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History and Origin of the Ketogenic Diet

James W. Wheless

1. INTRODUCTION

In the past, many dietary “cures” for epilepsy were advocated, and such treatments included the excess or limitation of almost every substance (animal, vegetable, or mineral) (1). However, fasting as a treatment for seizures was less recognized. Fasting is the only therapeutic measure against epilepsy recorded in the Hippocratic collection (1). In the fifth century BC, Hippocrates reported on a man who had been seized by epileptic convulsions after having anointed himself before the fire in a bath, in winter. Complete abstinence from food and drink was prescribed, and the cure was effective.

Fasting, as a therapy for seizures, was documented in biblical times. In a quotation from the King James Version of the Bible, Mark relates the story of Jesus curing an epileptic boy (2–4). When his disciples asked him privately why they had not been able to cure the boy, Jesus said “this kind can come out by nothing but prayer and fasting.” Raphael’s *Transfiguration of Christ*, probably the most famous painting of a person with epilepsy, is based on this passage from Mark (5). This painting is divided into two parts; the upper part depicts the transfiguration of Christ, the lower part portrays the healing of the boy with epilepsy (Fig. 1).

2. FASTING (A PRECURSOR TO THE KETOGENIC DIET)

It was not until the early twentieth century that medical use of the ketogenic diet emerged as a strategy to mimic the biochemical effects of fasting (or starvation) (Fig. 2). Guelpa and Marie, both French physicians, authored the first scientific report on the value of fasting in epilepsy (6). They reported that seizures were less severe during treatment, but no details were given. In the United States, contemporary accounts of fasting were also recorded early in the twentieth century (Table 1); the first was a report on a patient of an osteopathic physician, Dr. Hugh W. Conklin, of Battle Creek, Michigan, and the second concerned Bernarr Macfadden (7,8). Macfadden was a physical fitness guru/cultist and publishing genius of the early part of the 20th century (9). He called the medical profession an organized fraud and said that people who followed his rules could live to age 120. At age 31 (in 1899), he established his first magazine, *Phys-*

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Fig. 1. Raphael's *Transfiguration of Christ*. (Reproduced with permission from ref. 5.)

ical Culture. He advised readers how to develop themselves physically, how to maintain their health, and how to cope with illness. He illustrated it with photographs of himself lightly clad, with muscles bulging (Fig. 3A). Each issue carried articles about sickly men and women who became healthy, strong, and beautiful through proper diet and exercise. The magazine's circulation had reached 500,000 by the end of World War I. Macfadden was widely recognized, and one of his followers, Angelo Siciliano, won Macfadden's "America's Most Perfectly Developed Man" contest twice. Using the winnings, Siciliano went on to establish his own muscle-building business under the name of Charles Atlas.

Macfadden offered advice on a subject he knew very little about—coping with illness. He maintained that any disease could be cured by exercise and diet. He also emphasized fasting. His rationale was that because much of the body's energy goes into digesting food, if there is no food to digest, more energy could be applied to recovering health. Macfadden claimed that fasting for 3 d to 3 wk could alleviate and cure about any disease, including asthma, bladder disease, diabetes, prostate disease, *epilepsy*, impotence, paralysis, liver and kidney disease, and eye troubles. He had become nationally recognized, and his ideas were well known (Fig. 3B). Dr. Conklin began as an

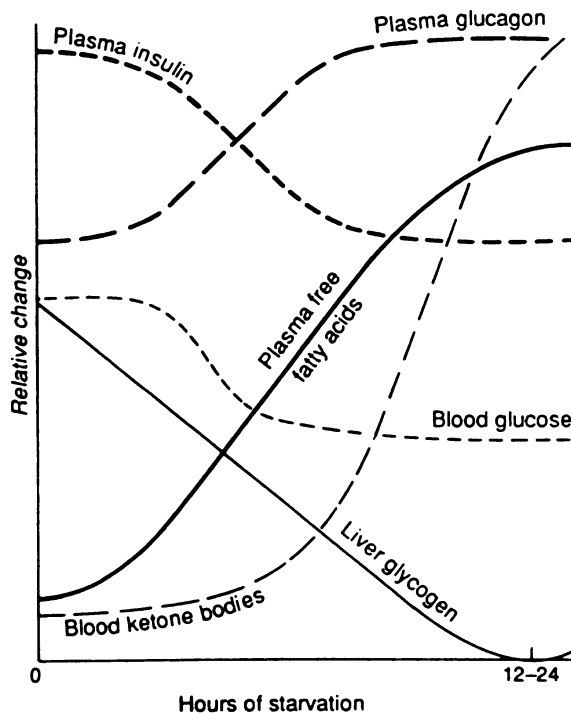


Fig. 2. Biochemical changes that occur with fasting (Reprinted with permission from ref. 94.)

assistant to Macfadden and adopted his method of fasting to treat various ailments (4). It was his practice of fasting to treat epilepsy and the results, which drew the attention of another pioneer in epilepsy studies, H. Rawle Geyelin, an endocrinologist at the New York Presbyterian Hospital.

Dr. Geyelin, a prominent physician from New York, first reported at the American Medical Association (AMA) convention in 1921 his exposure to fasting as a treatment of epilepsy (10). In 1919 he had the opportunity to observe a young cousin who had epilepsy for 4 yr (11). The patient's seizures were not controlled by numerous treatments that had been recommended by several neurologists. The patient also failed to respond to the conventional treatments of the day, bromides and phenobarbital. Then Dr. Conklin had the child fast four times over several months: the seizures stopped after the second day of fasting, and the boy had none in over 2 yr of follow-up. After observing two other patients who apparently had been cured of epilepsy by Dr. Conklin, Dr. Geyelin began using the same fasting treatment to see if he could confirm the results in a larger group of patients. Not knowing what the effects of the fast would be, Dr. Geyelin initially used variable periods of fasting. He finally adopted a 20-d period for the fast, although he admitted this was entirely arbitrary. Geyelin was the first to document that "when one wanted to turn a clouded mentality to a clear one it could almost always be done with fasting." This observation languished until recent times, when behavioral and developmental improvements attributed to the ketogenic diet were reported (12). Dr. Geyelin documented the efficacy of fasting in 36 patients (see Table 1) and closed his presentation by remarking that this was a preliminary report, and further study was needed.

Table 1
Efficacy of Fasting, 1921–1928

<i>First author</i>	<i>No. of patients</i>	<i>Age (yr) of Patients</i>	<i>Seizure type^a</i>	<i>Diet</i>	<i>Success rate (%)</i>	<i>Comments</i>
Geyelin R, 1921 (10)	30	3.5–35	PM, GM	Fasting	87% Seizure free	Results based on 20-d fast; no long-term follow-up
Weeks DF, 1923 (86)	64	7–61	PM, GM	Fasting	47% Seizure free during fast	Patients fasted for 3 wk; all had seizures after return to regular diet
Talbot FB, 1926 (37)	23	Children	UN	Fasting	Seizure free during fast	Seizures returned in all after fast
Lennox WG, 1928 (4)	27	13–42	UN	Fasting	50% had marked reduction in seizures during the fast	Phenobarbital stopped on admittance; fast lasted 4–21 d

^a GM, grand mal; PM, petit mal; UN, unknown.

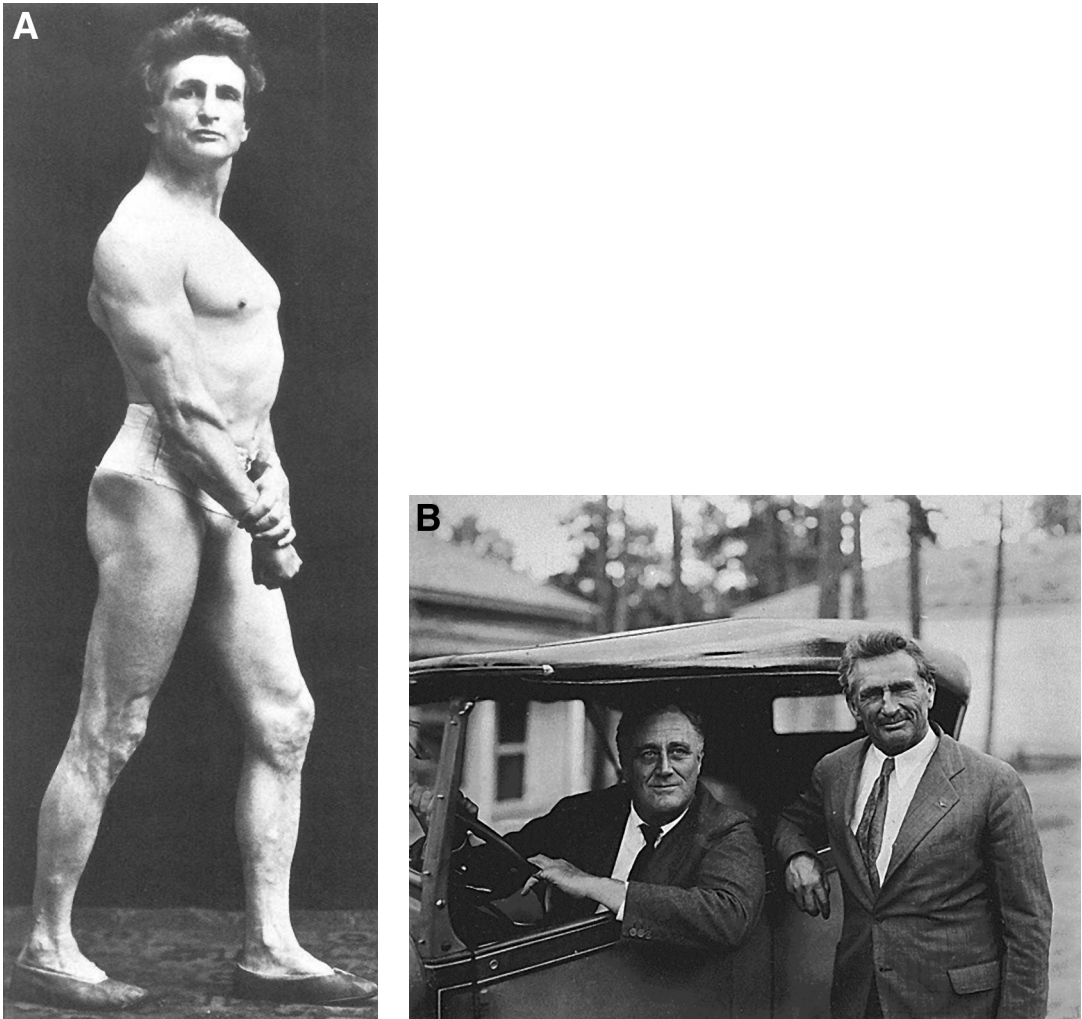


Fig. 3. Bernarr Macfadden. (A) As he appeared in a photograph in his magazine *Physical Culture*, illustrating his bulging muscles. (Reproduced with permission from the Qu'igley Photographic Archives, Georgetown University Library.) (B) With presidential candidate Franklin D. Roosevelt (in car) in 1931. Macfadden tried to ingratiate himself with Roosevelt as a part of a strategy to be appointed as the first Secretary of Health.

Dr. Stanley Cobb of Harvard was in the audience that day and commented that he had experimentally used starvation to prevent convulsions in an animal model. At that time, Cobb did not know that the father of the first child Geyelin had discussed would come to him in 1922 and ask him to explain the mechanism of action of starvation in treating epilepsy; we pick up this thread of the story again later in this section.

At this time, Dr. Conklin believed that epilepsy, which he labeled “intestinal epilepsy,” had its origin in the intestines and was curable (13). He thought that a toxin secreted from the Peyer’s glands was taken up in the lymphatics, stored in the lymph glands and other tissues, and from time to time discharged into the bloodstream, causing epileptic convulsions. He reasoned (based on influence from Macfadden) that dur-

ing a fast, the tissues freely pour their poison content into the bloodstream, through which means the toxins are eliminated. In his manuscript, he outlines his treatment for epilepsy and technique for initiating and breaking the fast. Typically, he deprived the patient of all food for 18–25 d, or as long as the person was physically able to stand it. Conklin reported that his cures of epilepsy were 90% in children younger than 10 yr, 80% in adolescents 10–15 yr old, 65% in patients 15–25 yr old, and 50% between 25 and 40 yr, above age 40, the percentage was very low.

However, even before Conklin published his results with fasting, word of his successful treatment had spread to others in more conventional neurology practices (4,14). Higgins, while addressing the Pennsylvania State Medical Society in 1928, commented, “About 1917 the attention of the medical world was drawn to the finding that the attacks in many cases of epilepsy were stopped, or lessened in severity and frequency, by starvation” (14). Dr. Penfield, of the Montreal Neurological Institute, and his colleague Dr. Erickson, also recognized Conklin’s fasting therapy in their 1941 textbook on epilepsy (15). Lennox acknowledged that Conklin, by 1928, had the most experience in treating patients with epilepsy by fasting (probably hundreds of patients over approx 20 yr [4]).

Conklin and Macfadden’s views on the origins and treatment of epilepsy were adopted by others (4). This is reflected in Dr. McMurray’s letter to the *New York Medical Journal* describing digestive disturbances as an impressive finding in his patients with epilepsy and the use of fasting followed by a starch- and sugar-free diet as a treatment beginning in 1912 (16). Dr. A. Goldbloom, a physician at the Children’s Memorial Hospital in Montreal, was more skeptical. He wrote, “A year or two ago we allowed ourselves to be startled by the news of an asserted real cure for epilepsy. A drugless healer in the middle west [Conklin] had been curing epileptics, it was said, by subjecting them to long periods of starvation” (17). He then related the story of a 10-yr-old girl who had failed therapy with bromide and Luminal® (phenobarbital), was having 60–100 petit mal seizures a day, and became seizure free on the fifth day of her fast. However, after the fast was broken, the seizures gradually returned.

Goldbloom stated, “It would seem from this case that the starvation treatment is effective only while it is continued and while the patient remains in bed, but that it has no enduring qualities. The explanation of the improvement is first that the patient is kept in bed, and secondly that the fermentative and putrefactive intestinal processes, so often the exciting causes of convulsions, even in a non-epileptic child, are reduced for the time being to a minimum. So far as children are concerned, one often sees children who have been considered epileptics in whom the epilepsy is found to be purely of intestinal origin, and who are therefore permanently cured by the application of strict dietetic measures” (17).

Lennox would later relate the relationship of Conklin’s practice to the origin of the ketogenic diet (4,18). In an interesting anecdote, he relates the story of HTH, the boy initially presented by Dr. Geyelin to the AMA convention.

Lennox stated, “a New York corporation lawyer and his wife were troubled because of the daily seizures of their son. The boy’s uncle (Dr. John Howland) was a professor of pediatrics, but the best medical advice and treatment of the day failed to help. In despair, the parents turned to Dr. Hugh Conklin, a disciple of Bernarr Macfadden, a physical cultist. The treatment was called, euphemistically, a water diet. This meant starvation for three or four weeks. Dramatically, the boy’s seizures left him.”

Around 1919, Charles Howland, the boy's father and a wealthy New York corporate lawyer, gave his brother \$5000 to determine whether there was a scientific basis for the success of the starvation treatment of his son (19,20). Dr. John Howland, professor of pediatrics at Johns Hopkins and director of the newly opened Harriet Lane Home for Invalid Children was H.T.M.'s uncle. The gift from Charles Howland was used to create the first laboratory at the Harriet Lane Home. By 1937, the John Howland Memorial Fund was established at Johns Hopkins and used to support research on the ketogenic diet (21). Lennox reports that initially two physicians sought confirmation and explanation for the surprisingly favorable results of fasting. One was Dr. James Gamble. In 1915 Dr. Howland recruited Gamble, who had recently developed an interest in clinical chemistry, to the Harriett Lane staff.

By 1919, Harvey reports, "Dr. Howland had developed a deep interest in the treatment of epilepsy by the ketosis of starvation. Gamble went to work on this problem..." (22). These children were ideal subjects for the metabolic balance studies of the 1920s because their intake was limited to water, and fecal material was greatly reduced. Gamble and his colleagues initially reported the study of the acid-base balance of two fasting children (23). This report produced little information regarding the mechanism of action of fasting on epilepsy, but it was the beginning of a 30-yr study by Gamble of factors affecting the water balance in children. His report formed a pattern for clinical research and created the basis for the fields of pediatric electrolyte physiology and nephrology. He also was the first to note increased calcium excretion on the ketogenic diet, with a resulting need for calcium supplementation (24).

The other doctor recruited by Howland was H. Rawle Geyelin, who had reported his results at the 1921 AMA convention in Boston. Urinary acid excretion had been highest in patients whose seizures were best controlled. At that time, W. G. Lennox was studying cardiology under Dr. Francis Peabody at Boston's Peter Bent Brigham Hospital. Lennox reported that he was "Thrilled by Geyelin's demonstration and having a compelling interest in epilepsy and its treatment, my missionary zeal was abruptly transferred from Chinese to the epileptic" (18). Geyelin's extensive clinical and laboratory data were never published, but he later told Lennox that long-term freedom from seizures occurred in 15 of 79 children treated (19%), but in only 1 of 200 adults (0.5%) (4,11). Lennox's personal review of Conklin's short case records of 127 patients with epilepsy indicated that 20% achieved seizure freedom, and some improvement occurred in 50% (4).

In 1922 the parents of H.T.H. asked Dr. Stanley Cobb, associate professor of neuropathology at Harvard Medical School, to explain why starvation worked as a treatment for epilepsy (18). Cobb enlisted the assistance of a young colleague, W. G. Lennox. Lennox and Cobb reported on a selected group of five patients during a 2-wk period of fasting (24). Lennox himself served as a control during one fast period of 14 d and several shorter ones. Chemical assays of the blood and urine were performed in the subjects and controls. All showed an increase in serum uric acid and acidosis, which was excreted in the urine if the fast was broken with carbohydrate or by a purine-free protein diet, but not if broken by the intake of 40% cream. Also, they noted the increase in serum uric acid and acidosis typically developed after 2 or 3 d and was accompanied by a decrease in seizures.

Lennox stated, "Initiation of the use of bromides in 1857 and of phenobarbital in 1912 had demonstrated that the chemical action of these sedative drugs could lessen seizures. The third decade of the twentieth century witnessed a measure of control

through a change of body metabolism. Simple absence of food or dearth of carbohydrate in the body forced the body to burn acid-forming fat" (18). The efficacy of fasting led to a flurry of clinical and research activity. Theories arose to explain the success of starvation. Dehydration (23,26), ketosis (24,27–29), and acidosis (25,30,31) were all advanced as mechanisms to explain the efficacy of fasting. Metabolic balance studies had been used by many investigators of this era to understand the interrelationships of fat, protein, and carbohydrate metabolism to the ketoacidosis and disturbed glucose utilization that occurs in diabetes.

3. THE KETOGENIC DIET

At about the same time as the study of Cobb and Lennox, in 1921, a review article about diet adjustments and diabetes by Woodyatt stated "acetone, acetic acid, and beta-hydroxybutyric acid appear ... in a normal subject by starvation, or a diet containing too low a proportion of carbohydrate and too high a proportion of fat. It [ketoacidosis] appears to be the immediate result of the oxidation of certain fatty acids in the absence of a sufficient proportion of 'oxidizing' glucose" (32).

Concurrently, Dr. Wilder at the Mayo Clinic proposed, probably based on the work summarized by Woodyatt, "that the benefits of ... fasting ... could be obtained if ketonemia was produced by other means. The ketone bodies ... are formed from fat and protein whenever a disproportion exists between the amount of fatty acid and the amount of sugar actually burning in the tissues. In any case, as has long been known, it is possible to provoke ketogenesis by feeding diets which are very rich in fat and low in carbohydrate. It is proposed therefore, to try the effects of such ketogenic diets on a series of epileptics" (27). Wilder suggested that a ketogenic diet should be as effective as fasting and could be maintained for a much longer period, compensating for the obvious disadvantages of a prolonged fast.

In a report issued the following day, he described the dramatic improvement in seizure control of three patients with epilepsy who had been admitted to the Mayo Clinic for initiation of the ketogenic diet (33). He concluded, "It is impossible to draw conclusions from the results of these few patients treated with high fat diets, but we have here a method of observing the effect of ketosis on the epileptic. If this is the mechanism responsible for the beneficial effect of fasting, it may be possible to substitute for that rather brutal procedure a dietary therapy which the patient can follow with little inconvenience and continue at home as long as seems necessary" (33). It was Wilder who coined the term *ketogenic diet*.

Peterman and other pediatricians eagerly acted on Wilder's suggestion (34,35). Peterman first reported the calculation and effectiveness of the ketogenic diet from the Mayo Clinic in 1924 (35). Peterman's ketogenic diet, composed of one gram of protein per kilogram of body weight in children, 10–15 g of carbohydrate per day, and the remainder of the calories in fat, is identical to the ketogenic diet that is used today. Peterman documented the importance of teaching the caregivers management of the diet before discharge, individualization of the diet, close follow-up, and the potential for further adjustments at home. He also made the early observation that excess ketosis could lead to nausea and vomiting, symptoms that were quickly relieved by orange juice (34). This clinical caveat is still useful to know and is employed as needed during initiation of the ketogenic diet (36).

Peterman also noted improvements in behavior and cognitive effects that accompanied the ketogenic diet.

“The mental development has been normal in all patients, and exceptionally good in seven of the twenty who are now free from attacks. In all the children treated with the ketogenic diet there was a marked change in character, concomitant with the ketosis, a decrease in irritability, and an increased interest and alertness; the children slept better and were more easily disciplined. This action of the diet warrants further study” (34).

This last comment is as true today as it was in 1925! M. B. Pulsifer and others, 75 yr later, performed the first prospective study of the effects of the ketogenic diet on development and behavior (12). She concluded, “At follow-up, mean developmental quotient showed statistically significant improvement ($p < 0.05$), with significant behavioral improvements in attention and social functioning,” verifying Peterman’s earlier observation.

These initial reports were rapidly followed by reports from Talbot and colleagues (Harvard) (28,37–39) and from McQuarrie and Keith (Mayo Clinic) (40) in 1926 and 1927. Talbot introduced the first report as follows: “In 1921, the children’s medical service of the Massachusetts General Hospital (MGH) initiated a study of the treatment of idiopathic epilepsy. The first method of attack was by the fasting method recommended by Conklin of Battle Creek” (37). This statement verifies the impact Macfadden ultimately had, even on such prestigious institutions as MGH.

Talbot noticed some seizure freedom in all 21 children during the fast, but the seizures returned after the fast was broken. As a result, in 1924 MGH adopted the ketogenic diet as performed by the Mayo Clinic (Dr. Peterman). Talbot also noted that the diet was well tolerated, “without causing any untoward symptoms in the patients. On the contrary, they seem to be more alert and less nervous” (37). Talbot also acknowledged the critical role of the dietician and noted that “a clever dietician works out various little tricks to get in fat” (37). Talbot’s 1930 textbook on the treatment of epilepsy included tables with complete discussion and instructions for the ketogenic diet (41). The current Johns Hopkins Hospital protocol (*see ref. 42*) for calculating and initiating the ketogenic diet after a period of fasting to hasten the production of ketosis, and gradually increasing the amount dietary fat introduced over several days, was well discussed by Talbot in 1926 (38).

By 1928, Talbot had experience with differing compositions of ketogenic diets and wrote that “the best therapeutic results in epilepsy are not obtained until the ratio has approached 4:1...” (24), which is now recognized as the most common composition for the ketogenic diet. McQuarrie and Keith, while studying the biochemistry of children on the ketogenic diet in 1927, made the initial observation that the proportion of acetone bodies in the blood runs parallel to that in the urine (40), a finding validated 62 yr later by Schwartz et al. (43). The Mayo Clinic investigators also were the first to note variations during the day in the intensity of ketosis, with a maximum in the late afternoon and the nadir in the early morning hours.

McQuarrie and Keith were aware of the recently rerecognized tendency of children to have seizures early in the morning, when ketosis is minimal, and they suggested the addition of a midnight snack to maintain early ketosis. They also recognized that the degree of ketosis to prevent seizures may vary across individuals, and as a result adjust-

ing the diet for the individual patient was necessary to ensure optimal ketosis. Such adjustments are routinely made in multidisciplinary epilepsy clinics today.

By 1927 Helmholz at the Mayo Clinic was aware that if the child did not have definite improvement in seizure control after 2 mo of the ketogenic diet, it was fair to say that a therapeutic failure had occurred and appropriate to abandon the diet (29). In 1927 the Section on Pediatrics and Nutrition at the Mayo Clinic prepared a pamphlet that describes in detail meal plans and recipes for a ketogenic diet (44). This was done in response to the demand for this type of practical information.

The use of the ketogenic diet was recorded in almost every comprehensive textbook on epilepsy in childhood that appeared between 1941 and 1980 (3,15,18,45–51). Most of these texts had full chapters describing the diet, telling how to initiate it and how to calculate meal plans. Extensive tables listed the nutritional composition of foods and discussed meal planning.

Throughout the 1920s and 1930s, the ketogenic diet was widely used (*see* next section). When Merritt and Putnam discovered diphenylhydantoin in 1938, the attention of physicians and researchers shifted focus from the mechanism of action and efficacy of the ketogenic diet to new antiepileptic drugs (AEDs) (*see* ref. 52). A new era of medical therapy for epilepsy had begun, and the ketogenic diet fell by the wayside. Medications were easier to administer and new chemical compounds were always on the horizon. As early as 1937, Ford, in a pediatric neurology text, found the ketogenic diet difficult, rigid, and expensive (53).

In an effort to make the classic ketogenic diet more palatable, Huttenlocher et al., in 1971, introduced a medium-chain triglyceride (MCT) oil diet that was more ketogenic per calorie, allowing less restriction of other foods (54). This 1971 report from Yale University documented a therapeutically significant anticonvulsant effect in 6 of 12 children with daily myoclonic and astatic seizures. As a result, other centers adopted the MCT diet in place of the classic ketogenic diet and reported it as the “ketogenic diet” (55–60). Almost 20 yr went by before Schwartz and colleagues conducted the only comparative trial of the MCT diet and the classic ketogenic diet (*see* Section 3.2.) (43,61). This report documented more side effects and less palatability of the MCT diet.

As new AEDs became available, the ketogenic diet was used less and less. After the introduction of sodium valproate, it was believed that this branched-chain fatty acid would treat children previously placed on the diet to treat the seizures of Lennox–Gastaut syndrome and that the diet could no longer be justified (62). Pediatric neurologists and epileptologists were led to believe that better understanding of central nervous system neurotransmitters and rationally designed AEDs were the hope for the future. Fewer children were placed on the ketogenic diet, resulting in fewer dietitians who were trained in the initiation and maintenance of the diet. As Lennox stated in 1960, “Though interest in fasting (or the ketogenic diet) as a treatment has almost vanished, doubtless much scientific gold remains in ‘them thar hills’” (18).

3.1. Ketogenic Diet in the 1990s

Use of the ketogenic diet decreased greatly until it received national media attention in October 1994, when NBC-TV’s *Dateline* aired a program on the treatment (7,8,42,63–66). This television program was based on the true story of Charlie, a 2-yr-old with intractable myoclonic, generalized tonic, and tonic–clonic seizures (Fig. 4). A videotape presentation made later summarizes Charlie’s condition in 1994: “Thousands



Fig. 4. Charlie Abrahams, age 4, with his parents Jim and Nancy, as they appeared in 1997 in a story on Charlie and the ketogenic diet published in the *New York Times* (Reproduced with permission from Bart Bartholomew.)

of seizures and countless medications later, after five pediatric neurologists, two homeopathic physicians, one faith healer, and one fruitless surgery, Charlie's seizures remained unchecked and his prognosis was for continued seizures and progressive retardation" (65).

While researching treatments for epilepsy on his own, Charlie's father found a reference to the ketogenic diet and Johns Hopkins (67). Charlie was brought to Johns Hopkins for initiation of the diet. There the diet continued to be used in the epilepsy center, under the discretion of Ms. Millicent Kelly, an experienced dietician. Charlie initiated the diet, became seizure-free, and soon posted developmental progress. Charlie's father was disturbed that no one had told him about the diet. He reviewed the references of the success rate (see Section 3.2.) and was determined that the information should be available so that other parents could become aware of the ketogenic diet. He created the Charlie Foundation and made videos for parents about the diet, as well as one directed at physicians and another, an instructional video, for dieticians. The foundation has distributed over 50,000 of these videotapes gratis.

The Charlie Foundation also funded the initial publication of *The Epilepsy Diet Treatment: An Introduction to the Ketogenic Diet* (8) and underwrote conferences to train physicians and dieticians from epilepsy centers nationwide. The first conference attendees were responsible for developing the first multicenter prospective report on the efficacy of the ketogenic diet (68). In 1995 Wheless concluded that the ketogenic diet compares favorably with other new treatments for epilepsy in children and should be available at every pediatric epilepsy center (69). This echoed a comment made by Dr. Geyelin at a presentation to the American College of Physicians in New Orleans on March, 7, 1928: "The results of fasting and the ketogenic diet are apparently the best that are obtained by any therapeutic procedure that we have to offer epileptics in childhood today" (see ref. 11).

The ketogenic diet has experienced a significant reemergence in recent years, and modern clinical studies have established the treatment as significantly effective (see

next section). This is reflected by the dramatic increase in scientific articles regarding this treatment. Between January 1965 and December 1995, PubMed recorded 93 publications pertaining to the with ketogenic diet; however, from January 1996 to January 2003, a website of the National Institutes of Health recorded 172 publications (www.ncbi.nih.gov/entrez/query.fcgi). This documents the increased interest in the diet in the scientific community over the last 5–10 yr, and the timeliness of this book.

3.2. Early Efficacy of the Ketogenic Diet

In the 1920s and 1930s, initial reports documented the efficacy of the ketogenic diet (Table 2) (14,29,70–78). These were all retrospective reports. Some included a small number of patients and provided few clinical details or specifications of epilepsy syndrome or seizure type. The studies clearly showed some patients had improved seizure control on the ketogenic diet. Over the next 60–70 yr, many more clinical reports appeared on the ketogenic diet (Tables 2 and 3) (79). Meta-analysis of the published data is not possible, given differences in study design and sparse clinical detail; additionally, it is often not clear what is meant by “good” or “partial” response to the ketogenic diet. Despite these limitations from older studies, however, the literature supports the consensus view that the ketogenic diet improves seizure control in some children. Overall, one-third to one-half of children have an excellent response to the ketogenic diet, defined by marked cessation of seizures or reduction in seizure severity. Younger children are more likely to have a favorable response than older children.

Few early studies evaluated the ketogenic diet treatment in adults (Table 4). Reports from the Mayo Clinic experience in 100 adults treated during the 1920s found that seizures were controlled in 12 patients and that an additional 44 benefited (80,81). Another early report of 20 institutionalized adult patients with epilepsy and mental impairment found an increase in seizure frequency upon initiation of the diet (82). However, all antiepileptic drugs have been stopped before diet initiation. In 1999, over 70 yr after the initial Mayo Clinic report, Sirven and colleagues, performed a modern, prospective study evaluating the efficacy and safety of the ketogenic diet as a treatment for adults with intractable, symptomatic partial, or generalized epilepsy (83). These patients had failed an average of 5.4 AEDs and had weekly to daily seizures. At 8 mo of follow-up, 54.5% (6 of 11) had a greater than 50% reduction in seizure frequency, and 4 patients discontinued the diet. All seizure types responded to the diet, and most patients tolerated the diet.

Some modern studies have looked more critically at the ketogenic diet and have provided good clinical details of the clinic population. Hopkins and Lynch reported on the first group of children in Australia (84). They followed 34 children who had not responded to adequate drug therapy, and this group experienced an overall success rate of 29%. Improvement was dramatic in some patients who had been earlier regarded as hopeless.

Schwartz et al. reported on the results of 24-h metabolic profiles performed on epileptic children receiving normal diets, the classic (4:1) ketogenic diet, the MCT diet, and the modified MCT diet (Radcliffe diet, which incorporates both long-chain and medium-chain fatty acids) (43). The authors hoped the study would establish relative efficacy of the various forms of the diet. They evaluated 59 patients who were fasted for 18 h and then placed on one of the three diets. Patients continued on the diet with recording of seizures and then were readmitted for a follow-up metabolic profile.

Several biochemical parameters were analyzed, but specifically, blood samples were assayed for the measurements of ketone bodies (acetoacetate, β -hydroxybutyrate), serum glucose, pyruvate, and lactate. The studies showed that all three therapeutic diets produced a significant increase in total ketone body levels, but this effect was most marked on the classic ketogenic diet. In addition, the work documented that ketone body concentrations elevated during the day, reached a maximum in the afternoon, and often were lower in the morning. Measured urinary ketones reflected changes noted in the serum. This led to the adoption of urine ketone body measurement as a standard method for determining the degree of ketosis on the ketogenic diet.

The study by Schwartz et al. documented that all three therapeutic diets resulted in seizure control and that one was not superior to another in this brief period; however, it also documented that the classic ketogenic diet, using the Johns Hopkins Hospital's protocol, induced the greatest degree of ketosis. Additionally, Schwartz et al. analyzed short-term clinical efficacy of the ketogenic diet in the treatment of epilepsy (61). They again used the three dietary therapies that were used in the 1980s: the classic (4:1) diet as administered at the Johns Hopkins Hospital, the MCT diet, and the modified MCT diet. They evaluated 59 patients who were followed for at least 6 wk and reported a very high (81%) responder rate (defined as >50% reduction in seizures). They noted that drowsiness, a frequent side effect during initiation of the diet resolved as the children obtained the full diet. They documented the efficacy of all forms of the ketogenic diet, but they also showed that there were more side effects associated with the MCT diet, including diarrhea and vomiting. In addition, the MCT diet was less palatable.

In 1992 a report updated the efficacy of the ketogenic diet in the modern era of antiepileptic drug therapy (85). The authors reviewed the results of 58 consecutive patients who were placed on the ketogenic diet at Johns Hopkins Hospital in the 1980s. All the children treated had severe, intractable epilepsy: 80% had multiple seizure types, and 88% were on multiple AEDs. Despite this high morbidity, improved seizure control occurred in 67% of the patients on the ketogenic diet, 64% were able to reduce their antiepileptic drugs, 36% became more alert, and 23% had better behavior. These findings are remarkable because they were reported in a group of patients with refractory epilepsy who also had mental retardation (84%), microcephaly (15%), and cerebral palsy (45%). In this study, seizure type did not predict success with the ketogenic diet. Additionally, 75% of the improved patients continued the diet for at least 18 mo, confirming the efficacy and palatability of the diet and patient willingness to continue with it. This study confirmed the earlier work by Livingston on a large number of patients at the same institution, demonstrating that 52% had complete control and an additional 27% had improved control (3).

The first multicenter study of the efficacy of the ketogenic diet was completed in 1998 (68). Seven comprehensive epilepsy centers prospectively entered 51 children into this study of the efficacy of the classic ketogenic diet. The parents recorded baseline seizure frequency for one month prior to initiation of the diet. These children had intractable epilepsy and an average of 230 seizures per month. Their seizure frequency was evaluated at 3, 6, and 12 mo on the ketogenic diet. Ten percent of the patients were seizure free at one year, and 54, 53, and 40% achieved greater than 50% decrease in seizure frequency at 3, 6, and 12 mo of follow-up on the diet. In addition, using an intention-to-treat analysis, 47% remained on the diet at one year. This study again showed that the patient's age, seizure type, and electroencephalographic results are not

Table 2
Efficacy of the Ketogenic Diet (KD), 1921–1976

<i>First author</i>	<i>No. of patients</i>	<i>Age (yr) of Patients</i>	<i>Seizure type^a</i>	<i>Diet</i>	<i>Success rate (%)</i>	<i>Comments</i>
Peterman MG, 1925 (34)	37	2.25–14.5	PM, GM	KD	60% Seizure free, 34.5% improved, 5.5% not improved	All idiopathic etiology; follow-up 0.33–2.5 yr; only 2 on phenobarbital
Talbot FB, 1926 (37)	12	Children	PM, GM	KD	50% Seizure free, 33% improved, 17% no change	Follow-up period 3–6 mo; all idiopathic etiology
Cooder HR, 1933 (87)	38	≤12	GM, PT	KD	50% Seizure free, 34% improved, 16% not improved	>3 mo follow-up
Helmholz HF, 1937 (88)	501	Children	UN	KD	Idiopathic etiology	92 had symptomatic epilepsy and 142 could not maintain diet. All children had > 1 yr follow-up. Results from children treated between 1922 and 1936; 1 child developed pella.
Wilkins L, 1937 (21)	30	3–14	GM, PT, MM	KD	27% Seizure free, 50% no benefit	Idiopathic etiology, follow-up >1.5 yr; all seizure-free patients resumed a normal diet
Keith HM, 1963 (49)	729	Unknown	UN	KD	Of 530 idiopathic patients, 31% seizure free, 24% improved, 39% no benefit	Patients treated between 1922 and 1944, follow-up 1–30 yr (some included in ref. 88). Excluded 84 with symptomatic epilepsy; 115 unable to follow diet No deaths from diet. 1 Renal calculus
Hopkins J, 1970 (84)	34	1–13	GM, MM	KD	29% Successful (seizure free or much reduced), 32% unsuccessful, 26% inadequate trial	
Livingston S, 1972 (3)	1001	Unknown	UN	KD	52% Seizures controlled, 27% seizures marked improvement, 21% no improvement	
Dodson WE, 1976 (89)	50	5–38	UN	KD	50% Seizure free, 20–30% seizures improved considerably	

^a GM, grand mal; MM, minor motor; ; PM, petit mal; UN, unknown; KD, classic ketogenic diet.

Table 3
Efficacy of the Ketogenic Diet, 1989–1999

<i>First author</i>	<i>No. of patients</i>	<i>Age (yr) of patients</i>	<i>Seizure type^a</i>	<i>Diet</i>	<i>Success rate (%)</i>	<i>Comments</i>
Schwartz RH, 1989 (61)	59	<5–54	M, A, IS, GTC, AB, SP, CP	KD-24 MCT-22 Modifield MCT-13	81% had a >50% reduction of seizures	MCT diet more unpalatable; prospective series
Kinsman SL, 1992 (85)	58	1–20	80% multiple seizure types	KD	29% seizure controlled >50% seizure reduction, 29% had	All had severe neurology handicaps: mental retardation (84%), cerebral palsy (45%), microcephaly (15%); 3 renal nodes
Swink T, 1997 (90)	18	6.5–1.75	934 seizures/mo average	KD	At 6 months: 50% seizure free; 42% have ≥50 seizure reductions, only 1 discontinued diet.	Prospective, all children <2 yr at enrollment
Vining EPG, 1998 (68)	51	1–8	230 seizures/mo average (IS, SP, GTC, AB, CP, A, M)	KD	At 1 yr 53% off diet (half poor seizure control, half poor tolerance), 40% of original group had ≥50% decrease in seizure frequency and 10% are seizure free	Prospective, multi center; failed average of 7 drugs previously
Freeman JM, 1998 (91)	150	0.34–16	410 seizures/mo average (multiple types)	KD	At 1 yr 55% on diet 27% had 90% decrease in seizure frequency; 7% were seizure free	Prospective; 70% had IQ <69, prior trials 6.24 AEDs on average
Hassan AM, 1999 (92)	52	Mean = 5.5	81% Mixed seizure types	KD-49 MCT-3	67% have > 50% decrease in seizures 11.5% seizure-free (no duration given)	Retrospective; no duration of follow-up given. 60% stopped diet in ≤ 3 mo.

M, myoclonic; A, atonic; IS, infantile spasms; GTC, generalized tonic-clonic; AB, absence; SP, simple partial; CP, complex partial; KD, classic ketogenic diet; MCT, medium-chain triglyceride diet; modified MCT, modified MCT diet; AEDs, antiepileptic drugs.

Table 4
Efficacy of the Ketogenic Diet in Adults

<i>Author</i>	<i>No. of patients</i>	<i>Age (yr) of patients</i>	<i>Seizure type*</i>	<i>Diet*</i>	<i>Success rate (%)</i>	<i>Comments</i>
Barborka CJ, 1928 (80)	49	17–42	GM, PM	KD	25% seizure free; 34% improved; 41% not benefited; 17 did not cooperate and stay on diet.	Idiopathic epilepsy in all. Only 5 on an AED (PB)*
Barborka CJ, 1930 (81)	100	16–51	GM, PM	KD	12% seizure free; 44% not benefited.	Idiopathic epilepsy in all.
Bastible C, 1931 (93)	45	19–51	GM, PM	KD	Of those staying on diet 7% seizure free; 69% improved; 21% seizures increased. 16/45 unable to maintain diet.	All females, diagnosed with epileptic insanity, all idiopathic etiology. 6-mo follow up. Best response seen in those with least mental disorder.
Notkin J, 1934 (82)	20	22–47	GM	KD	No improvement in any, 90% had an increase in seizure number.	All institutionalized patients And off AEDs, cryptogenic Etiology. Average time on the diet 11 mo.
Sirven J, 1999 (83)	11	19–4	CP, SGTC, GTC, Atonic Absence	KD	6/11 had >50% seizure decrease. None seizure free.	All symptomatic epilepsy. All seizure types responded. 8-mo follow-up.

GM, grand mal; PM, petit mal; GTC, generalized tonic-clonic; SGTC, secondary GTC; AED, antiepileptic drug; PB, phenobarbital.

related to outcome. Reasons that patients discontinued the ketogenic diet included insufficient seizure control, inability to medically tolerate the diet, concurrent medical illnesses, and inability to tolerate the nature of the dietary regimen. This study demonstrated that the ketogenic diet is effective in different epilepsy centers with different support staff. Children and families comply with the diet if it is effective, and results are similar to those obtained over the past seven decades.

Almost a century has passed since the ketogenic diet was initially used, and many more therapies are now available for children with epilepsy. The ketogenic diet continues to compare favorably with other new treatments that have been introduced to treat epilepsy in children. The renewed interest in the ketogenic diet has once again raised several research questions that, if answered, have the potential to improve our understanding of the neurochemistry of epilepsy and would allow better treatment of all patients with epilepsy. The ketogenic diet, a therapy that started at the beginning of the twentieth century, appears to have a definite role in the treatment of childhood epilepsy well into, and perhaps beyond, the twenty-first century.

4. CONCLUSION

Fasting, the precursor to the ketogenic diet, has been used to treat a spectrum of human maladies for centuries. The ketogenic diet emerged about 100 yr ago as a viable alternative, allowing the biochemical effects of fasting to persist, while providing fuel for the body. The ketogenic diet has a rich history in the United States and continues to be utilized to treat refractory childhood epilepsies. Its use has increased the last 10 yr, and now it is available at all major children's hospitals. Our understanding of the scientific underpinnings of this unique therapy has evolved dramatically, culminating in this medical textbook, the first ever devoted to the ketogenic diet. A better understanding of the scientific basis of this unique dietary therapy will continue to emerge with this renewed scientific interest, resulting in improved epilepsy care for all children. This will be a fitting legacy for the ketogenic diet.

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