Insulin response to a rapid intravenous injection of dextrose in patients with anorexia nervosa and obesity

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THE premorbid nutritional status of patients with anorexia nervosa is often one either of chronic obesity or else has included a phase of overeating and some weight gain just prior to the onset of illness. In some patients this phase may seem to be one aspect of the adolescent growth spurt, together with its attendant 'puppy fat'. The cause and effect relationship of eating behaviour to the adolescent growth spurt and puberty is complex (Tanner, 1962). Information concerning the nutritional history of patients with anorexia nervosa and also patients with obesity may be difficult to obtain, since these patients and also often their parents deny present and past fact concerning their feeding behaviour and weight, both to themselves and others (Crisp, 1965a; Quaade, 1955).

Recently, Crisp (1965b) has shown, in a series of forty-two patients with anorexia nervosa, that the 'typical' group of patients were characterized pre-morbidly by a state of high level of nutrition apparent from the time of birth. Some evidence was presented to suggest that this was initially associated with intrauterine nutrition. In conjunction with these findings, the adolescent growth spurt, as marked by the menarche, was also found to be significantly early in the probands. It was suggested that this life-long nutritional and metabolic 'set' of the patient was related to family attitudes and to the developing personality of the subjects. Furthermore, it was suggested that such subjects were thereby predisposed to react to some post-pubertal emotional conflicts by mobilizing their nutritional status, either towards obesity or towards anorexia nervosa, in an attempt to resolve such conflict.

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Some of the abnormal hunger experiences reported by patients with anorexia nervosa were also described and discussed in relation to possible concurrent disorders of carbohydrate metabolism. Patients with anorexia nervosa usually eat a bizarre diet containing variable but sometimes large quantities of salads, fruit, meat and cheese but they characteristically, at least in the early phase of the illness and except when suffering with intermittent bulimia, ingest very little carbohydrate. Their starvation is both elective and selective. Other workers (Bartels, 1946; McCullagh & Tupper, 1940; Russell & Bruce, 1964; Russell, 1965) have demonstrated an abnormal and impaired glucose tolerance in such patients who, in response to a load of oral glucose, produced blood-sugar curves which are similar to those found in people subjected to carbohydrate starvation of a few days' duration (Hales & Randle, 1963b; Himsworth, 1939) and which have encouraged the label 'hunger diabetes'. Hales & Randle (1963b) have also shown that 'normal' subjects who have been carbohydrate-deprived for several days show a sustained insulin response to a glucose load.

In view of such findings it was decided to examine some aspects of carbohydrate metabolism in patients with anorexia nervosa and others with obesity.

Method

In this study insulin response to a rapid i.v. injection of 25 g of dextrose has been measured in two groups of patients; one group suffering with anorexia nervosa and the other group with static obesity. The results are compared with those obtained from a group of 'normal' subjects.

The anorexia nervosa group consisted of fourteen female patients all grossly underweight (average -31%) when compared with appropriate

mean population body weights (Kemsley, 1951-52). Their ages ranged from 14 to 47 years with an average age of 23 years. Dietary assessment revealed that their daily carbohydrate intake before admission was in the region of 40 g. Glucose tolerance tests in the group were performed on admission (Test A) and after 8-10 weeks treatment (Test B) when the patients had gained an average of 38 lb in weight and were all except one within 12½% of the appropriate mean population body weight (average -3%). During the 2 months' treatment period they received psychotherapy, chlorpromazine, 400-800 mg/day, and a daily carbohydrate intake of 350-550 g (Crisp, 1966). The chlorpromazine was gradually withdrawn during the 14 days prior to the second glucose tolerance test so that no patient was taking chlorpromazine at the time of Test B. A third glucose tolerance test (Test C) was carried out on Patients 5 and 8 about a year after Test B. During this period both patients had been in clinical remission; their eating behaviour was judged to be qualitatively and quantitatively normal, their weights had remained constant and within 12½% of the appropriate mean population body weight, and they were menstruating regularly. They were not on drug treatment.

The obese group consisted of fourteen patients who were all at least 15% above the appropriate mean population body weight (average +48%). Most of these patients had been grossly overweight for many years. None was losing weight at the time of investigation and, with one exception, they were apparently on an unrestricted carbohydrate intake although it is quite probable that many of them had dieted at some time previously. The one exception (Patient 5) was on a 20 g carbohydrate diet prior to the test and it is interesting that the glucose tolerance and pattern of insulin response in this patient did not differ from those of the remainder of the group.

The mean age of the obese patients was 45 years with a range of 28-68 years. Nine were female and five male. None had glycosuria.

The 'normal' group consisted of thirteen subjects whose weight was constant and within 12½% of the appropriate mean population body weight. They were all on an unrestricted carbohydrate intake. They varied in age from 20 to 57 years with a mean of 36 years. Eight were male and five female.

Method of insulin assay

Insulin was measured using the double-antibody-precipitation method described by Hales & Randle (1963a) with minor technical modifications. Tracer insulin was iodinated with ¹³¹I using the chloramine T method (Banerjee & Gibson, 1962; Hunter & Greenwood, 1962). The antibodies to pork insulin and to guinea-pig gamma globulin used in the assay were prepared in the Middlesex Hospital Medical School using the technique described by Robinson & Wright (1961). Plasma insulin levels were assayed against standards made up from a human insulin preparation kindly supplied by Eli Lilly. Each plasma insulin level was determined in at least two separate assays and the assays were checked by including two standard plasma samples containing high and low insulin concentrations in each assay.

Blood sugar estimations were measured in the hospital's routine laboratory using the Auto-Analyzer. All determinations were performed on heparinized venous blood. The blood-sugar estimations were carried out on the day the blood was taken. Blood samples for insulin assay were centrifuged within 3 hr of the venepunctures and the plasma divided into aliquots and stored at -10°.

Results (Tables 1, 2 and 3).

The data are published in full because of the substantial variations of results within each group.

TABLE 1
'Normal' group results

Patient No.	Age (yr)	Sex	Weight (lb)	% mean* population body weights	Blood sugar (mg/100 ml) following 25g i.v. dextrose						Plasma insulin (μ U/ml) following 25 g i.v. dextrose						K values
					Fasting	5 min	10 min	20 min	30 min	45 min	Fasting	5 min	10 min	20 min	30 min	45 min	
1	29	F	123	- 8	70	254	185	108	90	61	8	28	34	25	17	10	4.10
2	37	M	184	+ 9	70	192	169	113	68	35	15	219	113	88	31	17	4.33
3	29	M	182	+ 2	77	202	190	147	89	68	18	46	35	25	25	25	3.47
4	57	F	112	- 11	70	286	246	177	118	86	10	48	44	38	28	15	3.30
5	20	M	150	+ 1	48	70	180	121	100	56	23	62	62	37	40	28	3.47
6	31	F	141	+ 1	72	265	234	161	120	83	17	63	53	41	33	25	3.15
7	57	M	158	- 2	67	218	190	133	111	80	20	62	39	35	33	41	2.67
8	40	M	164	+ 4	84	234	198	147	120	89	8	35	15	13	10	19	2.47
9	30	M	181	+ 5	85	216	201	155	129	92	27	65	39	36	41	45	2.24
10	39	F	131	+ 8	77	306	274	215	182	142	10	60	55	48	36	37	1.88
11	33	M	176	+ 4	80	200	189	158	138	107	23	56	41	38	36	35	1.83
12	29	F	120	- 8	80	275	275	218	168	114	6	31	36	29	28	28	2.40
13	33	M	189	+ 6	61	158	164	154	137	116	28	53	34	30	27	34	1.14
Average	36		155	+ 1	72	234	207	154	120	87	15.8	53.5	44.3	36.3	28.9	26.8	2.85

*Figures for mean population body weight (lb) for each sex, age and height (Kemsley, 1951-52).

TABLE 2
Anorexia nervosa group results

Pat- ient No.*	Age (yr)	Sex	Test†	Wt. (lb)	% mean popu- lation body weights	Blood sugar (mg/100 ml) following 25 g i.v. dextrose								Plasma insulin (μ U/ml) following 25 g i.v. dextrose								K values
						Fast- ing	5 min	10 min	20 min	30 min	45 min	60 min	80 min	Fast- ing	5 min	10 min	20 min	30 min	45 min	60 min	80 min	
1(33)	20	F	A	101	-25	87	253	198	207	162	164	111	102	10	33	18	25		23	34		0.88
			B	134	-1	77	232	202	184	160	136	91	86	16	39	31		30	33	35	33	1.26
2(43)	29	F	A	97	-26	71	252	250	185	136	103	91	74	9	47	49		31	35	26		2.24
			B	124	-5	76	270	178	146	120	100	74	61	17	80	55		41	35	33	23	2.33
3(23)	19	F	A	69	-41	62	306	260	189	155	143	114	62	20	126	95		53	42			2.10
			B	106	-9	69	254	216	104	66	52	118	118	19	248	127		52	43	26	25	3.46
4(34)	20	F	A	72	-37	77	261	217	211	207	180	160	135	13	26	22		26	30	22		0.70
			B	113	0	75	342	228	157	152	121	118	118	6	35	19		19	22	19	13	1.54
5(41)	28	F	A	105	-14	69	242	254	188	184	157	135	106	38	120	50	70					1.22
			B	131	+7	91	231	217	192	163	138	106	113	18	99	67		43	52			1.31
			C	122	0	73	249		139	119	113			25	62			54	53	37		1.78
6(59)	47	F	A	67	-48	74	500	402	344	263	225	200		9	99	111		76	61			1.74
			B	79	-39	91	289	260	228	206	181	157		10	77	55		41	45			1.08
7(37)	22	F	A	82	-35	43	261	272	244	230	200	174	170	14	29	26	25	23	27	26	27	0.96
			B	112	-12	66	259	224	164	110	69			19	110	70			47			3.30
8(25)	19	F	A	92	-23	77	267	203	161	129	98	80		10	41	34	31					2.04
			B	125	+4	72	275	263	186					10	16	12		40				2.93
			C	134	+12	80	268	298	245	217	279	133		22	38	47		43	40	45	37	1.65
9(10)	14	F	A	62	-45	65	263	248	245	193	158	135	98	9	51	37		26	31	32	23	0.73
			B	106	+11	82	348	315	263	222	176	109	64	20	26	28		58	63	53	36	1.70
10(24)	20	F	A	100	-25	71	202	211	178	170	163	144		12	48	42		38	39			0.71
11(8)	14	F	A	78	-22	81	333	252	227	204	159	140		20	50	47		46	43			1.39
12(29)	20	F	A	78	-34	82	259	312	276	199	203	168		20	59	53			40			1.24
13(27)	19	F	A	81	-34	53	260	206	168	159	123	124	130	13	30	25		20	22	24	24	1.16
			B	120	-2	75	209	195	180	139	108	102	79	22	64	55		40	41	37	34	1.85
14(48)	33	F	A	92	-24	72	324	251	186	164	122	108	97	26	82	52		41	39	43	36	2.10
			B	116	-4	78	241	233	208	194	170	155	123	23	33	36		32	41	50	47	0.85
Average	23		A	84	-31	70	283	254	216	189	164	142		15.9	60.0	47.2		38.0	29.5	36.9		1.37
			B	115	-3	77	268	229	193	157	130	108		16.4	75.0	50.0		41.0	41.0	38.0		2.04

*Numbers in parentheses are serial numbers of patients in overall study (Crisp, 1967).

†A, Before treatment; B, immediately after treatment; C, 1 year after full clinical recovery.

TABLE 3
Obese group results

Patient No.	Age (yr)	Sex	Weight (lb)	% mean population body weights	Fast-ing	Blood sugar (mg/100 ml) following 25 g i.v. dextrose						Plasma insulin (μ U/ml) following 25 g i.v. dextrose						K values	
						5 min	10 min	20 min	30 min	45 min	60 min	Fast-ing	5 min	10 min	20 min	30 min	45 min		60 min
1	55	F	280	+94	78	221	202	159	139	110		45	175	160	106	65	77	1.78	
2	28	F	140	+63	83	231	205	179	163	141		4	40	26	20	33	28	1.18	
3	28	F	224	+62	81	213	115	34	34	45		20	141	56		17	7	6.93	
4	43	M	238	+50	80	180	182	160	145	125		13	13	48	44	34	28	1.06	
5	28	F	192	+60	86	260	252	211	178	144		41	120	104	109	109	102	1.61	
6	53	F	182	+36	68	224	210	178	154	130		26	63	126	88	63	46	1.54	
7	39	F	182	+34	79	238	215	180	158	148		15	85	55	40	26	27	1.31	
8	50	F	172	+23	110	269	223	190	145			25		69	74	62	64	1.65	
9	54	M	186	+26	92	239	210	171	127	85		26	109	104	84	78	49	2.67	
10	54	M	203	+17	76		175	144	118	103		27		35	31	30	31	1.51	
11	68	M	180	+29	75	214	205	164	148	118	93	6	75	50	36	37	33	1.62	
12	38	F	181	+30	92	300	236	203	148	110	102	31	156	114	81	85	58	2.40	
13	46	M	242	+57	80	209	193	126	80	64		37	233	285	239	184	96	3.47	
14	48	F	265	+93	76	217	195	167	146	123	101	47	146	100	118	96	121	1.42	
Average	45		204	+48	83	228	204	174	137	113		24.3	110.0	94.7	79.3	63.3	49.6	2.15	

Despite these intragroup variations certain significant differences emerge between the groups.

Blood sugars

The mean fasting blood sugar levels in the 'normal' group and anorexia nervosa group before treatment were 72 and 70 mg/100 ml respectively. Following treatment the mean fasting blood sugar level in the anorexia nervosa group rose, but not significantly, to 77 mg/100 ml. The mean blood sugar level of the obese group was 83 mg/100 ml and significantly higher than that of the 'normal'

group ($P < 0.02$). Following the intravenous dextrose the mean blood sugar rise at 5 min was higher in the patients with anorexia nervosa than in the 'normal' or the obese group (283 mg/100 ml as compared with 234 and 228 mg/100 ml). This probably reflects the smaller glucose pool of the patients with anorexia nervosa who were all grossly underweight and some probably dehydrated at the time of Test A. Following treatment this blood sugar rise had decreased slightly although it was still greater than that seen in the 'normal' group.

The K values, which were calculated using the method described by Lundebaek (1962), were variable within each group but tended to be higher in the 'normal' group than the obese group. Thus in the 'normal' group the mean K value was 2.85 (range 1.14–4.25) and only three subjects had K values of less than 2, whereas in the obese group the mean K value was 2.15 (range 1.18–6.93) and ten patients had K values lower than 2. The K values of some of the patients with anorexia nervosa before treatment were particularly difficult to calculate as the blood sugar values did not fall even approximately in an exponential way and for this reason we have paid more attention to comparison of the blood sugar levels at 45 and 60 min in the three groups than to the K values. However, as a whole, the K values in the anorexia nervosa group were lower than those in the 'normal' group (before treatment mean $K = 1.37$, range 0.70–2.24, eleven patients with K less than 2) and rose slightly after treatment (mean $K = 2.04$).

The mean blood sugar level at 45 min in the 'normal' group fell to 87 mg/100 ml, whereas in the obese group it was significantly higher at 113 mg/100 ml ($P < 0.02$). This corresponds with the lower K value in the obese group. The mean blood sugar level at 45 min in the anorexia nervosa group was 164 mg/100 ml before treatment and 130 mg/100 ml after treatment, both values being highly significantly greater than the 45 min levels in the 'normal' group ($P < 0.01$). Furthermore the blood sugar levels in the anorexia nervosa group at 60 min remain notably higher than the 45-min levels in the 'normal' group.

Insulin levels

The mean fasting plasma levels were similar in the 'normal' and anorexia nervosa groups before and after treatment; namely 15.8, 15.9 and 16.4 $\mu\text{U/ml}$ respectively. In contradistinction the mean fasting plasma insulin level was significantly higher ($P < 0.02$) in the obese group at 25.9 $\mu\text{U/ml}$. The distribution of mean fasting plasma insulin levels and mean fasting blood sugar levels between the groups is similar.

The fasting insulin values in the 'normal' group are closely comparable to those found by other workers using the insulin immunoassay technique (Yalow & Berson, 1960; Hales & Randle, 1963b). Following the dextrose injection there was a rapid rise in insulin levels in all three groups. The mean insulin level at 5 min following the injection was similar in the 'normal' group and the anorexia nervosa group both before and after treatment, 53.5, 60.0 and 75.0 $\mu\text{U/ml}$ respectively, but was significantly higher in the obese group, 110.0 $\mu\text{U/ml}$ ($P < 0.01$). This is of interest for, if

the stimulus to insulin release by the pancreas is determined by the blood sugar concentration, one might expect a greater insulin response in the anorexia nervosa group than in the other two groups; both because of the higher blood sugar peak in the anorexia nervosa group and because of the relatively greater dose of dextrose given per kg body weight in this group. After treatment (Test B) the insulin level at 5 min in the anorexia nervosa group showed a greater variation than before treatment but tended to be somewhat higher despite the smaller blood sugar rise. The individual levels of insulin response within the anorexia nervosa group bore no relationship to ultimate clinical outcome.

After the peak insulin level, which was reached by the majority of each group within 5 or 10 min of the dextrose injection, the insulin levels started to fall. Although there was some overlap between the groups this fall was, on the whole, more rapid in the 'normal' than in the anorexia nervosa or the obese groups. Thus the mean plasma insulin level in the 'normal' group had fallen to less than twice the fasting level at 45 min whilst it remained at more than twice the fasting level in the obese group at this time. The data for plasma insulin levels at 45 min in the anorexia nervosa group are incomplete but the mean plasma insulin level at 60 min both before and after treatment remained higher than the 45-min level in the 'normal' group ($P < 0.01$).

The two patients (5 and 8) with anorexia nervosa who were studied a year after treatment showed a continued improvement of glucose tolerance but the insulin response although less sustained than before treatment, remained sustained in comparison with the mean of the 'normal' group.

Discussion

The anorexia nervosa and obese groups of patients both showed glucose intolerance and sustained insulin response when compared with the 'normal' group in the experimental situation.

The anorexia nervosa subjects before treatment were mainly in a state of severe and chronic carbohydrate depletion. Nevertheless there was often a history of them having once been obese. The chronic or static obese subjects had probably varied their carbohydrate intake over a wide range during the previous years. Thus it is probable that both the patient groups had restricted their carbohydrate intake at times during the previous years and this, and/or their common history of obesity, may be contributory to the present findings. Nutritional histories were not taken systematically from the 'normal' group of subjects but one who

showed a typical sustained insulin response was known to have lost about 7 lb in weight 6 months previously.

A number of workers have studied the effect of carbohydrate restriction or total starvation on glucose and insulin levels in 'normal' and obese subjects. Himsworth (1939) and more recently Hales & Randle (1963b) have shown that normal people, subject to a period of carbohydrate restriction, develop impaired tolerance to an oral glucose load. Unger, Eisentraut & Madison (1963) have demonstrated a similar phenomenon following a period of total starvation. Beck *et al.* (1964) and Samaan *et al.* (1965), working with obese patients, found that glucose intolerance was increased following a period of total starvation.

Hales & Randle (1963b) showed in their study that, following the restricted carbohydrate intake, the fasting plasma insulin level was raised and the insulin response to the oral glucose load was sustained. Unger *et al.* (1963) also demonstrated a sustained insulin response to oral glucose following total starvation but did not find a raised fasting level. Beck *et al.* (1964) demonstrated similar results studying their starved obese subjects. However, Samaan *et al.* (1965) found an increase in the fasting typical insulin-like activity as well as a sustained response to a glucose load in obese patients following starvation. Karam, Grodsky & Forsham (1963), using their immunoassay, reported comparable results in obese patients after an overnight fast.

It is probable that the glucose intolerance shown in the present study by both the anorexia nervosa and the obese groups is due to impaired peripheral utilization of glucose. The sustained insulin response may be secondary to this. A number of factors, which have been shown elsewhere to be associated with glucose intolerance, may be active in both these groups. Such factors include raised plasma non-esterified fatty acid levels (NEFA), raised levels of growth hormone and cortisol and possibly raised glucagon levels. Following on Himsworth's (1939) suggestion that ketosis may cause the glucose intolerance in carbohydrate starved subjects, Hales & Randle (1963b) have shown that plasma NEFA levels are raised in normal subjects following a period of carbohydrate starvation, and Schallch & Kipnis (1964) have demonstrated that in the experimental situation, an induced increase in plasma NEFA leads to glucose intolerance. Other workers have shown that plasma NEFA levels are high in obese subjects after an overnight fast, although thereafter, in response to extended starvation, they rise less rapidly than in normal subjects (Beck *et al.*, 1964; Opie & Walfish, 1963).

Karam *et al.* (1965) have demonstrated glucose intolerance following an injection of growth hormone, and Zierler & Rabinowitz (1963), using a forearm preparation, have shown decreased glucose uptake and increased NEFA release following growth hormone infusion. It is unlikely that such a process operates in obese subjects as both Roth and Beck and their respective co-workers have found low growth hormone levels in obese patients before and after starvation (Roth *et al.*, 1963; Beck *et al.*, 1964). However, Greenwood *et al.* (1965) have found raised growth hormone levels in anorexia nervosa which may contribute to the impaired glucose tolerance in these patients.

Plasma cortisol has been found to be high in obese subjects (Eckert, Green & Migeon, 1961) and around the upper limit of normal in some patients with anorexia nervosa (Bliss *et al.*, 1953; Greenwood *et al.*, 1965) and it is possible that this factor too may contribute towards the glucose intolerance found in such patients. Glucagon may also be of some importance in view of the findings of Unger *et al.* (1963) that glucagon levels rise in normal subjects after a period of fasting and remain high for several hours despite refeeding.

Any of these factors could account for the impaired glucose tolerance and sustained insulin response in the anorexia nervosa group before treatment but the findings in this group, both immediately and 1 year after treatment, pose a more interesting problem. Immediately after treatment, when the patients had received a large carbohydrate intake and had regained their lost weight, their mean insulin response had not changed whilst their glucose tolerance had returned towards normal. Furthermore, these changes persisted to some extent in the two patients studied after a year's full recovery. The reason for this is obscure but some of the factors already discussed could still be active. Thus Hales & Randle (1963b) found that 5 weeks after carbohydrate restriction for a 5-day period, normal subjects showed raised plasma free fatty acid levels and a sustained insulin response to an oral glucose load. This suggests that a short period of carbohydrate restriction may account for a prolonged alteration of insulin response. Raised growth hormone levels may also still be present. Furthermore, Karam *et al.* (1965) have shown that the administration of a single dose of growth hormone to normal subjects leads to a sustained insulin response to oral glucose, with no alteration of glucose tolerance.

Results overall show that there is a metabolic characteristic of subjects with anorexia nervosa which they share to some extent with the obese

subjects. It has been shown to be a relatively stable phenomenon in the adult patient with anorexia nervosa, not greatly sensitive to sudden dietary changes and, in two subjects examined, it has persisted after full clinical recovery. Although some of these changes may be explicable in terms of previous carbohydrate restriction they may also reflect one (metabolic) aspect of the life-long and characteristic nutritional histories of these subjects. A minority of the 'normal' subjects showed a similar metabolic pattern. An intriguing question is whether such subjects have a predisposition to mobilize their nutritional state either towards obesity or, less commonly, anorexia nervosa under certain circumstances.

Summary

This paper presents a study of the insulin response to a rapid intravenous injection of 25 g dextrose in three groups of subjects, 'normal' people, obese patients and anorexia nervosa patients before and after treatment. The insulin levels were measured by immunoassay.

The anorexia nervosa patients had a characteristic pattern of insulin response which they shared with the obese group of subjects, which persisted after recovery and which may be a measure of their life-long nutritional status.

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