arteriosclerotic patients and synovial membrane in the patients with rheumatoid arthritis were important sources.

At the same time the possibility remains that phenformin plus ethylœstrenol in some way directly influences the rate of fibrinogen-to-fibrin turnover. To what extent fibrinogen is converted to fibrin in vivo is at present uncertain, but studies with radioactive fibrinogen before and during treatment with this combination of drugs might throw light on this. In this connection our findings accord with the proposal first put forward by Nolf (1908) and subsequently espoused by others (Copley 1954, Astrup 1956, Fearnley 1961) that deposition and removal of fibrin is in continuous flux, in other words that coagulation and fibrinolysis are in a state of dynamic equilibrium. This concept has been extended to suggest that coagulation and fibrinolysis together form a whole, a physiological system of repair which uses fibrin as a cement; and that imbalance of either side of the system leading to increment and persistence of fibrin may be of pathogenic importance in vascular occlusion and other conditions (Fearnley 1965).

The behaviour of fibrinogen/fibrin may be of importance in conditions other than occlusive vascular disease—e.g., rheumatoid arthritis (Fearnley and Chakrabarti 1966), cancer (O'Meara 1958, Cliffton 1966), and nephritis (Kincaid-Smith et al. 1968, Wardle 1969). Phenformin plus ethylœstrenol may have application both as a research tool and therapeutic agent in such situations. Meanwhile our findings lend weight to the suggestion (Fearnley et al. 1967, Chakrabarti et al. 1968, Fearnley and Chakrabarti 1968) that phenformin plus ethylœstrenol, which increases fibrinolytic activity, lowers plasma-fibrinogen and serum-cholesterol levels, and reduces platelet stickiness to glass—all of these effects being sustained with continued treatment—merits trial as a prophylactic measure in survivors of vascular occlusions, and also in other situations where deposition of platelets and fibrin are detrimental (e.g., after vascular surgery and the insertion of cardiac prostheses).

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GROSS FRAGMENTATION OF CARDIAC MYOFIBRILS AFTER THERAPEUTIC STARVATION FOR OBESITY

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Summary Death from ventricular fibrillation consequent upon therapeutic starvation to her ideal weight is described in an obese but otherwise healthy 20-year-old girl. At the time of her death the plasma electrolytes, calcium, magnesium, pH, and blood-gas tensions were normal. The extracellular fluid volume was also normal although the lean body mass was reduced. The myocardial fibres were reduced to approximately half their normal diameter, and electron microscopy revealed gross loss and fragmentation of the myofibrils. It is concluded that prolonged total starvation is an unsafe procedure.

Introduction

DEATH as a result of total starvation in obese but otherwise healthy patients has not been described.

Cubberley et al. (1965) reported the death of a 44-year-old hypertensive diabetic woman after 3 weeks of total starvation. They attributed the death to idiopathic lactic acidosis and found focal stenosis of coronary arteries at necropsy. Spencer (1968) reported two deaths during total starvation, one in a 61-year-old woman with an old anteroseptal infarct and gross atheroma who had presented with acute left ventricular failure; the other in a 58-year-old severely hypertensive woman with right-bundle-branch block who had presented in gross congestive failure. These patients had starved for 3 and 8 weeks, respectively.

We report here the death (after 30 weeks of total starvation) of an obese but otherwise healthy young woman at a time when she had achieved her ideal weight.

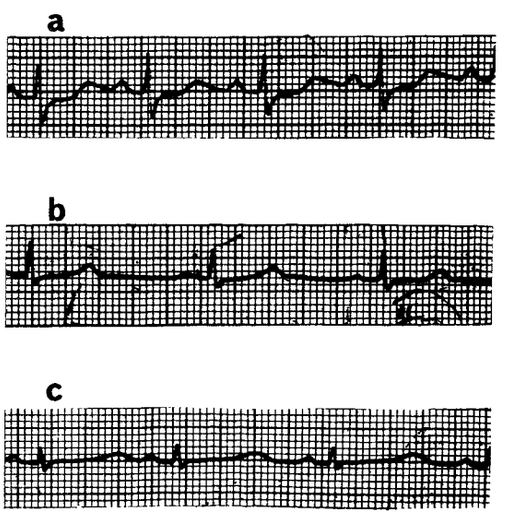

Fig. 1—E.C.G. with voltage adjusted to 1 mV=10 small vertical divisions.

(a) Hypokalæmia.
(b) 1 month before death.
(c) After cardiac arrest.

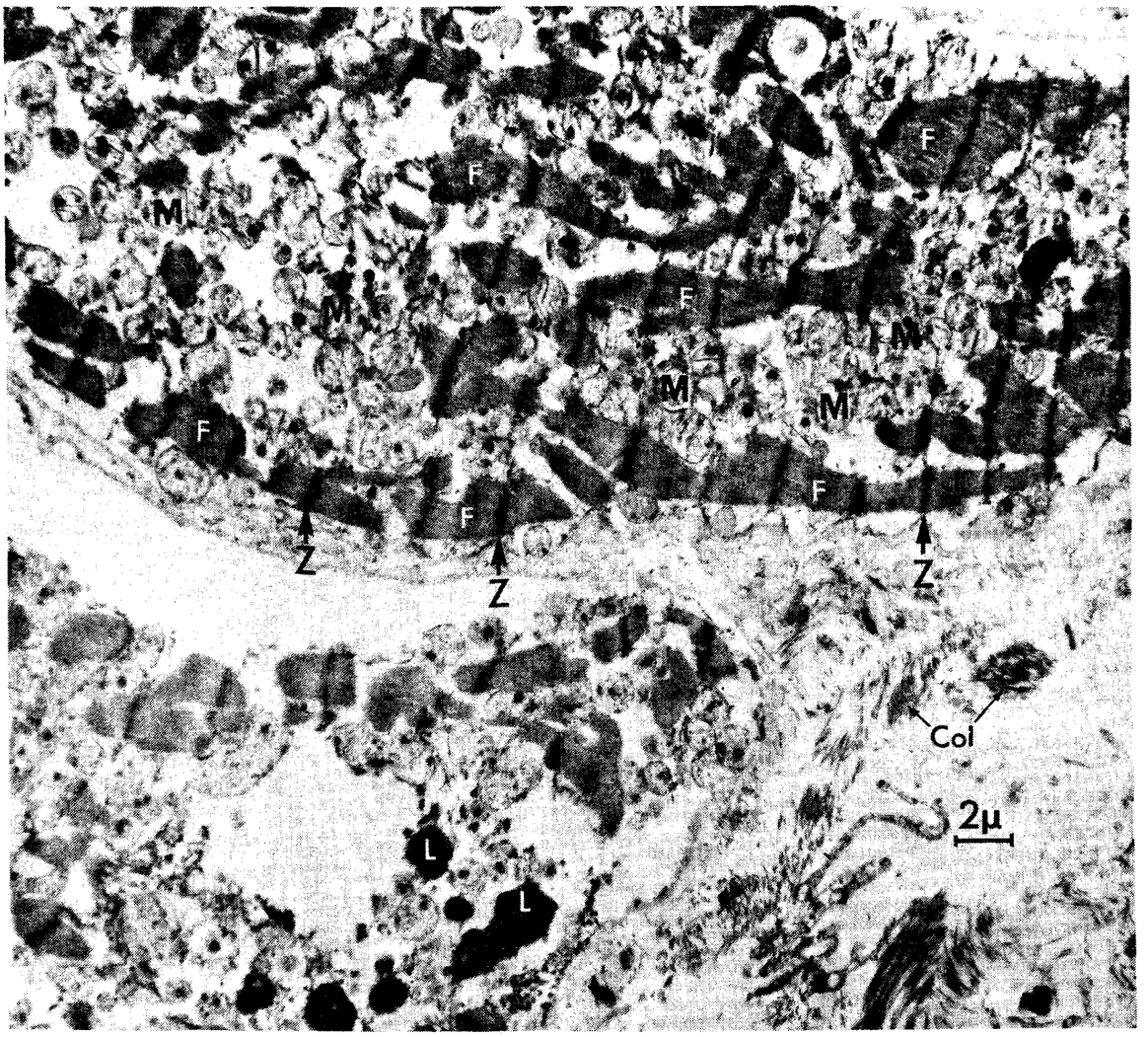

Fig. 2—Electron micrograph of myocardium fixed 4 hours after death.

Numerous mitochondria (M) replace disrupted and atrophied myofibrils (F). The Z lines persist. A small amount of collagen (Col) and lipofuscin (L) is present. (Reduced to $^2/_3$ of a total magnification of ×5000.)

Case-report

On Admission

Our patient was 20 years old and on admission weighed 118 kg. She had been fat since childhood and had not had any previous illnesses or head injury. On examination no physical abnormalities apart from obesity were found. Standing blood-pressure 110/80 mm. Hg; heart normal size and configuration; electrocardiograph (E.C.G.) normal. Tests of pituitary-adrenal axis and thyroid function, electrolytes, blood-urea, creatinine clearance, plasma pH and blood-gas tensions also normal.

Therapeutic Starvation

Total body water, exchangeable potassium, and sodium space were measured before starvation by standard isotope techniques. During starvation these body-fluid compartments were measured serially together with measurements of plasma electrolytes, urea, calcium, protein, blood-sugar, and blood-gas tensions every 2 weeks, and daily measurements of urinary electrolytes, nitrogen, and creatinine. E.C.G.S were recorded monthly.

The patient was closely supervised in a metabolic unit throughout treatment. She was given unrestricted acaloric salt-free fluids, folic acid, and allopurinol, and supplements of vitamin A, vitamin-B complex, and vitamin C.

After the initial rapid weight-loss and natriuresis, weight was lost at a steady rate of 0·2 kg. per day until she achieved her predicted ideal weight of 60 kg. Her fast was uncomplicated apart from one episode of hypokalæmia (plasma-potassium 2·3 meq. per litre) during the initial natriuresis. The E.C.G. at this time (fig. 1a), showed ST depression and a QT interval of 0·38 second (predicted maximum 0·37 second).

After this episode of hypokalæmia a daily potassium supplement of from 52 to 76 meq. was given. Despite this supplement her exchangeable potassium fell from a prefasting level of 3360 meq. to 1400 meq. (23 meq. per kg.) while the sodium space fell from 23·7 to 18·1 litres and the total body water fell from 52·6 to 32·4 litres—i.e., the decrease in exchangeable potassium of 1960 meq. was accompanied by a fall in the intracellular fluid volume of 14·6 litres and was therefore due almost entirely to a loss of lean tissue mass. This had happened even though the patient had been ambulant throughout the starve, had attended physiotherapy, and had been given supplements of essential aminoacids (12 g. daily for 47 days) and ' Casilan ' (a whole-protein powder) (25 g. daily for 56 days).

Refeeding

When the predicted ideal weight had been achieved, a refeeding regimen was instituted. This consisted of a diet of protein and fat providing 200 C. daily for the first 2 days, 400 C. daily for the third and fourth day, and 600 C. daily thereafter. Initially carbohydrate was omitted in an attempt to avoid salt and water retention. During the refeeding regimen the plasma-potassium ranged from 3·7 to 4·1 meq. per litre and the plasma-sodium from 141 to 144 meq. per litre, and there was no net change in the daily potassium and sodium balance.

The patient felt and looked well during this first week of refeeding. Her standing blood-pressure had fallen slowly during the fast to a steady level of 80/50 mm. Hg and it remained at this level while refeeding. Her pulse was regular

at 65 and although there was slight œdema of the legs, the jugular venous pulse was not raised and there were no crepitations at the lung bases. No other clinical abnormalities were detected, and her weight remained constant.

On the evening of the seventh day of refeeding the patient felt faint while standing and therefore went to bed. While lying in bed she became unconscious and very pale, but she recovered almost immediately. Her pulse and blood-pressure after this episode were normal.

The following morning she felt well, and routine blood analysis showed: electrolytes (meq. per litre) sodium 141, potassium 3·7, chloride 98; total carbon dioxide 26·2 mmole per litre, pH 7·39, P_{CO_2} 42·5 mm. Hg, total protein 6·0 g. per 100 ml. (albumin 3·4); and (in mg. per 100 ml.) urea 20, calcium 8·4, magnesium 2·25, blood-sugar 105.

Death

After a breakfast of one egg she had a cardiac arrest with loss of consciousness, absent respiration, pallor, impalpable pulses, inaudible heart sounds, and dilated pupils. After 2 minutes of external cardiac massage she recovered completely, with a normal pulse and blood-pressure. In contrast to the normal E.C.G. taken 1 month previously (fig. 1b), the E.C.G. taken immediately after this cardiac arrest (fig. 1c) was of low voltage with an obviously prolonged QT interval of 0·56 second (predicted maximum 0·41 second) and T-wave inversion in lead I, aVL, and aVR. Because of the prolongation of the QT interval a slow potassium infusion was started but this was stopped when the plasma-potassium report (3·7 meq. per litre) became available. However, the usual potassium supplement of 72 meq. was given during the day and carbohydrate in the form of ' Hycal ' was added to her diet.

The apparently low plasma-calcium had previously been accepted as within normal limits for a plasma-albumin concentration ranging from 2·7 to 3·4 g. per 100 ml., but in the absence of an explanation for the prolonged QT interval and in view of the possibility of further cardiac arrests, calcium chloride was given in 5% dextrose.

Multifocal ventricular extrasystoles developed after 1 hour when 1 g. of calcium chloride had been given. The calcium infusion was immediately stopped and lignocaine infused to control the extrasystoles. 7 hours later, the patient had an episode of ventricular fibrillation, from which she recovered completely after 1 minute of external cardiac massage.

The next morning the E.C.G. still showed a prolonged QT interval although 30 meq. of potassium had been given over night according to the Mittra regimen (Mittra 1965). At a time when there had been no extrasystoles for 4 hours ventricular fibrillation developed, and the patient died despite direct-current defibrillation and other resuscitative measures.

Necropsy

This was done 4 hours after death. The heart was dilated and weighed 250 g. The myocardium was soft and brown, but the valves and coronary arteries were normal. The liver weighed 600 g. No other abnormalities were detected macroscopically.

Microscopy of the heart showed myofibres of small diameter (0·64 compared with 1·0 arbitrary units for control tissue) and an increase in lipofuscin. Microscopy of the liver showed significant fatty degeneration.

Electron Microscopy (fig. 2)

Formalin-fixed samples of myocardium obtained at necropsy were post-fixed in buffered osmic acid and embedded in ' Epikote '. The most striking abnormalities were the paucity and disruption of myofibrils and the apparent increase in the number of mitochondria within the sarcolemma. The Z lines of the myofibrils were quite clear although interrupted in places by mitochondria. The mitochondria were normal apart from some swelling and minor changes in the appearance of the cristæ. The nuclei and blood-vessels were normal, and no virus particles were seen.

Discussion

We do not know the cause of death in this patient, but her mode of death and the electron-microscopy findings implicate myocardial failure, and it is interesting that Keys et al. (1950) suggested that the myocardium might be damaged after prolonged partial starvation in volunteers, when they found slight prolongation of the QT interval.

While prolongation of the QT interval may be a feature of potassium deficiency, the E.C.G. shown in fig. 1c was unlike that recorded in the same patient when hypokalæmic with a serum potassium of 2·3 meq. per litre (fig. 1b). Furthermore, the serum-potassium and the total carbon dioxide were normal at the time. Although the exchangeable potassium had fallen considerably during the fast (1940 meq.) this was accompanied by a commensurate fall in intracellular fluid (14·6 litres), body nitrogen (670 g.), and daily creatinine excretion (from 1·56 g. to 0·85 g.). The fall in exchangeable potassium was therefore due to a loss of lean tissue mass similar to that found in prolonged total starvation (Barnard 1969) and in pseudo potassium depletion in the muscular dystrophies (Nagant De Deuxchaisnes et al. 1961).

The QT interval may also be prolonged in hypomagnesæmia and hypocalcæmia. In this patient the plasma-magnesium was normal and the ionised calcium was almost certainly normal.

Finally no quinidine, digoxin, or diuretics were given at any stage—in contrast with Spencer's (1968) cases—and we should stress that our patient had at least one cardiac arrest before calcium was infused.

The electron-microscopic appearances of the myocardium after prolonged total starvation have not previously been described, as far as we know. To exclude the possibility that the changes shown (fig. 2) were artifacts, we compared the findings with those seen in normal myocardium obtained 9 hours after death from a healthy 23-year-old woman killed instantaneously in a road accident, and in myocardium from a 30-year-old woman who had had anorexia nervosa for at least 10 years. No significant fragmentation of the myofibrils was seen in either case.

It seems that prolonged total starvation produces gross destruction of cardiac myofibrils, and we suggest that this regimen should no longer be recommended as a safe means of weight reduction. Furthermore, it is apparent that the halving of the lean tissue mass, as evidenced by the changes in intracellular water, exchangeable potassium, body nitrogen, and creatinine excretion, is associated with similar changes in the myofibrils. This contradicts the widely held belief that the heart is spared during starvation.

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