STUDIES OF DIABETES MELLITUS

EVIDENCE THAT THE DISABILITY IS CONCERNED SOLELY WITH THE METABOLISM OF GLUCOSE. THE MODE OF ACTION OF INSULIN

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During the past several years a number of writers in this country and abroad have maintained that liberal additions of carbohydrate to the diabetic diet, usually accompanied by significant reduction in the fat, do not cause glycosuria, nor require an increase in the amount of insulin. They attribute this beneficial outcome to a variety of factors:—(1) the depressing effect of fat upon the utilization of glucose; (2) the stimulation of carbohydrate metabolism by ingested carbohydrate; (3) augmentation of the combustion of glucose brought about by under-nutrition; (4) and it is even suggested that the improvement is to be attributed to the increased activity of some hitherto unrecognized principle of nutrition brought to light by the high carbohydrate, low fat diet.

It is, for example, stated by Gray and Sansum (1), "That whether the beneficial clinical results which have been obtained by using these diets (carbohydrate-rich, fat-poor) are due to the increase in the carbohydrates or the decrease in the fats, is still debatable." Rabinowitch (2) writes, "Experiences with it (the high carbohydrate, low calory diet) are inconsistent with our present concept of the metabolism of diabetes." Barach (3) maintains that he has "repeatedly seen an increase in dietary fat followed by glycosuria." Later he (4) writes, "There is evidence that insulin applies to the total metabolism, or that one gram of fat creates the need for as much insulin as two grams of carbohydrate." Adlersberg and Porges (5) go so far as to postulate the secretion of insulin as the response of a complex reflex following stimulation of the buccal mucosa by contact with carbohydrate foods.

We believe that this bewildering divergence of opinion and experience has arisen because these investigators have failed to keep two totally unrelated processes apart. They have not taken pains to distinugish sharply between the tolerance of the individual for carbohydrate and the pharmacology of insulin. And yet the former deals solely with a specific attribute of a single person, while the latter is concerned with the behavior of a glandular extract when brought into contact with glucose.

In order to clarify the situation, we have accordingly first centered our attention upon the ability of the diabetic to metabolize carbohydrate

when he receives a high carbohydrate, low fat, low calory diet; and when he receives a low carbohydrate, high fat, high calory diet.

Tables 1 to 4, indicate the type of data we have secured. Table 1 shows that a middle aged, mild diabetic could dispose of 181 grams available glucose, but not 191 grams when she received a high fat, supermaintenance diet. The removal of 100 grams of fat from this diet did not increase her ability to metabolize glucose, since now glycosuria appeared when the available glucose was only 184 grams.

TABLE 1

Comparison of tolerance on low and on high fat diets

Hauver: Mild diabetes

Date	Protein	Fat	Carbohydrate	Calories	Available glucose	Insulin units	Urine sugar
	grams	*grams*	*grams*		*grams*		
January 1	55	190	130	2450	181	0	– – –
January 2	55	190	140	2490	191	0	– – –
January 3	55	190	140	2490	191	0	– – –
January 4	55	190	140	2490	191	0	2 grams
January 7	55	190	140	2490	191	0	2 grams
January 9	55	90	110	1490	151	0	– – –
January 13	55	90	125	1542	167	0	– – –
January 14	61	91	140	1618	184	0	– – –
January 15	61	91	140	1618	184	0	+ – –
January 16	61	91	140	1618	184	0	2 grams

TABLE 2

Comparison of tolerance on low and on high fat diets

Stoldt: Mild diabetes

Date	Protein	Fat	Carbohydrate	Calories	Available glucose	Insulin units	Urine sugar
	grams	*grams*	*grams*		*grams*		
February 23	49	51	80	975	113	0	– – –
February 24	52	51	95	1047	130	0	+ – +
February 25	52	51	95	1047	130	0	+ + +
February 28	30	130	20	1370	50	0	– – –
February 29	30	130	20	1370	50	0	– – –
March 10	58	220	50	2484	122	0	– – –
March 11	58	220	50	2484	122	0	– – –
March 12	58	220	50	2484	122	0	– – –
March 13	62	220	73	2520	131	0	– – –
March 14	62	220	73	2520	131	0	+ + +

In Table 2, the order of the test is reversed. It is shown that a mild diabetic, who received a low fat, low calory diet, had glycosuria when the

available glucose of the diet was 130 grams. A subsequent diet containing more than twice as much fat and only about one fourth as much carbohydrate, quickly abolished the glycosuria. The further striking increase in fat accompanied by only small additions of carbohydrate, was tolerated without glycosuria until the available glucose became 131 grams.

Similar results were obtained with patients whose disease was severe enough to require insulin with any dietary plan. These patients were first placed on a low fat, liberal carbohydrate diet and given much more insulin than needed to prevent glycosuria. The insulin was then slowly decreased without change in diet until glycosuria appeared. The diet was next abruptly changed to the high fat type and the insulin was increased sufficiently to overcome the glycosuria. Whereupon the insulin was slowly decreased again until glycosuria reappeared. A single example will suffice to show our experience with this group. For this purpose we selected a youth who had been under observation by us in the hospital for many months. Table 3 brings out the fact that 16 units of

TABLE 3

Comparison of tolerance on low and on high fat diets

Bryson: Severe diabetes

Date	Protein	Fat	Carbohydrate	Calories	Available glucose	Insulin units	Urine sugar
	grams	*grams*	*grams*		*grams*		
March 28	47	84	140	1506	174	20–15	− − −
March 29	47	84	140	1506	174	18–12	− − −
March 30	47	84	140	1506	174	15– 9	− − −
March 31	47	84	140	1506	174	13– 7	− − −
April 1	47	84	140	1506	174	10– 6	− − −
April 2	47	84	140	1506	174	8– 4	+ + +
April 3	47	84	140	1506	174	10– 6	− − −
April 5	55	220	120	2680	174	10– 6	− − −
April 6	55	220	120	2680	174	8– 4	− − −
April 7	55	220	120	2680	174	8– 4	− − −
April 8	55	220	120	2680	174	6– 4	+ − −
April 9	55	220	120	2680	174	6– 4	+ + +
April 10	55	220	120	2680	174	6– 4	7 grams

insulin were sufficient and that 12 units were insufficient to prevent glycosuria, when he was receiving a low fat, low calory diet, that yielded 174 grams glucose. The abrupt shift to a very high fat, high calory diet with the same available glucose, required no more insulin to prevent glycosuria. In fact, as the table shows, a slightly smaller dose was now adequate.

Since the experiments just described were of short duration, it might be contended that the prolonged ingestion of the high fat diets would

eventually injure the patient's tolerance. Evidence that this does not not take place was published by us (6) as long ago as 1923. Since insulin had not been used in the treatment of the groups of patients studied, it is clear that "downward progress" or loss of tolerance could be dealt with in terms of mortality. We accordingly compared the death rate of our patients who were receiving a high fat, maintenance diet, with the status of other patients treated by competent students who used a low fat, low calory diet. Thus we reported that Williams (7) treated 304 patients with the latter type of diet during a five year period, and had a mortality of 34 per cent, while we gave 176 patients the high fat diet and at the end of four years and four months 25 per cent of them had died. Allen (8) reported the outcome of a three years' trial of the low calory diet in 504 patients, the mortality was 17.1 per cent. During the same period we gave the high fat diet to 137 patients with a mortality of 18.8 per cent. Joslin (9) published his statistics for 536 patients who had taken the low fat, low calory diet from April 1, 1919 to December 31, 1922. The mortality was 23 per cent. During the same interval of time we treated 124 patients by means of the high fat, maintenance diet, with a mortality of 21 per cent. Only one conclusion could be reached.

Nevertheless, the question has recently been reopened, and it is accordingly worth while to cite further evidence that the persistent use of the high fat diet does not reduce the ability of the patient to metabolize glucose.

Dr. F. J., aged 35, first came under our care for the management of diabetes mellitus in 1920. He has taken a high fat diet continuously to date. From 1927 to the present, the diet has consisted of 73 grams of protein; 272 grams of fat; 68 grams of carbohydrate. Twenty-six units of insulin prevented glycosuria for four years. However, early in 1931, an acute upper respiratory infection made it necessary to increase the insulin temporarily to 50 units. Subsequently it was slowly decreased until he was again using 26 units daily without glycosuria.

V. B., aged 19, tolerated a diet consisting of 40 grams of protein, 240 grams of fat, and 30 grams of carbohydrate during a two weeks' trial in the hospital, in May 1931. He continued to take this very high fat diet with a fatty acid, glucose ratio of 3.2 and an available glucose of 77 grams, for six months, when he returned at our request. In the interval he had gained 10 kilograms in weight. In spite of these conditions his tolerance was unchanged.

We have cited the first example to show that the continued ingestion of a high fat diet for many years does not injure tolerance. The record of the second patient is evidence that a diet not only strikingly high in fat, but also one that permitted rapid gain in weight, was likewise without effect on tolerance.

These present studies have merely confirmed our earlier experience with many patients, that the capacity of a diabetic individual to dispose of

the available glucose of a diet, without glycosuria, is unrelated to either the fat or the energy content of the diet. The tolerance of a diabetic is the maximum number of grams of glucose from all sources that can be oxidized in twenty-four hours without insulin, and after he has had full opportunity to recover from interfering factors. It has been shown, over and over again, that tolerance is independent of the character of the diet.

We next took up the second question, that is, whether the ability of injected insulin to metabolize glucose is influenced by the composition of the diet. As a basis for this work, we had the enlightening studies of Campbell and of Allan. The substance of Allan's (10) investigations is contained in Table 4. Examination of the first section of the table shows

TABLE 4

Depancreatized dog

(From F. N. Allan, Am. J. Physiol., 1924, lxvii, 287)

Insulin units	Glucose		Ratio glucose : insulin	Glucose equivalent
	Available	Metabolized		
	grams	*grams*		
40	131	124	3.3	3.1
32	131	112	4.1	3.5
24	131	96	5.5	4.0
20	131	116	6.6	5.8
20	82	74	4.0	3.7
20	132	116	6.5	5.8
20	182	150	9.0	7.5
32	82	80	2.6	2.5
32	132	122	4.1	3.8
32	182	150	5.7	4.7

that the depancreatized dog, who daily received a diet that yielded 131 grams of glucose, metabolized relatively more of it as the insulin was reduced from 40 to 20 units. In the fourth column the relation between the available glucose and the insulin, is expressed as a ratio, while the last column shows how much glucose was disposed of by each unit of insulin. It will be seen that as the glucose increased in proportion to the insulin, so did the amount of glucose that was metabolized per unit of insulin. In sections two and three of the table, the procedure is reversed. Nevertheless, when the relation between dietary glucose and insulin is expressed as a ratio, it is again clear that an increasing ratio is attended by an increasing efficiency of insulin.

Entirely analogous evidence may be obtained from human diabetics. As indicated in Table 5, a well controlled young diabetic could tolerate 76 grams of available glucose without insulin. With each subsequent

TABLE 5

Glucose metabolized per unit of insulin with increasing glucose intake

Bryson

Total	Glucose beyond tolerance	Insulin	
		Units	Efficiency
grams	*grams*		
76	0	0	—
90	14	10	1.4
106	30	10	3.0
123	47	10	4.7
137	59	12	5.0
174	98	14	7.0
274	198	30	6.8

increase in the available glucose, insulin was also increased enough to surely prevent glycosuria. This amount was then slowly decreased until glycosuria appeared. Column 3 shows the least amount of insulin that would prevent glycosuria for each level of available glucose. It will be seen that as the glucose increased beyond tolerance, each unit of insulin disposed of a greater amount of glucose, until a maximum was reached beyond which further additions of glucose were without effect on the efficiency of insulin.

Experiments with the depancreatized dog and with the human diabetic agree in showing that the glucose equivalent of a unit of insulin is not a fixed quantity, but that it is dependent upon the absolute amount of glucose to be acted upon. The glucose equivalent may be strikingly augmented by increasing the available glucose in proportion to the insulin. This gives a high ratio. However, the reduction of the insulin in the presence of a small amount of glucose, which also increases the ratio, does not increase the efficiency. Hence, there must always be a large amount of glucose present, in order to obtain a high efficiency of insulin. The data also makes it clear that there is a definite upper limit to the amount of glucose that can be disposed of by a unit of insulin. The evidence at hand suggests that this maximum is about 7 grams of glucose per unit of insulin.

These investigations afford a quantitative basis for comparing the required dose of insulin when different types of diet are employed. For example, it is found that a hypothetical patient whose tolerance is 100 grams of available glucose, requires 14 units of insulin when he receives a diet containing 60 grams of protein, 190 grams of fat and 66 grams of carbohydrate. Since the total glucose of this diet is 120 grams, he will be receiving 20 grams more than his tolerance. Accordingly, 14 units of insulin disposes of 20 grams of glucose. The glucose equivalent is therefore 1.4 gram. The diet is now changed to 60 grams protein, 40 grams of

fat, and 150 grams of carbohydrate. The total glucose of this diet is 189 grams, which is 89 grams beyond tolerance. This additional glucose may also be completely utilized without increasing the insulin, since the required efficiency of 6.4 grams per unit of insulin has been demonstrated to occur. But the second diet yields only 1356 calories. If the first diet, that contains 2214 calories, is maintenance, the patient will obtain the extra calories when he takes the second diet by oxidation of about 95 grams of his body fat. The 9 extra grams of available glucose will not cause glycosuria if the efficiency of insulin may be relied upon for 7 grams of glucose per unit.

The study also shows that tolerance is independent of the type of diet. Accordingly, this patient's tolerance will not be increased by adding carbohydrate to the diet, nor diminished by increasing the fat. Such being the case, it is not necessary to use insulin at all in the treatment of this patient, since his tolerance of 100 grams of glucose permits him to obtain a satisfactory diet that will yield the desired calories. A diet consisting of 40 grams of protein, 208 grams of fat and 45 grams of glucose, will contain 89 grams of available glucose and 2212 calories.

SUMMARY

1. The tolerance of a diabetic individual is defined as the maximal capacity to dispose of the available glucose from all sources, without glycosuria, in the absence of insulin. This value is not depressed by dietary fat nor augmented by dietary carbohydrate. The continued administration of high fat, maintenance diets does not lower it.

2. The efficiency of insulin in the case of the human diabetic, as in the depancreatized dog, is related to the total amount of glucose upon which it acts. When the available glucose far exceeds the tolerance, each unit of insulin will cause the oxidation of six or seven grams of glucose. Under otherwise similar conditions except for a small excess of available glucose, only one or two grams of glucose are oxidized per unit of insulin.

3. A sharp maximal efficiency is also revealed.

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