CARBOHYDRATE UTILIZATION.

I. RATE OF DISAPPEARANCE OF D-GLUCOSE FROM THE BLOOD.

By VINCENT DU VIGNEAUD AND WALTER G. KARR.

(From the Biochemical Laboratories of the Philadelphia General Hospital and the Graduate School of Medicine of the University of Pennsylvania, Philadelphia.)

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Although the disappearance of d-glucose from the blood has been used as the basis of many clinical investigations for the testing of the tolerance of the body for glucose, very little is really known of the factors involved in this mechanism of regulating and maintaining the blood sugar level.

The alimentary sugar tolerance test depends on giving a definite amount of d-glucose per kilo body weight and on determining the blood sugar concentration before the test and at certain intervals thereafter. Normally the blood sugar rises to a maximum at about the hour period and returns to the normal level within 1 to 2 hours.

It has been shown by a number of investigators that the fall in the blood sugar is not due to absorption. Johansson (1), by x-ray examination, gave evidence that the absorption of 200 gm. of glucose is not complete until after about 4 hours. Indirect evidence was obtained by Janney and Isaacson (2) that absorption was not a factor in their experiments. They followed the excretion of nitrogen after the feeding of meat to their dogs before and after thyroidectomy in which they found a decreased tolerance. MacLean and de Wesselow (3) found that additional large doses of sugar given during the height of absorption failed to raise the blood sugar above the previous level. Furthermore, these same investigators, as well as Foster (4), Hamman and Hirschman (5), and others have found that a second dose of sugar, given after the return of the blood sugar level to normal from the effects of the first dose, gives little if any rise in the blood sugar value. Our own results support this.

When the glucose is introduced into the alimentary canal, it is readily absorbed from the gut, thence passing into the blood causing an increase in the blood sugar concentration. At some time during the rise of the blood
sugar a mechanism is stimulated that soon takes the sugar out of the blood at a faster rate than it is being absorbed, bringing the blood sugar back to normal or even slightly below normal. By tolerance for sugar, in this paper, we mean the ability of the organism to remove this excess sugar from the blood, or in other words the rate of disappearance of the sugar from the blood. We are not interested in the amount of sugar excreted in the urine. MacLean and de Wesselow (3) have put forth the hypothesis that it is the presence of an excess of sugar in the circulation that stimulates the mechanism that deals with sugar. This is strongly supported by Foster (4). Although sugar must stimulate this mechanism as shown by the successive tolerances, there must be some other factors than the concentration of the blood sugar itself, as we shall show later. Greenwald (5), although agreeing with the excess sugar stimulation hypothesis in part, nevertheless felt that hyperglycemia itself could not explain the results he obtained in the lowering of sugar tolerance by fat diets and not proteins. There seems no doubt, though, that there is some mechanism that is dormant during the first part of the tolerance test, which is then stimulated to action.

What this mechanism is, we can only hypothesize for the present. We do know though that the glycogenetic function of the liver and muscles is a major part, and that the endocrine secretions are intimately concerned.

Foster (4) has suggested that the ingestion of glucose or the hyperglycemia that ensues stimulates the pancreas to put out its internal secretions which then operates in some way to accelerate both glycogen formation and oxidation of sugar. This investigator further points out that the muscle tissues are more important in connection with glycogen storage than perhaps generally believed. Evidence for this is based on the great difference between the sugar concentration of the arterial and venous blood after the ingestion of glucose. Cori and Cori (7), Frank, Nothmann, and Warner (8), and Lawrence (9), have also found a greater difference between arterial and venous blood during the action of insulin. These facts emphasize the importance of the muscles and tissues in the mechanism of taking sugar out of the blood. Mann and Magath (10) have shown that the liver is not concerned with the fall in blood sugar due to insulin but that it is necessary for the return to normal.

We generally speak of the glycogen formation in connection with disappearance of sugar from the blood. However, there are many indications that this disappearance of the sugar is due to the formation of substances other than glycogen. Macleod (11) states in his review on insulin: "... the outstanding facts are that insulin causes the sugar of the blood (and tissues) to diminish both in the normal and diabetic animal partly because of the increase in the relative amount of carbohydrates that is metabolized and partly because some of the glucose is converted into non-saccharine material, which is mainly glycogen in diabetes but is some other substance in the normal animal." Palmer (12) came to the conclusion that there are present in muscle tissue higher sugars or polysaccharides of which maltose probably constituted the largest.
Since phosphorus has been found to decrease in the blood after the injection of insulin, it is highly indicative that the substance formed might be a phosphoric acid complex (6, 13-16). Although they found that there was a fall in the organic phosphates of the blood after insulin, Blatherwick, Bell, and Hill (13) did not find that the ingestion of glucose itself had any definite effect on the phosphates of the blood. This tends to support the idea that the process of taking excess sugar from the blood normally is different in principle from the effect of injected insulin, a point not in accord with the hypothesis of excess sugar in the blood stimulating the pancreas. However, Harrop and Benedict (14) claim a decrease in phosphates after the ingestion of glucose. Besides confirming the latter, Bolliger and Hartman (17) have presented curves showing that the phosphate level remains very constant in diabetes after the ingestion of glucose but that under the influence of insulin the curve behaves normally, showing a drop followed by a rise to normal. Since Cori and Golz (18) have demonstrated that the decrease of the free sugar of the liver is not due to the formation of a phosphate complex, our attention is once more directed to the muscles as the seat of this possible synthesis probably influenced by insulin.

Evidence pointing to the connection of the endocrines with sugar metabolism has been obtained both experimentally and clinically. The sugar tolerance curve has been used in many disorders. It has been used in diabetes, hyper- and hypothyroidism, hyper- and hypopituitarism, Addison's disease, cancer, arthritis, tuberculosis, mental diseases, infection, anemia, nephritis, and cirrhosis of the liver. Consideration of the behavior of these curves, especially in endocrine disorders, may throw some light on the part played by these glands normally or at least indicate whether or not they are connected with the sugar utilization mechanism.

We have already considered the rôle of the pancreas from the standpoint of insulin. The high and prolonged curve in diabetes again points to the importance of the pancreas in the ability of the organism to remove excess sugar from the blood.

Consistent results have also been found in hyperthyroidism; namely, an abnormally high curve indicating a reduced tolerance (19-23). Labbédé, Labbé, and Nepveux (24) suggest the test as a means of differentiating between simple goiter and Basedow's disease, the former giving little if any hyperglycemia while the latter gives a very marked hyperglycemia after the ingestion of 45 gm. of glucose. The reduced tolerance is not connected with the oxidation of sugar as shown by respiratory quotient studies (25). An increased diastatic activity of the blood besides the decreased tolerance has been found in hyperthyroid cases by Killian (23), while in hypothyroid cases the reverse was found. This seems to indicate that the thyroid secretion acts by increasing glycogenolysis rather than by decreasing or inhibiting glycogenesis. Also, Janney (2) has shown that thyroidectomy results in a distinct hypoglycemia. A similar fact was observed by Bodansky, Simpson, and Goldberg (26) in thyroidectomized sheep. McCurdy (27) found that removal of the thyroid
Carbohydrate Utilization. I

raises the assimilation limit for glucose. Furthermore, a great increase in sugar tolerance in myxedema (19, 28). Kuriyama (29) found feeding thyroid to white rats produced a decreased glycogen content of the liver. He did not find, however, that experimental hyperthyroid produced a change in sugar content of the blood in either rats or rabbits. This evidence rather points, although not necessarily, to an inhibition of glycogenesis rather than increased glycogenolysis. Nevertheless, it is certain that disturbances of the thyroid do cause disturbances in the mechanism controlling sugar metabolism, but it is still an open question whether this is done through the thyroid itself or indirectly through effect on the pancreas or on the nervous system.

The relationship between the parathyroid glands and carbohydrate metabolism is not clear, the evidence being somewhat conflicting. In general it is assumed that there is an increased mobilization of carbohydrates in tetany which is considered to be due to decreased parathyroid activity (30).

Cushing (31) has demonstrated the importance of the hypophysis in carbohydrate metabolism. Administration of the posterior lobe extract lowered the sugar tolerance to normal or below normal in animals in which it had been raised by excision of the posterior lobe. The decrease in sugar tolerance has been observed frequently in acromegaly. On the other hand, hypoglycemia and an increased tolerance have been associated with hypopituitarism (19, 28). In dystrophia adiposogenitalis, the carbohydrate tolerance is increased; sometimes it is almost unlimited (32). According to Cushing both the increased sugar tolerance and hypoglycemia can be remedied by injection of posterior lobe extract. Cushing believes that posterior lobe of the hypophysis has a glycogenolytic action. Furthermore, it has been shown that the simultaneous injection of the posterior lobe extract enhances the hyperglycemia induced by intravenous injection of glucose (33). It has also been found that pituitrin causes a rise in blood sugar concentration (34). Kojima obtained changes in the pancreas as a result of feeding pituitary gland (35). However, it must be borne in mind that in hypopituitarism and also in hypothyroidism there is an abnormal formation which may in part account for the increased tolerance.

It is generally accepted that adrenaline, the secretion of the adrenal glands, exerts a strong stimulation on the glycogenolytic function of the body causing a hyperglycemia. In Addison's disease, which is considered to be the result of a hypofunction of the adrenals, there is present a hyperglycemia and the tolerance for glucose is raised (23, 28). Achard, Boe and Binet (33) found that the simultaneous injection of adrenaline and glucose produced a greater hyperglycemia than the sum of the increases obtained from the injection of glucose and adrenaline separately. This indicates that adrenaline prevents the storage of sugar since it has also been shown by Lusk and Riche (36) that adrenaline does not affect the oxidation of glucose.

Tsubura (37) has reported that castration does not lower the fasting blood sugar but that the tolerance for glucose was lowered.
From time to time references have been made in the literature as to the effect of diet and fasting on the carbohydrate tolerance of the body. Kageura (38) found that the hyperglycemia resulting from the ingestion of the Sakeguchi test meal consisting of 100 gm. of rice and two eggs was greater after a carbohydrate-poor diet than after one rich in carbohydrates. He claimed that a protein diet was equally effective in lowering the tolerance to glucose as a fat diet (39). However, as pointed out by Greenwald (6), his protein diet consisted largely of fat. Greenwald found that in both man and dog a fat diet lowered the tolerance to glucose but that a protein diet did not produce this effect, in fact, it had a beneficial rather than detrimental effect. It was observed by Southwood (40) that an increased hyperglycemia resulted in men who had been on a carbohydrate-free diet for 36 hours before the test. Staub (41) found that the hyperglycemic reaction after the ingestion of 20 gm. of glucose was less after a fast of 10 to 15 hours than after one of 5 hours, but that it became more marked after a fast of 24 hours. An increased hyperglycemia was obtained after 2 days on a carbohydrate-free diet and also after severe work. During the work the hyperglycemia was less than at rest. Similar results have been reported by Traugott (42) who found that the ingestion of 20 to 100 gm. of glucose in a normal well nourished man produced a hyperglycemia of 30 to 50 per cent while after 3 days starvation it produced a hyperglycemia of 240 per cent.

We have found in rabbits that fasting greatly decreases the rate of disappearance of glucose from the blood after a hyperglycemia. We have endeavored to ascertain the cause of this decrease and what substances would bring the tolerance back to normal, in other words what stimulates the mechanism for taking the sugar out of the blood. By this we hoped light might possibly be thrown on the process involved in the regulation of the blood sugar level and removal of glucose from the blood.

**Methods.**

The rabbits used in these experiments were bled from the marginal ear vein. About 1 cc. of blood was taken for the determination of the blood sugar which was done by the method of Folin and Wu (43); for the determination of pH the blood was collected from the marginal vein of the ear. The blood was brought to the ear by applying xylol freely. The vein was cut and the blood allowed to collect on the ear in a little pool covered with paraffin oil and the blood pipetted from this. The pH was determined by the method of Hawkins (44). The carbon dioxide capacity was found by the method of Van Slyke and Stadie (45).

In the alimentary glucose tolerance tests the rabbits were given 3 gm. of pure d-glucose per kilo of body weight in 35 cc. of water. The blood sugar was determined at 1/2 hour intervals for
Carbohydrate Utilization.  

1½ hours and then at hourly intervals for 2 hours. In the intravenous tolerances 2 cc. of 50 per cent solution of d-glucosep kilo were injected into the marginal vein of the ear, and blood sugar determined at intervals of ½ hour.

In cases where the tolerance test was made after fasting, the dosage of sugar was based on the weight of the animal before fasting. During the fasting periods the rabbits had water libitum.

**TABLE I.**  
*Alimentary Glucose Tolerance after 1 Day Fast.*

3 gm. glucose per kilo.

<table>
<thead>
<tr>
<th>Rabbit No.</th>
<th>Normal blood sugar per 100 cc.</th>
<th>Periods after ingestion of glucose.</th>
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<tr>
<td></td>
<td>mg.</td>
<td>½ hr. 1 hr. 1½ hrs. 2½ hrs. 3½ hrs.</td>
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<td>17</td>
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<td>125</td>
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<td>11</td>
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<td>260 210 170 155 130</td>
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<tr>
<td>Average...</td>
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<td>184 190 167 138 138</td>
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</table>

EXPERIMENTAL.

*Effect of Fasting on Sugar Tolerance.*

Table I gives the results of feeding 3 gm. of glucose per lb to twelve rabbits that had been fasted 1 day. Table II presents the results of similar tests on nine rabbits that had been fasted for 4 days. The points of interest in these curves are, the height of the curve, the time at which it returns to normal, and especially the time that the maximum of the curve appears. In the case of the 1 day fast curves, the majority have their maximum the ½ hour point and have generally returned to normal with 2½ hours. On the other hand, in the 4 day fasted animals the
maximum comes later, in the majority at the 1½ hour point, and it is considerably higher. There is also a decided delay in the return of the blood sugar concentration to the normal level. At 3½ hours after the ingestion of the glucose the blood sugar is still elevated. The composite curves in Chart 1 bring these points out clearly. In no case has there been a failure to find a decreased tolerance after fasting. The two rabbits with no fast were taken from the pen after having eaten ground grain and bread for 2 to 3 hours ad libitum. The tolerance test was done about ½ hour later. The utilization of the ingested glucose was much better than that of the fasted animals and as we will show later was evidently due to the stimulation of the metabolism by the previous carbohydrate diet.

The effect on the glucose tolerance of separate 1 to 4 day fasts on the same animal is shown in Chart 2. These curves show the gradual decrease in tolerance that is brought about by fasting. This rabbit was fasted 4 days, the tolerance test performed, and the rabbit put back on food for 2 days. After this rest period it was then fasted for 3 days, the tolerance test made, and the animal was put back on food again. In the same way tests were carried out after a 2 day fast and then after a 1 day fast. The results show a gradual decrease in tolerance with the in-

<table>
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<tr>
<th>Rabbit No.</th>
<th>Normal sugar per 100 cc.</th>
<th>⅓ hr.</th>
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<th>1½ hrs.</th>
<th>2⅔ hrs.</th>
<th>3½ hrs.</th>
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<tr>
<td>Average</td>
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<td>192</td>
<td>225</td>
<td>238</td>
<td>220</td>
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crease in the fasting period. This is marked by the height of the curve and the shifting of the maximum point from the 2 hour period to a later one and a delayed return to normal. Loss of weight in itself or the handling of the animals tended to decrease the tolerance, then in this series the tolerance after

1 day fast should have been less than the one after the 4 day fast. The 4 day test was made first, while the 1 day test was made last.

Further evidence for this contention is given by the results on rabbit No. 17 (Chart 3). This one was fasted 19 days, decreasing in weight from 2250 to 1550 gm. After the tolerance test was performed it was put back on food for 3 days, during which time it increased in weight to 1660 gm. It was the
Chart 3. Effect of fasting.

Chart 4. Effect of fasting.
fasted for 1 day and the sugar tolerance repeated. About
weeks later, a tolerance test was made after a 4 day fast,
this time it weighed 1770 gm. before and 1570 gm. after the fed.

The effects of longer periods of fasting are shown in Chart 4. Here the rate of disappearance of sugar from the blood is greatly reduced.
When glucose was introduced intravenously, its rate of disappearance from the blood stream was decreased by fasting. This offers very definite evidence that in the decreased tolerance caused by fasting we are dealing with the rate of disappearance of glucose from the blood and not with the absorption of glucose from the intestine. The composite curves of the intravenous tolerance tests made after a 1 day fast, a 4 day fast, and after no fast at all, are shown in Chart 5.

![Chart 7. Alimentary tolerance following intravenous tolerance.]

The 4 day fast period was selected for the studies on the effect of various substances on the sugar tolerance. It is a fast of sufficient duration to produce a definite and typical change, and yet not too long to make it difficult for the animal to recover from the effects of the inanition.

*Successive Tolerances.*

The results obtained by giving a second dose of sugar, at a time when the blood sugar concentration was on the downward
trend from the height caused by the first dose, agree with those of Foster (4) in that little if any rise occurred as a result of the second dose. Three successive tolerances were tried, even the third dose produced no further rise. However, in this rabbit No. 32 (Chart 6), after a 4 day fast, a second dose of sugar given at a point where the sugar concentration was at the height caused by the first produced a second rise, the point a little higher than the maximum caused by the first dose. In other words, after a 4 day fast, the first dose of sugar is not effective in stimulating that mechanism which removes excess blood sugar.

In Chart 7 are presented alimentary tolerance tests following intravenous tolerances in animals that have been fasted 4 days. Here again there is a lack of noticeable stimulation of the mechanism by hyperglycemia in the 4 day fasted animals. The same is also brought out by two successive intravenous tolerances in Chart 8.
Effect of Various Foodstuffs on the Glucose Tolerance.

In this series of experiments to determine the efficacy of various foodstuffs in stimulating the sugar-regulating mechanism, the animals were fasted for 4 days before the tolerance test except for a specific foodstuff given at a stated interval before the test. Chart 9 compares the results obtained by the feeding of fat, glucose, and protein 18 hours before the tolerance test with the normal 4 day fast curve.

The results obtained from feeding 10 gm. of lard oil the night before the test showed a decrease in tolerance.

The effect of glucose was studied by giving 10 gm. of glucose 18 hours before the test. A slight increase in tolerance resulted.
Gelatin seemed to have the greatest effect in increasing sugar tolerance. 10 gm. given the night before, 18 hours before the test, in all cases produced a remarkable increase in glucose tolerance.

Chart 10 shows the glucose tolerance tests on a rabbit after a 4 day fast and the effects of 40 gm. of egg white given at the same time, at 4 hours before, and at 18 hours before the glucose was ingested. The protein given simultaneously with the glucose and that given 4 hours before the test had little if any effect on the sugar tolerance, but when given the night before the test resulted in a very greatly increased tolerance.

That the increased tolerance is not related with the presence of material in the alimentary tract is shown by the fact that a fat meal produced no favorable influence on the tolerance; anything, it decreased the tolerance still further. Furthermore, the feeding of agar-agar produced negative results.

**Effect of Adrenalin and Morphine.**

It is important to determine whether the increasing of blood sugar concentration from the body's own stores stimulates the sugar regulatory mechanism. This would eliminate the possibility of some probable dietary factor, lack of which, caused by fasting, decreased the tolerance of glucose. Adrenalin was selected for this purpose. When the blood sugar concentration was coming back to normal after the rise caused by the adrenalin, the glucose was given. In the case of rabbit No. 27, as shown in Chart 11, 0.3 mg. of adrenalin showed a rise in the blood sugar concentration.
was given hypodermically, causing a rise in the blood sugar from 125 to 220 mg. per 100 cc. in 2 hours. At the 3½ hour point 3 gm. of glucose per kilo were given by stomach tube. The tolerance was only slightly increased, yet more so than a tolerance performed after a previous dose of sugar in an animal fasted 4 days. However, when the adrenalin was given the night before, the tolerance was increased to a remarkable degree (Chart 11).

In considering why adrenalin should be so effective in increasing the tolerance, the rise in the blood sugar suggests itself as being the causative factor. Consequently a hyperglycemia was produced by other means to see if this also would increase the tolerance. 20 mg. of morphine sulfate were given to the fasted animal the night before the test. Even though the blood sugar concentration was increased as by adrenalin, there was no increase in the sugar tolerance (Chart 12). Evidently the increase of the blood sugar from its own stores with its subsequent removal does not in itself stimulate the sugar regulatory mechanism. The cause of the action of adrenalin in this respect must be found elsewhere.

Effect of Insulin.

Since the action of adrenalin with its resultant hyperglycemia tends to increase the rate of disappearance of the sugar from
the blood, it is important to note the effect of insulin with resultant hypoglycemia.

This was tried by testing the tolerance when the sugar was supplied intravenously. Tolerance tests were done in both the 1 and the 4 day fasted animals. The results are shown in Chart 13. The tolerance was decreased both the 4 and the 1 day fasted animals.

**Chart 13.** Insulin before tolerance.
As there is much work that points towards an effect on sugar metabolism by the administration of sodium bicarbonate, it was thought worth while to try the effect of it on the 4 day fasted animals. It was found that the administration of the sodium bicarbonate, when given simultaneously with, a few hours before, or the night before the tolerance test was not as effective in increasing the rate of disappearance of blood sugar as when 1 gm. was administered each day of the fast. In the latter the sugar tolerance at the end of the fasting period was increased similarly to that of an animal after no fast (Chart 14).

Effect of Fasting on the pH and CO₂ Capacity of Blood.

The decided effect of the sodium bicarbonate naturally suggests that an acidosis is the cause of the decreased tolerance after fasting. The urine of a number of rabbits fasted from 4 to 7 days gave negative tests for acetone and β-hydroxybutyric acid. It was decided then to study the effect of fasting on the pH and CO₂ capacity. As shown in Table III the results show little if any acidosis. Of course this does not preclude the possibility of this decreased tolerance being somehow connected with the acid-base balance of the body. Henderson (46) points out the intimacy between the oxidation of sugar and the blood alkali although he considers the oxidation of the sugar in the tissues as a controlling factor in the regulation of blood alkali. This question of the connection of the acid-base balance of the
blood and the decreased tolerance, also the effect of internal metabolites, and other substances are now being studied in these laboratories.

<table>
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<tr>
<th>Rabbit No.</th>
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**SUMMARY.**

Attention is directed to the metabolic mechanism which concerned with the rate of disappearance of glucose from blood after a hyperglycemia.

Further evidence is offered that this mechanism is practically independent of the rate of absorption from the intestine.

Fasting invariably decreases the rate of disappearance of glucose from the blood in a normal rabbit after a hyperglycemia from glucose ingestion.

After a period of fasting, specific foodstuffs vary the rate of disappearance of hyperglycemia. Protein fed 18 hours previous to glucose test meal exerts little or no influence on blood sugar curve, but given 18 hours previous greatly increases the rate of disappearance. Fat fed 18 hours previous to glucose test meal decreases the rate. Glucose given 18 hours before the usual glucose test meal slightly increases the rate of disappearance of the sugar from the blood.
Adrenalin given 18 hours previous to the glucose test meal greatly increases the rate of disappearance while morphine does not, although both produce hyperglycemias. This indicates that a previous hyperglycemia is not the only stimulating factor.

A glucose test meal immediately after an insulin hypoglycemia has returned to normal shows a decreased rate of disappearance of sugar from the blood.

Sodium bicarbonate administered during a fast prevents this decrease in rate of disappearance of blood sugar normally occurring after a glucose test meal. Blood pH and CO₂ studies indicate that acidosis is not the predominant factor in causing this change during a fast.

The experimental data presented emphasize greatly the importance of carefully controlling the diet, period of fasting, and medication before performing the customary sugar tolerance test used in clinical diagnosis.

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