Epilepsy's Big Fat Answer

By John M. Freeman, M.D.

Editor's Note: Epilepsy and seizures affect nearly 3 million Americans of all ages. The incidence is greater in African-Americans and in socially disadvantaged populations, and about 200,000 new cases of epilepsy are diagnosed each year. Despite these alarming figures, no magic pill exists to eliminate convulsions. While drugs work for some, others find them ineffective. What seems to work just as well, if not better, especially in children, is a relatively unknown, high-fat diet. The author, John M. Freeman, M.D., one of the nation's leading advocates for its use, writes about the evolution of the diet and its struggle for acceptance.

It took a Hollywood producer, a made-for-TV movie with Meryl Streep, two decades of research, and the retraining of a cadre of dietitians and physicians to bring the ketogenic diet back into the mainstream. One of the first and most successful therapies for epilepsy, the diet had fallen into obscurity with the introduction of anticonvulsant medications in the 1930s. Today, however, not only has the diet reemerged as a therapeutic option in epilepsy, its effectiveness for other neurological disorders, including brain tumors, autism, and even Alzheimer's disease, is being explored as well.

The hallmark feature of the diet is the production of ketones (beta-hydroxybutyrate, or BOHB), the residues left when fats are burned in the absence of sufficient glucose. Glucose is an important source of the brain's energy, but, contrary to popular belief, it is not the only potential source. Ketones are, in fact, a more efficient energy source for the brain and, for unknown reasons, make the ketogenic diet—high in fat, low in carbohydrates—more effective than current anticonvulsant medications in curbing difficult-to-control seizures.[1,2]

Our hunter-gatherer ancestors, who underwent long periods of quasi-starvation as they searched for game, burned their body fat, producing ketosis, and used BOHB to fuel their brains. Ancient Greek physicians treated diseases, including epilepsy, by altering their patients' diets. But it wasn't until the early 20th century that modern physicians stumbled upon clues that led them to use this tactic purposely, even if they didn't truly understand it.

During the pre-insulin era of the 1920s, starvation became a treatment of choice for managing children with diabetes, who lacked insulin to transport glucose to the brain. The morbid effects of diabetic ketoacidosis (lethargy, coma, and even death), however, led to the misbelief that ketosis per se was dangerous. In 1922, Hugh Conklin, an osteopath and faith healer from Battle Creek, Michigan, erroneously theorized that epilepsy arose from the intestine and attempted a cure by fasting a number of children

with epilepsy for up to 25 days, providing only limited liquids. This starvation, he found, controlled seizures, and its beneficial effect was reported by Rawle Geyelin at the American Medical Association convention in 1921.[1] Soon after, Russell Wilder of the Mayo Clinic reported that the effects of starvation could be mimicked by a diet high in fat and low in carbohydrates and documented that it was as effective as starvation for the treatment of epilepsy in children. Because this diet caused ketosis, it became known as the ketogenic diet.

Following Conklin's and Wilder's lead, physicians often recommended the ketogenic diet, resulting in seizure control in 30 to 50 percent of children placed on it. The diet was far more effective than phenobarbital and bromides, then the only available anticonvulsant medications. With the discovery of phenytoin (Dilantin) in 1938 and the introduction of other anticonvulsant drugs soon afterwards, the diet was gradually abandoned and largely forgotten. Yet, even today, with many new medications, 30 percent of children with epilepsy continue to have difficult-to-control seizures.

Then, as now, physicians found it easier to prescribe a pill than to teach their patients all that was required for the preparation of food within a rigid diet—and patients found it easier, too. Consequently, few physicians recommended the diet and not many dietitians knew of its benefits or were trained in its appropriate management.

In 1968, Guy McKhann, M.D., director of child neurology at Stanford, was asked to direct the newly created neurology department at the Johns Hopkins Medical Institutions. I was working under him at the time, and he invited me to join him to create and direct its new pediatric neurology section. Samuel Livingston, M.D., also at Johns Hopkins, directed one of the country's few centers for childhood epilepsy. There the diet remained in vogue and was administered under the supervision of Millicent Kelly, his dietitian. When Livingston retired in 1973, I was asked to become director of the seizure clinic as well, since I was familiar with the management of seizures. In 1990, I ceased directing the pediatric neurology division and focused my attention on pediatric epilepsy.

Although officially retired, Kelly continued to help me and my colleagues use the diet to treat six to eight children each year successfully. One of the few dietitians familiar with management of the diet, she designed specific meals—liquid, soft, Kosher, etc.—which helped parents whose children were on the diet. That meant prescribing foods that had twice the fat content of a McDonald's Happy Meal; it also meant counseling patients to drink heavy cream and eat butter without bread. Without Kelly's knowledge and 40-plus years of experience, we would not have been able to prescribe the diet. Together, we were the keepers of the flame, and we prepared for the flood of patients who were to come.

Diet vs. Drugs

An epileptic seizure is defined as a transient symptom of abnormal excessive or synchronous firing of some or many of the brain's cells, or neurons. The outward effect can be as dramatic as convulsions with wild thrashing movements (tonic-clonic seizure) or as mild as a brief loss of awareness (absence seizure). Sometimes seizures consist of repeated full body "slumps," with the person simply losing body control and crashing to the ground. Recurrent seizures are termed epilepsy. Which of these manifestations occurs depends on which neurons "fire" synchronously.

Epilepsy is usually controlled, but not cured, with medication. It has been found that initial, thoughtfully chosen medication can make almost 50 percent of patients seizure-free for extended periods of time. If an initial drug fails, another well-chosen drug may make an additional 14 percent of patients seizure-free. If that drug fails, too, then the likelihood of rendering someone with epilepsy seizure-free is poor. More than 30 percent of patients with epilepsy will not have seizure control even with the best available medications. Despite the introduction of many new anticonvulsant medications, these figures have remained consistent over time.

Working with families whose children had epilepsy, we realized that there were no books written for parents to help them cope. To fill the void, my colleague, Eileen Vining, M.D., my coordinator/counselor, Diana Pillas, and I decided to team up to write one. The

result was *Seizures and Epilepsy in Childhood: A Guide for Parents*,[3] published by the Johns Hopkins Press in 1993. It contained three pages on the ketogenic diet. Sensing a need for a separate book that focused solely on the diet, the dietitian Millicent Kelly and I collaborated with my daughter, Jennifer Freeman, a freelance writer, to write *The Epilepsy Diet Treatment: An Introduction to the Ketogenic Diet*, a shorter book specifically about the ketogenic diet. Sadly, we could not find a publisher.

A New Foundation

It was 1993, and Charlie Abrahams, the two-year-old son of Jim Abrahams, the Hollywood producer of *Airplane* and *Naked Gun*, continued to suffer many uncontrollable drop seizures each day, despite extensive medical intervention. As Abrahams has stated, "After thousands of epileptic seizures, an incredible number of drugs, dozens of blood draws, eight hospitalizations, a mountain of EEGs, MRIs, CAT scans, and PET scans, one fruitless brain surgery, five pediatric neurologists in three cities, two homoeopathists, one faith healer, and countless prayers, Charlie's seizures continued unchecked, his development delayed, and he had a prognosis of continued seizures and progressive retardation."

Researching epilepsy treatments himself, Abrahams found our book, *Seizures and Epilepsy: A Guide for Parents*,[3] with its three pages on the ketogenic diet. After a phone call, he brought Charlie to Johns Hopkins, where the toddler first fasted, according to our protocol. Within several days his seizures disappeared and he began the diet. Gradually taken off his medications, Charlie has remained seizure-free, on no medications, for the past 19 years.

Jim was outraged that in all his conversations with medical experts and other parents, he had never been told of the diet. Determined to make information about the ketogenic diet available to parents and physicians, he was instrumental in bringing the 1994 "Dateline NBC" news magazine program, "An Introduction to the Ketogenic Diet," featuring his friend, the actress Meryl Streep, to the public. The same year he created the Charlie Foundation to Help Cure Pediatric Epilepsy. The foundation funded a seven-year study

and published 2,500 copies of our shorter book, which sold quickly and attracted a more established publisher, demosHealth.

The foundation also funded the production of several DVDs explaining the diet to parents, dietitians, and physicians. Despite offering them free to physicians at national and regional epilepsy meetings, there were few takers—a sign that much work still needed to be done. A big breakthrough in promoting the diet finally came in 1997, when an Abrahams-directed, made-for-TV movie, "First Do No Harm," also with Streep, was followed by a flood of thousands of phone inquiries and about 150 patients seeking help with the diet from Johns Hopkins.

The new patients allowed us to gather important data about the diet's effectiveness and its side effects. The reports from Johns Hopkins were the first of an avalanche of abstracts and articles on the clinical outcomes of children who were treated, including outcomes of the diet's various aspects and modifications. The huge increase in the number of clinical abstracts was presented annually at American Epilepsy Society meetings.

The foundation has since been the moving force behind increasing physicians' knowledge about the diet and in training parents and dietitians in its use. At the Third International Conference on Dietary Therapies for Epilepsy and other Neurological Disorders, organized by the foundation in 2012, close to 500 physicians, dietitians, and parents from 30 countries around the world honored Streep for her role in reintroducing the diet. The conference—promoted in the foundation's newsletter, *KetoNews*—included cooking demonstrations and exhibits, testimonials from parents, and a professional symposium.

Anecdotal and Empirical Evidence

At first, most epileptologists did not believe that a diet could be as effective as drugs, although multiple large studies documented the diet's effectiveness. But these studies were uncontrolled, and since many were based on the large Johns Hopkins patient population, there was a tendency for physicians to discount the results as biased by

enthusiasts. Finally, two blinded crossover studies—one from the Cross group in England[4] in 2008, the other funded by the National Institutes of Health at Johns Hopkins in 2009—documented the diet's effectiveness in children in a controlled fashion. Although there are currently no large studies in adults, anecdotal reports indicate the diet's effectiveness, although it appears adults have more difficulty adhering to its rigidity.[5]

The outcome of children with uncontrolled seizures who are placed on the diet is shown in the figure (see below), which summarizes data from Johns Hopkins studies[6] and is similar to many reports from other centers. It is notable that 33 percent of the children with intractable seizures were seizure-free, or had only rare seizures, after being on the diet for one year, and 27 percent of the children whose seizures had previously been uncontrollable by medications had no seizures or only rare seizures three to six years after initiating the diet, although by that time most of the children were off the diet and all medications. Some with continued seizures remain on the diet because it has decreased the number of medications the children need to take as well as the consequent side effects. No anticonvulsant drugs have been studied for that duration or have shown that rate of beneficial effects.

Outcomes of children on the Ketogenic Diet
1 year and 3-6 years after initiation

		% of original 150	
Number Initiating	Seizure control	1 year	3 – 6 years later
Total N = 150	Seizure free	7%	13%
	> 90%	26%	14%
	50 -90%	22%	16%
	< 50%	5%	12%
	On Diet	83 (55%)	18 (12%)

The diet is rarely used as the initial treatment for epilepsy, but should be strongly considered when two anticonvulsants, properly used, have failed. However, the diet may be the initial treatment of choice in infantile spasms and other "drop" seizures.

Despite considerable recent research, how the diet exerts its beneficial effects remains unknown.[6] It is not solely the ketosis, the accompanying acidosis, the lipidosis, or any of the other chemical changes that have been investigated that are responsible. Glucose restriction appears to be a partial answer. A recent study[9] suggests that episodic fasting, in addition to the diet, is even more effective than the diet alone in controlling seizures. Learning the mechanisms by which the diet controls epilepsy may give us a better understanding of epilepsy itself.

Other Ketogenic-like Diets

Modifications of the ketogenic diet, such as the modified Atkins diet, the medium-chain triglyceride (MCT) diet, and the low-glycemic diet (LGD) have been developed as alternatives to the rigidity of the classic version. These diets, all of which have been found to have degrees of effectiveness, may be more acceptable to adolescents and adults.[5] Although large studies of these diets have yet to be performed, uncontrolled studies suggest that they may be effective. If tried, and the individual's seizure control is less than satisfactory, the more rigid, classic ketogenic diet is recommended.[1]

While the classic ketogenic diet may cause complications[1] such as kidney stones,[9] lipidemia, and gastrointestinal symptoms, problems are rarely serious and easily managed. Vomiting is common in the early stages of fasting and may be relieved with small doses of glucose. Constipation is common and may be relieved with small amounts of medium-chain triglyceride oil (MCT) or a readily available laxative such as MiraLAX. Carnitine is rarely needed, but sugar-free multivitamins and minerals such as calcium are recommended. Calcium oxalate and uric acid kidney stones occur in 15 to 20 percent of patients and can be treated or prevented by the administration of potassium citrate. Plasma lipids are also known to rise slightly, but they return to normal levels after six

months. The rare patient with familial dyslipidemias has been seen, and therefore lipid levels should be checked occasionally.[1]

Generally, children whose seizures are controlled by the diet are tapered off it after two years. But if seizures continue, or recur, the child should remain on the diet longer. Some patients have remained on the diet for more than 25 years without adverse effects.

Other Possible Uses

The resurgence of interest in the ketogenic diet has led to some very preliminary studies of its use in conditions other than epilepsy. Anecdotal reports are leading to controlled studies in various neurological conditions. Neurodegenerative disorders provide a unique opportunity to study cellular protection through diet.[6,9,11]

Animal models and anecdotal human reports suggest that glucose restriction and the ketogenic diet may have beneficial effects on brain tumors.[7,8] Tumors rapidly metabolize glucose but are unable to utilize ketones as an energy source. Brain tissue, on the other hand, is able to use both. Glioblastoma implanted in rodents rapidly regresses on a glucose-restricted ketogenic-like diet. Anecdotal reports and preliminary studies in humans have found tumor regression on ketogenic diets. The dramatic findings in glioblastoma may also be true of other brain tumors and perhaps other systemic tumors.

There are also anecdotal reports of the diet's benefits[6,9,11] in modifying Alzheimer's disease, Parkinsonism, amyotrophic lateral sclerosis, and possibly posttraumatic brain injury, stroke, and severe hyperactivity. No controlled studies of these conditions have yet been reported. However, such studies are needed to prove or disprove the diet's usefulness. The diet, or a modified form of it, may also be useful in the management of diabetes. Preliminary reports of its use in inflammatory disease and the management of pain are also of interest and deserve further study.[6]

Although it has taken 20 years to reintroduce the once-abandoned ketogenic diet, it has become an important new therapy—especially for difficult-to-control seizures in

children. As more dietitians are trained, and more physicians become aware of the diet, it is used increasingly throughout the world.[1] Guides to its use are now available in many languages and in many countries, thanks to the Charlie Foundation and its British cousin, Matthew's Friends. The idea of food as medicine has been a controversial topic in this country for many years. But the statistics don't lie, nor do the hundreds of young people who will tell you how their lives were changed because of it.

References:

1. Ketogenic Diets: Treatments for Epilepsy and Other Disorders Fifth Edition. Kossoff EH, Freeman JM, et al. demosHealth, New York, 2011.

2. Further information about the ketogenic diet may be obtained from the Charlie Foundation to Help Cure Pediatric Epilepsy.

3. Freeman JM, Vining EPG and Pillas DJ: Seizures and Epilepsy in Childhood: A Guide for Parents. Johns Hopkins University Press. Baltimore, Maryland. 3rd edition 2002.

4. Neal EG, Chaffe H, Cross JH, et al. The Ketogenic Diet for the Treatment of Childhood Epilepsy: a Randomized Controlled Trial. Lancet Neurol. 2008 Jun; 7(6):500-6

5. Payne NE, Cross JH, Sander JW. The Ketogenic diet and related diets in adolescents and adults: A Review. Epilepsia,52:1941-1948, 2011

6. Freeman JM, Kossoff EH. Ketosis and the Ketogenic Diet 2010: Advances in treating Epilepsy and Other Disorders. Advances in Pediatrics 2010 57; 315-329

7. Hartman AL, Rubenstein JE, Kossoff EH. Intermittent fasting: A "new" historical strategy for controlling seizures? Epilepsy Research, J Epilepsy Res.2012.10.011

8. Seyfried BT, Kiebish M, Marsh J, Mukherjee P. Targeting energy metabolism in brain cancer through calorie restriction and the ketogenic diet. J Can Res Ther 2009;5:7-15.

9. Baranano, KW and Hartman, AL The Ketogenic Diet: Uses in Epilepsy and Other Neurologic Illness, Treat Options Neurol. 2008;10(6):410.

10. Stafstrom, CE and Rho JM. The Ketogenic Diet as a Treatment Paradigm for Diverse Neurological Disorders Front Pharmacol. 2012; 3: 59.

11. Cunnane,S, Nugent S, Roy, M et al. Brain Fuel metabolism, aging and Alzheimer's Disease Nutrition 27 (2011) 3-2