Epilepsia, **49**(Suppl. 8):3–5, 2008
doi: 10.1111/j.1528-1167.2008.01821.x

History of the ketogenic diet

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SUMMARY

Fasting and other dietary regimens have been used to treat epilepsy since at least 500 BC. To mimic the metabolism of fasting, the ketogenic diet (KD) was introduced by modern physicians as a treatment for epilepsy in the 1920s. For two decades this therapy was widely used, but with the modern era of antiepileptic drug treatment its use declined dramatically. By the end of the twentieth century this therapy was available in only a small number of children's hospitals. Over the past 15 years, there has been an explosion in the use, and scientific interest in the KD. This review traces the history of one of the most effective treatments for childhood epilepsy.

KEY WORDS: Ketogenic diet, Intractable epilepsy, Children, Ketosis, Starvation, Epilepsy.

In the past, many dietary "cures" for epilepsy were advocated, and such treatments included the excess or limitation of almost every substance (animal, mineral, or vegetable). Additionally, while fasting has been recognized as a treatment for many ailments for over two and a half thousand years, fasting as a treatment for seizures is less recognized. Fasting is the only therapeutic measure against epilepsy recorded in the Hippocratic collection. Five centuries later, 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 (Huisjen, 2000).

FASTING—A PRECURSOR TO THE KETOGENIC DIET

The first modern use of starvation as a treatment for epilepsy was recorded by a pair of Parisian physicians, Gulep and Marie, in 1911 (Guelpa & Marie, 1911). They treated 20 children and adults with epilepsy and reported that seizures were less severe during treatment, but no specific details were given. The United States contemporary accounts of fasting were also recorded early in the 20th century: 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 (Freeman et al., 1994). Macfadden was a physical fitness guru/cultist and publishing genius of the early part of the 20th century. He advised readers how to develop themselves physically, how to maintain their health, and how to cope with illness. Each issue of his magazine, *Physical Culture,* carried articles about sickly men and women who became healthy, strong, and beautiful through proper diet and exercise. By the end of World War I, the magazine's circulation had reached 500,000. Macfadden claimed that fasting for 3 days to 3 weeks could alleviate and cure just about any disease, including epilepsy. He had become nationally recognized, and in 1931 tried to ingratiate himself with a presidential candidate, Franklin D. Roosevelt, as part of a strategy to be appointed as the first Secretary of Health (Wilkinson, 1997). Dr. Conklin began as an assistant to Macfadden and adopted his method of fasting to treat various ailments. It was Dr. Conklin's practice of fasting to treat epilepsy and the results, which drew the attention of another pioneer in epilepsy study, H. Rawle Geyelin, an endocrinologist at New York Presbyterian Hospital. Dr. Geyelin first reported at the American Medical Association Convention in 1921 his experience with fasting as a treatment of epilepsy (Geyelin, 1921). Dr. Geyelin was the first to document the cognitive improvement that could occur with fasting. Attending Dr. Geyelin's presentation were Drs. Stanley Cobb and W.G. Lennox of Harvard. The success of Dr. Conklin's results with fasting quickly spread and by 1941 it had achieved prominence in the textbook of Penfield and Erickson on epilepsy from

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the Montreal Neurologic Institute (Penfield & Erickson, 1941). In the early 1920s, Drs. Cobb and Lennox at Harvard Medical School began studying the effects of starvation at a treatment for epilepsy. They were the first to note that seizure improvement typically occurred after 2–3 days. Lennox documented that the control of seizures occurred through a change of body metabolism and that simple absence of food or dearth of carbohydrate in the body forced the body to burn acid-forming fat.

The Ketogenic Diet

In 1921, two pivotal observations were made. Woodyatt noted that acetone 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 (Woodyatt, 1921). Concurrently, Dr. Wilder at the Mayo Clinic proposed that the benefits of fasting could be obtained if ketonemia was produced by other means (Wilder, 1921). Wilder proposed that a ketogenic diet (KD) be tried in a series of patients with epilepsy. He suggested that the diet should be as effective as fasting and could be maintained for a much longer period of time. Wilder subsequently reported on patients treated with the ketone-producing diet at the Mayo Clinic and coined the term "ketogenic diet." Subsequently, Peterman at the Mayo Clinic reported the calculation of KD similar to that used today: 1 g of protein per kilogram of body weight in children, 10–15 g of carbohydrates per day, and the remainder of the calories in fat (Peterman, 1925). Peterman documented the importance of teaching caregivers management of the diet before discharge, individualization of the diet, and close follow-up. Peterman also noted improvements in behavior and cognitive effects that accompanied the KD. These initial reports were rapidly followed by reports from Talbot et al. from Harvard and McQuarrie and Keith at the Mayo Clinic. The use of the KD was recorded in almost every comprehensive textbook on epilepsy in children that appeared between 1941 and 1980. Most of these texts had full chapters describing the diet, telling how to initiate it, and how to calculate meal plans (Wheless, 2004). Throughout the 1920s and 1930s, the KD was widely used. In his 1972 textbook, Livingston, at Johns Hopkins Hospital, reported on the results of the diet in over 1,000 children with epilepsy that he had followed over the prior decades (Livingston, 1972). He suggested that 52% had complete control of the seizures and an additional 27% had improved control.

When Merritt and Putnam discovered diphenylhydantoin in 1938, the attention of physician and researcher shifted focus from the mechanism of action and efficacy of the KD to new antiepileptic drugs. A new era of medical therapy for epilepsy had begun and the KD fell by the wayside. In an effort to make the classic KD more palatable, Dr. Peter Huttenlocher, at the University of Chicago, in 1971 introduced a medium-chain triglyceride oil diet, allowing less restriction of other foods. As new antiepileptic drugs became available, the KD 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 the diet could no longer be justified. Pediatric neurologists were led to believe that rationally designed antiepileptic drugs were the hope for the future. Fewer children were placed on the KD, resulting in fewer dietitians trained in the use of the diet. A shortage of properly trained dietitians meant that the KD was often implemented without correct calculation, leading to the perception that the diet was ineffective. The use of the KD has always been dependent on public perception.

Modern Era of the Ketogenic Diet

Use of the KD decreased greatly and PubMed listed only two to eight publications per year from 1970 to 2000. However, this changed dramatically when the KD received national media attention when NBC-TV's *Dateline* aired a program on the treatment. Corresponding with this was a dramatic spike in PubMed publications averaging over 40 a year since then. This television program was based on the true story of Charlie, a 2-year-old boy with intractable generalized seizures, who presented out of desperation to Johns Hopkins Hospital for treatment. He was seen by Dr. Freeman and Ms. Millicent Kelly (the same dietitian who had worked with Dr. Livingston) and initiated on the KD. He quickly became seizure-free and The Charlie Foundation was formed by his father. This foundation disseminated informational videos for parents and instructional videos for physicians and dietitians about the KD. It also helped fund the initial publication of *The Epilepsy Diet Treatment: The Introduction to the Ketogenic Diet* (Freeman et al., 1994). The Foundation supported the first multicenter prospective study of the efficacy of the KD (Vining et al., 1998), and in 1997, Charlie's father directed the film "First Do No Harm" starring Merryl Streep, which aired on national TV.

The KD has experienced a reemergence in recent years and modern clinical studies have established the treatment as significantly effective (Freeman et al., 1998). The KD is now is available in over 45 countries (Kossoff & McGrogan, 2005). However, physician perception still greatly affects when this therapy is utilized by pediatric neurologists. Two recent expert opinion surveys, one conducted in the United States and one conducted in Europe, revealed that the KD was the next-to-the-last or last choice for

treatment of almost all childhood epilepsies. In addition, a recent survey of practicing child neurologists also ranked the KD as a therapy they typically used last, with many not using it at all (Mastriani et al., 2008). Much work still needs to be done to improve the perception of the utility of the KD, a treatment that compares favorably with other new treatments that have been introduced to treat childhood epilepsy.

Summary

Almost a century has passed since the KD was initially used, and many more therapies are now available for children with epilepsy. The KD has a rich history in the United States and continues to be utilized to treat refractory childhood epilepsy. It is available at almost all major children's hospitals. Our understanding of the scientific underpinnings of this unique therapy has evolved dramatically, culminating in this first international conference devoted to the KD. 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 KD.

Acknowledgment

I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure: The author declares no conflicts of interest.

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