DIETARY FACTORS THAT INFLUENCE THE DEXTROSE TOLERANCE TEST

A PRELIMINARY STUDY *

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The dextrose tolerance test is now being extensively employed as a diagnostic procedure. It is most beneficially used in the differentiation of mild diabetes mellitus and renal diabetes. It is also being used, and is believed to be of diagnostic value, in many pathologic conditions, such as encephalitis, malignant tumor, pituitary and thyroid dysfunctions and nephritis.[1]

Although it is definitely established as a diagnostic procedure, there is some diversity of opinion concerning what constitutes a normal response to the oral administration of dextrose. Some writers state that in a healthy person there may be a postprandial rise in blood sugar of from 14 to 16 per cent and a return to the normal within two hours.[2] There are other writers [3] who consider a postprandial hyperglycemia of 20 per cent within normal limits. It is generally believed that the persistence of the postprandial hyperglycemia is of more diagnostic significance than the degree of hyperglycemia.[4] In early cases of diabetes the blood sugar curve rises higher, stays up for a longer time and does not return to normal for several hours. Macleod says that "slight deviations from the normal must not be given too much weight in diagnosis, since they may occur in other diseases or even in perfectly normal persons." [5]

All who have studied dextrose tolerance curves have noted the variability exhibited by normal persons, to say nothing of those who are

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1. Gray, Horace: Blood Sugar Standards in Conditions Neither Normal nor Diabetic, Arch. Int. Med. **31**:259 (Feb.) 1923. John, H. J.: Ann. Clin. Med. **5**:340, 1926. Friedenwald, J., and Grove, J. G.: Am. J. M. Sc. **33**:163, 1922. Paullin, J. E., and Sauls, H. C.: South. M. J. **15**:249, 1922. Mosenthal, Herman O.: M. Clin. N. Amer. **9**:549, 1925.

2. Mosenthal (footnote 1, fifth reference). Macleod: Physiology and Biochemistry in Modern Medicine, ed. 5, St. Louis, C. V. Mosby Company, 1926, p. 876.

3. Hale-White, R., and Payne, W. W.: Quart. J. Med. **19**:393, 1926. Gilbert, Max; Schneider, Hans, and Bock, Joseph C.: J. Biol. Chem. **68**:629, 1926.

4. Mosenthal (footnote 1, fifth reference). John, H. J.: J. M. Research **4**:255, 1923.

5. Macleod (footnote 2, second reference).

diseased. These variations have been discussed and explained in different ways.[6]

It occurred to me that perhaps the character of the food and the amount of water that a person had been consuming for a few days prior to the time the tolerance test was made might be factors that would influence the dextrose tolerance curve. If these factors should prove to be capable of altering a tolerance curve, they could be controlled. This would eliminate some of the confusing variability that is so frequently observed. It was these thoughts that lead to the following experiments.

Young, healthy, male medical students were used to study the effect of different preceding diets. Four groups were formed. The subjects in one group were given a protein diet, those in another a fat diet, those in a third a rich carbohydrate diet, and those in the fourth group were not given any food—the starvation group. Those on the protein diet received only lean meat and the whites of eggs. The students on the fat diet received only olive oil, butter, mayonnaise made with egg yolk, and 20 per cent cream. Those in the group fed on carbohydrates were allowed sugar, candy, pastry, white bread, baked potatoes, syrup, bananas, rice and oatmeal. These diets were followed for two days. Meals were taken at the usual hours, and eating between meals was allowed, provided the diets were followed. Those in the starvation group did without food for two days. On the morning of the third day, each student was given by mouth 1.75 Gm. of dextrose per kilogram of body weight, on an empty stomach. Determinations of blood sugar were made from samples of venous blood removed immediately before the dextrose was given, and at 30, 60 and 120 minute intervals following its administration. I made all determinations of blood sugar by the Folin-Wu method.[7]

The results of these tests are listed in tables 1, 2, 3 and 4, and in charts 1, 2, 3 and 4. It will be noted that the curves are strikingly different. The persons who starved and those who were placed on the fat diet present the most abnormal responses to the administration of dextrose. In no instance did the blood sugar return to normal within two hours. The most atypical curve of these two groups is that of subject W, whose blood sugar rose to 0.286 mg. per hundred cubic centimeters of blood at the two hour observation. This student was nauseated, which probably explains not only the delayed rise, but also

6. Mosenthal (footnote 1, fifth reference). McCaskey, G. W.: The Basal Metabolism and Hyperglycemic Tests of Hyperthyroidism, J. A. M. A. **73**:243 (July 26) 1919. Rohdenburg, G. L.; Bernhard, A., and Krebbiel, O.: Am. J. M. S. **159**:577, 1920.

7. Folin and Wu: J. Biol. Chem. **38**:81, 1919.

TABLE 1.—*Results of Dextrose Tolerance Tests on Four Normal Young Adults (Medical Students) Who Had Been Eating Only Proteins for Two Days Prior to Tests*

			Blood Sugar Mg. per 100 Cc.			
				After Dextrose		
Subject	Age	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
S	23	95	69	143	148	154
T	25	140	75	148	182	...
C	25	110	62	125	168	155
Mc	25	136	71	155	172	125

TABLE 2.—*Results of Dextrose Tolerance Tests on Five Normal Young Adults Who Had Been Placed on the Fat Diet for Two Days Prior to the Tests*

			Blood Sugar Mg. per 100 Cc.			
				After Dextrose		
Subject	Age	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
W	26	71	69	100	95	286
B	25	137	78	143	178	133
S	23	119	80	170	232	190
B2	21	105	95	222	219	170
J	22	119	80	143	195	200

TABLE 3.—*Results of Dextrose Tolerance Tests on Eight Normal Young Adults Who Had Been Placed on the Carbohydrate Diet for Two Days Prior to Tests*

			Blood Sugar Mg. per 100 Cc.			
				After Dextrose		
Subject	Age	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
C	23	85	74	111	125	111
N	25	115	78	111	101	88
J	24	126	75	85	97	85
A	22	141	80	148	111	85
F	25	125	80	121	143	105
Jack	24	165	98	148	108	100
J2	22	119	82	121	114	82
S	23	119	89	111	73	83

TABLE 4.—*Results of Dextrose Tolerance Tests of Five Normal Young Adults Who Starved for Forty-Eight Hours, Only Water Being Taken*

			Blood Sugar Mg. per 100 Cc.			
				After Dextrose		
Subject	Age	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
J	24	124	71	133	167	235
A	22	145	61	143	182	229
M	25	143	58	114	160	129
D	25	149	67	113	178	131
R	21	139	72	157	242	174
C	23	119	74	211	200	205

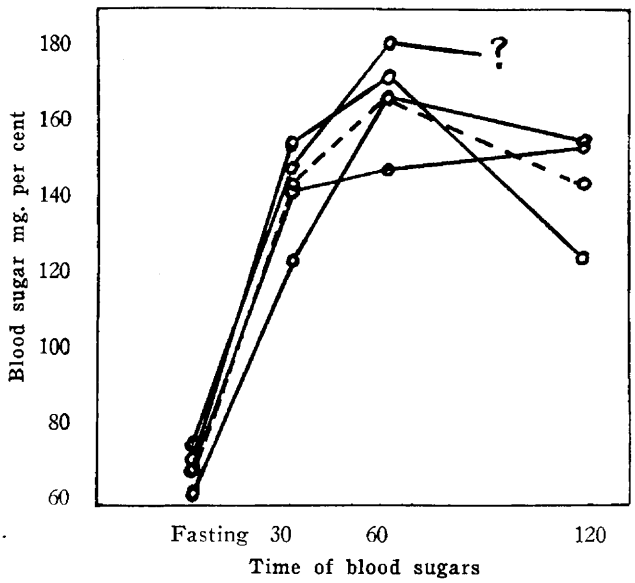

Chart 1.—Graph showing dextrose tolerance curves of four normal young adults who had been eating a protein diet for two days. The dash line in all charts is the average or type curve.

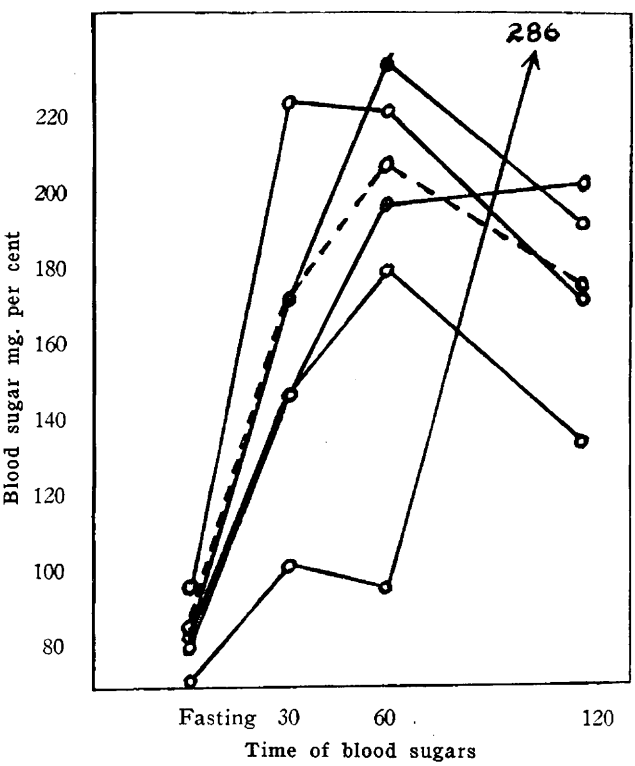

Chart 2.—Graph showing dextrose tolerance curves of five normal young adults who had been eating a fat diet for two days.

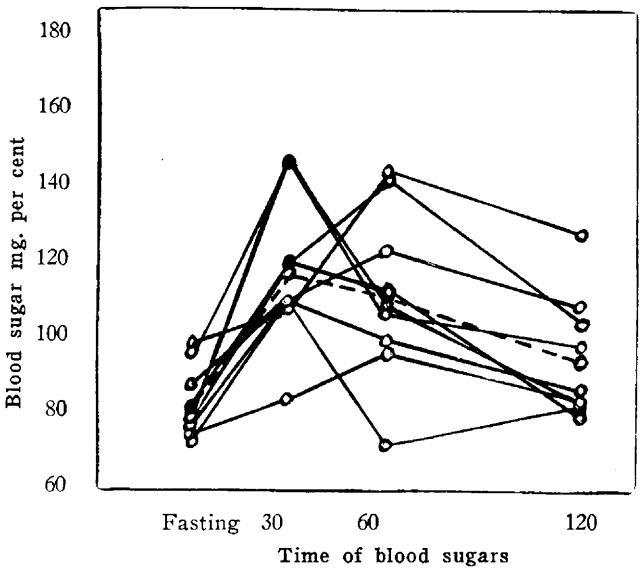

Chart 3.—Graph showing dextrose tolerance curves of nine normal young adults who had been eating a rich carbohydrate diet for two days.

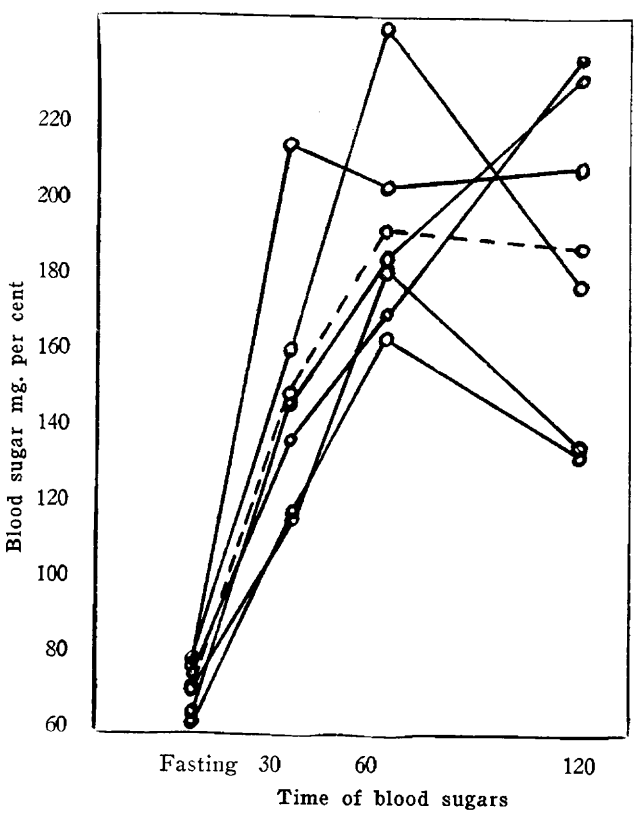

Chart 4.—Graph showing dextrose tolerance curves of six normal young adults who did without food for two days, taking only water.

the slight drop at the one hour observation. This effect of nausea has been pointed out previously.[8]

The groups fed on protein and on carbohydrates, especially the latter, showed a marked contrast to the other groups. Judged by some standards, none of the curves for the protein group should be considered normal. Those in the carbohydrate group are all strikingly within normal limits; in fact, the highest postprandial rise in this group was to a level of 0.148 mg. per hundred cubic centimeters of blood. The highest two hour observation was to 0.111mg.

A better comparison of these groups is obtained by examining table 5 and chart 5 in which are contained the average or type curves of each group. It will be noted that those students who were on the carbohydrate diet exhibited a marked increase in sugar tolerance and those on a protein diet a slight decrease in tolerance, while those who were placed on the fat diet and those who were starved manifested a definite

TABLE 5.—*Table Showing Average Dextrose Tolerance Curves or Type Curves of the Students in the Four Different Dietary Groups*

	Blood Sugar Mg. per 100 Cc.			
		After Dextrose		
Diet Groups	Fasting	30 Minutes	60 Minutes	120 Minutes
Fats *	83	170	206	173
Protein	69	143	167	145
Carbohydrate	84	118	113	96
Starvation	67	145	188	184

* Averages excluding curve of subject W, who was nauseated.

decrease in sugar tolerance. The differences in the average fasting blood sugars are noteworthy. The blood sugar in those of the protein and starvation groups was distinctly lower than that of the members of the fat and carbohydrate groups.

Because of the great difference in these groups, those students on the fat diet and those in the starvation group who showed the most extreme responses were placed on the carbohydrate diet. Similiarly, those in the carbohydrate group who showed an extreme response were placed on starvation restriction. This was obviously done to determine whether the curve of a person could be changed significantly by diet. The results are presented in table 6 and in charts 6 and 7.

Comparison of the curves of these five students is striking. The curves of all who had been placed on carbohydrate diets manifested a definite increase in their sugar tolerance. When three of these (the three most extreme) were placed on starvation restrictions, the curves were notably abnormal; there was a marked postprandial hyperglycemia,

8. Hale-White and Payne (footnote 3, first reference).

which persisted at the end of two hours; in other words, what was an increased sugar tolerance following the carbohydrate diet became a definitely decreased tolerance following two days of starvation. The remaining two persons who were placed on the fat diet showed a similar decreased tolerance. It should be stated that an interval of at least one week was allowed between the tolerance tests performed on the same subject.

It is plain from the foregoing experiments that the dextrose tolerance test may be significantly affected by the character of food taken prior to

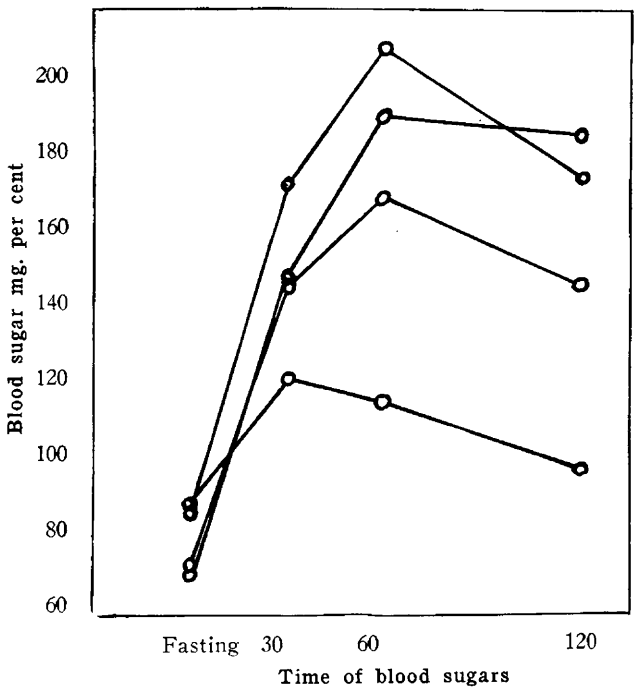

Chart 5.—Graph showing the average or type curves (figures in table 5). Reading from below upward on the two hour ordinate, the curves are as follows: first, carbohydrate; second, protein; third, fat, and fourth, starvation.

the test. Practically, this means that a standardized diet should be worked out to be followed prior to the performance of the dextrose tolerance test. It is reasonable to believe that if a dextrose tolerance curve can be so materially altered by two days of such restriction of the diet as has been shown, that a standardized diet would have the tendency to cause a less variable response. In this connection it is possible that some of the atypical curves that have been noted in different pathologic conditions may in reality be due to the diets indicated and

taken in such states. Likewise, some of the slightly abnormal curves noted in healthy persons may have the same basis of explanation.

Dogs were used for the purpose of studying the effect of hydration and dehydration on dextrose tolerance. To dehydrate the animal, all water was withheld for two days. To increase the body fluids, 500 cc. of physiologic sodium chloride was injected intraperitoneally on the day preceding the test, and 350 cc. more was injected two hours before

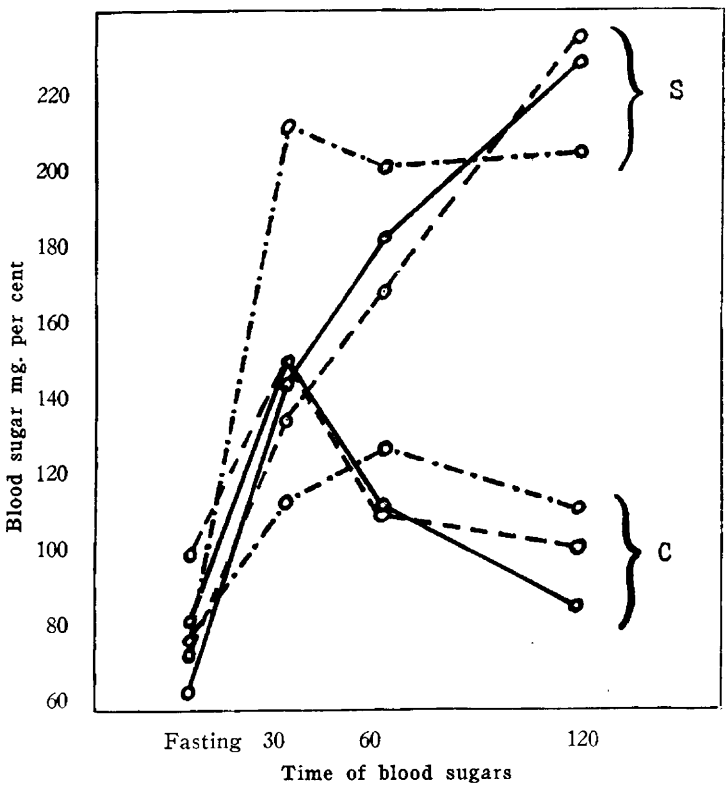

Chart 6.—Graph showing two curves for each of three normal young adults. In one instance—the curves marked S—the students were starved for two days prior to the test; in the other instance—the curves marked *C*—they were fed the carbohydrate diet. Similar lines represent the same subjects.

the dextrose was administered.[9] All dogs were given 2 Gm. of dextrose per kilogram of body weight by stomach tube. The dextrose was diluted with water to make a 20 per cent solution. Samples of blood were drawn as already described for medical students. All determinations were made by Mr. R. W. Lackey of the physiology department. The

9. Andrews, Edmund: Water Metabolism; Sugar Metabolism in Dehydration, Arch. Int. Med. **38**:136 (July) 1926.

Hartmann-Shaffer method was used.[10] All dogs received a mixed diet containing varying proportions of meat, bread and vegetables.

In tables 7 and 8 are listed the results obtained on five hydrated and two dehydrated dogs, respectively. The same results are presented graphically in charts 8 and 9. The dash line in each chart is the average

TABLE 6.—*Table Showing the Dextrose Tolerance Figures of Five Medical Students, Each of Whom Was Placed on Two Different Diet Restrictions, as Indicated, for Two Days Prior to the Tests. An Interval of at Least One Week Was Allowed Between Tests on the Same Individual*

				Blood Sugar Mg. per 100 Cc.			
					After Dextrose		
Subject	Age	Diet	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
A	22	Starvation	145	61	143	182	229
		Carbohydrate ..	141	80	148	111	85
Jack*	24	Starvation	124	71	133	167	235
		Carbohydrate ..	165	98	148	108	100
C*	23	Starvation	119	74	211	200	205
		Carbohydrate ..	85	74	111	125	111
J	22	Fat	119	80	143	195	200
		Carbohydrate ..	119	82	121	114	82
S	23	Fat	119	80	170	232	190
		Carbohydrate ..	119	89	111	73	83

* It will be seen that the amounts of dextrose given to students Jack and C differed for the two tests. This was due to an error in the arithmetic. It is noteworthy that these errors varied in such a way as to make the effect inconsequential.

TABLE 7.—*Results of Dextrose Tolerance Test on Five Dogs That Had Received 850 cc. Physiologic Sodium Chloride Intraperitoneally Prior to the Test*

		Blood Sugar Mg. per 100 Cc.			
			After Dextrose		
Subject	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
Dog 1.....	20	115	112	171	166
Dog 2.....	20	100	118	126	113
Dog 3.....	20	113	125	132	156
Dog 4.....	28	93	107	134	133
Dog 5.....	30	100	150	149	140

TABLE 8.—*Results of Dextrose Tolerance Test on Two Dogs That Had Not Received Any Water for Two Days Prior to the Test*

		Blood Sugar Mg. per 100 Cc.			
			After Dextrose		
Subject	Dextrose Gm.	Fasting	30 Minutes	60 Minutes	120 Minutes
Dog 1.....	25	87	169	201	113
Dog 2.....	32	90	139	162	148

curve. Three interesting differences are noted in the comparison of these two groups: First, there seems to be a lower blood sugar in the dehydrated animals while fasting; second, the postprandial hyperglycemia is distinctly less at the thirty minute observation in the hydrated

10. Hartmann, A. F., and Schaffer, P. A.: J. Biol. Chem. **45**:368, 1920.

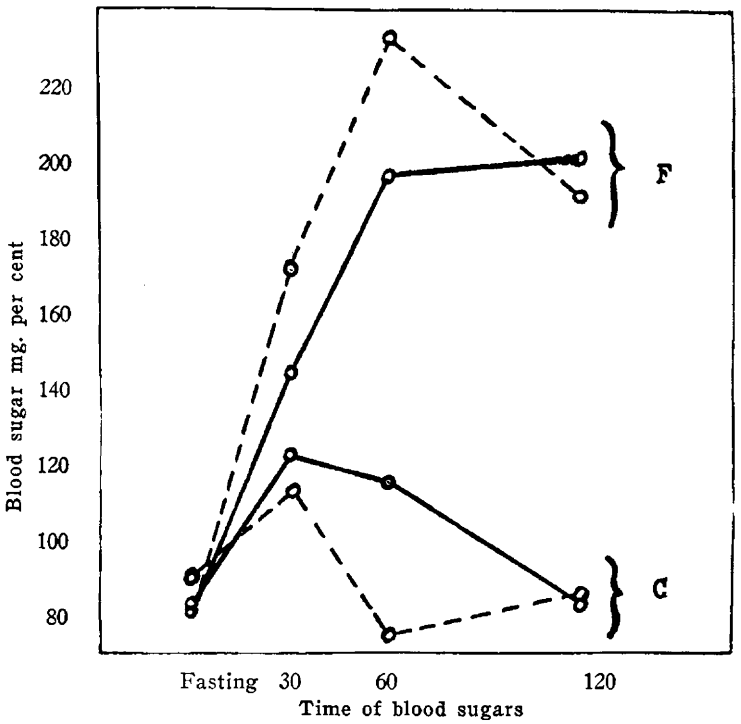

Chart 7.—Graph showing two curves each of two normal young adults. In one instance—the curves marked *F*—the students were fed the fat diet for two days prior to the test; in the other instance—the curves marked *C*—they were fed the carbohydrate diet. Similar lines represent the same subjects.

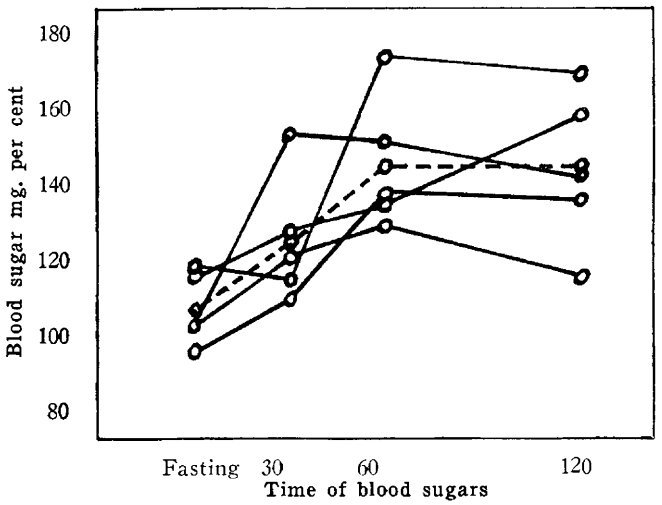

Chart 8.—Graph showing sugar tolerance curves of five hydrated dogs. These animals received 850 cc. of physiologic sodium chloride intraperitoneally.

dogs; and third, there seems to be a tendency toward a delayed return to normal at the two hour period in the hydrated animals. It will be noted that one hydrated dog (dog 5, table 7) showed a marked thirty minute rise in blood sugar as compared to the others in this group. This animal was extremely nervous. Every time he was handled he would become rigid and remain so until placed back in his cage. The factors involved in this phenomenon may explain the comparatively abrupt thirty minute rise in blood sugar.

It is unwise to conclude much from so few observations. It is believed, however, that the really significant result of this experiment is

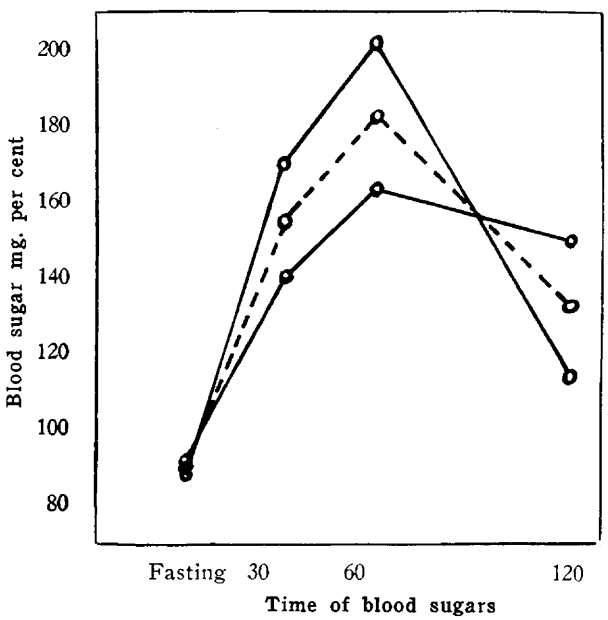

Chart 9.—Graph showing dextrose tolerance curves of two dehydrated dogs. All fluids were withheld for two days.

the delayed initial rise of blood sugar in the hydrated animals. This result is most probably explained on the basis that a mild transient hydremia was produced by intraperitoneal injections of physiologic sodium chloride. More experiments are being performed on hydrated and on dehydrated animals in which the diets are standardized.

COMMENT

It may be stated with reasonable accuracy that the major portion of the dextrose ingested during a dextrose tolerance test is converted into glycogen. The height of the postprandial hyperglycemia, the rapidity of the rise and the persistency of the hyperglycemia may be said to be

dependent on the degree of activity of this glycogenic function. Recent experimental evidence has been accumulated which tends to ascribe a strictly anabolic function to insulin.[5] Lawrence [11] has recently presented good experimental evidence favoring the anabolic function of insulin. By this conception, that is, that insulin has principally a glycogenic function, one may readily explain the behavior of the dextrose tolerance curves obtained not only in the subjects in this study, but also in healthy persons and in patients with diabetes mellitus. One assumption, however, is necessary; namely, that the ingestion of carbohydrates activates an intermediate hormone which in turn stimulates the production of insulin. This is certainly reasonable from a physiologic point of view.

With these points in mind it may be said, in explanation of the normal dextrose tolerance curve, that when dextrose is taken, a hormone is produced which stimulates the production of insulin. The result is only a moderate postprandial rise in blood sugar until the insulin that has been produced has caused active glycogenesis.[12]

In health and as a result of daily eating of the usual mixed diet, this mechanism is working smoothly and flexibly; in other words, the response to carbohydrate ingestion is normal. In case of diabetes, although the hormonic response is normal after the ingestion of dextrose, the amount of insulin that is produced is insufficient to store the dextrose as glycogen, and there is a resultant hyperglycemia and a prolonged curve.

In the curves of the subjects fed on carbohydrate there is an insignificant rise in the blood sugar. This phenomenon, therefore, may be explained by the more active functioning of the hormone stimulating process as a result of an excessive intake of carbohydrates. Consequently, when dextrose was administered, there was no delay in this mechanism, and the stimulation with insulin was more prompt; the result was quick and active glycogenesis.

In those persons who were on protein diets only a slight variation from the normal was found in their response to dextrose. This may possibly be explained on the basis of the carbohydrate content of protein.

In the next group of patients, namely, those receiving fats, the curves fall just where one would expect them to according to the theory proposed. As a result of much ingestion of fat, the activation of the insulin stimulating hormone has been reduced. This would cause a sluggish response when dextrose is ingested; therefore, a rather steep rise in the blood sugar occurs until the insulin stimulating process has been completed.

11. Lawrence, R. D.: Quart. J. Med. **20**:69 (Oct.) 1926.

12. This term is used rather loosely. I am aware of other probable actions of insulin (reference 5).

What has been said of the curves for the subjects on the fat diet may be said for those of the subjects in the starvation group. It is interesting to note that the average curve for the subjects fed on fats showed evidence of a slightly quicker response, that is, a reduction in blood sugar, than did the average curve for the starvation group. This may possibly be due to the small percentage of carbohydrate that fat yields.

Joslin, as well as others, for a long time has stressed the overeating of starches and sugars as important etiologically in diabetes mellitus. The foregoing results tend to strengthen this belief. Whatever lies behind the innate desire for sweets, overeating of them by some persons may impair an inherently weakened insulin producing organ. As a result, when glycogenesis is lessened, the storage of fat increases and the weight increases, an almost invariable fact in the anamnesis of any diabetic person. Diabetes mellitus follows varying periods of obesity.

CONCLUSIONS

1. The dextrose tolerance test, as usually employed, has been shown to be materially influenced by different antecedent foods or diets, and to some degree by the preliminary intake of water. It is suggested that a standardized antecedent diet might eliminate the variability produced by different foods. It is further suggested that some of the dextrose tolerance curves believed to be peculiar to different pathologic conditions might result from the diets indicated or taken in such conditions.

2. The principal effect of hydration or dehydration on the dextrose tolerance curve appears to be a delayed thirty minute postprandial rise in blood sugar in hydrated animals. This was interpreted on the basis of a transient hydremia.

3. Dextrose tolerance tests performed on medical students are shown to vary definitely with the character of the antecedent diet. Four different types of curves are presented: the protein, fat, carbohydrate and starvation curves. These curves are distinctly different and are obtained by simply restricting the diet to protein, fat, carbohydrate and starvation for two days prior to the test.