STUDIES IN COELIAC DISEASE: GLUCOSE ABSORPTION

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A consecutive series of 46 children suffering from coeliac disease presented an opportunity to study various aspects of this strange condition. The beneficial effect upon fat absorption resulting from a withdrawal of starch from the diet has already been described (Sheldon, 1949), while in a later communication (Sheldon and MacMahon, 1949) the failure to produce a similar response in pancreatic fibrosis was noted, together with the conclusions to be drawn from a study of chylomicron counts in coeliac disease.

Oral Glucose Curves

It is widely acknowledged that glucose administered orally to coeliac children causes a relatively flat blood sugar curve, the rise of blood sugar above the fasting level being less than 40 mg. per 100 ml., which is usually accepted as the lower limit of the normal rise. During the initial period at the onset of the disease the blood sugar curve according to Ross and Tonks (1938) may show a high rise, which, within a few weeks, as the illness becomes established, changes to the typical flat curve. Macrae and Morris (1931), and Hardwick (1939) have pointed out that during periods of clinical improvement the blood sugar curve tends to become more normal. It seems clear that in estimating the significance of the blood sugar curve, account must be taken of the phase of the illness at the time of the investigation.

We have been able to confirm that the blood sugar curve improves as the children respond to treatment. Our results are shown in Fig. 1. The continuous line represents the average curve† for normal children between 1 and 5 years of age, and was obtained by averaging the figures from 29 normal children.

The broken line shows the average curve obtained from 33 children at the time of their admission to hospital with coeliac disease; in them the illness was

firmly established, and recovery had not yet begun. The dotted line shows the average curve from 31 children with coeliac disease at a time when their weight had risen by several pounds, and their clinical condition had much improved although they had not yet completely recovered. It will be seen that, as the clinical condition improves, the blood sugar curve tends to move towards the normal.

The method employed in the coeliac and the normal children was the same. The amount of glucose in grammes was calculated from the formula

$$\left(\frac{\text{weight in lb.}}{140} \right)^{\frac{2}{3}} \times 50.$$

The children fasted from 6 p.m. Fifteen hours later the blood sugar was estimated, and the dose of glucose given in about 50 ml. water, further blood sugar estimations being made at half-hour intervals by a modified Folin and Wu method.

FIG. 1.—Oral glucose curves.

Continuous line=average normal curve for children between 1 and 5 years (29 cases).

Broken line=average curve in coeliac children before treatment (33 cases).

Dotted line=average curve in coeliac children during recovery (31 cases).

* Working with grants from the Sebag-Montefiore Fund, and the Cheyne Hospital Research Fund.

† We are indebted to Dr. W. W. Payne of The Hospital for Sick Children, Great Ormond Street, for supplying us with the data necessary for the compilation of this curve.

The Size of the Liver

The cause of the flat oral glucose curve in coeliac children is not fully understood, but it is usually attributed to defective absorption from the intestine. When glucose is given intravenously to these children it is removed from the circulation at a normal rate, and therefore is presumably utilized in a normal manner, and this has been regarded as supporting the contention that the flat oral curve is due to defective absorption. Emery (1947) dissents from this view, bringing forward evidence to suggest that the liver in coeliac children lacks available glycogen, and the amount of glucose given in performing a standard oral glucose curve is almost entirely taken up by this organ. In this connexion the smallness of the liver in children with coeliac disease, to which Still (1918) drew attention, may be of significance.

We have attempted to study the size of the liver in 29 coeliac children by taking tracings at weekly or fortnightly intervals of the lower edge of the liver in relation to the costal margin. This is admittedly a rough method, as the position of the liver may well vary according to the degree of abdominal distension, but the changes were often sufficiently great to make it seem likely that actual variations were taking place in the size of the organ. The method of recording was certainly simple and caused no discomfort to the children; it was carried out by several observers. The results of this investigation are recorded as changes in the distance of the liver edge from the tip of the xiphisternum, that is to say, as measurements in the midline. Changes of less than half-an-inch have been recorded as 'no change'. What changes there were, were gradual, developing over a period of from one to four months during a phase of clinical improvement, and at a time when the diet contained from 1 to 4 oz. of glucose daily.

Our findings showed that the position of the liver edge did not change in seven cases. The liver edge lowered its position from $\frac{1}{2}$ to 1 in. in seven cases; from 1 to $1\frac{1}{2}$ in. in six cases; and from $1\frac{1}{2}$ to 2 in. in six cases.

In eight children, at the time of admission to hospital, the liver was too small for its edge to be palpable. In three children the lower edge of the liver retreated towards the costal margin by distances respectively of $\frac{1}{2}$, 1, and 2 in.

Intraduodenal Glucose Curves

A delay in the emptying time of the stomach has been advanced as one possible cause of defective absorption, and May and McCreary (1940) investigated this aspect by observing the character of the blood sugar curve after giving glucose by tube directly into the duodenum. They used a 10% aqueous solution of glucose, allowing 0.75 g.

glucose per lb. body weight, and found that in normal children there was little difference in the maximum rise of blood sugar whether the glucose was fed by mouth or intubated into the duodenum. In a study of 22 coeliac children with 'flat' oral curves, they found that in 16 the rise in blood sugar was normal when glucose was put into the duodenum while in six children intraduodenal glucose gave a scarcely higher rise than had oral glucose.

Our experience with duodenal glucose curves, the results of which are shown in Fig. 2, has not been quite the same. In the first place we found that the rise of blood sugar in normal children (Fig. 2, continuous line) was considerably higher when glucose was put into the duodenum than when given by mouth, the maximum rise after duodenal glucose averaging 164 mg. per 100 ml. compared with a rise of 50 mg. per 100 ml. after oral glucose. In coeliac children a total of 24 duodenal glucose curves were

FIG. 2.—Duodenal glucose curves.

Continuous line = average normal curve for children between 1 and 5 years (6 cases).

Broken line = average curve in coeliac children before treatment (8 cases).

Dotted line = average curve for coeliac children during recovery (16 cases).

carried out. Of these, eight estimations were made shortly after the children had been admitted to hospital at a time when the disease was definitely established but before improvement had set in (Fig. 2, broken line), and in these the maximum rise in the blood sugar averaged 57 mg. per 100 ml. The remaining 16 estimations were made several weeks after admission to hospital, when the weight was steadily rising, and the clinical condition improving (Fig. 2, dotted line), and in these the maximum rise approached that of the normal children, averaging 143 mg. per 100 ml.

Our technique differed in some respects from that employed by May and McCreary, although it seems doubtful whether these would account entirely for the apparent difference in our results; the difference may, however, be more apparent than real, as May and McCreary have not indicated whether their patients were static or improving at the time of the investigation. In our method, the amount of glucose was calculated by the same formula as for oral glucose curves. No food was given during the previous night. The glucose was given at the isotonic strength of 5% in aqueous solution. Having passed a radio-opaque tube into the duodenum, and confirmed its position under the x-ray screen, an attempt was made to mimic the natural emptying of the stomach by giving the glucose solution in jets each minute, spreading the entire dose evenly over half-an-hour. Having taken a sample of fasting blood, further samples were taken every 15 minutes for the first hour, and thereafter at half-hourly intervals up to two-and-a-half hours. It follows that the administration of glucose was not completed until half-an-hour after the beginning of the test, which explains why the maximum rise in blood sugar was delayed until three-quarters-of-an-hour later.

Barium Meal Studies of Stomach and Intestinal Motility

Studies of the passage of barium through the stomach and small intestine, combined with simultaneous oral glucose curves, led May and McCreary (1940) to conclude that the flat blood sugar curve after oral glucose in coeliac children could be explained either by delay in the emptying rate of the stomach, or by inactive peristalsis and defective segmentation in the small bowel, or by a combination of both. As a result of these abnormal motilities, glucose is prevented from coming into adequate contact with the intestinal mucosa, and it was concluded that there was no specific defect in absorption of glucose inherent in the mucosa in coeliac children. It was also shown that the defects in gastro-intestinal motility could be surmounted by giving glucose together with mecholyl into the duodenum, the absorption of glucose then becoming normal.

A delay in the emptying time of the stomach in

coeliac children has not been a universal finding; in fact Parsons (1932), in his Rachford lectures, quoted Friese and Jahr as having found by radiological examination that food passed rapidly through the stomach, small intestine and beginning of the colon, not allowing adequate time for absorption.

Our barium meal investigations were made by giving 1 oz. per year of age of a suspension of 1 lb. barium sulphate in 1 pint of tap water. We studied 23 coeliac children and 14 normal children as controls. The age of the normal children lay between 3 months and 6 years. The time taken for their stomachs to empty varied between one-and-a-half and three hours; three of the children showed a tendency to a segmentation defect in the lower ileum, indicated by 'clumping' of the barium, otherwise the small intestine pattern was normal.

In the coeliac children the stomach-emptying time varied between one and three hours, which was the same as in the control cases, and we were therefore unable to confirm that the flat glucose curve might be due to delay in the emptying time of the stomach. The passage of the meal through the small intestine was rapid enough for the head of the meal to reach the caecum in one-and-a-half hours, and in 11 of the children the whole of the meal had reached the large intestine in three hours. Forward peristaltic movement through the small intestine tended to be rapid, but in all but three of the 23 children a segmentation defect in the small intestine was apparent, the normal feathery pattern being replaced by 'clumping' of the barium into pellet-like masses. As a rule clumping appeared after an interval of from half to one-and-a-half hours, but in two children with severe coeliac disease there was no preliminary normal pattern, clumping being present throughout the passage of the meal in the small intestine.

Clumping is a well-known occurrence in coeliac disease, but is in no sense diagnostic as it occurs in other intestinal disorders, notably in sprue and idiopathic steatorrhoea of adults. Nevertheless the common occurrence of this segmentation defect in coeliac children must have the effect of preventing a proper contact of the intestinal contents with the mucosa, and could well play a part in accounting for the flat blood sugar curve, and this effect would be aggravated by a combination of clumping with a rapid passage through the small bowel. As, however, clumping does not occur in all cases, and often does not make its appearance until the barium has been in the small intestine for an hour or more, it can hardly be the sole explanation of the flat sugar curve, but must be regarded as a contributory cause.

Stomach Emptying Time for Glucose

Although we were unable to demonstrate that the stomach emptying time in coeliac children was

delayed when an inert substance such as barium was used, it was felt that this might not necessarily be true for glucose. It was therefore decided to approach the question in a different way, avoiding the use of barium.

The method employed was to allow no food or drink from midnight, and next morning a fasting blood sample was taken for sugar estimation. A Ryle's tube was then passed into the stomach and the stomach contents withdrawn by syringe as completely as possible. An amount of glucose calculated according to the standard formula for blood sugar curves was then made up with approximately 50 ml. of warm water, and given down the tube. At subsequent half-hour intervals for two-and-a-half hours the stomach contents were withdrawn through the tube as completely as possible with the child lying on his right side, the total amount at each withdrawal was measured, and then returned to the stomach except for a small sample kept for estimation of the amount of glucose. Blood sugar estimations were also made at half-hour intervals. In this way it was possible to determine how much glucose had left the stomach in each half-hour, and to correlate these findings with the blood sugar curve. The investigation was carried out on seven normal children and on 17 coeliac children. Of the latter, six were investigated shortly after admission to hospital before clinical improvement had begun, and 11 were examined several weeks after admission at a time when clinical improvement was manifest, and the weight was steadily rising. Any method of this sort must invoke a risk of some degree of psychological interference with the stomach emptying rate, but there seemed no reason to suppose that this would affect normal and coeliac children differently, and it must be recorded that the children were singularly good during the procedure, thanks in large measure to the nursing staff who were already on very friendly terms with them.

The results are shown in Fig. 3, where the continuous line represents the stomach emptying rate for glucose in normal children, and the broken and dotted lines represent the stomach emptying rate for glucose in coeliac children at the time of admission to hospital and during the phase of recovery respectively. It will be seen that coeliac children

both before and during a period of clinical improvement tend to empty glucose from the stomach slightly faster than did the children who served as controls. The evidence is therefore against the view that in coeliac disease the stomach emptying time is delayed.

In the preparation of Fig. 3 the results of the

FIG. 3.—Stomach emptying rate for glucose.

Continuous line = average stomach emptying rate for glucose in normal children (7 cases).

Broken line = average stomach emptying rate for glucose in coeliac children before treatment (6 cases).

Dotted line = average stomach emptying rate for glucose in coeliac children during recovery (11 cases).

individual investigations that make up each group have been added together, and the amount of glucose leaving the stomach in successive half-hours has been expressed as a percentage of the total amount of glucose received by the group as a whole. The actual figures for each of the three groups are given in Table 1.

TABLE 1
STOMACH EMPTYING TIME FOR GLUCOSE

Total Amount of Glucose Received by	Amount of Glucose (g.) Leaving the Stomach in				
	First $\frac{1}{2}$ hr.	Second $\frac{1}{2}$ hr.	Third $\frac{1}{2}$ hr.	Fourth $\frac{1}{2}$ hr.	Fifth $\frac{1}{2}$ hr.
7 control cases, 113.5 g. ..	47	31.4	14.6	9.3	9.3
6 coeliacs before treatment, 93.5 g.	59.7	15.8	8.7	7.0	1.0
11 coeliacs during recovery, 184.5 g.	107.3	41	24.4	8.0	3.3

TABLE 2
STOMACH EMPTYING TIME FOR GLUCOSE IN COELIAC BOY AGED 4 YEARS*

Time	Volume (ml.) of Stomach Contents	Glucose (%) in Stomach Contents	Weight of Glucose (g.)	Weight of Glucose (g.) Leaving Stomach in Previous $\frac{1}{2}$ Hour	Blood Sugar (mg. per 100 ml.)
<i>First investigation on July 8, 1949 (weight 22 lb.)</i>					
Fasting (15 g. glucose orally)					96
$\frac{1}{2}$ hour	30	6.25	1.9	13.1	114
1 hour	5	1.8	0.1	1.8	107
$1\frac{1}{2}$ hours	4	1.4	0.06	0.04	109
2 hours	3	0.55	0.02	0.04	90
$2\frac{1}{2}$ hours	1	0.46	0.005	0.01	95
<i>Second investigation on October 5, 1949 (weight 33 lb.)</i>					
Fasting (18 g. glucose orally)					94
$\frac{1}{2}$ hour	44	13.4	5.9	12.1	141
1 hour	33	5.4	1.8	4.1	113
$1\frac{1}{2}$ hours	8.5	1.95	0.15	1.65	105
2 hours	1.5	0.85	trace	0.15	97
$2\frac{1}{2}$ hours	1.5	0.1	trace	trace	86

* Admitted June 29, 1949.

The method used in expressing the results obtained in any individual case can best be illustrated by quoting an actual example. Thus Table 2 gives the results obtained from a boy with coeliac disease, who was admitted to hospital when 4 years old, having been ill for two years. His first investigation was carried out nine days after admission, when his weight was only 22 lb.; it was repeated three months later when considerable clinical improvement had taken place, and his weight had risen to 33 lb.

The blood sugar figures from this child illustrate what was a general finding, namely that the rate at which glucose emptied from the stomach bore a relation to the shape of the blood sugar curve. Thus, when most of the glucose escaped from the stomach during the first half-hour, the maximum rise in the blood sugar level also occurred after half-an-hour. When the amount of glucose leaving the stomach was more evenly spread over the first hour or hour-and-a-half, the maximum rise in the blood sugar level was correspondingly delayed. This is illustrated in Table 3, which gives the figures for a coeliac child aged $2\frac{1}{2}$ years who was investigated several weeks after admission to hospital at a time when the

weight was steadily rising. His stomach emptying time for glucose was the slowest of all the children examined, and his blood sugar curve, although showing a rise of 40 mg. per 100 ml., was correspondingly prolonged.

Summary

The flat blood sugar curve after oral glucose in coeliac children is confirmed, and evidence is produced to support the claim of previous writers that this curve tends to move towards the normal as recovery proceeds.

In normal children the blood sugar curve shows a considerably higher rise when glucose is put into the duodenum than when given by mouth.

In active coeliac disease, glucose put into the duodenum gives a relatively flat curve when compared with the curve in normal children. As the clinical condition improves the curve recovers towards the normal.

Barium meal studies did not reveal delay in the emptying time of the stomach. Forward peristalsis

TABLE 3
RELATION OF BLOOD SUGAR TO GLUCOSE

	Fasting	First $\frac{1}{2}$ hr.	Second $\frac{1}{2}$ hr.	Third $\frac{1}{2}$ hr.	Fourth $\frac{1}{2}$ hr.	Fifth $\frac{1}{2}$ hr.
Glucose (g.) leaving the stomach after initial dose of 18 g. ..		4.85	5.5	3.0	3.1	0.7
Blood sugar (mg. per 100 ml.) ..	98	120	134	120	138	105

in the stomach and small intestine was at least as rapid as in normal children. A segmentation defect in the small intestine was apparent in most of the coeliac children, and may well be a contributory factor in accounting for the flat blood sugar curve.

The rate at which glucose leaves the stomach has been studied, and the conclusion has been drawn that in general glucose leaves the stomach of coeliac children a little faster than in normal children. It has not been possible to establish that the stomach emptying rate in coeliac children is delayed, and therefore this is not regarded as a factor contributing to the flat blood sugar curve.

Attention is drawn to the change in position of the lower border of the liver during the course of coeliac disease. It is thought that this may indicate an actual change in the size of the organ.

It is a pleasure to record our indebtedness to Dr. W. W. Payne and the Biochemical Department of The Hospital for Sick Children, Great Ormond Street, where the numerous sugar estimations embodied in this report were carried out.

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