Sudden death associated with very low calorie weight reduction regimens[1, 2]

Harold E. Sours,[3] M.D., Victor P. Frattali, Ph.D., C. Daniel Brand, B.S., Roger A. Feldman, M.D., Allan L. Forbes, M.D., Richard C. Swanson, B.S., and Allen L. Paris, M.D.

ABSTRACT We studied the cases of 17 individuals who died suddenly of ventricular arrhythmia after prolonged use (median 5 months) of very low calorie weight reduction regimens consisting entirely or largely of protein. The deaths appeared to be independent of type of medical supervision received during the diet, daily dosage of potassium supplementation, and biological quality of the protein product used. Factors common to all cases were marked obesity at the onset of dieting, prolonged use of extremely low calorie diets (approximately 300 to 400 kcal daily), and significant and rapid weight loss. Our review of available electrocardiograms and pathological specimens revealed a pattern of cardiac changes previously described in starvation. We conclude that use of very low calorie weight reduction regimens should be curtailed until further studies determine what modifications, if any, can insure their safety. *Am. J. Clin. Nutr.* 34: 453–461, 1981.

KEY WORDS Obesity, weight reduction regimens, protein diets, cardiac arrhythmia, rapid weight loss, starvation

Introduction

After the widespread use of the so-called liquid protein diet popularized by *The Last Chance Diet* (1), reports of deaths associated with the use of this and similar very low calorie weight reduction regimens were received by the Food and Drug Administration. An investigation by the Food and Drug Administration and the Center for Disease Control revealed a recurrent pattern of either sudden death or death due to intractable ventricular arrhythmia in individuals who had been dieting for prolonged periods and who had lost large amounts of weight. After the results of this initial investigation were publicized, further reports of diet-associated deaths were received and investigated. Of these reports, the deaths of 17 individuals, 16 females and one male, were found to fit this pattern and are summarized here.

Methods

The 17 cases were among 58 reports of death associated with the use of the liquid protein and similar weight reduction regimens and were those not readily attributable to underlying disease. Fourteen of the 41 other reported deaths had histories that proved to be unreliable or were incomplete because of physician or family refusals to provide needed information. One of these reports was a spontaneous abortion in a woman on the diet. Underlying disease may have been partially responsible for the remaining 26 reported deaths, 18 of which occurred in individuals with either clinical or pathological evidence of atherosclerotic coronary artery disease and/or diabetes.

All reports were received from voluntary sources. We investigated these reports by telephone interviews and/or personal visits with physicians and surviving family members and reviewed available medical and pathological records. Information on past medical history, details of the dietary regimen, and circumstances of death were collected. Reports of several of the cases presented here have already appeared in the literature (2–4).

Pathological material from the heart was obtained from 14 cases and was reviewed at the National Heart,

[1] From the Bureau of Epidemiology, Center for Disease Control, Atlanta, Georgia and the Food and Drug Administration, Washington, D.C.

[2] Address reprint requests to: Victor Frattali, Ph.D., Food and Drug Administration (HFF-261) 200 C St. S.W., Washington, D.C., 20204.

[3] Presently in private practice.

The American Journal of Clinical Nutrition 34: APRIL 1981, pp. 453–461. Printed in U.S.A.

Lung, and Blood Institute. A detailed discussion of this pathological review is presented elsewhere (5).

Results

Dietary histories

The 17 persons all died between July 1, 1977 and the 1st wk of January 1978. They were from 10 states and the province of Ontario. Five were from Minnesota. All 17 were white. All were relatively young (median 35 yr) who were morbidly obese (median 106.5 kg) before they started the regimen. They remained on the diet for 2 to 8 months and lost substantial weight (median 39 kg) at a rapid rate (median 2.1 kg/wk) (**Table 1**). All had histories of numerous unsuccessful attempts at weight reduction.

In cases 1 through 13, the patients' total caloric intake came from "liquid protein", i.e., aqueous solutions of collagen or gelatin hydrolysates to which various amounts of tryptophan, preservatives, and artificial flavorings had been added. Two patients (cases 14 and 15) supplemented liquid protein once a day with protein food of high biological value. The other two (cases 16 and 17) used powdered products that were based on lactalbumin and/or casein and containing carbohydrates. The product used in case 17 also contained mineral supplements. No single brand product was used by more than two individuals. Daily energy intake was approximately 300 to 400 kcal in all cases. All took a vitamin or vitamin-mineral supplement of the prenatal variety. Daily dosage of potassium ranged from none in one case to an estimated 75 mEq in another. Five also took a calcium supplement (**Table 2**). All consumed 2 to 3 L of noncaloric fluids daily. Adherence by the patient to the regimen was described by relatives and friends as compulsively strict in all cases.

Twelve patients were under some form of medical supervision, which varied from thorough to infrequent follow-ups without laboratory studies. Eleven were taking no medication other than the vitamin and mineral supplements consumed with the diet (Table 2). One woman (case 1) smoked cigarettes.

None of the patients who had standard clinical laboratory tests done while they were on the diet had persistent hematological or biochemical abnormalities, but six had at least one documented episode of hypokalemia (**Table 3**). In addition to those having routinely available laboratory tests performed, one individual (case 17) was found to have normal serum zinc and copper levels shortly before going off the diet.

TABLE 1
Anthropomorphic and dietary data

Case	Age	Height	Prediet weight	Weight loss	Percentage weight loss	Duration of diet	Rate of weight loss	Death during refeeding
	yr	*cm*	*kg*	*kg*		*mo*	*kg/wk*	
1	33	163	112	41	36	7.5	1.4	Yes
2	32	168	98–104	29–36	30–35	5	1.5–1.8	Yes
3	34	168	107	41	38	4	2.5	No
4	25	168	126	63	50	5	3.2	Yes
5	32	165	113	49	44	6	2.0	No
6	44	164	103	40	39	4.5	2.2	No
7	44	160	97	18	18	2	2.2	Yes
8	33	163	106	33	31	4	2.1	No
9	33	164	85	25	30	3	2.1	Yes
10	38	173	153	63	41	8	2.0	No
11	45	173	91–95	9–14	10–15	2.5	0.9–1.4	No
12*	50	157	73	18	25	2	2.3	No
13	23	175	128	38	30	4	2.4	No
14	51	173	108	44	41	5	2.2	No
15	36	160	135	49	36	7	1.7	No
16	41	164	104	36	35	5	1.8	Yes
17†	43	188	184	82	44	7	2.7	Yes
Median	35	164.5‡	106.5‡	39‡	36	5	2.1‡	

* Second time on diet. Had previously lost 27 kg, but had regained 18 kg.
† Male.
‡ Females only used in tabulation.

TABLE 2
Dietary supplements and medication

Case	Daily dosage of potassium	Vitamin-mineral preparation	Calcium supplement	Other medications
	mEq			
1	54	Multivit + Ca, Fe, I, Mg	Yes	No
2	5	Multivit; folic acid	Yes	No
3	25	Multivit + Ca, Fe, I, Mg	No	No
4	0	Multivit	No	Birth control pills
5	40	Multivit; folic acid, Fe, vitamin C	No	Clorazepate, Cimetidine, antacids
6	3	Multivit + Ca, Fe, Mg, K, I, Cu, Mn, Zn, folic acid	No	No
7	3	Multivit + Ca, Fe, Mg, K, I, Cu, Mn, Zn, folic acid	No	Rare Marax*
8	20	Multivit + minerals; Fe	No	No
9	24	Multivit + Ca, Fe, Mg, K, I, Cu, Mn, Zn; folic acid	No	No
10	24	Multivit + Fe; folic acid	Yes	No
11	7	Multivit; folic acid	No	Thioridazine, Fuorsemide, Flurazepam
12	75	Multivit + minerals	No	Triavil,* Thioridazine
13	24	Multivit; folic acid; Fe	Yes	No
14	25–50	Multivit + Ca, Fe, I, Mg	Yes	No
15	Unknown	Multivit + folic acid, Fe	Unknown	Rare α-methyldopa
16	32–48	Multivit + Ca, P, I, Fe, Mg	No	No
17	42–62	Multivit; Ca, P, Fe, Mg, Cu, Zn, K, Na, Mn†	Yes†	No

* Use of trade names is for identification only and does not constitute endorsement by the Public Health Service, United States Department of Health and Human Services.
† Minerals supplied in protein supplement.

TABLE 3
Laboratory data

Case	Range of serum K during diet	Studies on hospital admission							
		Serum K	Serum Ca	Serum Mg	Serum PO_4	Total protein	Albumin	EKG	
								Low voltage	Long QTc*
	mEq/L	*mEq/L*	*mg/dl*	*mg/dl*	*mg/dl*	*g/dl*	*g/dl*		
1	3.6–5.2	3.6	8.8	1.7	3.0	6.5	3.9	Yes	Yes
2	NA†	2.9	9.0	1.5	NA	4.7	2.9	Yes	Yes
3	3.1–3.9	3.6	8.9	2.2	3.7	5.5	4.4	Yes	Yes
4	NA	3.0	NA	NA	NA	NA	NA	No	No
5	3.3–5.1	2.8	9.2	2.1	3.7	6.3	3.5	Yes	Yes
6	3.4–4.1	NA	NA	NA	NA	NA	NA	NA	NA
7	4.2–4.8	3.3	7.8	NA	NA	NA	NA	Yes	Yes
8	3.0–4.3	3.1	8.8	2.3	0.9	6.0	3.9	No‡	Indeterminate
9	NA	NA	NA	NA	NA	NA	NA	NA	NA
10	3.8–4.1	4.2	8.7	1.8	2.7	6.3	3.8	Yes	Yes§
11	NA	NA	NA	NA	NA	NA	NA	NA	NA
12	NA	NA	NA	NA	NA	NA	NA	NA	NA
13	3.5–4.9	3.9	8.5	1.6	NA	NA	NA	Yes	No
14	3.9–4.2	3.8	8.7	1.8	NA	NA	NA	No	Yes
15	2.2	NA	NA	NA	NA	NA	NA	NA	NA
16	3.3–4.7	4.1 |	8.8 |	2.2 |	3.3 |	NA	NA	Yes |	Yes |
17	3.6–4.6	3.2	NA	NA	NA	NA	NA	Yes	Yes

* $QTc = \frac{QT}{\sqrt{RR}}$ (6).
† Not available.
‡ Voltage not low, but decreased from base-line.
§ QTc prolonged prior to diet; further prolonged after weight loss.
\| Studies performed shortly before patient's sudden death outside of hospital.

None had signs or symptoms suggestive of cardiac decompensation. Most were feeling very well and pleased with their marked weight loss, although hair loss and cold intolerance were frequently reported.

Circumstances of deaths

Six patients died suddenly, six died while under observation in the hospital after being admitted for syncope, and five suffered cardiac arrest outside of the hospital and never regained consciousness after admission. Seven patients were in the early stages of refeeding at the time of their death; the refeeding regimens consisted mainly of low sodium, low calorie diets with protein supplements substituted for one or more meals daily.

Ventricular tachycardia and fibrillation were documented in the 11 persons who died under observation. These cases of arrhythmia were surprising to the clinicians taking care of the patients and markedly refractory to standard antiarrhythmia therapy. All 11 were repeatedly cardioverted, and lidocaine was ineffective in 10 cases, propanolol in seven, procaine amide in six, and phenytoin sodium in five. None of the 11 received quinidine. Left stellate ganglion blockade (without associated Horner's syndrome) was ineffective in one patient and ventricular overdrive pacing was ineffective in another. Attempted replacement of presumed intracellular deficits of potassium (11 cases), calcium (six cases), and magnesium (six cases) was also unsuccessful in controlling the arrhythmia.

For those who were admitted to the hospital, limited clinical data are available. Serum electrolytes on admission were normal except as shown in Table 3. Six of 11 patients were hypokalemic, one of nine was hypocalcemic, although no serum protein values are available to document this fully, and three of eight were hypomagnesemic. Two patients (cases 1 and 10) were found to be hypothyroid, one having had this condition documented before dieting. Arterial blood gas analyses were only performed in the setting of respiratory arrest and/or cardiovascular collapse, and no serum measurements of lactic acid or ketones were performed.

Electrocardiograms were taken near the time of death in 12 cases, 10 of which were available for detailed analysis. All but one patient were taken during the final hospitalization; the exception was in case 16 where the finding of an abnormal electrocardiogram had prompted the initiation of a refeeding regimen 3 wk before the patient's sudden death outside of the hospital. Nine of 10 electrocardiograms showed low QRS voltage (sum of QRS deflections in leads I, II, and III $\leq$ 15 mm). Accurate measurement of the QT interval could be made in nine cases, and in each of these the QT interval corrected for rate (using Bazett's formula (6)) was prolonged.

In four of the 10 cases, prediet electrocardiograms were available for comparison; all four of these showed that QRS voltage decreased significantly after dieting. Three of four patients had a normal and one had a prolonged prediet QT interval (**Fig. 1**).

In two cases, only descriptions of the electrocardiograms taken on admission to the hospital were available. In case 4, the patient was in sinus tachycardia with aberrant ventricular conduction; QRS voltage and QT interval measurements were not mentioned in the report. In case 13, the patient was in normal sinus rhythm, and the electrocardiogram showed low voltage, however, the criteria used to make this judgment and the QT interval are not reported.

Pathological studies

Autopsies were performed in 16 cases. On gross examination all organs appeared normal. Organ weights were generally in the range anticipated from body weight at the time of death. None had pulmonary or systemic embolization or pericardial effusion.

Heart weights ranged from 260 to 430 g (median 300) and did not differ significantly from predicted values (7). The coronary arteries were normal in origin and distribution in all cases and were free of significant atherosclerosis. The cardiac valves were normal in all cases.

Histological examination revealed that abnormal findings were generally restricted to the myocardium. Six individuals were described as having "myocarditis" by the pathologists performing the original studies. In the evaluation of specimens from 14 cases by pathologists of the National Heart, Lung, and

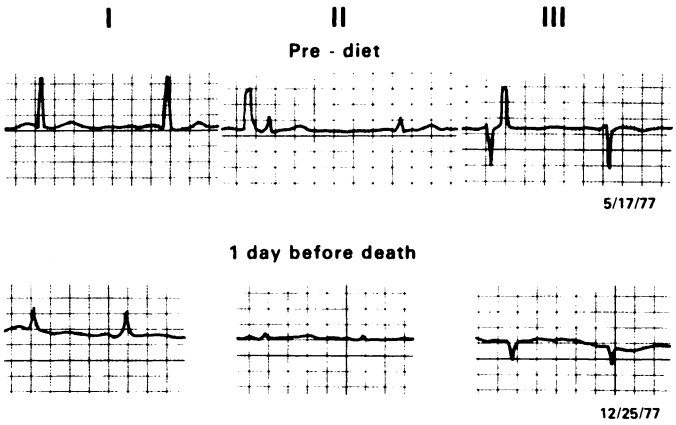

FIG. 1. Prediet and postdiet electrocardiograms from case 17 showing a decrease in QRS voltage and prolongation of the QT interval.

Blood Institute, an interstitial mononuclear cell myocarditis was found in only one of the diet-associated cases (case 4). With this exception, the incidence of sparse mononuclear cell infiltrates did not differ between the study and control groups. Myocardial atrophy was the most prominent finding. Other myocardial abnormalities included increased perinuclear pigment deposition and poorly characterized nuclear changes (5).

Other histological findings were mild fatty change in the liver in five cases and chronic thyroiditis in the two hypothyroid individuals. None had renal changes suggestive of hypokalemic nephropathy.

Discussion

The unique pattern of these 17 deaths, their association with extremely low calorie weight reduction regimens, and their occurrence over a 6-month period coincident with the widespread popularity of a dietary fad make a cause and effect relationship highly probable. Unfortunately the retrospective nature of the investigation and the lack of adequate specimens for thorough pathological and biochemical analysis make the determination of the precise mechanism of the deaths difficult. The variety of products used by the individuals in our study makes an exogenous toxin unlikely. Although mineral deficiency syndromes, drug interactions, hereditary prolongation of the QT interval, and hypothyroidism may have been involved in some of the cases, the overall pattern of the deaths is most consistent with the effects of protein-calorie malnutrition on the heart. Understanding of this area remains incomplete because much of the information is derived from the uncontrolled environment of war and famine.

The lack of antecedent symptoms referable to the heart seen in our cases is consistent with the well-documented cardiac effects of protein-calorie malnutrition (8–10). Cardiac size and output decrease in proportion to weight loss, changes to a certain extent representing normal adaptation to decreasing energy supply and demand. Venous pressures are decreased, and overt congestive heart failure is rare. Starvation edema cannot be explained on a cardiac basis. There are indications, however, that the seemingly healthy adaptation of the heart to starvation may have a pathological component.

With refeeding there is a tendency to volume overload. The starved myocardium does not have sufficient functional reserve to handle additional stress. Keys et al. (8) reported increased complaints of dyspnea during the rehabilitation stage of their classic volunteer study on semistarvation, and there are reports of clinical congestive heart failure with refeeding (11, 12). Sudden death, presumably cardiac in origin as was seen in our cases, has been described in starvation, especially during the early refeeding phase (9, 13).

Myocardial atrophy, the most consistent finding in our cases, is fairly specific for protein-calorie malnutrition, both in clinical

settings (14–20) and in animal models (21, 22). Other myocardial findings reported and also seen in our cases are increased perinuclear pigment deposition and nonspecific nuclear changes.

The seemingly contradictory findings of normal heart weights as predicted from body weights at death and myocardial atrophy on microscopic examination are most likely explained in terms of atrophy of a previously hypertrophied myocardium. Hypertrophy of the myocardium is well documented in obesity and heart weights tend to remain a constant fraction of total body weight (7). With regression of the hypertrophy, a relative increase in the ratio of connective tissue to myocardial fibers is consistent with the above observations.

Myocarditis, found in one of our cases, has also been reported in animal models of protein deficiency where calorie and electrolyte intakes have been well controlled, although the interstitial mononuclear cell infiltrates are usually not extensive enough to justify this diagnosis (21). Interestingly, Gopalan (14) described an overdiagnosis of myocarditis on autopsy in areas of severe malnutrition. He attributed this to most pathologists being unfamiliar with the myocardial changes of starvation.

Although myocardial lesions have been associated with certain mineral deficiencies, the changes described are not those seen in our cases. Deficiencies of potassium (23, 24), calcium (25), magnesium (26–28), and selenium (29) have been described as causing focal necrosis of the myocardium with myofibrillar destruction. In our diet-associated cases, including the case of myocarditis, there was little, if any, destruction of the atrophied myofibrils. Deficiency of copper (30–32) is associated with myofibrillar hypertrophy, presumably representing an attempt to overcome a lack of specific enzymatic activity. Myofibrillar hypertrophy was not seen in our cases.

The electrocardiographic pattern of decreased voltage and prolonged QT interval adjusted for rate (QTc) has previously been described in various states of protein-calorie malnutrition, including famine (14, 33, 34), controlled human experimentation (11), cachexia of chronic diseases (35, 36), and highly restrictive weight reduction regimens (37, 38). The decreased voltage and prolonged QTc interval appear to reflect independent processes with different rates of recovery on refeeding; the QTc interval may actually increase during the early stages of rehabilitation (11, 38), an event that could increase the risk of ventricular arrhythmias and possibly explain the sudden deaths which sometimes occur in this stage. There is suggestive evidence that the electrocardiographic changes tend to parallel the severity of the deficiency and that mortality increases as they become more pronounced (9, 11).

The decreased voltage may be an indication of the myocardial atrophy of starvation. The prolonged QTc interval is not as readily explained. Hypocalcemia and hypomagnesemia are potential explanations, although in the diet-associated deaths presented here, it is unlikely that deficiencies of these 2 ions would have been present in all cases; serum levels were normal in the majority, several were receiving supplementation, large stores were available in bone, and repletion of presumed deficits was ineffective in controlling the arrhythmias. QTc interval prolongation has been attributed to hypokalemia, although this is generally considered to be only an apparent prolongation owing to the superimposition of a prominent U wave on the T wave. It seems most likely that in starvation the QTc changes reflect myocardial damage and/or alterations in the normal hormonal and neurological environment.

Recently, Lantigua et al. (38a) have reported that three of six obese subjects studied in a metabolic ward on a 300-kcal diet of hydrolyzed collagen with added tryptophan developed transient arrhythmias that were recorded during 24-h Holter monitoring. These arrhythmias, many of which were clinically significant and potentially life-threatening (e.g., ventricular tachycardia and 1st- and 2nd-degree heart block), were not detected by standard 12-lead electrocardiograms performed weekly during the experimental period.

The deaths presented here occurred in individuals after various extreme weight reduction regimens. These regimens are based on the concept that by feeding small amounts of protein to a person with restricted caloric

intake, the negative nitrogen balance associated with strict fasting will be prevented and lean body mass will be "spared". At the same time, the rapid weight loss seen with strict fasting can be achieved. Evidence in support of this concept is based on nitrogen balance studies and measurements of total body potassium as an index of lean body mass (39–43). The localized loss of lean tissue seen in our cases and certain theoretical and experimental considerations raise serious questions about the safety of the very low calorie weight reduction regimens consisting mainly of protein.

Limited numbers of patients have been studied with reference to nitrogen balance, and there are limited published data specifically addressing the question of protein preservation, although several large series have been published documenting the success of such regimens in achieving notable weight loss (44, 45). Nitrogen balance can be achieved for the short term, especially after a period of negative nitrogen balance (42). It has not been satisfactorily shown that such balance can be maintained for prolonged periods in outpatients or that balance can be equated with protein preservation. This is of particular importance given the documented capability of obese individuals to achieve nitrogen balance more efficiently than lean individuals on restricted diets (46). It is not known at what stage an obese individual losing weight "breaks through" and begins to act like a lean one.

In a single study where patients had nitrogen balances performed after up to a year of dieting, two of three individuals were losing nitrogen (40). Genuth et al. (47) found a continued tendency toward nitrogen loss, especially among men. Baird et al. (48) reported achieving nitrogen balance during prolonged studies of low calorie chemically defined diets, however, they did not correct for fecal and skin losses and noted that there were marked individual variations in the balance studies.

Internal shifts of protein may not be reflected in overall balance studies, and it is possible that some organ systems may be spared at the expense of others. Biochemical studies in animals suggest that at low caloric intake certain enzyme systems and structural proteins are affected differently and that some organs have a net protein uptake (49–52). The distinction between healthy adaptation and pathological change remains unclear. Animal studies using very low calorie protein diets for prolonged periods and which address internal biochemical changes have not been published.

All of the experimental work cited above supporting the use of very low calorie weight reduction regimens has been based on using protein of high biological quality. There are no data in the literature supporting the claim that use of low quality protein products such as the collagen derived liquid protein is effective in maintaining body protein. Bolinger et al. (53) specifically state that collagen derivatives are ineffective. Although liquid protein was used in a majority of our cases, several of the individuals in our study used products based on higher quality protein, a fact raising further questions about this general approach to weight reduction.

Recommendations for micronutrient supplementation of the very low calorie regimens have, with few exceptions, been largely empirical. No studies have been published looking at the effect of these regimens on vitamin, electrolyte, and trace mineral requirements. To assume that commercially available vitamin-mineral preparations, designed as supplements to normal diets, are adequate during the altered metabolism of near-starvation may not be warranted. Such supplementation is likely to give a false sense of security to both dieters and their physicians.

The long-term effects, if any, of such highly restrictive dietary regimens are unknown. There is epidemiological and experimental evidence that near-starvation may adversely affect the future course of patients with hypertensive and cardiovascular diseases (54, 55). There have also been suggestions that chronic malnutrition may play a role in certain poorly understood cardiomyopathies, although this point remains controversial (18).

At present it is not possible to determine whether deaths associated with the use of very low calorie weight reduction regimens consisting entirely or largely of protein can be prevented by some as yet unknown modifications of the regimens, or whether they represent the inevitable outcome of a pro-

longed period of near-starvation. Until resolution of these viewpoints can be made, we recommend that all very low calorie weight reduction regimens be limited to use in research settings controlled by protocols approved by committees on human experimentation and only with the informed written consent of the participants.

References

1. Linn R, Stuart SL. The last chance diet. Secaucus, NJ: Lyle Stuart, Inc, 1976.
2. Michiel RR, Sneider JS, Dickstein RA, Hayman H, Eich RH. Sudden death in a patient on a liquid protein diet. N Engl J Med 1978;1005–7.
3. Singh BN, Gaarder TD, Kanegae T, Goldstein M, Montgomerie JZ, Mills H. Liquid protein diets and torsade de pointes. JAMA 1978;240:115–9.
4. Brown JM, Yetter JF, Spicer MJ, Jones JD. Cardiac complications of protein-sparing modified fasting. JAMA 1978;240:120–2.
5. Isner JM, Sours HE, Paris AL, Farrans VJ, Roberts WC. Sudden unexpected death in avid dieters using the liquid protein modified fast diet. Circulation 1979;60:1401–12.
6. Bazett HC. An analysis of the time relations of electrocardiograms. Heart 1970;7:353–67.
7. Amad KH, Brennen JC, Alexander JK. The cardiac pathology of chronic exogenous obesity. Circulation 1965;32:740–5.
8. Keys A, Henschel A, Taylor HL. The size and function of the human heart at rest in semi-starvation and in subsequent rehabilitation. Am J Physiol 1947;150:153–69.
9. Smythe PM, Swanepoel A, Campbell JAH. The heart in kwashiorkor. Br Med J 1962;1:67–73.
10. Alleyne GAO. Cardiac function in severely malnourished Jamaican children. Clin Sci 1966;30:553–62.
11. Simonson E, Henschel A, Keys A. The electrocardiogram of man in semistarvation and subsequent rehabilitation. Am Heart J 1948;55:584–602.
12. Wharton BA, Howells GR, McCance RA. Cardiac failure in kwashiorkor. Lancet 1967;2:384–7.
13. Cruickshank EK. In: Waterlow JC, ed. Protein malnutrition. Proceedings of a conference in Jamaica (1953). Cambridge: University Press, 1955;107.
14. Gopalan C. In: Waterlow JC, ed. Protein malnutrition. Proceedings of a conference in Jamaica (1953). Cambridge: University Press, 1955;126–31.
15. Bablet J, Normet L. Les lésions histopathologiques de la bouffisure d'Annam. Bull Acad Med (Paris) 1937;117:242.
16. Stein J, Fenigstein H. Anatomie pathologique de la maladie de famine. In: Apfelbaum E, ed. Maladie de famine. Recherches clinques sur la famine executées dans le ghetto de Varsovie en 1942. Warsaw: American Joint Distribution Committee, 1946;21–77.
17. Schnitker MA, Mattman PE, Bliss TL. A clinical study of malnutrition in Japanese prisoners of war. Ann Intern Med 1951;35:69–96.
18. Ramalingaswami V. Nutrition and the heart. Cardiologia 1968;52:57–68.
19. Piza, J, Troper L. Cespedes R, Miller JH, Berenson GS. Myocardial lesions and heart failure in infantile malnutrition. Am J Trop Med Hyg 1971;20:343–55.
20. Wharton BA, Balmer SE, Somers K, Templeton AC. The myocardium in kwashiorkor. Q J Med 1969;38:107–16.
21. Chauhan S, Nayak NC, Ramalingaswami V. The heart and skeletal muscle in experimental protein malnutrition in rhesus monkeys. J Pathol Bact 1965;90:301–9.
22. Racela AS, Grady HJ, Higginson J, Svoboda DJ. Protein deficiency in rhesus monkeys. Am J Pathol 1966;49:419–44.
23. Follis RH, Orent-KE, McCollum EV. The production of cardiac and renal lesions in rats by a diet extremely deficient in potassium. Am J Pathol 1942;18:29–39.
24. Molnar Z, Larsen K, Spargo B. Cardiac changes in the potassium depleted rat. Arch Path 1962;74:339–47.
25. Weiss DL, Surawicz B, Rubenstein I. Myocardial lesions of calcium deficiency causing irreversible myocardial failure. Am J Pathol 1966;48:653–66.
26. Heggtveit HA, Herman L, Mishra RK. Cardiac necrosis and calcification in experimental magnesium deficiency. Am J Pathol 1964;45:757–82.
27. Seelig MS, Heggtveit HA. Magnesium interrelationships in ischemic heart disease. A review. Am J Clin Nutri 1974;27:59–79, 1974.
28. Burch GE, Giles TD. The importance of magnesium deficiency in cardiovascular disease. Am Heart J 1977;94:649–57.
29. VanVleet JF, Ferrans VJ, Ruth GR. Ultrastructural alterations in nutritional cardiomyopathy of selenium-vitamin E deficient swine. I. Fiber lesions. Lab Invest 1977;37:188–200.
30. Shields GS, Coulson WF, Kimball DA, Carnes WH, Cartwright GE, Wintrobe MM. Studies on copper metabolism XXXII. Cardiovascular lesions in copper deficient swine. Am J Pathol 1962;41:603–21.
31. Leigh LC. Changes in ultrastructure of cardiac muscle in steers deprived of copper. Res Vet Sci 1975;18:282–7.
32. Mills CF, Dalgarno AC, Wenham G. Biochemical and pathological changes in tissues of Friesian cattle during the experimental induction of copper deficiency. Br J Nutr 1976;35:309–31.
33. Apfelbaum E, Pakszwer R. Zarchi J, Heller A, Askansas Z. Recherches cliniques sur la pathologie du système circulatoire dans la cachexie de famine. In: Apfelbaum E, ed. Maladie de famine. Recherches cliniques sur la famine executées dans le ghetto de Varsovie en 1942. Warsaw: American Joint Distribution Committee, 1946;189–225.
34. Ellis LB. Electrocardiographic abnormalities in severe malnutrition. Br Heart J 1946;8:53–61.
35. Hellerstein HK, Santiago-Stevenson D. Atrophy of the heart: a correlative study of eighty-five proved cases. Circulation 1950;1:93–126.
36. Burch GE, Phillips JH, Ansari A. The cachectic heart. Dis Chest 1968;54:403–9.
37. Garnett ES, Barnard DL, Ford J. Goodbody RA, Woodehouse MA. Gross fragmentation of cardiac

myofibrils after therapeutic starvation for obesity. Lancet 1969;1:914–6.
38. Sandhofer F, Dienstl F, Bolzano K, Schwingshackl H. Severe cardiovascular complication associated with prolonged starvation. Br Med J 1973;1:462–3.
38a. Lantigua RA, Amatruda JM, Biddle TL, Forbes GB, Lockwood DH. Cardiac arrhythmias associated with a liquid protein diet for the treatment of obesity. N Engl J Med 1980;303:735–8.
39. Apfelbaum M, Boudon P, Lacatis D. Effets métaboliques de la diete protidique chez 41 sujets obèse. Presse Med 1970;78:1917–20.
40. Bistrian BR, Blackburn GL, Flatt JP, Sizer J, Scrimshaw NS, Sherman M. Nitrogen metabolism and insulin requirements in obese diabetic adults on a protein-sparing modified fast. Diabetes 1976;25:494–504.
41. Bistrian BR, Blackburn GL, Stanbury JB. Metabolic aspects of a protein-sparing modified fast in the dietary management of Prader-Willi obesity. N Engl J Med 1977;296:774–9.
42. Bistrian BR, Winterer J, Blackburn GL, Young V, Sherman M. Effect of protein-sparing diet and brief fast on nitrogen metabolism in mildly obese subjects. J Lab Clin Med 1977;89:1030–5.
43. Marliss EB, Murray FT, Nakhooda AF. The metabolic response to hypocaloric protein diets in obese man. J Clin Invest 1978;62:468–79.
44. Vertes V, Genuth SM, Hazelton IM. Supplemented fasting as a large-scale outpatient program. JAMA 1977;238:2151–3.
45. Lindner RG, Blackburn GL. Multidisciplinary approach to obesity utilizing fasting modified by protein-sparing therapy. Obesity Bariatr Med 1976;5: 198–216.
46. Van Itallie TB, Yang M-U. Nitrogen balance during weight reduction: effect of body stores of protein and fat. In: Bray GA, ed. Recent advances in obesity research II. London: Newman Publishing, 1978:379–84.
47. Genuth SM, Castro JH, Vertes V. Weight reduction in obesity by outpatient semistarvation. JAMA 1974;230:987–91.
48. Baird IM, Parsons RL, Howard AN. Clinical and metabolic studies of chemically defined diets in the management of obesity. Metabolism 1974;23:645–57.
49. Waterlow JC. Factors influencing protein metabolism in the organism. Protein malnutrition and replenishment with protein in man and animals. In: Gross F, ed. Protein metabolism. Berlin: Springer Verlag, 1962;90–108.
50. Waterlow JC. The adaptation of protein metabolism to low protein intakes. In: McCance RA, Widdowson EM, eds. Calorie deficiencies and protein deficiencies. Boston: Little, Brown and Co., 1968;61–73.
51. Ramalingaswami V. Perspectives in protein malnutrition. Nature 1964;201:546–51.
52. Nettleton JA, Hegsted DM. Protein-energy interrelationships during dietary restriction: effects on tissue nitrogen and protein turnover. Nutr Metabol 1975;18:31–40.
53. Bolinger RD, Lukert BP, Brown RW, Gueuara L, Steinberg R. Metabolic balance of obese subjects during fasting. Arch Intern Med 1966;118:3–8.
54. Brozek J, Chapman CB, Keys A. Drastic food restriction: effect on cardiovascular dynamics in normotensive and hypertensive conditions. JAMA 1968;137:1569–74.
55. Smith GS, Smith JL, Mameesh MS, Simon J, Johnson BC. Hypertension and cardiovascular abnormalities in starved-refed swine. J Nutrition 1964;82: 173–82.