electrical cardioversion without a suitable period of withdrawal of digoxin (Gilbert and Cuddy, 1965). It seems likely that many patients with atrial fibrillation have latent digoxin toxicity which can readily become manifest without any increase in plasma concentration of the drug.

In view of the wide variations in dose requirements needed to achieve control of the heart rate in atrial fibrillation, and the fact that many patients with atrial fibrillation may have slow heart rates with or without digoxin, the poor correlation between ventricular rate and plasma levels was to be expected. The extent to which plasma levels reflect myocardial concentrations in chronically digitalized patients, however, remains to be defined.

Daily Dose and Plasma Levels

The relationship between the size of the daily dose and the plasma levels of digoxin was investigated. Because most of the drug is excreted unchanged by the kidneys (Marcus *et al.*, 1964), renal function is as important as dose in determining blood levels. We therefore restricted the analysis to those patients who had normal or near-normal renal function indicated by blood urea concentrations of less than 40 mg./100 ml. The data presented in Fig. 3 show a significant relationship between oral dose and plasma levels. Several factors must have militated against more uniform blood levels. The patients were of different heights and weights; blood urea provides only a rough index of glomerular filtration rate; the potency of some commercially available digoxin tablets may vary widely (Feinberg, 1969); and blood samples were taken at intervals after the previous dose ranging from about 8 to 24 hours. Clearly, however, 0·5 mg. of digoxin daily will usually provide plasma levels in a satisfactory therapeutic range of 1 to 2 ng./ml. in the presence of normal renal function. Larger doses, or moderate doses in the presence of considerably impaired renal function, are associated with levels which fall within the toxic range.

Digoxin toxicity is particularly common in the elderly (Soffer, 1961), and the suggestion has been made that this may be due in part to increased sensitivity to the drug (Feibush, 1959). We found, however, that blood levels in patients aged 60 and over with controlled atrial fibrillation were closely similar to the levels in younger patients (Fig. 4). The blood levels in the older age group were attained with a smaller mean dose, and the blood urea of these patients tended to be higher than those found in the under-60 group. This observation is consistent with the findings of Ewy, Kapadia, Yao, Lullin, and Marcus (1969), who used tritiated digoxin to show that a given dose of the drug resulted in higher blood concentrations in the elderly compared with younger subjects, and that the difference was associated with smaller body size and diminished urinary excretion of digoxin.

The present findings indicate that the ventricular response to atrial fibrillation is not well correlated with plasma concentration of digoxin. Patients receiving more than 0·5 mg. daily or those having smaller doses in the presence of impaired renal function may have blood concentrations in the range often associated with toxicity, irrespective of heart rate. Though high blood levels are often well tolerated, the risk of digoxin toxicity must be carefully weighed against the need for large doses of the drug.

We are grateful to the physicians at St. Bartholomew's Hospital and the National Heart Hospital for allowing us to study patients under their care. We are also indebted to Dr. Edgar Haber, Dr. G. W. Hayward, Dr. J. Hamer, Professor J. Landon, Dr. T. Chard, and Dr. D. Gibson for help and advice. The crystalline digoxin was kindly supplied by Messrs. Burroughs Wellcome & Co.

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Prolonged Starvation—A Dangerous Procedure?

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Summary: Experience with 18 obese patients who have undergone prolonged (60 days) therapeutic starvation shows that in general this is a safe procedure, but there are significant associated hazards, particularly a breakdown in electrolyte homoeostasis. The need for close biochemical control of such patients is stressed.

Introduction

Spencer (1968) reported the deaths of two patients while they were undergoing therapeutic starvation. Garnett *et al.* (1969) reported the death of a young woman on the seventh day of refeeding following a fast of 30 weeks. At necropsy fragmentation of the cardiac myofibrils was found. This led them to stigmatize therapeutic starvation as an unsafe procedure. These reports have stimulated us to review our experience in particular the possible hazard to the patient during therapeutic starvation. We also wish to describe some side-effects of fasting which, to our knowledge, have not previously been reported.

Probably the incidence of any hazard due to therapeutic starvation will rise with increasing length of fast of patients. In this context we have arbitrarily defined prolonged starvation as for a minimum period of 60 days. To date, in this series, 18 patients have undergone periods of fasting of at least 60 days. The details of these patients—length of fast and weight loss—are shown in the Table.

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Duration of Fast and Weight Loss in 18 Patients

Case No.	Duration of Fast (Days)	Weight Before Fast		Weight Loss		
		lb.	kg.	lb.	kg.	% of Initial Weight
1	249	264	119·7	75	34·0	28·4
2	236	281	127·5	97	44·0	34·5
3	210	420	190·5	140	63·5	33·8
4	138	287	130·2	62	28·1	21·6
5	134	254	115·2	83	37·6	32·6
6	119	220·3	99·9	78	35·4	25
7	112	296	134·3	84	38·1	28·3
8	72	220·5	100·0	45	20·4	16·2
9	71	270·6	122·7	82	37·2	30·3
10	71	219	99·3	60	27·2	27·3
11	66	207	93·9	53	24·0	25·6
12	62	204·9	92·9	58	26·3	28·3
13	177	399	181·0	135	61·2	33·8
14	124	310·2	140·7	112	50·8	36·1
15	101	355·7	161·3	143	64·9	40·2
16	89	317	143·8	84	38·1	26·4
17	74	459·7	208·5	97	44·0	21·1
18	69	238	108·0	69	31·3	28·9

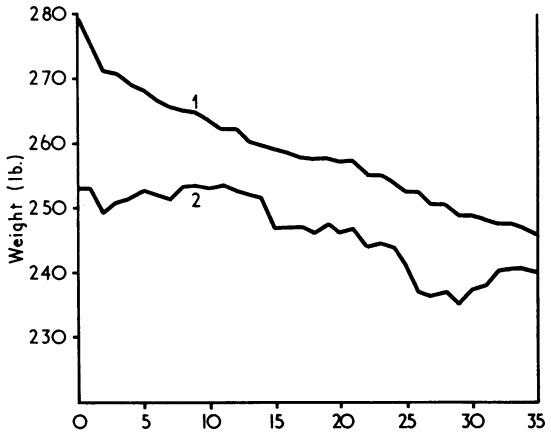

FIG. 1.—Weight loss patterns. 1=Normal progressive weight loss. 2=Irregular, unpredictable weight loss.

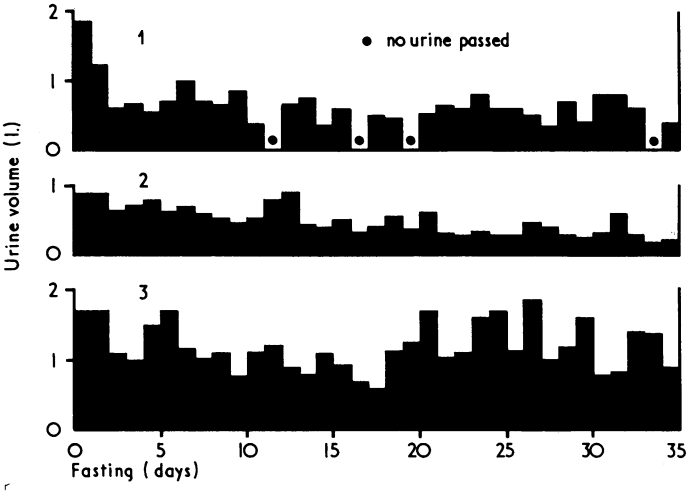

FIG. 2.—Patterns of urine excretion (Volume). 1=Normal response. 2=Normal oliguric response. 3=Atypical oliguric response.

Treatment Regimen.—The basic management of these patients has been described by Thomson *et al.* (1966). When the importance of the renal adaptive response to fasting was realized all urine passed by the patients was collected in 24-hour periods and analysed for its content of sodium, potassium, nitrogen, and acetoacetic acid. The osmolality of the urine was also measured. In selected patients measurements of the 24-hour exchangeable sodium of renal plasma flow and of glomerular filtration were performed before fasting and again at intervals throughout the fasting period.

Results of Fasting

(1) *Effectiveness.*—The weight loss of the patients is given in the Table. This is shown in lb. (kg.) and as a percentage of the patients' weight before starvation. It is apparent that large amounts of weight, varying from 16 to 40% of the total body weight, have been lost. From the Table therapeutic starvation is an obviously effective method of losing weight. Moreover, large percentages of the initial body weight can be so lost.

(2) *Weight Loss Responses.*—Two forms of weight loss are seen in fasting patients. The commonly observed pattern is that of progressive weight loss (Fig. 1, 1). In some patients weight loss occurs in an irregular and unpredictable manner (Fig. 1, 2). This response is most obviously associated with variation in the volume of urine passed by the patients.

(3) *Urine Output During Fasting.*—Measurement of the urine output shows three differing responses in fasting subjects. In some a normal urine output of 1-2 litres/day is maintained throughout fasting. In others the urine output falls with the starting of fasting and is maintained at this reduced volume, varying between 100 and 700 ml./day throughout (Fig. 2, 1 and 2). These responses are associated with a progressive weight loss. A third, and abnormal, response is seen in a few patients, wherein periods of oliguria, or even suppression of urine formation, alternate with periods of relative diuresis. In the extreme case oliguria results in an expansion of the extracellular fluid which is visible as dependent oedema. This is associated with irregular weight loss, and on occasions this effect may result in weight gain (Fig. 2, 3).

Other Side-effects.—Some patients have complained of vague malaise—headache, dizziness—early in the fasting period, but these have all settled as the patients develop increasing confidence in the treatment.

Abdominal Pain.—This is a significant symptom in fasting patients. One man (Case 13) suffered from attacks of midgut colic on the 8th and 17 days of fasting. In the second attack he obtained relief by lying prone. Three other patients have developed, early in fasting, typical midgut colic which settled without treatment. Finally, a middle-aged man complained of colicky umbilical pain on the 11th day of fasting. His condition deteriorated rapidly and he died on the 13th day. At necropsy there was infarction of the small bowel due to an acute volvulus. Possibly fasting patients may develop abnormal bowel motility, perhaps related to increased tone in the smooth muscle of the small bowel, and this may predispose to the development of mechanical obstruction. This effect must be rigorously excluded in fasting patients who develop abdominal pain.

Fall in Blood Pressure.—The blood pressure falls in all fasting subjects. In some this may present as postural hypotension early in the fasting period. This settles spontaneously. Two patients (Cases 9 and 5) complained of weakness about the 55th and 98th day of fasting respectively and were found to be suffering from postural hypotension, associated with a sudden increase in the renal excretion of sodium and potassium. These cases are discussed more fully below.

Biochemical Lesions.—Increased retention of bromsulphthalein in the plasma following intravenous injection has been found. It is not associated with alteration in the standard liver function tests nor with raised serum transaminases. It begins to fall within 24 to 48 hours of refeeding and reaches normal levels between the 5th and 7th days (Runcie, 1970). The possible significance of this is discussed below. Carbohydrate intolerance, as judged by the blood glucose response to an oral glucose load, has developed in several patients. It does not develop in all patients, nor does intolerance appear to increase with increased length of fast. Glucose

tolerance rapidly reverts to normal on refeeding—that is, fasting causes a rapidly reversible form of carbohydrate intolerance.

Serious Side-effects

In addition to the patient who died, two others have become dangerously upset while fasting.

Case 9.—A 34-year-old woman fasted without incident for 55 days. She then complained of being dizzy and weak. The only abnormality found on examination was a fall in blood pressure, with a further fall on standing. An increased urinary excretion of sodium and potassium was also noted. The fast was continued. She became increasingly prostrated and lapsed into hyponatraemic shock. The emergence of this syndrome was paralleled by an increasing urinary loss of sodium and potassium (Fig. 3). The renal mechanism for conservation of sodium and potassium had broken down. Oral potassium supplements failed to improve the patient's condition; on day 71 the fast was abandoned and she was given an 800-calorie diet. This resulted in the rapid restoration of her well-being. In this refeeding phase she developed pronounced fluid retention.

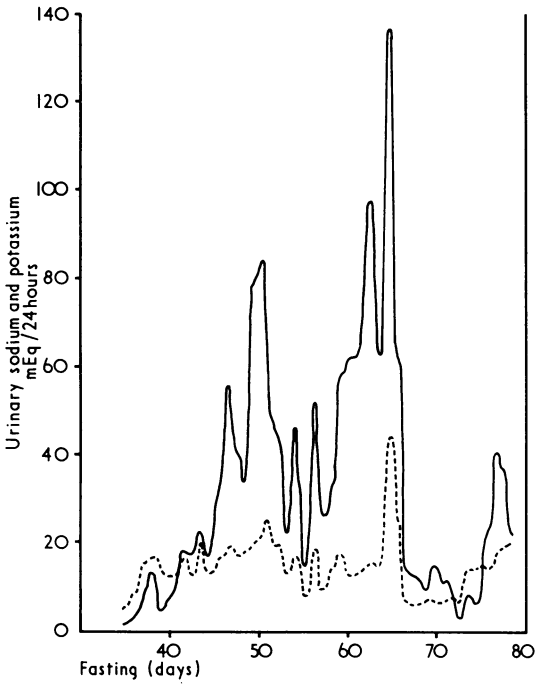

FIG. 3.—Case 9. Renal leak of sodium (———) and potassium (- - - - -).

Case 5.—A 54-year-old woman fasted without incident for 98 days. She then complained of being weak and dizzy. She was found to be hypotensive, with a further fall in blood pressure on standing. An increased excretion of sodium and potassium was found (Fig. 4). Treatment with bed rest and oral potassium supplements was begun. The fast was continued. Her condition steadily improved over a period of 24 to 48 hours. The urinary sodium and potassium excretion fell. Hypotension was no longer present. The fast was continued without incident for a further 22 days. In the refeeding phase she developed gross fluid retention. This responded to oral diuretic therapy.

Finally, acute and potentially dangerous biochemical changes may occur. We have noted the development of hypokalaemia in several patients, both spontaneously and more usually after an oral glucose load as a test for carbohydrate intolerance. In one patient (Case 10) the serum potassium fell to 2·4 mEq/l. following this procedure. She was also found to have latent tetany as evidenced by carpopedal spasm and a positive Chvostek's sign. Despite this the serum calcium was 9·2 mg./100 ml. and the serum magnesium 2·2 mEq/l.

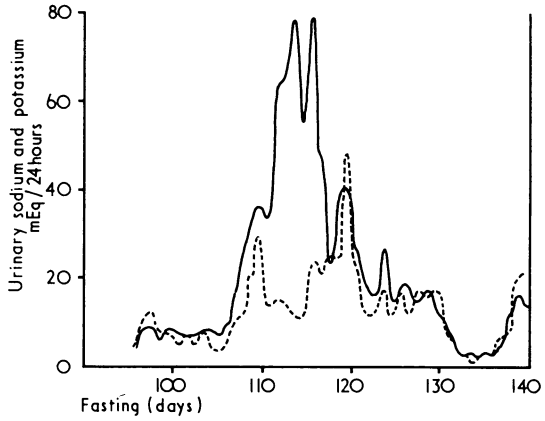

FIG. 4.—Case 5. Renal leak of sodium (———) and potassium (- - - - -).

Discussion

The acceptable morbidity of any therapy must be related to the severity of the disease for which it is prescribed. The morbidity of uncontrolled obesity is such that any effective therapy would have a considerable acceptable toxicity. Man's survival during starvation is related to his ability to conserve the essential, but limited, protein reserves of the body. This is achieved in part by an adaptive response of the liver, whereby hepatic gluconeogenesis is reduced (Felig *et al.*, 1969), and also by the utilization of liver cell protein to an unknown extent. This effect can be seen in the fatal case reported by Garnett *et al.* (1969). At necropsy the liver was found to weigh only 600 g.

Despite these effects liver function is little affected when judged by the tests currently available. These remain normal even after many months of fasting. The significance of the increased retention of bromsulphthalein in the plasma, following intravenous injection, is not clear. In some patients gross retention of the dye is seen, with plasma values of 40 to 70% at 45 minutes. Possibly this is due to diminished bile production by the liver in the absence of the normal stimulus for its production, food. Bromsulphthalein excretion therefore may not be a valid test of liver function in fasting patients. Nevertheless, any additional hepatic insult, such as cardiac failure, may result in pronounced deterioration in liver function, with all its attendant dangers.

The association between the hyperuricaemia of fasting and acute gout is well known. This has led some workers to use uricosuric or other antigout agents routinely in fasting patients (Gilliland, 1968). In our view this is unnecessary (Runcie and Thomson, 1969). It is potentially dangerous in that such drugs may impair or abnormally stress the renal adaptive response to fasting. Cases 5 and 9 show a hitherto unrecognized hazard of fasting—namely, that the renal response to starvation—that is, electrolyte conservation—may break down. Unless urinary sodium excretion is being measured routinely the significance of such non-specific symptoms as dizziness, weakness, and lethargy may be misinterpreted and a dangerous degree of sodium depletion allowed to develop.

All the patients who have died during or in association with therapeutic starvation (Spencer, 1968; Garnett *et al.*, 1969) have manifested abnormalities of the extracellular fluid. Spencer's two cases had been in cardiac failure. This may have obscured the development of a renal leak of electrolytes or impaired the renal response to fasting. In the case described by Garnett *et al.* (1969) ankle oedema was noted to be present in the refeeding phase. The maintenance of sodium homoeostasis is an integral part of the metabolic response to fasting. In obese patients this is effected by a reduction in the systemic blood pressure coupled with diminished excretion of sodium by the kidney. The latter effect can be

accurately measured. The general form of this response can be seen to be a series of oscillations of decreasing amplitude (Fig. 5). This behaviour is common to many biological systems in which there is feed-back control of function, and can be anticipated on theoretical grounds (Morowitz, 1966).

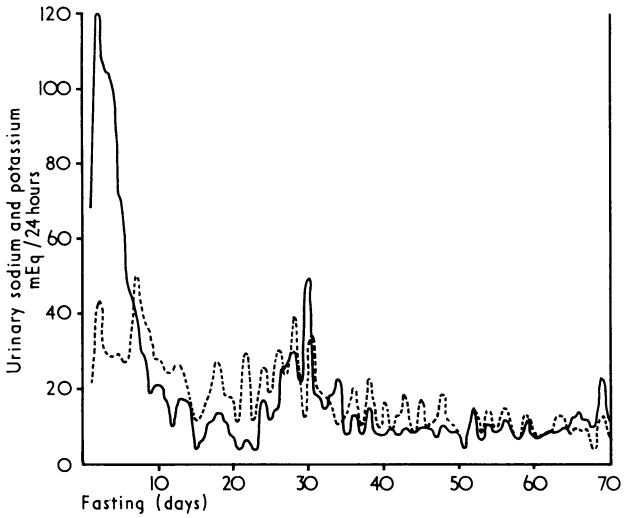

FIG. 5.—Normal urinary sodium (———) and potassium (- - - - -) excretion in a fasting obese patient.

In Cases 5 and 9 this response had broken down. After a varying period of normal behaviour the stable sympathetic oscillations of urinary sodium and potassium excretion give way to a system of increasingly unstable and irregular oscillations. In Case 9 this abnormality arose spontaneously and was more severe—hence its failure to respond to measures other than refeeding. In Case 5 the abnormality was of lesser degree and may have been induced by giving her a series of drugs—namely, potassium supplements followed by the aldosterone antagonist spironolactone. These artificial, or exogenous, perturbations on the stable oscillations of normal urinary sodium and potassium excretion may have induced a period of temporary instability in the system (Fig. 6). Recovery was ultimately effected by giving further potassium supplements. That measures as diverse as giving an 800-calorie diet containing about 20 mEq of sodium per day, an amount in itself unlikely to make good a sodium deficit, and the exhibition of potassium supplements, could reverse the established features of hyponatraemic shock is an indication of the numerous interacting forces whose function is to maintain sodium homoeostasis. In the refeeding phase both patients developed severe fluid retention, as shown by rapid weight gain and oedema of the legs, suggesting that renal dysfunction had persisted into this phase and was not immediately reversible by eating.

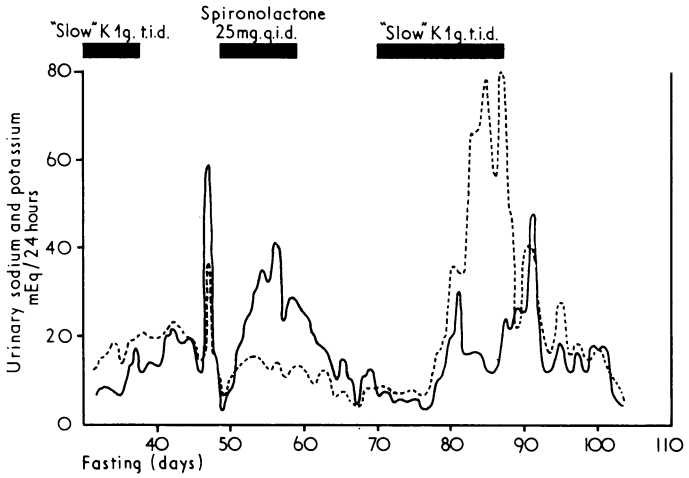

FIG. 6.—Effect of exogenous stimuli (perturbations) on urinary sodium (———) and potassium excretion (- - - - -) in fasting obese subjects.

Thus the metabolic abnormalities of fasting evolve progressively and, provided that the necessary biochemical measurements are made, they can be identified and the necessary corrective action taken to restore homoeostasis.

In our experience intercurrent disease is not a contraindication to therapeutic starvation; the presence of cardiac failure is a possible exception to this. In particular, several patients suffering from degenerative vascular disease, including acute myocardial infarction, have undergone varying periods of fasting without ill effect. We believe that prolonged therapeutic starvation is a safe and effective procedure. Though it is well tolerated by most obese patients, it should be undertaken only in a hospital where adequate facilities are available for following the associated metabolic changes. We would particularly stress the need for close surveillance of the changes in renal function during therapeutic starvation.

We wish to thank Professor Stanley Alstead for permission to study patients under his care, and Mr. Peter Waldie, of the department of photography, Stobhill General Hospital, for preparing the figures. We wish to record our gratitude to Dr. J. Wilson Chambers, department of biochemistry, Stobhill General Hospital, for the large number of tests he has performed in these patients.

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