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Protein Sparing Therapies in Acute Illness and Obesity: A Review of George Blackburn's Contributions to Nutrition Science

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Abstract

Protein sparing therapies were developed to mitigate the harms associated with protein-calorie malnutrition and nitrogen losses induced by either acute illness or hypocaloric diets in patients with obesity. We review the development of protein sparing therapies in illness and obesity with a focus on the pioneering contributions of George Blackburn, MD, PhD. He recognized that protein-calorie malnutrition is a common and serious clinical condition and developed new approaches to its treatment in hospitalized patients. His work with stable isotopes and with animal models provided answers about the physiological nutritional requirements and metabolic changes across a spectrum of conditions with varying degrees of stress and catabolism. This led to improvements in enteral and parenteral nutrition for patients with acute illness. Blackburn also demonstrated that lean body mass can be preserved during weight loss with carefully designed very low calorie treatments which became known as the protein sparing modified fast (PSMF). We review the role of the PSMF as part of the comprehensive management of obesity.

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Introduction

The World Health Organization classified obesity as a disease in 1948, but it was not until 2013 that the American Medical Association adopted a policy that "recognizes obesity as a disease requiring a range of medical interventions to advance obesity treatment and prevention"[1]. This shift in the perception of obesity occurred in parallel with increasing recognition of the harms associated with both obesity and protein-calorie malnutrition.

George Blackburn, MD, PhD (1936 – 2017) was a central figure in nutrition and obesity medicine in the United States over the past half century that catalyzed this shift. He raised awareness about hospital acquired protein-calorie malnutrition and advocated that obesity should be recognized as a disease that has effective treatments[2]. He was a pioneer in the field of hospital nutrition and also performed the first Roux-en-Y procedure for severe obesity treatment in New England in 1973, at a time when bariatric surgery was still in its infancy.

We review here his contributions to the field of nutrition over the past several decades with a focus on protein sparing therapies. Blackburn described how common protein-calorie malnutrition was in hospitalized patients and how this led to increased complications and morbidity. To mitigate this, he developed the concept of nutrition support teams to administer therapies that met full nutritional needs via both enteral and parenteral routes and pioneered peripheral intravenous protein-sparing therapies to limit the requirement for more invasive TPN. He also pioneered the development of a system of nutritional assessment techniques that identified the patients who might best benefit from these therapies. This new model for the diagnosis and treatment of malnutrition in the hospitalized setting was quickly adopted nationwide in many academic medical centers. From this early work with protein-sparing therapies, he realized that the therapeutic effects of ketosis could be harnessed for the treatment of obesity, which led to the creation of the protein sparing modified fast (PSMF), a modified very-low-calorie diet (VLCD) designed to preserve lean body mass during major weight loss.

We review how Blackburn's contributions altered the treatment of obesity. His research used stable isotopes and new technologies to elucidate the physiology of fuel metabolism, energy expenditure, and the effects of changes in nutrient load on body composition and energy balance. These discoveries led to changes in total parental nutrition and refinements in the PSMF. Finally, we review the role of PSMF in the modern era as part of the comprehensive management of obesity and type 2 diabetes (T2D).

Protein-calorie malnutrition and a new paradigm for nutrition support for hospitalized patients

Importance of nutrition and lean body mass

Studley conducted one of the earliest studies in hospital protein-calorie malnutrition associating preoperative weight loss due to chronic peptic ulcers with significantly increased mortality in 1936[3]. The recognition of the severe consequences of acute unintentional

weight loss led to research into its mechanisms and the development of therapies to improve the nutritional state of patients.

In the following decades, it was established that essential physiological processes including hematopoiesis, wound healing, and immunity require adequate energy and supplemental amino acids for protein synthesis in order to function properly. When dietary protein or micronutrients are inadequate, clinically significant malnutrition can develop very quickly in critical illness without nutritional support which can lead to poor wound healing, immunodeficiency, infectious complications, and increased mortality. Protein-calorie malnutrition, also known as protein-energy malnutrition, is the ultimate outcome if underfeeding is severe and prolonged or more rapidly if metabolic stress is severe, and is subdivided into marasmus, kwashiorkor, or marasmic kwashiorkor. To address the widespread malnutrition across many war-affected countries following World War 2, the World Health Organization began to issue guides to the assessment of nutritional status. In 1962 the World Health Organization Expert Committee on Medical Assessment of Nutritional Status proposed a classification of physical signs and biochemical assessments for nutrition survey purposes in populations. Nationwide surveys of arm circumference and triceps skin fold thickness were initiated across the world to characterize the prevalence of malnutrition[4].

Despite these advancements, protein-calorie malnutrition was generally considered to be limited to underdeveloped nations until Bistrian and Blackburn demonstrated how common they were in hospitalized patients in Boston. In 1974, Bistrian and Blackburn surveyed the nutritional state of all of the surgical patients in an urban municipal teaching hospital and found that half of these patients had evidence of severe protein-calorie malnutrition based on triceps skin fold, arm muscle circumference, and serum albumin[5]. Next, they turned their attention to hospitalized patients on the medical service at the same hospital. Bistrian and Blackburn examined the overall caloric depletion with weight, height, and triceps skin fold, and the overall protein status with arm circumference, albumin, and hematocrit. They found that medical patients had significantly more caloric malnourishment than surgical patients based on triceps skin fold and weight/height criteria, but had less protein-calorie malnutrition based on arm circumference[6]. This is consistent with surgical illnesses inducing a more protein catabolic state leading to loss of muscle mass. In addition, 47% of patients had anemia and 34% had lymphopenia concerning for impaired cellular immunity. Following these papers, greater attention was given to assessment of nutritional state by anthropometric data (skinfold thickness and arm circumference), laboratory tests, and clinical assessment based on history and physical exam findings[7].

Blackburn showed that malnutrition had clinically important implications for hospitalized patients. He demonstrated that mortality is higher in malnourished cancer patients with low serum albumin and decreased cell-mediated immunity[8]. In 1976, Bistrian and Blackburn demonstrated that cellular immunity is compromised in adult marasmus induced by recent illness-related weight loss that could be reversed upon adequate nourishment[9]. Because of this, they advocated for preoperative screening and treatment of protein-calorie malnutrition for at least two weeks prior to elective surgery in malnourished patients to minimize subsequent complications. Nitrogen is an essential component of protein and its urinary

excretion can be quantified. Inadequate nutrition produces a negative nitrogen balance and reflects the loss of lean body mass, which is the major determinant of the body's metabolic rate. The clinical relevance of this became clear with landmark studies of total fasting and severe semi-starvation in normal adults.

Harms of total fasting induced loss of lean body mass

In 1915, Francis Benedict published the first report of the effects of prolonged fasting on metabolism assessed via indirect calorimetry and demonstrated that the majority of weight loss in fasting people of normal weight is from lean body mass[10]. This reflects the fact that lean body mass is 80% water whereas fat contains 5%.

In the 1940s, Ansel Keys' experiments on human starvation established that there was a substantial loss of lean body mass and cardiac mass in lean men with prolonged caloric restriction of 1570 kcal/day after 24 weeks[11]. However, in subsequent decades fasting increased in popularity, especially after Bloom re-introduced fasting as a treatment for obesity in 1959[12] and Drenick subsequently reported good short-term outcomes from fasting in eleven morbidly obese subjects[13]. This dichotomy in outcome between lean and obese individuals is a consequence of the greater protein sparing with fasting in the obese due to the ample energy stores as fat which provide most of the energy required in fasting. Thus lean individuals can only fast for less than 2 months before death due to fat depletion[14] whereas morbidly obese individuals have fasted for periods of more than 1 year[15]. In 1963, Garfield Duncan popularized a fasting protocol based upon his study of 50 patients that he treated with periods of 5–14 days of total fasting followed by 1 day of fasting per week which he found to be safe and effective under qualified supervision[16,17].

In the following years, several reports of adverse events associated with total fasting were published. In 1969, Garnett and colleagues reported a case of sudden death in an otherwise healthy 20 year-old woman who completed 30 weeks of therapeutic starvation in a closely supervised metabolic unit. She was found to have gross destruction of cardiac myofibrils on autopsy, contradicting the belief that the heart could be spared from the loss of lean body mass during starvation[18]. This report along with other similar cases contributed to abandoning medically monitored starvation as a treatment for obesity. However probably even more important for the abandoning of fasting as a therapeutic strategy was Ernst Drenick's studies at the Wadsworth VA Hospital in Los Angeles where he followed up on the morbidly obese subjects who had lost vast amounts of weight during inpatient studies of the metabolism of fasting. He reported that with 7-year follow up, all of the lost weight from fasting was regained[19]. This points out two concerns with therapeutic fasting. The lean tissue lost is likely to foster the drive for weight regain as a physiologic imperative, and substantial fat regain is likely due in part to the inefficiency of lean tissue repair. However most importantly the return to initial weight and greater after fasting treatment emphasizes the importance of long-term behavior change necessary to reduce energy intake and promote increases in energy expenditure.

Blackburn and others began to investigate how to protect muscle mass during weight loss to avoid some of these consequences. He recognized that adequate nutrition support for critically ill patients can mitigate their loss of muscle, and saw a similar need to mitigate the

protein catabolism and nitrogen loss induced by hypocaloric mixed diets that did not increase the protein intake over the usual required amount when energy intake was adequate.

Determinants of nitrogen balance

Urinary nitrogen excretion is closely correlated with protein catabolism under most conditions[20]. Hence, Blackburn and Bistrian proposed that this be measured twice weekly in hospitalized patients using urinary urea nitrogen excretion as a simple measure of urinary nitrogen loss to guide treatments seeking to offset urinary losses with adequate intake of enteral amino acids or proteins or parenteral amino acids[21,22].

In addition to the nitrogen-sparing effect of dietary protein, a nitrogen-sparing effect of glucose was already demonstrated in 1946 in a study by Gamble. In healthy fasting volunteers, Gamble administered either 50, 100, or 200 g of glucose for six days and measured the nitrogen balance. He showed that 100 g of glucose daily achieves near maximal protein sparing effect and prevents about half of the oxidation of body protein seen in the fasting state[23]. However, glucose may have a protein-sparing effect of limited duration and only in healthy volunteers, since carbohydrates do not spare protein in the early phase of acute illness as shown in 1974 by Giddings who demonstrated no difference in the urinary nitrogen excretion of patients given saline or dextrose on the first two days after elective abdominal surgery[24]. In this study, dextrose had a mild protein sparing effect only 48 hours after surgery. Thus, at the time when Blackburn started his studies in human subjects, the role of diet in the regulation of protein metabolism was an evolving field of research.

Mentors of Blackburn: Cahill and Flatt's studies in metabolism and ketosis

Studies by George Cahill and his group were crucial for clarification of the physiology of starvation and the protein-sparing effect of ketosis. By providing alternative fuel for the brain, thus reducing the need for gluconeogenesis, ketones could reduce the demand for muscle protein breakdown during starvation[25,26]. In this adaptive process, insulin plays a significant role as master metabolic regulator[27]. Cahill measured the arteriovenous difference in the concentration of amino acids under post-absorptive and prolonged starvation conditions and showed that prolonged starvation leads to a substantial drop in muscle amino acid release with the largest decline in alanine[28]. These and other studies demonstrated that ketones have a protein-sparing effect by reducing the oxidation of branched chain amino acids in muscle.

Around this time, the concept of insulin sensitivity and resistance were being elucidated. In 1954, Howard showed that battlefield injuries induce glucose intolerance and insulin resistance[29]. Conversely, fasting improves adipose tissue insulin sensitivity[30]. Blackburn's mentor Jean-Pierre Flatt theorized that excess adipose tissue in obesity increases free fatty acid (FFA) release, which decreases glucose uptake and consequently increases insulin secretion, thus establishing a crucial role for insulin in regulating fuel availability in overfed individuals[31]. As a result of these homeostatic shifts, a state of insulin insensitivity to the antilipolytic effect of insulin could develop with obesity[32].

To further describe their model of metabolic regulation, Flatt and Blackburn posited that an insulin-glucose-fatty acid loop and insulin-amino acid-glucose loop control the metabolic

fuels in a coordinated system that integrates the metabolism of fat, carbohydrates, and proteins. Their model provided a theoretical basis for the changes in protein and calorie metabolism during starvation[33]. They proposed that a protein-sparing effect could be achieved in either the treatment of obesity or in the feeding of critically ill patients by restricting carbohydrate intake, which would lower insulin levels and allow for mobilization of endogenous fat stores. Cahill contributed to Blackburn's ideas and served on his PhD thesis committee.

Blackburn's PhD thesis work on protein sparing

Blackburn recognized that loss of lean tissue is a major limitation of fasting and applied Cahill and Flatt's theories to develop a new treatment paradigm. Muscle is more insulin sensitive than adipose tissue, hence low insulin concentrations can maintain muscle protein synthesis while allowing for lipolysis in adipocytes to meet the body's metabolic demands[34]. Carbohydrates stimulate insulin secretion to a much greater degree than fat or protein. Hence, maintaining lower insulin concentrations by restriction of carbohydrates could spare muscle mass in acutely ill inpatients and in outpatients with obesity.

The prevailing nutrition doctrine aimed to suppress ketosis by providing intravenous 5% dextrose as a sole source of nutrition in critically ill patients. He argued that restricting carbohydrates would reduce insulin secretion and allow the continued mobilization of body fat to meet the body's energy requirement. These conceptual developments paralleled efforts to introduce total parenteral nutrition (TPN) protocols by Dudrick et al. in 1968[35]. The calories in TPN were historically largely from dextrose due to difficulties in obtaining a safe, FDA-approved fat emulsion. These formulations of TPN were hyperosmolar and frequently hypercaloric to promote positive nitrogen balance using relatively small infusion volumes. The benefits of TPN in improving survival in malnourished patients became clear although this treatment was associated with acute metabolic complications such as glycosuria and hyperosmolar coma[36]. Hyperalimentation with dextrose was subsequently found to be associated with chronic complications including liver lipogenesis, steatosis, cholestasis, and liver dysfunction[37].

Within this context of determining the optimal TPN solutions for surgical patients, Blackburn conducted a series of studies in 1973 as part of his PhD thesis at MIT entitled "A new concept and its application for protein-sparing therapies[38]." For his thesis, he studied the effect of protein (in the form of lean meat in the obese and amino acid infusions in surgical patients) and dextrose in these two populations: patients after surgery for trauma and ambulatory patients with obesity. We first discuss his contributions to in-patient nutrition before turning to his contributions to obesity treatment.

Blackburn's studies in surgical patients

In 1973, Blackburn published a study of peripheral intravenous feeding with amino acids[39]. This cross-over study of 10 patients that required intravenous support compared the effects of three parenteral solutions on nitrogen balance and glucose, FFA, and insulin. These solutions were a either dextrose-free solution with 90 g IV amino acids, a 100 g dextrose solution with 70 g amino acids, or a 100 g dextrose solution without amino acids. He

demonstrated that the dextrose-free 90g amino acid solution was associated with the best nitrogen balance, the highest concentration of FFA and ketones, and the lowest serum insulin.

In 1975, Bistrian, Blackburn, Scrimshaw and Flatt showed that protein-free dextrose infusions in hospitalized catabolic patients are associated with a decrease in plasma protein concentrations and impairment in delayed hypersensitivity reactions[40]. These data were consistent with his hypothesis that dextrose infusions increase insulin and consequently reduce amino acid release from skeletal muscle and hence reduce amino acid availability for visceral protein synthesis, creating an iatrogenic kwashiorkor-like state with detrimental consequences.

The problem of acute “metabolic stress” induced by illness, and the role of nutritional support

The catabolic effects of trauma were recognized in the early work of Cuthbertson in the 1930s who described excessive losses of nitrogen and electolytes following long bone fractures[41]. Subsequent studies demonstrated that injury and sepsis activate the sympathetic nervous system leading to the secretion of catecholamines and glucocorticoids that mediate the catabolic responses to injury. This prompted the search for an optimal nutritional support to counteract this catabolic response.

In 1973, O’Connell et al. compared total fasting with 150 g or 700 g per day of dextrose in healthy volunteers and showed that dextrose decreased urinary nitrogen excretion but could not totally eliminate the negative nitrogen balance[42]. Hence, although carbohydrates may exert a protein sparing effect, there is a limit to their nitrogen conserving power. Ryan, Blackburn, and Clowes showed that illness can further limit the protein sparing effect of dextrose. They compared the effects of fasting with or without sepsis induced by cecal ligation in rats. Fasting animals with sepsis demonstrated decreased fat mobilization with lower FFA levels and serum ketones, and higher insulin levels and epididymal fat pad weight[43]. Blackburn’s group also demonstrated that rats following femur fracture had a 24% and 63% increase in synthesis of liver and plasma proteins, which could be increased by an amino acid infusion or partially inhibited by a protein-free dextrose infusion[44]. Hence, dextrose infusions may impair this response to injury. In parallel, he found that a high carbohydrate and minimal nitrogen diet led to a loss of delayed hypersensitivity in fasting rats when compared with a diet that contained only fat and no protein[45]. These experiments demonstrate an important concept. Although limiting lean tissue loss is an important goal, maintaining protein synthesis in the critically ill can be an even more important outcome. Nitrogen-free, high energy intakes can limit nitrogen excretion but at the cost of impairing the protein anabolic response to injury which importantly includes immune competence and wound healing.

Starting in the late 70’s, Vernon Young at MIT conducted detailed studies with stable isotopes of amino acids as tracers to investigate “whole body protein metabolism” in humans. Blackburn and his group used these same techniques to understand the physiology of fasting and to test the impact of nutritional therapies on protein catabolism during acute illness. In a study using ^{15}N glycine as a tracer, Steffee et al. found that 0.38 g protein/kg

body weight was inadequate to maintain nitrogen balance but 1.5 g/kg was sufficient in six healthy adults fed 45 kcal/kg/day[46]. This study highlighted the importance of sufficient dietary protein in protecting lean body mass.

Blackburn collaborated with many colleagues to use stable isotopes to study the effects of nutrition after surgery. His laboratory helped Skillman et al. conduct a randomized controlled trial of 10 patients after elective gastrointestinal surgery that compared the effect of peripheral, parenteral amino acids with IV dextrose on albumin synthesis using ^{14}C-leucine[47]. They found that albumin synthesis was significantly higher in the parenteral amino acid group. However, whether this effect was due to the ketosis associated with parenteral amino acids was subsequently questioned. Greenberg, Marliss and colleagues randomized 30 patients after elective abdominal surgery to either parenteral glucose, parenteral amino acids, parenteral amino acids and soybean oil, or parenteral amino acids and 150 g glucose for their first four postoperative days[48]. They did not find any difference in nitrogen sparing between the three groups that received parenteral amino acids and concluded that the major determinant of protein sparing may be sufficient dietary protein and that ketosis or low insulin concentrations are not required. However, it is unclear whether any of the patients in this study developed postoperative sepsis, which may alter the net effect of glucose on nitrogen metabolism. Dextrose may favorably reduce the demand for gluconeogenesis from amino acids but also unfavorably inhibit fat mobilization and increase glucose consumption. Hence, the net effect of dextrose on nitrogen balance may depend on the degree of insulin resistance in the muscle, adipose tissue, and liver. However peripheral venous feeding is limited by the final osmolality of the solution, and amino acids are the most efficient substrate for nitrogen sparing.

Rutten, Blackburn, and Flatt found that stress increases protein catabolism and raises the caloric requirement needed to achieve nitrogen balance in hospitalized patients. Thus, patients with greater stress required greater amounts of amino acids to achieve nitrogen balance, consistent with a greater demand for protein synthesis and amino acid-derived energy production (Cerra, Blackburn et al[49]).

The practice of total parenteral nutrition and Blackburn's contribution

In 1975, the contribution of individual elements to regrowth of various tissues during intravenous hyperalimentation of underweight subjects was defined[50]. In the early days, the practice of TPN emphasized the administration of excess calories (hence, "hyperalimentation"). However, subsequent studies documented the deleterious effects of overfeeding. Blackburn and Bistrian's work played a major role in rectifying these early concepts leading to the modern principles of TPN. These include more modest energy intakes in the first 7–10 days of TPN at less than 80% of energy expenditure to limit glucose intolerance with ample amino acids of at least 1.5 g/kg. In many patients fluid restriction is also required due to an underlying condition that further limits energy and protein intake initially which appears to be well provided by 1 liter of containing 70 g amino acids and 210 g glucose compared to greater amounts of both in the first 7–10 days[51].

Collaborative studies in Boston led by Wolfe et al. further defined the effects of the macronutrient content and overall caloric content of TPN on the endocrine milieu and

protein synthesis[52]. In 1980, Wolfe et al. studied the effect of different ^{13}C-glucose infusion rates on gluconeogenesis, glucose clearance, glucose oxidation, metabolic rate, and respiratory quotient by indirect calorimetry in postoperative patients requiring TPN[53]. They found that above a threshold of 7 mg/kg/min of dextrose, further increases in the dextrose infusion rate do not lead to increased glucose oxidation but rather conversion into fat via de novo lipogenesis.

Maini, Blackburn, Bistrian and Flatt et al. developed a cyclic hyperalimentation protocol as an alternative to continuous hyperalimentation with dextrose, which was the dominant TPN method at the time[54]. They reported that by alternating between a dextrose-containing infusion and a dextrose-free amino acid infusion, they could achieve equivalent nitrogen sparing while improving serum albumin levels and liver function tests.

Studies by Blackburn's group to understand the mechanisms behind the catabolic response to injury led to the investigation of the roles of pro-inflammatory cytokines such as IL-1 and TNF-α[55,56]. They found that muscle proteolysis is increased by TNF-α, which can be synergistically augmented with IL-1 leading to increased urinary nitrogen excretion. Moldawer reviews these studies in greater depth in his article published in this issue of Metabolism.

Blackburn investigated branched chain amino acids (BCAA) that have a unique protein sparing effect in muscle and liver. The main mechanism for this was uncovered by the elegant work of Jefferson and his group who showed that administration of leucine by itself could increase protein synthesis rates through an effect on initiation of protein translation[57]. Based on this, Blackburn and his group hypothesized a beneficial role for BCAA supplementation to counter the catabolic effects of sepsis and trauma in surgical patients. Tayek, Bistrian, and Blackburn examined the effect of BCAA-enriched TPN on whole body leucine kinetics using ^{14}C-leucine and albumin synthesis[58]. They demonstrated that compared with standard TPN, BCAA-enriched TPN improved leucine balance and the albumin synthetic rate. In a follow up study with a similar crossover design using both ^{13}C-leucine and ^{14}C-tyrosine in cancer patients, they also demonstrated that leucine balance was improved and tyrosine oxidation was reduced, consistent with improved protein utilization[59]. However, whether these metabolic effects translate into clinical benefits remains uncertain.

In addition to BCAA, Blackburn and his group investigated the potential benefits of "alternative fuels" in metabolic support of surgical patients. For example, they showed that addition of xylitol in TPN promotes fatty acid oxidation and reduces gluconeogenesis[60]; and that the combination of amino acids and xylitol improved the nitrogen balance compared with amino acids and glucose or amino acids alone in rats after burn injury[61]. This was consistent with his hypothesis that mobilization of fat can spare protein. Other alternative fuels studied by the Blackburn group included medium chain triglycerides (MCT) and "structured lipids" where specific fatty acids were introduced into the composition of triglycerides[62]. He worked with Yamazaki to show that administration of MCT in the form of structured lipids spared body protein after bilateral femur fracture in rats[63]. Blackburn

also demonstrated metabolic advantages to these lipids after burn injury in rats and in guinea pigs[64].

These early developments led Blackburn and Bistrian to revise the principles of nutritional care of the injured or septic patient, taking into consideration the major hormonal changes associated with acute injury and the recovery phase of illness. They advocated that indiscriminate use of dextrose infusions should be replaced by careful nutritional support with adequate protein to preserve and restore body cell mass[65]. Blackburn's studies starting with his thesis work contributed to the scientific basis behind the evolution of TPN. The American Society of Enteral and Parenteral Nutrition (ASPEN) was founded in 1976, and Blackburn was elected president in 1978 in recognition of his contributions. In parallel, Blackburn studied the effects of protein sparing for the treatment of obesity. Although there are many physiological differences between critical illness and obesity, Blackburn recognized that protein-sparing was important to the treatment of both. We review Blackburn's contributions to obesity medicine next.

Protein Sparing Modified Fast in the Treatment of Obesity

Early studies of fasting and hypocaloric diets

Banting published one of the most famous early reports of his experience following low calorie diet in 1863, which emphasized restriction of bread, butter, milk, sugar, beer, and potatoes with portion controlled meat for breakfast and dinner which allowed him to lose 50 pounds in one year[66]. His pamphlet was translated into multiple languages and widely sold widely for decades.

The key metabolic changes during fasting were quantified in 1915 by Folin and Denis. They studied two morbidly obese subjects who underwent intermittent total fasts lasting between 3 and 6 days and demonstrated that beta-hydroxybutyric acid was the major excreted organic acid in the urine and that with successive fasts there was a metabolic adaptation with decreased urinary nitrogen excretion[67].

In 1931, Evans and Strang presciently suggested criteria for a low caloric diet to be successful including maintenance of nitrogen balance by providing at least 1 g protein/kg ideal body weight[68].

However, standard non-pharmacologic obesity treatments remained largely ineffective as demonstrated by Stunkard based on a literature review and the results of 100 consecutive patients treated in a nutrition clinic which recommended a hypocaloric mixed diets of 800 – 1500 kcal[69]. He found that only 12% of these patients were able to achieve a weight loss of 20 lbs.

Bolinger and colleagues compared the nitrogen balance and ketone excretion during total fasting or a lean protein diet and concluded that the addition of 40g of protein per day resulted in a much more favorable ratio of fat loss to lean body mass loss[70]. Ernst Drenick pioneered fasting diets in the 1960s and published a practical guide to the VLCD in 1967 in which he recommended a diet of 500 kcal with 50g protein because he considered that the

protein sparing effect of dietary protein was minimal and hence he considered loss of lean body mass with weight loss unavoidable[71]. Blackburn was not convinced that this was true and developed the PSMF, a specific type of VLCD that provides much more protein than these early studies which he demonstrated could maintain lean body mass during weight loss.

Recognition of the potential harms of VLCD and inadequate medical supervision

Following the publication of *The Last Chance Diet*[72] in 1976, liquid protein diets of varying composition became widely popular. In 1979, Isner published a report of 17 deaths associated with low-quality liquid protein VLCD, which were frequently preceded by QT interval prolongation and on autopsy histological changes in the left ventricle were seen[73].

Hence, in the early days of the development of the PSMF by Blackburn and Bistrian, there was substantial concern about the safety of VLCD. In 1978, Bistrian published a high-profile review of the clinical use of PSMF that highlighted its differences with these liquid protein diets and emphasized the importance of close medical monitoring during the fast and refeeding periods[74]. In 1980, Lantigua et al. published a detailed report of cardiac arrhythmias in previously healthy subjects that developed during treatment with 300 kcal hydrolyzed collaged liquid protein diet and documented a total body protein loss[75] measured by ^{40}K and nitrogen balance. Thus, in 1983, the potential harmful effects of low quality liquid VLCD became widely publicized[76].

Early contributions of Blackburn and Bistrian to PSMF

The PSMF is considered to be a subset of VLCD that provides sufficient protein in order to preserve lean body mass during weight loss. It consists of a diet providing < 800 kcal per day composed of conventional foods which contain high biological value protein (lean meat, egg whites, fish, poultry) to provide 1.5 g protein / kg ideal body weight along with mineral, multivitamin, and micronutrient supplements, particularly potassium as the bicarbonate salt.

To understand the effect of mild illness on metabolism during a PSMF, Bistrian studied the effect of yellow fever vaccination in five obese patients who were following a PSMF for at least three weeks prior to vaccination[77]. They found that vaccination induced a rise in serum glucose and insulin and a decrease in beta-hydroxybutyrate. The subject with the highest fever in response to vaccination had the largest increase in glucose and insulin and developed a negative nitrogen balance. This is consistent with their earlier finding that infections induce insulin resistance and have anti-ketogenic and catabolic effects.

In early clinical studies, Blackburn and colleagues investigated the effects of PSMF in 16 obese pediatric patients in a metabolic unit for four weeks and demonstrated that half of the patients were able to achieve a positive nitrogen balance by the fourth week. They also showed that cell mediated immunity remained normal[78]. In another study, PSMF was found to be associated with only slight decreases in serum retinol binding protein and complement β1c after 4 weeks in obese adolescents[79]. Blackburn, Bistrian, and Stanbury showed that in Prader Willi syndrome the PSMF can achieve substantial weight loss while preserving a positive nitrogen balance and lean tissue (assessed by ^{40}K)[80].

In 1985, Bistrian and Blackburn and colleagues published the largest case series of the PSMF (consisting of lean meat, fish, or fowl) in 668 outpatients[81]. The mean weight loss was 41 lbs with a mean duration of 17 weeks and mean total duration of follow up of 31 weeks. Wadden performed a randomized controlled trial that compared a 500 kcal PSMF with a 1200 kcal balanced diet and found that after 1 month there was significantly greater weight loss and less hunger with PSMF[82]. As PSMF and VLCD emerged as viable options for the treatment of obesity, they started to be used for only moderately overweight patients. Wadden, Van Itallie and Blackburn did not endorse the use of the PSMF for these patients, and recommended that PSMF be used only in patients that were more than 30% overweight for 12–16 weeks followed by 3 to 6 weeks of refeeding[83].

New technologies allowed further study into the effects of diets on body composition and energy expenditure

In 1967, Ball used helium dilution densitometry to characterize the changes in body composition after 16 days of total caloric deprivation followed by refeeding with VLCD. He found that although total starvation induced rapid weight loss, less than 15% of the lost weight was adipose tissue[84]. He also compared changes in body composition between a 600–800 kcal/day diet and a 150 kcal/day diet and found that both induced similar rates of fat loss but there was significantly more fat-free body mass loss with more severe caloric restriction[85]. These findings were confirmed in a follow up study in a metabolic ward with tritiated water as well as nitrogen balance to assess body composition[86].

Benoit et al. studied nitrogen balance and total body potassium using ^{40}K to estimate changes in body composition starting with 10 days of total fasting, followed by 4 days of a 1000 kcal mixed diet (20% fat, 20% protein, 60% carbohydrate), and then 10 days of a 1000 kcal ketogenic diet (82% fat, 14% protein, 4% carbohydrate)[87]. He found that fasting-induced weight loss was 65% lean tissue, whereas ketogenic diet-induced weight loss was only 3% lean tissue.

This led to more detailed investigations using tracers on the effects of PSMF on protein synthesis and breakdown by Blackburn, Bistrian, and Young. Following a three week PSMF with 1.5 g protein / kg ideal body weight, protein turnover assessed with ^{15}N-glycine was maintained with equal rates of protein synthesis and breakdown[88]. In contrast, a one-week total fast that followed this period induced a significant decrease in protein synthesis with no change in the protein breakdown and hence a net negative nitrogen balance.

Bistrian showed that a diet consisting of only 0.8 g protein and 0.7 g carbohydrate / kg ideal body weight cannot achieve nitrogen balance using [^{15}N]glycine[89]. Hoffer et al. using [1-^{13}C]leucine and [^{15}N]alanine confirmed that a 0.8 g protein / kg ideal body weight diet providing 500 kcal cannot achieve nitrogen balance, whereas a 1.5 g protein / kg ideal body weight 500 kcal diet can achieve nitrogen balance[90]. These studies elegantly demonstrated that the standard protein recommendation of 0.8 g / kg, the recommended dietary protein intake for a diet with adequate energy intake, is insufficient to attain nitrogen balance under hypocaloric conditions. A follow up study compared a hypocaloric 800 kcal high carbohydrate diet and high protein diet (providing 90 g protein / day) and demonstrated

decreased fat-free mass loss, reduced 3-methylhistidine excretion, and improved insulin sensitivity assessed by euglycemic hyperinsulinemic clamp in the high protein diet[91].

In 1985, Van Gaal studied the effect of a commercial 500 kcal VLCD that provides 60 g protein per day on body composition and metabolism using indirect calorimetry and urinary nitrogen excretion[92]. They found a significant increase in lipid oxidation with a decrease in carbohydrate oxidation and no significant change in protein oxidation resulting in a decrease in fat mass with sparing of lean mass. Apfelbaum performed several studies of PSMF and reached similar conclusions and also demonstrated that there is no decrease in physical vigor or neuromuscular performance after 3 weeks[93].

Goals of obesity therapies and current clinical use of PSMF

Current clinical use of PSMF and VLCD

Blackburn recognized that sustained weight loss improves comorbid diseases associated with obesity. Blackburn showed that even 5% weight loss has significant health benefits for diabetes, hypertension, hyperlipidemia, and cardiovascular disease[94]. This prompted a reassessment of the goals for the treatment of obesity for many patients and physicians with a shift towards maintaining moderate weight loss rather than attempting to achieve large amounts of weight loss quickly. However, for selected and engaged patients without contraindications, PSMF remains an attractive option.

PMSF is used as a treatment for highly motivated patients to achieve rapid weight loss that usually is administered for 6 – 16 weeks. In patients with class III obesity, the PSMF diet can be continued for beyond 16 weeks as long as it continues to be well tolerated. A PSMF is often used as a treatment prior to bariatric surgery with either foods (lean meats) or liquid meal replacement shakes which result in comparable weight loss over a two-week period[95]. Wadden et al. examined in a randomized trial whether a PSMF based on lean meats was better tolerated than a protein-formula-liquid diet that provided a similar amount of protein and calories. They found that both groups achieved similar amounts of weight loss over 1 month but patients in the PSMF group reported significantly less hunger, preoccupation with food, and social disruptiveness compared with the formula-based VLCD[96]. A clinical guide to the PSMF administration, which is beyond the scope of this review, has been recently published from the Cleveland Clinic[97].

Blackburn collaborated on a study of patients who had participated in at least two cycles of a PSMF, which found that the rate of weight loss was significantly less during the second cycle than the first[98]. However, body composition was not assessed and it has been shown that the lipolysis rate is proportional to the lean body mass[99]. Hence, if there had been some loss of lean body mass between the first and the second cycle, that could explain why weight loss is less rapid during the second cycle of that study. If repeated cycles of weight loss and weight regain contribute to gradual net loss of lean body mass, then that may have detrimental metabolic consequences. However, a study of rural African population that undergoes profound weight cycling due to an annual hungry season and obese women who underwent three cycles of VLCD found no evidence for excessive loss of lean tissue as a result of weight cycling[100].

Studies of PSMF and VLCD in type 2 diabetes

PSMF have the potential to be beneficial for patients with T2D (not on insulin) due to their glycemic benefits which are greater than those associated with more moderate diets even for similar amounts of weight loss[101].

Genuth described different effects of VLCD in patients with mild and severe T2D. He observed that weight regain in the months following VLCD does not consistently cause relapse in patients with mild T2D, but in patients with severe T2D there is inevitable relapse of hyperglycemia[102].

Bistrian, Blackburn et al. investigated the effects of PSMF on insulin and nitrogen requirements in seven patients with T2D on insulin and obesity[103]. They found that the PSMF reduced insulin and glucose concentration and allowed for the withdrawal of exogenous insulin after a mean 6.5 days, while maintaining nitrogen balance as long as 1.3 g protein/kg IBW was given. However, after discontinuation of the PSMF treatment, their subjects often regained substantial fractions of their lost weight.

Wing et al. studied a combination of PSMF of lean meat, fish, or fowl with the option of using Optifast 70 (Sandoz nutrition) with behavioral modification compared with behavioral modification alone in obese subjects with T2D. This study included a run- in period, then 8 weeks of VLCD, followed by a maintenance phase and found significant improvement in glycemic control in the combination VLCD and behavioral modification group which persisted at 1 year[104]. Wing et al. subsequently performed a study that randomized patients with T2D to either LCD or a similar choice of VLCD treatments. The VLCD treatment was separated into two 12-week periods. Subjects assigned to the VCLD group were significantly more likely to remain off diabetes medications after 2-years of follow up[105]. Wing et al. randomized 93 patients with type 2 diabetes to either 1000 kcal / day balanced diet or 400 kcal/day VLCD consisting of either lean meat, fish, or fowl or Optifast formula for 12 weeks and examined changes in insulin sensitivity by frequently sampled intravenous glucose tolerance testing. She found a greater degree of improvement in insulin sensitivity in the 400 kcal group and concluded that caloric restriction improves insulin sensitivity independent of weight loss[106].

In 1984, Hughes et al. studied 12 patients with T2D and compared a PSMF for 6 months with RYGB[107]. Patients in the PSMF group consumed 1.4 g protein/kg ideal body weight for up to six months. Both treatments produced significant weight loss and improvements in hemoglobin A1c and lipids.

Hence, PSMF is a promising therapy for patients with T2D given improvements in A1c, decrease in triglycerides, decrease in insulin resistance, and potential improvement in beta cell function. This is reflected in the clinical practice guidelines including the 2013 AACE/ACE/TOS guidelines for healthy eating for the prevention and treatment of metabolic diseases, which state that a very low calorie meal plan may be recommended for 12 to 16 weeks in selected patients with a BMI > 30[108]. Similarly, the American Diabetes Association 2017 Standards of Care acknowledge that short term VLCD may be beneficial if led by trained practitioners and followed by a structured weight loss maintenance program to

prevent weight regain[109]. PSMF is a tool whereby safe and rapid weight loss can be achieved for many patients, but the maintenance of the weight loss is problematic[110].

Weight maintenance after weight loss

Sustaining weight loss and preventing weight regain is an important problem for many obese patients, which Blackburn recognized even with his thesis work. The difficulty in maintaining a reduced body weight is compounded by a reduction in energy expenditure[111].

Wadden and Stunkart performed a randomized controlled trial of PSMF, behavioral therapy alone, or the combination of both also found that after 1 year follow-up the combination group maintained a mean 12.9 kg weight loss which was significantly greater than the PSMF alone group[112]. A similar trial in Japan compared VLCD with Optifast, behavioral therapy alone, or the combination of both with two year follow up also found significantly greater weight loss in the combination group which achieved 12.8 kg weight loss after 2 years[113]. Hence, behavioral and lifestyle changes are paramount after any VLCD.

A meta-analysis in 2006 of randomized controlled trials that compared LCD and VLCD with at least 1 year follow up after maximal weight loss identified six trials and found no significant differences in long term weight loss between these two diets[114].

A randomized controlled trial of a low calorie diet compared with a very low carbohydrate ketogenic diet for 45–60 days followed by a re-education phase and maintenance phase in Spain demonstrated a significantly greater reduction in BMI, waist circumference, and visceral fat mass assessed by DEXA in the VLCD which persisted for 24 months[115]. Similarly, a recent observational study of 127 consecutive patients who followed a PSMF found that at 24 months post-intervention 25% were able to maintain ≥ 10% weight loss[116].

There may be a role for pharmacotherapy for sustaining weight loss following a PSMF. Wadden et al. found that sertraline was not efficacious at reducing weight regain after VLCD in a placebo controlled randomized trial of 53 women[117]. Apfelbaum conducted a placebo-controlled randomized controlled trial of sibutramine for 1 year in 160 patients following a 4-week VLCD. She found that sibutramine was significantly more effective than placebo at maintaining > 5% weight loss[118]. However, the Sibutramine Cardiovascular Outcome Trial (SCOUT) trial found increased cardiovascular adverse events in the sibutramine group compared with placebo so it was withdrawn from the market in 2010[119]. Wadden and colleagues performed the SCALE Maintenance trial of 422 patients who lost a mean of 6% of initial weight with a low calorie diet and were randomized to liraglutide or placebo for 56 weeks. 81% of patients receiving liraglutide maintained the >5% weight loss compared with 49% of patients receiving placebo, and liraglutide induced an additional 6% weight loss[120]. It is unknown whether liraglutide would have the same effect following a PSMF. A recent systematic review and meta-analysis of obesity drugs (including orlistat and sibutramine), meal replacements, and protein diets were all moderately efficacious at maintaining weight loss after a VLCD[121]. Further research is needed to optimize the prevention of weight regain following weight loss. It is clear that a multidisciplinary approach combining physical activity, nutrition and behavioral education is crucial.

Areas for future research

- What is the role for PSMF for the treatment of childhood obesity?
  - In a case series from the pediatric Obesity Management Program at Cleveland Clinic, PSMF was safe and effective in 12 adolescents and resulted in a mean 9.8% weight loss over a 6 month period[122]. Another study of 10 obese adolescents who followed the PSMF for a mean of 92 days showed that they were able to remain in positive calcium, magnesium, and potassium balance and mean weight loss was 14.7 kg[123].
- What is the role of resistance weight training during caloric restriction with PSMF to enhance lean body mass and strength[124]? Can a regimen that combines exercise, behavioral, and pharmacotherapy after VLCD prevent weight regain?
  - Blackburn collaborated with Whatley and colleagues to investigate the combination of Optifast VLCD with a supervised exercise program emphasizing walking and resistance training. They found that the combination group achieved additional loss of fat mass with similar preservation of fat free mass[125].
  - The preservation of fat- free mass and muscle strength during a 4-month very-low calorie ketogenic diet was recently demonstrated in a study of 20 obese patients with dual-energy X-ray absorptiometry, multi-frequency bioelectrical impedance, and air displacement plethysmography to assess body composition[126].
- What is the optimal duration of PSMF? How many cycles should patients undergo? How to maintain weight loss following each cycle?
  - The National Weight Control registry described the habits of people who were able to maintain 10% weight loss for at least one year and found that most people consistently engage in high levels of physical activity and eat a diet low in calories and fat along with daily self-monitoring of weight[127]. Whether these techniques can help prevent weight regain after PSMF remains to be seen.
  - Blackburn predicted the growing interest in new technologies to assist with weight maintenance and behavioral modification[128]. In addition, new means of delivering care in community settings will be necessary to meet the demand for treatment[129].

Conclusions

The acute hormonal and metabolic stress responses to surgery were extensively studied by Blackburn throughout his career and he made landmark contributions to our understanding of these processes[130]. His laboratory studied animal models of sepsis, burns, and trauma and made seminal contributions to our understanding of protein-calorie malnutrition, obesity, and insulin resistance[131]. Over the course of his career, Blackburn contributed to the study

of enteral and parenteral feeding of critically ill subjects and patients with obesity. He participated in the development of TPN into a widely used therapy and the development and use of disease specific enteral formulas and became a leader in the field of parenteral and enteral nutrition[132]. To implement these findings, Blackburn developed the model of nutrition support teams in hospitals, and this legacy contributed to the large reductions in morbidity and mortality from protein-calorie malnutrition and improved surgical outcomes in the hospital setting.

With the evolution of obesity treatments from fasting to PSMF and VLCD to its current emphasis on pharmacotherapy and bariatric surgery, a deficiency in the current state of field has emerged. The emphasis has become to achieve and sustain weight loss by any means necessary and different therapies that can maintain total body weight are sometimes considered as equivalent: behavioral treatments, small caloric deficits, exercise interventions etc. Current studies are often limited by the fact that the primary outcome is weight change with no assessment of change in body composition or lean body mass. This is partially driven by the FDA requirement for efficacy: mean weight loss of a drug compared with placebo at 1 year of ≥5% or proportion of subjects who lose ≥ 5% from baseline to be ≥ 35% and approximately twice the proportion as the placebo group. This outcome does not consider lean body mass or body composition. Although the FDA has also indicated that visceral adiposity, blood pressure, glycemic control, and plasma lipid profiles are important clinical outcomes for obesity medications[133], Blackburn's emphasis on the preservation of lean body mass during weight loss should be heeded. Obesity medicine has benefited greatly from the growing body of scientific knowledge that Blackburn and his colleagues built upon and expanded. However, the recent ACC/AHA/TOS guidelines concluded that there is still insufficient evidence to answer the many of questions that Blackburn raised in the 1970s and further research is still needed[134].

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Abbreviations

VLCD	Very Low Calorie Diet
PSMF	Protein Sparing Modified Fast
FFA	free fatty acid
TPN	total parental nutrition

BCAA	branched chain amino acid
FDA	Food and Drug Administration
DEXA	dual-energy x-ray absorptiometry
T2D	type 2 diabetes

Glossary

Protein-calorie malnutrition
A state of severe deficiency of protein and calories that can result in either marasmus or kwashiorkor in children and related conditions in adults

PSMF
A treatment for obesity developed by Blackburn and colleagues designed to spare body protein during weight loss

VLCD
A diet consisting of less than 800 kcal per day

TPN
a method of intravenous feeding providing full nutritional needs that bypasses the gastrointestinal tract

DEXA
A radiologic technique for measuring lean body mass and fat as major components of body composition

Marasmus
a form of severe malnourishment due to underfeeding characterized by major weight loss and cachexia when accompanied by chronic inflammation as with some cancers and other chronic conditions

Kwashiorkor
a form of severe protein malnourishment characterized by edema, apathy, thinning hair, and fatty liver in children and with increased morbidity and mortality due to impaired organ function and immunocompetence in hospitalized adults with underfeeding and severe metabolic stress

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