

seen in the colon in 11 (and in the gallbladder in 2 of the 11) on delayed films. They make the interesting suggestion that protein binding of diatrizoate is increased in patients with uræmia.

Experimental work has also shown heterotopic excretion of urographic media, especially when renal function is diminished. McChesney and Hoppe (1957) found that when hypaque 50% was injected into dogs in a dose of 2 ml. per kg., 2% was excreted in the fæces, while in cats given 0.5 g. per kg., 3.5–6.9% was in the liver and bile up to three hours after injection. Salzman and McClintock (1963) injected hypaque and 'Miokon' (sodium diprotrizoate) into intact cats in doses of 1–3 g. per kg. and observed opacification of the small intestine and later the gallbladder. By ligating the intestine at various levels they showed that the medium was excreted from the small-intestine wall as well as in the bile, but not from the large intestine. Opacification was enhanced by nephrectomy. Hansson and Lindholm (1963) gave hypaque tagged with ¹³¹I intravenously to rabbits. In intact animals, about 1% of the medium was excreted in the bile; after bilateral nephrectomy about a quarter was excreted in the bile and a seventh through the intestinal wall. Chamberlain and Sherwood (1966) gave hypaque 85% in doses of 2 ml. per kg. intravenously to rats and found that the small and large intestine were opacified, but only if the rats had been made anuric and not if the common bile duct had been ligated.

Evidently, if the normal pathway is blocked, diatrizoates (or at least their iodine) can be excreted by the liver. Excretion from the wall of the small intestine has been shown in some species and seems likely in man, since in several patients the bowel but not the gallbladder was opacified. The reason for heterotopic excretion in occasional patients with functioning kidneys remains obscure.

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"... we have a system of scientific education which is almost unbelievable. Because of the incredible myopia which has proliferated over the years, we are left with a syllabus that need not, in the slightest degree, pay heed to modern developments of the qualities that the student will need as a qualified man; we have a system of selection which passes students with abilities which are quite different from (in some cases contradictory to) the basic essentials of the true scientist; and we employ staff to teach who are neither trained to teach, nor selected for their teaching ability. The position is intolerable, and long overdue for change."—BRIAN J. FORD, *New Scientist*, May 30, 1968, p. 453.

DEATH DURING THERAPEUTIC STARVATION FOR OBESITY

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Summary 12 cases of obesity, complicated by a variety of conditions, have been treated by periods of starvation varying from two to eight weeks. 2 cases started in severe heart-failure and both died suddenly after three and eight weeks treatment during which time their clinical condition improved considerably. It is suggested that the combination of obesity and severe heart-failure should not be treated by starvation for there would seem to be a very real risk of inducing ventricular fibrillation.

Introduction

TOTAL starvation as a means of treating obesity was first reported in America by Bloom (1959), and in this country by Thomson et al. (1966). It would seem to be the rational form of treatment if it can be shown to be without risk, for there is no doubt that it is effective and that it is the quickest way of losing weight. Hitherto no risk inherent in the procedure has been reported: the one death (Cubberly et al. 1965) was thought to be due to lactic acidosis, whilst Duncan et al. (1965) treated nearly 900 patients by periods of fasting varying from ten to fourteen days without a single death. Believing this method to be safe I adopted it for some of my patients at the beginning of 1967, but of the first 12 patients, 2 have died, probably from ventricular fibrillation.

Method

From January to October, 1967, 12 cases were admitted with gross obesity often accompanied by other forms of illness. They were treated with a calorie-free diet, but all were allowed unrestricted amounts of fluid which could be taken as tap water, plain tea or coffee, or diabetic-type fruit drinks. Vitamins A, B, C, and D, together with calcium lactate were prescribed, and it was so arranged that patients received some tablets during each medicine round in order to mitigate feelings of victimisation at being excluded from distributions of food. Serum-electrolytes, blood-urea, and electrocardiogram (E.C.G.) were regularly monitored and their weights were recorded daily, for a reduction in weight acts as great encouragement during this Spartan form of treatment.

Results

Table I gives the individual details concerning each patient and table II shows their weight loss week by week, together with the average weekly weight loss of the group.

TABLE I—AGE, SEX, DIAGNOSIS, WEIGHT, AND BLOOD-PRESSURE

Case no.	Age	Sex	Diagnosis	Weight (lb.)		Blood-pressure (mm. Hg)	
				Start	Finish	Initial	Final
1	64	F	Diaphragmatic hernia, œsophageal ulcer ..	235	208	180/120	135/100
2	57	F	Obesity	288	271
3	68	M	Myocardial infarction	221	197	140/90	130/80
4	58	F	Left ventricular failure	330	255	230/120	140/80
5	75	M	Obesity	259	230	230/130	130/85
6	45	F	Obesity	301	261	170/110
7	64	M	Ischæmic heart-disease	229	210	160/110	140/80
8	49	M	Diabetes	221	202	165/115	145/90
9	62	F	Left ventricular failure	212	185	150/110	120/70
10	58	F	Obesity, varicose ulcer	242	204	200/100	120/65
11	29	F	Obesity	250	223	150/100	140/90
12	61	F	Left ventricular failure, ischæmic heart-disease, varicose ulcer	233	196	150/100	140/50

TABLE II—WEIGHT LOSS DURING FASTING AND AT FOLLOW-UP

Case no.	Weight loss (lb.) in week:								Total loss after fasting (lb.)	Follow-up (mo. from start of fast)	Weight at follow-up compared with end of fast (lb.)
	1	2	3	4	5	6	7	8			
1	11	3	6	3	4	0	27	11	+5
2	10	-4	10	1	17	11	+9
3	10	10	4	24	11	-4
4	31	9	8	7	4	6	6	4	75	..	Dead
5	15	8	6	29	10	+1
6	9	12	2	5	4	4	4	..	40	10	-3
7	12	7	19	9	-23
8	11	8	19
9	21	3	3	0	27	5	-7
10	13	6	2	9	3	2	2	..	38	2	0
11	16	5	6	27	2	0
12	16	9	12	37	..	Dead
Mean	14.6	6.3	5.9	4.2

The period of starvation varied from two to eight weeks, and table II also shows the number of months from the start of the fast to follow-up in November, 1967.

Case-reports

The case-histories of the 2 patients who died (cases 4 and 12) after fasting fifty-nine and twenty-one days, respectively, will be described in detail.

Case 4

Aged fifty-eight years, this woman had weighed 136 lb. (61 kg.) when she married at the age of twenty-four but when admitted as an emergency in January, 1967, she weighed 330 lb. (150 kg.). She had severe orthopnoea, which had started two weeks previously, and she was massive in all dimensions. Her legs presented an almost tubular appearance, because of oedema of almost solid consistency, and measured in circumference 23 in. (57.5 cm.) at the knee, 21 in. (52.5 cm.) at the calf, and 18 in. (45 cm.) at the ankle. The dorsum of the feet were raised about 2 in. (5 cm.) with equally solid swelling, and she had been unable to wear ordinary shoes for almost ten years. Heart considerably enlarged, blood-pressure 230/120 mm. Hg; E.C.G. showed right-bundle-branch block. She was immediately started on treatment with digoxin, diuretics, and potassium supplements together with a calorie-free diet. In spite of losing 31 lb. (15 kg.) in the first week, and large amounts subsequently, the measurements of her legs only altered by an inch or two, and remained unusually hard to the touch until she died. She followed a starvation diet for eight weeks but never complained of hunger and, as her weight dropped, so her breathlessness decreased and her morale rose, and she busied herself with odd jobs in the ward and, in general, made herself useful. Her electrolytes, blood-sugar, and blood-urea remained normal throughout and her blood-pressure gradually dropped until it averaged 140/80 mm. Hg, though her E.C.G. continued to show right-bundle-branch block.

We were all encouraged by her progress and, on the day before her death, she walked about 200 yards to the front of the hospital to watch an Easter parade, and she came back to the ward excited at walking, without distress, a distance greater than at any time during the previous ten years. After a good night's sleep she got up, washed herself in the bathroom and returned to bed, where a few minutes later she was found collapsed, and an E.C.G. showed ventricular fibrillation, from which resuscitative measures failed to revive her. Necropsy showed hypertrophy of all chambers of her heart (weight 525 g.) but the coronary arteries were almost free from atheroma.

Case 12

This 61-year-old woman had weighed 112 lb. (51 kg.) at the age of twenty-one, but over the years this had increased to 233 lb. (106 kg.). She had had a varicose ulcer on her left leg for seven years and in 1964 she had inpatient treatment in hospital for this for seven months, but it failed to heal. She was admitted in October, 1967, with acute left ventricular failure.

Breathlessness had started painlessly three months previously and had become increasingly severe in the preceding two weeks. On admission she was orthopnoic, cyanosed, and had tachycardia and swelling of both her legs and her right arm. Blood-pressure 150/100 mm. Hg; cardiac enlargement and pulmonary engorgement; E.C.G. showed old anteroseptal infarction. She was a small woman with gross obesity and she was immediately started on a calorie-free diet with digoxin, diuretics, potassium supplements, and anticoagulants.

For the first four days there was no material change in her condition, then she had a significant diuresis and there was considerable improvement. Three weeks after admission all were encouraged by her progress. She no longer was breathless though she still had slight oedema of her legs and right arm. However, her varicose ulcer had healed for the first time in seven years and her morale was high. Her electrolytes and blood-urea remained normal, her E.C.G. continued to show evidence of old anteroseptal infarction, but her pulse-rate had slowed, her cyanosis had disappeared and her blood-pressure averaged 140/80 mm. Hg. In three weeks she had lost 37 lb. (17 kg.) including a moderate amount of oedema.

At 8.30 p.m. one evening a patient called the nursing staff's attention to her and she was found dead. Necropsy showed enlargement and hypertrophy of the left ventricle, with old anterior infarction and mural thrombi, but no evidence of any emboli. Both coronary arteries showed striking atheromatous changes and it would seem probable that she had died of ventricular fibrillation.

Effect of Treatment

Table II shows that the average loss of weight in the first week was marginally over 14 lb., and after three weeks was almost 28 lb. Thereafter the number of cases involved was relatively few but the rate of weight loss decreased considerably. Occasionally there was an inexplicable gain in weight of a few pounds, but this could well have been due to a slight increase in aldosterone secretion, as suggested by Thomson et al. (1966).

Cases 1 and 2 ceased to show ketonuria after ten to fourteen days and were thought to be eating surreptitiously in the lavatory. How they rationalised this behaviour whilst outwardly following a starvation regimen is a matter of interesting speculation but, since they continued to lose weight, we did not tax them with their defection for it was thought that to do this would inevitably result in them abandoning any further efforts at weight reduction.

Cases 1 and 10 experienced mild postural hypotension, but this was not sufficiently severe to interfere with further dieting, and it gradually subsided. All patients, in fact, had quite a striking reduction in blood-pressure and towards the end of their spell of starvation it was well within the normal range, even though some had started with quite significant hypertension. One has, of course, to allow for the effects of rest, but case 8 had a final blood-pressure of 145/90 mm. Hg and this was the highest in the entire group.

Perhaps the most unexpected effect was the rapid healing of varicose ulcers. Case 10 had had ulceration continuously for eighteen years following an operation on her varicose veins, but after six weeks starvation the ulcers had completely healed, whereas case 12 had ulcers which had remained active for seven years in spite of seven months treatment in hospital in 1964, yet they healed in three weeks. Since completing this series of patients I have treated a man, who also had hypothyroidism, with a regimen of spells of two weeks starvation interspersed with one week on a diet of 500 C. composed largely of protein, and the varicose ulcers which he had endured for fifteen years healed within two months, during which time he lost over 50 lb. None of these patients had treatment

for their ulcers other than 'Aserbine' dressings, so perhaps this method is worthy of further study by those concerned with this condition.

Discussion

This method of treating obesity has always shown gratifying results as regards weight loss, especially if one considers that these cases provide the hard core of patients who are overweight. The method is far from unpleasant and none of my patients complained of undue hunger and many, after two or three days, did not experience a sensation of hunger at all, which is in keeping with the findings of others (Duncan et al. 1962, 1963, van Riet et al. 1964, Duncan et al. 1965, Harrison and Harden 1966, Thomson et al. 1966). In fact most felt a new sense of well-being due, in all probability to the effect of grappling successfully with a problem which had baulked them for so long.

Successful weight-loss would not be worth the effort and time spent in hospital, to say nothing of the cost, if it were only temporary, but table II shows that weight-loss was generally maintained and in some cases even continued after returning home. This was also reported by Duncan et al. (1963) and Harrison and Harden (1966), but by not MacCuish et al. (1968). However, it may be that the time spent following a calorie-free regimen allows those doing so to pause and reflect on their dietary habits and consider whether eating in their former manner is worth while when it results in such crippling obesity.

Cardiac illness and obesity have been treated successfully by starvation in other series (Duncan et al. 1965, Thomson et al. 1966) but I have not found any reference to cases starting in heart-failure being treated by this method. Hitherto there has been little mention of cardiac complications though the patient described by Cubberley et al. (1965) was temporarily revived from an episode of ventricular fibrillation; she had lactic acidosis and was probably dying before fibrillation developed. The only other arrhythmias reported have been by Duncan et al. (1965) who had 3 cases of atrial flutter, but they survived and were thought to have developed this complication because they were too energetic.

Both the deaths in this series were admitted in severe heart-failure, complicated by gross obesity; but both had improved greatly whilst undergoing starvation therapy. I had been treated for eight weeks and had had no cardiac distress for at least a month before her death, whilst the other had lost almost all evidence of heart-failure during the three weeks she had been in hospital. Neither were thought to be in any particular risk when they died suddenly, the first due to ventricular fibrillation, and this was probably the cause of death in the other.

The outcome of these 2 cases would suggest therefore that starvation therapy should not be used in cases of obesity complicated by cardiac failure, for the combination would seem to carry a very real risk of inducing ventricular fibrillation.

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Preliminary Communication

URIC-ACID METABOLISM IN MANIC-DEPRESSIVE ILLNESS AND DURING LITHIUM THERAPY

Summary Plasma-uric-acid in manic-depressive patients does not seem to be higher than in the healthy controls; and remains at a steady value during manic-depressive cycles. Cyclic changes in manic-depressive illness are followed closely by changes in daily urinary uric-acid excretion. Lithium seems to have an uricosuric effect when it is used in the treatment of manic-depressive illness. Uric-acid-clearance studies indicate that uric-acid excretion during manic-depressive illness becomes substantially increased in the early phase of remission (whether natural or lithium induced) suggesting an alteration in tubular reabsorption or secretion. It is postulated that lithium may interfere with the active transport of organic acids both in the kidney and in the brain.

INTRODUCTION

AN association between manic-depressive illness, gout, uric-acid excretion, and hyperuricæmia was suggested by Kraepelin,¹ Jaspers,² and others. Jaspers,² citing Luxemberger, stressed the possible genetic nature of this association. Lange³ was the first of many workers to claim beneficial results from the use of lithium in both gout and mental depression. Whilst lithium has been discarded in gout in favour of newer drugs, its role in the management of manic-depressive illness is of continuing interest.

The mode of action of lithium is uncertain. Most authorities favour the view that its influence in manic-depressive illness is mediated via an effect on sodium transport.⁴ Schou⁵ pointed out that lithium urate is soluble in water and that urinary calculi containing urates could be dissolved in a solution of lithium carbonate, but he added that since sodium and potassium formed insoluble urates and were present in the human body, lithium would not exert a "solubilising" effect *in vivo*.

We have re-examined the temporal relationship of plasma and urinary uric acid to phasic mood changes, and have examined a hypothesis relating the action of lithium on these phasic mood changes to variations in plasma and urinary uric acid.

PATIENTS AND METHODS

Patients and Controls

Five patients (two men, three women) diagnosed by at least two consultant psychiatrists as manic-depressive (Kraepelin concept) were investigated for periods ranging from 1 to 8 months. Two other patients (subjects 6 and 7) admitted because of atypical mood swings, and five "healthy" volunteers (subjects 8-12) were also studied. The study of healthy volunteers lasted only 5 days, its specific purpose being to provide a picture of daily plasma and urinary uric acid values. The patients with personality disorders were studied during the whole period of hospital admission ranging from 1 to 3 months. The clinical descriptions of the manic-

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