RESEARCH NEEDS
IN MANAGEMENT OF OBESITY
BY SEVERE CALORIC RESTRICTION

December, 1979

Prepared for

BUREAU OF FOODS
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D.C. 20204

under

Contract Number FDA 223-75-2090
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by

John M. Talbot, M.D.

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This technical report was prepared for the Bureau of Foods, Food and Drug Administration (FDA), by John M. Talbot, M.D., Senior Medical Consultant, LSRO, FASEB, in accordance with the provisions of Contract No. FDA 223-75-2090.

The LSRO acknowledges the contributions of the investigators and consultants who assisted with this study. The report reflects the opinions expressed by participants in an ad hoc study group that met at the Federation on November 30 and December 1, 1978. A judicious attempt has been made to incorporate the various viewpoints and opinions. The report was reviewed by these consultants; however, the listing of their names in Section XII does not imply that they endorse the study. The author and LSRO accept responsibility for the contents of the report.

The report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to FDA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
SUMMARY

Sixteen white women and one white man between 22 and 52 years-of-age died suddenly and unexpectedly in 1977 or early 1978 during or shortly after completing massive, rapid, weight reduction resulting from prolonged, strict adherence to very low-calorie protein diets. In most cases, the protein used was a solution of hydrolysed gelatin or collagen, commonly referred to as "liquid protein" or "predigested protein" product. The decedents had been free from manifest cardiovascular disease, and, except for gross obesity, were considered healthy. The deaths were all associated with demonstrated or presumed cardiac conduction disturbances and ventricular tachydysrhythmias that proved refractory to therapy. The estimated mortality rate for the decedent women of 59 per 100,000 per year contrasted sharply with about 2 per 100,000 per year for nondieting white women in the same age range who died from cardiac disorders of a similar nature.

Prolonged total fasting supplemented with vitamins, minerals, and noncaloric liquids has been used in the past two decades for treatment of severe obesity by several medical clinics. In most carefully supervised programs, it results in rapid weight loss and has proved safe. However, a few patients have had serious side-effects and complications including rare instances of death. Most authorities currently favor other dietary regimens over total fasting for major weight reduction.

The protein-sparing modified fast described in the medical literature differs from total fasting by providing 1.25 to 1.5 g per kg ideal body weight of high-quality protein daily. It has been shown to diminish the loss of lean body mass during prolonged fasting, thus improving nitrogen balance. Available data suggest that, with one exception, it has been used safely in the treatment of approximately 2600 severely obese adults who followed the regimen for 60 days or more and lost at least 0.5 lb per week. When used in conjunction with careful clinical monitoring, dietary counseling, prescribed exercise, and behavioral therapy, it is said to achieve long-term beneficial results. However, some authorities consider it an investigative-type procedure, not yet ready for widespread use on an outpatient basis.

So-called "predigested proteins" including "liquid proteins" marketed as an aid to rapid weight reduction reached peak popularity in 1977. When used as the sole source of calories, typical daily intakes of these products provide about 300 to 500 kcal. These products are a poorly defined mixture of amino acids, peptides, and polypeptides. Sample analyses revealed harmless levels of such elements as arsenic, cadmium, and lead, and no significant amounts of possible environmental contaminants such as pesticides. Most samples lacked certain essential amino acids or
contained them in inadequate amounts. They did not sustain growth in standardized rat feeding studies designed to determine protein efficiency ratios of several protein sources.

With further reference to the 17 dieters, the events shortly preceding hospitalization and death of those who were hospitalized fitted a pattern including syncopal attacks, weakness, collapse, and intractable ventricular tachydysrhythmias. Electrocardiographic manifestations typically included prolongation of the QT interval, low voltages, ventricular tachycardia, and ventricular fibrillation.

Repeated, independent examination of the heart specimens showed only one of the original six diagnoses of myocarditis could be sustained. Consistent findings in all the examined hearts included overall decrease in cardiac mass, fiber-size attenuation with marked variation and an absolute reduction in size, disappearance of myofibrils, and excessive lipofuchsin deposition. Similar findings have been noted in cachectic patients who died of non-diet-related causes. One individual had unequivocal myocarditis, with lymphocytic infiltration, but no history of a preceding viral infection. Several of the heart specimens had foci of five or six inflammatory cells that were judged to be insufficient evidence to support a diagnosis of cardiac necrosis or myocarditis, and their significance remains to be identified. Similar manifestations have been reported in otherwise normal hearts of persons dying of trauma.

The exact pathogenesis of the fatal cardiac disturbances could not be identified from the available evidence; however, the commonly observed QT interval prolongation appeared to be the underlying cause of the associated dysrhythmias. The origin of the prolonged QT intervals is obscure in all but one of the decedents, in whom it may have been congenital.

One consultant regarded the deaths as idiosyncratic while another, referring to known pathologic effects of starvation on the hypothalamic-pituitary axis, suggested that unidentified central nervous system effects may have occurred that led to disturbances of the electrical system of the heart.

Possible mineral and electrolyte deficiencies, which are known to affect cardiac function, were difficult to assess because of inadequate laboratory data on most of the decedents, and a lack of certain basic scientific knowledge relating deficiencies of these micronutrients to the development of pathologic lesions. Potassium supplements in doses ranging from 3 to 75 mEq per day were taken by 15 of the 17 dieters, and 13 took additional mineral preparations which varied markedly in content. Borderline hypokalemia was reported in two of the dieters on at least one occasion; however, this was considered clinically insignificant. Furthermore, the notion that hypokalemia may lead to fatal cardiac
dysrhythmias in the human lacks scientific documentation. Phosphorus depletion may be associated with cardiac dysfunction, especially during refeeding of fasted or malnourished persons without phosphorus supplementation; but, with one exception, serum phosphate levels, when measured, were within normal range. A majority of the dieters were thought to have consumed adequate phosphate via noncaloric cola beverages. The available evidence does not support possible mineral and electrolyte deficiencies as a significant factor in the 17 deaths.

Attempts to demonstrate the cardiac lesions found in the decedents in fasted rats fed "predigested protein" have been negative or equivocal except for a recent report of pronounced dysrhythmias.

The effects of starvation include amino acid deficiencies, loss of lean body mass, and negative nitrogen balance. In acute starvation, myocardial protein synthesis decreases; however, little is known about the effects of amino acid availability on protein degradation in the heart. Hypothetically, such amino acid deficiencies may lead to myocardial protein degradation sufficient to disturb cardiac conduction and contractility. Such effects may complicate the prolonged use of protein products as the sole source of a 300 to 500 kcal per day diet.

The apparent influence of sex, race, and age suggested by the epidemiologic data could not be confirmed by the available information, and was thought to represent reporting artifacts. Four additional observations were considered noteworthy. First, recent preliminary human data show a greater cumulative nitrogen deficit during 40 days of protein-supplemented fasting using "predigested protein" than with high-quality protein. Second, the high average rate of weight loss and the reported avidity with which most of the dieters followed their restrictive regimens may be significant as it is apparently atypical of persons on such modified fasts. Third, six of the dieters died after the start of refeeding. Fourth, the apparent tendency for the less obese to die sooner than the more obese suggested that a maximum safe period exists for some individuals for this mode of weight reduction and that it may vary directly with the degree of obesity.

The most compelling fact in this review is that 17 basically healthy but obese adults died suddenly and unexpectedly of ventricular tachydysrhythmias associated with prolonged QT intervals and low voltages, during or shortly after completing massive, rapid, weight reduction by fasting supplemented with protein products. A definite cause-effect relationship could not be established between the use of such products and the deaths.

The specific etiology and pathogenesis of the fatal cardiac complications could not be established on the basis of available data, suggesting that additional research should be undertaken. Suggestions for future investigation are offered.
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ABBREVIATIONS USED IN THIS REPORT

AMP  adenosine monophosphate
ATP  adenosine triphosphate
BCAA branched-chain amino acids
BMR basal metabolic rate
B-cell bursal lymphocyte
BSP sulfobromophthalein
CDC Center for Disease Control
DOA dead on arrival
ECG electrocardiogram
Em resting transmembrane potential
FDA Food and Drug Administration
FFA free fatty acid
GFR glomerular filtration rate
HANES Health and Nutrition Examination Survey, United States
IgA immunoglobulin A
IgG immunoglobulin G
IgM immunoglobulin M
LQTS long QT syndrome
3-MeHis 3-methylhistidine
PAH p-aminohippuric acid
PBI protein-bound iodine
PCM protein-calorie malnutrition
PG prostaglandin
PGA prostaglandin A
PG E1 prostaglandin E1
PG E2 prostaglandin E2
PSMF protein-sparing modified fast
QRS QRS complex of the ECG; represents ventricular depolarization
QT part of the ECG from start of ventricular depolarization to end of repolarization
ST the S-T segment; part of ECG tracing immediately following ventricular depolarization
T-wave part of ECG tracing corresponding to ventricular repolarization
T-cell thymic lymphocyte
T3 triiodothyronine
T4 thyroxine
USPHS United States Public Health Service
U-wave an ECG deflection that may occur in delayed repolarization
17-KS 17-ketosteroid
17-OH-CS 17-hydroxycorticosteroids
I. INTRODUCTION

Serious questions concerning the safety of weight reduction regimens with very low-calorie, high-nitrogen diets arose as a result of unexpected deaths in 1977 and early 1978 of grossly obese adults who were reducing by means of severely restricted energy intakes of approximately 300 kcal per day from such diets. The dieters adhered strictly to the regimens for prolonged periods and, with few exceptions, used protein products derived from hydrolysates of collagen or gelatin. In a few instances, protein of higher biologic value was used. However, because of the predominant use by the decedents of the gelatin- or collagen-derived products, this report emphasizes the possible role of such products. This emphasis does not imply that the association between illness or death and the use of such products is exclusively limited to hydrolysed gelatin- or collagen-derived products.

Obesity exists when energy intake exceeds energy requirements for growth and physical activity and when the excess calories are stored as fat in adipose tissue (Thorn and Cahill, 1977). Obesity in the United States is excessively prevalent. It is considered by many medical authorities to be the most important public health problem and the number one nutritional problem in this country.

Historically, treatment of obesity has focused mainly on reduction of energy intake by total or partial fasting and increasing energy expenditure by exercise. A host of "special" weight reduction diets has come and gone along with the use of anorectic drugs, surgical procedures, and behavior modification. Regardless of the approach, loss of weight, while highly desirable, is not easily achieved and maintained. In addition, drastic weight reduction may have serious metabolic and behavioral sequelae.

While there is no question of the efficacy of total fasting in mobilizing fat and reducing body weight, the accompanying loss of body protein and essential micronutrients may compromise this approach. An important refinement of total fasting has been the development of the protein-sparing modified fast (PSMF)*, which mitigates the nitrogen imbalance that is characteristic of total fasting. Experience with PSMF techniques has been favorable in several leading centers of bariatric medicine over the past two decades. Most investigators and clinicians consider close medical supervision by experts skilled in PSMF procedures as a mandatory aspect of the safe use of PSMF. Such supervision includes prescreening of patients to detect contraindicating conditions and frequent clinical assessment with laboratory backup during the fasting.

*Abbreviations used in this report are listed on page x.
Reports of increasingly favorable clinical experiences with PSMF and related techniques led to widespread awareness of the success of such treatments by the general public. In addition, various "do-it-yourself" techniques were spawned by the favorable results with PSMF. One such approach is based upon use of "predigested protein" products. These products are frequently termed "liquid proteins" although they are marketed as powders, wafers, tablets, and capsules in addition to the liquid forms. Typically these products are formulations containing enzymatically or acid hydrolysed collagen or gelatin. Over 200 brand name, protein products became available as over-the-counter items in drug, grocery, and health food stores (Schucker and Gunn, 1978).

Use of the "predigested protein" products became popular in the United States in recent years, particularly after publication of "The Last Chance Diet" (Linn and Stuart, 1976). Estimates in 1977 suggest that close to 100,000 white females, 25 to 44 years old, used a "predigested protein" product for at least one month as a sole source of nutrition (Schucker and Gunn, 1978).

The widespread marketing of protein supplements as freely available over-the-counter items and the rapid popularity of the protein product-supplemented fast as a magical new "do-it-yourself" way to lose weight generated major concern not only in the Congress and federal regulatory agencies, but also among medical authorities. These concerns are associated with the safety and welfare of users as well as the abuse of an experimental approach to treatment of obesity (PSMF) and its conversion to a weight reduction scheme widely available and inadequately controlled (Blackburn, 1978a; Van Itallie, 1978; Vertes et al., 1977a,b).

Increasing concern and recognition of possible life-threatening complications of prolonged use of protein products led to investigations by the Center for Disease Control and the Food and Drug Administration. As of mid-1978, 58 deaths had been reported to be associated with the use of very low-calorie protein diets used for weight reduction. Of this group, 17 grossly obese but otherwise healthy adults (16 white women and 1 white man) 25 to 44 years old, who were reducing body weight by strict adherence to a fasting regimen supplemented by small daily intakes of protein products, died suddenly of cardiac dysrhythmias and arrest (Center for Disease Control, 1979). A summary and details of the cardiac pathology of the 17 confirmed heart-related deaths are given in Appendix I. These unexpected deaths led, in December 1977, to the formation of the U.S. Public Health Service Protein Diet Task Force (Food and Drug Administration, 1977a); to Congressional hearings such as that by Congressman Waxman (U.S. Congress, 1978); and to a proposed FDA rule that would require warning labels on protein products (Food and Drug Administration, 1977b, 1978).
The USPHS Protein Diet Task Force consists of representatives of the Food and Drug Administration, the Center for Disease Control, the National Institutes of Health, and the National Center for Health Statistics. Among the actions initiated by the Task Force were:

- CDC review of data from each fatal case;
- development of epidemiological data such as estimates of total numbers of serious users of "predigested protein" products and cardiac death rates among women who had not used protein-supplemented fasting;
- emphasis on the field compliance program of inspection of manufacturers of "predigested protein" products;
- analysis and tests of product samples;
- FDA intramural studies on obese rats; and
- a request that LSRO conduct a study to identify the immediate and long-term research needs on the health problems associated with very low-calorie protein diets and "predigested protein" products used in rapid weight loss.
II. SCOPE OF THE STUDY

In response to the actions initiated by the USPHS Protein Diet Task Force, the FDA requested that LSRO undertake a study to meet the needs of the USPHS Protein Diet Task Force with respect to suggestions for immediate and long-term research. This study was initiated in June 1978, and its primary objective has been to identify research necessary for evaluation of the health aspects of using diets that provide less than 800 kcal per day for rapid weight reduction. Emphasis on possible serious adverse effects of such regimens was considered essential as were answers to the following questions:

- What are the metabolic and pathophysiological consequences of total caloric deprivation?

- What are the metabolic and pathophysiological consequences, particularly cardiopathological alterations, of severe caloric restriction; that is, diets providing less than 800 kilocalories per day for voluntary rapid weight reduction?

- What research is necessary to identify, delineate, and characterize the alterations that underlie adverse health effects, including life-threatening pathological changes, resulting from the use of low-calorie diets for rapid weight reduction?

- Are there special advantages or disadvantages of high-nitrogen low-calorie dietary regimens in treating obesity as compared with other types of low-calorie diets or total caloric deprivation?

- Do the following factors influence the safety and efficacy of diets providing less than 800 kilocalories per day for rapid weight reduction?
  
  a. race, age, and sex
  
  b. physiological states (e.g., adolescence, pregnancy, postmenopausal state)
  
  c. various disease states (hypertension, thyroid disorders, coronary heart disease, diabetes)
  
  d. degree of obesity
  
  e. genetic predisposition to cardiac dysrhythmias
f. state of immunological competence

g. duration and regimen of diets

h. degree and rate of weight loss

i. drugs

- What research strategies should be evolved to identify those factors most likely to influence the safety and efficacy of diets for rapid weight reduction?
III. OVERVIEW OF OBESITY

A. DEFINITION

Webster defines obesity as, "a bodily condition marked by excessive generalized deposition of fat". The Council on Foods and Nutrition of the American Medical Association (1973) defined it as "...an accumulation of fat in undesirable excess". Obesity results when energy intake exceeds the energy requirements of the body for growth and physical activity, the excess calories being stored as fat (Thorn and Cahill, 1977). However, this basic metabolic fact fails to explain the elusive causal factors of obesity, and it probably is a fact that some individuals grow corpulent more readily than others. Although not completely valid, obesity is often defined as being 20 to 30 percent over so-called ideal body weight; thus moderate degrees of overweight under 20 to 30 percent are not necessarily obesity. Individuals with large frames and bulky muscles may be overweight according to arbitrary standards, but not obese. Stated otherwise, a body fat content greater than about 15 percent of body weight in a 60 kg individual represents obesity (Bray, 1975a). Morbid or massive obesity may be defined as weight at least twice the ideal weight for height, sex, and age (Blackburn, 1978b).

Among the etiologic factors involved in obesity, hormone imbalances and disturbances of endocrine gland function are probably least important, involving only a small fraction of obese individuals. Cushing's disease and noninsulin-dependent maturity-onset diabetes are examples of disorders that are associated with obesity. Genetic predisposition is thought to influence the incidence of obesity, but it is difficult to separate this tendency from familial and cultural practices in which foods, including high-calorie items, are consumed in excess. In affluent countries, the abundance of rich foods and beverages seems to promote overeating, and psychologic factors associated with the stresses of modern living appear to induce overindulgence in alcohol and food by some. Such factors, as well as an increasingly sedentary lifestyle, appear significant in the etiology of obesity.

The lack of a completely acceptable, practical classification of the obesities is related in part to the obscurity of their etiologies and the fact that they are signs of underlying diseases or disorders, rather than being diseases themselves. This subject was recently reviewed by the Editorial Board of "Obesity in Perspective" (Bray, 1975a), and Table 1 lists some of the systems of classification. While most of these schemes have merit, none is completely satisfactory. Consequently, the Editorial Board (Bray, 1975a) recommended a problem-oriented approach to the clinical classification of the obesities. This provides for a comprehensive data base for description of the
patient's particular syndrome, guides for both anatomic and etiologic classification, and a personalized listing of problems that may influence the therapeutic approach. An additional advantage of this recommended scheme would be the systematic accumulation of data needed for clinical investigation of obesity and its management.

---

Table 1. Some Historical Approaches to Classifying Obesity (Bray, 1975a)

---

I. Noorden's Classification
   A. Exogenous
   B. Endogenous

II. Jarlov's Classification
   A. The Hypertrophic Type (Exogenous)
   B. Myxematoid
   C. Lipomatoid

III. Anatomic Classification
   A. Hypercellular -- Hypertrophic
   B. Hypertrophic

IV. Kemp's Classification by Age of Onset
   A. Childhood
   B. Young Adult
   C. Pregnancy
   D. Middle Life

V. Mayer's Experimental Models
   A. Regulatory
   B. Metabolic

VI. Etiologic Classification in Animal Models
   A. Dietary
   B. Physical Inactivity
   C. Endocrine
   D. Hypothalamic
   E. Genetic
Accurate measurement is one of the problems of defining obesity and determining its prevalence. Although a number of acceptable methods are available for measuring obesity including direct estimates by using inert gases and indirect methods such as body density, total body water, or total body potassium, these are laboratory procedures not readily available to the average clinician. Height-weight-age standards for men and women are most frequently used. These are somewhat arbitrary and inaccurate for assessing adiposity; however, they offer the most practical approach in regular clinical practice. Since it is desirable to improve accuracy, other readily available, quick, and inexpensive methods are of interest. For instance, the skinfold thickness measurements appear to offer a reasonable approach, and their reliability may be expected to improve with better training in techniques, standardization of calipers and procedures, further validation with measures of body fat of greater specificity, and increased experience with different racial and cultural groups (Bray, 1975b; Garn and Clark, 1976).

B. PREVALENCE

Although acceptable data are scarce, it is widely held that the prevalence of obesity is high. In a review of various estimates of its prevalence in the United States, the Public Health Service, in 1966, noted several reports suggesting that obesity was increasing and that food abundance, labor-saving devices, and sedentary life-styles were contributing factors (U.S. Department of Health, Education, and Welfare, 1966). The report concluded that no data were available to support estimates of the incidence of obesity in the total population or in any particular population group. Christakis (1975) alluded to estimates of 40 to 50 percent of certain adult populations as obese. Prevalence data on adult obesity from the First Health and Nutrition Examination Survey, United States, 1971-1972 (Abraham et al., 1975) are classified by age group, sex, and race, but do not permit generalization to the adult population of the United States. Nevertheless, the authors concluded that, based on HANES criteria, the prevalence of adult obesity is high and is relatively higher for women, particularly black women. In the age group 45 to 74 years the prevalence of obesity in black women was 32.4 percent compared with 7.7 percent of black men in the same age group. Sixteen percent of white men and 18.9 percent of white women 20 to 44 years old were obese.

Estimates from HANES 1971-1974 indicated that among men 20 to 74 years-of-age in the United States, 4.9 percent or about 2.8 million were severely obese (Abraham and Johnson, 1978). Among women in the same age range, 7.2 percent, or about 4.5 million were severely obese. In these studies, severe obesity was defined statistically as the skinfold thickness measurement (triceps plus subscapular) greater than the 95th percentile of such measurements for men and nonpregnant women aged 20 to 29 years.
A gross estimate of the total numbers of obese persons in the United States from another source was from 40 to 80 million (19 to 38 percent of the population) (Stuart and Davis, 1972).

Recent data from the American Cancer Society are presented below.

Table 2. Excess Weight in U.S. Citizens 29 to 90 Years-of-age (Lew and Garfinkel, 1979)

<table>
<thead>
<tr>
<th>Extent of overweight (% above standard)</th>
<th>Percent of surveyed population</th>
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<tr>
<td></td>
<td>men&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10 - 19</td>
<td>14.0</td>
</tr>
<tr>
<td>20 - 29</td>
<td>4.0</td>
</tr>
<tr>
<td>30 - 39</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;40</td>
<td>0.5</td>
</tr>
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<sup>a</sup>336,442 men  <sup>b</sup> 419,060 women

Obesity is thought to be related generally to increased morbidity and mortality. It has been associated with a series of diseases and disorders including hypertension; cardiovascular, respiratory, and gallbladder diseases; diabetes, hyperuricemia, and gout; renal problems; damage to weight-bearing bones and joints; increased surgical risk; increased risk of cancer, especially colonic; dysmenorrhea; and psychologic consequences ranging from feelings of inferiority to serious incapacitation (Bray, 1970; Bray et al., 1972; Heaton and Williamson, 1978; Hirsch, 1975; Kempner et al., 1975).

Unpublished data discussed during the LSRO ad hoc review group meeting suggest that mortality in a group of grossly obese males compared with expected mortality for all United States males was >11-fold in the age range 25 to 34, >5-fold for ages 35 to 44,
3-fold for ages 45 to 54, and about 2.5-fold from 55 to 74 years-of-age. Provisional data from the New Build and Blood Pressure Study support the association of gross obesity with increased mortality rates (Lew, 1978). For example, men 40 percent above average weight showed an excess mortality of 50 percent from all causes, 60 percent for coronary disease and cerebral hemorrhage, 120 percent for digestive diseases, and >400 percent for diabetes. Mortality rates for obese women were somewhat lower than for obese men.

C. TREATMENT OF OBESITY

1. Total fasting

Although, as noted by Apfelbaum (1976), "Total starvation has been used for centuries to purify the body before approaching a sacred place and also to obtain health by the expiation of sin," therapeutic fasting as a treatment for "refractory" obesity was first recommended in 1915 (Anonymous, 1978). It has been the subject of reports of clinical investigations such as those of Bloom (1959), Drenick (1972), Duncan et al. (1965), Johnson and Drenick (1977), Oster et al. (1977), Runcie and Hilditch (1977), and Thomson et al. (1966). While there is no question of the efficacy of total fasting in mobilizing fat and reducing body weight, the accompanying loss of body proteins and essential micronutrients as well as other side-effects has raised serious questions regarding the relative safety and desirability of total fasting as a therapeutic procedure.

2. Protein-sparing modified fast*

Studies of protein-sparing led to the introduction of the protein-sparing modified fast as a refinement aimed at mitigating the nitrogen loss of total fasting (Apfelbaum, 1976; Apfelbaum et al., 1967; Baird et al., 1979; Blackburn et al., 1973, 1975; Bolinger et al., 1966; Genuth et al., 1974; Howard and Baird, 1977; Lindner and Blackburn, 1976; Marliss et al., 1978; Vertes et al., 1977a; and Willard et al., 1978). Medical authorities in the PSMF field stress the importance of a multidisciplinary program to ensure patient safety and success in weight reduction and control. Such programs feature: (a) strict adherence to a daily food intake of high-quality protein limited to 1.25 to 1.5 g per kg ideal body weight; (b) daily supplements of vitamins, magnesium, potassium, calcium, and sodium; (c) selected physical exercise; (d) behavioral therapy to alter food consumption habits and attitudes; and (e) close medical supervision. The latter is

*Range of total daily caloric intake approximately 300 to 450 kcal.
considered mandatory and should include careful medical preselection of patients to screen out those with contraindications for PSMF (p.15) as well as periodic medical examinations, and close laboratory monitoring including chemical assays of urine constituents, urine specific gravity and electrocardiograms during the treatment period.

To date, the reported experiences with the PSMF in some medical clinics have been favorable, and the use of the PSMF appears to be growing in popularity among clinics specializing in bariatric medicine as well as with individual clinicians. However, not all authorities agree that the procedure has been proved safe and superior to other methods for treating obesity (Felig, 1978; Marliss, 1978). For example, Felig (1978) suggests that, in view of certain limitations of knowledge about its effects, PSMF should be considered an experimental procedure not yet ready for unrestricted outpatient use. Other investigators also question the safety of PSMF even when used in well regulated medical programs (Foege, 1978; Van Itallie, 1978). Bray et al. (1972) summed up one school of thought about therapeutic starvation and modified fasting in the treatment of obesity: "Rapid and steady weight loss can be achieved by semistarvation or total fasting, but these methods are complicated by hypotension and electrolyte imbalances as well as by metabolic derangements owing to protein loss and the use of body fat as the primary fuel source".

During the LSRO ad hoc review meeting, preliminary data were discussed from clinical trials in which obese patients were treated using fasting regimens supplemented daily with 1.5 g per kg ideal body weight of a high-quality protein versus a hydrolysed product from low-quality protein sources. Results showed a mean 40-day cumulative nitrogen loss of 137 g in patients taking the high-quality protein compared with 176 g for those taking the low-quality product.

In another study, Pinney and Blackburn (1979) investigated the effect of tryptophan-supplemented collagen hydrolysate (CH) on nitrogen balance in five morbidly obese subjects during a ketogenic diet in which two nitrogen sources were alternately used. After a 3-week dietary adaptation period, subjects received CH for 2 weeks at 1.5 g protein per kg ideal body weight followed by 2 weeks of CH-egg albumin, 2:1 mixture (CH-Egg) at 1.4 g protein per kg ideal body weight. The regimens were supplemented daily with 3 g sodium chloride, 50 to 75 mEq potassium bicarbonate, 8 mEq magnesium sulfate, 0.6 to 1.2 g calcium carbonate, 100 mg phosphate, and 100 percent of the Recommended Dietary Allowances for vitamins and trace minerals. Mean daily nitrogen balances of the five subjects for the final 7 days of each test period were 0.3±1.4 g during the CH regimen and -2.6±1.4 g during CH-Egg. The authors concluded that, despite its apparent low biologic value, CH supported positive nitrogen balance, and
protein quality tested by limiting nitrogen intake may not apply to hypocaloric diets that provide protein above the minimum daily requirement. The decrement in nitrogen balance during the CH-Egg regimen could not be readily explained.

3. Other low-energy diets

For the purposes of this review, a daily energy intake of less than 800 kcal has been arbitrarily defined as severe caloric restriction, and is considered as a form of modified fasting.

Genuth et al. (1974) treated 75 massively obese individuals as outpatients for up to 50 weeks using a semistarvation regimen that supplied 75 g daily of casein calcium (Casec®; calcium caseinate) and glucose (total energy intake about 300 kcal) along with noncaloric fluids ad libitum, one complete multivitamin tablet daily, and 5 mg folic acid weekly. Typically the diet contained 45 g casein calcium and 30 g glucose, although proportions were varied for some patients. Forty-seven (63 percent) of the patients achieved successful weight reduction and were able to continue their daily activities during the process. No major adverse effects were reported. Kemper and his associates (1975) reported weight reduction of at least 45 kg per person in 106 massively obese patients whose regimens consisted of the "rice/reduction diet", a prescribed exercise program, environmental alteration, and motivational enhancement. The initial modified rice/reduction diet was 90 to 96 percent carbohydrate, consisting of rice and fruit and providing an estimated 400 to 800 kcal per day. After several weeks, vegetables were added and later, lean poultry or meat; however the protein content remained low and the energy intake never exceeded 1000 kcal per day.

An example of the "ketogenic diet" has been described as a low-calorie (800 to 1000 kcal per day) diet containing about 70 percent of calories as fat, 20 percent as protein, and 10 percent as carbohydrate (Piscatelli et al., 1969). Ten obese patients on the ketogenic diet for 10 days lost an average of 6.8 kg; six who remained on the regimen for 21 days had a mean weight loss of 10.9 kg. The authors noted that while this diet offered no advantage over other low-calorie diets in terms of rate and degree of weight loss, patient acceptance and the absence of severe side-effects were advantageous. It is of interest that the PSMF is also a ketogenic diet, the lipid component being supplied by the fat stores of the obese dieter.

Numerous variants of ketogenic diets have been promoted including several with "unrestricted calories". Common to all so-called ketogenic diets are a high proportion of calories from fat and a low carbohydrate content. The Council on Foods and
Nutrition of the American Medical Association (1973) found little scientific rationale for high-calorie ketogenic diets and cautioned physicians about the probable atherogenic effects of such diets used over prolonged periods.

Van Itallie et al. (1975) compared the rates and nature of weight loss that occurs in obese subjects during the first 10 days of three types of treatment regimens: total starvation, an 800 kcal mixed or "balanced" diet, and an 800 kcal "ketogenic diet". Despite difficulties in matching the data from various studies reported in the literature, the authors found remarkably similar results. They noted that, if such factors as the excess water losses and the relatively high protein losses during the first few days of total starvation are taken into account, the loss of stored triglyceride during total starvation, corrected for the total caloric deficit, is no greater than that resulting from a mixed low-calorie diet.

4. Weight control maintenance

Experts agree that the main challenge in treating obesity is not the initial or first phase reduction of weight, but the follow-up task of maintaining reduced body weight. The success rate for long-term maintenance of reduced weight has been very discouraging for both patients and their doctors (Apfelbaum, 1976; Bray, 1970; Felig, 1978; Stunkard and McLaren-Hume, 1959; Swanson and Dinello, 1970; Vinnick and Peterson, 1975; West, 1973). Consequently, a great deal of emphasis is now placed on efforts to alter the eating habits and life-style of patients via multiple techniques including various methods of behavior modification and programming of physical exercise. The multidisciplinary approach employed at several leading clinical centers includes expertise in bariatric medicine, nutrition, physical education, and behavioral science (Abramson, 1973; Altschul*, 1979; Blackburn and Greenberg, 1978; Stunkard, 1975). These authors concluded that preliminary results with such multidisciplinary techniques appear promising in terms of improvement in duration and degree of reduced body weight maintenance.

5. Risk-benefit in therapeutic fasting

Table 3 lists some diseases and disorders that, according to some authorities, are contraindications to the use of the PSMF (Bistrian, 1978; Drenick, 1972; Marliss, 1978). However, other specialists in the treatment of obesity regard the items listed in Table 3 not as contraindications, but as conditions requiring careful supervision by experts highly experienced in administering the PSMF.

*Altschul, A.M. Personal communication.
Table 3. Absolute and Relative Contraindications for the PSMF

<table>
<thead>
<tr>
<th>Contraindication</th>
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<tr>
<td>Recent myocardial infarction*</td>
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<tr>
<td>Recent cerebrovascular accident</td>
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<tr>
<td>Juvenile type diabetes*</td>
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<tr>
<td>Clinically significant disease of:</td>
</tr>
<tr>
<td>kidneys**</td>
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<tr>
<td>liver**</td>
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<tr>
<td>cardiovascular system**</td>
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<tr>
<td>cerebrovascular system**</td>
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<tr>
<td>Pregnancy and lactation**</td>
</tr>
<tr>
<td>Depressive psychiatric illness**</td>
</tr>
<tr>
<td>Childhood (under 5)**</td>
</tr>
<tr>
<td>Adolescence</td>
</tr>
<tr>
<td>Old age</td>
</tr>
<tr>
<td>Serious illness with expected malnutrition and poor prognosis</td>
</tr>
<tr>
<td>Diseases and disorders requiring:</td>
</tr>
<tr>
<td>adrenergics</td>
</tr>
<tr>
<td>high-dose steroids</td>
</tr>
<tr>
<td>lithium</td>
</tr>
<tr>
<td>high-dose aspirin</td>
</tr>
<tr>
<td>History of thrombophlebitis</td>
</tr>
<tr>
<td>Nutritional deficiency states</td>
</tr>
<tr>
<td>Porphyria</td>
</tr>
</tbody>
</table>

*Absolute contraindication (Bistrian, 1978).
**Absolute contraindication (Marliss, 1978).

In deciding whether total fasting or severe caloric restriction may be contraindicated in the grossly obese subject, the clinician must weigh the potential benefits of these approaches to substantial weight reduction against the possible side-effects and complications because the benefits often out-weigh the risks (Bistrian, 1978; Duncan et al., 1965). In a review of 890 obese patients, many of whom had coexisting diseases and who were treated by intermittent total fasting, Duncan et al. (1965) noted that patients with cardiovascular diseases usually improved clinically with weight reduction. Runcie and Thomson (1970) stated that, in their experience, coexisting disease, with the possible
exception of cardiac failure, was no contraindication for the use of prolonged starvation in the treatment of obesity. They cited several obese patients with degenerative vascular diseases, including acute myocardial infarction, who underwent therapeutic fasting without ill effect. More recently, Runcie and Hilditch (1977) listed among their patients who successfully reduced weight by therapeutic starvation, some with electrocardiographic evidence of ischemia, some who were in the immediate postmyocardial infarction phase, two with nephrectomies, and one with chronic tophaceous gout.

Beneficial effects of weight reduction by therapeutic starvation or modified fasting include reduction of blood pressure in hypertensive patients, improvement of carbohydrate tolerance resulting in termination of insulin therapy in some diabetic patients, reduction of dyspnea in patients with pulmonary or cardiac diseases, alleviation of back and joint pain, and improvement in exercise tolerance and agility (Genuth et al., 1974). Certain surgical procedures that are impractical in morbidly obese patients become feasible after substantial weight loss. The fatty liver associated with obesity usually improves with fasting or severe caloric restriction (Drenick et al., 1970). Kempner et al. (1975) listed the following improvements in coexisting clinical disorders in massively obese patients treated with a low-calorie rice/reduction diet followed by a low-calorie mixed diet: significant decrements in blood pressure, fasting and 2-hour postprandial blood glucose, serum triglycerides, serum uric acid, and heart-chest ratios. In addition, retinal venous fullness or papilledema in 14 patients was resolved via the rice/reduction diet, as were electrocardiographic abnormalities in all but 6 of 45 patients with ECG changes on the initial, prediet examination.

It is apparent that substantial differences of expert opinion have prevailed about the safety of therapeutic starvation and severe caloric restriction for use by obese persons with concomitant diseases and disorders. It would seem that any clinical condition coexisting with massive obesity that might contribute to cardiac conduction disturbances should represent at least a relative contraindication for therapeutic starvation or severe caloric restriction.

Review of the literature and the opinions of the LSHO consultants indicate that additional experience and substantial additional research including some prospective, controlled studies with obese human subjects are needed to determine the relative merits of various severely restricted dietary regimens. Suggestions for such studies are listed in Section X of this report.
IV. BIOLOGIC EFFECTS OF STARVATION AND SEVERE CALORIC RESTRICTION*

A. GENERAL METABOLIC EFFECTS

Treatment of obesity by therapeutic starvation or severely restricted caloric intake (less than 800 kcal per day) has been advocated by numerous authorities as a procedure that, with careful medical supervision and attention to supplemental nutrients, is safe, effective, and well tolerated (Blackburn and Greenburg, 1978; Bloom, 1959; Drenick, 1972; Duncan et al., 1965; Genuth et al., 1974; Howard and Baird, 1977; Runcie and Hilditch, 1977; Runcie and Thomson, 1970). However, because serious side-effects and deaths have occurred during such regimens, albeit with questionable patient selection and supervision in some cases, it is essential to reexamine the reported complications and the biologic effects of starvation and severe caloric deprivation.

For the purposes of this review, it was impractical to prepare separate treatments of the biologic effects of starvation (total fasting) and severe caloric restriction because the effects of the two modes, in grossly obese persons, are essentially similar, differing mainly in degree and temporal aspects. In some respects, the effects are identical. Consequently, both types of caloric deprivation are presented in this section, with differences stated when they appear significant. The single, most important difference is the continuing, obligatory protein loss of starvation, which contrasts sharply with the improvement in nitrogen balance achieved within 2 weeks after initiating a fast supplemented with approximately 1.25 to 1.5 g protein per kg body weight per day.

Excellent reviews of the biologic effects of starvation are available, for example in Cahill (1970), Grande (1964), Keys et al. (1950), and Moore (1959). In reviewing the effects of starvation in man, Ashley and Whyte (1961) alluded to the rapid loss of weight, particularly in the first week, and disappearance of hunger. The losses of weight are composed of "all elements" of the body tissues including water, fat, protein, minerals, and glycogen. Glycogen is depleted rapidly; fat is lost continuously.

*The following terms, taken from the literature, are used interchangeably with starvation in this report: involuntary starvation, therapeutic starvation, fasting, total fasting, therapeutic fasting. Except for involuntary starvation, it is implicit that subjects are allowed no food but presumably adequate daily doses of vitamins and minerals and unlimited amounts of noncaloric liquids. Terms pertaining to daily food intake of less than 800 kcal include severe caloric restriction, protein-sparing modified fast, protein-supplemented fast, semifasting, and semi-starvation.
serving as the main energy source; and the rate of protein depletion declines after an initial interval, accompanied by a reduction in urea and creatinine excretion and an increase in ammonia excretion. Oxygen consumption and carbon dioxide production decrease steadily, and the respiratory quotient declines to about 0.73, reflecting depletion of available carbohydrate and conversion to fat as the primary fuel source.

Complete food deprivation for several weeks without irreversible damage is possible in nonobese adults; for instance, survivals of between 17 and 76 days of complete starvation have been reported (Grandjean, 1964). Survival time varies directly with stored body energy reserves, ambient temperature, and age, and inversely with metabolic rate and physical activity. Others have documented man's ability to adapt to reduced energy intake levels and have shown that caloric balance can be achieved after a period of time as a part of the adaptation process (Grandjean, 1964; Keys et al., 1950; Taylor and Keys, 1950).

As the major source of energy during starvation, fat stores may be sufficient to supply the body's energy needs for several weeks, provided that physical activity is reduced. Grossly obese subjects have fasted successfully for periods of about 200, 245, and 384 days (Runcie and Hilditch, 1977).

Taylor and Keys (1950) studied human adaptation to semistarvation. Male subjects consumed a diet that was mostly carbohydrate, provided an average of 1570 kcal per day, and included about 54.5 g of protein and 27 g of fat. After 6 months of this regimen, the subjects had lost 24 percent of body weight and showed manifestations typical of famine victims such as weakness, depression, anemia, polyuria, bradycardia, and edema. The authors concluded that the subjects, at 75 percent of their original body weight, had adapted to a 55 percent reduction in energy intake based on the 3492 kcal diet used during the 3 months' pretest period. Table 4 shows examples of weight losses that may be expected in normal and obese adults undergoing complete fasting or severely restricted energy intakes.

During the first few days of total fasting, serum glucose and insulin decrease, while FFA levels increase, all then tending to remain stable for several weeks of fasting (Platt and Blackburn, 1974). Serum triglycerides always decline during prolonged fasting (Bistrian, 1978).

Prior to a fast, carbohydrate stored in the body amounts to only a few hundred grams, mainly liver and muscle glycogen. Its rapid depletion in starvation results in increased hepatic gluconeogenesis using protein derived mainly from skeletal muscles. During the first 10 days of starvation, body protein
Table 4. Human Adult Body Weight Losses in Conditions of Caloric Deficit (kg)

<table>
<thead>
<tr>
<th>Duration of caloric deficit (days)</th>
<th>4</th>
<th>14</th>
<th>30</th>
<th>40</th>
<th>60</th>
<th>75</th>
<th>84</th>
<th>120</th>
<th>168</th>
<th>224</th>
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</thead>
<tbody>
<tr>
<td>A. Nonobese Subjects</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Short term starvation</td>
<td>2.85&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>7.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Semistarvation with work</td>
<td>-</td>
<td>6.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
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<tr>
<td></td>
<td>-</td>
<td>8.3&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>B. Obese Subjects</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Therapeutic fasting</td>
<td>-</td>
<td>17.5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-</td>
<td>37.8&lt;sup&gt;f&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>-</td>
<td>21.1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>-</td>
<td>50&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>-</td>
<td>32&lt;sup&gt;g&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Therapeutic semi-starvation</td>
<td>-</td>
<td>5&lt;sup&gt;h&lt;/sup&gt;</td>
<td>10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>10.8&lt;sup&gt;h&lt;/sup&gt;</td>
<td>-</td>
<td>14&lt;sup&gt;h&lt;/sup&gt;</td>
<td>-</td>
<td>17&lt;sup&gt;h&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

| Reference                          |    |    |    |    |    |    |    |     |     |     |
| Brennan, 1977                      |    |    |    |    |    |    |    |     |     |     |
| Grande, 1964                       |    |    |    |    |    |    |    |     |     |     |
| Taylor and Keys, 1950              |    |    |    |    |    |    |    |     |     |     |
| Bray et al., 1972                  |    |    |    |    |    |    |    |     |     |     |
| Howard and Baird, 1977             |    |    |    |    |    |    |    |     |     |     |

<sup>a</sup> Sedentary
<sup>b</sup> Assumed energy expenditure = 1500 kcal per day
<sup>c</sup> 1200 kcal per day energy expenditure
<sup>d</sup> 1570 kcal daily intake, walked 20 miles per week
<sup>e</sup> Initial weight = 250 lb (113.6 kg)
<sup>f</sup> Initial weight = 375 lb (170 kg)
<sup>g</sup> Initial weight = 550 lb (250 kg)
<sup>h</sup> Mean values for 20 patients on semisynthetic diet not exceeding 320 kcal per day
<sup>i</sup> Mean values for 67 patients on PSMF (1.2 g protein per kg body weight per day for females; 1.4 g for males)
loss in obese subjects is about 50 g per day or about 8 to 12 percent of the caloric expenditure (Van Itallie et al., 1975; Yang and Van Itallie, 1976). Brennan (1977) noted that a rate of loss of muscle protein of 75 g per day, as occurs in acute starvation, would, if unabated, lead to a 30 percent loss of muscle mass in 20 days. Lindner and Blackburn (1976) pointed out that in the first month of starvation, about 5 kg of lean tissue are metabolized, decreasing to about 2.7 kg in the second month. However, following partial protein depletion and in the presence of low insulin levels during the second or third week of starvation, body protein is less readily mobilized and primary consumption of metabolic fuel shifts to the fat stores (Flatt and Blackburn, 1974; Guyton, 1976).

The effects of protein and energy restriction on rapid-turnover transfer proteins were investigated in obese women who were consuming low-energy, restricted-protein diets for 24 days (Shetty et al., 1979a). Although no significant changes were observed in plasma concentrations of albumin and transferrins, prealbumin and retinol-binding protein were sensitive to both protein and energy restriction, and responded promptly to refeeding.

Starvation ketosis develops, reflected by a rise in serum acetoacetate and β-hydroxybutyrate and by ketonuria, and the brain adapts to ketone bodies as the major energy source (Cahill, 1970). However, the brain requires a minimum obligatory amount of glucose (Owen et al., 1967). During this adaptation process, the rate of protein catabolism decreases to one-third to one-fifth of normal for the nonfasting person, and gluconeogenesis declines in the liver, but increases in the kidneys so that, in prolonged starvation, kidney gluconeogenesis matches that of the liver. Owen et al. (1969) estimated that in obese subjects fasted for 5 to 6 weeks, glucose production is about 86 g per day, of which liver and renal gluconeogenesis each contributes about one-half.

Hyperuricemia occurs early in fasting, and has been occasionally associated with such complications as gout, urate stones, and renal insufficiency (Drenick, 1973). During a protein-sparing fast, the serum uric acid falls to baseline levels or below after several months (Bistrian, 1978). The hyperuricemia of fasting is thought to be caused by interference by ketone bodies with renal uric acid transport and by reduced glomerular filtration secondary to diminished effective plasma volume.

According to Runcie and Hilditch (1974), in the later stages of starvation in obese subjects, about 96 percent of expended energy comes from triglycerides. Owen and Reicard (1971) observed that, on the 24th day of starvation, forearm muscle of obese human subjects extracted plasma free fatty acids as the principal energy substrate. Thus protein is spared so that a chronically starved person will lose only about 400 g of muscle mass in 20 days rather than up to 1500 g (Brennan, 1977).
Atrophy of organs occurs in starvation carried to the point of general emaciation. It is thought by many investigators that there is a tendency for such critical organs as brain, liver, heart, and kidneys to be partially spared at the expense of other body tissues. Keys (1948) and others have challenged this concept. Even in the absence of general emaciation, atrophy apparently takes place to some extent during therapeutic starvation or severe caloric restriction. For example, the liver of a young obese woman who died after 30 weeks of mixed total and protein-supplemented fasting, weighed only 600 g compared with liver weights of 1.2 to 1.4 kg in well nourished adult women (Garnett et al., 1969).

Death from starvation is said to result from reduction of body weight to about 50 percent of ideal weight (Law, 1977). Mechanisms of death from starvation are not well defined, but appear to be more than the consequence of depletion of body energy stores. Experiences with malnourished victims of World War II in western Netherlands suggested that in the final stages of starvation, digestion became disturbed to such an extent that no form of available treatment could resuscitate the patients (Goodhart and Shils, 1973). Cahill (1970) noted the frequency of deaths from bronchopneumonia in debilitated, malnourished patients, and emphasized the need for at least a minimal intake of glucose to spare body protein and help maintain the respiratory musculature.

Normal adult volunteers fed a 500 kcal per day diet for 10 days and exposed to gradually decreasing oxygen concentrations in their breathing atmosphere demonstrated reduced metabolic rates and markedly reduced hypoxic ventilatory responses which, the authors suggested, could contribute to hypoxemia and respiratory failure during such degrees of semistarvation (Doekel et al., 1976).

B. INFLUENCES ON ELECTROLYTES AND MINERALS*

During the first 2 weeks of total fasting, water excretion, which may be influenced by several mechanisms such as lack of carbohydrate intake, metabolic acidosis, and natriuresis, accounts for most of the weight loss (Drenick, 1972). In general, mineral excretion in the first few days of starvation exceeds the amounts liberated by catabolized tissues although serum mineral levels tend to remain within normal limits. Sodium loss, which

*Cardiac effects of altered electrolyte and mineral metabolism associated with starvation and severe caloric restriction are presented on pages 32 to 35; those related to specific organs and systems are on pages 38, 40, and 41. Cardiac effects of minerals and electrolytes in experimental animals are treated on pages 57 and 58.
may be as much as 80 mEq per 24 hours during the first 5 days, tapers to minute amounts within 3 weeks. Food and salt intake as well as body sodium content just prior to fasting affects the sodium excretion rate. Sigler (1975), studying urinary sodium, potassium, and ammonium excretion in fasting subjects, found support for the hypothesis that obligatory cation balance of metabolically generated anions is a major factor in fasting natriuresis. Serum sodium levels are usually within the normal range throughout fasting, and clinical symptoms of depletion have not been documented (Drenick, 1973).

Potassium excretion during starvation gradually decreases from about 48 mEq per 24 hours in the first few days to about 5 mEq after about 4 weeks of fasting. Lawlor and Wells (1969) reported that whole body exchangeable potassium levels are low in prolonged starvation. In their investigation of potassium loss during fasting, Drenick et al. (1966) found in obese patients without mineral supplementation only slight decreases in serum potassium during the first month and in most subjects, low-normal levels even after 3 to 4 months. Three of 15 patients who received no potassium supplements showed significant hypokalemia (2.6 to 2.8 mEq per l), but no symptoms of potassium deficiency. Serum levels <3 mEq per l after 2 or more months of fasting are exceptional. It is thought that renal tissue potassium depletion may adversely affect the ability of the kidney to concentrate urine and lower its pH. According to Drenick (1973), the electrocardiographic changes that often accompany acute potassium depletion do not occur in fasting.

Magnesium is continuously lost during fasting. In some obese individuals after 2 months of fasting, total body magnesium may be reduced by 20 percent reflecting gross losses of 150 to 450 mEq (Drenick, 1969, 1973; Drenick et al., 1969). Plasma magnesium levels show no consistent trends, and the degree of depletion of muscle magnesium during typical periods of therapeutic fasting, such as 2 months, has been considered physiologically insignificant. Fouty (1978) mentioned a normal magnesium balance in two patients who were using "liquid protein" diets, but no details were reported. He stated that a reliable diagnosis of magnesium deficiency requires muscle analysis, a concept that is supported by the studies of MacIntyre et al. (1961). According to Moore (1978), it is virtually impossible to correct hypokalemia in the presence of hypomagnesemia.

Calcium and magnesium excretion usually parallel each other, the calcium losses being slightly greater than those of magnesium. Drenick (1973) noted a range of calcium depletion of 550 to 900 mEq in a 50-day fast. Serum calcium levels tend to remain normal, and a need for calcium supplementation during fasting appears questionable.
Phosphorus is excreted in large quantities in the urine, especially during the early phases of fasting; for example, up to 80 mEq phosphate per day. However, the rate of phosphate loss soon declines so that, at 15 to 20 days, typical daily outputs range between 20 to 30 mEq. Serum levels remain in the normal range, and phosphate losses during therapeutic fasting appear to have no clinical significance. On the other hand, serum phosphorus levels do not necessarily reflect tissue levels, and severe phosphorus depletion is known to be associated with serious pathophysiologic effects (Knochel, 1977).

In their study of therapeutic fasting in 20 obese patients, Rooth and Carlström (1970) found reduced hemoglobin and serum iron concentrations as well as decreased total iron-binding capacity.
V. CARDIAC ASPECTS OF STARVATION AND SEVERE CALORIC RESTRICTION

The occurrence of intractable ventricular fibrillation and cardiac arrest in apparently healthy, obese people using prolonged, severe, caloric restriction supplemented with about 300 to 500 kcal per day of protein products to reduce body weight, focusses this review on the heart. Thus, it is necessary to examine in detail the effects of such regimens on cardiac metabolism and function.

A. ANIMAL STUDIES

Chauhan et al. (1965) reported atrophy of myocardial muscle fibers and in some cases, changes suggesting cardiac myolysis in rhesus monkeys fed a protein-deficient diet. Focal cellular infiltrates, mostly lymphocytes, were found in some specimens. As the protein deficiency progressed, the myocardial atrophy increased, with an apparent increase in interstitial connective tissue.

Smith (1977) reported massive intracellular destruction of rat heart cells after 6 days of starvation and, based on analyses of whole heart homogenates, elevated intracellular K⁺ and Ca²⁺ levels, increased activities of autolytic neutral and alkaline proteases, and the proliferation of lysosomes and their acid hydrolytic activities, particularly cathepsin D. She suggested the observed changes may aid in understanding the marked ECG changes that have been reported in some patients undergoing therapeutic fasting.

Hansen-Smith et al. (1977) observed that while oxygen consumption in papillary muscle declined in young male Sprague-Dawley rats on involuntary food restriction combined with a reduction in protein, restriction of dietary protein per se had no such effect. The appearance and distribution of mitochondria in rat cardiac muscle were not affected by food restriction used in these studies.

Moldauer et al. (1979) studied the effects of hypocaloric, ketogenic diets in male Sprague-Dawley rats fed for 45 days using protein supplements with or without added electrolytes, trace minerals, and vitamins (micronutrients). Protein supplements consisted of 2.7 g protein as lactalbumin (LA), commercial hydrolysed collagen (LP), or hydrolysed collagen plus egg albumin (LP + E). Diets containing LA or LP+E, with or without micronutrients, were superior to LP diets in preserving body weight, nitrogen balance, and liver protein. Regardless of the protein source, animals receiving micronutrient supplements demonstrated better protein status than those not receiving them. Myocardial
and skeletal muscle potassium were decreased 15 and 35 percent in
16 rats not receiving micronutrients, and the myocardia of 4 of
this group of 16 had microfoci of lymphocytic infiltration. Of
the four with lymphocytic microfoci, two had received LP+E, one
LA, and one LP.

Previously fattened Sprague-Dawley rats fed a hypocaloric
diet consisting of a "liquid protein" product, vitamins, and min-
erals for 21 days lost weight rapidly, and liver, but not heart
weights decreased (Timmons, 1979). There was no myocardial histo-
pathology as observed by light microscopy.

Groups of male weanling Osborne-Mendel rats that were fed
a high-fat diet for 11 weeks were then subjected to weight loss of
45 to 50 percent by starvation or hypocaloric diets consisting of
"liquid protein" hydrolysate with or without vitamin-mineral
supplements (Ahn et al., 1979). Weekly electrocardiograms were
normal in starving rats and those fed the "liquid protein"
hydrolysate plus vitamins and minerals. However, rats fed the
"liquid protein" hydrolysate alone showed markedly dysrhythmic
electrocardiograms.

Young Sprague-Dawley rats fed various "predigested pro-
tein" diets for 28 days demonstrated emaciation, rough hair coats,
decreased body fat and skeletal muscle, reduced bone marrow hemato-
poeisis, and testicular atrophy (Food and Drug Administration,
1977c). The hearts demonstrated no histopathologic changes by
light microscopy that could be related to diet. However, a very
small focus of mononuclear cells of unknown significance was found
in the myocardium of one control animal fed a protein-free diet.

Amino acid imbalances. Young rats force-fed a purified
diet (nutritionally-balanced, chemically-defined) free of single
essential amino acids for periods of 1 to 10 days developed
morphologic changes in some organs which resemble those in humans
suffering from kwashiorkor (Sidrinsky, 1976). The livers enlarged,
and hepatocytes showed increases in fat, glycogen, number of
free polyribosomes, number and size of lysosomes, and enlarged
nucleoli. Instead of decreased hepatic protein synthesis, which
might be expected with diets lacking one or more essential amino
acids, protein synthesis in the liver and heart increased in the
young rats force-fed this diet for one or more days. Protein
synthesis decreased in skeletal muscle and spleen and remained
unchanged in kidney and brain. As reviewed by Sidransky (1976),
fasted animals given a single feeding of good quality protein or
a complete amino acid mixture quickly increase hepatic protein
synthesis, with an increase in heavier aggregates of hepatic
polyribosomes. A similar response occurs with amino acid mixtures
devoid of single amino acids except for tryptophan; in the latter
case hepatic polyribosomes remained as in the fasted controls.
Further experiments showed that tryptophan alone, but no other
single amino acid, induced rapid stimulation of hepatic protein
synthesis and the polyribosome response. Other data from the same

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Laboratory showed that young rats fasted for 2 days, then tube-fed a protein-free diet responded similarly, with stimulated hepatic polyribosome aggregation and increased protein synthesis. These studies led to the concept that kwashiorkor-like pathologic changes can be induced in certain organs (the liver, pancreas, salivary glands, and gastrointestinal tract) by single amino acid deficiencies in young rats while overall protein synthesis in liver and heart may be increased. In addition, individual dietary components can rapidly create imbalances that strongly influence hepatic polyribosome metabolism and protein synthesis (Sidransky, 1976).

Studies of the biologic functions of taurine have suggested it exerts a calcium and potassium stabilizing effect on the heart under conditions of electrolyte depletion, thus helping to preserve cationic and membrane integrity (Hayes, 1976). Recently Hilton (1979) suggested that prolonged use of "liquid protein" preparations that are deficient in the sulfur amino acids may eventually lead to taurine deficiency with associated adverse effects on cardiac function. Analyses of 23 "liquid protein" products indicated that two were substandard in methionine-cystine content while 21 contained methionine in excess of amounts needed for normal taurine synthesis (Appendix II, Tables 1 to 4).

In their review of heart and skeletal muscle protein turnover, Rannels et al. (1977) noted that omission of any of 11 amino acids from the perfusate of isolated rat livers inhibited protein synthesis. In vivo, this effect was most easily demonstrated by omitting tryptophan. The branched-chain amino acids stimulated protein synthesis in heart and skeletal muscle, but the mechanism has not been elucidated. Protein synthesis during acute starvation declined rapidly in skeletal muscle and less rapidly in the heart. In the perfused rat heart, five times normal levels of amino acids in the perfusate increased the rate of synthesis of whole heart protein and myosin by about 40 percent, and higher levels of the BCAA had the same effect as the complete mixture of amino acids. Similar results were observed in studies using the isolated rat diaphragm. The BCAA are oxidized in both skeletal and heart muscle and the rate is increased by fasting. The authors pointed out that very little is known about the effects of amino acid availability on proteolysis in heart muscle.

B. HUMAN CARDIAC EFFECTS

Keys (1948) challenged the widespread notion that the heart is resistant to undernutrition, pointing out that both acute and prolonged undernutrition result in decreased cardiac size roughly comparable to the loss in body weight. For example, a 30 percent loss in body weight may include a 20 percent loss in heart weight. Keys (1948) reported that an early histopathologic change in a starved heart is decreased myocardial fiber size, followed by
brown atrophy with cloudy swelling, loss of striation, and vacuolization. Bradycardia of <50 beats per minute at rest is said to characterize the undernourished heart; in semistarvation, the heart rate is slowest during the first months. Typical ECG changes include reduced voltages in all deflections, most marked in the standard leads, and prolongation of both systole and diastole. Both arterial and venous pressures fall in starvation, cardiac output may be reduced, and maximal oxygen consumption during exercise may decrease by as much as 80 percent in a person who is 20 percent underweight. Prominent signs and symptoms referable to the cardiovascular system include postural hypotension and excessive sensitivity to cold. Keys (1948) advised caution in the nutritional rehabilitation of undernourished people, noting that the heart and circulation do not return to normal "along a simple recovery pathway" and that heart failure may supervene, with dyspnea, tachycardia, cardiac dilation, and edema.

In the CDC series of decedents, a prominent electrocardiographic feature during the last hours before death was prolongation of the QT interval (see Appendix I). Isner et al. (1979), noting the evidence that starvation may lead to pathologic hypothalamic-pituitary changes, suggested that "information supporting a critical role for the nervous system in the genesis of cardiac arrhythmias, including those related to QT interval prolongation, might provide a link between starvation or semistarvation and secondary electrocardiographic changes". However, the mechanisms involved in QT interval prolongation under such circumstances remain essentially unknown.

Three deaths, presumably from cardiac causes, among obese subjects undergoing therapeutic starvation or semistarvation have been reported in some detail. Most impressive in terms of cardiac involvement was the case of a 20-year-old woman who died in ventricular fibrillation during the refeeding phase following 30 weeks of total and semistarvation during which she reduced her body weight from 118 to 60 kg (Garnett et al., 1969). Except for obesity, she was in apparent good health and was asymptomatic during the fast except for one episode of hypokalemia during the initial natriuresis. In this episode, the ECG showed ST depression and a slightly prolonged QT interval. Although she was given daily supplements of potassium, amino acids, and whole protein powder, her exchangeable potassium declined from a prefasting level of 3360 mEq to 1400 mEq. Postmortem examination showed a dilated, soft, brown heart weighing 250 g, with no gross abnormality of valves and coronary arteries. Microscopically there were small diameter myofibers (0.64 compared with an arbitrary 1.0 for control tissue) and increased lipofuscin. Electron microscopy showed a paucity and disruption of myofibrils and an apparent increase in numbers of sarcolemmal mitochondria, which, aside from some swelling and apparent changes in the cristae, appeared normal. Arteries appeared normal and no virus particles were found.
In 1965, Cubberly et al. reported the death of a 44-year-old obese woman after 3 weeks of therapeutic starvation. Preexistent clinical diagnoses were diabetes and hypertension, and, at autopsy, coronary artery stenosis. Shortly before death she was temporarily revived from an episode of ventricular fibrillation; however, lactic acidosis was considered to be the cause of death. Spencer (1968) described two cases of death during therapeutic starvation in obese women 58 and 61 years old, both of whom had started the fast with a diagnosis of severe heart failure. The 58-year-old patient, who had right bundle branch block, enlarged heart, and blood pressure 230/130 mm Hg, fasted for 8 weeks during which she steadily lost weight and enjoyed general clinical improvement. She died suddenly in refractory ventricular fibrillation. Postmortem examination showed "hypertrophy of all chambers of the heart (weight 525 g)" but nearly normal appearing coronary arteries. The 61-year-old obese woman started the fast with an enlarged heart, pulmonary congestion, and ECG indication of an old anteroseptal infarct. During her 3 weeks fast, she lost 37 pounds and her general clinical condition improved. She was found dead, apparently from ventricular fibrillation. Necropsy revealed an enlarged, hypertrophied left ventricle and mural thrombi but no emboli. Spencer's series of obese patients treated by starvation included three others with heart disease, who fasted between 2 and 3 weeks, apparently without cardiac disturbances.

Brown et al. (1978) described in detail the ante- and postmortem cardiac manifestations of one of the fatal cases collected by the CDC (Center for Disease Control, 1979; Gregg, 1977). The patient was hospitalized for evaluation of a syncopal episode while she was reducing by using a hydrolysed protein-supplemented fast. Prior to developing refractory ventricular tachycardia, she displayed hypotension, persistent QT interval prolongation, and low QRS voltage. Noting the commonality of QT interval prolongation, low ECG deflection voltage, and refractory ventricular tachycardia in the CDC series, the authors suggested that QT interval prolongation may indicate an unpredictable ventricular instability in patients who semistarve. In another patient in the CDC series, histopathologic changes in the myocardium included small myofibers, increased lipofuchsin, paucity and disruption of myofibrils, and increased numbers of mitochondria (Michiel et al., 1978) (see also Appendix I, p.114). As reviewed by Keys et al. (1950), cardiac atrophy (mean estimated loss of heart weight 19.3 percent) nearly proportional to whole body weight loss was found in 85 percent of nearly 500 starved inmates of the World War II Warsaw Ghetto.

Five of nine patients with anorexia nervosa were reported to have slightly prolonged QT intervals in the absence of recognized heart disease and with normal serum electrolytes (Thurston and Marks, 1974). Gottdiener and associates (1978) reported bradycardia, relative hypotension, ventricular dysrhythmia, and abnormal
T-waves in some members of a group of 11 young female anorexia nervosa patients. In addition, they found reversible decreases in end-diastolic cardiac dimensions in some patients; however, left ventricular systolic function was normal. They did not find prolonged QT intervals in these patients. They posed the question of whether an unusually small left ventricular end-diastolic dimension in anorexia patients might aid in detecting risk for ventricular ectopic beats and possible dysrhythmic death.

Nonfatal cardiac abnormalities associated with total and partial fasting have been observed by several investigators. Keys et al. (1950) found slight prolongation of the QT interval in young men after prolonged undernutrition on a 1570 kcal diet; however, when corrected for heart rate, the average QT intervals were shortened. In their series of nearly 900 patients whose treatment included 10 to 14 day periods of fasting, Duncan et al. (1965) reported three cases of atrial fibrillation in patients with preexisting cardiovascular disease; excessive physical activity during the fast was considered the responsible factor. Oster and associates (1977) in a review of 200 obese patients treated by total fasting, described a 44-year-old patient, digitized because of a "questionable" cardiac insufficiency, who developed auricular fibrillation.

On the other hand, members of the LSRO review group indicated that in several leading clinics in the United States with major PSMF programs, cardiac complications, including dysrhythmias, have not been encountered. For example, in over 700 obese patients who used the PSMF as part of their treatment, no instance of QT interval prolongation was observed, and in approximately 200 obese patients who reduced their weight by more than 60 or 70 lb using total starvation, no electrocardiographic changes were discovered.

Analysis of ECG's of 900 obese patients who were treated by protein-supplemented fasting revealed that approximately 1 percent had "slight deviations" of the QT, with prolongations of 10 to 15 ms, and that none had the marked QT prolongation as reported by Brown et al. (1978) and Singh et al. (1978) (Goldberg and Dornfeld, 1978). The group of 900 patients included some with coronary artery disease, hypertension, and diabetes mellitus as well as some with apparently normal hearts. The authors reported they were continuing to gather ECG data including Holter monitor recordings at 3-month intervals. No significant changes in systolic time intervals, ejection fraction, and myocardial contractility index were observed in 12 obese patients during 2 weeks of therapeutic starvation (Aigner et al., 1977).

Theorell et al. (1978) reported significant decreases in heart rate and in the ratios between QRS and T-wave amplitudes in leads I and II in 14 healthy adult men fasted for 10 days. Blood
glucose and serum triiodothyronine decreased while urinary adrenaline excretion increased. The authors concluded that other hormonal, neural, and metabolic mechanisms have greater influence on the heart than sympa tho-adreno-medullary activity during fasting.

Gopalan (1955) described ECG changes including low voltages, inverted T-waves, and prolonged QT intervals in cases of kwashiorkor and adult hunger edema. Cardiac atrophy and myocardial fibrosis were found in victims of adult nutritional edema. He suggested that the origin of some of the cases of myocarditis of unexplained etiology in patients from regions where kwashiorkor and adult nutritional edema are common is probably nutritional; however, this has not been confirmed.

Children suffering from severe protein-calorie malnutrition become hypovolemic and, as the malnutrition worsens, may change from an adaptive hypocirculatory state to frank peripheral circulatory failure (Viertl, 1976; 1977a,b; 1978). The circulatory failure is associated with a high death rate even after treatment has been instituted. Although hypovolemia may be responsible, the exact cause of the circulatory failure is unclear; however, available data indicate that the heart plays no direct role.

Gillanders (1957) observed a form of congestive heart failure in 30 adult Bantu men and women whose staple diet was porridge made from refined maize, supplemented with white bread, tea, and sugar. Meat and milk in very small quantities or not at all, and rarely, vegetables or fruit were consumed as well. This was considered by the author a qualitatively and quantitatively deficient diet. Extreme edema was the most striking sign; enlargement of the whole heart, gallop rhythm, and coexistent liver disease were commonly observed. Marked clinical improvement occurred when the patients consumed an adequate, balanced diet; however, when the disease was long-standing, the cardiac enlargement and congestive failure were irreversible. Except for cardiac enlargement and ventricular hypertrophy, the postmortem heart findings were not striking. The author considered the evidence strong for nutritional deficiency as a factor in the etiology of the syndrome.

Smythe et al. (1962) described the cardiovascular effects associated with kwashiorkor including radiologic and pathologic evidence suggesting cardiac atrophy, a clinical finding of low cardiac output, x-ray evidence of cardiac enlargement, and distinctive groups of ECG changes. Cardiac arrest was suspected as a cause of sudden death in this series. The authors drew attention to similarities between the cardiac findings in kwashiorkor and the myocardiopathy of unknown origin in the Bantu (Gillanders, 1957).
MINERAL AND ELECTROLYTE EFFECTS ON THE HEART*

Mineral nutrients that may influence cardiac function include potassium, sodium, calcium, copper, iodine, iron, magnesium, phosphorus, and zinc (Burch and Giles, 1977; Fisch, 1973; Seelig and Heggtveit, 1974; Shils, 1969; 1973; Surawicz, 1967; Underwood, 1977). In particular, potassium, calcium, sodium, and magnesium are said to be factors in the genesis of experimental cardiac dysrhythmias (Fisch, 1973).

Isolated rat hearts perfused at potassium levels of 1.19 mmol per l developed ventricular fibrillation in 15 to 20 minutes (Emerson and Muir, 1969). About half the myofibrils showed disintegration and the remainder appeared normal to electron microscopy. Areas of insertion of myofilaments into plaques of the intercalated disc regions were markedly altered, with disappearance of insertion plaques. When the perfusate contained potassium at concentrations above 2.5 mmol per l, normal cardiac ultrastructure was preserved. Dietary potassium deficiency in the rat leads to reversible renal tubular and cardiac lesions (Welt et al., 1960).

Fouty (1978) briefly reviewed reports that high-protein diets produce severe magnesium deficiency in rats (which is associated with an obligate potassium depletion that cannot be repleted by potassium alone) and that magnesium deficiency in the rat causes myocardial necrosis and focal inflammation. Such effects have not been reported in control animals whose diets contained adequate amounts of magnesium.

The effects of calcium on the electrophysiologic properties of the heart are influenced by the potassium concentration. Surawicz (1967), using isolated, perfused heart preparations, showed that intraventricular and atrioventricular conduction disturbances associated with reduced extracellular potassium concentrations could be prevented or reversed by lowering extracellular calcium levels.

Clinical conditions that may interfere with normal electrical activity of cells include those that induce electrolyte imbalances, and, for purposes of this review, those characterized by nutrient deficiencies that may result from therapeutic starvation or severe caloric restriction.

*This section concerns the cardiac effects of not only mineral and electrolyte changes resulting from undernutrition, but also changes in these nutrients associated with certain diseases and disorders. Other aspects of minerals and electrolytes are treated on pages 21 to 23, 38 to 41, 57 and 58.
It is commonly accepted among clinicians that hypokalemia may be associated with a syndrome that includes muscular weakness, postural hypotension, and cardiac conduction and rhythm disturbances (Fisch, 1973; Fourman, 1954; Hyatt et al., 1975; Sobel and Braunwald, 1977; Surawicz, 1967). While the cardiac dysrhythmias of hypokalemia in man are most commonly associated with digitalis administration, they are also said to occur in the absence of digitalis. Hence, in prescribing and supervising PSMF and therapeutic starvation, careful attention has been given to attempts to prevent hypokalemia via potassium supplements.

Electrocardiograms of patients with large deficits of total body potassium are reportedly normal provided their plasma potassium concentrations remain normal (Surawicz, 1967). However, Nieper and Blumberger (1966) reported that, while the electrocardiogram was often used to diagnose cardiac potassium depletion, this method was unreliable. A serum potassium level of 1.4 mEq per l (hypokalemia) in the presence of a myocardial tissue level of 46 mEq per 100 g fat-free dry weight measured in a human patient illustrates one problem of interpreting serum potassium levels.

Otherwise healthy obese subjects who were not given potassium supplements maintained low-normal values of serum potassium even after 3 to 4 months of total fasting; however, total body potassium decreased markedly and then increased promptly when a 300 kcal diet with 30 g protein and 30 mEq potassium daily was instituted after total fasting (Drenick et al., 1966). No cardiac dysrhythmias or changes in conduction were observed. Serum potassium generally failed to indicate tissue potassium depletion. In addition, during the LSRO discussions, it was noted that cholera victims with massive potassium depletion and hypokalemia that persisted for many months showed some prolongation of the QT interval but no cardiac dysrhythmias; the QT intervals were not corrected for weight loss.

None of the decedents who had laboratory tests during their diets had persistent serum electrolyte abnormalities (Center for Disease Control, 1979). Upon admission to hospital, six had slight hypokalemia (range 2.8 to 3.3 mEq per l), and five had normal serum potassium concentrations (range 3.5 to 4.3 mEq per l). The other six dieters expired outside the hospital. Participants in the LSRO review group noted a lack of scientific evidence that hypokalemia may cause fatal cardiac rhythm disorders in the non-digitalized subject. According to Isner et al. (1979), hypokalemia, by itself, has not been adequately documented as a cause of QT interval prolongation or fatal ventricular tachyarrhythmias. These authors suggest that reports of prolonged QT intervals in hypokalemic patients represent, instead, QU intervals resulting from superimposition of U-waves on T-waves. Most of the consultants for this review did not consider hypokalemia a significant factor in the deaths.
Burch and Giles (1977) observed that, despite abundant information on magnesium metabolism and the pathologic effects of magnesium depletion in animals, knowledge of its role in human cardiovascular disease is incomplete. In part, this results from the lack of routine magnesium measurements in patients. About one-half the total body content of approximately 2000 mEq of magnesium is in bone, hence not readily available; about 1 percent is extracellular, and the largest amount that is kinetically active is intracellular (about 28 mEq per l). There is clinical evidence associating chronic alcoholism with hypomagnesemia and decreased skeletal muscle potassium. Electrocardiographic data from alcoholic patients suggest the presence of myocardial magnesium deficiency. However, the state of human myocardial magnesium metabolism is essentially unknown, and the question of ECG changes that may be characteristic of magnesium deficiency is open (Burch and Giles, 1977). According to Seelig and Heggteviet (1974), magnesium is important in retaining intracellular potassium and in maintaining normal cardiac rhythmicity in the presence of myocardial ischemia.

Shils (1969, 1973) noted that in the one reported prospective study in which symptomatic magnesium deficiency was induced in human subjects, hypocalcemia occurred in six of seven patients despite adequate calcium intake, and most of the subjects developed hypokalemia and negative potassium balance. The observed electrocardiographic changes were considered to be compatible with the coexisting calcium or potassium depletion, and the author concluded that magnesium depletion itself does not cause any reproducible, characteristic, electrocardiographic changes. Loeb et al. (1968) considered hypomagnesemia as a possible cause of paroxysmal ventricular fibrillation in two patients, both of whom also exhibited prolonged QT intervals; however, one patient was an alcoholic; the other suffered from anxiety and hyperventilation.

Klevay (1979) estimated that, in general, typical "liquid protein" products alone would provide less than one-tenth the adult daily requirement of copper. In view of the demonstrated adverse cardiac effects of copper deficiency in domestic and experimental animals, he suggested that a daily copper supplement for dieters might prevent cardiac arrhythmias.

The magnitudes of the transmembrane resting potential and phase 4 of the action potential, variations of which are important in inducing cardiac dysrhythmias, are apparently not altered by changes in calcium concentration encountered in most clinical situations (Fisch, 1973). Rumancik et al. (1978) measured QT intervals in human subjects in relation to serum ionized calcium concentrations, and concluded that, while a prolonged QT interval may indicate the presence of hypocalcemia, a normal QT interval does not exclude the presence of acute hypo- or hypercalcemia.
It appears that before sodium deficiency could appreciably alter the electrophysiology of cardiac fibers, fatal levels of depletion would be necessary; the effects of survivable hypornatremia cannot be recognized in the electrocardiogram (Fisch, 1973; Surawicz, 1967).

Among the situations that may be associated with hypophosphatemia or phosphorus depletion are therapeutic refeeding after major weight loss or PCM, and prolonged use of phosphorus-binding antacids (Darsee and Nutter, 1978; Fuller et al., 1976; Knochel, 1977). Congestive heart failure is one of the possible untoward effects of phosphorus depletion. Darsee and Nutter (1978) described three male patients with congestive cardiomyopathy associated with markedly depressed serum phosphorus levels. Each patient had been consuming large amounts of phosphate-binding antacids when symptoms of cardiac failure developed. Phosphate repletion restored serum phosphorus to normal levels and, within 2 to 5 weeks, reversed the cardiomyopathies. One concept of a cardiovascular effect of hypophosphatemia involves increased circulatory demand and high-output cardiac failure resulting from peripheral tissue anoxia and secondary to a marked fall in erythrocyte 2,3-diphosphoglycerate (2,3-DPG) (Knochel et al., 1975). The ability of red cells to release oxygen to the tissues is markedly affected by the presence of 2,3-DPG.

The question of whether the rhabdomyolysis associated with hypophosphatemia in experimental animals and man (see pages 40 and 41) or the rhabdomyolytic effects of combined hypophosphatemia and potassium depletion may induce similar degenerative effects in the heart has not been sufficiently investigated. Although serum phosphate was reported for only three of the 16 decedent women, two of these values were below normal levels (0.8 mg per 100 ml in case No. 8; 2.3 mg per 100 ml in case No. 10) (Appendix I). Several of the dieters consumed liberal amounts of noncaloric cola beverages which contain substantial amounts of phosphate or phosphoric acid; however, there is no firm evidence that cases No. 8 and 10 supplemented their diets with any phosphorus sources. Whether or not these two patients whose single-instance serum phosphorus determinations were subnormal actually had significant hypophosphatemia of meaningful duration cannot be determined from the available data.
VI. EFFECTS ON OTHER ORGANS AND SYSTEMS

A. HEPATIC

The liver has a central role in adaptation of the organism to caloric deprivation (Cahill, 1970). Liver gluconeogenesis from amino acids decreases as the body shifts to the fat-based fuel economy and as body protein depletion decreases. Through a series of enzyme changes, the ability of the liver to convert glycerol, lactate, and pyruvate to glucose becomes enhanced. The reduced hepatic gluconeogenesis from amino acids is reflected by a decrease of urinary nitrogen, and ammonia replaces urea as the main nitrogenous excretion product (Owen et al., 1969). Hyperbilirubinemia has been observed during fasting of obese subjects (Barrett, 1971) as have increased sulfobromophthalein retention and reduced hepatic steatosis (Rozental et al., 1967). The possible clinical significance of these changes has not been reported, and the validity of BSP retention as a test of liver function in fasting subjects has been questioned (Runcie and Thomson, 1970). Barrett (1971) noted that a fall in the elevated serum bilirubin levels occurred as early as 2 hours after starting refeeding of fasted subjects.

An extensive study of liver damage in pellagra led Gillman and Gillman (1945) to conclude that the pigmented cirrhosis seen in 15 percent of adult pellagrins, clinically and pathologically indistinguishable from hemochromatosis, is a manifestation of chronic undernutrition. The liver biopsies reported by Rozental et al. (1967) showed prominent hemosiderin deposits after therapeutic starvation. Elevated serum glutamic oxaloacetic and pyruvic transaminase levels during fasting have been reported (Wildenhoff et al., 1969).

Rats starved for 7 days lost 40 percent of liver protein compared with 8 percent losses in muscle, skeleton, and skin (Addis et al., 1936). Livers of newborn beagle puppies that were semistarved for 10 days by restricting caloric intake to glucose at 60 kcal per kg per day showed slight cholestasis and slightly more prominent hemosiderin pigmentation than controls (Pulito et al., 1976). Enzyme changes in the livers of young and old rats subjected to 1, 2, 3, or 4 days' starvation were reported by Freedland (1967). In general, those enzymes associated with gluconeogenesis, glycolysis, and the citric acid cycle were most stable; those thought to be related to lipogenesis were least stable under the experimental conditions, suggesting the preferential maintenance of some enzymes at the expense of others.
B. RENAL

As already noted, during adaptation to fasting, renal gluconeogenesis increases, urea excretion falls dramatically, and ammonia excretion rises markedly as a means of titrating the urinary loss of ketone bodies with ammonium ions (Cahill, 1970; Owen et al., 1969). Another important aspect of the adaptation process is renal conservation of ketone bodies. Sapir and Owen (1975) estimated reabsorption increases of approximately 2-fold for acetoacetate and 2.6-fold for β-hydroxybutyric acid in obese subjects during the first 24 days of fasting. The authors concluded that there is no tubular maximal transport rate for acetoacetate and β-hydroxybutyrate during physiologic ketonemia and that conservation of 450 to 500 mmol of ketone bodies per day prevents large urinary losses of cations during starvation.

Edgren and Wester (1970) studied renal clearance of p-aminohippuric acid, inulin, and endogenous creatinine in obese subjects during fasting and found a reduced glomerular filtration rate, but little change in PAH clearance. GFR slowly returned to normal after refeeding. Drenick (1973) noted that renal concentrating ability is somewhat impaired in fasting and that, because of elective reduction of fluid intake during the later phases of therapeutic fasting, marked oliguria may occur. Although the need for obligatory water excretion is small because of greatly reduced excretion of urea, the major osmotic solute (Cahill, 1970), most clinicians recommend a minimum daily fluid intake of 2 liters to avoid oliguria.

Although normal kidneys appear to function without impairment during prolonged fasting, subjects with preexisting renal disease are susceptible to hyponatremia because of failure of the kidneys to conserve sodium (Lindner and Blackburn, 1976). This may lead to rapid deterioration of renal function. Runcie and Thomson (1970) recommend close surveillance of renal function during therapeutic fasts. In 1969, Lawlor and Wells reported reduction in renal clearance of urea, uric acid, and endogenous creatinine in fasting obese subjects. They considered the possibility of urate lithiasis remote because of the decreased uric acid excretion. However, Zürcher et al. (1977) reported two cases of acute urate nephropathy during starvation for weight reduction, and cautioned that the use of uricosuric agents or sudden intake of a normal calorie diet may cause massive uricosuria and renal damage.

C. SKELETAL MUSCLE

Goodhart and Shils (1973) observed that there was no way to measure how much of total body protein can be mobilized (during caloric restriction) without functional interference. Drenick (1973) speculated that in the fatality reported by Garnett et al.
(1969), the subject may have fasted to the point where obligatory catabolism of critical protein stores occurred. Studies of forearm muscle metabolism in fasting obese subjects revealed relatively constant oxygen consumption and lactate and pyruvate production after overnight, 3-, and 24-day fasts (Owen and Reichard, 1971). Glucose consumption decreased while that of acetoacetate and β-hydroxybutyrate increased markedly after 3 days of fasting. After 24 days, FFA were the main fuels extracted by forearm muscle, and glucose and ketone body consumption was reduced.

Drenick (1973) noted that electron microscopic examination of human striated muscle after 2 months of fasting revealed intact muscle fibers with normal diameters.

Pozefsky et al. (1976) measured arterial amino acid concentrations and amino acid balance across forearm muscles of nonobese volunteers who were fasted overnight or for 60 hours. Although the concentrations of most amino acids in arterial plasma decreased during the 60-hour fast, levels of valine, isoleucine, and leucine rose strikingly. The balance of several amino acids measured across the forearm muscles became markedly more negative during the fast, the average increase in release of all amino acids amounting to 69.4 percent for the 60-hour period. During prolonged starvation, there is a gradual reduction in the initially heightened release of amino acids from skeletal muscle, which occurs in parallel with the attenuation of gluconeogenesis during adaptation of the fasting organism (Pozefsky et al., 1976). Amino acids most consistently released from muscle are glutamine, serine, threonine, alanine, and glycine, which are those most rapidly taken up by splanchnic tissues (Marliss et al., 1971; Pozefsky et al., 1976).

Urinary output of 3-methylhistidine has been shown to be a reliable index of the rate of myofibrillar protein breakdown in human and rat skeletal muscle (Young and Munro, 1978). Its output in obese human subjects decreases with protein or energy restriction, and may offer a convenient, noninvasive method of monitoring muscle protein catabolism during starvation or severe caloric restriction (Young et al., 1973).

Using isolated perfused hindquarters of rats, Ruderman et al. (1977) found that neither glucose uptake nor glycolysis was depressed after 48 hours of fasting; however, glucose oxidation was depressed by approximately 75 percent in starved rats and by 30 percent in rats perfused with acetoacetate. The authors suggested that in starvation, glucose metabolism in skeletal muscle is inhibited at the step of pyruvate oxidation and that diminished glucose uptake by skeletal muscle during starvation may be unrelated to the presence of an abundance of FFA and ketone bodies.
Ogata et al. (1978) reported the rate of myofibrillar protein catabolism increased six-fold over control values in young rats fasted for 72 hours and remained above control values despite restoration of high positive nitrogen balance. The authors noted that the excess myofibrillar protein catabolism may have provided amino acids for protein synthesis in "higher priority" tissues such as liver or brain.

Rhabdomyolysis and myoglobinuria are reported to be possible complications of potassium depletion (Bilbrey et al., 1973; Knochel and Schlein, 1972). Knochel and Schlein (1972) conducted experiments in dogs to test the hypothesis that, if potassium release from potassium-deficient muscle were subnormal, potassium-dependent arteriolar dilation and blood flow during exercise would be insufficient to maintain muscle viability. Gracilis muscles of dogs that were 50 percent potassium-deficient showed frank rhabdomyolysis following faradic stimulation for 60 minutes. However, nonexercised, potassium-deficient muscle showed only irregular and minor histologic abnormalities. Heart muscle of the potassium-deficient dogs appeared normal. The authors suggested that the rhabdomyolysis occurred as a result of ischemia in the exercised muscles.

Resting transmembrane potentials of skeletal muscles of dogs with moderate, and rats with severe, potassium deficiency increased, while in severely potassium-deficient dogs, the \( E_m \) declined (Bilbrey et al., 1973). Skeletal muscle paralysis observed in unexercised, potassium-deficient dogs, associated with the reported fall in \( E_m \) suggested that muscle membrane function may be involved in kaliopenic myopathy. According to participants at the LSRO meeting, in potassium-deficient rats, myocardial cells hyperpolarize and the animals die of heart failure before any change in transmembrane potential occurs.

Measurements of \( E_m \) in myocardial cells in vivo have not been conducted in potassium-deficiency. Because myocardial potassium content either remains normal or becomes only slightly depressed in severe total body potassium-deficiency, the predicted \( E_m \) would be elevated since the ratio of intracellular to extracellular potassium is abnormally high. In the potassium-deficient rat that ingests sodium chloride, myocardial lesions are commonly the cause of death. Simultaneous sodium deprivation in the potassium-deficient rat prevents these lesions (Cannon et al., 1953). According to Smith et al. (1950), skeletal muscle paralysis had not been reported in rats with very low serum potassium levels; Knochel (1978) noted that skeletal muscle lesions or paralysis in the potassium-deficient rat are highly unusual. In contrast, skeletal muscle of man and the dog as well as other species shows necrosis and becomes paralyzed in severe potassium-deficiency (Knochel, 1978).
Another essential nutrient that may influence the integrity of skeletal muscle is phosphorus, and there is good clinical and laboratory evidence that skeletal muscle weakness and rhabdomyolysis may be induced when hypophosphatemic undernourished individuals are abruptly refed carbohydrates without phosphorus supplementation (Knochel, 1977). In dogs fed a phosphorus-deficient diet for 28 days, serum inorganic phosphorus declined from 4.2 to 1.7 mg per 100 ml; total muscle phosphorus fell from 28.5 to 22.4 mmol per 100 g fat-free dry weight; and average Em decreased from 92.6 to 77.9 mV (Fuller et al., 1976).

Changes in total muscle water, sodium, chloride, and potassium occurred during the phosphorus depletion. All values returned toward normal after 28 days of phosphorus repletion. Fuller et al. (1976) concluded that reversible changes in skeletal muscle composition and transmembrane potential in dogs can occur as a result of moderate phosphorus depletion and independently of profound hypophosphatemia (serum inorganic phosphorus <1.0 mg per dl). In a subsequent study at the same laboratory, dietary phosphorus deprivation and undernutrition were used to induce subclinical myopathy in dogs (Knochel et al., 1978). Refeeding with excess calories but no phosphorus caused severe hypophosphatemia and acute rhabdomyolysis in contrast to the absence of these complications when the refeeding with excess calories included an abundant phosphorus supplement. The authors noted similarities between the skeletal muscle changes induced by phosphorus deprivation and undernutrition in these experiments and effects that have been observed in patients with subclinical alcoholic myopathy (Knochel et al., 1975).

Among the causes of profound hypophosphatemia, Knochel (1977) lists the nutritional recovery syndrome, which has been observed during refeeding of patients with severe protein-calorie malnutrition. The important clinical aspects, which seem to result mainly from overzealous refeeding with simple carbohydrates, included edema, ascites, hydrothorax, and death. Blood and urine analyses were not feasible in these patients, who were prisoners of war or concentration camp inmates.

Sidransky (1972) reviewed the effects of acute (1 to 3 days) amino acid deficiencies on organ weights and protein content in rats force-fed diets devoid of threonine, methionine, valine, lysine, leucine, isoleucine, phenylalanine, tryptophan, or arginine. Skeletal muscle weight and protein were decreased in all tests except with the arginine-devoid diet. In vivo protein synthesis declined in rats force-fed diets devoid of threonine, leucine, isoleucine, phenylalanine, or tryptophan.

The effects of chronic undernutrition on rat quadriceps muscle were investigated by Hansen-Smith et al. (1978). Young Sprague-Dawley rats (124 ± 2 g) were fed for 10 weeks protein-
restricted (8 percent casein) or marginal protein, energy-restricted diets (15 percent casein, 35 percent of control ad libitum intake). These dietary restrictions did not change muscle weights relative to body weights. Significant decreases in muscle fiber diameters occurred in the "white" (low-oxidative) portions, but not in the red (high-oxidative) regions in the protein-restricted group. While most of the fibers in each region appeared normal, a few showed moderate degenerative changes, with myofibrillar disorganization more prominent in the white portion, especially in the protein-energy restricted group. However, the authors concluded that while a few fibers were adversely affected after chronic dietary restriction of protein or energy, most were structurally similar to those of the controls.

In a review of research on protein metabolism in heart and skeletal muscle, Rannels et al. (1977) listed evidence that the availability of the branched-chain amino acids was the major factor responsible for effects of amino acids on protein synthesis in heart and skeletal muscle. For example, increased rates of protein synthesis in the isolated rat diaphragm after addition of normal or supranormal plasma levels of complete mixtures of amino acids could also be achieved by addition of the BCAA alone. The BCAA have been shown to inhibit protein degradation in rat diaphragm, as do increased levels of complete plasma amino acid mixtures. The mechanisms of these effects have not been fully worked out.

The rate of oxidation of BCAA in skeletal muscle was increased during fasting (Rannels et al., 1977). In postinjury states, which are frequently accompanied by undernutrition, muscle protein catabolism yields amino acids needed in the healing process (Benotti et al., 1976). This involves oxidation of BCAA of muscle protein, resulting in increased circulating alanine levels, accelerated gluconeogenesis, and decreased muscle protein synthesis. The authors concluded that amino acid infusions and adaptation to the metabolic ketosis help to maintain BCAA levels needed for protein synthesis and preservation of body cell mass (Benotti et al., 1976). However, the effects of amino acid availability and fatty substrates on proteolysis in the heart are mostly unexplored.

D. NEUROLOGIC

In animals, semistarvation is accompanied by diminution of well established conditioned responses and interferes with establishment of new conditioned responses (Brozek and Grande, 1960). Depletion of specific nutrients, which may occur in starvation, leads to the well known mineral- and vitamin-deficiency syndromes, many of which have neurologic components. These are not reviewed here.
Young and Landsberg (1977) reported a significant reduction of norepinephrine turnover in the hearts of rats that were fasted for 2 days, a finding thought to be consistent with a suppression of centrally mediated sympathetic activity during fasting. The authors noted a lack of other reported physiologic or pathophysiologic states that consistently reduce norepinephrine turnover and that there was no consensus concerning the functional state of the sympathetic nervous system during fasting. They alluded to unpublished data from their laboratory suggesting that norepinephrine turnover in other sympathetically innervated organs also declines during fasting. In addition, preliminary data reported by Jung et al. (1979a,b) suggest that the fall in systolic and diastolic blood pressures of normotensive as well as hypertensive obese women during restricted energy dieting is associated with a reduction in autonomic output.

Practically all organs lose weight during starvation except the central nervous system (Grande, 1964; Keys et al., 1950). During prolonged fasting, the brain adapts to β-hydroxybutyrate and acetoacetate as its primary energy sources, thereby sparing gluconeogenesis and extending the potential survival of the organism from weeks to months (Cahill, 1970).

In prospective studies of prolonged semistarvation in healthy volunteers (the Minnesota Experiment), sensory function and intellectual performance were essentially preserved and neurologic status did not deteriorate except for paresthesia in two of 32 men. Some degree of neurasthenia, a decrease in spontaneous mental and physical effort in all subjects, and diminished patellar and Achilles tendon reflexes in some subjects were noted (Keys et al., 1950; Taylor et al., 1948). Psychomotor performance declined in healthy young volunteers who were doing hard physical work during a 5-day fast (Henschel et al., 1954). The authors considered the loss of coordination of eye-hand movements to be dependent upon blood sugar levels. Neuromuscular performance as measured by grip strength, fatigability, eye-hand coordination, and reaction time was not compromised in moderately obese subjects under sedentary conditions who were on protein-supplemented fasts (Apfelbaum, 1976).

The literature on neurologic changes in semistarvation is extensive, but it does not always clearly differentiate the effects of nutrient deficiencies from those that may result from caloric deficits (Keys et al., 1950). However, a large part of this literature is devoted to the effects of specific mineral or vitamin deficiencies, which will not be reviewed extensively in this report. Keys and his associates (1950) emphasized major differences in neurologic manifestations reported from war-famine studies in Europe (relatively unremarkable) compared with those from the Far East (extensive and severe).
Authorities on starvation agree that manifestations reported in human beings during prolonged semistarvation, as in famines, which may be partially or wholly referable to the nervous system include irritability, restlessness, asthenia, adynamia, ataxia, amblyopia, nerve deafness, mental lethargy, slow cerebration, inability to concentrate, sluggish tendon reflexes, increased sensory thresholds, retarded pupillary light reaction, and deterioration of moral standards (Brozek and Grande, 1960; Keys et al., 1950). So-called nutritional neuropathies reported from the Spanish Civil War included paresthesias, neurasthenias, visual disturbances, cold sensations, and disturbances of gait. Under conditions of involuntary semistarvation, the individual is often exposed to multiple stresses that may influence nervous system integrity such as excess cold, lack of sanitation, lack of pure water, infectious diseases, and extreme anxiety. Hence, the data obtained during famine situations, especially those associated with wars, are of limited scientific value.

Whether neurologic manifestations of undernutrition in otherwise healthy test subjects and in victims of famine may be relevant to weight reduction of severely obese persons by fasting or modified fasting is debatable, particularly since the obese dieter does not experience total caloric deficit. Few instances of frank neurologic disturbances associated with dietary reduction of weight in obese individuals have been reported. Rooth and Carlström (1970) described a 29-year-old female patient who developed polyneuritis with bilateral peroneal palsy following 13 weeks of fasting during which she lost about 68 lb body weight. Details of her fasting regimen were not reported except for prescribed vitamin supplements and noncaloric liquids without restriction. Sherman and Easton (1977) reported reversible peroneal nerve palsies that developed in seven patients while they were on weight-reduction diets. The authors stated that the cause of the nerve palsies in these patients was unknown but that prolonged leg crossing, which had been suggested as a cause of such palsies by other authors, was probably not a factor in their "active and generally healthy" patients.

Symptoms that may be derived from neurologic disturbances in obese subjects undergoing weight reduction by severe caloric restriction include apathy, indifference, and headache (Lawlor and Wells, 1969; Runcie and Thomson, 1970). Episodes of reversible cerebral ischemia in three middle-aged, hypertensive, obese patients undergoing total fasting to reduce body weight were reported by Oster et al. (1977). The neurologic effects included hemiparesis in one patient, and motor aphasia and hemianopsia in another. Angiography revealed multiple stenoses of the cerebral arteries in these patients.
It is recognized that specific nutrient deficiencies that could be associated with poorly regulated therapeutic fasting or semifasting may ultimately lead to some of the well-known vitamin- or mineral-deficiency syndromes that have neuropathologic components. Although the subject was not discussed during the LSRO ad hoc review, the effect of rapid weight loss in obese subjects on vitamin metabolism and daily requirements may be significant in terms of safety of treatment by severe caloric restriction.

Possible neurological sequelae of severe caloric restriction in obese persons were mentioned during the LSRO review as a subject worth investigation. The scarcity of reported neurologic problems associated with well regulated therapeutic fasting and modified fasting suggests that if adverse neurologic effects occur, they are mostly too subtle or transient to be recognized by ordinary clinical monitoring.

E. ENDOCRINE

Van Itallie (1977) noted that in starvation, the thyroid gland and pancreas lose mass approximately in proportion to total body loss; the adrenal glands lose relatively less, and the brain shows minimal changes. In general, the consultants at the LSRO conference considered that good data on the endocrine effects of starvation and semistarvation in obese and nonobese human subjects are limited. Gardner et al. (1979) studied certain endocrine effects of 80-hour fasts in normal men and concluded that fasting is accompanied by a lower "set point" of thyroid stimulating hormone secretion and that the pituitary remains responsive to changes in serum thyroid hormone concentrations.

Mean serum levels of growth hormone did not appear to change significantly from pretreatment values in 11 obese individuals who starved for 38 days (Owen et al., 1969). On the other hand, patients with protein-calorie malnutrition commonly exhibit elevation of growth hormone concentrations (Dietze et al., 1974; Munro, 1978). Growth hormone, however, is released in spurts, and an appropriate evaluation requires repeated determinations throughout a 24-hour period.

Starvation studies in animals and man have generally shown atrophy of the endocrine organs (Keys et al., 1950). The overall endocrine effect has been called a "pseudohypophysectomy"; however, a number of variables including animal species, duration, and degree of caloric deficit influence the endocrine response, and the evidence suggests that, despite depression of pituitary function, some production of pituitary hormones is maintained in starvation. Investigations of children with protein-energy malnutrition suggest that their failure to grow results from
deficiencies of dietary protein and energy intake rather than from hormone deficiency (Hansen, 1975). Evidence of impaired or altered adrenotrophic and thyrotropic hormone production in anorexia nervosa patients has not been reported (Grande, 1964).

Studies in 10 successive generations of female pigs on a 30 percent calorie restriction showed no significant changes in the weights of pituitary, thyroid, and adrenal glands. Decreased growth rates and regressive changes in the thyroid gland, thought to be caused by diminished growth hormone and thyrotropin have been reported (Grande, 1964).

Thyroid gland. Decreases in basal metabolic rate in obese subjects undergoing prolonged semistarvation for weight reduction have been described as unremarkable compared with substantial reductions of BMR in nonobese persons under similar dietary restrictions (Van Itallie and Yang, 1977). That the BMR decreases in undernutrition is well established (Huseby et al., 1959). In physically active, healthy young men consuming a 1000-kcal carbohydrate diet for 16 days, basal oxygen consumption declined about 20 percent during the first 14 days; however, as indicated by $^{131}$I uptake and plasma PBI levels, thyroid function was not depressed. Similarly, in cases of anorexia nervosa, $^{131}$I uptake and serum PBI are usually normal or only slightly depressed (Huseby et al., 1959).

The LSRO review group noted that fasting obese patients treated with large doses of thyroid extracts did not develop cardiac dysrhythmias, but in a few cases, experienced angina pectoris, which disappeared on discontinuing the thyroid extracts. Hypophysectomized rats demonstrated depression of all phases of thyroid activity including marked reduction of iodide transport and binding, $^{131}$I uptake, and $^{131}$I-T$_4$ formation (Taurog, 1974). According to Grande (1964), results of $^{131}$I uptake studies in starving animals have varied so much as to be equivocal. During the LSRO discussions, it was pointed out that a condition of "physiological hypothyroidism" is said to occur in human subjects fasted for several weeks, featuring such manifestations as reduced oxygen consumption, slowed tendon reflexes, and decreased T$_4$-T$_3$ conversion. With whole protein, essentially carbohydrate-free diets supplying about 400 kcal per day, more T$_4$ is apparently converted to reverse T$_3$ (an inactive form of the hormone), resulting in a relatively hypothyroid state (Marliss, 1978). Restoration of serum T$_3$ levels to normal by oral replacement therapy results in increased oxygen consumption, increased heart rate, and normal tendon reflex responses, but the rate of nitrogen loss doubles.

Endocrine pancreas. A rapid decline in plasma insulin and a prompt increase in plasma glucagon levels are two of the principal hormonal changes of fasting (Cahill, 1977; Kolanowski, 1977; Marliss et al., 1970). In fasting obese subjects, these
changes were well developed within 3 days of the start of fasting, at which time insulin levels reached a plateau and glucagon concentration, having doubled, declined to levels at or above postabsorptive values (Marliss et al., 1970). Acutely starved rats demonstrated inactive pancreatic beta cells and hyperactive alpha cells, which was interpreted as a functional inactivity of the beta cells with suppression of insulin production (Grande, 1964). Hyperinsulinism occurs in obesity; weight loss improves carbohydrate tolerance and lowers serum insulin levels (Bistrian et al., 1976).

Adrenal glands. The increased 24-hour excretion of urinary 17-hydroxycorticoids or 17-ketogenic steroids characteristic of obese persons tends toward normal upon reduction of weight, while 17-ketosteroid excretion is unchanged (Bray et al., 1972). Six grossly obese young and middle-aged women who fasted for 23 days showed diminished urinary excretion of 17-OH-CS and 17-KS (Haag et al., 1967). Semistarvation with protein deprivation leads to a reduction of urinary excretion of 17-OH-CS but no change in plasma levels of unconjugated 17-OH-CS, suggesting that caloric restriction combined with protein-deprivation changes the catabolism of adrenal steroids, but does not significantly alter the level of hormonally active corticosteroids (Grande, 1964).

In anorexia nervosa patients with prolonged undernutrition, levels of urinary 17-KS and 17-OH-CS excretion are reduced; however, results of analytic methods that measure primarily unconjugated urinary metabolites were equivocal (Grande, 1964). In 12 healthy young men subjected to 16 days of caloric restriction combined with protein-deprivation, urinary excretion of steroid metabolites declined rapidly during the first 6 days, and then stabilized at about one-half control values; however, plasma levels of unconjugated 17-OH-CS were not depressed (Huseby et al., 1959).

In studies of obese women on weight reducing, low-carbohydrate diets that provided 9.2 kcal per kg ideal body weight, Shetty et al. (1979b) found a striking decrease in urinary concentrations of catecholamine metabolites and diminished venous levels of noradrenaline within 48 hours of the start of caloric restriction.

A transient increase in aldosterone secretion is another change that occurs in fasting (Kolanowski, 1977). Eight obese subjects on a total fast for 7 days demonstrated markedly increased secretion and plasma levels of aldosterone by day 4 of the fast while plasma cortisol remained unchanged. After day 7 of fasting, plasma aldosterone levels decreased (Chinn et al., 1970).

Prostaglandins. While it is recognized that the prostaglandins do not fit the classical definition of endocrine substances, they are included with this section for convenience and because some of their effects are hormonal in nature.
Despite large temporal differences, the initial effects of PGA infusion in hypertensive patients (marked natriuresis, kaliuresis, diuresis, and fall in blood pressure and blood volume) are strikingly similar to those of fasting (Lee, 1974). However, in the former group, the effects occur in minutes, but in fasting subjects, only after days.

A direct relationship between potassium depletion and PGE renal synthesis and urinary excretion has recently been reviewed by Ferris (1978). Such effects have been reported from in vitro studies and in vivo animal studies as well as in human subjects. Excessive amounts of prostaglandins produced by the kidney in potassium-deficient dogs bypass the lungs where they are normally catabolized, enter the general circulation, and cause a high cardiac-output state (Ferris, 1978; Galvez et al., 1977). Abnormal hemodynamic responses in the potassium-deficient animal, typified by impaired pressor responsiveness to angiotension II, are improved by indomethacin (Bay et al., 1976; Galvez et al., 1977).

There appears to be antagonism between norepinephrine or nerve stimulation and the E series prostaglandins in vascular tissue (Hedquist, 1973). Concentrations of $3 \times 10^{-9}$ to $1.5 \times 10^{-6}$ M PGE$_1$ and PGE$_2$ reversibly depress mechanical responses in the perfused rabbit heart as well as the norepinephrine overflow response to sympathetic nerve stimulation. This appears to result from reduced transmitter release from the nerve terminals. Horrobin (1978) noted evidence, particularly in the heart, that prostaglandins may exert a negative feedback effect on acetylcholine release from parasympathetic nerve endings. Several investigators have shown that intravenous administration of PGE$_1$ increases heart rate significantly in human subjects and experimental animals (Nakano, 1973). Finally, Flatt and Blackburn (1974) noted that the prostaglandins represent a group of substances that can interfere with fat mobilization and might be involved in the development of protein-wasting states. While there is some evidence that prostaglandins inhibit the mobilization of fat from adipose tissue and stimulate lipolysis, the question of whether they may have a fundamental role in obesity has not been elucidated (Kather et al., 1978). In addition, little has been reported on possible relationships of prostaglandins to adverse effects, including cardiac effects, of severe caloric restriction in the treatment of gross obesity.

Consultants for this review noted the precursor role of linoleic acid in prostaglandin synthesis, and raised the question of whether total fasting or severe caloric restriction without linoleic acid supplementation in obese individuals might result in linoleic acid deficiency. This appears to be an open question.
Finally, it should be apparent that the pathophysiologic significance of endocrine changes associated with undernutrition or starvation is not completely understood. Marliss (1978) suggested the possibility that altered catecholamine metabolism, especially in the heart, might be involved in some aspects of the cardiac response to "liquid protein" diets including the dysrhythmias. Bistrian et al. (1976) pointed out that, in their experience, 1.2 to 1.4 g of protein, as egg albumin or lean beef, per kg ideal body weight as the sole source of calories in PSMF in obese subjects maintains nitrogen balance and preserves normal liver, endocrine, and hematopoietic functions. Dietze et al. (1974) concluded that the metabolic adaptations observed during starvation are not the result of hormone effects. It is of interest that endocrine effects have not received much emphasis in the recent literature on the use of severe caloric restriction in the treatment of obesity. On the other hand, some of the participants in the LSRO review meeting were convinced that endocrine changes are critical in determining when to modify or stop a drastic weight reduction regimen, and that such changes deserve additional investigation.

F. IMMUNOLOGIC

The influence of nutritional deficiency on immunologic function has been the subject of considerable activity by investigators involved with protein-calorie malnutrition, so-called hospital malnutrition, starvation, and severely restricted-calorie regimens in the management of overt obesity (Beisel, 1979; Bistrian, 1978; Bistrian et al., 1977; Edelman, 1975; Fernandes et al., 1976; Good et al., 1976; Scrimshaw, 1975; Wannemacher, 1977). The LSRO review group observed that interrelationships of immunologic and caloric deficits have been recognized, but only recently have investigators been studying the basic aspects; hence, available information is rather general in nature. For example, generalized PCM tends to suppress cell-mediated, humoral, and secretory immune competence. There are also limited data indicating that immunosuppression may result from deficiency of single essential nutrients such as iron, zinc, magnesium, and several of the vitamins (Beisel, 1979).

Malnutrition leads to lymphoid tissue atrophy, which can be clearly demonstrated in children with kwashiorkor or marasmus and in starved experimental animals. PCM is known to interfere with humoral and cellular immunity and to impair leukocyte response and function. As reviewed by Scrimshaw (1975), children with untreated kwashiorkor, as well as malnourished concentration camp survivors, demonstrated impaired antibody responses to a variety of antigens, and malnourished tuberculous children had falsely negative tuberculin tests.
Kwashiorkor may be associated with absent or reduced leukocytosis in infections, and leukocytes of PCM patients tend to have diminished phagocytic competence. On the other hand, elevated levels of specific immunoglobulins have been reported in children with PCM, as have increased resistance to certain virus diseases and reduced numbers of T-cells in the presence of a normal delayed hypersensitivity response. In mice, rats, and guinea pigs, antibody production and humoral immunity are inhibited by PCM or chronic protein deprivation while cell-mediated immunities that are depressed by severe protein restriction seem to be enhanced when the protein restriction is moderate (Good et al., 1976). In general, most studies have shown that refeeding quickly corrects immunologic deficits associated with undernutrition.

Members of the LSRO review group indicated that while the evidence for impairment of T-cell functions by various types of malnutrition is fairly firm, B-cell dysfunction has been more difficult to document because immunoglobulin concentrations do not differ much from normal. Children with kwashiorkor or other forms of malnutrition usually show a deficit in response to a new antigen even though their serum IgG, IgA, and IgM values are about normal. Some of the confusion in attempting to interpret such apparent discrepancies stems from the fact that a large majority of malnourished people also have infections. Thus, while it is recognized that T-cell and B-cell dysfunction occurs in malnutrition, it has not been possible to define precisely what occurs. The development of better animal models is expected to aid investigators in achieving more precise definition of the nutritional-immunologic relationships. For example, what specific nutrient deficit produces what sort of immunologic deficit?

Blackburn and his colleagues have assessed cellular immune function by delayed hypersensitivity skin testing in obese patients undergoing weight reduction by protein-sparing modified fasts (Bistrian, 1978). They found no impairment, even after major weight loss (Bistrian et al., 1975). Similar studies should be done by other groups to validate these findings and perhaps to learn more about the nutritional deficit-immunologic relationship. Nevertheless, when compared with other factors such as possible amino acid or severe electrolyte imbalances, immunologic dysfunction appears to be an unlikely candidate for priority consideration in the etiology of deaths among users of very low-calorie protein diets.
VII. DYSRHYTHMIAS AND CARDIOMYOPATHIES

Because of the cardiogenic nature of the deaths of the "liquid protein" dieters, aspects of clinical and experimental cardiology and cardiovascular physiology, mostly not associated with caloric deprivation but possibly related to the observed cardiac changes of the decedents, were reviewed. The 16 women and one man were generally described as free from cardiovascular disease with the exception of one person with "borderline" hypertension, two with "minimal" hypertension, and one with hypertension of unspecified degree.

During hospitalization in 1973 for minor surgery, Case No. 10 (Appendix I) was found to have slightly depressed thyroid function, and a routine ECG showed prolonged QT interval. Thyroid function studies in connection with her "liquid protein" diet revealed hypothyroidism, but whether she received treatment for this is not stated in the clinical summary. The 43-year-old man was under treatment for hypertension prior to starting his diet, at which time antihypertensive therapy was discontinued.

Thus the apparently noteworthy cardiovascular abnormalities among the 17 individuals were one case of frank hypertension with blood pressure controlled by treatment before the diet, another case of hypertension of unknown degree, and a case of possible congenital prolonged QT interval syndrome. The types of structural changes found in the hearts of the decedents and the absence of evidence of prediet cardiac pathology, except as noted above, support the impression that most of the decedents had no preexisting significant cardiac disease.

A. CONDUCTION DISTURBANCES AND DYSRHYTHMIAS

Rare but well-known cardiac dysrhythmias such as the paroxysmal tachycardias are among the conditions that should be considered in seeking the etiology of the deaths among dieters. However, except for one woman with a history of alleged episodes of "tachycardia" for which no cardiologic or ECG supporting evidence could be found, none of the 17 decedents had a history of any cardiac rhythm disturbance.

Experimental procedures and clinical conditions that increase the QT interval of the electrocardiogram are commonly associated with ventricular tachycardia, syncopal attacks, and sudden death (James, 1969; Ratshin et al., 1971; Schneider et al., 1977; Schwartz et al., 1975; Vincent et al., 1974). Among the factors that may increase the QT interval, James (1969) listed excess digitalis, quinidine, diuretics, certain phenothiazine drugs, hypokalemia, and hypocalcemia. The alleged association
between hypokalemia and cardiac disorders is treated on pages 32 and 33. Another type of QT interval prolongation, not well understood, is associated with cerebrovascular disease. Experimentally, QT interval prolongation may be induced by a variety of agents including certain aliphatic aldehydes and proplphenone derivatives such as phenylethyl ketone used in perfume.

A heritable form of QT prolongation, the long QT syndrome occurs in children, sometimes with congenital deafness, and is associated with syncope and sudden death. Of 203 cases of LQTS reviewed by Schwartz et al. (1975), the overall mortality was 34 percent, of which 73 percent were untreated. Among cases for whom adequate data were available in this series, 27 died before age 13, nine between 13 and 20, and 3 after age 20. The pathogenesis of LQTS is unknown. A current hypothesis relates LQTS with a non-homogeneous, asymmetrical cardiac sympathetic innervation that results in an imbalance between the right and left sympathetic outflows to the heart. The pharmacologic treatment of choice in patients with LQTS is the sustained use of beta-blockers in full blocking dosages.

The signs and symptoms of LQTS usually appear in childhood and diminish in survivors after adolescence; survival into middle age has been reported (Schwartz et al., 1975). The number of syncopal attacks in LQTS varies from many episodes per month to one or two throughout life. A noteworthy aspect of LQTS mentioned by James (1969) is that the fatal dysrhythmias occur in hearts that frequently show a normal myocardium at autopsy. However, in some cases of LQTS, pathologic anatomic lesions of the conduction system and the vascular supply have been described (Schneider et al., 1977).

Of possible special interest in this review is the report of Schneider et al. (1977) of a 45-year-old woman with previously undiagnosed, asymptomatic, congenital prolongation of the QT interval who experienced over a 7-day period several episodes of light-headedness, palpitation, diaphoresis, and vomiting, culminating in a syncopal attack and hospitalization to control recurrent bouts of ventricular tachyarrhythmias and syncope that proved unresponsive to the usual antidysrhythmia therapy. This patient was on a low-potassium, weight-reduction diet and was taking a combination tranquilizer-antidepressant, both of whose components (amitriptyline and perphenazine) may have contributed to the onset of conduction disturbance and ventricular tachyarrhythmia. The authors suggested that a number of asymptomatic individuals with prolonged QT intervals may be at risk when exposed to factors that aggravate disturbances of repolarization.

In adults, congenital LQTS must be differentiated from so-called acquired prolonged QT interval syndrome, which features spontaneous syncopal attacks and ventricular fibrillation without precipitating episodes of physical or emotional stress commonly
involved in the congenital version (Schneider et al., 1977). A specific cause for the increased QT interval in these cases, such as drugs, electrolyte disturbances, or a conduction defect, is implicit in the diagnosis.

Only one of the 17 decedents (Appendix I, Case 10) had presumptive evidence of congenital QT interval prolongation that was noted in an ECG done approximately 4 years before she started her diet. Three other patients in this series had records of prediet ECG's, which were normal. Of these, two had an ECG during their diets, and both were described as normal. The ECG of another patient done after 4.5 months of a 5-month diet showed abnormalities including prolonged QT interval. The possibility that asymptomatic prolonged QT interval existed in 13 of the 17 decedents cannot be ruled out although the probability seems small.

A type of ventricular tachycardia that may exhibit clinical and ECG features similar to those observed in the 17 decedents is torsades de pointes (Krikler and Curry, 1976; Singh et al., 1978). Although its pathogenesis is unclear, it is said to be a definable dysrhythmia that may be induced by a variety of factors including severe hypokalemia or hypomagnesemia; as a complication of quinidine or quinidine-like drug therapy; and by such non-cardiac drugs as the phenothiazines and the tricyclic antidepressants. Characteristically, the electrocardiogram reflects paroxysms of ventricular tachycardia and undulating rotations of the QRS axis in runs of 5 to 20 beats. Frequently there is associated prolongation of the QT or QU interval. Accurate diagnosis is critical because quinidine or similar cardiac agents administered to patients with torsade on the mistaken assumption that the manifestations represent ventricular hyperexcitability may severely aggravate the dysrhythmia. Illustrative of torsade de pointes was a 27-year old woman who survived several episodes of syncope with ventricular tachycardia following the loss of 90 lb during a 5-month "liquid protein" reduction regimen. Her experience in-hospital included repeated bouts of syncope and ventricular tachydysrhythmia along with apnea. Treatment included cardio-pulmonary resuscitation, cardiac defibrillation, repeated intravenous infusions of phenytoin sodium, intravenous lidocaine, and finally oral phenytoin sodium (Singh et al., 1978).

Whether the postulated mechanism leading to disturbances of norepinephrine turnover in the hearts of fasted rats reported by Young and Landsberg (1977) (see page 43) is consistent with the sympathetic innervation imbalance hypothesis in the LQTS (see page 52) remains to be elucidated.

Fozzard's (1976) review of the dysrhythmia problem mentioned reports of victims of sudden cardiac deaths, the majority of whom had no evidence of myocardial infarctions at autopsy, apparently having died of their dysrhythmias. Similarly, 7 of 87
patients who died of sudden cardiovascular collapse had no significant vascular disease, acute coronary thrombosis, myocarditis, or valvular disease that could account for the sudden deaths (Reichenbach et al., 1977). A postulated explanation of apparently spontaneous ventricular fibrillation and sudden death in presumably healthy persons is the occurrence of ganglionitis of cardiac nerves located close to the sinus node or other parts of the cardiac conduction system (James et al., 1979). Such neuropathies appear to be clinically silent until sufficient pathology has developed to cause cardiac conduction disturbances. The cause of the condition is unknown.

The "pickwickian syndrome" consists of an association of gross obesity with hypoventilation, somnolence, polycythemia, and excessive appetite (Murray, 1977). When fully developed, the manifestations include periodic respiration, cyanosis, right ventricular hypertrophy, and right-sided heart failure. Daly et al. (1979) listed the pickwickian syndrome as one of a series of clinical conditions that may be associated with intermittent alveolar hypoventilation and arterial hypoxemia that could hypothetically place a patient at risk of chemically-induced bradycardia or cardiac arrest. While none of the 17 decedents had a history of the pickwickian syndrome prior to dieting, the nature of the clinical features of some of the victims during their last few hours of life suggests it should be included with the differential diagnosis in terms of the possible pathogenesis of their cardiac dysrhythmias. In addition, despite negative clinical histories, some of the victims may have had the sleep-induced apnea syndrome, which has been shown by continuous, overnight electrocardiographic and electroencephalographic monitoring to be associated with cardiac rhythm disturbances such as severe sinus dysrhythmias, extreme sinus bradycardia, transient asystole, and ventricular dysrhythmias (Anonymous, 1979; Flick and Block, 1979; Tilkian et al., 1977).

In view of the increased levels of circulating FFA that result from total fasting or severe caloric restriction (Bistrian, 1978; Cahill et al., 1967; Dietze et al., 1974), the possible dysrhythmogenicity of FFA holds special interest. Ople and Lubbe (1975) reviewed their own work and the literature on this subject and concluded that while experimental elevations of FFA in the presence of adrenaline infusion may disturb cardiac rhythm in experimental animals (for example, FFA:albumin molar ratio of 6:1 in rats) and the use of antilipolytic agents decreased dysrhythmias after myocardial infarcts in human patients, the question of the possible dysrhythmogenicity of FFA in clinical and experimental settings remained open. Merin (1978) suggested that increased FFA levels that are associated with a shift from glycolytic to lipolytic metabolism in the heart might (in combination with the antiglycolytic effects of halothane) contribute to an increased sensitivity of myocardial cell membranes to beta-adrenergic stimulation.
In studies of arrhythmogenesis in the early stages of myocardial infarction, Opie et al. (1978) perfused isolated rat hearts with dibutylryl cyclic AMP and observed a decrease in the ventricular fibrillation threshold. Phosphodiesterase inhibition from low tissue pH was suggested as a possible factor leading to elevated cyclic AMP in ischemic myocardium. Another arrhythmogenic factor thought to be involved was compromise of the ability of FFA in ischemic myocardium to maintain action-potential duration; in a similar setting, lactate has proven inferior to glucose in maintaining duration of the action-potential.

Administration of catecholamines has frequently been used experimentally to produce cardiac injury. For example, Maling and Highman (1958) reported that intravenous infusion of a large dose (0.51 mg per kg) of norepinephrine, and subsequent small doses of either epinephrine (1.03 μg per kg) or norepinephrine (0.95 μg per kg) resulted in ventricular tachycardia and fat deposition in the myocardia of dogs. Sensitivity to the small test doses of these catecholamines persisted for 2 to 4 days following the initial infusion of norepinephrine.

B. CLINICAL CARDIOMYOPATHIES

James (1964) described a form of heart disease associated with various systemic diseases in which there is a progressive cardiac enlargement that goes on to congestive failure commonly associated with conduction disturbances, arrhythmias, syncope, and sudden death. The predominant pathologic feature in the heart is focal fibrosis. Another prominent feature, thought to be a heritable trait, was medial necrosis in small coronary and pulmonary arteries (0.1 to 1.0 mm in diameter), which may be overlooked at postmortem examination, particularly in view of the usual absence of such disease in the larger coronary arteries. The associated diseases, mostly heritable (Marfan's syndrome, progressive muscular dystrophy, LQTS, Friedreich's ataxia, and "primary" pulmonary hypertension) were not diagnosed in any of the 17 decedents except for the possibility of asymptomatic LQTS in Case 10 (Appendix I).

Congestive cardiomyopathy as defined by Goodwin (1970) comprises severe myocardial damage of unknown origin that results in dilated, flabby ventricles and patchy myocardial fibrosis, usually leading to left ventricular failure, often rapid in onset. Possible etiologic factors in Goodwin's series of 74 patients were alcohol, pregnancy and puerperium, and upper respiratory infections.

The original autopsy reports of 9 of the 17 decedents in the CDC collection included pulmonary congestion, associated in several instances with congestion of other organs (Center for Disease Control, 1979). These findings were generally described
as being consistent with acute heart failure. However, authorita-
tive reviews of the pathology of the decedents by the CDC (Center
for Disease Control, 1979) and Isner et al. (1979) did not mention
pulmonary changes, nor were they suggested for consideration by
the group of LSRO consultants for this review. Ventricular dila-
tion was reported in Case No. 9; soft, flabby cardiac muscle in
Case No. 35 (Appendix I). No myocardial fibrosis was reported in
any of the cases.

A type of cardiomyopathy frequently found in human
hearts and reproducible in experimental animals has been termed
myofibrillar degeneration (Reichenbach and Benditt, 1970) (see
page 57).

In a review of toxic cardiomyopathies, Balazs and Herman
(1976) noted that bronchodilators such as isoproterenol and vaso-
dilating antihypertensive drugs like hydralazine can produce
subendocardial necrosis. Both classes of drugs may evoke signs of
myocardial hypoxia, and the sympathomimetic bronchodilators cause
tachycardia and vasodilation. The authors described signs and symp-
toms of extreme cardiovascular response to these types of drugs,
including deaths preceded by dysrhythmias. Two of the decedents
in the CDC collection (Cases 7 and 22, Appendix I) had histories
of asthma, but there is no history of an attack during their
dieting periods. Nevertheless, this could have occurred. Case 35
took methyldopa for hypertension during her diet; however, this is
not in the hydralazine class of drugs and is reported to have no
direct effect on cardiac function (Physician's Desk Reference,
1979). Cardiomyopathy associated with phosphorus depletion during
consumption of large amounts of phosphate-binding antacids is
described on page 35 (Darsee and Nutter, 1978).

Patchy myocardial necrosis and hemorrhage in decedent
patients who had sustained infusions of norepinephrine for shock
have been described, as has histopathologic evidence of acute
patchy necrosis or myocardial fibrosis in patients who died with
pheochromocytomas (Haft et al., 1972). Possible mechanisms for
these cardiotoxic responses include hypoxia, effects on vagal
tone, or direct cardiotoxicity of catecholamines.

Empirical evidence was reported of abnormal hemoglobin-
oxxygen dissociation in 14 of 15 women under 40 years-of-age who
had objective signs of myocardial ischemia or necrosis in the
presence of normal coronary arteriograms and, in three of this
group who died, evidence of subendocardial infarcts but normal
small and large coronary arteries (Eliot and Bratt, 1969). The
possible significance of these observations may justify additional
study including the question of "silent" myocardial ischemia
possibly related to anomalous hemoglobin-oxygen dissociation.
C. EXPERIMENTAL CARDIOMYOPATHIES

When young female Sprague-Dawley rats (initial weight ~52 g) were fed a potassium-deficient diet for 1 week, the myocardium showed no structural changes (Selye and Bajusz, 1959). However, exposure of other potassium-deprived rats to a variety of factors that had no effect on normally fed controls caused extensive myocardial necrosis. The test factors included noradrenaline, vasopressin, thyroxine, dihydrotachysterol (sterol closely related to calciferol), forced restraint, heat, cold, vagotomy, quadriplegia, and intestinal injury. The authors concluded that a brief period of nutritional deficiency can selectively condition the myocardium to the cardiotoxic effects of stresses produced by various agents. They noted that the magnesium content of the potassium-deficient diet was only at the base maintenance level and that supplementary potassium or magnesium prevented the cardiac necrosis. In a review of experimental metabolic cardiac necroses, Pioreschi (1967) listed the results of many studies that demonstrated a striking capacity of potassium administration to protect the myocardium against a wide variety of cardiotoxic agents including desoxycorticosterone combined with sodium chloride in unilaterally nephrectomized animals, 9α-fluorocortisol (and other glucocorticoids) together with sodium salts; papain, dihydrotachysterol, stress plus 9α-fluorocortisol, neomycin, polymyxin, isoproterenol, ligature of abdominal aorta, and magnesium depletion combined with sodium salts. However, the author noted that doses of cardiotoxic substances to man equivalent to those used experimentally in animals would be enormous.

The myocardia of rats given 9α-fluorocortisol and sodium phosphate revealed numerous pathologic changes, most striking of which were multiple dense granules in the mitochondria (D'Agostino and Chiga, 1966). The authors believed these granules were accumulations of minerals and suggested that an accumulation of calcium and phosphate within mitochondria can interfere with the formation of ATP in the process of oxidative phosphorylation.

Table 5 is a partial list of chemical, metabolic, and physical factors that have produced cardiotoxic responses in several species of animals; many of the responses were similar to the myofibrillar degeneration type of cardiomyopathy described by Reichenbach and Benditt (1970). Local release of norepinephrine at cardiac sympathetic nerve endings has been shown to induce a lesion similar to the myofibrillar degeneration caused by administration of norepinephrine. The relevance to man of experimental cardiomyopathy induced by administration of catecholamines has often been questioned because the amounts used in animal studies have usually been much larger than doses causing physiologic effects. Reichenbach and Benditt (1970) estimated that the amount of norepinephrine that is released from sympathetic nerve endings in the heart upon moderately excessive sympathetic stimulation is comparable to concentrations following parenteral injection, and is sufficient to cause myofibrillar degeneration.
Table 5. Factors Associated with Experimental Cardiac Myofibrillar Degeneration*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Factor</th>
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<tbody>
<tr>
<td>Potassium deficiency**</td>
<td>Catecholamines plus corticoids</td>
</tr>
<tr>
<td>Potassium deficiency plus stress (cold, heat, trauma)</td>
<td>Mineralocorticoids plus sodium phosphate</td>
</tr>
<tr>
<td>Potassium deficiency plus sodium salts (except sodium chloride)</td>
<td>Magnesium deficiency</td>
</tr>
<tr>
<td>Potassium deficiency and corticoids</td>
<td>Cobalt</td>
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<td></td>
<td>Hypoxia</td>
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<tr>
<td></td>
<td>Hypothermia</td>
</tr>
<tr>
<td></td>
<td>Catecholamines</td>
</tr>
</tbody>
</table>

*Modified from Reichenbach and Benditt (1970).

**Other aspects of minerals and electrolytes are treated in sections IV, V, VI, and on pages 57 and 58.

Prolonged, severe magnesium deficiency in young dogs resulted in a variety of adverse effects of which degeneration of some of the small coronary arteries and associated focal myocardial necrosis hold particular interest in this review (Wener et al., 1964). No consistent electrocardiographic changes were observed that could be directly related to the magnesium deficiency, nor could a direct effect on the myocardium be demonstrated. The diets of the test animals afforded adequate nutritive potential except for the lack of magnesium.

James (1967) called attention to experimental data indicating that magnesium deficiency in young dogs may lead to medial necrosis of small coronary arteries (0.1 to 1.0 mm in diameter). He suggested that a relationship might exist between the myocardial pathology of chronic alcoholism and magnesium deficiency, which is frequently associated with alcoholism. During the LSRO review, it was pointed out that the myocardia in chronic alcoholism resemble histopathologically those of the 17 decedent subjects of this review.

As already noted, rhesus monkeys maintained on a protein-deficient diet for up to 12 weeks showed, in the early stages of protein deficiency, focal myocardial cytoplasmic coagulation,
fragmentation and edema of myocardial fibers, and focal interstitial round cell infiltration. In the later stages, myocardial fiber atrophy and interstitial fibrosis were prominent (Chauhan et al., 1965). On the other hand, hearts of juvenile rhesus monkeys subjected to dietary protein deficiency, although somewhat atrophic, showed less severe pathologic changes compared with those reported by Chauhan and colleagues (Deo et al., 1965).

The sudden onset of myocardial ischemia, as in acute coronary thrombosis, may be followed immediately by cyanosis, lowered tissue temperature, decreasing pH, and ECG changes, all directly related to the development of local hypoxia (Jennings et al., 1969). In such a setting, myocardial cells may be injured reversibly or irreversibly. The authors investigated changes in myocardial cells of the dog in an attempt to determine events that dictate the onset of irreversible injury. This is relevant to the present review because of the possibility of myocardial hypoxia in undernourished subjects in a chain of events that includes decreases in physical activity, oxygen consumption, cardiac output, and heart rate as well as relative or absolute hypotension.

Haft et al. (1972) reviewed numerous investigations which demonstrated the capacity of infused epinephrine, norepinephrine, and isoproterenol to cause myocardial necrosis in dogs, rats, rabbits, turtles, and man. The authors tested the hypothesis that the necrosis results from ischemia caused by platelet thrombi in occluded small vessels of the coronary circulation. Platelet antiaggregating agents (aspirin, dipyridamole) were shown to protect against the cardiotoxicity of norepinephrine in dogs.

Recent clinical reports suggest that creatine phosphokinase isoenzyme MB is highly specific for damaged myocardium as in infarction (Model et al., 1979) and acute coronary ischemia (Marmor et al., 1978, 1979). A newly developed radioimmunoassay method reportedly allows rapid detection of serum creatine kinase MB without interference from other forms of creatine phosphokinase (Montgomery, 1979). Such an assay may offer a convenient method of detecting possible myocardial damage during investigations involving starvation or severe caloric restriction.

The foregoing examples of clinical and experimental dysrhythmias and cardiomyopathies have been included in the hope of provoking additional thought about possible leads to the cardiac derangements of the 17 decedents. Suggestions for future investigation may be derived from consideration of these as well as the factors reviewed in other parts of this report.
VIII. INFLUENCE OF AGE, SEX, RACE, AND OTHER FACTORS ON SAFETY OF SEVERE CALORIC RESTRICTION

Age, sex, and race. With the exception of one male subject (Case 56), the fact that the decedents in this study were all white premenopausal women suggests that age, sex, and race influenced the susceptibility of the dieters to the fatal set of circumstances. Discussion of these topics during the LSRO ad hoc review meeting suggested that numerous factors probably contributed to the apparently highly skewed concentration of fatalities among young-to-middle-aged white women. Among the probable factors are failure of the voluntary reporting system to include all diet-related fatalities; the likelihood that sudden, unexplained deaths in obese males would, in the absence of postmortem contradiction, be recorded as deaths caused by myocardial infarction; the higher incidence of obesity in women than in men; and the greater tendency of women compared with men to correct their excess weight.

It is important to note that 16 records of deceased women dieters were selected for biostatistical reasons from 58 reports of deaths of persons reportedly using protein-supplemented fasting. The 42 cases that did not fit the statistical selection criteria included 19 males and 3 blacks, many of whom had evidence of coronary heart disease and/or diabetes (Center for Disease Control, 1979).

The absence of males and blacks fitting the chosen criteria may be an artifact of the data collection and reporting process. The use-rate of the "liquid protein" diet did not appear to differ significantly between black and white women (Schucker and Gunn, 1978), and on a proportional population basis, only one or two deaths would be expected among black women using the diet provided the death rate were the same as that of white women (Center for Disease Control, 1979).

The one male decedent had a dietary and clinical history and postmortem findings essentially identical with the typical picture in the 16 female decedents except that he used a protein product that was reportedly of high-quality. The scientific literature does not appear to distinguish among sex, age, and race in terms of the safety of total or partial fasting or in terms of untoward effects of such regimens except that childhood and adolescence have been listed as contraindications by some authorities (page 15). Scientific evidence that sex may exert a significant influence is lacking despite the epidemiologic data suggesting that premenopausal women may be more susceptible than others. However, in the absence of scientific data, possible influence of these factors cannot be ruled out despite the judgment that they probably are not significant.
Amount and rate of weight loss and duration of diet. The duration of dieting in the group of decedents ranged from 2 to 8 months, averaging about 5 months. Total weight loss varied from 20 to 139 lb, with a mean of 83 lb and an average rate of 4.6 lb per week. By comparison, the planned range of weight loss on a carefully supervised PSMF is about 2.5 to 4 lb per week. Three women who died after 2 to 2.5 months of dieting lost an average of about 33 lb at rates that varied from about 2.5 to 5 lb per week. The lowest rate of weight loss, 2 to 3 lb per week, occurred in a 45-year-old woman who weighed about 205 lb before starting the diet that terminated in death after 2.5 months. The two women who died after 2 months of dieting lost weight at nearly identical rates, 4.9 and 5 lb per week. The percentage weight loss in the group of 16 ranged from about 12.5 to 50 with an average of 34 percent. The two longest dietary regimens, 7.5 and 8 months, were by women with prediet weights of 247 and 337 lb, rates of weight loss of 3 and 4.3 lb per week, and percentage weight losses of 36 and 41 percent, respectively (Appendix I Table 1).

The one male decedent, 43 years-of-age (Center for Disease Control, 1979), dieted for about 7 months and lost 180 lb at a rate of 6 lb per week. The 20-year-old woman reported by Garnett et al. (1969) died after about 6.5 months of total and protein-supplemented fasting and the loss of about 128 lb. After an initial period of rapid weight loss and natriuresis, the rate of weight loss steadied at about 3 lb per week. Sandhofer et al. (1973) described a severe cardiac response in a 37-year-old obese woman who was treated for 18 weeks by total fasting. Her weight decreased from a prefast level of 237 lb to 150 lb at a rate of 4.3 lb per week. On the 129th day of starvation she became exhausted after an "excursion", demonstrating signs of shock, hypotension, tachycardia, and ECG signs of low voltage and prolongation of electrical systole. The QT interval, which was only slightly prolonged at the start of the episode, increased to 59 percent over normal 5 days later. The patient slowly recovered over a period of 11 weeks during which she complained of extreme weakness. The authors suggested that therapeutic starvation, under close supervision, is a safe procedure in grossly obese but otherwise healthy persons but that it should not exceed 3 to 4 weeks in duration on a continuous basis.

The question of maximum safe duration of weight reduction regimens featuring severe caloric restriction or total fasting supplemented with vitamins and minerals cannot be fully answered on the basis of available information. Members of the LSHO review group observed that experience with the PSMF in approximately 2600 cases treated by 61 physicians in this country included only one death, which was one of the cases in the CDC series. This group included only cases who lost at least 0.5 lb per week and continued the PSMF for at least 60 days. The fact that 3 of the fatal 17 cases in the CDC collection died after 2 to 2.5 months' dieting while others survived 7.5 to 8 months suggests major differences in individual response.
Of the various factors considered important in the etiology of deaths by the group of consultants, the rapid and massive weight loss seemed to be very significant, coupled as it was with extremely strict observance of the dietary restrictions. Another point of special interest was the fact that 6 of the 17 decedents had started refeeding shortly before their deaths. They were using a slow refeeding schedule including use of a protein supplement several times daily with perhaps one low-calorie, low-carbohydrate meal daily. There was no suggestion of excessive food intake.

Degree of obesity. The data in Appendix I Table 1 suggest a direct relationship between the degree of excess weight and duration of dieting before death. Cases 9, 15, and 22, who survived 3 months or less, were only moderately obese in comparison with others who survived for 4 or more months and were at least 100 lb over desirable weight (Cases 1, 4, 5, 8, 10, 35, 37, 44, and 56). This apparent relationship may be real, but documented evidence is not available. However, authorities generally agree that an obese, otherwise healthy individual can survive starvation for considerably longer periods of time than the nonobese, and it has been shown that obese persons on calorie-restricted diets achieve nitrogen balance more efficiently than the nonobese (Van Itallie and Yang, 1978). It is noteworthy that one of the criteria used by some clinics for admission of patients to weight-reduction programs using severe caloric restriction is that they fit the classification of massive obesity (at least twice the ideal weight).

Finally, a question arose as to whether fat mobilization during severe caloric restriction might release harmful levels of toxic substances stored in body fat. For example, increased plasma concentrations of DDT (1,1,1-trichloro-2,2-bis[p-chlorophenyl] ethane) and its metabolites were measured in starved rats previously fed DDT in the diet (Dale et al., 1962; Fitzhugh and Nelson, 1947). However, Backman and Kolmodin-Hedman (1978) reported that while the plasma concentrations of DDT increased significantly in obese patients during weight reduction following intestinal bypass operations, the levels were well below those of a control group selected from non-occupationally-exposed office workers. In the opinion of the LSRO consultants, little scientific information is available about mobilization of fat-stored toxic substances during massive weight loss.
IX. CONCLUSIONS

BACKGROUND

Sixteen white, premenopausal women and one white man, who were essentially healthy except for gross obesity, died unexpectedly of cardiogenic causes in 1977 and early 1978 during or just after completing long-term supplemented fasts. For most of the decedents, the sole or principal source of calories was from "liquid protein" or other "predigested protein" products. However, protein supplements of high biologic value were used in a few instances; thus the deaths were not exclusively associated with the use of gelatin- or collagen-derived products. Available evidence has not elucidated the nature of the individual susceptibility to the development of severe cardiac disturbances in any of these circumstances.

"Predigested proteins", including "liquid proteins", marketed as aids to rapid weight reduction when used as the sole source of calories in amounts equivalent to 350 to 500 kcal per day, are poorly defined mixtures of amino acids, peptides, and polypeptides obtained from digests of collagen or other protein sources mostly of poor nutritional quality. These products generally contain nutritionally insufficient concentrations of certain essential amino acids and trace minerals. They have demonstrated low protein efficiency ratios. However, none of the samples analyzed has been shown to contain environmental contaminants, other toxic substances, or hazardous levels of minerals such as the heavy elements.

Three separate studies of rats fed commercial hydrolysed protein demonstrated no cardiac pathology by light microscopy except for myocardial lymphocytic infiltration in 4 of 16 animals whose dietary supplements did not include micronutrients. Only one of the four had received collagen hydrolysate alone. Regardless of the type of protein supplement used, myocardial potassium levels were depressed in all animals not receiving a micronutrients supplement. In another study, electrocardiograms showed pronounced dysrhythmias in rats fed "liquid proteins" without vitamin and mineral supplements.

Fasting obese men receiving commercial "liquid protein" for 40 days as their sole source of calories showed significantly greater cumulative nitrogen loss than control fasting subjects whose isocaloric supplements consisted of high-quality protein. In a separate study, grossly obese men reportedly maintained positive nitrogen balance during 2 weeks of fasting supplemented by 1.5 g per kg ideal body weight of tryptophan-enriched collagen hydrolysate.
Thus, a limited number of tests suggest that the so-called "liquid proteins" or "predigested protein" products are inferior to proteins of high biological value in terms of weight gain and growth in rats and in preventing excess nitrogen loss in obese men during prolonged, supplemented fasts. However, the available evidence is insufficient to allow a firm conclusion regarding the nitrogen-sparing ability of such products in fasting, obese human adults. Cardiotoxicity of these substances in rats has not been convincingly demonstrated, but cardiac dysrhythmias have been observed in rats. Long-term animal feeding studies using these products have not been reported.

The following pages contain detailed conclusions presented according to the main topical headings of the report.
• While improved prevalence, morbidity, and mortality data on obesity are becoming available, the true incidence is unknown; thus better data are needed to permit estimation of incidence of obesity and its associated morbidity and mortality. Of equal or greater significance, the etiologies and pathogeneses of the obesities are not fully understood. Hope for improved classification, prevention, and treatment of the obesities depends in part on resolution of these inadequacies in scientific knowledge.

• Most reported experiences with dietary treatment of gross obesity have been disappointing, particularly with respect to maintaining reduced weight status. However, balanced deficit diets tailored to individual needs as well as extremely low-calorie diets such as the protein-sparing modified fast, when used as part of a multidisciplinary program including diet counseling, prescribed exercise, and behavior modification, are said to achieve significant, enduring results.

• While the protein-sparing modified fast using high-quality protein under careful medical supervision has enjoyed a nearly unblemished safety record as a means of rapid weight reduction of severely obese adults and appears to be increasing in popularity among physicians, some authorities consider it an investigative-type procedure not yet suitable for general outpatient use.

• Clinical, physiological, and other contraindications for using extremely low-calorie, protein regimens for weight reduction have been published. However, some experienced clinicians regard most common adult ailments, including heart diseases, not to be contraindications. The decision to use total or modified fasting should involve expert medical assessment of expected benefits versus risk on an individual basis.
EFFECTS OF STARVATION AND SEVERE CALORIC RESTRICTION
(pages 17 to 23)

- Survivals of between 17 and 76 days of complete starvation of nonobese human adults have been reported while grossly obese persons have survived for many months on nothing but noncaloric liquids and energy from their own bodies, primarily fat stores. Death from starvation reportedly occurs after the loss of about 50 percent of ideal body weight; however, the exact mechanism(s) of death from starvation is unknown.

- Nearly all organs atrophy during starvation, the central nervous system showing the least effect. In starving animals, a state of "pseudohypophysectomy" occurs, reflected by generally depressed endocrine functions. In fasting obese humans, reversible "physiologic hypothyroidism" features the adapted state.

- The continuing, obligatory loss of lean body mass in starvation is the most significant difference between the effects of starvation and those of protein-supplemented fasting at levels of severe caloric restriction (for example, 300 to 500 kcal intake per day).

- Circulating levels of the biologically important minerals and electrolytes usually stabilize within normal limits during prolonged total fasting in obese individuals; however, little is known about their tissue concentrations in such circumstances.

- Consumption of protein products that contain insufficient amounts of essential amino acids, when used as the sole source of dietary protein over prolonged periods, may lead to critical amino acid imbalances and impaired protein metabolism. While information about the effects of amino acid imbalances in obese subjects undergoing therapeutic fasting is incomplete, such imbalances are thought to be potentially hazardous.

- Serious deficiencies in knowledge include the minimum human nutritional requirements for protein, fat, carbohydrate, and all other essential nutrients to prevent irreversible metabolic and functional changes in the myocardium, cardiac conduction system, central nervous system, and the neuroendocrine system including such requirements for grossly obese individuals. Knowledge of the pathogenic tissue deficiency levels of the biologically important minerals and their corresponding blood levels is incomplete.
Seventeen obese, otherwise healthy adults died unexpectedly of ventricular tachyarrhythmia and cardiac arrest during or just after completing long-term fasts supplemented with protein products as the sole or principal source of calories. The only consistent pathologic findings in the hearts of these decedents were fiber-size attenuation, featuring marked variation but an absolute reduction in fiber size, and excess lipofuschin deposition. Similar changes have been found in hearts of cachectic patients dying of cancer or other nondietary causes. Several of the specimens showed focal aggregates of five or six inflammatory cells, but only one contained sufficient round cell infiltration to support a diagnosis of myocarditis.

Unequivocal prolongation of the QT interval and decreased QRS voltage were demonstrated in nine of the decedents shortly before death or toward the end of their dieting periods. These are evidently characteristic features in susceptible individuals undergoing massive and rapid weight reduction by severe caloric restriction. The mechanism(s) of such cardiac changes is unknown.

In total starvation, the heart undergoes atrophy along with the rest of the body, and a characteristic histologic change is decreased myocardial fiber size. Bradycardia of 50 beats per minute characterizes the undernourished heart, and typical electrocardiographic changes include reduced voltages in all deflections and prolongation of both systole and diastole.

The notion that hypokalemia may lead to fatal cardiac dysrhythmias in man, a generally accepted principle among clinicians, lacks adequate scientific documentation. In addition, the question of whether significant hypokalemia occurs in obese subjects on prolonged fasts without potassium supplements remains open.

The only prospective study of human magnesium deficiency found in this review showed that magnesium deprivation led to hypocalcemia despite calcium supplementation, and to hypokalemia and negative potassium balance. Magnesium depletion, per se, did not appear to cause electrocardiographic changes.
• Evidence suggests that only at fatal levels of calcium deficiency would hypocalcemia be associated with any significant effect on myocardial resting transmembrane potentials and phase 4 depolarization, both of which are important in the genesis of dysrhythmias. Such profound degrees of calcium depletion are not anticipated in therapeutic fasting of obese individuals.

• It has been suggested that persons using "liquid protein" diets as the sole source of mineral nutrients would consume less than one-tenth the adult daily requirement of copper. Although copper deficiency has been investigated in domestic and experimental animals, the possible pathophysiological significance in otherwise normal human adults is largely unknown.

• The availability of branched-chain amino acids is known to be a key factor responsible for the effects of amino acids on protein synthesis in heart and skeletal muscle; however, the effects of amino acid availability and fatty substrates on cardiac proteolysis have not been extensively investigated.
EFFECTS ON OTHER ORGANS AND SYSTEMS
(pages 37 to 50)

• The liver atrophies during prolonged fasting, but seems to retain metabolic capabilities sufficient for the fasted state. Hyperbilirubinemia of unknown clinical significance has been observed during therapeutic fasting, as have increased sulfobromophthalein retention and reduced hepatic steatosis.

• Normal kidneys appear to tolerate prolonged fasting without functional impairment. However, subjects with renal disease are susceptible to hyponatremia during fasting.

• Except for valine, leucine, and isoleucine, which increase, arterial plasma amino acid concentrations measured across human forearm muscle decrease in nonobese subjects during a 60-hour fast. Human striated muscle appeared normal to electron microscopy after 2 months' fasting; however, in prolonged, unsupplemented fasting, the continuing obligatory loss of lean body mass may deplete critical protein stores, leading to irreversible tissue changes including damage to the myocardial conduction system.

• Young rats fasted for 72 hours demonstrated a 6-fold increase over control values in myofibrillar protein catabolism, and dietary omission of certain single amino acids, except arginine, resulted in decreased skeletal muscle weight and protein content. The branched-chain amino acids as well as complete plasma amino acid mixtures inhibit protein degradation in rat diaphragm.

• Skeletal muscle paralysis, rhabdomyolysis, and myoglobinuria associated with severe potassium depletion have been demonstrated in dogs and man, but are unusual in potassium-depleted rats.

• In undernourished, phosphorus-deficient dogs, refeeding with excess calories and no phosphorus caused severe hypophosphatemia and rhabdomyolysis. Clinical and laboratory evidence suggests that when hypophosphatemic undernourished individuals are abruptly refed carbohydrate without phosphorus supplementation, muscle weakness and rhabdomyolysis may occur.

• Neurologic signs and symptoms during therapeutic starvation or protein-sparing modified fasting are rarely reported; however, there is evidence of possible catecholamine imbalances in sympathetically innervated organs during fasting.
The significance of endocrinologic changes associated with severe caloric restriction is not well understood. The thyroid and pancreas undergo atrophy approximately in proportion to total body weight loss, the adrenal glands less, and the brain least of all. Some investigators believe that in a carefully conducted therapeutic fast supplemented by about 1.5 g per kg ideal body weight of high-quality protein, essential endocrine functions are preserved. Others consider that endocrine changes may represent a critical point at which to stop or modify weight reduction regimens based on severe caloric restriction. However, good data on the endocrinologic effects of severe caloric restriction are scarce.

While respiratory failure, per se, may have been a contributing factor in the deaths in the CDC series (pages 21 and 55), insufficient information is available on respiratory effects of starvation to determine their possible significance.

Malnutrition leads to atrophy of lymphoid tissues and tends to suppress cell-mediated, humoral, and secretory immune competence. Immunosuppression may result from deficiency of a single essential nutrient. On the other hand, in children with protein-calorie malnutrition, elevated levels of specific immunoglobulins have been reported as has increased resistance to certain viral infections.

Delayed hypersensitivity skin testing in obese patients undergoing prolonged protein-supplemented fasting has not revealed any impairment of cellular immunity even after major weight loss. While it is evident that only limited studies of the relationship between caloric deficits and immunocompetence have been done in obese subjects using severe caloric restriction to reduce body weight, immunologic dysfunction did not appear to be a significant factor in the 17 decedent dieters or in large numbers of obese subjects who have achieved major weight reduction with the protein-sparing modified fast.
DYSRHYTHMIAS AND CARDIOMYOPATHIES
(pages 51 to 59)

- Severe, reversible, congestive cardiomyopathy has been reported in patients using phosphate-binding antacids for long periods. One of the decedents in this review used antacids for esophageal reflux; her serum phosphates were normal one day before death. Two others had subnormal serum phosphate values upon hospital admission. However, none of the 17 decedents had a diagnosis of congestive heart failure.

- Bronchodilators such as isoproterenol and vasodilating antihypertensives such as hydralazine have been shown to produce myocardial hypoxia and subendocardial necrosis, and the sympathomimetic bronchodilators cause vasodilation and tachycardia. Although two of the decedents had histories of asthma, only one took an occasional dose of a noncardiotoxic antiasthmatic drug during the dieting period.

- Conduction disturbances, dysrhythmias, and cardiac necrosis have been induced in experimental animals by exposure to excessive amounts or degrees of agents such as norepinephrine, thyroxine, sodium salts (except sodium chloride), cold, heat, and restraint, particularly under conditions of potassium deficiency. Potassium has been shown to protect the heart against most of these agents. However, there is no evidence that any of the foregoing factors was involved in the deaths reviewed in this report.

- Local release of norepinephrine at cardiac sympathetic nerve endings has been shown to induce a lesion similar to the myofibrillar degeneration caused by administration of exogenous norepinephrine. The amounts of norepinephrine released in the heart during moderately excessive sympathetic stimulation are theoretically comparable to levels achieved by parenteral injections and are therefore considered sufficient to induce myofibrillar degeneration.

- The hearts of rhesus monkeys that were fed protein-deficient diets for 12 weeks showed some pathologic changes that were similar to those found in specimens from most of the decedents.

- Somewhat uncommon cardiac disorders, not diet- or obesity-related, which predispose to sudden death and may go undetected for years, include the heritable and acquired long QT interval syndromes and torsade de pointes. One
of the decedents in this review had prior electrocardio-
graphic evidence of increased QT interval (uncorrected),
but no history of cardiac symptoms. Another was thought
to be a possible case of torsade de pointes. In addi-
tion, sudden, presumably cardiac deaths have been
reported in persons with no previous history of heart
disease whose hearts at necropsy revealed no morphologic
pathology. Although these types of disorders cannot be
absolutely excluded in most of the 17 decedents, the
probability of their involvement, except as described
above, appears slight.
INFLUENCE OF AGE, SEX, RACE, AND OTHER FACTORS
(pages 61 to 63)

- The fact that 16 of the 17 decedent subjects of this review were white premenopausal women appears to indicate that sex, age, and race influenced the risk of death in these cases. However, all available data from the CDC, the scientific literature, and consultant opinion suggest that an artifact in reporting may be responsible for the apparent importance of these factors.

- Consultants for this review regarded the high rates of weight loss (average 4.6 lb per week, range about 2.5 to 7.0 lb per week) and the zealous adherence to the severely restricted diets as possible factors in the deaths.

- Data from the 16 female decedents suggest there may be a direct relationship between degree of obesity and safe duration of very low-calorie, protein diets. Three subjects who survived 3 months or less were only moderately obese as defined in this review. The fact that three of the 16 died after 2 to 2.5 months of dieting while others survived 7.5 to 8 months suggests marked individual differences in adaptability to such regimens.

- In addition, the consultants considered significant the fact that 6 of the 17 decedent dieters had discontinued the very low-calorie, protein diet and had commenced the limited refeeding phase.
X. SUGGESTIONS FOR FUTURE CONSIDERATION

OBESITY (EPIDEMIOLOGICAL INVESTIGATIONS)

Current inability to estimate the true incidence of the obesity in the United States, and their associated morbidity and mortality, hampers the development of urgently needed improvements in classification, diagnosis, prevention, and treatment. Reliable incidence figures for selected population subgroups should aid, as well, in elucidating the etiologies of various types of obesity.

- Despite some recent progress, better data on the prevalence of obesity in the United States are needed. These data should be based on a larger sample of the population than has been used to date. Provision should be made to differentiate morbid from moderate obesity.

- Additional data are needed on the prevalence of sudden, unexpected, cardiogenic death in the United States population (including grossly obese individuals) with no prior history of heart disease and no demonstrable cardiac pathology.

- Improved data are also needed on obesity-associated morbidity and mortality. Such data should be so classified that the high-risk obese person can be identified.

- Opportunities exist to collect morbidity and mortality information associated with the use of very low-calorie diets (<800 kcal per day) for weight reduction in thousands of obese individuals. Some of the larger clinics specializing in weight control could be sources of such information, and additional data could be obtained via the Society of Bariatric Physicians.

- Little is known about the pathology associated with obesity. Such information could be gathered from apparently healthy individuals who die in accidents.

- With regard to the deaths associated with the very low-calorie protein diets, better data are needed to validate the estimated mortality rate. Information is being collected to improve the denominator for selected types of cardiac deaths among premenopausal women. A better estimate of the number of persons using such diets who exceed their ideal body weight by 100 percent or more, and reliable, associated mortality data would improve the basis for public education related to the safety of severely restricted energy diets.
• Information on electrocardiographic changes in individuals who experience major weight loss should be collected systematically. This should include measurements of possible diurnal variations such as may occur with nocturnal hypoxemia.

• Epidemiologic data should be collected on clinical improvements in severely obese subjects with cardiac, respiratory, hepatic, renal, and metabolic diseases following major and sustained weight reduction.
Although much is known about the physiologic and pathologic effects of severe undernutrition, knowledge is only fragmentary in certain areas, including some that may have critical importance in the safety of severe caloric restriction as a means of treating gross obesity. Several areas in which knowledge is incomplete are indicated in the following suggestions.

- Identification of critical, irreversible pathophysiologic changes during prolonged starvation and severe caloric restriction should be attempted in experimental animals. Biologic indicators of such changes should be sought, and possible factors influencing adaptability to such regimens should be investigated. Examples of factors might include age, sex, degree of overweight, duration of energy deprivation, nature and degree of essential mineral and/or vitamin deficiency. Finally, the applicability of possible biologic indices to human subjects undergoing severe caloric restriction for massive weight reduction should be assessed in carefully controlled, prospective studies in medically supervised clinical settings.

- The precise mechanisms of death by starvation should be determined in appropriate animal models, isolated organs, and tissue culture systems.

- There is a need for better data to aid in defining safe refeeding strategies for persons who have starved or who complete major weight reduction by severe caloric restriction.

- Experiments should be devised to determine whether starvation with obesity versus starvation without obesity makes a difference in adaptation to and tolerance for severely restricted energy intakes.

- Investigations of relationships between serum and tissue levels of electrolytes and essential minerals and associated pathophysiology should be stimulated. Improved methods short of biopsy are needed for the estimation of tissue levels. Special emphasis is needed on methods of detecting tissue depletion of magnesium, potassium and phosphorus, including myocardial levels, in the presence of normal or low-normal serum levels.

- Additional studies should be done to determine optimal daily intakes of supplementary vitamins during rapid weight reduction of grossly obese persons by severe caloric restriction.
- An unresolved question concerns the possibility of essential fatty acid deficiency occurring during treatment of gross obesity by severe caloric restriction. Clinical investigation should be conducted to determine the influence of such dietary regimens on levels of circulating essential fatty acids. If deficiencies were demonstrated, clinical trials should be done to establish appropriate dosages of supplemental essential fatty acids.

- A review should be conducted to determine the possible need for additional research on the effects of prolonged or supplemented fasting on gastrointestinal function including absorption of nutrients and the frequency of such complications as blind loops and bacterial overgrowth.

- An effort should be made to consider the total impact of all stresses, including psychologic, acting on individual obese subjects undergoing drastic weight reduction by severe caloric restriction in terms of adaptability to the regimen. Does the highly-stressed individual represent a greater risk than the relatively unstressed?

- The question of the possible mobilization of significant quantities of toxic substances stored in adipose tissues during prolonged caloric restriction in obese subjects should be investigated more thoroughly to determine what is known and whether additional studies should be done. Appropriate studies could then be devised to measure such substances in obese human subjects during major weight reduction programs.

- The influence of "liquid protein" products on blood volume should be compared with that of high-quality protein in otherwise fasting animals.

- The possible effects of "liquid protein" products on blood-oxygen dissociation should be determined.

- Evidence suggests that urinary 3-methyl histidine excretion may be a good, noninvasive method of estimating protein degradation. Its value in monitoring major weight reduction should be assessed and compared with other methods.

- Serum creatinephosphokinase and creatine kinase MB (myocardial) isoenzyme assays should be further investigated as methods for monitoring the integrity of skeletal and cardiac muscle during severe caloric restriction.
• The potential of plasma prealbumin and retinol-binding protein concentrations as clinical indices of protein-energy malnutrition should be investigated in obese persons undergoing rapid, massive weight reduction by severe caloric restriction.

• Qualitative and quantitative determinations of peptides and polypeptides in commercial hydrolysed collagen and hydrolysed gelatin ("liquid protein", "predigested protein") should be done.

• Variation in composition of commercial "liquid protein" and "predigested protein" products means that different investigators use test lots of different composition. Consideration should be given to convening a workshop of investigators to establish standards of experimental approach, animal models, and test substances including standard formula hydrolysed protein products, as well as how best to control all variables so that results from different laboratories may be meaningfully compared.
CARDIAC EFFECTS OF CALORIC DEPRIVATION AND MINERAL-ELECTROLYTE IMBALANCE

Those parts of this review that deal with the cardiovascular effects of severe undernutrition and nutrient deficiencies and imbalances have helped to identify several areas of incomplete knowledge. Investigations of these areas should assist in developing concepts of the pathogenesis of associated cardiac pathology and dysfunctions. It is hoped that some of the suggested studies may lead to an understanding of the mechanisms of cardiac dysfunctions that occurred in the recent series of deaths involving rapid weight reduction in obese persons associated with the use of very low-calorie, protein diets.

Animal Studies

- If a suitable obese animal model can be identified, tests using the "predigested protein" products should be done in an attempt to simulate closely the dietary regimens and cardiac responses of the decedents. Miniature pigs or obese dogs may be suitable animal models. Results of a recent major meeting at the Oregon Primate Center should be considered regarding possible primate models. Cats have proved useful in studies of taurine deficiency. Experimental variables should include electrolytes and trace minerals. Such tests should be designed to probe the hypothesis that a poor-quality protein product, unbalanced in amino acids, containing excess proportions of hydroxy amino acids, would add sufficient stress to the otherwise starving organism to cause the type of cardiac responses observed in the decedents. An extension of the hypothesis is that marginal deficiencies in potassium, magnesium, and phosphorus might, in combination with the hydrolysed collagen diet, cause cardiac changes that would not be found in either circumstance separately.

- A similar animal model study should be done using high-quality protein in a simulated protein-sparing modified fast. In all such experiments, body composition studies should be done to determine rates and sources of protein loss. In addition, all organs should be carefully examined for histopathologic changes.

- Recently reported cardiac dysrhythmias in rats fed "liquid protein" without mineral supplements should be confirmed and extended by additional investigations.
Basic studies of myocardial cell composition in fasting animals should be done using modern tissue analytical techniques to determine molecular anatomy; also, nuclear magnetic resonance procedures should be used to examine intracellular ATP and adenylic acid metabolism and to locate the compartmentalization of electrolytes within the cell. Correlation of the measurements with electrophysiologic changes should be attempted; changes in cell permeability and cell wall structure and the location of lipid changes should be determined in such undernourished hearts. The influence of the thyroid hormone, T₃, insulin, and individual specific nutrients on such changes should be studied.

Cellular composition should be determined not only of the cardiac muscle cells, but also of all other cells in the hearts of fasted animals fed supplements of high-quality protein or hydrolysed collagen supplements as well as non-fasted controls. Parameters should be included that can be readily assessed by quantitative electron microscopy such as lysosomal and mitochondrial changes.

The mechanism of changes in cardiac conduction including the QT interval in various nutritional states including fasting supplemented with high- or low-quality protein should be investigated. His bundle electrocardiography in animals is one feasible approach.

The energy metabolism of perfused working hearts of animals that have been subjected to typical protein-sparing modified fasts and to fasts supplemented by hydrolysed collagen should be measured. Identification of the energy substrates actually used by hearts in such circumstances is needed. Nuclear magnetic resonance is a feasible technique for quantitative studies of carbon-13 and phosphorus metabolism.

Another hypothesis that should be tested in animals is that, superimposed on continuing, rapid losses of lean tissue, individual or aggregate deficiencies of potassium, magnesium, phosphorus, and other biologically important minerals induce electrical changes in the myocardium that result in conduction disturbances, reduced systolic voltages, and dysrhythmias.

Investigation should be conducted of possible abnormalities in the hormonal regulation of protein turnover in the hearts of animals, including obese animals, that are subjected to caloric restriction or unbalanced amino acid mixtures and whether specific proteins whose turnover may be affected in such circumstances can influence cardiac performance.
The hearts of animals fed hydrolysed collagen or gelatin as the sole source of protein should be analyzed to detect possible effects on amino acid balance including the branched-chain amino acids and possible disturbances of protein metabolism such as taurine depletion secondary to insufficient intake of the sulfur amino acids.

Metabolic patterns and possible effects on cardiac performance should be determined in working hearts perfused with mixtures of amino acids that contain hydroxyproline and hydroxylsine at levels found in commercial hydrolysed collagen or gelatin.

Possible effects on heritable receptor sensitivity in the cardiac conduction system of specific amino acid or hormone deficiencies that might occur in supplemented fasting regimens should be investigated.

Clinical Studies

Very little, if any, information is available on the possible 24-hour electrocardiographic changes in grossly obese subjects undergoing rapid weight reduction by severe caloric restriction. A study should be done using ambulatory electrocardiographic recording (Holter monitoring) periodically in such a group.

The question of whether severe caloric restriction in obese persons may induce relative tissue hypoxia via its influence on cardiovascular function and by other possible mechanisms should be investigated. If myocardial hypoxia should prove to be a potential consequence, its relationship to other dysrhythmogenic factors such as increased myocardial cyclic AMP or the degradation of the ability of free fatty acids to maintain action-potential duration should be studied.

The question of possible changes in norepinephrine turnover and their relationship to cardiac dysrhythmias during severe caloric restriction in obese subjects should be clarified.

Systolic ejection fractions, systolic time intervals, and left and right ventricular volumes using noninvasive radionuclide techniques could be added to experimental protocols in order to determine their utility and practicality as an alternate cardiac monitoring method.
• In view of a concept that an unusually small left ventricular end-diastolic dimension in anorexia nervosa patients might aid in identification of risk for ventricular ectopic beats and possible dysrhythmic deaths, dimensional changes of this sort in obese subjects undergoing weight reduction by severe caloric restriction should be investigated, using available noninvasive technics.

• The relation between the natriuresis of semistarvation and orthostatic hypotension should be assessed quantitatively.

• The orthostatic tolerance test should be considered as a clinical monitoring technique for patients undergoing rapid weight reduction.
EFFECTS ON OTHER ORGANS AND SYSTEMS

- A search for possible effects on the central nervous system of very restricted-calorie diets, supplemented with high- or low-quality protein, should be undertaken. It should include the pituitary-adrenal axis as well as the central cardiac innervation and its neurophysiology. If effects are found, possible mechanisms should be investigated such as involvement of energy depletion or amino acid depletion.

- Neurological aspects of major weight loss in severely obese subjects should be investigated to identify possible changes, and, if found, to relate them to variables in the mode of weight reduction such as rate, degree of energy deprivation, and quality of supplemental protein. Such investigations should include consideration of neuroendocrine effects.

- The role of total caloric intake and of individual nutrients on the immune response and on susceptibility to infectious challenge should be studied.

- While no significant changes in cellular immune function or in resistance to infection have been documented in otherwise healthy obese subjects undergoing therapeutic fasting or protein-supplemented fasting, some doubts exist regarding possible alterations in immunocompetence during such regimens. Additional studies on the effects of severe caloric restriction in the management of severe obesity should be done to validate existing information in this area and to develop possible alternate methods of monitoring immunocompetence.

- The effects of starvation and extremely low-calorie, protein diets on respiratory physiology should be investigated to determine pulmonary susceptibility and adaptability to such regimens.

- The mechanisms of increased serum bilirubin and serum glutamic oxaloacetic and pyruvic transaminase that are observed in obese subjects on protein-sparing modified fasts should be investigated.
DYSRHYTHMIAS AND CARDIOMYOPATHIES

- Kinetic studies of intracardiac norepinephrine turnover in response to sympathetic nervous system function should be expanded to include variables involved in protein-supplemented fasting of obese animals.

- The possible dysrhythmogenicity of elevated levels of free fatty acids should be investigated as should the effect of diurnal variations in lipoprotein lipase levels on FFA uptake in the undernourished heart.

- The feasibility and desirability of additional investigation of abnormal hemoglobin-oxygen dissociation as a possible factor in inducing myocardial ischemia and necrosis in normal hearts should be determined.

- Decreased capillary density is found in deconditioned muscle. This should be looked for in hearts of fasted animals because of its potential importance in terms of impaired supply of nutrients and oxygen to the myocardium.

INFLUENCE OF AGE, SEX, AND OTHER FACTORS

- The influence of the rate of weight loss in fasting animals on cardiovascular function and other parameters should be studied.

- The influence of exercise on the maintenance of cardiovascular fitness and possible risks of over- or under-exertion during major weight reduction should be investigated.


Thomson, T.J.; Runcie, J.; Miller, V. 1966. Treatment of obesity by total fasting for up to 249 days. Lancet 2:992-996.


XII. STUDY PARTICIPANTS

A. ATTENDEES, AD HOC CONFERENCE, NOVEMBER 30 AND DECEMBER 1, 1978

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APPENDIX I

SUMMARY OF CARDIAC COMPLICATIONS AND DEATHS ASSOCIATED WITH THE USE OF VERY LOW-CALORIE, PROTEIN DIETS FOR RAPID WEIGHT LOSS

As of mid-1978, 58 deaths reported to have been associated with the use of very low-calorie, protein diets for weight reduction had been investigated by FDA and CDC (Center for Disease Control, 1979). Of the 58 decedents, 17 were identified who fitted a distinctive set of criteria:

- All were Caucasians between 25 and 44 years old, and all but one were women.
- Except for gross obesity, all had been essentially healthy, with no evidence of significant heart disease.
- All had undergone massive weight reduction by strict fasting supplemented with commercially available protein products as the sole source of calories.
- All died unexpectedly and rather suddenly during or shortly after completing their weight reduction regimens.
- The deaths were cardiac in nature, featuring syncope, intractable ventricular tachyarrhythmias, and cardiac arrest.
- Postmortem examination revealed no significant coronary heart disease.

None of the 17 decedents chosen for detailed follow-up study showed evidence of underlying medical problems that could have caused their deaths. All reportedly followed the dietary guides strictly. Most consumed daily caloric intakes provided by 85 to 200 ml (3 to 7 ounces) of hydrolysed collagen or gelatin products (estimated to supply approximately 300 kcal). Most included a daily multivitamin and mineral supplement of the prenatal type. During a portion of their dieting, three of the women added high-quality protein to their "predigested protein" supplements, and the one man in the series reportedly consumed a protein product of high biologic value. The completeness and dosages of the mineral supplements undoubtedly varied; for example, among various mineral supplements available over-the-counter, some contain no copper, phosphorus, manganese, or zinc, and quantities of other mineral components are nonuniform. While compliance in taking the protein supplements, vitamins, and minerals may have been good, it remains conjectural.
The duration of dieting by the 16 women varied from 2 to 8 months, with a mean of approximately 5 months. Average weight loss was 38 kg (83 lb), range 9 to 63 kg (20 to 139 lb), and mean rate 2 kg (4.6 lb) per week. Eleven subjects had medical supervision which varied from thorough, with laboratory backup, to intermittent without laboratory data.

While hair-loss and cold-intolerance were frequently reported, most of the dieters felt well during the dieting and expressed pleasure with their progress in weight reduction. Ten of the women took no medication during the dieting period. Of the other six women, one took birth control pills; one an occasional dose of Marax® for asthma; one took cimetidine for esophageal reflux and a benzodiazepine tranquilizer; two took phenothiazine tranquilizers (one with a monosulfamyl diuretic for dependent edema caused by incompetent veins and the other with an antidepressant); and one took an occasional tablet of alpha-methyldopa, which she had formerly taken for borderline hypertension.

Six of the women had begun refeeding programs shortly before the fatal episodes (duration of refeeding varied from 1 day to 2 to 3 weeks). Six died in-hospital following admission for syncope; four had cardiac arrests outside the hospital but died in-hospital, without regaining consciousness; and six died suddenly outside the hospital. The ten subjects who died under medical observation had ventricular tachycardia and fibrillation which were very refractory to the usual antidysrhythmia treatment. Appendix I, Tables 1 to 3 list clinical and laboratory data of the 17 decedents.

The originally reported cardiac pathology is listed in Appendix I Table 2. In addition, representative tissue specimens from 14 of the hearts were independently examined at the National Heart, Lung, and Blood Institute (Isner et al., 1979). Data presented during the meeting of the LSRO review group indicated that all the hearts consistently showed fiber-size attenuation with marked variation in fiber size, an absolute reduction in size, disappearance of myofibrils, and excessive lipofuchsin deposition. Similar findings have been noted in cachectic patients who died of nondiet-related causes. Case No. 4 had unequivocal evidence of myocarditis with lymphocyte infiltration. There was no history of a preceding viral infection in this patient. Several of the heart specimens had focal aggregates of five or six inflammatory cells of unknown significance but insufficient to support a diagnosis of cardiac necrosis or myocarditis. Similar phenomena have been found in otherwise normal hearts of persons dying of trauma. Thus, based upon the follow-up examinations, only one of the six original diagnoses of myocarditis could be sustained.
Appendix I Table 1. Clinical Data on 17 Decedents (Center for Disease Control, 1979)

<table>
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<th>Case #</th>
<th>Age (years)</th>
<th>Height in Inches (cm)</th>
<th>Pre-Diet Weight in Pounds (kg)</th>
<th>Weight Loss in Pounds (kg)</th>
<th>Percent Weight Loss</th>
<th>Duration of Diet (mos)</th>
<th>Rate of Weight Loss in Pounds (kg)/wk</th>
<th>Death During Refeeding</th>
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<td>41</td>
<td>5</td>
<td>4.9(2.2)</td>
<td>No</td>
</tr>
<tr>
<td>35</td>
<td>36</td>
<td>63(160)</td>
<td>298(135)</td>
<td>107(49)</td>
<td>36</td>
<td>7</td>
<td>3.8(1.7)</td>
<td>No</td>
</tr>
<tr>
<td>37</td>
<td>41</td>
<td>64.5(164)</td>
<td>229(104)</td>
<td>80(36)</td>
<td>35</td>
<td>5</td>
<td>4.0(1.8)</td>
<td>Yes</td>
</tr>
<tr>
<td>44</td>
<td>23</td>
<td>69(175)</td>
<td>281(128)</td>
<td>83(38)</td>
<td>30</td>
<td>4</td>
<td>5.2(2.4)</td>
<td>No</td>
</tr>
<tr>
<td>56a</td>
<td>43</td>
<td>74(188)</td>
<td>405(184)</td>
<td>180(82)</td>
<td>44</td>
<td>7</td>
<td>5.9(2.7)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*a Male
| Case No. | Admission ECG | Precipitating Events | Circumstances of Death | Cardiac Findings at Autopsy$^2$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low volt; prolonged QT$_C$</td>
<td>Syncope</td>
<td>in hospital, intract vent tach</td>
<td>Round cell infilt of myocardium</td>
</tr>
<tr>
<td>2</td>
<td>Low volt; prolonged QT$_C$</td>
<td>Disorient; collapse</td>
<td>in hospital, intract vent tach</td>
<td>Round cell infilt of myocardium</td>
</tr>
<tr>
<td>3</td>
<td>Low volt; prolonged QT$_C$</td>
<td>Syncope</td>
<td>in hospital, intract vent tach</td>
<td>Round cell infilt of myocardium</td>
</tr>
<tr>
<td>4</td>
<td>LAD, VPCs, LBBD$^3$</td>
<td>Syncope</td>
<td>in hospital, supravent tach, vent fibr</td>
<td>Round cell infilt of myocardium$^4$</td>
</tr>
<tr>
<td>5</td>
<td>Low volt; prolonged QT$_C$</td>
<td>Syncope; seizure?</td>
<td>in hospital, intract vent tach</td>
<td>Round cell infilt of myocardium</td>
</tr>
<tr>
<td>6</td>
<td>Low volt; prolonged QT$_C$; sinus tach</td>
<td>—</td>
<td>found dead at home</td>
<td>No pathol reported</td>
</tr>
<tr>
<td>7</td>
<td>Sinus tach</td>
<td>Syncope</td>
<td>repeated cardiac arrests; decerebrate</td>
<td>No autopsy</td>
</tr>
<tr>
<td>8</td>
<td>—</td>
<td>Severe dyspnea in bed</td>
<td>severe dyspnea, DOA hospital</td>
<td>PMN infilt of myocardium</td>
</tr>
<tr>
<td>9</td>
<td>—</td>
<td>Syncope; dyspnea; seizure</td>
<td>repeated vent tach and fibr</td>
<td>Dilated ventricles</td>
</tr>
<tr>
<td>10</td>
<td>Low volt; prolonged QT$_C$</td>
<td>—</td>
<td>found dead at home</td>
<td>Atrophy, focal frag-mentation myocardial fibers</td>
</tr>
<tr>
<td>11</td>
<td>—</td>
<td>—</td>
<td>found dead at home</td>
<td>No pathol reported</td>
</tr>
<tr>
<td>22</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>29</td>
<td>Sinus tach; low volt; elevated ST</td>
<td>Unconscious; resuscitated</td>
<td>dizzy, arrhythmias, vent fibr</td>
<td>No cardiac pathol reported</td>
</tr>
<tr>
<td>35</td>
<td>—</td>
<td>Collapsed</td>
<td>DOA hospital</td>
<td>Soft flabby heart</td>
</tr>
<tr>
<td>37</td>
<td>LGL syn; prolonged QT$_C$</td>
<td>—</td>
<td>found dead at home</td>
<td>Round cell infilt of myocardium</td>
</tr>
<tr>
<td>44</td>
<td>Vent fib; low volt; prolonged QT$_C$</td>
<td>Collapsed</td>
<td>coma, vent fibr, cardio-resp fail</td>
<td>Abnormal size, shape, stain of myocardial cell nuclei</td>
</tr>
<tr>
<td>56</td>
<td>Low volt; prolonged QT$_C$</td>
<td>Syncope</td>
<td>coma, vent fibr</td>
<td>Atrophy myocardial fibers possible early infarct</td>
</tr>
</tbody>
</table>

$^1$ QT$_C$ = QT/$\sqrt{RR}$

$^2$ Based on original autopsy reports. Subsequent independent examination of tissues at the National Heart, Lung and Blood Institute consistently revealed variation and absolute reduction of myocardial fiber size, disappearance of myofibrils, and abnormal lipofuscin deposits in myocardium. Several specimens showed focal aggregations of 5-6 inflammatory cells, insufficient to diagnose myocarditis or cell necrosis.

$^3$ Left axis deviation; ventricular premature contraction (ventricular ectopic beat); left bundle branch block (from a description of the ECG).

$^4$ Unequivocal myocarditis with lymphocyte and polymorphonuclear leukocyte infiltration.

$^5$ QT prolonged prior to diet, but further prolonged after weight loss.

$^6$ Routine office ECG about 4 wk antemortem; Lown-Ganong-Levine syndrome (short PR interval but no delta wave or QRS widening).
### Appendix I Table 3. Laboratory Data of 17 Decedents (Center for Disease Control, 1979)

<table>
<thead>
<tr>
<th>Case #</th>
<th>Daily Dosage of K⁺ (mEq)</th>
<th>Range of Serum K⁺ During Diet (mEq/l)</th>
<th>Laboratory Data on Hospital Admission</th>
<th>ECG</th>
<th>Long QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>3.6-5.2</td>
<td>3.6</td>
<td>8.8</td>
<td>1.7</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>—</td>
<td>2.9</td>
<td>9.0</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>3.1-3.9</td>
<td>3.6</td>
<td>8.9</td>
<td>2.2</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>—</td>
<td>3.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>3.3-5.1</td>
<td>2.8</td>
<td>9.2</td>
<td>2.1</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3.4-4.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>4.2-4.8</td>
<td>3.3</td>
<td>7.8</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>3.0-4.3</td>
<td>3.1</td>
<td>8.8</td>
<td>2.3a</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>3.8-4.1</td>
<td>4.2</td>
<td>8.7</td>
<td>1.8</td>
</tr>
<tr>
<td>15</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>22</td>
<td>75</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>29</td>
<td>25-50</td>
<td>3.9-4.2</td>
<td>3.8</td>
<td>8.7</td>
<td>1.8</td>
</tr>
<tr>
<td>35</td>
<td>Unknown</td>
<td>2.2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>37</td>
<td>32-48</td>
<td>3.3-4.7</td>
<td>4.1c</td>
<td>8.8c</td>
<td>2.2c</td>
</tr>
<tr>
<td>44</td>
<td>24</td>
<td>3.5-4.9</td>
<td>3.9</td>
<td>8.5</td>
<td>1.6</td>
</tr>
<tr>
<td>56d</td>
<td>42-62</td>
<td>3.6-4.6</td>
<td>3.2</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

---

a Voltage not low, but decreased from baseline values.

b QTc prolonged prior to diet; further prolonged after weight loss.

c Studies performed shortly before patient's sudden death outside hospital.

d Male
To determine the dimensions of the public health problem, the government sought data on the numbers of citizens exposed to "liquid protein" diets. On the basis of a recent telephone survey of 6,616 females selected for interview from 19,200 households screened in the United States, Schucker and Gunn (1978) estimated that, during 1977, about 98,000 white women between 25 and 44 years old, most of whom were overweight, used "predigested protein" products as their sole or principal source of nourishment for at least 1 month. Of these, about 37,000 used the products for at least 2 months.

For estimating the mortality rate among women using "predigested protein" products in the United States, the CDC omitted from the group of 16 decedents the four women whose ages were outside the 25 to 44 years range and the one Canadian. Thus, 11 cases of unexpected cardiac deaths occurred in white women 25 years-of-age or older, but less than 45. They died between July 1 and December 31, 1977 (Center for Disease Control, 1979). Hence, the estimated mortality rate for this 6-month period was 11 per 37,000 women who used the "predigested protein" products for at least 2 months, or 59 deaths per 100,000 dieters per year.

The expected mortality rate among nondietering white women in the same age range who die as a result of heart diseases or abnormalities selected by the CDC as appropriate for comparison (acute myocarditis, cardiomyopathy, cardiac arrests, ventricular fibrillation) is 1.6 per 100,000 per year. The ratio of the two rates, 59/1.6, yields a relative risk of 37 for obese white women between 24 and 45 years-of-age who followed the "predigested protein"-supplemented fast for 2 months or more. Some of the participants in the LSRO review group questioned the accuracy of the denominator derived from the telephone survey. They noted that less than 3 percent of those surveyed could be classified as morbidly obese, and that the survey yielded a low frequency of matched controls. However, since these projections are based upon upper limits (95 percent confidence), the net effect is to overestimate the denominator and thus underestimate the risk.

In prior years, a few deaths among obese subjects who were undergoing therapeutic starvation or protein-supplemented fasts were reported (Cubberly et al., 1965; Garnett et al., 1969; Kahan, 1968; Spencer, 1968). In most of these cases, the subjects had manifest clinical disease, including heart disease in the cases reported by Spencer (1968); however, the young woman reported by Garnett and associates (1969) was apparently in good health at the start of her 30-week protein-supplemented fast and essentially asymptomatic until the 7th day of refeeding.

In their recent telephone survey of "liquid protein" product users in the United States, Schucker and Gunn (1978) noted that 70 percent had no medical supervision and only 13.5 percent had "continuous" medical supervision. At least one-third were not
taking supplemental potassium and 14 percent were taking no vitamin or mineral supplements. In addition, the survey projected that more than 200 per 100,000 white women between 24 and 45 years-of-age in this country undertook total fasts during 1977 for periods of 1 month or longer. Nearly half took no vitamin or mineral supplements and few took a potassium supplement.

Of the reasons given by survey respondents for stopping the "predigested protein" diets, 30 percent reported illness as a result of the diet, and of these, about one-fourth required hospitalization. Respondents not wishing to repeat the use of a liquid, powdered, or solid* product reported one or more of the following signs or symptoms: fatigue, tiredness, weakness, dizziness, "blackouts", "cardiac problem", swollen ankles, blood clots in legs, and loss of hair. Over 165 Complaint/Injury reports of adverse reactions and effects attributed to consumption of "predigested protein" products by consumers attempting to lose weight have been received by FDA; in addition, approximately 60 Drug Experience reports of adverse reactions have been received from users of "predigested protein" products (Food and Drug Administration, 1977).

*Wafers, capsules, or tablets
APPENDIX I

LITERATURE CITED


APPENDIX II

COLLAGEN- AND GELATIN-DERIVED PRODUCTS

Introduction. "Predigested protein" products are typically manufactured from whole protein of low nutritional quality such as collagen or gelatin. In the literature as well as in this report, they are often referred to as "liquid proteins". A key step in their production is the chemical breakdown of the protein molecules into peptides and amino acids by enzymic or acid hydrolysis. These protein hydrolysates are marketed in liquid form as "predigested liquid protein" or in powder, wafer, capsule, and tablet forms. Nomenclature for these products includes such terms as "PDLP", "protein-sparing fast", "protein supplement", "amino acids", "collagen", and "gelatin with tryptophan" (Anonymous, 1978a).

Such products should not be confused with the whole protein products of high biologic value that are widely used as components of nutritionally complete diets, with the hydrolysed protein components of prescription-quality chemically-defined diets (Fisher et al., 1977), or with the generally recognized as safe protein hydrolysates (Select Committee on GRAS Substances, 1978).

Use of the "predigested protein" products became popular in the United States in recent years, particularly after publication of a book entitled "The Last Chance Diet" (Linn and Stuart, 1976). Schucker and Gunn (1978) estimated that, in the 25 to 44 years-of-age group, at least 98,000 white women in the United States used a "liquid protein"-derived product in 1977 as the main or sole source of nutrition for at least one month. These products are available over-the-counter from various sources such as drug, grocery, and health food stores, and the existence of at least 218 brand names reflects the manufacturing and marketing interest (Schucker and Gunn, 1978). However, it is understood that the market for these products has recently declined (Forbes, 1979; Kramer, 1978).

Analyses of randomly obtained product samples suggest that their composition is variable; with some exceptions, they contain no significant quantities of free amino acids, and they may lack certain essential amino acids (unless supplemented by the manufacturer). They contain only traces of most elements, and the amounts of such essential minerals as calcium, magnesium, iron, zinc, and copper are extremely low compared with the Recommended Dietary Allowances (Anonymous, 1978b; Food and Nutrition Board, 1974). Sample analyses of some of these products are shown in Appendix II, Tables 1 to 5.
### Appendix II Table 1. Essential Amino Acid Content of a Liquid Protein (Food and Drug Administration, 1977a)

<table>
<thead>
<tr>
<th>Essential amino acids</th>
<th>Liquid protein mg/g N</th>
<th>Reference protein (egg albumin) mg/g N</th>
<th>Chemical score (percent ref. protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoleucine</td>
<td>61</td>
<td>250</td>
<td>24</td>
</tr>
<tr>
<td>Leucine</td>
<td>133</td>
<td>440</td>
<td>30</td>
</tr>
<tr>
<td>Lysine</td>
<td>176</td>
<td>340</td>
<td>52</td>
</tr>
<tr>
<td>Methionine + 1/2 cystine</td>
<td>57</td>
<td>220</td>
<td>26</td>
</tr>
<tr>
<td>Phenylalanine + tyrosine</td>
<td>113</td>
<td>380</td>
<td>30</td>
</tr>
<tr>
<td>Threonine</td>
<td>108</td>
<td>250</td>
<td>43</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>57</td>
<td>65</td>
<td>89</td>
</tr>
<tr>
<td>Valine</td>
<td>108</td>
<td>310</td>
<td>35</td>
</tr>
<tr>
<td>Total essential</td>
<td>813</td>
<td>2255</td>
<td>36</td>
</tr>
</tbody>
</table>

### Appendix II Table 2. Amino Acid Label Data of a Liquid Protein Compared with an Independent Laboratory Analysis (modified from Timmons, 1979)

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Label information mg/ml</th>
<th>% of protein</th>
<th>Independent analysis mg/ml</th>
<th>% of protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoleucine</td>
<td>7.3</td>
<td>1.5</td>
<td>4.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Leucine</td>
<td>14.3</td>
<td>2.9</td>
<td>9.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Lysine</td>
<td>20.0</td>
<td>4.0</td>
<td>11.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Methionine</td>
<td>3.3</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>10.3</td>
<td>2.1</td>
<td>9.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Threonine</td>
<td>9.2</td>
<td>1.8</td>
<td>6.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>2.2</td>
<td>0.4</td>
<td>2.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>1.3</td>
<td>0.3</td>
<td>1.7</td>
<td>0.3</td>
</tr>
</tbody>
</table>
### Appendix I Table 3. Amino Acid Analysis of a Typical "Predigested Protein" Product (Food and Drug Administration, 1977b)

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Label Declaration</th>
<th>Assay</th>
<th>% of Label Declaration</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Alanine</td>
<td>1,300</td>
<td>937</td>
<td>72</td>
</tr>
<tr>
<td>L-Arginine</td>
<td>1,200</td>
<td>453</td>
<td>38</td>
</tr>
<tr>
<td>L-Aspartic Acid</td>
<td>900</td>
<td>538</td>
<td>60</td>
</tr>
<tr>
<td>L-Cystine</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>L-Glutamic Acid</td>
<td>1,500</td>
<td>1,074</td>
<td>72</td>
</tr>
<tr>
<td>Glycine</td>
<td>3,500</td>
<td>2,604</td>
<td>74</td>
</tr>
<tr>
<td>L-Histidine</td>
<td>110</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>L-Hydroxylysine</td>
<td>150</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>L-Hydroxyproline</td>
<td>1,000</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L-Isoleucine</td>
<td>200</td>
<td>139</td>
<td>70</td>
</tr>
<tr>
<td>L-Leucine</td>
<td>450</td>
<td>297</td>
<td>66</td>
</tr>
<tr>
<td>L-Lysine</td>
<td>650</td>
<td>221</td>
<td>34</td>
</tr>
<tr>
<td>L-Methionine</td>
<td>110</td>
<td>90</td>
<td>82</td>
</tr>
<tr>
<td>L-Phenylalanine</td>
<td>350</td>
<td>209</td>
<td>60</td>
</tr>
<tr>
<td>L-Proline</td>
<td>2,300</td>
<td>1,437</td>
<td>62</td>
</tr>
<tr>
<td>L-Serine</td>
<td>1,000</td>
<td>247</td>
<td>25</td>
</tr>
<tr>
<td>L-Threonine</td>
<td>300</td>
<td>176</td>
<td>59</td>
</tr>
<tr>
<td>L-Tryptophan</td>
<td>65</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>L-Tyrosine</td>
<td>100</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>L-Valine</td>
<td>350</td>
<td>261</td>
<td>75</td>
</tr>
</tbody>
</table>
Appendix II Table 4. Amino Acid Analysis of a Higher Quality "Predigested Protein" Product (Food and Drug Administration, 1977b)

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Label Declaration</th>
<th>Assay</th>
<th>% of Label Declaration</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Alanine</td>
<td>1,300</td>
<td>1,279</td>
<td>98</td>
</tr>
<tr>
<td>L-Arginine</td>
<td>1,200</td>
<td>2,332</td>
<td>194</td>
</tr>
<tr>
<td>L-Aspartic Acid</td>
<td>900</td>
<td>849</td>
<td>94</td>
</tr>
<tr>
<td>L-Cystine</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>L-Glutamic Acid</td>
<td>1,500</td>
<td>1,571</td>
<td>105</td>
</tr>
<tr>
<td>Glycine</td>
<td>3,500</td>
<td>3,613</td>
<td>103</td>
</tr>
<tr>
<td>L-Histidine</td>
<td>110</td>
<td>236</td>
<td>215</td>
</tr>
<tr>
<td>L-Hydroxylysine</td>
<td>150</td>
<td>323</td>
<td>215</td>
</tr>
<tr>
<td>L-Hydroxyproline</td>
<td>1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-Isoleucine</td>
<td>200</td>
<td>255</td>
<td>128</td>
</tr>
<tr>
<td>L-Leucine</td>
<td>450</td>
<td>484</td>
<td>108</td>
</tr>
<tr>
<td>L-Lysine</td>
<td>650</td>
<td>1,055</td>
<td>162</td>
</tr>
<tr>
<td>L-Methionine</td>
<td>110</td>
<td>234</td>
<td>213</td>
</tr>
<tr>
<td>L-Phenylalanine</td>
<td>350</td>
<td>311</td>
<td>89</td>
</tr>
<tr>
<td>L-Proline</td>
<td>2,300</td>
<td>2,300</td>
<td>100</td>
</tr>
<tr>
<td>L-Serine</td>
<td>1,000</td>
<td>520</td>
<td>52</td>
</tr>
<tr>
<td>L-Threonine</td>
<td>300</td>
<td>277</td>
<td>92</td>
</tr>
<tr>
<td>L-Tryptophan</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-Tyrosine</td>
<td>100</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>L-Valine</td>
<td>350</td>
<td>340</td>
<td>97</td>
</tr>
</tbody>
</table>
**Appendix II Table 5.** Mineral Composition of "Predigested Liquid Protein" Products (Food and Drug Administration, 1977c)

| PRODUCT NUMBER | Ca mg/ml | Mg µg/ml | P µg/ml | Na µg/ml | K µg/ml | Fe µg/ml | Zn µg/ml | Cu µg/ml | Mn µg/ml | Se ng/ml | As ng/ml | Cd ng/ml | Pb ng/ml | F µg/ml | Ni µg/ml |
|----------------|---------|----------|---------|----------|---------|----------|---------|---------|---------|----------|---------|----------|----------|---------|---------|---------|
| 1.             | 1.53    | 198      | 38.4    | 843      | 275     | 5.52     | 5.67    | 2.44    | 2.96    | 37.2     | 120     | 2.0      | 96.3     | 5.8     | 2.6     |
| 2.             | 0.55    | 108      | >2500   | 3350     | 154     | 8.13     | 1.26    | 0.18    | 1.70    | 93.7     | 91      | 26.5     | 16.5     | 1.9*    | 0.4     |
| 3.             | 1.76    | 139      | 27.7    | 1640     | 254     | 7.38     | 1.27    | 2.19    | 4.67    | 148      | 8.2     | 4.0      | 135.7    | 1.5*    | 1.6     |
| 4.             | 0.043   | 16       | 20.3    | 223      | 179     | 0.87     | 0.55    | 0.24    | 0.03    | 159      | ND**    | 15.7     | 81.3     | 0.4*    | 0.6     |
| 5.             | 0.287   | 84       | 1600    | 1260     | 259     | 9.00     | 1.10    | 0.30    | 2.30    | 141      | 22      | 3.3      | 79.0     | 5.3     | 0.1     |
| 6.             | 0.275   | 77       | 135     | 5480     | 300     | 2.80     | 3.00    | 0.40    | 0.20    | 104      | 60      | 8.5      | 79.5     | 6.8     | 0.6     |
| 7.             | 1.06    | 93       | 123     | 504      | 235     | 7.94     | 0.98    | 0.36    | 4.07    | 86       | 24      | 8.3      | 64.0     | 6.2     | 0.4     |
| 8.             | 0.83    | 73       | 119     | 564      | 394     | 6.97     | 0.93    | 0.32    | 3.43    | 98       | 50      | 6.7      | 31.7     | 5.2     | 0.3     |

* Approximate values

**ND**, not detectable. Other elements that were not detectable in significant amounts in these products [values shown in parentheses are the analytical limits for the size sample that was used for these analyses (µg/ml)]: Mo(0.2), Cr(0.05), V(0.2), Be(0.02), Co(0.125), Ti(1.25), Al(0.125), Te(1.25), Sn(0.20), Sb(0.50), and As(0.005).
Their content of toxic elements including arsenic, cadmium, and lead is reportedly below hazardous levels (Anonymous, 1978b). Eight samples tested for chlorodioxin contamination were negative at detection limits of 15 to 30 parts per trillion. Analyses for organochlorine, organophosphorus, and organonitrogen pesticides and pentachlorophenol contamination were negative (Food and Drug Administration, 1977d). Finally, according to Hilton (1979), these products contain significant amounts of hydroxyproline and hydroxylysine, neither of which contributes directly to protein synthesis.

The protein efficiency ratios (PER) for three samples varied from \(-0.89 \pm 0.27\) (SD) to \(-1.17 \pm 0.17\) (SD) as compared with an Animal Nutrition Research Council casein standard of \(3.19 \pm 0.12\) (Food and Drug Administration, 1977e). It is recognized that protein quality tests in which test animals do not gain weight should yield PERs of zero; however, the foregoing PERs were expressed as negative values to indicate that the animals actually lost weight. Recently, Brooks et al. (1979), analyzed samples of commonly used "liquid proteins" and reported that significant deficiencies of each essential amino acid could occur if the "liquid proteins" were consumed in the recommended doses. Noting that the branched-chain amino acids have a major role in cardiac and skeletal muscle protein economy, the authors estimated that a combined deficit of BCAA of 348 g could result during an 8 months' fast supplemented only with "liquid protein".

The labels of most brands of "predigested liquid protein" indicate that tryptophan has been added as well as, in some instances, both nutritive and nonnutritive sweeteners, flavoring, and preserving agents. Bistrian (1978) noted, "The liquid protein diet resembles the [protein-sparing modified...] fast superficially but contains 3 g of carbohydrate per 30 ml and hydrolysed collagen as the source of protein. It also suffers from deficiency of potassium and other essential micronutrients".
APPENDIX II

LITERATURE CITED


