LXXVIII. STUDIES IN CARBOHYDRATE METABOLISM.

III. THE INFLUENCE OF DIHYDROXYACETONE UPON THE RESPIRATORY METABOLISM AND UPON THE INORGANIC PHOSPHATE OF THE BLOOD.

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Two divergent views are at present held regarding the path by which dihydroxyacetone is metabolised. According to one view—that of Campbell, Fletcher, Hepburn and Markowitz [1926]—it is first of all entirely converted into glucose which is then metabolised in the ordinary way.

According to the second view, dihydroxyacetone may be in part directly oxidised, although, in the diabetic, it may be more or less completely converted into glucose according to the severity of the condition, whilst even in the normal individual a certain amount may go into glucose, particularly after large doses [Kermack, Lambie and Slater, 1927]. Indirect evidence pointing to direct utilisation is afforded by the observation that the blood-sugar curves, both in diabetic and in normal subjects, after administration of dihydroxyacetone (50 g.) not only do not rise to so great a height as after an equivalent amount of glucose, but return more rapidly to the original level [Isaac and Adler, 1924; Rabinowitch, 1925; Kermack, Lambie and Slater, 1926; Mason, 1926, 1]. As regards recovery from insulin hypoglycaemia, Kermack, Lambie and Slater [1927] could find no significant difference between the time taken to remove the symptoms after administration of the same dose of glucose and of dihydroxyacetone. Moreover, after dihydroxyacetone recovery sometimes occurred in spite of the fact that the blood-sugar had apparently not risen to the "convulsion level." More direct evidence, suggestive of direct utilisation, was furnished by the experiment upon the decerebrated cat with the liver excluded from the circulation, in which it was shown that the muscles removed dihydroxyacetone from the blood much more rapidly than glucose when the two substances were transfused at an equal rate. This experiment does not, however, tell us whether the dihydroxyacetone which is removed by the muscles is oxidised or whether it is merely stored in some form.

In order to settle the question of direct oxidation it would be necessary to show that dihydroxyacetone could raise both the respiratory quotient and

the oxygen consumption more rapidly than glucose. If it could be demonstrated that these changes in the respiratory metabolism occur in the diabetic after administration of dihydroxyacetone under conditions where they are absent or less marked after glucose, the evidence in favour of direct oxidation would be further strengthened.

Mason [1926, 2] has found that dihydroxyacetone when administered by the mouth does, as a matter of fact, raise the respiratory quotient and the metabolic rate more rapidly and more markedly than an equal amount of glucose, and this occurred both in diabetic and in normal individuals. A possible objection, may, however, be raised to the conclusions drawn from his experiments owing to the consideration that the differences observed may have been due to dihydroxyacetone being more rapidly absorbed from the alimentary canal than glucose. It was therefore decided to repeat Mason's observations and to compare the effects of dihydroxyacetone and glucose upon the metabolism after intravenous administration. A few similar experiments were also performed with laevulose. In order to see whether the observations of Campbell, Fletcher, Hepburn and Markowitz regarding the identical behaviour of the inorganic blood-phosphate curves after administration of glucose and dihydroxyacetone could be confirmed, these were followed simultaneously with those of the respiratory metabolism and the blood-sugar.

EXPERIMENTAL.

In all experiments the subject was in the post-absorptive condition. The expired air was collected in 6-minute samples, using the Douglas bag method, and was analysed by means of Haldane's apparatus. The basal metabolic rate was first determined and a sample of blood for blood-sugar, blood-dihydroxyacetone and blood-inorganic phosphate was taken. The blood-sugar was determined by MacLean's method, the inorganic phosphate by Briggs' [1922] modification of the Bell and Doisy method and dihydroxyacetone by Campbell and co-workers' [1926] method. After administration of the carbohydrate, similar determinations were made at intervals.

In the first series of experiments oral administration was employed.

Oral administration.

Exp. 1 (a). Respiratory metabolism and curves of blood-sugar and blood-phosphate in normal student after ingestion of 50 g. glucose.

Time mins.	Metabolic rate % of normal B.M.R.	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood- sugar mg. %	Blood- inorganic phosphate mg. %
0	- 3	1.484	0.81	31.5	94	3.629
Glucose 50 g.						
18	± 0	1.486	0.91	32.1	111	3.629
31	+ 10	1.712	0.75	35.0	109	3.605
46	+ 10	1.700	0.76	34.0	100	3.358
61	+ 4	1.663	0.79	34.5	87	3.388
91	+ 4	1.695	0.84	33.25	84	3.750
128	+ 1	1.564	0.76	32.0	75	3.308
173	- 13	1.378	0.8	27.85	87	3.358

Exp. 1 (b). Same as preceding after ingestion of 50 g. dihydroxyacetone.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-dihydr. mg. %	Blood-inorganic phosphate mg. %
0	+ 3	1.643	0.75	28.32	86	0	3.432
Dihydroxyacetone 50 g.							
15	+ 21	1.779	1.10	39.36	86	5	2.848
20	+ 35	1.976	1.10	46.50	105	30	2.526
44	+ 31	1.941	1.10	48.90	106	49	2.368
67	+ 10	1.614	1.10	45.21	87	25	2.586
97	+ 4	1.469	1.10	40.56	68	5	2.884
127	+ 13*	1.909	0.707	35.10	76	5	2.960
157	- 3	1.593	0.67	35.10	68	0	2.960

* Mask readjusted.

Exp. 2 (a). Respiratory metabolism and curves of blood-sugar and blood-phosphate in normal student after ingestion of 50 g. glucose.

Time mins.	Metabolic rate % of normal B.M.R.	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-inorganic phosphate mg. %
0	- 1	1.750	0.81	37.2	117	3.243
Glucose 50 g.						
19	+ 2	1.789	0.72	36.0	123	3.236
38	+ 18	2.092	0.76	41.6	113	3.000
47	+ 15	1.957	0.85	43.5	110	2.925
59	+ 19	2.091	0.73	42.5	76	2.703
88	+ 13	2.005	0.7	40.2	67	2.928
116	+ 7	1.865	0.76	37.6	80	2.756

Exp. 2 (b). Same as preceding after 50 g. laevulose.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-laevulose mg. %	Blood-inorganic phosphate mg. %
0	+ 15	1.620	0.8	40.5	110	0	2.008
Laevulose 50 g.							
25	+ 26	1.817	0.72	40.0	98	25	1.825
39	+ 20	1.716	0.75	39.0	69	0	1.759
49	+ 1	1.409	0.84	35.5	—	—	—
68	+ 8	1.460	0.82	35.0	—	—	—
95	+ 10	1.555	0.85	36.0	70	0	1.715

Exp. 3 (a). Respiratory metabolism and curves of blood-sugar and blood-phosphate in a diabetic patient after ingestion of 50 g. glucose.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-inorganic phosphate mg. %
0	+ 18	1.339	0.60	26.35	168	3.571
Glucose 50 g.						
15	- 7	1.051	0.66	23.10	192	3.562
34	- 3	1.149	0.62	23.50	204	3.556
49	+ 15	1.317	0.59	24.25	251	3.571
69	+ 11	1.259	0.63	24.25	295	2.777
109	+ 7	1.200	0.65	24.25	341	2.900
149	+ 5	1.192	0.63	23.75	312	3.409
190	- 5	1.091	0.56	24.35	255	3.333

Exp. 3 (b). Same as preceding after ingestion of 50 g. dihydroxyacetone.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-dihydr. mg. %	Blood-inorganic phosphate mg. %
0	+ 2	1.147	0.65	24.50	187	0	3.1846
Dihydroxyacetone 50 g.							
24	+ 9	1.173	0.85	26.65	206	60	2.568
46	+ 50	1.615	0.80	37.39	230	70	2.272
65	+ 29	1.423	0.71	32.50	270	55	2.343
98	+ 14	1.285	0.66	28.43	249	25	2.922
132	+ 2	1.150	0.65	23.00	231	10	2.445
160	+ 5	1.182	0.63	23.61	243	5	2.445

Exp. 3 (c). Same as preceding after ingestion of 50 g. laevulose.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-inorganic phosphate mg. %
0	± 0	1.227	0.57	24.15	133	3.703
Laevulose 50 g.						
15	- 7	1.234	0.63	24.25	173	3.703
30	+ 16	1.370	0.69	27.5	202	3.750
46	+ 15	1.367	0.68	28.0	222	3.571
60	+ 18	1.390	0.72	29.75	222	3.845
90	+ 5	1.227	0.68	25.0	222	?
123	+ 2	1.140	0.99	25.0	202	3.488

Exp. 4 (a). Respiratory metabolism and curves of blood-sugar and blood-phosphate in a diabetic patient after ingestion of 50 g. glucose.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-inorganic phosphate mg. %
0	- 15	1.063	0.79	24.90	152	3.304
Glucose 50 g.						
51	± 0	1.360	0.6	27.34	253	3.300
82	+ 6	1.371	0.62	28.50	400	2.905
143	- 23	0.801	0.51	22.50	444	3.321

Exp. 4 (b). Same as preceding after ingestion of 50 g. dihydroxyacetone.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-dihydr. mg. %	Blood-inorganic phosphate mg. %
0	- 12	1.134	0.65	30.50	145	5	3.289
Dihydroxyacetone 50 g.							
12	- 11	1.116	0.74	30.50	190	25	2.952
33	+ 44	1.818	0.74	46.25	202	55	2.686
53	+ 37	1.819	0.73	48.25	253	35	2.343
73	- 10	1.159	0.66	28.20	—	—	—
140	- 10	1.159	0.65	28.75	222	5	2.393
179	- 20	1.047	0.61	27.50	210	5	2.678

Intravenous administration.

In the next series the substances were injected intravenously.

The solutions for intravenous injection were made by dissolving 25 g. glucose or dihydroxyacetone in physiological saline in the cold and making up the volume to 50 cc. Sterilisation of the solution was effected by passing it through a Seitz germicide (EK) filter No. 6, using special pads impermeable to micro-organisms. 40 cc. of the fluid, previously warmed to 37°, were injected into a superficial vein at the bend of the elbow, the injection being made at a uniform rate and occupying a period of exactly 5 minutes. Strong solutions were employed in order to avoid excessive blood-dilution, and to minimise any disturbing effects upon metabolism occasioned by the injection of large volumes of fluid. Great care must, however, be exercised in the use of such hypertonic solutions owing to the risk of producing venous thrombosis. While the injection was in progress there occurred, with dihydroxyacetone, an obvious increase in the depth and frequency of the respiratory movements. At first it was thought that this might have been due to the direct stimulation of the respiratory centre by dihydroxyacetone, or to something of the nature of a "specific dynamic action." The analyses of 3-minute samples of expired air taken during this period show, however, that the increased breathing was accompanied by a rise in the total metabolism, in the oxygen consumption and in the R.Q., indicating that the carbohydrate itself was being rapidly metabolised. These phenomena were not observed in the case of glucose.

Exp. 5 (a). Respiratory metabolism and curves of blood-sugar and blood-phosphate in a normal student after intravenous injection of 20 g. glucose.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-inorganic phosphate mg. %
0	+ 7	1.766	0.73	37.5	85	3.515
1-5 Glucose 20 g.						
16	+ 8	1.760	0.79	43.35	156	3.260
31	+ 24	2.441	0.80	43.75	112	3.571
44	+ 19	1.887	0.82	42.5	75	4.40
58	+ 17	1.904	0.70	40.0	67	3.571
74	+ 16	1.927	0.78	41.8	67	3.375
103	+ 15	1.898	0.73	41.35	76	4.40
136	+ 8	1.774	0.72	37.20	73	—

Exp. 5 (b). Same as preceding after intravenous injection of 20 g. dihydroxyacetone.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-dihydr. mg. %	Blood-inorganic phosphate mg. %
0	- 7	1.59	0.83	39.35	90	15	3.125
1-5 Dihydroxyacetone 20 g.							
1-3	+ 15	1.94	0.87	42.00	—	—	—
3-6	+ 50	2.51	0.92	61.50	—	—	—
17	+ 49	2.54	0.86	57.00	92	20	2.240
27	+ 36	2.35	0.81	51.00	93	15	2.312
40	+ 12	1.91	0.84	47.00	82	15	2.351
52	+ 7	1.85	0.80	46.50	70	15	2.700
67	+ 3	1.8	0.76	40.25	69	15	2.725

Exp. 6 (a). Respiratory metabolism and curves of blood-sugar and blood-phosphate in a diabetic patient after intravenous injection of 20 g. glucose.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-inorganic phosphate mg. %
0	+ 1	1.239	0.5	25.5	168	3.750
1-5 Glucose 20 g.						
12	- 1	1.188	0.5	25.0	245	3.685
25	+ 8	1.381	0.51	27.0	236	3.597
40	+ 10	1.274	0.62	28.0	205	3.456
60	- 4	1.220	0.56	27.0	212	3.658
68	- 4	1.125	0.56	25.0	195	3.658
105	- 4	1.115	0.52	25.0	167	3.428

Exp. 6 (b). Same as preceding after intravenous injection of 20 g. dihydroxyacetone.

Time mins.	Metabolic rate	Oxygen consumption l. per 6 mins.	R.Q.	Expired air l. per 6 mins.	Blood-sugar mg. %	Blood-dihydr. phosphate mg. %	Blood-inorganic phosphate mg. %
0	+ 2	1.227	0.55	27.50	202	80.0	3.333
1-5 Dihydroxyacetone 20 g.							
1-3	+ 46	1.735	0.59	35.20	—	—	—
3-6	+ 59	1.792	0.85	41.00	—	—	—
16	+ 56	1.749	0.88	41.75	253	35.0	2.884
33	+ 21	1.687	0.88	34.00	246	27.5	2.812
47	- 10	1.030	0.73	29.00	246	20.0	2.585
63	- 6	1.071	0.79	31.00	222	15.0	2.585
95	± 0	1.201	0.60	29.30	214	12.0	3.409?
126	- 18	0.952	0.77	28.25	200	10.0	2.884

DISCUSSION.

The above experiments amply confirm the results of Mason regarding the differences which occur in the respiratory metabolism following administration of dihydroxyacetone and of glucose when the substances are given by the mouth. In fact, by taking air and blood samples at shorter intervals, the more rapid rise in the total metabolism, in the oxygen consumption and in the respiratory quotient is even more strikingly shown. Thus, within 15 minutes of the ingestion of 50 g. dihydroxyacetone by the normal individual, a rise of about 18 % in the total metabolism was observed, whilst after a similar amount of glucose a rise of only 3 % was obtained. *Exp. 1 (a)* is exceptional in that the respiratory quotient, high to begin with, rose to a maximum 15 minutes after the administration of glucose, but there was no corresponding rise in the oxygen consumption or in the metabolic rate. Overbreathing is the probable explanation of this result. In all other experiments, both in diabetics and normals, the R.Q. attained its maximum about 45 minutes after administration of glucose, as did also the total metabolism and the oxygen consumption. On the other hand, after dihydroxyacetone the various maxima were reached in 20 to 30 minutes. After this there was a rapid fall in all values. The experiments in which intravenous injection of this substance was employed show that more rapid absorption from the intestine is not sufficient to account for the observed results. Thus, after 20 g. glucose intravenously, the total

metabolism, oxygen consumption and respiratory quotient gradually rose, reaching their maximum in approximately half an hour. Simultaneously with the rise in the respiratory metabolism, the blood-sugar fell and had regained the normal level or fallen below it about the time that the metabolism was at its height. With dihydroxyacetone, on the other hand, the rise in the total metabolism, the oxygen consumption and the respiratory quotient was not only more marked than with glucose, but was immediate, attaining its maximum about the time that the injection was completed, after which there was a fall *pari passu* with the disappearance of dihydroxyacetone from the blood. The maximal increase in the total metabolism of normal individuals after glucose was about 16 %, while after dihydroxyacetone the metabolism rose to 57 % above the basal level. In the diabetic, the rise in the metabolism after glucose was much smaller than in the normal individual. Thus, in Exp. 6 (a) there was an increase of not more than 9 % in the total metabolism after 20 g. glucose intravenously, the respiratory quotient and oxygen consumption also showing only a slight rise. On the other hand, after injection of a similar amount of dihydroxyacetone, the resultant increase in metabolism was comparable to that met with in the normal individual—namely 57 %—the oxygen consumption and respiratory quotient showing a corresponding rise. Dihydroxyacetone, therefore, produced a much greater increase in the metabolism in the diabetic than did glucose in the normal (cf. Exps. 5 (a) and 6 (b)).

These facts would seem to indicate that dihydroxyacetone can either be directly and immediately oxidised or very rapidly changed into some substance—possibly an active form of dihydroxyacetone—which is oxidised with great ease. Glucose, on the other hand, would appear gradually to undergo some transformation prior to its oxidation. It is evidently this transformation which the diabetic has difficulty in effecting.

The above observations seem to be in accord with the hypothesis advanced in a previous paper [Kermack, Lambie and Slater, 1927]—namely, that the essential feature of insulin action is to facilitate the transformation of glucose into dihydroxyacetone, which is then directly oxidised.

Although dihydroxyacetone may be converted into glucose to a greater or lesser extent in the diabetic, especially after repeated small doses by the mouth, the sudden injection of a large quantity intravenously would cause a certain amount to be rapidly oxidised, thus raising the metabolism in the manner above described, before any considerable amount would have time to be converted into glucose.

This more rapid oxidation of dihydroxyacetone in the animal body is paralleled by its more ready oxidation *in vitro*, as compared with glucose. Thus Wind [1925] has found that in neutral phosphate solution it takes up atmospheric oxygen much more readily than laevulose, while glucose takes up hardly any oxygen at all. Experiments, which will be reported by one of us in detail in a future communication, have been performed which show that, in neutral phosphate solution at p_H 7.4 and 37°, permanganate is much more

rapidly decolorised by dihydroxyacetone than by glucose and that dihydroxyacetone reduces methylene blue under anaerobic conditions whereas glucose does not. The latter observation is of interest in connection with the experiments of Ahlgren [1924], who found that the muscles of depancreatized animals, unlike those of normal animals, were unable to convert glucose into a hydrogen donor as tested by the methylene blue method, whereas addition of insulin restored the capacity to do so. Evidently some intermediary metabolite must have been formed from glucose under the influence of insulin which could act as a hydrogen donor. Dihydroxyacetone, which is a suggested intermediary, could at least fulfil this rôle.

It is now well established that increased metabolism of carbohydrates, whether brought about by ingestion of glucose or by injection of insulin, is accompanied by a fall in the inorganic phosphate of the blood, due in all probability to the formation of phosphoric acid esters of carbohydrate [Wigglesworth, Woodrow, Winter and Smith, 1923; Harrop and Benedict, 1924]. In view of this close connection between phosphate and carbohydrate metabolism together with the differences above described in the respiratory metabolism after administration of glucose and of dihydroxyacetone, there might naturally have been expected to be corresponding differences in the phosphate metabolism. Our protocols show that this is indeed the case. The curves of inorganic blood-phosphate follow closely those of the respiratory metabolism; the fall in inorganic blood-phosphate is more marked and more rapid after dihydroxyacetone than after glucose whether administered by the mouth or intravenously. Moreover, in the diabetic, where very little drop in the inorganic phosphate occurred after glucose, a marked fall followed the administration of dihydroxyacetone. It is difficult to reconcile these findings with those of Campbell, Fletcher, Hepburn and Markowitz [1926]. The fall in the inorganic blood-phosphate is not accounted for by increased excretion in the urine, since it was immediate after intravenous injection of dihydroxyacetone, while in some experiments little if any urine was eliminated during the whole period of the experiment. In other experiments the elimination of phosphate in the urine varied with the urine volume, rather than with the concentration of inorganic blood-phosphate.

These results would appear to indicate that administration of dihydroxyacetone causes the more rapid formation of a phosphoric acid ester than does the administration of glucose. The extremely rapid fall in inorganic phosphate following intravenous injection suggests that dihydroxyacetone may be directly esterified, forming a triosephosphate. Raymond [1925] and Kluver and Struyk [1926] have proposed schemes in which triosephosphate figures as an intermediary in carbohydrate metabolism, without, however, bringing forward any experimental evidence in support of their views. Glucose, as suggested by Euler [1925] and Meyerhof [1926], is represented as being esterified to hexose-monophosphate, and the latter splits into one molecule of triose and one molecule of triosephosphate. Two molecules of triosephosphate then condense

to form one molecule of hexosediphosphate. This would seem to account more readily for the formation of hexosediphosphate than the explanation offered by Meyerhof, namely, that it is formed by the splitting of two molecules of hexosemonophosphate into hexosediphosphate (1 mol.) and lactic acid (2 mols.). It would be premature to speculate upon the nature or fate of the phosphoric esters actually involved in these processes, as this is a matter for further investigation, but the above experiments serve to draw attention to the possible importance of esters of dihydroxyacetone.

The experiments with laevulose show that this substance is utilised somewhat more easily than glucose, but not nearly as readily as dihydroxyacetone. Its effects upon metabolism appear to be intermediate between the two, but more closely approximating to those of glucose. In experiments upon the normal subject (including some not recorded in the above protocols) the R.Q. after oral administration of 50 g. dihydroxyacetone rose above unity, indicating that fat was being formed from carbohydrate. Respiratory quotients above unity were not obtained with either glucose or laevulose in the doses employed, namely, 50 g. Benedict and Carpenter [1918] have, however, shown that with 100 g. or after repeated administration of smaller quantities, respiratory quotients above unity may be obtained with laevulose but not with glucose. Dihydroxyacetone can therefore produce these high respiratory quotients with smaller doses than laevulose.

Only a small number of experiments upon the respiratory metabolism in diabetics following administration of laevulose have been recorded above, and these show that, in the doses employed, the effects were not very different from those obtained with glucose. It has, however, been demonstrated by numerous investigators [Minkowski, 1890; Lusk, 1915; Verzar, 1914; Tögel and co-workers, 1913; Johansson, Billström and Heijl, 1904] that with larger or repeated doses laevulose produces a much greater rise in the total metabolism and in the R.Q. than similar amounts of glucose. Joslin [1924] has even obtained respiratory quotients of unity or above in diabetics.

Laevulose, like dihydroxyacetone, is not only more easily oxidised in the animal body, but it is a better glycogen former than glucose. This is all the more remarkable in view of the fact that glycogen yields only glucose on hydrolysis. As far as can be ascertained there is no difference between the glycogen formed from glucose and that formed from laevulose [Cremer, 1902; Macleod, 1926]. Neither laevulose nor hexosediphosphate [Harden and Young, 1911; Young, 1911], which is probably a derivative of laevulose, can, therefore, presumably be the immediate precursors of glycogen. There would therefore seem to be some intermediary common to laevulose and to glucose from which glycogen is formed. Another fact pointing to the existence of a common intermediary is that in the diabetic laevulose is excreted for the most part as glucose [Minkowski, 1890]. It has been supposed that in the formation of glycogen from laevulose, the latter is converted into glucose through the common enol form of the hexoses. This would not, however, explain satisfactorily the greater

ease with which laevulose forms glycogen, nor why such a substance as dihydroxyacetone is a better glycogen former than glucose. The simplest hypothesis would seem to be that dihydroxyacetone is the intermediary common to laevulose and glucose and that glycogen is formed from it by condensation and polymerisation. In the diabetic, dihydroxyacetone would be converted into glucose and thus the increased elimination of the latter after administration of laevulose would be accounted for. It at first seems an objection to this assumption that laevulose, in spite of its being more readily oxidised in the animal body, even in diabetes, does not cause recovery from insulin hypoglycaemia as rapidly as does glucose [Noble and Macleod, 1923] or dihydroxyacetone. It is possible, however, that laevulose, being structurally more closely related to dihydroxyacetone than glucose, may be converted into dihydroxyacetone without the aid of insulin, and in this way its more ready utilisation by the diabetic, observed especially after large doses, would be accounted for. On the other hand, insulin may be supposed to be specifically adapted for the conversion of glucose (? and mannose, whose structure closely resembles that of glucose) into dihydroxyacetone, a reaction occurring with difficulty, if at all, without it. In the presence of excess of insulin, however, as in animals suffering from experimental hypoglycaemia, the conversion of glucose into dihydroxyacetone might be even more rapid than the formation of the latter from laevulose. Hence, under these conditions, recovery would be more rapid with glucose than with fructose.

Finally, it may be noted that it is probable that dihydroxyacetone, like other ketoses, can exist in forms other than the stable variety [cf. Fischer and Taube, 1924] and we therefore cannot exclude the possibility that it is in fact a reactive form of the substance which is biologically important.

SUMMARY.

1. Dihydroxyacetone produces, both in diabetics and normals, a more rapid and more marked rise in the respiratory quotient, the oxygen consumption and the total metabolism than does glucose, whether administered intravenously or orally.

2. Dihydroxyacetone can be directly utilised by the diabetic. After intravenous injection of 20 g. over a period of 5 minutes, the immediate rise in the metabolism, respiratory quotient and oxygen consumption is comparable to that obtaining in normal individuals.

3. The fall in the inorganic phosphate of the blood in both diabetics and normals is more rapid and more marked after dihydroxyacetone than after glucose, whether administered intravenously or orally. The curves of inorganic blood-phosphate follow closely those of the respiratory metabolism.

4. Laevulose produces effects intermediate between those of glucose and dihydroxyacetone, but more closely approximating to those of the former when small doses are employed.

5. Respiratory quotients above unity were obtained after oral administration of 50 g. dihydroxyacetone in normals, indicating the formation of fat from carbohydrate.

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