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Following the administration of dihydroxyacetone there is a temporary increase in the carbon dioxide production and a secondary increase in the oxygen consumption, as has been shown by others as well as ourselves (1, 2, 3, 4, 5). In some respects the results differ from those following glucose administration. The increase in CO_2 occurs more sharply, that of oxygen gradually, but at the end of four hours the average oxygen consumption approximates that of the preliminary control period in both cases. The so-called respiratory quotient becomes very high (1.0 to 1.31) on account of the increased CO_2 elimination and this has been interpreted as indicating a difference in the metabolism of the triose (increased combustion) as compared with glucose and has been advanced as evidence that dihydroxyacetone is metabolized more readily than glucose and is, therefore, more suitable for the treatment of diabetics than glucose itself.

The bulk of the other evidence on accurately controlled experimental animals is definitely opposed to this view and supports the opinion that the triose is converted into glucose prior to its utilization. On examination two inconsistencies reveal themselves: First, that a respiratory quotient above 1.0 should be regarded as signifying that a substance with a respiratory quotient of 1.0 is being burned; secondly, that the CO_2 elimination precedes the increased oxygen intake. When we consider that a similar rise in oxygen absorption and CO_2 elimination occurs in completely depancreatized animals fed the triose, even while they are excreting the equivalent of the triose given as glucose in the urine, this interpretation becomes remarkable and, we believe, untenable.

Examination of the data (1, 2, 4, 5) indicates that hyperventilation has taken place and a cause for this is of interest. Increased oxygen consumption occurring later can then be explained on the basis of

TABLE 1

Dihydroxyacetone tolerance tests

Case	Time	Blood glucose	Blood dihydroxy-acetone	Blood lactic acid	CO₂ combining power
		mgm. per cent	*mgm. per cent*	*mgm. per cent*	*volumes per cent*
1	Fasting	85	0	18	58*
	30 minutes	90	17.5	50	52
	1 hour	90	15.8	40	60
	2 hours	95	13.2	26	59
	3 hours	95	8.8	23	62
2	Fasting	100	0	17	64
	30 minutes	120	13.2	24	56
	1 hour	135	8.8	21	52
	2 hours	100	8.8	18	61
	3 hours	80	4.4	11	63
3	Fasting	80	0	11	67
	30 minutes	110	45.5	31	60
	1 hour	85	28.0	26	63
	2 hours	65	8.8	19	67
	3 hours	85	4.4	9	67
4	Fasting	95	0	21	64
	30 minutes	80	8.8	38	60
	1 hour	60	4.4	33	56
	2 hours	85	1.8	15	59
	3 hours	80	0	17	63
5	Fasting	100	0	12	67
	30 minutes	100	26.3	37	59
	1½ hours	75	13.2	31	66
	2½ hours	80	8.8	23	65
6	Fasting	85	0	16	68
	30 minutes	105	17.5	42	58

* First blood hemolyzed.

increased work necessitated by the hyperventilation and possibly also in other ways. Since it seemed apparent that hyperventilation was a

probable feature of a period following administration of dihydroxyace-
tone and only to a minor extent follows glucose administration, it

TABLE 2

Fructose tolerance tests

Case	Time	Blood glucose	Blood fructose	Blood lactic acid	CO₂ combining power
		mgm. per cent	*mgm. per cent*	*mgm. per cent*	*volumes per cent*
7	Fasting	90	0	12	59
	30 minutes	100	11.5	29	53
	1 hour	110	11.5	33	49
	2 hours	100	8.6	26	50
	3 hours	85	5.8	14	59
8	Fasting	90	0	12	61
	30 minutes	90	8.6	23	59
	1 hour	90	8.6	25	59
	2 hours	95	5.8	19	58
	3 hours	85	2.9	14	59
9	Fasting	80	0	16	62
	30 minutes	100	17.2	25	62
	1 hour	110	26.0	24	61
	2 hours	100	14.4	19	63
	3 hours	80	0	9	62
10	Fasting	95	0	15	64
	30 minutes	105	11.5	27	60
	1 hour				
	2 hours	100	5.8	21	61
	3 hours	90	0	14	63
11	Fasting	85	0	14	58
	30 minutes	90	2.9	24	60
	1 hour	110	5.8	19	61
	2 hours	125	5.8	16	57
	3 hours	95	0	12	61
12	Fasting	110	0	21	63
	30 minutes	130	17.2	31	61
	1 hour	145	23.0	34	58
	2 hours	115	11.5	28	61
	3 hours	110	8.7	26	61

became important to discover wherein the difference in the behavior
of the sugars lies. As fructose, another ketose, sometimes causes the

respiratory quotient to rise above 1.0 and similar claims have been made for it in diabetic treatment, it was included in the investigation along with cane sugar, which splits into glucose and fructose.   Maltose, lactose, glucose and galactose, examples of aldoses, and the triatomic alcohol, glycerine, were selected for comparison with the above mentioned sugars.

TABLE 3

Sucrose tolerance tests

Case	Time	Blood glucose	Blood fructose	Blood lactic acid	CO₂ combining power
		mgm. per cent	*mgm. per cent*	*mgm. per cent*	*volumes per cent*
13	Fasting	105	0	17	63
	30 minutes	150	15.6	23	59
	1 hour	190	21.0	25	54
	2 hours	145	15.6	24	60
	3 hours	110	0	17	60
14	Fasting	95	0	28	60
	30 minutes	115	0	29	61
	1 hour	85	0	24	62
	2 hours	85	0	24	61
	3 hours				63
15	Fasting	100	0	10	65
	30 minutes	175	15.6	15	59
	1 hour	150	10.4	17	61
	2 hours	95	10.4	11	62
	3 hours	65	0	9	65
16	Fasting	100	0	11	61
	30 minutes	120	5.2	12	59
	1 hour	155	10.4	17	56
	2 hours	130	5.2	11	60
	3 hours	95	0	10	61

Disturbance of the acid alkali balance is perhaps the most potent cause of hyperventilation, and for its measurement the CO_2 combining power (Van Slyke's precision method (6)) was employed.   For certain reasons which will be discussed later the change encountered cannot be the maximal one, but it is sufficiently great to exceed many times the possible error.   The origin of the change in CO_2 combining power which preliminary tests showed to be present was not far to

seek. Embden and co-workers (7) found that, as well as the triose becoming glucose when perfused through surviving liver, the perfused blood also contains much lactic acid. In our work estimations of blood lactic acid were made by the Clauson method as improved by Shaffer and his co-workers (8).

TABLE 4

Glucose tolerance test

Case	Time	Blood glucose	Blood lactic acid	CO$_2$ combining power
		mgm. per cent	*mgm. per cent*	*volumes per cent*
17	Fasting	95	10	65
	30 minutes	130	10	65
	1 hour	160	11	62
	2 hours	150	11	66
	3 hours	75	11	65
18	Fasting	95	15	65
	30 minutes	125	17	62
	1 hour	100	17	64
	2 hours	95	15	63
	3 hours	80	14	63
19	Fasting	90	10	57
	30 minutes	85	15	60
	1 hour	105	12	‚60
	2 hours	95	9	59
	3 hours	105	9	59
20	Fasting	90	14	61
	30 minutes	135	15	64
	1 hour	135	14	64
	2 hours	120	11	61
	3 hours	100	12	61

Because of the amounts of blood required for duplicate analyses and the effect of hemorrhage on the blood lactic acid of small animals these experiments were carried out on man. In most cases convalescent patients were the subjects, care being taken that no metabolic abnormalities were present and the patient well recovered from his disease. Some cases were patients awaiting operations of election. A few were selected deliberately because they were suffering from liver in-

jury due to arsphenamine and were undergoing a parallel investigation at the time. (Cf. table 10.) The preparation was the same as for the ordinary blood sugar tolerance test, the patient remaining quiet in bed, fasting for fifteen hours and receiving 100 grams of the particular sugar dissolved in 250 cubic centimeters of water. Blood samples

TABLE 5

Maltose tolerance test

Case	Time	Blood glucose	Blood lactic acid	CO_2 combining power
		mgm. per cent	*mgm. per cent*	*volumes per cent*
	Fasting	90	11	64
	30 minutes	130	11	61
21	1 hour	90	11	65
	2 hours	65	11	65
	3 hours	75	11	65
	Fasting	90	11	58
	30 minutes	130	11	(Lost)
22	1 hour	120	11	59
	2 hours	70	10	59
	3 hours	80	10	59
	Fasting	100	11	59
	30 minutes	160	11	Not taken
23	1 hour	190	12	58
	2 hours	95	12	59
	3 hours	75	10	59
	Fasting	90	14	67
	30 minutes	130	15	65
24	1 hour	170	15	67
	2 hours	65	12	66
	3 hours	75	12	67

were removed while fasting, 30 minutes, and also one hour, two hours and three hours after administration of the sugar, and the appropriate analytical treatment for the various tests commenced at once. The results of the analyses after administration of dihydroxyacetone, fructose, cane sugar, glucose, maltose, lactose, galactose, and glycerine are tabulated in tables 1 to 8.

TABLE 6

Lactose tolerance test

Case	Time	Blood glucose	Blood lactic acid	CO_2 combining power
		mgm. per cent	*mgm. per cent*	*volumes per cent*
	Fasting	95	15	61
	30 minutes	100	17	61
25	1 hour	105	17	62
	2 hours	105	17 .	61
	3 hours	120	14	59
	Fasting	90	14	61
	30 minutes	95	17	60
26	1 hour	95	16	60
	2 hours	90	15	61
	3 hours	95	15	61
	Fasting	95	15	63
	30 minutes	145	21	61
27	1 hour	155	19	61
	2 hours	140	18	63
	3 hours	75	16	65

TABLE 7

Galactose tolerance test

Case	Time	Blood glucose	Blood lactic acid	CO_2 combining power
		mgm. per cent	*mgm. per cent*	*volumes per cent*
	Fasting	95	14	66
	30 minutes	15	17	65
28	1 hour	205	12	64
	2 hours	235	14	66
	3 hours	190	13	67
	Fasting	95	14	62
	30 minutes	125	15	62
29	1 hour	170	15	61
	2 hours	240	14	62
	3 hours	215	19	62
	Fasting	100	17	65
	30 minutes	155	17	64
30	1 hour	210	18	62
	2 hours	150	19	61
	3 hours	105	18	63

TABLE 8

Glycerine tolerance test

Case	Time	Blood glucose	Blood lactic acid	CO₂ combining power
		mgm. per cent	*mgm. per cent*	*volumes per cent*
	Fasting	90	10	57
	30 minutes	95	10	57
31	1 hour	95	15	61
	2 hours	95	12	58
	3 hours	95	10	58
	Fasting	90	14	62
	30 minutes	105	14	61
32	1 hour	110	12	62
	2 hours	110	12	62
	3 hours	100	(Lost)	61
	Fasting	85	12	67
	30 minutes	80	14	69
33	1 hour	80	12	70
	2 hours	80	12	68
	3 hours	80	12	68

TABLE 9

Lactic acid tolerance test

Case	Time	Blood glucose	Blood lactic acid	CO₂ combining power
		mgm. per cent	*mgm. per cent*	*volumes per cent*
	Fasting	90	11	63
	30 minutes	90	19	60
34	1 hour	95	19	56
	2 hours	100	14.5	61
	3 hours	95	11	61
	Fasting	95	11	61
	30 minutes	90	19	58
35	1 hour	90	17	60
	2 hours	90	14.5	60
	3 hours	90	11	60

TABLE 10

Clinical diagnoses of subjects

Test	Case number	Diagnosis
Dihydroxyacetone............	1	Catarrhal jaundice
	2	Duodenal ulcer
	3	Arsphenamine jaundice
	4	Cerebrospinal syphilis
	5	Arsphenamine jaundice
	6	Arsphenamine jaundice
Fructose.....................	7	Rheumatic fever
	8	Osteoarthritis, tarsal joints
	9	Arsphenamine jaundice
	10	Rheumatic myocarditis
	11	Acute pharyngitis
	12	Rheumatic fever; aortic stenosis and regurgitation
Sucrose.....................	13	Polycythemia rubra vera
	14	Pneumonia
	15	Chronic tonsillitis
	16	Carcinoma of nasopharynx
Glucose.....................	17	Morphinism
	18	Epilepsy
	19	Psychasthenia
	20	Lateral sclerosis
Maltose.....................	21	Degenerative myocarditis
	22	Hemorrhoids
	23	Psychasthenia
	24	Seborrheic dermatitis
Lactose.....................	25	Mitral insufficiency
	26	Tonsillitis
	27	Chronic proctitis
Galactose....................	28	C. N. S. syphilis
	29	Sciatic neuritis
	30	Psychoneurosis
Glycerine....................	31	Osteoarthritis, cervical spine
	32	Duodenal spasm
	33	Psychasthenia
Lactic acid..................	34	Rheumatic myocarditis
	35	Rheumatic fever

DISCUSSION

It will be noted that the results fall into two groups, the first three sugars causing a reduction in CO_2 combining power, the others not. Associated with the fall in CO_2 combining power is a definite increase in the blood lactic acid, more marked in the case of dihydroxy-acetone than with fructose or cane sugar as would be expected from the relative amounts of reduction of the CO_2 combining power in these cases. Moreover, the return to previous values for CO_2 combining power and blood lactic acid runs parallel. As in the case of the CO_2 combining power alterations in the blood lactic acid after administration of the other sugars are practically negligible. In order to gain some idea of the changes involved two men were given five grams of pure lactic acid dissolved in 250 cubic centimeters of water sweetened with saccharin, and tests similar to the foregoing carried out. Table 9 shows the results obtained. In this connection it should be pointed out that lactic acid in the body is constantly being burned or reconverted to glucose or glycogen so that the values obtained for blood lactic acid as well as the resultant lowering of CO_2 combining power fall short of measuring the total change taking place. Particularly will this be important in the later phases owing to the increased oxygenation consequent upon the hyperventilation. (Also since the respiratory muscles work on carbohydrate we must expect a shift of respiratory quotient toward 1.0.)

To take one method of calculating the CO_2 eliminated: Palmer and Van Slyke (9) have shown that it requires 1.0 gram of $NaHCO_3$ to raise the CO_2 combining power one volume per cent in an individual weighing 38 kilograms. Taking the average depression[1] of the CO_2 combining power at the half hour period as amounting to eight volumes per cent in an individual of 70 kilograms, 14 grams of $NaHCO_3$ have been lost, equal to one-sixth of a formula weight or 3,750 cc. of CO_2 released. Providing this patient were in a basal state, 1 calorie per kilogram hour should approximate his needs, or 35 calories the requirement for the half-hour, or 7,300 cc. of oxygen. With a true respiratory quotient of 0.80 (it would undoubtedly be higher on ac-

[1] Omitting from the average Case IV which requires one hour to attain this reduction in CO_2 combining power.

count of the increased muscle work of respiration) the CO_2 production would be 5,840 cc.   Adding to this 3,750 cc. CO_2 driven off by the production of lactic acid the CO_2/O_2 ratio becomes 1.31.   Had the basal respiratory quotient actually been 1.0 the additional liberation of CO_2 would have forced it up to 1.50.   It may be recalled that using a method for determining total oxygen consumption and carbon dioxide elimination we have not found CO_2/O_2 ratios exceeding 1.10 (5).

Or to take an example from Mason's paper (Jour. Clin. Invest., 1925, ii, 522) in which he administers 50 grams of dihydroxyacetone to a man of twenty-six with a surface area of 1.525 sq. m.:

> Basal CO_2 elimination at true rate of 10,780 cc. per hour
> Basal O_2 absorption at true rate of 12,120 cc. per hour
> True basal R.Q. = 0.888

After 30 minutes a second examination shows the

> CO_2 elimination at the rate of 14,910 cc. per hour or 7,455 cc. in 30 minutes
> O_2 absorption   at the rate of 13,610 cc. per hour or 6,805 cc. in 30 minutes
> R.Q. = 1.090.

Evidently this rate is near the maximal since in the examination made one hour after the dihydroxyacetone administration the O_2 and CO_2 are nearly back to the basal and the respiratory quotient is again 0.890. Evidently, also, since the discontinuous method of examination was used during the period 20 to 30 minutes after ingestion of the triose the additional CO_2 actually eliminated in the first half hour cannot be more than one-quarter the difference between the basal value per hour and the observed value per hour, or about one liter.   As we have seen, a minimal average depression of the CO_2 combining power of eight volumes per cent would provide 3,750 cubic centimeters of CO_2 to be eliminated but as 100 grams of the triose were used instead of 50 grams, as in Mason's work, 1,875 cc. might be expected to be eliminated by a 70 kgm. man.   The margin appears to be quite adequate to explain the actual result even in an individual weighing much less than 70 kgm., even without regard to the fact that such an additional amount of CO_2 to be eliminated would require increased respiratory work as must have been the case from the additional amount of oxygen consumed.

No doubt also, considering that all the sugar cannot have been

absorbed in the first half hour, the formation of more lactic acid may be expected as this remaining sugar reaches the liver. It is evident from the tables that some lactic acid has disappeared at the end of an hour but a continuance of a high respiratory quotient may depend in part on incomplete re-establishment of acid alkali equilibrium, or combustion of the lactic acid, or many other factors. Should the initial CO_2 released be eliminated over a longer period, as there is good reason to believe possible, there is quite sufficient to maintain high CO_2/O_2 ratios for a considerable period. Attention may be called to the fact that the higher values for these ratios reported have been obtained for a very limited period and calculated on the hour basis, a procedure which examination of the protocols in the preceding paper shows is unsuitable and liable to lead to erroneous conclusions.

Turning now to another aspect of these results, we wish to call attention to the remarkable parallelism between the changes in CO_2 combining power and blood lactic acid in these cases with the results of the respiratory examination in man (Mason's) or in normal dogs following the administration of dihydroxyacetone as recorded in the preceding paper. In contrast the fixation of CO_2 and blood lactic acid in man and the slow rise and fall of the CO_2/O_2 ratio after glucose administration to man or animals inspires confidence that such extraneous factors play little, if any, part in the alterations of the respiratory quotient after administration of the normal body sugar.

Corresponding to the decreased frequency with which the CO_2/O_2 ratio exceeds 1.0, the results with fructose are somewhat less striking both in the reduction of CO_2 combining power and increase in the lactic acid level (table 2). With them, however, it is still possible to calculate a CO_2/O_2 ratio well above 1.0. Sucrose also shows a smaller change in the CO_2 combining power and blood lactic acid (table 3). Half the administered carbohydrate was really glucose when it reached the liver and, as shown in table 4, glucose has no effect on either CO_2 combining power or blood lactic acid. Likewise, maltose and lactose and galactose have no influence on these (tables 5, 6 and 7).

It would seem apparent that the extraordinary CO_2/O_2 ratios reported by others (1, 2, 3, 4), as well as ourselves (5), after administration of certain carbohydrates are consequentially related to the production of lactic acid in the body and the blowing off of CO_2 neces-

sitated thereby. In such case the inferences drawn from them by various observers who have regarded them as true respiratory quotients must be revised and the problem becomes exceedingly complex. To eliminate an extra amount of CO_2 only somewhat smaller than the elimination under basal conditions must entail additional muscular work. According to the present accepted opinion this work must be done principally at the expense of the muscle glycogen stores, and in turn these stores kept full by transfer of carbohydrate from elsewhere. In all probability, as Hill and his co-workers have shown, the respiratory quotient of the additional work for short periods will approach unity and necessarily the output of CO_2 and the oxygen consumption will rise independently of any considerations as to the kind of foodstuff being ingested. In addition, however, we have to deal with a rapid production of lactic acid in considerable amounts. The heat production in this case is anerobic but additional oxygen is required to convert it into its final forms—glycogen, carbon dioxide and water— and this must tend to increase the oxygen consumptions and CO_2 elimination and raise the respiratory quotient toward unity since the respiratory quotient of this process is 1.0.

Now that it is becoming clearer that all, or about all, foodstuffs must be utilized as glucose, the latter assumes a unique position in the body. The site of transformation into glucose in the case of dihydroxyacetone (10) and fructose (11, 12) has been shown to be the liver and other evidence points to this organ playing an important rôle in the transformation of proteins and fat. The meaning of the production of considerable amounts of lactic acid when certain sugars are being converted to glucose presents some speculative interest. It may be suggested that when glycogen is present in the liver it can be used to furnish energy for other processes. In this case the first step is conversion of glycogen to lactic acid, an anerobic process yielding 0.72 calorie per gram of lactic acid produced. It may be suggested that this energy would provide the small energy deficit between fructose and glucose and presumably (though no data on this point exists) between dihydroxyacetone and glucose. The other sugars tested have as high, or higher, energy value as glucose. Because of its high energy value and the fact that it also is known to be converted to glucose in the depancreatized animal (13) glycerine was tested in the same

way as the sugars.   As table 8 shows, no lowering of CO_2 combining power or rise in blood lactic acid occurs, a result which is at least consistent with this viewpoint, though by no means confirmatory of it.

Whether it be true or not that it provides the necessary chemical energy for the conversion of the ketoses to glucose, a further implication of the lactic acid production by these sugars occurs to one.   For some reason lactic acid is produced when the triose or fructose is fed.   The only source of lactic acid known to occur in the body is glucose or glycogen.   If it could be produced from triose itself the triose administered intravenously to eviscerated animals would not remain unchanged (9).   The process glycogen→lactic acid involves an energy reduction change which must be charged against the foodstuffs initiating the lactic acid production.   As, according to Meyerhof, this reduction amounts to 0.72 calorie per gram of lactic acid produced, a considerable reduction in the physiological caloric value of the foodstuff is caused directly as well as through the extra work induced by the acid stimulating respiration.   In our opinion such an action does not enhance the therapeutic value of either sugar in diabetes.   It is perhaps not a fortuitous circumstance that most of the important carbohydrate used by man and animals is convertible directly to glucose before absorption.

<div align="center">SUMMARY AND CONCLUSIONS</div>

The results of the examination of the carbon dioxide combining power and blood lactic acid after the administration of certain carbohydrates have been tabulated and discussed.   Certain sugars—dihydroxyacetone, fructose and cane sugar—cause a lowering of the carbon dioxide combining power and a rise in the blood lactic acid, while glucose, maltose, lactose, galactose and glycerine do not.   These changes take place at the proper time to cause stimulation of respiration and the increased elimination of carbon dioxide noted when such substances are fed and explain the extraordinarily high CO_2/O_2 ratios found.   We would conclude that such ratios cannot be used as an index of food transformation, combustion or storage of the first substances mentioned.   There appears no reason to believe that these factors interfere in the use of the ratios as respiratory quotients in the case of the other sugars examined.   In view of the additional energy

required, because of the stimulation of respiration and that lost by conversion of glycogen to lactic acid we cannot regard the first named sugars as being more valuable in the treatment of diabetes than glucose itself.

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