

Editorial Commentary

The Ketogenic Diet Revisited: Back to the Future

Douglas R. Nordli, Jr. and Darryl C. De Vivo

*Division of Pediatric Neurology and the Comprehensive Epilepsy Center, Columbia Presbyterian Medical Center,
New York, New York, U.S.A.*

There has been a recent extraordinary resurgence of interest in the ketogenic diet. Some commentaries in the professional and lay literature have been instructive and informative, others have been less so, and some have been frankly contentious. Books, an informative videotape, a made-for-television movie starring Meryl Streep, and many websites are just some of the current venues that are providing information regarding the diet (1). An unfortunate byproduct of this popularization has been a fruitless dialectic: “Does the ketogenic diet deserve a prominent role in the management of children with refractory epilepsy?”

The answer to this question has always been yes. In our view, this is a distracting issue and one that should be put aside, because the diet is a time-tested, effective, and safe method for treatment of intractable childhood epilepsy. Only bromides, discovered in 1857, and phenobarbital, discovered in 1910, can match the 76 years of experience with the ketogenic diet. Numerous centers have documented its efficacy, and clinical reports indicate that at least one-third to two-thirds of patients benefit substantially from the diet (2–5). Results of treatment with few antiepileptic drugs (AEDs) can match these statistics.

Like AEDs the ketogenic diet has also demonstrated efficacy in experimental models of seizures (6–8). At the Neurological Institute of New York, clinicians have used the conventional long-chain diet as a mainstay for the treatment of drug-resistant childhood epilepsy for >30 years, with good success (9). In the last several years, our dietitians and nutritionists have used a novel and effective approach. The diet is organized into food groups so that substitutions among different foods can be made easily. This makes the diet simpler to use and provides parents with greater flexibility. The broad picture regarding the mechanics and the effectiveness of the ketogenic diet has been clear since 1921. Therefore, we regard

continued discussion of the applicability of the diet as a poor utilization of time and energy. The article by Hori et al. (10) in this issue of *Epilepsia* provides an excellent opportunity to study other important aspects of the ketogenic diet in an attempt to answer more compelling and fundamental questions.

SCIENTIFIC ISSUES CONCERNING THE KETOGENIC DIET

The ketogenic diet produces a state of chronic ketosis, and considerable information regarding the relations among cerebral metabolism, ketosis, and anticonvulsant effects is available. Well before a modern understanding of the role of ketone bodies was achieved, Wilder (11) devised the ketogenic diet with a simple objective in mind: He sought to mimic the positive effects of starvation while providing patients with sufficient calories and other requirements to maintain their nutritional state. He was aware of studies conducted by Geyelin et al. (12) at the Presbyterian Hospital in the City of New York which showed that fasting improved seizure control in patients with epilepsy. Wilder (11) speculated that the sedative effect of ketosis, which he ascribed to increasing levels of acetoacetic acid and acetone, was the critical factor in producing an antiepileptic effect. These ketone bodies were assumed to act as anesthetic agents, a reflection of the then current belief that a drug must be a sedative—like phenobarbital—to be an effective anticonvulsant. Later, other investigators attributed the ketogenic diet's antiepileptic effect to alterations in electrolytes, acid-base perturbations, increased concentrations of serum lipids, and dehydration (13).

Ketone bodies were first discovered in the 19th century in the blood and urine of patients with diabetes mellitus; these metabolites were believed to be waste products of fatty acid degradation (14). Subsequently, however, investigators found that β -hydroxybutyrate and acetoacetate were synthesized by a separate metabolic pathway (15). Thirty years ago, Cahill et al. (16) reasoned that if glucose were the sole source of fuel for the

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Address correspondence and reprint requests to Dr. D. R. Nordli at The Neurological Institute of New York, 710 W. 168th St., New York, NY 10032, U.S.A.

brain, then the body would be depleted of 30–50% of its protein mass within a few weeks of fasting. A series of careful studies of cerebral arterial-venous oxygen differences in fasting obese adults showed that glucose utilization, after correction for lactate and pyruvate recovery, accounted for only 29% of the brain's oxygen consumption, whereas β -hydroxybutyrate extraction accounted for 52% of oxygen consumption, and acetoacetate accounted for 8% (17). These seminal studies showed unequivocally that under certain conditions the human brain could utilize ketone bodies for fuel.

In 1974, Appleton and De Vivo (18) developed an animal model to study the effects of the ketogenic diet on cerebral metabolism. Adult male albino rats were given either a high-fat diet containing (by weight) 38% corn oil, 38% lard, 11% vitamin-free casein, 6.8% glucose, 4% U.S. P. salt mixture, and 2.2% vitamin diet fortification mixture or a high-carbohydrate diet containing (by weight) 50% glucose, 28.8% vitamin-free casein, 7.5% corn oil, 7.5% lard, 4% U.S. P. salt mixture, and 2.2% vitamin diet fortification mixture. Parallel experiments were conducted to evaluate responses to electroconvulsive shock and biochemical alterations. The electroconvulsive studies showed that the mean voltage necessary to produce a minimal convulsion remained constant for 12 days before the high-fat diet was started and for ~10 days after the feedings were started (69.75 ± 1.88 V). About 10–12 days after the high-fat diet was started, the intensity of the convulsive response to the test voltage decreased, necessitating an increase in voltage to reestablish the same degree of minimal convulsive activity as before. Approximately 20 days after the high-fat diet was started, the convulsive threshold was stabilized at a new level (81.25 ± 2.39 V), $p < 0.01$. When the high-fat diet was replaced by the high-carbohydrate diet, there was a rapid and dramatic change in response to the electrical stimulus. Within 48 h, the electrical stimulus that had previously produced only a minimal seizure now resulted in a maximal convulsion, and the mean voltage required to produce the standard minimal convulsion returned to a value close to that observed before study (70.75 ± 1.37 V). Blood concentrations of β -hydroxybutyrate and acetoacetate were significantly increased in rats fed the high-fat diet; concentrations of chloride, esterified fatty acids, triglycerides, cholesterol, and total lipids were also higher in ketotic animals.

In a subsequent study, De Vivo et al. (19) reported changes in cerebral metabolites that occurred in chronically ketotic rats. There were no alterations in brain water content, electrolytes, or pH. As expected, fat-fed rats had significantly lower blood glucose concentrations and higher blood β -hydroxybutyrate and acetoacetate concentrations than control animals. More important, the brain concentrations of ATP, glycogen, glucose-6-

phosphate, pyruvate, lactate, β -hydroxybutyrate, citrate, α -ketoglutarate, and alanine were higher and the brain concentrations of fructose 1,6-diphosphate, aspartate, ADP, creatine, cyclic nucleotides, acid-insoluble CoA, and total CoA were lower in rats fed a high-fat diet. Cerebral energy reserves were significantly higher in the ketotic group (26.4 ± 0.6) than in controls (23.6 ± 0.2) ($p < 0.005$). Many of these metabolic changes could be explained by the higher energy state of brain cells from fat-fed animals and specifically by the ratio of ATP to ADP. For example, the higher ATP/ADP ratio inhibits phosphofructokinase and pyruvate dehydrogenase (Fig. 1A and B), thus explaining the increases in glucose-6-phosphate and pyruvate.

Tricarboxylic acid (TCA) cycle activity is governed by the availability of oxaloacetate, the rate-limiting substrate, and the kinetics of α -ketoglutarate dehydrogenase, the rate-limiting enzyme. α -Ketoglutarate dehydrogenase (Fig. 1C) is regulated mainly by the concentration of succinyl-CoA through a product inhibition feedback mechanism. Conversion of β -hydroxybutyrate and acetoacetate to acetoacetyl-CoA requires a stoichio-

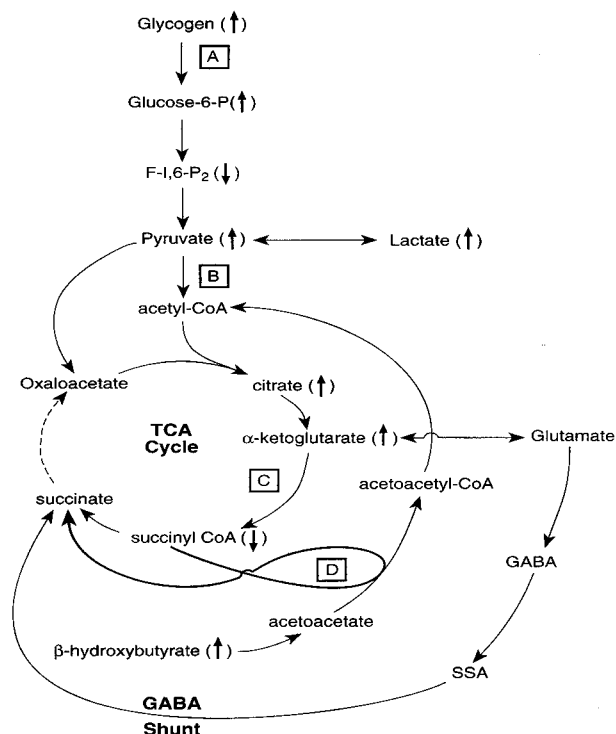


FIG. 1. Summary of the relevant metabolic pathways affected by the ketogenic diet. The arrows (↑) and (↓) indicate significant differences of brain metabolites between ketotic animals and nonketotic animals. A, phosphofructokinase; B, pyruvate dehydrogenase; C, α -ketoglutarate dehydrogenase; D, 3-oxoacid-CoA transferase. The biochemical observations imply that cerebral energetics are improved by chronic ketosis. These findings also suggest that flux rates through the tricarboxylic acid cycle and the γ -aminobutyrate (GABA) shunt may be maximized and that GABA effects may be augmented. Adapted from De Vivo et al. (19). TCA, tricarboxylic acid; SSA, succinic semialdehyde.

metric conversion of succinyl-CoA to succinate. This reaction is catalyzed by the enzyme, 3-oxo-acid CoA transferase (Fig. 1D). The observations of normal oxaloacetate, increased α -ketoglutarate, and decreased succinyl-CoA imply maximal TCA cycle activity, a situation quite contrary to the metabolite profile of anesthetic-sedative agents. Increased α -ketoglutarate levels also raise the possibility of increased flux through the γ -aminobutyric acid (GABA) shunt (Fig. 1). Al-Mudallal et al. (20) recently showed that neither cerebral pH nor total cerebral GABA levels were altered in adult male rats fed a high-fat ketogenic diet as compared with controls. Although whole brain GABA concentrations are unchanged during chronic ketosis, local or regional differences may well occur. In addition, ketosis may produce GABA-mimetic effects because of the structural similarities of GABA, β -hydroxybutyrate, and acetoacetate.

Additional observations provide useful information and allow further speculation. The ketogenic diet is the treatment of choice for the glucose transporter protein syndrome (21) and for pyruvate dehydrogenase deficiency (22,23). Both disorders cause cerebral energy failure and seizures. In the glucose transporter protein syndrome, seizures result from hypoglycorrachia and neuroglycopenia. The seizure disorder responds dramatically to the ketogenic diet because it provides alternate fuel sources. The benefit of the ketogenic diet as treatment for pyruvate dehydrogenase deficiency is less well documented, but the metabolic basis for its use is clear. The diet provides an alternative source for brain acetyl-CoA and facilitates TCA cycle activity (Fig. 1). Seizures, if present, subside with dietary treatment.

These observations suggest that the ketogenic diet favorably influences cerebral energetics, and that increased cerebral energy reserves may be the most important factor in endowing ketotic brain tissue with an increased resistance to seizures. However, the precise way in which improved cerebral energetics raises the seizure threshold is unclear. Further research is needed to define this, and the results of such experimental studies will have important consequences. First, they will provide insight into a novel method of suppressing seizures that might be duplicated pharmacologically. Second, they will identify factors that may predict whether a particular child will respond to the diet. Finally, they should offer clues to enhancing the diet's effectiveness. It is equally important, however, to recognize that animal models offer more than just a means to study the diet's mechanism of action. As discussed by Hori et al. (10), animal models allow investigators to study issues in a controlled fashion that cannot be studied easily in children. These models may help address unanswered clinical questions, including the impact of successful dietary

treatment on learning and the natural history of the epileptogenic process.

CLINICAL ISSUES REGARDING THE KETOGENIC DIET

Is seizure type important?

Despite the ketogenic diet's respectable longevity, several important clinical questions still require answers (Table 1). The obvious first question is: Who should be treated? In 1963, Keith (2) wrote that at the Mayo Clinic the ketogenic diet was reserved for patients with idiopathic epilepsy because patients with "so-called symptomatic epilepsy, as a result of encephalitis, or associated with cerebral palsy and other conditions, probably would not respond to a dietary regimen." A 10-year follow-up of patients treated with the diet at the Mayo Clinic reflects this approach. For example, only 51 of 369 patients were classified as having symptomatic epilepsy. Yet the material provided on 132 patients followed for 5 years, showed that 66% of 12 patients with symptomatic epilepsy had improved seizure control. In the group as a whole, 22.2% achieved complete seizure control, 17.6% improved, and 28.2% had no change or worsening. Lack of cooperation limited the diet's use in 15.8%.

Livingston (3) reviewed his extensive experience with the diet in the 1972 edition of his textbook. Among 1,001 patients who underwent dietary treatment, seizures were controlled in 52%, were reduced in 27%, and were unchanged in 21%. Of particular note, he reported improved seizure control in patients with organic brain damage and noted especially impressive results in children with akinetic and myoclonic seizures. Patients with "major motor seizures" alone responded less well, as did children with idiopathic absence seizures and 3-Hz spike-wave discharges on EEG. Livingston's data suggest that patients with idiopathic epilepsy are less likely to improve than are those with symptomatic epilepsy, a conclusion diametrically opposite to that reached by Keith (2).

Neither Keith (2) nor Livingston (3) mentions partial seizures specifically, but this reflects the seizure classification systems in use at the time. Unfortunately, the lack of data about partial seizures, the most common seizure type, limits our ability to draw conclusions from these early large studies that can be easily applied to

TABLE 1. *Clinical questions about the ketogenic diet*

Which are the most appropriate candidates for the ketogenic diet in terms of seizure type, epilepsy syndrome, and etiology?
How do the efficacy and tolerability of the diet vary as a function of age, including infancy and early adulthood?
How does the diet affect cognition, learning, and behavior?
Does the ketogenic diet influence the natural history of epilepsy?
What are the incidence, severity, and risk factors for adverse effects?

today's patients using the classification scheme of the International League Against Epilepsy (24–26). Furthermore, there are no data comparing the efficacy of the diet in different epilepsy syndromes.

Since valproate was introduced, the need for the ketogenic diet in patients with idiopathic generalized epilepsies has been reduced substantially. The diet has its greatest role in patients with hard-to-control symptomatic forms of epilepsy, especially epileptic encephalopathies. Such patients commonly have atypical absence, myoclonic, and atonic seizures. Animal models may offer the best initial approach for determining the diet's efficacy in partial and generalized seizures, and comparative animal studies might provide justification and guidelines for clinical trials, as Hori et al. (10) suggest.

Interaction with age

Is the patient's age a factor in choosing the ketogenic diet as a treatment option? The diet has traditionally been used in children past infancy. There are both theoretical and practical justifications for this. The brain's ability to utilize ketone bodies is a function of age: It is greatest in the young, because the relative fractional extraction of ketone bodies decreases with age (27). Haymond et al. (28) demonstrated that children produce more ketone bodies than adults after 38 h of fasting, but maintain serum glucose concentrations in the same range as their adult counterparts. Many physicians have avoided using the ketogenic diet in infants because of ill-founded concerns either that it is not well tolerated or does not work in children in this age group. Our own experience (29) using the diet in this age group has been quite favorable, and the ketogenic diet is the treatment of choice for infants with the glucose transporter protein defect or pyruvate dehydrogenase deficiency. It is important, however, to provide infants with enough substrate to meet the growing brain's metabolic demands and to provide adequate nutrition to support the child's growth and development. We administer a regimen of 85–100 kcal/kg/day and often will provide as much as 2 g protein/kg/day. The pattern of ketone body utilization in the brain is regionally specific and varies across different cortical layers (30). Whether this regional variability is itself age-dependent and whether this influences the efficacy of dietary treatment is not known. These issues, too, must be addressed in experimental studies in both animals and humans.

Effects on cognition and behavior

When the ketogenic diet is effective, AEDs can be reduced or discontinued, which should result in less sedation and which might be expected to improve behavior and cognition, as has been reported previously (4,5). As Hori et al. (10) reported, the effects of the diet on behavior have never been subjected to rigorous scrutiny, either in an experimental animal model or prospectively

in humans with use of appropriate neurobehavioral tests. Such information would be very helpful for parents who are considering placing their children on the diet.

Are dehydration and caloric restriction necessary?

We know of no methodologically sound studies that demonstrate the need for dehydration or severe caloric restriction when the ketogenic diet is started. Such an approach is probably a carry-over from the dehydration regimen proposed in 1930 by Fay (31). On the contrary, we try to avoid both dehydration and severe caloric restriction, and indeed take special care to ensure that our patients are adequately hydrated and have adequate nutrients to maintain weight–height percentiles. β -Hydroxybutyrate and acetoacetate require facilitated transport across the blood–brain barrier that is mediated by the monocarboxylic transport system, which also transports lactate and pyruvate. In theory, dehydration could lead to poor tissue perfusion, thereby increasing lactate and pyruvate. These organic acids would compete with β -hydroxybutyrate and acetoacetate, effectively reducing the amount of ketone bodies transported into the brain and limiting supply of this essential fuel source. This speculation should be investigated clinically and in animal models to determine if fluid restriction affects the diet's efficacy or complication rate, especially lethargy and renal stones. We use a standardized 38-h fast to initiate the diet (28,32,33).

Is ketogenic diet antiseizure or antiepileptogenic?

Most available AEDs seem to be effective at suppressing seizures without altering the underlying epileptogenic process. This has best been demonstrated for phenytoin in patients who have had head injuries (34), but experimental data from studies of kindling are generally supportive of this distinction (35). There is no information about whether the ketogenic diet affects the subsequent course of the epileptic disorder, especially the likelihood of an enduring remission of seizures. A related question that could be addressed is whether the ketogenic diet affects developmental neuroplasticity.

Adverse effects

The ketogenic diet, although generally well tolerated, is not without potential side effects. Treated patients may experience a significant reduction in bone mass (36), and renal calculi have been reported (3). Lipemia retinalis developed in two of Livingston's patients. Thinning of the hair and, rarely, alopecia may occur. Long-term cardiovascular complications due to atherosclerosis have not been seen in the few adult patients who have been examined (3), but this is a concern that deserves systematic study. We have had patients who developed mental status changes, including coma (33,37), although this is rare. Recently, the issue of carnitine depletion has been raised (38), but carnitine supplementation may have

TABLE 2. Effects of ketogenic diet on blood metabolites in seven patients (mean $\pm$ SE)^a

Metabolite	Control	End 38-h fast	Day 5	Day 10	Day 14
Glucose (mM)	5.11 $\pm$ 0.20	3.78 $\pm$ 0.28	4.23 $\pm$ 0.30	4.27 $\pm$ 0.33	4.47 $\pm$ 0.27
β OHB (mM)	0.14 $\pm$ 0.06	1.83 $\pm$ 0.79	2.67 $\pm$ 0.54	2.06 $\pm$ 0.30	2.09 $\pm$ 0.31
AcAc (mM)	0.08 $\pm$ 0.04	0.41 $\pm$ 0.12	0.92 $\pm$ 0.11	0.92 $\pm$ 0.12	0.87 $\pm$ 0.12
Lactate (mM)	0.93 $\pm$ 0.05	1.04 $\pm$ 0.19	0.78 $\pm$ 0.10	0.70 $\pm$ 0.09	0.70 $\pm$ 0.07
Pyruvate (μ M)	45 $\pm$ 9	33 $\pm$ 14	36 $\pm$ 8	23 $\pm$ 5	32 $\pm$ 5

β -OHB, β -hydroxybutyrate; AcAc, acetoacetate.

^a Data from De Vivo (41).

competing effects. On the one hand, carnitine may increase glucose transport into cells; carnitine deficiency, on the other hand, may restrict metabolism of fats by β -oxidation (39). We do not routinely supplement the diet with carnitine unless a frank carnitine deficiency is documented in the patients. There is a need for clinical studies to document the frequency of carnitine deficiency in children treated with the ketogenic diet and to determine if any comorbid factors exist, such as occult metabolic disease, that can be identified as predisposing to this complication (40). Would routine early screening of urinary calcium excretion or ultrasonography of the kidneys aid in detecting renal stone formation and permit treatment, rather than discontinuation of the diet? What is the optimal dose of vitamin D, and what is the need for calcium supplements?

From bedside to laboratory

It is essential that disease-oriented laboratory experiments reflect the clinical condition as closely as possible, not the other way around. The article of Hori et al. (10) represents the work of skilled investigators and offers a valuable model suitable for exploring many of the questions raised in this Editorial Comment. At the same time, a note of caution regarding their findings and conclusions is warranted. For example, a notable feature of the ketogenic diet is that it often produces sustained benefit that lasts for months or years. In contrast, Hori et al. (10) showed only a transient effect on afterdischarge thresh-

old and stage 5 seizure threshold. This discrepancy may relate, at least in part, to the level of ketosis achieved in their experimental animals. The β -hydroxybutyrate levels indicate ketosis but correspond to a concentration of only 0.67 mM. Appleton and De Vivo (7) measured β -hydroxybutyrate levels of 1.63 mM in rats receiving high-fat diets, values >10 times those in their control animals and 2.4 times greater than those in rats in the study of Hori et al. (10). The degree of ketosis achieved in children treated successfully with the ketogenic diet are even higher.

We measured blood metabolites in 7 children during the initiation of ketogenic dietary therapy (Table 2) (41). The total ketone body concentrations in blood ranged from 2 to 4 mM. We also measured blood and cerebrospinal fluid metabolites during chronic ketosis in 11 children being treated with the ketogenic diet (Table 3) (41). Again, the total ketone body concentrations in blood were 3–4 mM. The corresponding cerebrospinal fluid concentrations were 0.6–0.7 mM. Owen et al. (17) reported that β -hydroxybutyrate levels in fasting adults averaged 6.67 mM. They also demonstrated that the brain had great ability to extract these ketones, as reflected in an arteriovenous difference of 0.34 mM.

Another factor that may have contributed to the transient nature of the effects observed by Hori et al. (10) is the age of the rats they studied; the investigators themselves recognize the need to study younger animals.

TABLE 3. Effect of ketogenic diet on arterial and CSF metabolites (mean $\pm$ SE)^a

Metabolite	Control subjects (n = 14)		Ketogenic diet patients (n = 11)	
	Arterial	CSF	Arterial	CSF
Glucose (mM)	5.23 $\pm$ 0.15	3.19 $\pm$ 0.10	4.80 $\pm$ 0.22	3.20 $\pm$ 0.13
Lactate (μ M)	752 $\pm$ 57	1317 $\pm$ 56	619 $\pm$ 31 ^b	1419 $\pm$ 52
Pyruvate (μ M)	55 $\pm$ 4	95 $\pm$ 4	30 $\pm$ 3 ^c	96 $\pm$ 12
β -OHB (μ M)	120 $\pm$ 29	15 $\pm$ 2	2538 $\pm$ 255 ^c	432 $\pm$ 48 ^c
AcAc (μ M)	53 $\pm$ 8	16 $\pm$ 4	854 $\pm$ 96 ^c	248 $\pm$ 28 ^c

CSF, cerebrospinal fluid; other abbreviations as in Table 2.

^a Data from De Vivo (41).

^b $p < 0.05$.

^c $p < 0.005$.

TABLE 4. *Projected focus and objectives of clinical trials of ketogenic diet*

Bedside	Laboratory
<i>Vexing clinical observation/issue</i>	<i>Possible experimental model/study</i>
The diet is more effective in children	Effect of diet in kindled rats of different ages
The diet is not as sedating as AEDs	Comparison of AED treatment to dietary therapy in kindled rats; performance on various tests requiring learning (e.g., water platform test)
The diet is more effective in generalized seizures than partial seizures	Comparison of kindled seizures to generalized electroshock seizures
Fluid restriction increases efficacy	Comparison of fluid-restricted ketogenic diet-treated rats with control ketogenic diet-treated rats
Does the diet affect long-term prognosis for epilepsy?	Comparison of seizure remission in rats treated with varying degrees of ketosis as compared with AED-treated rats and controls

AEDs, antiepileptic drugs.

Other laboratory data as well as clinical experience suggest that younger animals would probably have a more pronounced and possibly sustained dietary effect.

In evaluating any therapy, and especially when trying to understand its mechanisms of action, laboratory and clinical investigators must collaborate closely. We have identified several clinical issues that could be addressed in part by appropriate animal experiments. The results of these would in turn serve to focus and define objectives in clinical trials (Table 4). We end as we began by emphasizing that the question is not "Does the ketogenic diet have a role in the treatment of epilepsy?" but rather "How can we maximize using the ketogenic diet and learn from it to benefit all children with epilepsy?" The report by Hori et al. (10) in this issue is an important step in fulfilling this goal.

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