HYPOGLYCEMIC REACTIONS FOLLOWING GLUCOSE INGESTION

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The blood sugar in normal individuals is maintained at a relatively constant level from day to day. The sugar is being continually drained from the blood stream for storage or oxidation in the tissues and is constantly being supplied to it from the liver. After taking carbohydrate food the blood in the portal vein is enriched with glucose and the liver storehouses are replenished. The blood in the systemic circulation has a greater amount of sugar for a short time after the meal than is found in the fasting condition. When insulin is given an increase both in the storage of glycogen in the liver and in the oxidation of glucose has been noted but the exact rôle played by insulin in performing these functions is still obscure. Conditions which may affect the level of the blood sugar include disturbances in the liver which may affect storage in and release of sugar from this organ and changes in the amount or quality of the internal secretion of the pancreas—insulin.

There is some variation in the normal level of the blood sugar depending on the method used. Most observers consider blood sugar readings between 80 and 120 mgm. per 100 cc. of blood as normal. Some would place the normal range between 85 and 115 mgm. In this discussion any blood sugar reading below 80 mgm. is taken as evidence of hypoglycemia. In a recent review of blood sugar methods Folin and Svedberg (1) pointed out that if plasma is used for the determination of the blood sugar instead of whole blood the discrepancies noted by many observers between the amount of fermentable sugar and the amount of reducing substances in the blood will disappear.

Many conditions have been reported where hypoglycemia was found either with or without symptoms and a brief review of some of these reports may be of interest.

1. Fasting. Griffith (2) found levels between 28 and 54 mgm. in 9 children who were having convulsions which could be relieved temporarily by glucose ingestion. Some of these children were vomiting and some had infections but all were taking very little nourishment. He considered

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the possibility that the muscular contractions during the convulsions may have been in part responsible for depleting the blood sugar. Josephs (3) reported 10 children who had fasting blood sugars between 36 and 60 mgm. and he discussed fasting, infections, and constitutional factors as possible causes. Talbot, Shaw, and Moriarty (4) in epileptic children who fasted noted that the blood sugar usually fell below 50 mgm. sometime between the 3rd and the 6th days of the fast period. They found that symptoms of a hypoglycemic nature were more common if the fluid intake was inadequate and that the younger the child the greater the fall of the blood sugar as a result of fasting. Ashe, Mosenthal and Ginsberg (5) in a man with chronic nephritis who was having muscular twitchings and vomiting noted a blood sugar as low as 30 mgm. They did not feel that the twitchings which were present at this time were due to the hypoglycemia alone for they were present when the blood sugar was raised to 750 mgm. by the injection of glucose.

2. Physical exhaustion. The prolonged demand for glucose in continued muscular activity may lead to depletion of sugar in the body. Levine, Gordon et. al. (6, 7) classified the condition of runners in a Marathon race on the basis of the sugar in the blood at the end of the race. They found that the men who showed the most exhaustion had blood sugars below 50 mgm., those who finished in fair condition were between 60 and 70 mgm. and those who were in the best condition were above 80 mgm. Winans (8) studied a patient with a fasting sugar between 70 and 80 mgm. who after an hour of exercise was exhausted and had a blood sugar of 68 mgm. Comment has been made in the preceding section on the influence of convulsions on the blood sugar. Nervous exhaustion also may play its part as pointed out by Hoxie and Lisherness (9), who found that 95 subjects out of 307 reported had fasting blood sugar levels below 70 mgm. They point out that most of these patients showed symptoms of overwork, debilitating disease, or worry.

3. Low renal threshold for glucose. In patients with renal glycosuria a moderate depression of the blood sugar is sometimes found. Fischler and Ottensoozer (10) observed symptoms in phlorizinized dogs which were similar to those seen after injections of insulin.

4. Diseases of the liver. The removal of the liver in animals is followed by a sharp fall in the blood sugar (Mann and Magath, 11). Hypoglycemia has been reported in patients whose liver has been severely damaged by hydrazin, chloroform, phosphorus or white snake root. Cross and Blackford (12) found blood sugars of 27 and 35 mgm. with definite symptoms of hypoglycemia in a patient with severe toxic hepatitis resulting from neosalvarsan. Nadler and Wolfer (13) noted low blood sugars in a patient with primary liver cell carcinoma. The changes in the liver must be marked to result in hypoglycemia for it is not present in patients with cirrhosis of the liver. Wakeman and Morrell (14) noted
that the blood sugar of monkeys which had been infected with yellow fever fell below normal between 24 and 36 hours before death. The level of 45 mgm. was reached in their animals without symptoms of hypoglycemic reaction. They found also a marked depletion of the glycogen in the liver.

5. Oversupply of insulin in the body. The effect of overdosage of insulin in producing hypoglycemia is so well recognized at present that it needs no special consideration.

A relative accentuation of the effect of insulin in the body has been suggested by Pettersson (15) and by Stenström (16) in patients where they noted evidence of diminished activity of other glands and blood sugars between 25 and 50 mgm. Further consideration of the interrelation of internal glandular secretions will be given in the next section. In the past four years reports of patients who have had hypoglycemia with severe symptoms which were due to tumors of the islets of the pancreas have appeared (17, 18, 19, 20, 21). Gray and Feemster (22) reported the case of a child whose mother had diabetes and who died when 3 days old, with a blood sugar of 67 mgm. At autopsy they estimated that the pancreas contained approximately 24 times the normal amount of islet tissue and that there was some hypertrophy of the medullary cells of the adrenals. They suggested that the high sugar level in the maternal blood might have been the stimulus which caused the marked development of the islets in the pancreas of the infant.

6. Endocrine disturbance. Holman (23) reported a patient with exophthalmic goiter who lapsed into coma 24 hours after a thyroidectomy. He found a blood sugar of 48 mgm. The coma was relieved by glucose intravenously. In two other postoperative thyroid patients, the blood sugars were 78 and 80 mgm. He felt that the manipulation of the gland resulted in an excess thyroid secretion which caused a rapid utilization of the available carbohydrate with hypoglycemia.

Porges (24) reported blood sugars between 33 and 67 mgm. in three patients with Addison's disease, Bernstein (25) found the range between 47 and 84 mgm. in four cases and Longcope (26) between 73 and 91 mgm. in five cases. Chapman (27) found only slight elevation in blood sugar after 50 grams of glucose in a patient with Addison's disease, which suggested an increased tolerance for carbohydrate in this condition.

In dogs after removal of hypophysis, Houssay and Biasotti (28) found that some animals developed convulsions and coma with the blood sugar dropping to 70 mgm. and that sugar would relieve the symptoms. They noted that doses of insulin which produced no effect in controls would quickly kill the hypophysioprival animals. The tolerance to sugar was the same in both groups.

Deficiency of adrenal, pituitary or ovarian secretion has been suggested as the cause of the hypoglycemia noted in patients by Laroche,
Lelourdy and Bussière (29), Pettersson (15), Stenström (16), Wilder (30), Oppenheimer (31) and Pribram (32). Experimental evidence has been presented by Blotner and Fitz (33) to show that injections of pituitrin and adrenalin will prevent the usual fall in blood sugar when injected with insulin. Also injections of adrenalin and pituitrin relieve symptoms which are associated with hypoglycemia. Cammidge (34, 35) reported hypoglycemia of 70 mgm. or less in 200 patients. He suggested that patients with low kidney threshold for glucose and with low blood calcium may be suffering from hypoparathyroidism.

The sugar level in the blood appears to be the result of a balance between the internal secretions of the thyroid, pituitary, and adrenal glands on one side and of the islets of the pancreas on the other.

7. Miscellaneous conditions. Hypoglycemia has been noted in progressive muscular dystrophy, in scleroderma (26), and in a small series of 15 patients with bronchial asthma where the blood sugar varied between 68 and 80 mgm. (36). The influence of changes in the nervous system in producing hypoglycemia has been considered by Hoxie and Lisherness (9) and by Pemberton (37). Schmidt (38) obtained blood sugar readings between 28 and 75 mgm. in 12 out of 33 patients tested one hour or less before death. At autopsy these patients showed no striking pathological lesions which have been identified with the production of hypoglycemia. The rôle of infection as a possible cause has been presented by Pribram (32) and by Cammidge (35).

8. The ingestion of carbohydrate. It seems paradoxical to consider the influence of carbohydrate, which is recognized as the best means of relieving the symptoms related to hypoglycemia, among the causes of hypoglycemia. It has been noted, however, by a number of observers. Folin and Berglund (39) found that after giving 100 grams of glucose the blood sugar rose at first but later it fell below the fasting level with ranges between 54 and 95 mgm. between two and four hours after the meal. Hamman and Hirschman (40) showed that repeated tolerance tests resulted in smaller elevations of the blood sugar, and they point out that the evidence of an increased tolerance for carbohydrate is present when there is only a slight rise after the glucose meal. In this group they noted a greater tendency toward hypoglycemia after the meal. In a patient with renal glycosuria Gibson and Larimer (41) found a fasting blood sugar of 58 mgm. and after 50 grams of glucose the level was at 40 mgm. three and one half hours later and the patient had mild symptoms. Then they gave another 50 grams of glucose and three and one half hours later it was 58 mgm. and slight symptoms were noted again. In three patients with fasting blood sugars between 100 and 105 mgm., Foster (42) found the level between 61 and 81 mgm. two hours after giving 100 grams of glucose. Stenström (43) noted in four patients with fasting blood sugars between 76 and 95 mgm. hypoglycemia about two hours after they had taken 1
gram of glucose per kilo of body weight with readings between 46 and 53 mgm. John (44) found in a tolerance test with 100 grams of glucose that his own blood sugar fell to 45 mgm. at the end of three hours and at that time he noted extreme hunger. Harris (45) studied a patient who felt weak and hungry every day before lunch time and found a blood sugar of 65 mgm. In a tolerance test following 100 grams of glucose the blood sugar was 67 mgm. three hours after the meal. Then one hour later on the way home, this patient became so faint and weak that he could hardly walk. He was very hungry and his symptoms were entirely relieved after taking a meal. Winans (8) reported a patient who had fasting blood sugars between 70 and 80 and who felt worse in the afternoon about three hours after lunch when the blood sugar was found to be 59 mgm.

After fructose Meyer (46) noted in eleven patients that the level of the blood sugar was from 0 to 22 mgm. below the fasting levels. He associated this with a labile vegetative nervous system and after giving atropine to the same patients he found a rise of the blood sugar following the ingestion of fructose. Cathcart and Markowitz (47) after the ingestion of 50 grams of dihydroxyacetone found blood sugars between 50 and 78 mgm. which were associated with flushing, restlessness, and muscular tremors. McClellan, Biasotti, and Hannon (48) after the same amount of dihydroxyacetone found similar depressions in the blood sugar but noted no symptoms.

**CASE HISTORY**

In the patient to be reported we noted on three separate occasions, following the ingestion of 100 grams of glucose, symptoms which were similar to those observed in patients who have had an overdose of insulin. On one occasion the blood sugar taken at this time was 40.6 mgm.

The patient, F. R., was admitted to Bellevue Hospital, December 4, 1930, complaining of swelling of the legs and feet. This had been present about two weeks. He was 37 years of age, German by birth, and a cook by occupation. The past history and family history gave no information which could be related to his present condition. The patient had been out of work for about three months. He had been living entirely on soup and vegetables with no meat except an occasional piece of smoked ham. Two weeks previous to admission he noted that both feet and legs were swollen and that there was occasional itching and burning of the feet. The swelling decreased only slightly after a night's rest in bed. There had been numerous blisters on his feet and when he removed his shoes to ease the discomfort it required two to three hours for the swelling to recede sufficiently to allow him to put on his shoes again. There were no symptoms particularly referable to either heart or kidney.

On admission, the physical examination showed an adult, white male who was not acutely ill. There was marked pitting edema of both feet and ankles and in the left leg this extended almost to the knee. There was no evidence of phlebitis. There were no ulcerated areas on the feet at this time.

The condition was considered one of nutritional edema and he was admitted to the metabolism ward for special observations.
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The laboratory data showed that his urine was normal and his blood Wassermann negative. The findings for his blood chemistry on December 11, 1930, are presented in Table I.

**TABLE I**

*The blood chemistry findings of F. R. on December 11, 1930, one week after admission to the hospital*

<table>
<thead>
<tr>
<th>Nonprotein nitrogen</th>
<th>45.0 mgm. per 100 cc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sugar</td>
<td>81.0 mgm. per 100 cc.</td>
</tr>
<tr>
<td>Blood chlorides</td>
<td>480. mgm. per 100 cc.</td>
</tr>
<tr>
<td>Blood phosphorus</td>
<td>5.0 mgm. per 100 cc.</td>
</tr>
<tr>
<td>Blood calcium</td>
<td>12.4 mgm. per 100 cc.</td>
</tr>
<tr>
<td>CO₂ combining power</td>
<td>57.6 volumes per cent</td>
</tr>
<tr>
<td>Total serum protein</td>
<td>6.28 grams per 100 cc.</td>
</tr>
<tr>
<td>Albumin protein</td>
<td>3.53 grams per 100 cc.</td>
</tr>
<tr>
<td>Globulin protein</td>
<td>2.75 grams per 100 cc.</td>
</tr>
</tbody>
</table>

In the ward he was placed on a diet of 3000 calories and his edema entirely disappeared at the end of 48 hours. He was observed for a period of two months with diets containing both large and small amounts of carbohydrate. Details of the food taken and the analyses of the urine for the period of observation are presented in Table II.

**TABLE II**

*Data of food ingested and the analyses of urine given as the average daily findings for each period of the observation*

<table>
<thead>
<tr>
<th>Period number</th>
<th>Number of days</th>
<th>Weight kgm.</th>
<th>Calories</th>
<th>Protein grams</th>
<th>Fat grams</th>
<th>Carbohydrate grams</th>
<th>N₂ grams</th>
<th>Acetone bodies cc.</th>
<th>Acidity 0.1 N cc.</th>
<th>Volume cc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>5</td>
<td>55.7</td>
<td>2800</td>
<td>80</td>
<td>134</td>
<td>300</td>
<td>12.8</td>
<td>12.5</td>
<td>339</td>
<td>1632</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>56.4</td>
<td>2976</td>
<td>79</td>
<td>133</td>
<td>344</td>
<td>12.6</td>
<td>9.8</td>
<td>319</td>
<td>1900</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>56.2</td>
<td>3000</td>
<td>80</td>
<td>133</td>
<td>350</td>
<td>12.8</td>
<td>9.1</td>
<td>310</td>
<td>1656</td>
</tr>
<tr>
<td>IV</td>
<td>7</td>
<td>56.7</td>
<td>2911</td>
<td>75</td>
<td>128</td>
<td>344</td>
<td>12.0</td>
<td>8.4</td>
<td>156</td>
<td>1310</td>
</tr>
<tr>
<td>V</td>
<td>10</td>
<td>57.1</td>
<td>2962</td>
<td>76</td>
<td>131</td>
<td>350</td>
<td>12.2</td>
<td>8.6</td>
<td>249</td>
<td>1376</td>
</tr>
<tr>
<td>VI</td>
<td>9</td>
<td>57.4</td>
<td>2922</td>
<td>78</td>
<td>237</td>
<td>90</td>
<td>12.5</td>
<td>9.5</td>
<td>352</td>
<td>1484</td>
</tr>
<tr>
<td>VII</td>
<td>7</td>
<td>56.6</td>
<td>2878</td>
<td>78</td>
<td>264</td>
<td>25</td>
<td>12.5</td>
<td>11.1</td>
<td>529</td>
<td>1411</td>
</tr>
<tr>
<td>VIII</td>
<td>6</td>
<td>57.5</td>
<td>2847</td>
<td>73</td>
<td>127</td>
<td>333</td>
<td>11.7</td>
<td>8.4</td>
<td>0.80†</td>
<td>224</td>
</tr>
</tbody>
</table>

* First day omitted.
† First 2 days of period.

The special studies carried out included observations of his respiratory metabolism in the calorimeter following the ingestion of 100 grams of glucose. In each of the three observations made he developed symptoms about four and one-half hours after the ingestion of the glucose, which made it necessary on each occasion to terminate the observation. It was not until the second occurrence of the symptoms that their similarity to those following the injection of insulin was considered. For that reason actual observation of the blood sugar was made only once, when it was found to be 40.6 mgm.
The finding of this low level of blood sugar suggested the possibility that this man might be suffering from a mild degree of hyperinsulinism. A single blood sugar time curve was obtained after giving him 100 grams of glucose. Mild symptoms including slight dizziness, flushing of the face and moisture on the skin were noted three and one-half hours after giving the glucose when his blood sugar was 60.5 mgm. He left the hospital against our advice on February 12, 1931, with a diagnosis of alimentary hyperinsulinism.

DISCUSSION

A. The effect of the ingestion of glucose on the blood sugar

As has been pointed out in the review of previous work on this subject, the response of the body to the ingestion of glucose depends in a large part on the previous diet which the patient has been receiving. The relatively high levels to which the blood sugar rises in the tolerance test with patients in whom the carbohydrate in the diet has been markedly restricted is well established by the work of Malmros (49) and others. Tolstoi (50) found that the Arctic explorers who had lived on an exclusive meat diet for one year showed high levels of the sugar in the blood during tolerance tests following 100 grams of glucose.

We have made a few observations of the blood sugar tolerance curves of five subjects, some of whom were receiving high carbohydrate diets and others of whom received only 25 grams of carbohydrate per day. While our series is not of sufficient size to warrant statistical consideration, still the curves obtained seem worth reporting. After the fasting blood was obtained the men were given 100 grams of glucose in the form of 104 grams commercial glucose, 100 grams orange juice and 200 cc. of water. The samples of blood were obtained at 45, 90, 150, 210 and 270 minutes after the ingestion of the glucose. The analyses of sugar in the blood were made in duplicate samples by the modified Hagedorn-Jensen method (51). In a few of the tests the analyses were checked by the Folin-Wu method (52). Curves showing the results of these tolerance tests and the composite curve for each group are presented in Chart 1.

There was some scatter in the observations of the men who had been receiving in their diets large amounts of carbohydrate. In two subjects, F. R. and W. C., scarcely any elevation in the blood sugar was noted; in the subject E. A. following a period on a low carbohydrate diet, the highest level of the blood sugar was found. It should be pointed out that this subject received only 45 grams of protein in his diet when the test was made, while the other two subjects were receiving 90 grams per day. This may in part account for the higher level observed in this subject. Another point of particular interest was the finding that after four and one-half hours following the ingestion of glucose the level of the blood sugar in all subjects was at almost the same level regardless of whether they had been receiving high or low carbohydrate diets. No
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Chart 1. The Blood Sugar Time Curves of Five Subjects with Reference to the Nature of the Previous Diet. The first group were made when the patients were receiving 350 to 400 grams of carbohydrate daily in the diet, and the second group when they were receiving only 25 grams daily. The broken line is the composite curve for each group.
symptoms referable to hypoglycemia were noted in any subject except F. R., the one whose special observations are being presented in this paper.

B. Relation of level of the blood sugar to the occurrence of symptoms

Most observers consider that a blood sugar of 80 mgm. is the lower limit of the normal range. Below this point blood sugars ranging between 60 and 80 represent a mild hypoglycemia and are usually not associated with definite symptoms. When the level is below 60 some symptoms are usually expected. In our subjects levels below 60 occurred four times but in only one instance were any symptoms noted. One observation of the subject F. R., who developed symptoms of hypoglycemic reaction while in the calorimeter, showed at that time a level of 40.6 mgm. In the subject E. A. a level of 34.0 mgm. was reached in one tolerance test without the development of symptoms. It would appear from our observations that the development of symptoms must be associated with some other factor than just the level of sugar in the blood alone. Inasmuch as the symptoms are similar to those seen in overactivity of the sympathetic nervous system, it seems possible that the development of symptoms may be in some way associated with different degrees of sensitivity in this system.

C. The respiratory metabolism

The basal metabolism of the subject F. R. as determined in the Sage calorimeter was 62 calories per hour, which represented 97 per cent of the average normal metabolism determined by the Aub-DuBois standards (53). The metabolism following the glucose meals which resulted in the hypoglycemic reaction described above is presented in Chart 2. In each observation the record covers the second, third, and fourth hours following the ingestion of the glucose. The reaction in each case occurred early in the fifth hour so that no accurate results were obtained of his metabolism at that time. The first two observations were made while he was receiving a diet containing 80 grams protein, 133 grams fat and 350 grams carbohydrate. The last observation followed a period when he received only 25 grams carbohydrate in his diet. His response to the ingestion of glucose under these conditions showed two striking differences. First, a marked rise in the respiratory quotient to nearly 1.00, which shows that his energy was being derived almost exclusively from carbohydrate in the observations following the high carbohydrate diet. Second, the absence of any marked rise in the respiratory quotient in the observation following the low carbohydrate diet, which indicates that he was using only slightly greater amounts of carbohydrate in this observation than he did when in basal condition. The hatched portion at the bottom of each column represents the calories derived from the protein
metabolized, the clear portion of the column the calories derived from fat and the vertical lining the portion from carbohydrate.

The disposal of the 100 grams of carbohydrate in this subject under the two conditions studied differs materially. In the three hours observed in the first two observations 42 grams of carbohydrate were ac-

![Graph](chart2.png)

**Chart 2. The Respiratory Metabolism of F. R. in Basal Condition and After Glucose Ingestion**

The nature of the previous diet and the excess metabolism is indicated. The height of the columns shows the total metabolism per hour and the calories resulting from the metabolism of protein are represented by the hatched portion at the bottom of the column, those from fat by the clear space and those from carbohydrate by the vertical lined portion at the top. The curves show the changes in the level of the respiratory quotient.

actually oxidized while in the last observation only 23 grams were metabolized. At no time did we find more than a trace of glucose in his urine. It appears then that when there was an adequate supply of glycogen in the body, the subject actually metabolized a much greater portion of the ingested glucose than he did when the glycogen stores were depleted by a
restriction of his carbohydrate preceding the last observation. We assumed, then, that in the last case storage of the ingested carbohydrate was the principal method of its disposal in the body. A more complete discussion of the metabolism of glucose under these conditions is to be presented in another communication.

As far as we can find in the study of the literature this subject is the first in whom observations of the respiratory metabolism have been made during the period preceding the development of a spontaneous hypoglycemic reaction. The fact that he developed reactions both when he had an adequate supply of glycogen in his body and also when the supply of glycogen had been depleted indicates that a lowering of the blood sugar to a level at which reactions may occur can result either from the excessive oxidation of carbohydrate in the body or from excessive storing of the glucose ingested, or from both factors working together.

D. The treatment of hyperinsulinism

The use of frequent ingestion of carbohydrate food has been recommended in the treatment of patients who suffer from spontaneous hypoglycemia. While this definitely relieves the symptoms in these patients the possibility that it may stimulate the natural production of insulin in the body must be considered. For that reason some people have advocated the use of diets containing greater amounts of fats. The fact that in our subject a reaction occurred after giving the glucose at the end of one week on a high fat, low carbohydrate diet seems to indicate that the use of high fat diets may not be of much value in treating these conditions although the evidence which we have presented only indirectly supports this conclusion.

SUMMARY AND CONCLUSIONS

1. Observations have been made of the respiratory metabolism of a patient who on three different occasions developed symptoms of hypoglycemia about four and one-half hours after the ingestion of 100 grams of glucose.

2. A review of the conditions which may produce hypoglycemia is presented.

3. In the patient studied a depression of the blood sugar to the level which resulted in symptoms occurred twice as a result of excessive oxidation of carbohydrate, and once as a result of excessive storage.

4. The blood sugar time curves of five patients were studied and wide variations were found which depended largely on the diet which the individuals had previously received. The interpretation of every blood sugar time curve should be based on a knowledge of the previous diet.
BIBLIOGRAPHY

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