.33 gm. per kilo of body weight.

The second half of Fig. 1 details four experiments with Subject
164, a patient with diabetes insipidus. The second injection curve
of this subject was somewhat lower than the first. An hour and
a half after the ingestion of 100 gm. of glucose, blood sugar had
risen to a height of 315 mg. Ingestion of a second 100 gm. of
glucose at the end of 2 hours did not prevent the continued fall of blood sugar. On another occasion, a blood sugar curve test was begun 10 minutes after intramuscular injection of 1 cc. of pituitrin. The effect of the pituitrin was reflected in an excretion of only 370 cc. of urine against an output of 1470 cc. during the corresponding 2 hour period of the previous test. In spite of this fact, however, the blood sugar curve (marked "after pit." in the chart) was similar to the previous curve. On another occasion injection of 1 cc. of pituitrin intramuscularly resulted in no increase in the level of sugar in the blood. In this individual, therefore, the alimentary hyperglycemia which he showed did not seem to be influenced by the injection of pituitrin.

The first half of Fig. 1 illustrates an experiment in which a double dose of 0.75 gm. of glucose was ingested. In this instance there was a rise of blood sugar following the second ingestion. In other instances in which the subjects drank the second solution of glucose while blood sugar was yet elevated, the concentration of sugar in the blood continued to fall.

![Fig. 2. One duplicate injection and three duplicate ingestion curves of Subject 13. Ingestion curves which are marked by solid and dotted lines followed the ingestion of 0.75 gm. of glucose per kilo. The lowest curve with broken lines followed ingestion of 0.33 gm. per kilo. The upper ingestion curve of normal Subject 165 followed ingestion of 1.5 gm. and the lower curve ingestion of 0.33 gm. of glucose per kilo.](http://www.jbc.org/)

Fig. 2. One duplicate injection and three duplicate ingestion curves of Subject 13. Ingestion curves which are marked by solid and dotted lines followed the ingestion of 0.75 gm. of glucose per kilo. The lowest curve with broken lines followed ingestion of 0.33 gm. per kilo. The upper ingestion curve of normal Subject 165 followed ingestion of 1.5 gm. and the lower curve ingestion of 0.33 gm. of glucose per kilo.
FIG. 3. Two duplicate injection and ingestion curves of Subject 122. In the experiment marked A the interval between injections was 90 minutes. In that marked B the interval was 20 minutes. In Experiment C 0.75 gm. of glucose per kilo was ingested, and in Experiment D 0.33 gm. per kilo.

FIG. 4. Two duplicate injection and three duplicate ingestion curves of Subject 75. In the ingestion experiments the amounts of glucose used were 1.5, 0.75, and 0.33 gm. per kilo. Other injection curves of this subject are shown in Fig. 5.

The response to the second dose of glucose differed so greatly in different individuals that we wished to determine the extent of
the variation at different times in the same individual. In making the eighteen double curves shown in Figs. 2 to 5 four subjects were used. Subject 13 (Fig. 2) was a patient whose ingestion curve was constantly diabetic in type. On two occasions, double

![Graph showing sugar regulation](http://www.jbc.org/)

Fig. 5. Duplicate curves following intravenous injection of 1.5 gm. of glucose per kilo of body weight in normal Subject 165 and in Patient 75. The dotted zones indicate the period during which injections were made. In the case of Subject 165, injection was at the rate of 3 gm. of glucose per minute, 35 minutes being required. In Subject 75, injection was at double this rate; namely, 6 gm. per minute, the time required being approximately 15 minutes. In this chart solid lines indicate initial curves and broken lines duplicate curves. The two are superimposed. During the period of injection blood was drawn from the arm not being used for injection. In both subjects second injection of glucose resulted in marked degree of hypoglycemia, 48 and 50 mg. per 100 cc., respectively.

ingestion curves were made using 0.75 gm. of glucose per kilo. The resulting curves were approximately the same. Fig. 3 shows four experiments on one subject. When sugar was injected after an interval of 1½ hours (Curve A), the second curve was
slightly lower than the first. When the interval between the two injections was only 20 minutes (Curve B), the second curve, except for the measurement at the end of injection, was again slightly lower than the first. When a second 0.75 gm. per kilo of glucose was ingested (Curve C), there was no consequent rise in blood sugar. When only 0.33 gm. per kilo was used (Curve D), the second rise was greater than the first. Fig. 4 presents five double sugar curves of Subject 75. In both instances in which glucose was injected, the second injection curve was higher than the first. Varying results were obtained when different amounts of glucose were ingested.

Inspection of the foregoing figures makes it evident that with relation to initial curves second intravenous curves were higher than second ingestion curves. This may be due to the fact that only small amounts of glucose were injected. Fig. 5 presents two experiments in which duplicate injections of 1.5 gm. of glucose per kilo were made. Previous double injection curves of these subjects, with use of 0.33 gm. per kilo of glucose, are shown in Figs. 2 and 4. In two injection experiments of Subject 75 (Fig. 4), second curves had been considerably larger in area than first curves. In the experiments detailed in Fig. 5, more than 4 times the previous amounts of glucose were injected. In both experiments second curves were lower than initial curves. Another point of difference between large and small injections of glucose was the more marked hypoglycemia which followed the use of the larger amount. After the double injection of 0.33 gm. of glucose per kilo, the lowest concentration of blood sugar was 87 mg. for Subject 165 and 74 mg. for Subject 75. After the double injection of 1.5 gm. of glucose, the corresponding values for these subjects were 50 and 48 mg. In each subject, if all the sugar had remained in the blood during the period of injection, blood sugar at the end of injection would have been approximately 1700 mg. per 100 cc. of blood. Instead, blood sugar of Subject 75 was 606 mg. and of Subject 165, 505 mg. In other words 64 per cent of the injected glucose disappeared from the blood during the 15 minute injection of Subject 75, and 70 per cent during the 35 minute injection of Subject 165. During second injections, 66 per cent of the injected glucose disappeared from the blood of Subject 75, and 80 per cent from the blood of Subject 165. Therefore, 8 per cent more of
glucose disappeared from the blood when glucose was injected more slowly. During the last 11 minutes of the second injection of Subject 165, when glucose was being introduced at the rate of 3 gm. a minute, the concentration of the sugar remained constant. During the 11 minute period after the injection was finished, glucose disappeared from the blood at the rate of approximately 0.5 gm. a minute. The impetus which the sugar-disposing mechanism received by this double injection of glucose is shown most strikingly in Subject 75. During the 65 minute period after the second injection, concentration of blood sugar decreased 500 mg., a rate of nearly 8 mg. per 100 cc. a minute. In a diabetic person, it would require the injection of large amounts of insulin to produce such a rapid and extensive fall in the concentration of blood sugar. During the period when blood sugar was approximately 50 mg. per 100 cc., Subject 165 experienced symptoms of a mild hypoglycemic reaction.

In order to make comparison of these double curves, it is necessary to express the degree of hyperglycemia which follows administration of glucose by a number. Because of the variability in the form of curves and also because of the different intervals at which blood was drawn, the use of a formula is not feasible. Therefore, we have expressed the height of curves in terms of the area covered. To do this, we drew curves on cross-ruled paper, transferred them to tracing cloth which weighed approximately 0.1 mg. per sq. mm. of surface, cut out the areas which were above or below the base line formed by the fasting blood sugar, and weighed. Areas below the fasting base line were subtracted from those above.

Areas of second injection curves were from 280 to 29 per cent of the areas of the first injection curves. Of the twenty-six double injection curves, areas of second curves were greater than areas of first curves in twelve experiments and smaller in fourteen. Second ingestion curves showed an even greater variation. Of the thirty ingestion experiments, areas of second curves were greater than areas of first curves in six experiments and smaller in twenty-four. In nine instances second curves had a negative value; i.e., after the ingestion of glucose blood sugar for the most part was below the preingestion level. For individuals, there was no constant relationship between the relative areas of double ingestion and in-
jection curves. A subject with a relatively high second injection curve might have a relatively low second ingestion curve and *vice versa*.

Certain data are summarized in Table I. Comparison of the first two lines of Table I shows that increase in blood sugar following a second dose of glucose was much smaller if blood sugar was still elevated when the second dose was given. Apparently there was increased speed in the disposal of glucose when blood sugar was elevated. This is seen also by the shape of intravenous curves; *e.g.*, those shown in Fig. 5. The rate of removal of sugar from the blood was greatest during the latter part of the period of injection.

**Table I.**

*Summary of the Average Relative Areas of Various Curves.*

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Blood sugar at beginning of 2nd curve.</th>
<th>Glucose administered per kilo.</th>
<th>1.5 gm.</th>
<th>0.75 gm.</th>
<th>0.33 gm.</th>
<th>All cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>2nd curve, percent of 1st curve</td>
<td>No. of cases</td>
<td>2nd curve, percent of 1st curve</td>
<td>No. of cases</td>
<td>2nd curve, percent of 1st curve</td>
</tr>
<tr>
<td>Ingested.</td>
<td>Normal.</td>
<td>7</td>
<td>54</td>
<td>7</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Elevated.</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>45</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Both groups.</td>
<td>11</td>
<td>28</td>
<td>15</td>
<td>53</td>
<td>4</td>
</tr>
<tr>
<td>Injected.</td>
<td>Normal.</td>
<td>2</td>
<td>75</td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>All experiments.</td>
<td></td>
<td>13</td>
<td>52</td>
<td>15</td>
<td>53</td>
<td>28</td>
</tr>
</tbody>
</table>

and immediately after, when hyperglycemia was greatest. After injection the curves gradually flattened out into a straight line.

A general summary of the relative areas of the 56 duplicate blood sugar curves is presented in Fig. 6. Inspection of this figure shows the following: First, the amount of glucose being equal, the area of a blood sugar curve was much greater following intravenous injection than following oral administration of the glucose. This was especially true when large amounts of glucose were used. In Fig. 6 the area of the first double column (representing the curves following injection of 1.5 gm. per kilo of glucose) is more than 8 times the area of the second double column (representing curves following ingestion of the same amount of glucose). Second, with
both methods of administration the area of the second curve with relation to the first was much smaller when larger amounts of glucose were used. This is seen most clearly in the heights of the columns at the bottom of the figure. Following the oral administration of 1.5 gm. per kilo, the second curve was approximately one-fourth the area of the first. With 0.75 gm., it was one-half the area of the first, and with 0.33 gm., it was of approximately the same area. In other words, the relative area of second curves, roughly speaking, was inversely proportional to the amount of glucose ingested. The contrast in the response to

![AREAS OF DUPLICATE CURVES](chart.png)

**Fig. 6.** Graphic representation of the relative areas of first and second injection and ingestion curves following administration of various amounts of glucose. In the upper part of the chart the ordinate represents the area of the curves expressed in sq. mm. The method used in measuring the area is explained in the text. In the lower part of the chart the ordinate represents the area of the second curve with reference to the area of the first. The measurements are grouped into the experiments in which 1.5, 0.75, and 0.33 gm. per kilo of glucose were used. In the upper half of the chart areas of initial curves are represented by solid columns and of duplicate curves by dotted columns.
large and small doses was not so marked when glucose was injected. It would seem clear that small amounts of glucose do not over-stimulate the sugar-regulating mechanism to the same degree as large amounts. Third, with large amounts of glucose the sugar-disposing mechanism was stimulated more by ingestion than by injection of glucose. Following intravenous injection of 1.5 gm. per kilo (two experiments) the second curve was three-fourths the area of the first, whereas where glucose was ingested the second curve was but 28 per cent of the first (first two columns at the bottom of Fig. 6). If we exclude the four experiments in which the second dose of glucose was ingested when blood sugar was elevated, the proportion is 54 per cent.

There are various possible explanations of this fact that a second dose of glucose when given by mouth does not cause as great an increase of blood sugar as when injected intravenously. First, in contrast with injected glucose, the second dose of ingested glucose may not enter the blood as rapidly as the initial dose. We have no means of knowing how important this factor is. Second, the fact that ingested glucose enters the blood stream more slowly than we injected it may influence the height of curves. Holm (13) has reported that a given dose of insulin has a more marked effect when injected over a period of hours than when injected in one dose. As we have already pointed out, in the experiments shown in Fig. 5, when sugar was injected at a slow rate, at the end of injection 8 per cent more sugar had disappeared from the blood than when sugar was injected at a faster rate. However, if the total areas of the second curves, instead of the height of glycemia, are considered, we find that the experiment in which glucose was injected more slowly showed the larger area for the second curve. Our observations are too few to permit conclusions on this point. Third, it is possible that glucose which is injected directly into the blood stream causes less stimulation of the blood sugar-regulating mechanism than glucose which passes first through the intestines and liver. The experiments of Franke and Wagner (14) in which they find that after peritoneal injections of glucose the fermentable sugar is transformed into higher non-fermentable carbohydrates only after a certain period of time, suggest this. It is evident that the sugar-regulating mechanism receives greater stimulus from ingested than from injected glucose, but we have no means of judging which of the factors named is most concerned.
Our experiments confirm the importance of glucose as a stimulator of the blood sugar-regulating mechanism of the body. Elsewhere (11) we shall present observations concerning the alimentary hyperglycemia which occurs in fasting, a condition which apparently is due to lack of stimulation of the sugar-regulating mechanism. Maclean and de Wesselow (2) thought that such stimulation became effective only when concentration of sugar in the blood exceeded the renal threshold. Although, as we have seen, the process of removal of sugar from the blood was greatly increased when glycemia was great, in many of the ingestion experiments this process was hastened when there was but slight increase in blood sugar. Our experiments would seem to demonstrate that the degree of stimulation of the sugar-disposing mechanism is dependent not on the height of blood sugar per se, but rather on the amount of glucose introduced into the body. Our experiments do not permit analysis of the possible factors concerned in the increased rapidity with which sugar is removed from the blood. Such factors are an increased rate of oxidation of glucose or of its absorption into the tissues or an increased rate of glycogen formation. Foster (1) believes the last named factor is the one of most importance.

The foregoing observations are concerned only with non-diabetic subjects. In such subjects preliminary administration of 0.33 gm. per kilo—about 20 gm. in all—of glucose seems to have little influence in hastening removal from the blood of a subsequent similar dose of glucose. The behavior in diabetic patients would seem to deserve some study. It is possible that patients could utilize carbohydrate food better if it were given in small amounts frequently repeated.

SUMMARY.

We have performed 56 experiments in which duplicate amounts of glucose were administered at intervals of from 20 minutes to 2 hours. In twenty-six of the experiments glucose was given intravenously, and in thirty it was given by mouth.

1. The response of various subjects, and of the same subjects to the two methods of administration, differed greatly.

2. Following ingestion of various amounts of glucose, the average area of the second curves was inversely proportional to the amount of glucose ingested.
3. Areas of curves were much larger following injection than following ingestion of glucose. Also, areas of second duplicate curves (in relation to initial curves) were larger when glucose was injected than when it was ingested. Following double injection of glucose, hypoglycemia as low as 48 mg. per 100 cc. of blood was reached.

4. These observations emphasize the importance of glucose as a stimulator of the blood sugar-regulating mechanism of the body.

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