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SUGAR TOLERANCE AND ALCOHOL.

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The experiments about to be described are an outcome of some investigations on the effect of alcohol on sugar absorption in cats [Edkins and Murray, 1928]. In those experiments it was found that alcohol made the absorption of sugar more rapid and possibly more complete; for the sugar in the arterial blood rose to a maximum more quickly, and this maximum was generally higher than without alcohol. These cats were under amytal anæsthesia, which is known to depress metabolism generally and carbohydrate metabolism more particularly. These animals, when given the amount of glucose comparable to that used in the glucose tolerance test, showed incomplete utilization of carbohydrate; the blood sugar, having risen considerably, did not return to normal within eight hours, sometimes not at all. When given alcohol with the sugar there was apparently more utilization or storage, since the level of sugar in the blood fell to normal on an average in about six hours.

This last-mentioned result seemed important; for if it might be assumed that the non-utilization of the sugar in cats under amytal was comparable to the diabetic state, then it might be of benefit to give alcohol to diabetic subjects. Alcohol has been used as a source of fuel for diabetics repeatedly with very varying results. Hunt [1930] has obtained results in experiments on diabetic patients which show that alcohol lowers the fasting sugar level in the blood. He also showed that giving alcohol with sugar caused a more rapid absorption of the latter. Given in small quantities at suitable intervals it has been used to supply 2000 cals. per diem. The question then arises, does alcohol help the combustion of sugar? Determinations of the R.Q. and total ventilation after the ingestion of sugar alone and sugar with alcohol have been made by Togel, Brezina and Durig [1913]. In their experiments on normal human subjects, they found that with sugar alone there was a rise in R.Q. which lasted for over 2½ hours, accompanied by an increased total ventilation and hence a much greater increase in CO_2 output than in oxygen consumption. When alcohol was administered with the sugar the R.Q. fell

immediately and continued below normal for 2 hours. The total ventilation was smaller than with sugar alone, and hence the increase in CO_2 output above the normal was small as compared with the increased O_2 consumption. Their results prove that the fall in R.Q. is really due to the burning of alcohol in preference to sugar, so that the alcohol spares the sugar from oxidation. They definitely stated that this "spared" sugar was not to be found in the circulating blood, nor was it excreted, though they gave no figures for blood or urine sugar. In their experiments the quantities of sugar and alcohol used were strictly comparable to those of the experiments to be described. Allen and Wishart [1922] found that alcohol diminished hyperglycæmia and glycosuria in diabetic subjects on a low caloric diet, and in normal subjects was burnt in preference to other foods; that is, it had a sparing action. Fuller [1922] obtained similar results and arrived at the same conclusions.

In the following experiments glucose was given to normal human subjects with and without alcohol. The subjects had a cup of weak tea, without sugar, first thing in the morning, came to the laboratory at about 9 a.m., rested for half an hour, and then a blood sample was collected. Further samples were taken at intervals to be certain that the blood sugar was constant. The bladder was emptied. Then the sugar was taken in the following way: 75 g. of glucose were dissolved in water, 50 c.c. lemon juice added and the final volume made up to 300 c.c. When alcohol was given it was included in the 300 c.c., the quantity of alcohol being 0·57 c.c. absolute alcohol per kg. body weight, amounting to about 30 c.c.; the strength of alcohol then was 10 p.c. by volume. The liquid was drunk at a temperature of 25°–30° C. and the room temperature maintained between 19° and 20° C. in all the experiments.

All the blood samples were arterial in composition, being taken by stabbing the thumb or finger behind the nail with a very sharp ophthalmic surgery knife after the hand had been in hot water. The samples (oxalated) were placed directly on ice and measured from the ice. Determinations of sugar were made by the method of Hagedorn and Jensen at ¼-hour intervals during the rise of sugar and later at ½-hour intervals.

Urine samples were collected at definite intervals, the volumes noted and the sugar estimated. The amount of sugar was always too small to be detectable by ordinary rough sugar tests, though it could be determined by more refined methods. The estimations of sugar in urine were done as follows: 5 or 10 c.c. of urine (according to the dilution) were accurately measured, to it added 10 or 5 c.c. of water and then 5 c.c. of $N/10\,H_2SO_4$. To this diluted acid urine was added Lloyd's alkaloidal reagent recom-

mended by Folin and Berglund [1922]. This mixture was shaken for 2 minutes and filtered; the filtrate contained neither uric acid nor creatinine. Sugar was estimated in this filtrate, after neutralization, by the method of Hagedorn and Jensen. All blood and urine estimations were completed on the same day as the experiment.

The effect of alcohol alone on the blood sugar.

It was first necessary to know what effect alcohol taken alone had on the blood sugar in the subjects of these experiments. Alcohol given in the same dilution as in the other experiments caused very little alteration of blood sugar. In four subjects the blood sugar never varied much from the normal level during the 2 hours after the alcohol; after that the level tended to fall slightly. It has been shown by Southgate [1925] that alcohol reaches its maximum in blood in 1–2½ hours.

The effect of alcohol on sugar tolerance.

A series of experiments was carried out to compare the rate of rise of the blood sugar, the degree of hyperglycæmia and the rate of return to the normal level when sugar was taken alone and when it was taken together with alcohol. The conditions of these experiments were according to the details already stated and were entirely comparable in the two types of experiment. The graphs in Fig. 1 show three typical experiments in each subject. The complete set of experiments is given in Table I. The rate of return to normal or rate of disappearance of the hyperglycæmia is obtained by taking the maximum rise and dividing by the time taken to fall to the normal level. During the course of these experiments it was noted that the degree of diuresis caused by the alcohol was of importance; the figures for the urine secretion are therefore also given. The experiments are arranged in two series for each subject, (*a*) sugar alone, (*b*) sugar and alcohol.

From a study of the figures in the table, it is clear that the tendency for alcohol to quicken the absorption of sugar and so give a higher degree of hyperglycæmia, which we were able to show clearly in anæsthetized cats, is not a constant phenomenon in these experiments: although in two of the subjects the average maximum rise of blood sugar was greater when alcohol was taken with the sugar than when it was not. But there is another effect that the alcohol had in most of the experiments, namely to cause diuresis, and the extent to which this effect is manifested has a marked influence on the degree of hyperglycæmia. When there is no diuresis (subject A, Exps. 7 and 9) the rise of blood sugar is at its highest;

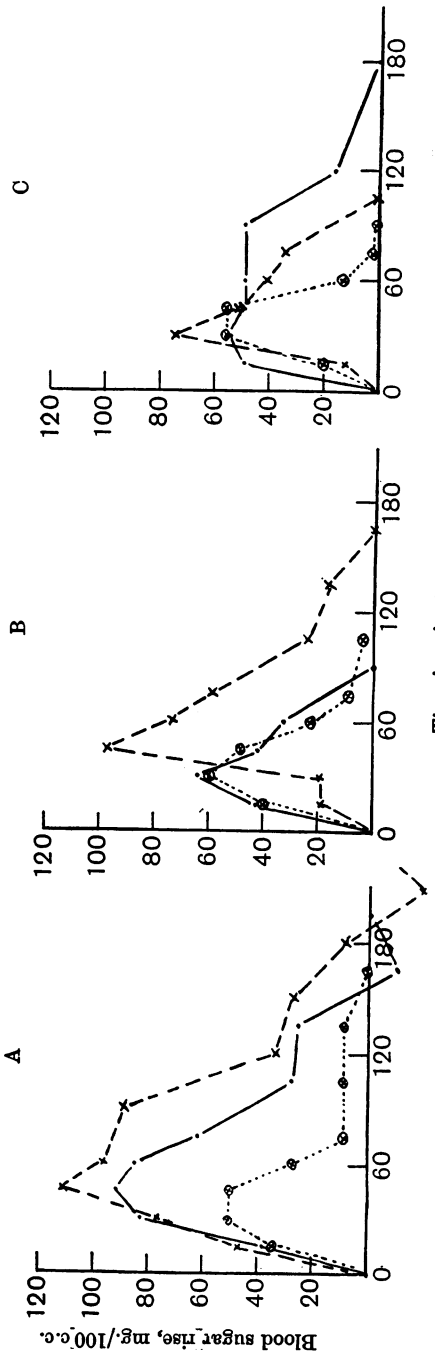

Fig. 1.

Subject A. —— Sugar alone. Urine in 2 hr. 170 c.c.
– – – – Sugar + alcohol. " " 270 "
. . . . . " " " 565 "

Subject B. —— Sugar alone. Urine in 2 hr. 250 c.c.
– – – – Sugar + alcohol. " " 415 "
. . . . . " " " 565 "

Subject C. —— Sugar alone. Urine in 2 hr. 270 c.c.
– – – – Sugar + alcohol. " " 280 "
. . . . . " " " 503 "

TABLE I.

	Expt. no.	Max. rise in blood sugar (mg./100 c.c.)	Time taken to reach this max. (min.)	Time taken to return to normal (min.)	Rate of fall	Urine vol. in 2 hr. (c.c.)	Sugar excreted in 2 hr. (mg.)
Subject A. Age 38 years. Weight 56·25 kg. Height 162 cm.							
Sugar alone	4	92	45	150	0·61	220	73
	5	87	45	165	0·53	170	36
	11	82	45	165	0·50	125	36
	16	71	30	195	0·36	410	70
	Average	84	41	169	0·50	230	54
Sugar and alcohol	7	97	45	165	0·59	236	Not deter.
	9	111	45	165	0·67	270	80
	19	28	30	60	0·47	640	91
	8	41	45	75	0·55	545	130
	10	50	30	75	0·67	565	120
	12	70	60	165	0·42	410	Not deter.
	Average	66	43	118	0·56	444	105
Subject B. Age 30 years. Weight 52·7 kg. Height 166 cm.							
Sugar alone	1	64	30	90	0·71	300	116
	2	63	30	105	0·60	250	118
	8	42	30	105	0·40	235	Not deter.
	12	64	30	105	0·61	255	„
	Average	58	30	101	0·58	260	117
Sugar and alcohol	7	75	30	75	1·00	490	91
	15	80	30	135	0·59	475	65
	5	84	60	180	0·47	320	80
	4	97	45	150	0·65	415	Not deter.
	10	57	30	120	0·48	500	„
	9	59	30	120	0·49	525	„
	6	60	30	90	0·67	565	200
	13	75	30	105	0·71	590	140
	Average	73	36	122	0·63	485	115
Subject C. Age 29 years. Weight 72·5 kg. Height 174 cm.							
Sugar alone	1	63	15	120	0·53	294	97
	2	54	30	120	0·45	270	111
	10	46	30	60	0·77	273	99
	11	51	15	105	0·48	373	101
	Average	54	23	101	0·56	302	102
Sugar and alcohol	3	56	30	120	0·47	425	128
	4	81	45	120	0·68	415	133
	5	47	15	105	0·45	448	142
	6	42	15	90	0·47	515	126
	7	74	30	105	0·70	380	80
	8	74	15	105	0·70	395	87
	9	55	30	75	0·73	503	100
	Average	61	26	103	0·60	440	115

when the diuresis is most marked, more than twice as great as without alcohol (subject A, Exps. 8, 10 and 19), the rise of blood sugar was actually less than when the sugar was taken alone. In the subjects B and C the degree of diuresis did not vary so much, but here too the tendency for the hyperglycæmia to vary inversely as the diuresis is evident, especially when plotted as is done in Figs. 2, 3 and 4 for the three subjects respectively.

That alcohol does tend to increase the hyperglycæmia we have other evidence, obtained in several experiments in which the alcohol was taken not at the same time as the sugar, but ¾ to 1 hour later, when the blood sugar was beginning to fall. In subject A a definite secondary rise was then obtained which did not occur if water was taken instead of alcohol. In similar experiments on subject B, although there was no such secondary rise, the fall of the sugar level was arrested for some time.

There are two ways in which this tendency to increase hyperglycæmia may be accounted for: it may be that the alcohol has speeded up the rate of absorption from the alimentary tract; evidence for this occurring in animals we have already given [1928]; or it may be that the alcohol has slowed down the rate at which the sugar is taken up from the blood by the tissues, especially the liver. The evidence furnished by our experiments definitely is against this latter possibility. In all three subjects the average rate of return from the maximum hyperglycæmia to the normal level was greater, not less, with alcohol than without. But the rate of return from the maximum hyperglycæmia is not the only measure of the rate at which sugar is removed from the blood by transfer to the tissues. In the extreme case, if the rate of removal were so rapid that it kept pace with the absorption into the blood, there would be no hyperglycæmia from which to measure the rate of return. The extreme case obviously does not occur, but a degree of hyperglycæmia less than might otherwise be expected may be evidence of rapid removal from the blood. Bearing in mind that although alcohol increases the rate at which sugar is taken up into the blood, we find as is shown in Figs. 2, 3 and 4 that, if it causes diuresis it gives less hyperglycæmia. It is therefore a fair inference that when alcohol causes diuresis it causes the sugar to leave the blood more rapidly, that is it increases the sugar tolerance.

That diuresis with or without glycosuria is associated with low hyperglycæmia after administration of sugar by itself has been observed by Goto and Kuno [1921].

The diuretic action of alcohol is apparently not due to direct action on the kidney. Loewy and Bornstein [1927] have shown that the

addition of alcohol to the blood circulating in a heart-lung-kidney preparation stops the secretion of urine; this was the case with a concentration of alcohol, 0·058 p.c., which in man would give a marked diuresis.

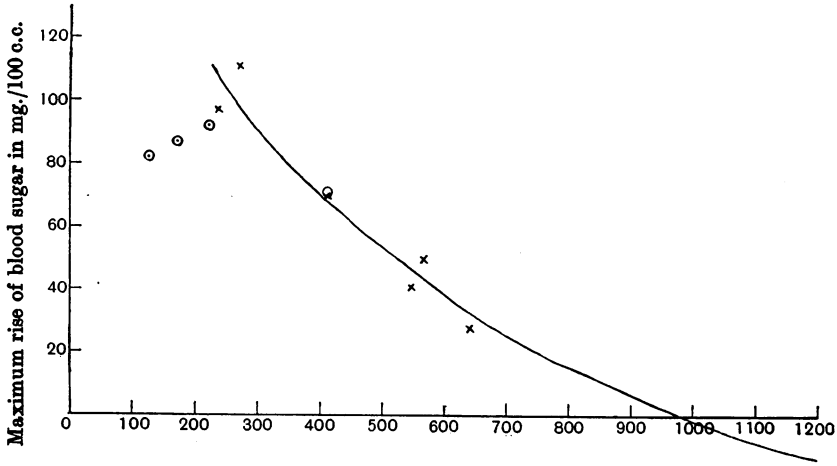

Fig. 2. Subject A. $m=26$. Sugar alone ⊙. Sugar + alcohol ×.

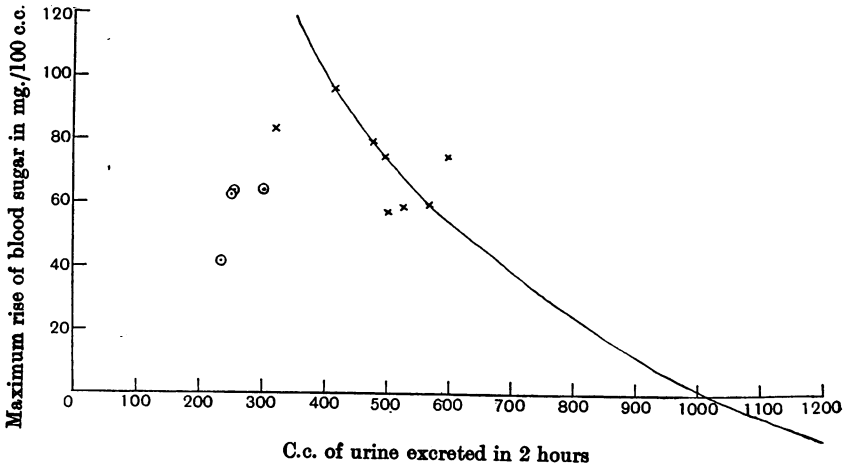

Fig. 3. Subject B. $m=54$.

This diuretic action of alcohol must, therefore, depend upon an influence exerted through some organ outside those included in the heart-lung-kidney preparation, unlike the action of such diuretics as theobromine and digitalis [Gremels, 1928].

The possibility that the organ through which alcohol acts on the kidney might be the pituitary suggests itself, not only on account of the well-known effect of injection of extracts of the posterior lobe in diabetes insipidus and in arresting the diuresis set up by drinking water, but also because we find that alcohol when it causes diuresis lowers the hyperglycæmia. The posterior lobe of the pituitary contains something which raises blood sugar by releasing sugar from the liver [Clark, 1928]. If, therefore, alcohol depressed the activity of the pituitary body, the association of diuresis with a lower level of blood sugar found in these experiments might be explained.

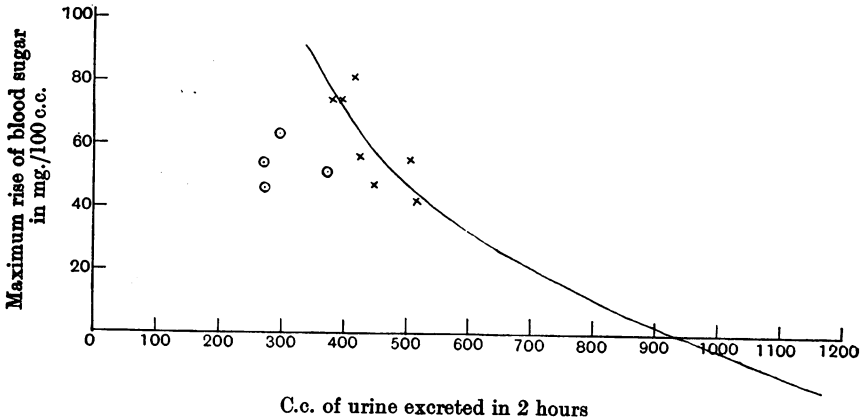

Fig. 4. Subject C. $m=37$.

In order to test this possibility, experiments have been made to see whether the diuresis induced by alcohol was accompanied by the diminished excretion of chloride which Starling and Verney [1925] found was characteristic of the diuresis resulting from the absence of the influence of the pituitary body. We find that this is so, as is illustrated by the following figures.

TABLE II.

Subject B. Exp. 25. Given 30 c.c. alcohol in 300 c.c. water.

	1 hr. before alcohol	Successive ½ hours after alcohol	Average per hour after alcohol
Urine volume	55·5	22·5, 126, 230, 124, 15	—
Urine chloride mg. per 100 c.c.	458	480, 76, 29, 53, 363	—
Mg. chloride excreted	231	108, 96, 67, 66, 54	156
Urine phosphate mg. per 100 c.c.	68	75, 16, 8, 13, 87	—
Mg. phosphate excreted	36	17, 20, 19, 16, 13	34

Here there is a marked increase in the volume of urine excreted, the rate at which chloride was excreted was considerably decreased, while the rate of excretion of phosphate was unchanged.

Summary and conclusions.

1. Experiments have been made comparing the tolerance to 75 g. glucose taken alone and with alcohol.

2. The alcohol increases absorption, as shown by a more rapid rise in blood sugar.

3. After alcohol the sugar in the blood falls more rapidly.

4. The more diuresis the alcohol causes the less the rise in blood sugar.

5. The diuresis is associated with increased sugar tolerance and diminished output of chloride.

6. The associated results in 3, 4 and 5, suggest a common origin in a depression of the activity of the pituitary body by the alcohol.

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