CX. THE EFFECT OF HYPNOTICS ON GLUCOSE TOLERANCE.

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IN the course of an investigation into the glucose tolerance of mental patients, four extremely abnormal curves were obtained. In these there was little or no initial rise in blood sugar after the ingestion of 50 g. glucose and the blood sugar fell to low levels. The only abnormality found in the circumstances of these curves was that in each case the patient received a dose of a hypnotic previous to the ingestion of the glucose. It was found, furthermore, that in each case the drug had been administered at such a time previous to the administration of the glucose that the patient was just coming under the influence of the drug when the test was commenced. Thereafter, hypnotics were not given before carrying out the tests, but time did not permit of a more detailed investigation of the problem.

Subsequently, this question has been examined more closely. A search of the literature shows that while numerous workers have investigated the effects of hypnotics on the fasting blood sugar, the only workers who have investigated their effects on glucose tolerance tests are Högler and Zell [1933] who state that they find that neither veronal nor chloral has any marked effect on alimentary hyperglycaemia in rabbits. An examination of their results shows, however, that eight out of nine experiments carried out with these drugs show the effect described below.

In the following research a glucose tolerance test was carried out on the fasting patient and within a few days, often the next day, the test was repeated with the patient fasting and under the influence of a drug. In a number of cases a repetition of the "normal" curve was carried out, and in each case the results were comparable.

This work has been carried out on two classes of patients: (a) cases showing marked lack of emotion and apathetic behaviour. These cases showed also considerable intellectual deterioration and for descriptive purposes are referred to as cases of "dementia" in this paper in contrast to (b) cases which showed the typical emotion consonant with their type of psychosis and had fairly well-maintained personalities. It is noticeable, however, that the phenomenon is manifested independently of the type of disorder.

The drugs used were:

- (1) Nembutal, gr. iii;
- (2) Veronal, gr. vii or x;
- (3) Chloral, gr. xx;
- (4) Morphine sulphate, gr. $\frac{1}{4}$ or $\frac{1}{8}$;

i.e. the ordinary clinical doses used in hospital practice.

No very profound variations were found in the fasting levels whether the patient was under the influence of the drug or not, and for clarity the

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fasting levels of the two curves have been made equal. Blood sugar estimations were carried out on oxalated-fluorided blood by the Hagedorn-Jensen technique.

The tables show the fasting level, the maximum level attained and the 2 hour level or the minimum if that is attained before 2 hours. In addition, the hyperglycaemic index (H.I.) and the hyperglycaemic area (H.A.) are shown for, in each case, first the normal curve and, second, the curve after the drug has been administered. In each case the age, sex and diagnosis for the patient are given.

It will be seen that in most cases following the administration of the drug there is a fall in the H.I., excepting where the "normal" was zero. In each case, however, the hyperglycaemic area shows a fall. This is expressed as a percentage decrease, calculated from the formula:

$$\% \text{ decrease} = \frac{(\text{Area}_{(\text{no drug})} - \text{Area}_{(\text{drug})}) \times 100}{\text{Area}_{(\text{no drug})}}$$

The hyperglycaemic area was found by actual measurement by counting squares when the curves were plotted on 1/10 in. graph paper. The hyperglycaemic index (H.I.) is that of McCowan and Quastel [1931]:

$$\text{H.I.} = \frac{(2 \text{ hour level} - \text{fasting level}) \times 100}{(\text{maximum} - \text{fasting level})}$$

Where a minimum is reached before 2 hours this value is used. In addition to the H.I. and decrease in H.A. the change in the curves may be seen from the maxima and minima in the tables. In the following tables the curves marked (a) are the "normal" curves and those marked (b) are those obtained when the patient was under the influence of the drug.

Table I.

A. *Nembutal*.

Case	Blood sugar mg./100 ml.			H.I.	H.A.	% decrease in H.A.	Sex	Age	Diagnosis
	Fasting	Max.	Min.						
i (a)	70	80	72	20	9	—	M	45	Mania
(b)	70	(40)	55	—	0	100			
ii (a)	80	105	92	50	32	—	M	56	Melancholia
(b)	80	100	75	0	18	56			
iii (a)	75	115	60	0	24	—	M	66	Inv. Mel.
(b)	75	95	45	0	17	29			
iv (a)	80	150	135	80	152	—	M	57	Acute Dep.
(b)	80	130	65	0	52	66			
v (a)	120	240	210	75	280	—	F	64	Dementia
(b)	120	220	170	50	194	31			
vi (a)	70	120	80	20	64	—	F	68	Dementia
(b)	70	95	70	0	32	50			
vii (a)	75	151	120	60	130	—	M	76	Dementia
(b)	75	120	120	100	63	49			

Inv. Mel. = Involutional melancholia, Dep. = Depression.

In case (i) the hyperglycaemic rise is entirely abolished, the blood sugar content falling to a minimum at 1 hour and then rising slowly. Case (i) was very excited at the time of the test. The other cases show the typical lowering of the curve. Case (vii), however, shows a rise in H.I., although the H.A. shows a 49 % decrease.

Owing to lack of space, it is not possible to show the individual pairs of graphs and accordingly the following method has been used for a graphic representation. At each time period, *i.e.* $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2 and $2\frac{1}{2}$ hours after the

ingestion of glucose the blood sugar level for the curve on the drug was subtracted from the blood sugar level on the control curve, and the difference was termed the "depression" for that time. The means of these "depressions" for each time and for each drug were determined and are shown in Table V together with the maximum and minimum depressions.

Table II.

B. *Veronal*.

Case	Blood sugar mg./100 ml.			H.I.	H.A.	% decrease in H.A.	Sex	Age	Diagnosis
	Fasting	Max.	Min.						
viii (a)	75	100	70	0	12	—	F	37	Ag. Depr.
(b)	75	75	55	—	0	100			
ix (a)	80	140	90	17	57	—	F	52	Ag. Depr.
(b)	80	105	80	0	23	40			
x (a)	95	127	90	0	25	—	M	62	Ag. Depr.
(b)	95	120	90	0	11	44			
xi (a)	80	107	85	20	33	—	F	49	Inv. Mel.
(b)	80	102	70	0	17	48			
xii (a)	80	140	65	0	68	—	F	?	Mania
(b)	80	125	35	0	38	44			
xiii (a)	75	140	90	23	70	—	F	59	Dementia
(b)	75	105	70	0	30	57			
xiv (a)	60	140	130	88	161	—	F	49	Dementia
(b)	60	125	95	54	102	37			

Ag. Depr. = Agitated depression.

In case (viii) also, the hyperglycaemic rise is abolished; a small transitory rise may however have been missed between the fasting sample and the sample drawn 30 minutes after the ingestion of the glucose. No case showed a rise in H.I. and the other cases show the typical increase of tolerance.

Table III.

C. *Chloral*.

Case	Blood sugar mg./100 ml.			H.I.	H.A.	% decrease in H.A.	Sex	Age	Diagnosis
	Fasting	Max.	Min.						
xv (a)	80	175	110	32	130	—	F	54	Inv. Mel.
(b)	80	150	105	36	94	28			
xvi (a)	80	113	100	61	63	—	M	24	Melancholia
(b)	80	103	75	0	26	59			
xvii (a)	90	118	80	0	26	—	M	40	Melancholia
(b)	90	98	70	0	8	69			
xviii (a)	80	135	95	27	61	—	F	70	Dementia
(b)	80	107	75	0	18	70			
xix (a)	80	115	105	71	67	—	F	28	Dementia
(b)	80	100	90	50	35	48			
xx (a)	85	130	115	67	75	—	F	63	Dementia
(b)	85	125	105	50	57	52			
xxi (a)	75	100	85	40	39	—	F	37	Dementia
(b)	75	90	70	0	8	79			

No case with chloral showed the abolition of rise in blood sugar. One case (xv) shows a rise in H.I., the other values for this case show depression.

Table IV.

D. *Morphine.*

Case	Blood sugar mg./100 ml.			H.I.	H.A.	% decrease in H.A.	Sex	Age	Diagnosis
	Fasting	Max.	Min.						
xxii (a)	90	145	105	27	83	—	M	77	Sen. Hyp.
(b)	90	127	113	62	43	48			
xxiii (a)	85	169	85	0	78	—	M	41	Schiz.
(b)	85	94	80	0	7	89			
xxiv (a)	80	142	135	40	125	—	M	77	Sen. Dem.
(b)	80	124	118	86	94	25			
xxv (a)	80	135	95	27	30	—	F	60	Dementia
(b)	80	92	88	66	13	57			
xxvi (a)	75	121	100	54	72	—	F	52	Dementia
(b)	75	108	68	0	17	76			
xxvii (a)	85	97	64	0	9	—	F	37	Dementia
(xxi) (b)	85	87	74	0	1	89			
xxviii (a)	85	125	105	50	65	—	M	74	Dementia
(b)	85	99	99	100	22	66			

Sen. Hyp.=Senile hypochondriasis, Schiz.=Schizophrenia, Sen. Dem.=Senile dementia.

In this series only one case showed a fall in H.I., four showed a rise and two did not change (H.I.=0). A reason for this will be suggested later. The areas, however, show a marked decrease with the drug.

Table V. *Differences in blood sugar content due to hypnotics.* (mg./100 ml.)

Hours	...	...	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$
Nembutal	Mean		-17	-23	-24	-24	-11
	Max.		-40	-60	-40	-70	-25
	Min.		-5	+5	-5	0	+25
Veronal	Mean		-20	-16	-21	-14	-3
	Max.		-45	-25	-40	-35	-25
	Min.		-5	-10	-10	+5	+10
Chloral	Mean		-18	-16	-13	-15	-11
	Max.		-40	-25	-20	-30	-35
	Min.		-10	0	0	-5	0
Morphine	Mean		-31	-30	-21	-4	+8
	Max.		-50	-55	-35	-25	-10
	Min.		-5	-15	+5	+5	+25

A normal blood sugar curve [Stewart and Dunlop, 1932] was taken as a standard, and the mean "depressions" were subtracted from its values for each drug. Figs. 1-4 show the depressed curves so obtained.

From Fig. 4 it will be seen that at 2 hours the depression is small and at $2\frac{1}{2}$ hours an increase is actually found. Further, the maximum of the curve ($\frac{1}{2}$ and 1 hour) is heavily depressed (Table V). This accounts for the elevation of the H.I. in so many of the morphine cases.

Seven cases of schizophrenia were used, and an interesting point was shown. In all cases but one (xxiii) the drugs had no clinical action whatever, and in each case the two curves obtained were identical. Case (xv), for some reason had no clinical reaction to the drug in the first instance and two identical curves

were obtained. On a subsequent occasion the drug was effective with the results shown above. This fact is particularly clear and seems to indicate that the biochemical manifestations run closely parallel with the clinical effects.

Fig. 1. Nembutal.

Fig. 2. Veronal.

Fig. 3. Chloral.

Fig. 4. Morphine.

SUMMARY.

1. It has been shown that hypnotics in clinical doses show a marked effect on the results of the glucose tolerance test.
2. This effect is shown by lowered maxima or shortened hyperglycaemia, or both, with markedly decreased hyperglycaemic area. The effect on the H.I. is less constant.
3. This effect is shown by chloral and morphine and is, therefore, not peculiar to drugs of the barbituric group.

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