MELANCHOLIA, GLUCOSE TOLERANCE AND BODY WEIGHT

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A DECREASE of glucose tolerance in mental illness has been observed for over forty years (Kooy, 1919; Mann, 1925). Although this change in carbohydrate metabolism has been described in all types of mental disorders, the majority of investigators report that it occurs most frequently in melancholia (Kooy, 1919; Mann, 1925; McCowan and Quastel, 1931; Holmgren and Wohlfahrt, 1944). The phenomenon has usually been regarded as a secondary effect, and several theories have been suggested to explain how it is produced (Kooy, 1919; Mann, 1925; McCowan and Quastel, 1931; Holmgren and Wohlfahrt, 1944); however, no single explanation is firmly established, and the mechanism or mechanisms are still uncertain.

The present investigation was undertaken to re-examine glucose tolerance in depressions. To obviate the possible effect of variations in the intestinal absorption of glucose, a factor previously held to be of paramount importance in determining the shape of glucose tolerance curves in depressions (Greville, 1945), intravenous are preferable to oral tests. Moreover, since the absorption factor is eliminated, the curve obtained by the intravenous test reflects the rate of glucose utilization alone, and this curve corresponds closely to an exponential equation (Greville, 1943). Thus, by means of a suitable technique and appropriate mathematical treatment, it is now possible to express glucose tolerance as a single numerical index (Duncan, 1956); this facilitates statistical analysis in studies of glucose tolerance.

A control group of mentally healthy subjects of similar age distribution to that of the depressions was examined concurrently. Systematic observations of various physical and mental factors were made in both experimental and control groups in the hope of establishing correlations should any change in glucose tolerance be found.

METHOD AND MATERIALS

A slight modification of the method of Duncan (1956) was used in the present investigation. The subject was fasted for 15 hours (overnight) and remained in bed on the morning of the test. Three samples of 0·1 ml. capillary blood were taken from a stab in the lobe of the ear, over a period of 10–15 minutes. Fifty ml. of 50 per cent. dextrose were then injected into an arm vein within 3 minutes, the time exactly 4 minutes from the end of the injection was taken as zero, and the first post-injection blood sample obtained. Further samples of 0·1 ml. capillary blood were obtained at approximately 7 minute intervals over the next hour, alternative samples usually being duplicated. The time of collection of each sample was accurately recorded, the time half-way between beginning and end of collection being taken when collection took longer than 30 seconds. Dabbing the stab wound with cotton wool soaked in

heparin prevented blood clotting. Since a fairly large needle (Record fitting "VIM" 18 gauge) was needed for the injection of the syrupy dextrose solution, its site of introduction into the skin of the arm was anaesthetized with a small intra-dermal wheal of 2 per cent. procaine. The glucose content of the samples was estimated by the micro-method of Folin and Wu, with the aid of a null-point photoelectric colorimeter. By plotting the logarithm of the difference between the mean fasting blood glucose and post-injection blood glucose values (log. glucose-increment) against time from zero, a linear relationship is obtained. The slope of this line, as given by $k=\log_e 2/t_r$, where t_r is the time taken for the blood glucose increment at any point to be halved, is an index of the rate of glucose utilization (Duncan, 1956).

The experimental group (Table I) consisted of 19 patients admitted to a mental hospital because of depression. These patients were mainly consecutive admissions and were unselected. Those who gave such scattered blood glucose values that an unequivocal linear relationship between time and log. glucose increment could not be obtained, were rejected from the group; some of these were early cases, and the scatter was possibly due to errors of technique. The group included 17 women and 2 men, ranging from 45 to 72 years of age, with mean age, weight and height for the women, of 57·4 years, 54·6 kgm., and 159 cm. respectively. Fifteen were recent admissions. Eleven gave histories of attacks of severe depression in the past, ten had a family history of mental illness or suicide, and sixteen either a past personal history or a family history of mental illness. In seven the depression was classified as an episode of manic-depressive psychosis, in eight as involutional melancholia, one was regarded as reactive (but she had a strong family history of depression), one was labelled neurotic depression, and two were unclassified depressions. Fifteen patients were treated with E.C.T.; fourteen gave a good response, in one the response was fair, and in four the improvement obtained was temporary. Recent admissions were tested during their first week in hospital, before commencing E.C.T.; all patients were depressed at the time of testing. Each patient's symptoms and signs were recorded on a check-list; and systematic observations of behaviour during testing were made on fourteen patients.

The control group (Table II) consisted of nine women, aged 42 to 71 years, with a mean age, weight and height of 61·1 years, 67·6 kgm., and 159 cm. respectively. Four had had surgical operations 10 days to 3 months previously, two had long-standing hemiplegias and one multiple arthritis.

Information was sought from subjects and relatives in both groups concerning past history and family history of illness; weight over the year and diet and appetite during the three to six months before admission; type of onset and length of illness; and (from nursing staff) amount of diet during the four days before the glucose tolerance test was carried out.

Results

Table III shows that there is a highly significant decrease in glucose tolerance in the group of depressions compared with the control group. Duncan (1956) gives an "increment index" of 3·68 (range 3·15–4·62; s.d. 0·4) for healthy adults between 20 and 60 years; and a value of 1·83 (range 1·33–2·34; s.d. 0·31) for mild diabetics. The mean value found in depressions thus lies near the upper limit of that given for mild diabetes.

The mean weight of the depressions is 13 kgm. (2 stones) less than the mean weight of the controls; this difference is highly significant (Table IV). The mean

TABLE I

No.	Sex	Age	Weight (kgm.)	Height (cm.)	Past History	Family History	Weight Before Admission	Appetite Before Admission	Pre-test Diet	Length of Illness	Onset	Response to E.C.T.	"Increment Index"
1	F	51	61·7	163	Dep. 26, 3, 2 years ago	Nil	Constant	Normal	Decreased	2 weeks	Acute	Good	1·87
2	F	47	55·3	165	Dep. 13 years ago	S. suicide, B. in M.H.	Constant	Normal	Normal	8 months	Subacute	Good	2·39
3	F	63	71·7	155	Nil	M. obese	?Decrease	Poor	Normal	6-7 weeks	?Acute	Good	2·27
4	F	72	40·4	157	Dep. 8 and 6 years ago	Nil	Decrease	Poor	Decreased	3 months	Subacute	Good	1·98
5	F	61	52·6	160	Dep. 3 and 1 year ago	M. and sisters "nervous"	Decrease	Fair	Normal	6 weeks	Subacute	Good	2·16
6	F	72	49·0	163	Chronic Dep. since 1937	S. to 10	Constant	(Fair)	Normal	19 years	Insidious	Good	2·77
7	M	56	53·1	157	Nil	Nil	Decrease	Poor	Normal	6-8 months	Insidious	Good	2·10
8	F	47	63·0	142	Rec. dep. since 1947	Obesity	Decrease	Fair	Decreased	4-6 weeks	Subacute	Good	1·44
9	F	65	48·5	183	Nil	S. suicide	Decrease	(Fair)	Normal	3 years	Subacute	—	2·04
10	F	62	45·8	163	"Breakdown" in 1924	S. to 6	Constant	(Fair)	Normal	16 years	Subacute	—	3·01
11	F	56	51·3	152	Rheum. arth. 10 years	S. to 12	Decrease	Fair	Normal	6 weeks	Acute	Good	2·16
12	F	66	57·2	155	Ost. arth. Rec. dep. 1 year	S. to 11	Decrease	Poor	Not observed	1 year	Subacute	Fair	2·20
13	F	63	49·4	155	"Breakdown" in 1929	Nil	Increase	(Normal)	Normal	3½ years	Subacute	Good	2·99
14	F	53	43·1	157	Nil	GF., M. and Aunt were in M.H.	Decrease	Fair	Normal	1 year	Insidious	—	3·46
15	M	45	54·4	165	Rec. dep. since 1936	Aunt in M.H.	Increase	Normal	Normal	5-6 weeks	Subacute	Good	2·66
16	F	48	56·2	163	Rec. dep. since 1952	Nil known	Constant	Fair	Normal	1 week	Acute	Good	2·17
17	F	61	60·8	150	Rec. dep. since 1935	B. was in M.H.	Decrease	Poor (3 weeks)	Normal	3 weeks	Acute	Good	3·15
18	F	52	59·4	152	Rec. dep. since 1952	S. was in M.H.—Dep.	Constant	Normal	Decreased	4 months	Insidious	—	2·31
19	F	37	62·6	175	Dep. 17 and 3 years ago	Nil	Decrease	Poor	Normal	1 year	Subacute	Good	2·66

TABLE II

No.	Sex	Age	Weight (kgm.)	Height (cm.)	Past History	Family History	Weight Before Admission	Appetite Before Admission	Pre-test Diet	"Increment Index"
20	F	42	68·5	155	Vaginal repair under G.A. 10 days previously	M. died of diabetes	Decrease (1st)	Normal	Normal	3·22
21	F	54	74·4	152	Multiple arthritis	Nil	Increase	Normal	Normal	2·77
22	F	67	67·6	165	Always "nervous"	S. has nervous breakdown	Decrease	Fair	Normal	3·33
23	F	65	74·4	163	"Nervous breakdown" years ago	Nil	Increase	—	Normal	3·22
24	F	63	72·1	165	Right hemiplegia 3 years	Nil	Constant	Normal	Normal	4·06
25	F	71	72·1	147	Right hemiparesis 6 years	Nil	Increase	Normal	Normal	2·31
26	F	54	70·8	155	Hysterectomy under G.A. 10 days previously	M. obese and diabetic	Increase	Normal	Decreased	3·65
27	F	70	50·8	165	Arthrodesis knee under G.A. 1 month previously	Nil	Constant	Normal	Normal	3·46
28	F	64	58·1	163	Osteotomy under G.A. 3 months previously	Nil	Decrease	Decrease	Normal	3·15

Abbreviations used in Tables I and II:
Dep. = Depression. Rec. dep. = Recurrent Depression. Rheum. arth. = Rheumatoid Arthritis. Ost. Arth. = Osteoarthritis. M. = Mother. S. = Sister. B. = Brother.
GF. = Grandfather. M.H. = Mental Hospital. G.A. = General Anaesthesia.

TABLE III

		Increment Index		
Depressions (females) ..	range 1·44–3·46;	mean 2·41;	s.d. 0·52	
Controls	range 2·31–4·06;	mean 3·24;	s.d. 0·50	
Difference	of means 0·83;	t=3·87;	D.F.=24;	p<0·001

TABLE IV

		Wt. in kgm.		
Depressions (females) ..	range 40·4–71·7;	mean 54·6;	s.d. 7·43	
Controls	range 50·8–74·4;	mean 67·6;	s.d. 8·04	
Difference	of means 13·0;	t=4·14;	D.F.=24;	p<0·001

weight of the controls, 67·6 kgm., approximates closely to 65·7 kgm., which is the mean weight of 24 normal subjects of similar mean age (63 years) given by Silverstone *et al.* (1957). No significant difference between the two groups is obtained in the history of change of weight before admission (Table V); and a history of decrease in appetite and diet during the three to six months before admission in the depressions compared with the controls is barely significant (Table VI).

TABLE V

Weight	Depressions	Controls	Total
Decreased	9	3	12
Constant or increased	8	6	14
Total	17	9	26

χ^2=0·292; D.F.=1; p<0·7>0·5

TABLE VI

Appetite Before Admission	Depressions	Controls	Total
Fair or decreased	10	2	12
Normal or good	3	6	9
Total	13	8	21

χ^2=3·538; D.F.=1; p<0·1>0·05

The diet during the four days before testing was reported to have been decreased in four of the seventeen female depressions, and in one of the nine controls; the difference between the two groups is not statistically significant (χ^2=2·38; D.F.=1; p<0·2>0·1). The usual hospital diet offered adequate carbohydrate as was shown by weighing the daily intake of four patients (not included in the investigation) on four separate days; values of 306, 510, 231 and 306 gm. carbohydrate were obtained.

The relation between the glucose tolerance of the depressions and history of weight change before admission, diet and appetite before admission, and diet during the four days before testing, is as follows. The mean increment index of the ten who reported a decrease in weight is 2·33, and in the nine whose weight was reported to have been constant or increased the index is 2·49; the difference (0·16) is not statistically significant (t=0·691; D.F.=17; p>0·1). The mean indices for the eleven with decreased appetite, and the four with normal appetite before admission, are 2·34 and 2·31 respectively. The mean indices of the four with decreased food intake during the four days before

testing and the fourteen with normal intake before testing are 1·90 and 2·56 respectively; the difference (0·66) is highly significant ($t=11$; D.F.$=16$; $p<0·001$).

The mean increment index for the seven patients diagnosed manic-depressive psychosis (Cases 6, 8, 10, 14, 15, 16, 17) is 2·66, and that for the eight involutional melancholias (Cases 4, 5, 7, 9, 11, 12, 13, 18) is 2·24. The difference (0·42) is highly significant ($t=5·872$; D.F.$=13$; $p<0·001$). Although the involutional melancholics are slightly older and weigh slightly less than the manic-depressive group (mean ages 61 and 55 years; mean weights 50·2 and 53·2 kgm. respectively), the differences are not statistically significant ($K=0·369$ and 0·245 respectively; D.F.$=13$; $p>0·5$).

No correlation was found between various symptoms of melancholia and glucose tolerance. Thirteen patients were judged to have shown agitation, twelve retardation, and twelve anxiety or panics during the course of their illness. But there was considerable overlap, for eight patients had displayed both agitation and retardation at different times, while of the twelve anxious patients, ten were also agitated. The symptomatology of the two main groups of depression was essentially similar. Six involutional and five manic-depressive melancholics were agitated and/or anxious; six involutional and six-manic-depressive melancholics were retarded.

Of the fourteen depressions whose behaviour was recorded during testing, eight remained still and six were slightly resistive or agitated. The mean increment indices are 2·38 and 2·68 respectively. The mean pulse rate at the end of the test in twelve patients is 73/min. (range 60–84/min.). Of the nine controls, six were still, two rather restless, and one (Case 21) was in obvious pain from arthritis of the hip. Case 25 perspired freely throughout, and her pulse was 120/min. at the end; it was a fairly warm day. The mean pulse rate at the end of testing in five others is 78/min. (range 60–88/min.).

Discussion

It has recently been shown that glucose tolerance decreases with age (Silverstone *et al.*, 1957). The two groups in the present investigation were however of similar mean age (57·4 and 61·1 years for depressions and controls respectively). Surgical procedures and arthritis are also known to be associated with decreased glucose tolerance (Epstein and Aschner, 1916; Fletcher, 1922), so that these complications in the controls tend to decrease rather than increase the difference in glucose tolerance observed between the two groups.

It is well known that deficiency of carbohydrate in the previous diet lowers sugar tolerance (see review by Chambers, 1938). The evidence obtained during this investigation suggests that the diet taken during the four days before testing supplied adequate carbohydrate in most cases, although more detailed knowledge of dietary intake would be needed to establish this conclusively. Other investigators have reported that their subjects took a diet adequate in carbohydrate content during the days before testing (Freeman *et al.*, 1944; Henneman *et al.*, 1954). The depressions, with a mean weight 13 kgm. less than the mean weight of the control group, which represents a loss of body-weight of almost 20 per cent., were however probably in a state of chronic under-nutrition. Now, the corrective influence on glucose tolerance of a few days' adequate carbohydrate intake has been shown in well-nourished subjects who had undergone a short period of fasting. The disturbance of carbohydrate metabolism in chronic under-nutrition may be different, and not so easily reversible. Indeed, animal experiments have shown that chronic under-nutrition

produces its own characteristic disturbance of carbohydrate metabolism (Halmi and Spirtos, 1956); and Lingjaerde (1956), from observations on mental patients, states that certain of them, especially acute schizophrenics and depressives, need relatively large quantities of carbohydrate for a relatively long time before glucose tolerance returns to normal. He suggests, as have others (Ström-Olsen, 1932; Robinson and Shelton, 1940), that the decrease in glucose tolerance found in certain mental illnesses is due to previous refusal to eat and its duration.

Data obtained during the present investigation are relevant to the problem. Although a greater percentage of depressions than controls gave a history of loss of weight and poor appetite before admission, the differences are not statistically significant. Such data, obtained from patients and relatives, are however of low reliability, and in view of the impairment of appetite known to occur in depression it remains probable that the decreased weight of the group of depressions is due to decreased food intake. The relationship of body weight and diet on the one hand to glucose tolerance on the other, within the group of depressions, is not however a simple one. The highly significant lower mean increment index in the four depressions with a decreased food intake during the four days before testing, suggests that the lower food intake may have been the cause of the lower glucose tolerance. When however the mean increment index (2·53) of the ten depressions with weights below the mean weight for the depressions, is compared with the mean index (2·27) of the nine with weights above the mean weight, no correlation between low body weight and low glucose tolerance is found. However, it remains possible that changes in body weight may correlate with simultaneous changes in glucose tolerance, but the data needed to establish this have not been obtained. At present, although both low glucose tolerance and loss of body weight are known to occur in depressions, a dependence of impaired glucose tolerance on loss of weight has not been shown, and both could be due to common underlying factors.

It has been stated that the most important factor determining the shape of the oral glucose tolerance curve in depressions is probably absorption from the alimentary tract (Greville, 1945). In the present investigation absorption was eliminated by giving the glucose intravenously. The results with the intravenous test indicate a delay in glucose utilization, and it has been shown that hyperglycaemia in depressions is correlated with inhibition of the hexokinase reaction by plasma from the same patient (Weil-Malherbe and Bone, 1951); this suggests that the hyperglycaemia is due to inhibition of the initial step in glucose metabolism. The inhibitory factor in the plasma is thought to be of hormonal origin, possibly from the adrenal cortex (Weil-Malherbe and Bone, 1951). It is of interest that in the rat liver a short period of fasting can likewise inhibit the hexokinase reaction (Wyshak and Chaikoff, 1953).

Other explanations relate the decrease in glucose tolerance in mental illness to emotion or "stress", the effect being mediated by the secretions of the medulla or cortex of the adrenal glands (Kooy, 1919; McCowan and Quastel, 1931; Holmgren and Wohlfahrt, 1944; Lingjaerde, 1956; Rames and Simon, 1955). Strong emotion, such as acute fear, is well known to cause hyperglycaemia, through increased secretion of adrenaline. The twelve patients in the present investigation judged to show symptoms of anxiety, had a somewhat better glucose tolerance than the seven who showed little evidence of anxiety (mean increment indices 2·58 and 2·11 respectively). But it could be argued that all patients were in the grip of an affect more powerful than anxiety, and

indeed it has been shown that among the various categories of mental illness, plasma adrenaline occurs in highest concentration in the depressions (Weil-Malherbe, 1955).

The data available provide no explanation for the significant difference in glucose tolerance between the groups of involutional and manic-depressive depressions.

Summary

Glucose tolerance values and various physical and mental data were obtained from two groups: 19 depressions and 9 controls, of similar age distribution. An intravenous test which gave a numerical index for glucose tolerance was used.

A highly significant decrease in glucose tolerance and in body weight is found in the depressions compared with the controls. However, within the group of depressions, there is no correlation between glucose tolerance and body weight. Low food intake during the four days before testing (4 cases) is correlated with a low glucose tolerance. The glucose tolerance in 8 patients with involutional melancholia is significantly lower than in 7 patients with manic depressive psychosis. Explanations for these findings are discussed.

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Addendum

Since the above was written, a paper has appeared in which is presented a convincing argument for regarding the total or absolute index as a better measure of glucose utilization than the increment index used above.* The absolute index is obtained by plotting log. absolute glucose concentration against time, and drawing the straight line through the values (above fasting level) after the 25th minute from the beginning of the injection; then, $K = \log_e 2/t_r$, as used for calculating the increment index. The absolute index has therefore been obtained (from the data) for each patient in the above investigation, and all the relevant values recalculated. Statistical analysis gives results which are in full agreement with those obtained using the increment index. The absolute indices for cases 1 to 19 are, respectively: 0·83, 1·20, 0·99, 0·89, 1·06, 1·49, 1·04, 0·94, 1·04, 1·12, 0·97, 1·31, 1·44, 1·46, 0·88, 0·91, 1·15, 1·01, 1·01; and for cases 20 to 28: 1·46, 1·28, 1·54, 1·56, 2·24, 1·37, 1·87, 1·47, 1·59; mean absolute index for depressions: 1·09, s.d. 0·16; and for controls: 1·60, s.d. 0·31.

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