Epilepsy has been a disease battled by mankind since its inception. As noted by Temkin (1), through the ages seizures have been treated with practically every variety of magic, religion, and medicine, from powdered human skull, to the gall of a boar dried with urine, to the blood or liver of a recently slain gladiator. In the 1920s, researchers at the Johns Hopkins Hospital developed a high fat-low carbohydrate diet- named the ketogenic diet, for the treatment of epileptic seizures in children. The namesake comes from the fact that ketone bodies are derived from fat. With the advances in development of anti-epileptic drugs (AED's) in the ensuing decades, the ketogenic diet was overlooked as a viable treatment, even though AED's fail to control seizures completely in 20 to 30% of patients (2).

With national publicity initiated by the NBC Dateline report on "The Ketogenic Diet" in 1994 (3) on the treatment of AED refractory seizures, this non-toxic therapy has gradually regained popularity amongst physicians and patients. Confirming the results obtained seven decades ago, the most recent study showed that when treated by the ketogenic diet, two-thirds of the patients (age 1 to 20) had their seizure frequency reduced by at least 50% (4). Of patients who responded to the diet, 10% had both the diet and all AED's discontinued with continued seizure control. However, partially due to scarce funding for research on the ketogenic diet, the precise mechanism of the anti-convulsant effect of the diet remains unclear. Moreover, although the ketogenic diet has considerably fewer damaging side effects compared to AED's, it nevertheless may have certain clinical manifestations that must be monitored carefully by physicians and caregivers. This report will first discuss the present understanding of the mechanism of the ketogenic diet, and then briefly identify side effects associated with the diet.

What is the ketogenic diet?

The ketogenic diet is presently prescribed to young patients whose epileptic seizures either cannot be completely controlled by AED's, or to patients who cannot tolerate the AED-associated toxicity. Patients undergo a 24 to 72 hour fasting in the hospital until ketouria is observed, an indicator that the body has switched from utilizing glucose to ketone bodies as its energy source during "starvation." Patients then initiate on the classic 4:1 diet, where there are 4 grams of fat for every gram of carbohydrate or protein (including 1g protein/kg body weight to maintain adequate growth), such that 90% of the patient's caloric intake comes from fat, whose predominant food source includes cream and butter (2, 5). Each meal is weighed and isocaloric to meet growth need without causing weight gain. Because the diet imposes a strict limitation of food source, carbohydrate-free multivitamin and calcium supplements are given to meet the recommended daily allowances of various nutrients (2). Fluid intake is also restricted to 800 to 1000 ml per day to prevent dilution of blood ketone concentration (6). Due to these restrictions, adult patients as well as families of young patients often find the diet unpalatable.

If seizure control improves, patients are maintained on the diet for two years, after which they are gradually taken off the diet, and sometimes their AED treatment is also discontinued (4). Kinsman et al. showed that of the 67% of patients whose seizure

frequency improved (reduction of at least 50%), 64% of them had 1 or more AED's decreased, and 10% had AED discontinued.4 Moreover, 36% of all patients had increased alertness, while 23% had improved behavior. Besides its ineffectiveness in treating temporal lobe and absence seizures, (1) seizure type does not appear to be of predictive value in determining success with the ketogenic diet. (4, 7)

Mechanism of the ketogenic diet

While several factors in the ketogenic diet have been hypothesized as the anti-convulsant agent, only ketone bodies and fatty acids have consistent experimental support as such. Support for ketone bodies come from a variety of animal and human studies. Adult rats feeding on a high fat diet showed increased threshold to electroshock seizures; their brain tissues were later found to have elevated levels of ketone bodies (8). Patients on the ketogenic diet also have elevated levels of ketone bodies in their blood and CSF. (1,9) Moreover, it is believed that epileptic children are more responsive to the diet than adults, (7) because children's ability to extract ketone bodies from the blood into the brain is four to five times better than the adults'(10). Intravenous glucose infusion to children, who had been seizure free on the ketogenic diet, resulted in lowered serum ketones; subsequently, seizures were observed (11). Finally, ketogenic diet treatment of two children suffering from seizures due to a glucose transporter type I defect, resulted in complete seizure control. Presumably, the seizures ceased because the brain could use ketone bodies as oxidizable fuels independent of the glucose transporter, although the role of ketone bodies per se was not explicitly studied(12). Unfortunately, how ketone bodies trigger the downstream cascade of events leading to seizure control is not understood. Hence, it is unclear whether the association of high levels of ketone bodies with its role as an anti-convulsant is actually the result of ketone bodies or its metabolic byproduct (either upstream or downstream).

Although the cascade between ketone bodies and decreased cortical excitability is not known, it is clear that chronic ketosis, rather than the presence of ketosis per se, is accountable for improved seizure control. (1) After all, ketosis is established in the first few days of the ketogenic diet, but its anti-convulsant effect may not be evident for a week or two, suggesting that the brain requires a time period to adjust to utilizing ketone bodies as an energy source. (1)

Besides ketone bodies, fatty acid -- another breakdown product of fat, has also been hypothesized as an anti-convulsant. Rats injected with a mixture of non-esterified a -linolenic acid and linoleic acid had a higher seizure threshold in four different seizure models (13). The elevated seizure threshold was clearly not the result of the fatty acid treatment acting as barbiturates, since the rats were not sedated. It is more likely that the fatty acids reduced seizure frequency by preventing excessively strong stimuli from activating the epileptic focus. The authors postulate that the injection of free, essential fatty acids mediates the anti-convulsant effect by modulating the membrane lipid composition and the membrane fluidity of brain neurons. Any consequent stabilizing effect may counteract uncontrolled electric discharges to the brain. (13)

## Side effects

Unlike anti-epileptic drugs which have side effects on most patients, including nausea, vomiting, drowsiness, lethargy, headache, gingival hypertrophy, tremor (14), there is no common side effect with the classic ketogenic diet other than constipation, which can be alleviated with mineral oil or intermittent pediatric enemas. (2) Nevertheless, there are rare adverse effects of the diet of which physicians must be aware. Due to the prolonged fasting and restriction of fluid prior to starting the diet, there is a risk of hypoglycemia and dehydration occurring in the child, (1) all the more emphasizing the importance of hospitalization during this phase of the treatment. There also appears to be an increased rate of urolithiasis (0.5 to 5% compared to 0.01 to 0.1% in the general US pediatric population)(15) and renal stone formation (4) associated with the diet. Herzberg suggests that the presence of high urinary levels of ketones as a byproduct of the diet lowers urinary pH; coupled with prolonged fluid restriction, these effects may contribute to the formation of uric acid stones. (15) In addition, transient hypercalciuria associated with some patients on the diet may promote calcium stone formation. Since hematuria is a manifestation of any kind of urolithiasis, occasional screening should be done. (15)

Because many of the children treated with the ketogenic diet are also on AED's, it should be noted that valproate, commonly used in the treatment of generalized tonic-clonic seizures, has been shown to reduce fasting ketonemia in children (16). The danger lies in valproate's ability to inhibit ketogenesis (in infant mice and in children) and deplete liver glycogen stores (in mice). When children are then placed on a highly restrictive diet consisting predominantly of ketogenic substance, body tissues may resort to breakdown of proteins for energy production, which may become life-threatening. (16) Impaired neutrophil function has also been documented in children with seizures treated with the ketogenic diet (17), although the cause of this functional decline was unknown, nor were the researchers able to compare the results with neutrophil function of children on the conventional drug therapy. Finally, another obvious concern in the context of a high fat diet is the long term risk of cardiovascular disease. To date, the only long-term study was conducted on adults between 40 and 55 years of age who had been treated during their childhood with the classic 4:1 ketogenic diet. No evidence of adverse effects on cardiovascular function, including arteriosclerosis, hypertension, or cardiac abnormalities was found (18). It must be stressed that while the aforementioned urolithiasis and toxicity associated with valproate use and the ketogenic diet are alarming, these are rare pathologies that may be prevented or detected early on. Moreover, these are no more threatening than the rare side effects of AED's, which include agranulocytosis, Stevens-Johnson syndrome, aplastic anemia, hepatic failure, dermatitis, serum sickness, and pancreatitis. (14)

## Conclusion

Compared to the systemic and neuro-toxicity prevalence caused by anti-epileptic drugs used to treat epileptic seizures in children, the ketogenic diet--free of cognitive side effects, is a much more benign alternative therapy. However, the ketogenic diet is still not considered a standard treatment. Of the various treatment options for epilepsy, the diet

was omitted from American Family Physician's latest monograph on epilepsy. (14) Wheless believes that physicians consider it a treatment only when the children have failed multiple medications and are not surgical candidates, because of their lack of exposure and understanding of the diet during their training. (2)

While the success of ketogenic diet has been well documented, its anti-convulsant mechanism remains to be characterized with more animal studies and well-designed clinical trials. Outcome measurements to these studies should also be standardized, such that reports of "behavior improvement" and "increased alertness" can be evaluated objectively and compared across studies. Not only will such research answer questions such as to which types of seizures does the ketogenic diet represent a cure, and to which types does it remain a temporary alleviation of symptoms, it will also enhance our understanding of epilepsy itself. Combined with physician and dietitian training for the ketogenic diet, the diet may become an additional choice for patients and their families in the early stages of epileptic seizure diagnosis.

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