OBSERVATIONS ON THE USE OF DIHYDROXYACETONE IN THE TREATMENT OF DIABETES MELLITUS

(Preliminary Report)

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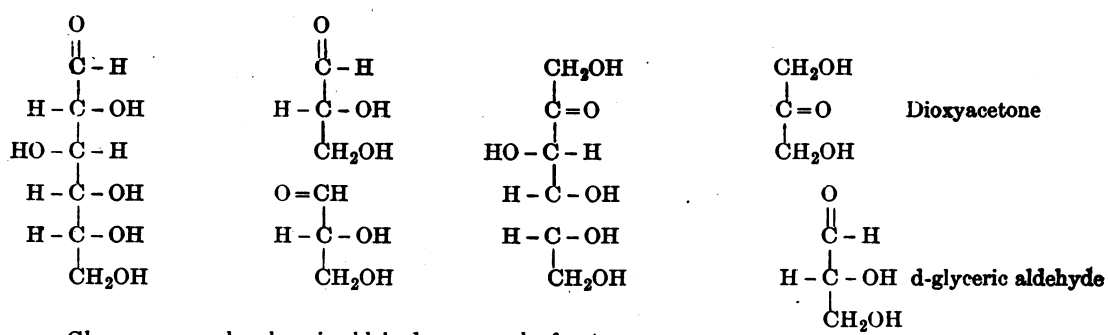
DIHYDROXYACETONE, $\begin{matrix}CH_2\,OH\\ C{=}O\\ CH_2\,OH\end{matrix}$ is a white crystalline substance with a sweet, cooling and slightly astringent taste. It dissolves slowly when triturated with one part of water at 20° C. and readily in greater dilution. It is a keto-triose, and like the other trioses, d and l glyceric aldehyde, is very unstable in alkaline media, readily undergoing rearrangement and condensation. It is readily oxidized. Polymerization is also noted to occur when, in solution, it is heated above 60° C. It is non-toxic when taken by mouth in the usual doses for sugar. No manifestation of kidney damage (albuminuria, suppression of urine, etc.), have been noted to occur as have been, following the administration of the aldoses, d and l glyceric aldehyde. Different results are recorded in the literature regarding fermentation. The product used in this investigation could not be fermented by fresh yeast. Dioxyacetone is optically inactive.*

Theoretical considerations.—It may be stated, generally, that in a diabetic, glycosuria is produced because of a disproportion between the rate of absorption of glucose from the alimentary canal or rate of production in the body, and the rate at which it is oxidized or stored. The failure to oxidize or store is probably partly due to failure of the necessary chemical transformations of the sugar molecules between the glucose phase and that representing their complete oxidation, namely, carbon dioxide and water.

There is much experimental evidence that the trioses, d and l glyceric aldehyde and dihydroxyacetone, are products of the normal chemical transformations. Thus Emden, Schmidt and Wittenberg[1] picture the cleavage of glucose and fructose as shown in chart below.

Von Lebedew and Griaznoff[2] also regarded that dextrose is first split into dioxyacetone and glyceric aldehyde. According to Buchner and Meisenheimer[3] dihydroxyacetone is the first disintegration product obtained during the fermentation of glucose . Numerous such examples may be found in the literature on the subject of the intermediate metabolism of carbohydrates. These hypothetic cleavage products may either be oxidized or reunited and retransformed into glucose, and subsequently glycogen, and stored in the liver. All trioses when administered to a phlorhizined dog are completely converted into glucose (Lusk[4]).

*For more detailed chemical and physical properties see *Bioch. Handlexicon* (Abderhalden) 2. Band, 270 (1911).



An attempt has been made to employ the two aldoses, d and l glyceric aldehyde, in the treatment of diabetes[5]. Both have been found wanting. Any decrease in the excretion of sugar or acetone bodies noted could apparently be attributed to impairment in renal efficiency caused by these substances. Dioxyacetone has received little consideration. Though not an aldose, it has been assumed it would have, practically, the identical properties of the other trioses.

Emil Fischer first suggested the therapeutic use of dioxyacetone. This suggestion was based purely upon chemical consideration and attracted apparently little clinical attention. At that time it was obtained by bacterial action on glycerine and the quantities available were obviously insufficient to permit anything in the nature of an extended clinical trial.* Recently, some of the physiological properties of this substance have been investigated[5]. In animals glycogen storage in the liver was found to be greater for given doses of dioxyacetone than for glucose. In healthy subjects a lowering of the blood sugar was noted following the administration of 60 gms. and no marked hyperglycæmia was noted following the administration of 150 gms. In diabetics similar results were noted, and in only severe cases was there noted a hyperglycæmia and this was less marked than when glucose was given.

The value of a product of such physiological characteristics in the treatment of diabetes is obvious. This applies especially to the severer type of diabetic requiring insulin. If the diabetic individual could more readily tolerate dioxyacetone than glucose, relatively, more of the former could be given. If its caloric and antiketogenic properties approximate those of glucose more fat could then be given without a tendency to disturb the body weight and the antiketogenic balance. Since more food could be given, less insulin would be required. This was tested by clinical and laboratory observations.

Blood sugar time curves were first obtained in normal individuals and then in diabetics. The usual procedure was followed. A blood and urine specimen were first obtained in the post-absorptive state. The dioxyacetone was then given, and blood and urine specimens were obtained 30, 60, 120 and 150 or 180 minutes later.

Methods.—The blood sugar estimations were made by Myers-Benedict method, and the urine sugars by employing the same principle. After preliminary removal of interfering substances with blood charcoal, the urines were suitably diluted, saturated with dry picric acid and filtered. The picric acid filtrate was then treated in the same manner as in the case of blood. As a result of a large number of experiments with this procedure, the dioxyactone used here has been found to have an average of 1.53 times the reducing capacity of a corresponding concentration of a solution of pure glucose. Dioxyacetone was qualitatively detected in the urine by treating the latter with an equal quantity of the copper reagent employed in the Folin and Wu[7] blood sugar method. If dioxyacetone is present the reduction of the copper solution becomes apparent *at room temperature* within five to thirty minutes. In the case of blood, dioxyacetone was qualitatively detected by treating the clear tungstate filtrate (Folin) with an equal quantity of the above copper reagent, after making the filtrate slightly alkaline with 5 per cent NaOH.

In normal individuals, within one hour following the oral administration of 50 gms. dioxyacetone, either the usual, or an insignificant increase in the blood was noted, as in the case of glucose. Following this, the blood sugar decreased and at the end of three hours, still remained below the level originally noted in the post-absorptive state. Dioxyacetone was detected qualitatively in the urien. The threshold, if there be one, is thus apparently lower than that for glucose. Examples of results in the case of normal individuals are recorded in the following table. These are graphically recorded in charts 1 and 2.

In the case of diabetics, curves were obtained from patients with varying degrees of severity of the disease, but under control and having either only a slight or no hyperglycæmia in the post-absorptive state. In each case, for comparative purposes, a dioxyacetone and glucose curve were obtained on separate days.

*The dioxyacetone used in this work was made by Farbwerke v. Meister Lucius & Bruning, Hoechst a Main, under the trade name of "Oxantin." The writer is indebted to the Mallinckrodt Chemical Works, Ltd. for the free supply of this product during this investigation.

Subject	Time	Blood Sugar Per cent.	Urine		Remarks
			Vol. cc.	Benedict Sugar Reaction	
1. Laboratory Worker (D)	Basal	0.102		0	
	50 minutes after	0.109	90	+	Dioxyacetone reaction positive
	60 minutes after	0.078	50	+	" " "
	120 minutes after	0.088	70	+	" " "
	150 minutes after	0.098	95	+	" " "
					Total sugar excreted 0.38 gms.
2. Laboratory Worker (G)	Basal	.092	85	0	Dioxyacetone reaction positive
	30 minutes after	.161	25	+	" " "
	60 minutes after	.108	20	+	" " "
	120 minutes after	.066	205	+	" " "
	180 minutes after	.078	120	0	
					Total sugar excreted 0.49 gms.

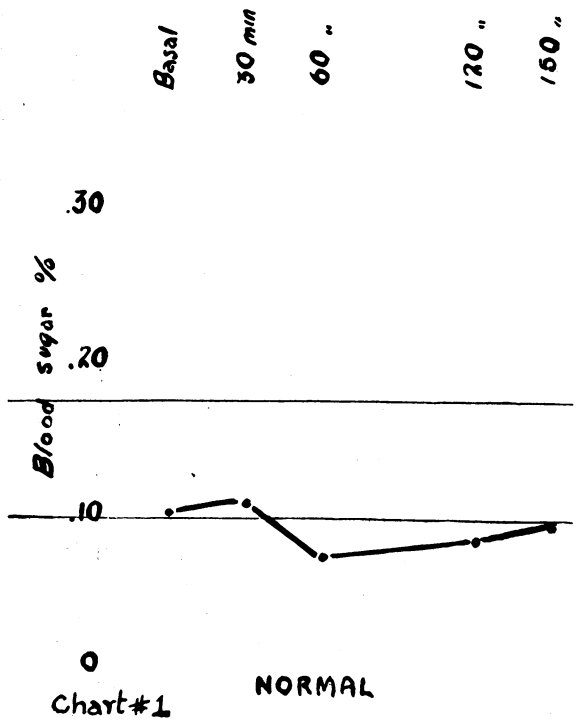


Chart #1 NORMAL

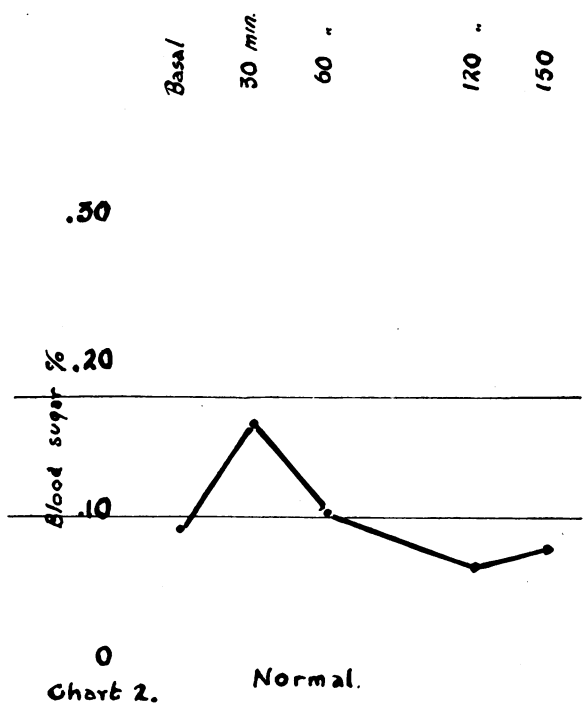


Chart 2. Normal.

Case No. 5258.—Mild. Discharged on a diet of 30 per cent above the basal caloric requirement, with the urine free of sugar and acetone bodies and the blood sugar normal.

100 gms. of dioxyacetone were given with the following results:

	Blood sugar %
Before administration	0.103
30 minutes after administration	0.145
60 minutes after administration	0.165
120 minutes after administration	0.173
180 minutes after administration	0.165

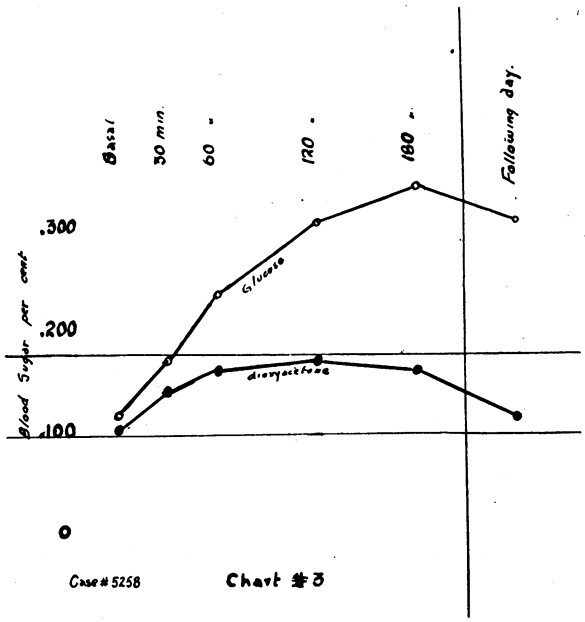
The total sugar excreted during this period amounted to 0.73 gms. The total for the entire day was 1.32 gms. The following morning the blood sugar was normal (0.127 per cent) and there was no sugar in the urine.

100 gms. of glucose were then given with the following results:

	Blood sugar %
Before administration	0.127
30 minutes after administration	0.176
60 minutes after administration	0.238
120 minutes after administration	0.312
180 minutes after administration	0.344

The total sugar excreted during this period was 3.8 gms. The total for the days was 19.6 gms. The next moring the blood sugar was .320 and the urine contained sugar.

The results are graphically recorded in Chart 3.



Thus, in the case of glucose the excretion of sugar was greater and the hyperglycæmia was more marked and persistent than in the case of the dioxyacetone.

Case No. 5233.—A mild diabetic discharged on a diet of 45 per cent above the basal caloric requirement, with the urine free of sugar and acetone bodies and the blood sugar normal.

100 gms. of dioxyacetone were given with the following results:

	Blood sugar %
Before administration	0.126
30 minutes after administration	0.140
60 minutes after administration	0.160
120 minutes after administration	0.190
180 minutes after administration	0.208

Here there was noted a gradual rise in the curve, reaching a 0.08 per cent increase in three hours. (0.12 to 0.20 per cent). During this period only 1.6 gms. of sugar were found in the urine, and the urine for the entire period of the rest of the day contained only 0.5 gms. sugar.

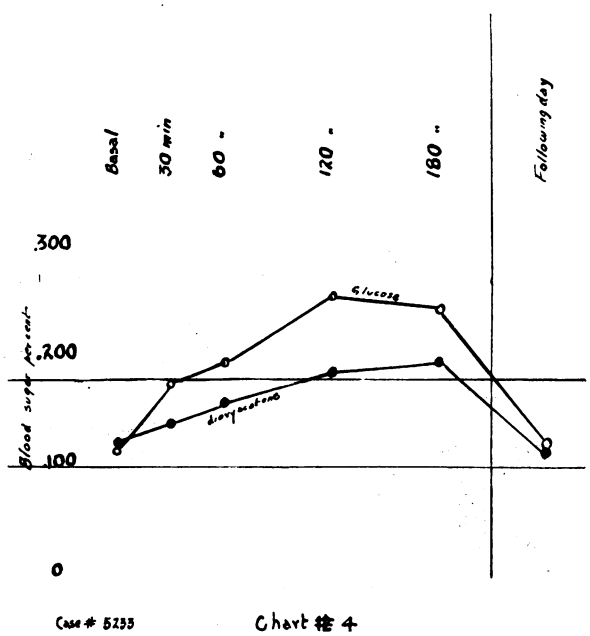
The following morning, in the post-absorptive state, the blood sugar was again normal (0.116 per cent).

100 gms. of dioxyacetone were given with the following results:

	Blood sugar %
Before administration	0.116
30 minutes after administration	0.178
60 minutes after administration	0.196
120 minutes after administration	0.256
180 minutes after administration	0.250

Here again it will be noted that the blood sugar curve had reached a higher level in the case of the glucose than when the same amount of dioxyacetone was given. During this three-hour period 9.9 gms. of glucose were excreted and the total sugar excreted for the day was 13.5 gms. The following morning, in the post-absorptive state, the blood sugar was, however, again within normal limits.

The results are graphically recorded in Chart 4.



Case No. 4966. — Severe diabetic. Glucose tolerance (Woodyatt) (in the absence of insulin) G = 46 gms.

On a diet of 50 carbohydrates, 150 fat and 50 protein (G=94), 35 units of insulin a day were required. On this diet and with the same amount of insulin the urine was kept sugar free and the blood sugar, in a post-absorptive state, was slightly increased (maximum-minimum variation 158 to 0.169 per cent). A blood sugar time curve was obtained following the administration of 50 gms. of dioxyacetone, with the following results:

	Blood sugar %
Before administration	0.158
30 minutes after administration	0.181
60 minutes after administration	0.211
120 minutes after administration	0.187
180 minutes after administration	0.187

It will be seen that the maximum rise noted was 0.15 to 0.21. On the morning of the test no insulin was given. During the period of the test 0.38 gms. of sugar were excreted in the urine. The noon and evening meals, preceded by 10 units of insulin in each case, were then

given. The total food value for the day, including the dioxyacetone, was 82 gms. carbohydrates, 100 gms. fat and 33 gms. protein. The remaining part of the twenty-four hour specimen of urine contained no sugar. The blood sugar the following morning was practically the same as on the day previous to the test (.160). The total value for "G" for the day of the test was 111.0. Thus it appeared that the patient was able to take 17 gms. more of "G" than the day before, though the dose of insulin was reduced from 35 to 20 units. A factor to be considered here, however, is that of the effect of starvation. Though only of a mild degree, by eliminating the breakfast, the total food value for the day was diminished by approximately 390 calories, in spite of the caloric value attributed to the 50 gms. of sugar given during the test. A corresponding curve was obtained the next day with 50 gms. of glucose with the following results:

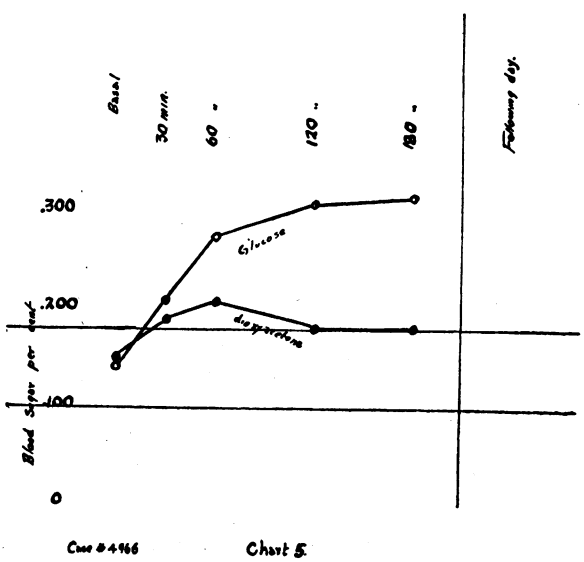
	Blood sugar %
Before administration	0.150
30 minutes after administration	0.212
60 minutes after administration	0.276
120 minutes after administration	0.311
180 minutes after administration	0.319

During this period 7.2 gms. of sugar were excreted and 8.4 gms. the rest of the day. Insulin was given with following meals, and the blood sugar the following morning was again within his usual range of variation.

The results are graphically recorded in Chart 5.

The slight excretion of sugar in the case of dioxyacetone as compared with glucose, could hardly be attributed to the same phenomenon as in the case of d and l glyceric aldehyde, namely, renal damage (suppression of urine). In none of the cases studied was there any albuminuria, nor other evidence of renal damage (urea retention, &c.) noted.

Blood sugar time curves were obtained in four untreated cases on the morning following their admission to the hospital. In each case there was a marked degree of hyperglycæmia and glycosuria in the post-absorptive state. In each case 25 gms. of dioxyacetone were given. The increase in the blood sugar above the basal value, noted in three of these cases, was not greater than that found in normal individuals. In one case a slight, though definite, decrease was noted. In each case, with one exception, the total amount of sugar excreted during the two and a half or three hours following the administration of the dioxyacetone was less than the amount excreted during the hour prior to the administration. It thus appeared that dioxyacetone had some influence on the excretion of glucose. The following table shows the combined data. These are graphically recorded in Charts 6, 7, 8 and 9.



Case #466 Chart 5.

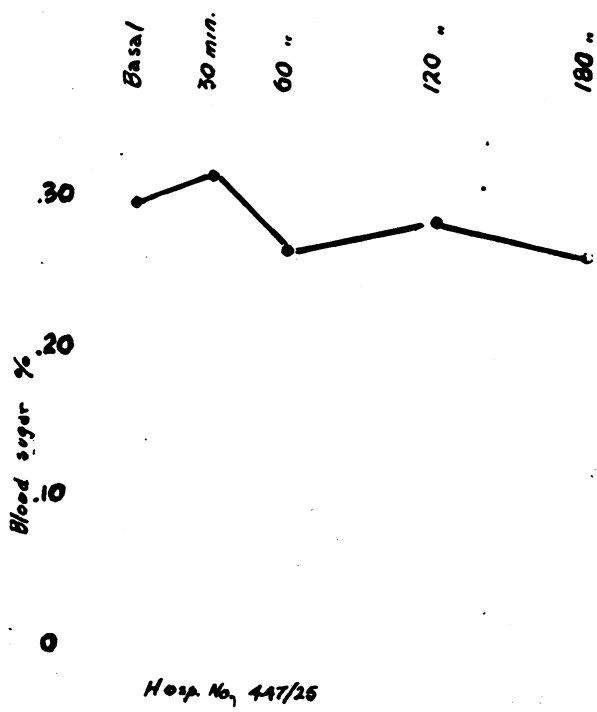
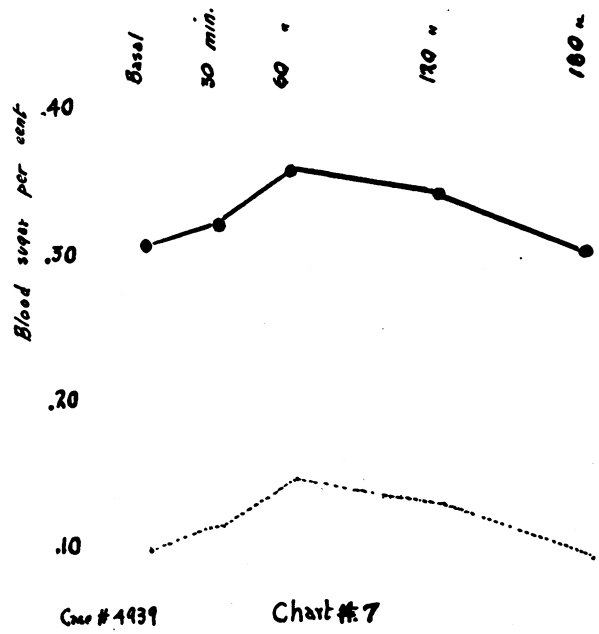
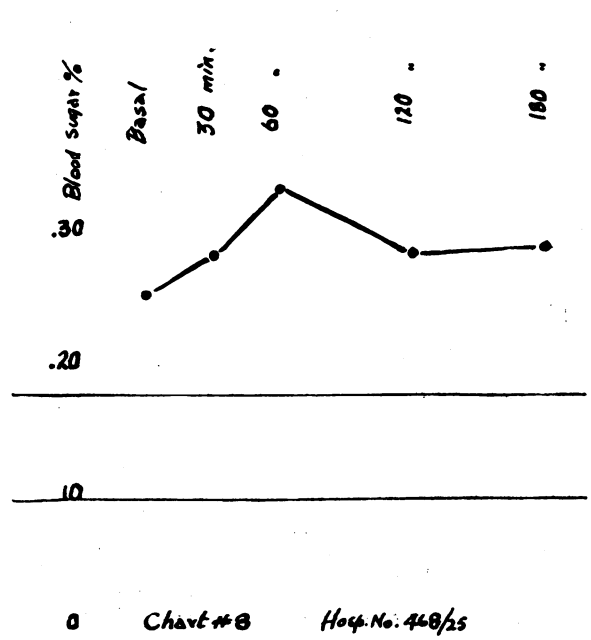
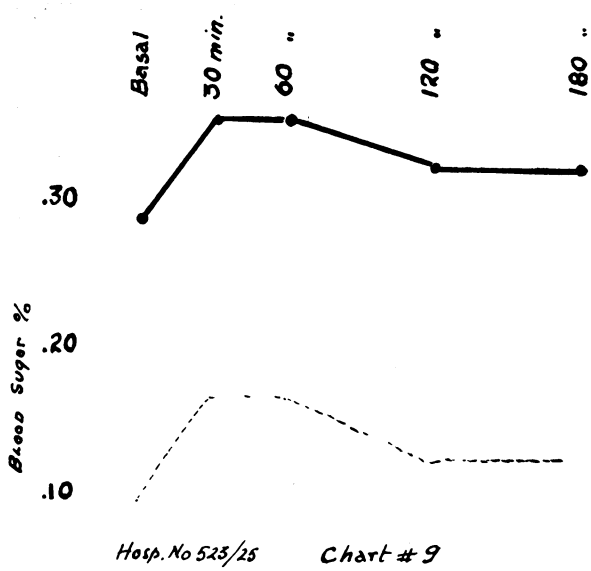


Chart #6

Case No.	Time	Blood Sugar %	Urine cc	Urine %	Urine gms.	Remarks
447	Basal	0.300	200	4.2	8.4	Total for 1 hour before.
	30 minutes after	0.327	38	2.5	1.77	
	60 minutes after	0.270	28	2.1	1.67	
	120 minutes after	0.293	65	2.8	2.35	
	180 minutes after	0.271	100	1.0	1.55	
					7.34	Total for 3 hours after.
4939	Basal	0.312	120	6.6	7.92	Total for 1 hour before
	30 minutes after	0.333	50	4.4	2.20	
	60 minutes after	0.357	35	2.9	0.91	
	120 minutes after	0.344	85	2.4	2.04	
	180 minutes after	0.302	110	1.8	1.98	
					7.13	Total for 3 hours after
468	Basal	0.256	165	3.8	6.27	Total for 1 hour before
	30 minutes after	0.285	175	2.1	3.67	
	60 minutes after	0.336	115	1.6	1.84	
	120 minutes after	0.285	175	0.61	1.06	
	150 minutes after	0.290	175	0.83	1.45	
					8.02	Total for 3 hours after
523	Basal	0.287	215	7.0	15.1	Total for 1 hour before
	30 minutes after	0.363	70	5.9	4.1	
	60 minutes after	0.360	40	7.0	2.8	
	120 minutes after	0.331	40	6.4	2.5	
	150 minutes after	0.338	45	5.5	2.5	
					11.9	Total for 3 hours after







That dioxyacetone may be retained after the limit of tolerance for glucose is reached, is suggested by the following case:

Hosp. No. 447.—Male, age twenty-seven years. Service of Dr. A. H. Gordon.

On January 31st on a "basal" diet of 48 gms. carbohydrates, 150 gms. fat and 50 gms. protein, the total excretion or sugar for twenty-four hours was 93.1 gms. There were acetone bodies in the urine, and the nitrogen metabolism was increased (12.6 gms.). The blood sugar in the post-absorptive state was 0.322 per cent. The low tolerance (Woodyatt "G") is obvious. The following day 10 gms. of dioxyacetone were given every hour for twelve hours (120 gms.). No insulin nor other food was given. The sugar excretion fell to 21.3 gms. and the acetone bodies decreased. During the next two days, the same treatment was continued, the sugar excreted for twenty-four hours was 26.3 and 17.8 gms. respectively. The degree of hyperglycæmia on these days in the post-absorptive state was 0.294 and 0.320 per cent respectively. An explanation of this decrease in the excretion of sugar may have been that it was due to starvation alone, the patient having received no other food. The patient was then replaced on the basal diet. The glycosuria increased daily, and within five days (on February 8th, 1925) the patient was excreting 81 gms. of sugar per day. Acetone bodies in the urine had reappeared. On the following day, 45 gms. of dioxyacetone were added to the diet. The excretion of sugar, however, for that day was 90 gms. Even assuming that the excretion of sugar would not have further increased on the basal diet alone, the body had apparently retained 36 gms. of the added sugar. The acetone bodies had slightly decreased.

Simultaneous blood sugar and respiratory quotients curves were also obtained. Since the quotients obtained from oxidation of acetone bodies may simulate those of carbohydrate, fat and protein, no patients excreting these bodies were utilized for the purpose of these observations. The standard technical procedure for this work was followed and the usual precautions taken to minimize the numerous sources of error, increased pulmonary ventilation, etc. One curve is recorded in the following table. This it will be noted was obtained from the same individual whose blood sugar time curve is recorded (Case No. 5258).

A definite rise in the R.Q. and an increase in the total metabolism is noted. Both were maintained throughout the period of observation. The R.Q. at no time reached the value of 1.00. Thus, evidence of oxidation of the dioxyacetone given was obtained, but at no time was there any evidence that the latter was supplying the total energy requirement. The calculations for the total sugar oxidized was the same as formerly used.[8] Fifteen per cent of the total metabolism was attributed to protein and deducted. The remaining calories, assumed to be derived from the carbohydrates and fats were apportioned according to the Zuntz and Schumberg tables as modified by Williams, Riche and Lusk. In spite of the possible fallacy of assuming a definite metabolism for protein and short

Time	*Blood Sugar %*	*R.Q.*	*Cal. per Hour*	*Cal. from CO H and Fat*	*Cal. from CO H*	*GMS. CO H*
Basal	0.103	0.706	78.79	.....	.....	.....
30 minutes after	0.145	.....	.....	.....	.....	.....
60 minutes after	0.165	0.773	87.17	74.09	16.15	4.07
120 minutes after	0.173	0.817	89.69	76.23	29.58	7.47
180 minutes after	0.165	0.753	82.32	69.97	10.49	2.64
						14.18

period experiment the results appear significant.*

Substitution of dioxyacetone for insulin.—If dioxyacetone has the same food and antiketogenic value as glucose and is more readily tolerated than the latter, it should be possible to lessen the dose of insulin. This was tested. The following case demonstrated that at least for a period of time dioxyacetone can replace small amounts of insulin.

Hosp. No. 294/25.—Male, age nineteen years. Service of Dr. Campbell Howard.

On December 29th, 1924, the patient was discharged from the hospital on a diet of 53 gms. carbohydrates, 148 fat and 48 gms. protein. The case was regarded as one of the severe type. On 25 units of insulin a day (15 in a.m. and 10 in p.m.) the urine was kept sugar free and the blood sugar normal (0.111 per cent). The weight was 119 pounds. The patient returned to the diabetic clinic one week and two weeks later. On each occasion the urine was sugar free and on the last visit the blood sugar was normal (0.100 per cent). On January 20th, 1925, he was readmitted for treatment with dioxyacetone. He was kept on the same diet and dose of insulin until January 24th, and on this day the carbohydrate content of the diet was lessened by 10 gms. Twenty gms. of dioxyacetone were then substituted for this and the evening dose of insulin was discontinued. During the following nine days (January 24th to February 1st inclusive) the urine remained sugar free and the blood sugar normal. The body weight was unchanged and there were no acetone bodies in the urine. On February 22nd the remainder of the insulin, 15 units, was discontinued. During the next four days the blood sugar increased and glycosuria reappeared. Ten units of insulin were then given daily and the urine again became sugar free and the hyperglycæmia decreased. It would appear that, for the present at least, in this case, dioxyacetone replaces the use of 15 units of insulin.

*The results of a more analytical study of the R.Q. and total metabolism are now in preparation for publication. The similarity between some of these and those obtained by Joslin in the case of lævulose is striking. It may be noted that dioxyacetone is one of the hypothetical cleavage products of lævulose.

This appears to hold also in the case of more severe diabetics who, though aglycosuric on insulin, still have mild degrees of hyperglycæmia in the post-absorptive state (0.15-0.16 per cent), as the following case demonstrated:

Hosp. No. 5477.—Male, age forty-eight years. Service of Dr. F. G. Finley.

In this case the diet consisted of 51 gms. of carbohydrates, 175 fat and 53 proteins. On this diet with the use of ten units of insulin twice a day, the urine could be kept sugar free, but there was a persistent, though mild, hyperglycæmia in the post-absorptive state (0.15-0.16 per cent). By substituting 15 gms. of dioxyacetone for 15 gms. of carbohydrate in the diet, it was found possible to diminish the evening dose of insulin (10 units).

No one method of procedure has as yet been found suitable for all individuals.

This applies especially to the partition of the total daily dose required, and the time of day it should be administered. Individuals given small doses at frequent intervals, apparently tolerate much more than when the total allowance for the day is divided between the three meal periods only. The readiness with which dioxyacetone is oxidized at room temperature, and the ease with which it may undergo rearrangement and condensation even in slightly alkaline media, may be the possible explanation of this phenomenon. Owing to the fact that polymerization takes place when solutions are heated above 65° C. these are to be sterilized by the fractional process. In spite, however, of the difficulties encountered, the results obtained appear sufficient to stimulate further study of the use of this product.

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