The Ketogenic Diet and Epilepsy

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Introduction

Epilepsy often starts during childhood and has a substantial impact on the quality of life of affected individuals and on their family [1]. A schematic diagram of the course of seizures and epilepsy and of the role of the ketogenic diet are shown in Figure 1. As indicated, 70% of individuals who have a single seizure will have no more, with or without treatment. Approximately 70% of individuals who have epilepsy (defined as two or more seizures) will have their seizures controlled with medication. Treatment of epilepsy with anticonvulsant medications can also have substantial impact on the individual’s quality of life, both for good and for bad. Indeed, the choice between anticonvulsant medications used is often based more on the medication’s side effects than on the differences in their efficacy. Despite the many new anticonvulsant drugs that have become available, approximately 20% of children and adults with epilepsy have ongoing seizures that remain difficult to control. Some individuals with difficult-to-control seizures are candidates for epilepsy surgery to remove a seizure focus. Many, not surgical candidates, must continue trying medications. For some children, the ketogenic diet represents a promising, alternative therapeutic approach to improved seizure control. The ketogenic diet is also a potential, but untested therapy for adults as well.

The history of the development of the ketogenic diet has recently been summarized [2]. The ‘classic’ ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet, developed in the 1920s, when few effective medications were available for seizure control. The diet was initially designed to mimic the effects of starvation which had been shown to have dramatic and long-lasting effects on the control of seizures. The diet was successfully utilized in the 1920s and 30s and many reports showed a better than 50% decrease
in seizure frequency. However, after the discovery of diphenylhydantoin (Dilantin), in the late 1930s and with the subsequent introduction of many new antiepileptic medications, the ‘classic’ ketogenic diet was used less frequently. Recent, prospective studies [3, 4], although uncontrolled and unblinded, have documented the continued efficacy of the diet in children with uncontrolled seizures (Table 1). An independent review of the role of the efficacy of the ketogenic diet by the Blue Cross and Blue Shield Technology Assessment Center [5] concluded that ‘the ketogenic diet appears efficacious in reducing the frequency of seizures in children with refractory epilepsy…’ ‘…this improvement is in the range of, or greater than, that reported with the addition of newer AEDs.’ As we begin to learn how the diet works, and about the effects of the utilization of ketones on brain function and metabolism, we may also learn more about the mechanisms underlying seizures [6] and develop new approaches to seizure control.

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**Fig. 1.** The place of the ketogenic diet in the management of seizures.

**Table 1.** Outcomes of the ketogenic diet at various times after diet initiation by intention to treat – Johns Hopkins 1998

<table>
<thead>
<tr>
<th>Number initiating and diet status</th>
<th>Seizure control</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-free</td>
<td>4 (3%)*</td>
<td>5 (3%)*</td>
<td>11 (7%)*</td>
<td></td>
</tr>
<tr>
<td>Total n = 150</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90%</td>
<td>46 (31%)</td>
<td>43 (29%)</td>
<td>30 (20%)</td>
<td></td>
</tr>
<tr>
<td>50–90%</td>
<td>39 (26%)</td>
<td>29 (19%)</td>
<td>34 (23%)</td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>36 (24%)</td>
<td>29 (19%)</td>
<td>8 (5%)</td>
<td></td>
</tr>
<tr>
<td>Continue diet</td>
<td>125 (83%)</td>
<td>106 (71%)</td>
<td>83 (55%)</td>
<td></td>
</tr>
</tbody>
</table>

*% is of those initiating the diet [data from 4].
The Ketogenic Diet

The ‘classic’ ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet developed in the 1920s to mimic the biochemical changes associated with prolonged starvation. Starvation (drinking only water) for 10–20 days had been reported in the 1920s to produce a dramatic decrease in otherwise uncontrollable seizures [2, 7]. Metabolic studies, designed at that time to learn more about diabetes, found that starvation forced the body to burn stored fat for energy. When there were insufficient carbohydrates available, the fat was incompletely metabolized by the tricarboxylic acid cycle, resulting in residual ketone bodies which could then be utilized as the energy source. The metabolic changes associated with starvation could be mimicked by a diet which was high in fat (90% of the calories) and low in carbohydrate. The diet is designed to provide adequate protein for growth [2]. This ‘ketogenic’ diet forces the individual to first burn the body’s stored fats for energy, and then provides exogenous fat, with minimal carbohydrates, as the primary energy source. With sufficiently low carbohydrates, the ingested fats are incompletely metabolized and ketone bodies result.

Multiple clinical studies during the 1920s and 30s reported that 41–95% of children placed on the diet at multiple different institutions achieved better than 50% control of their seizures. And yet, with many new anticonvulsant medications available, interest in and experience with the ketogenic diet waned, and the diet was not often used. In 1994, interest was reawakened after the airing of a TV documentary regarding a child whose difficult-to-control seizures had been controlled by the diet. With the assistance of the Charlie Foundation created by the child’s father and mother, a multicenter prospective study of the diet was initiated [3], and a prospective study of 150 consecutive children with difficult-to-control seizures was carried out. In this latter study [4], the average age of the children at the time of initiating the diet was 5.3 years and the children averaged 410 seizures, of various types, per month prior to initiating the diet. The percentage of children remaining on the diet at each time period after initiating the diet, and their degree of seizure control is shown in Table 1.

Eighty-three percent of all children initiating the diet remained on the diet for 3 months, 71% for 6 months. And 55% remained on the diet at least 1 year. Eleven (7%) of those 150 children starting the diet became seizure-free and 30 additional children (20%) had a 90% or greater decrease in seizures. (These include children who suffered only one seizure with illness during the month prior to the assessment.) A total of 41 of the 150 original children (27%) had achieved a better than 90% decrease in their seizure frequency at 12 months and an additional 34 children (23%) had a 50–90% decrease in seizures at 1 year. Thus, 75 of the original 150 children (50%) had achieved a better than 50% decrease in their otherwise difficult-to-control seizures. If the diet was insufficiently effective, most families discontinued it after a 3- to 6-month trial.
Only 8 children (5%) with less than a 50% decrease in seizures remained on the diet.

There were no statistically significant differences in seizure control based on age at diet initiation, sex, or seizure type. Even teenage children tolerated the diet – if it was effective – but were somewhat more likely to discontinue the diet if it did not result in a substantial decrease in seizure frequency.

Efficacy and tolerability of the diet were closely interrelated in this study. If the diet was effective in decreasing the seizure frequency by at least 50%, most children remained on the diet. Only a minority (10%) of the children remaining on the diet at 1 year had less than a 50% decrease in seizure frequency. The remainder, whose seizures had not been substantially controlled, had discontinued the diet, most after a 6-month trial. At 1 year, 74% of those on the diet had their medications reduced, and 48% were off medications. Despite its effectiveness in repeated studies, the ketogenic diet has never been subjected to the ‘rigorous’, blinded testing of efficacy required for marketing new drugs. Recent prospective studies [8], discussed below, enabled us to design a double-blind placebo-controlled crossover study (Fig. 2) evaluating the efficacy of the ketogenic diet in the control of the frequent atonic/myoclonic (drop) seizures associated with the Lennox-Gastaut syndrome (LGS). This study is currently in progress.

The diet must be carefully and individually calculated, rigidly controlled, and only used under medical and nutritional supervision [9–11].

**Initiation and Calculation of the Ketogenic Diet**

Children are admitted to the hospital, fasted for 48 h, and usually started on the ‘classical’ 4:1 diet (ratio of grams of fat to grams of protein plus carbohydrate) according to the Johns Hopkins protocol (Table 2).

Each of the 4 days while the child is hospitalized, the parents (and older children) are involved in classes to learn the rationale behind the diet, the calculation of meals, the weighing of foods, the reading of labels, and the management of the diet during the usual childhood infections.

Calculation of the diet, with examples, is discussed in more detail in *The Epilepsy Diet Treatment: An Introduction to the Ketogenic Diet* [10]. Calculation of the diet is generally based on 75% of the recommended daily allowance (RDA) of calories for the child’s *ideal* weight and height, and must be modified for the child’s activity level. Children who are overweight for their height must be calculated to lose weight if the diet is to be effective. Those underweight may be allowed to gain to their ideal weight. Calculating the ketogenic diet is three parts science and one part art. The art is a combination of common sense, empathy, and intuition. Each child’s individual needs and food preferences must be taken into account. The calculated number of calories/kilogram varies with the child’s age: under age 1, 75–80 kcal/kg; ages
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Table 2. The Johns Hopkins Protocol for initiating the ketogenic diet

For 1–2 days before fasting, the family is instructed to decrease their child’s intake of carbohydrates and starches. Fasting is begun after dinner, the evening before admission. Whenever possible, carbohydrate-free anticonvulsant medications should be used.

Day 1: The child is admitted to the hospital. Fluids (caffeine and carbohydrate-free) are limited to 60–75 ml/kg of body weight with an upper limit of 1,200 ml/day. Blood glucose is measured by Dextrostix every 6 h unless the level falls below 40 mg/dl in which case it is measured every 2 h. Symptoms simulating hypoglycemia warrant an immediate blood glucose test. Symptoms, or glucose levels below 25 mg/dl, warrant giving 30 ml of orange juice and measuring the blood glucose level again. Symptomatic hypoglycemia during this fasting is uncommon, even in small children.

Day 2: Lack of energy and lethargy are common during the second 24 h of fasting. Hunger is uncommon. On the evening of the second day, after 48 h of fasting, 1/3 of the calculated ketogenic diet is given as an ‘eggnog’. The diet is generally calculated on the basis of a given number of calories/kg to be provided in a given day, divided into three equal meals. Usually a 4:1 ratio is used. A 4:1 ratio eggnog would contain 60 g of 36% cream, 25 g, of egg, vanilla and saccharine for flavor. This would yield 245 calories, approximately 4 g of protein, 2 g of carbohydrate and 24 g of fats (24:6 or 4:1 ratio). Therefore, if 120 cm³ of a 4:1 ratio eggnog would usually serve as a meal for a given child, 1/3 would be 60 ml of the eggnog and 2/3 would be 120 ml of the eggnog. Although most children will have reached 4⁺ urinary ketosis (>160 mmol/dl on Ketostix) by this time, we begin feeding even if this degree of ketosis is not reached. Excess ketosis may be manifested by nausea or vomiting and may be relieved with small amounts of orange juice followed by continuation of the protocol.

Day 3: One third of the calculated diet is given as eggnog for breakfast and lunch. Two-thirds is given beginning with dinner. As the body is shifting to the utilization of ketones as the primary energy source, general lack of energy and lethargy persist; they will be regained over the ensuing 2 weeks.

Day 4: The child continues 2/3 of the calculated diet as eggnog and dinner is the first full meal. Occasionally, the child becomes too ketotic or acidic as evidenced by failure to drink, Kussmaul breathing, pallor or limpness. In such an event the child is re-hydrated with carbohydrate-free fluids and the diet is continued.

Day 5: The child receives a full ketogenic breakfast and is discharged.

Every child should receive a sugar-free multivitamin supplement and additional calcium.

1–3, 70–75 kcal/kg; ages 4–6, 65–68 kcal/kg; ages 7–10, 55–60 kcal/kg; age 11 and over, 30–40 kcal/kg.

Our most common mistake is beginning with too many calories and thereby not producing sufficient ketosis. This is particularly true of severely handicapped children who may be quite inactive, and therefore require fewer calories per kilogram of body weight. It is better to underestimate the caloric requirements of the child and later add more calories than to initially overestimate, and thereby have insufficient ketosis and insufficient seizure control. To obtain the child’s ideal caloric allotment per day, multiply the child’s ideal weight by the child’s caloric requirement (above).
A 4:1 ratio diet has 4 g of fat for each 1 g of protein + carbohydrate and a 3:1 diet has 3 g of fat for each 1 g of protein + carbohydrate. Fat contains 9 calories/g, while protein and carbohydrate each have 4 calories/g. Therefore, a 4:1 diet has 36 calories as fat \( (9 \text{ calories/g} \times 4 \text{ g} = 36 \text{ calories}) \) and 4 calories from protein and carbohydrate combined \( (4 \text{ calories/g} \times 1) = 4 \). Therefore a dietary unit on a 4:1 ratio contains \( 36 + 4 = 40 \) calories. Dividing the caloric requirements by the number of calories in a dietary unit gives the number of dietary units the child receives each day.

The amount of fat in the diet is derived by multiplying the number of dietary units by the number of units of fat in the prescribed ketogenic diet ratio to determine the number of grams of fat required daily. The protein allotment is 1 g/kg to permit minimal protein for growth. Younger, rapidly growing children may require 1.2–1.5 g/kg. Subtracting the protein requirement from the total protein + carbohydrate allotment results in the grams of carbohydrate permitted per day. These total allotments can then be divided into 3 meals per day or for smaller children into 3 meals and one or two snacks. Liquids have traditionally been restricted to 60–70 cm\(^3\)/kg as caffeine-free, carbohydrate-free liquid, but it is unclear that this is necessary, and may not be advisable. In hot or dry climates, more liquids are required to prevent kidney stones.

Once the diet order is calculated, meal plans are calculated by hand using a system of exchange lists and average food values [10] or a computer program (contact The Pediatric Epilepsy Center: Tel. +1 410 955 9100/Fax +1 410 614 0373).

The ketogenic diet is deficient in fat soluble vitamins and in calcium. All children on the diet must be supplemented with sugar-free multivitamins, with calcium, and with trace minerals.

After discharge the diet is individually adjusted by phone, changing the calories meal plans, and on occasion the ratio; to provide maximum seizure control; to maintain the child in 3–4 ketosis, and to avoid both significant weight gain and weight loss. Parents are instructed to measure urinary ketones daily in the morning. We do not routinely monitor blood glucose or electrolytes after discharge, nor do we follow serum lipids, except for research purposes. We do not alter or abandon the diet even if the serum lipids are elevated.

Does the Ketogenic Diet Work?

Multiple retrospective and recent prospective studies, as discussed above, indicate that the ketogenic diet is very effective in children with difficult-to-control seizures. However, the diet has never been tested clinically in a blinded, crossover fashion. In the course of our prospective, unblinded studies
we found that children with the atonic ‘drop’ seizures associated with the Lennox-Gastaut syndrome often had a dramatic decrease in frequency within days of the onset of the fasting (Fig. 2A). We also found that the ketosis of the fasting and the diet could be rapidly negated with small amounts of glucose. We further found that we could quantify the electroclinical seizures with a 24-hour ambulatory EEG. Therefore, we could design a protocol (Fig. 2B) which would allow a child to be assessed with a 24-hour EEG, before being started on the diet and again at the end of each arm of a study in which one arm the fluid intake would have added glucose, thereby negating the ketosis while on the other arm the glucose would be omitted. This blinded protocol (Fig. 2B) is currently in progress.
Mechanisms of Action of the Ketogenic Diet

A brief summary of fatty acid catabolism is shown in Figure 3. The biology of starvation, which the ketogenic diet was designed to mimic, has been well reviewed by Cahill [cited in 2]. To paraphrase, he states, . . . over 2–3 days of starvation, muscle and adipose tissue become progressively more efficient at decreasing their glucose utilization. The muscle stops using carbohydrate, and the liver uses available oxaloacetate (OAA) for gluconeogenesis, thus less OAA is available for the tricarboxylic acid cycle (TCA). Free fatty acids which are split into two carbon fragments are exported to the liver as the 2-carbon fragments β-hydroxybutyrate (β-OHB) or acetoacetate – the ketone bodies. However, since with the decreased OAA, they cannot be further broken down by the TCA cycle, they circulate in the blood. The brain then begins to preferentially utilize those ketoacids as fuel diminishing its glucose utilization accordingly. Fats are selectively utilized by muscle preventing the breakdown of protein and thus the terminal nitrogen catabolic effects of total starvation. The ingestion of only small amounts of energy as protein is able to replace the nitrogen depletion that would otherwise accompany total starvation. The resultant decrease in serum bicarbonate due to the circulating ketoacids produces a mild compensated metabolic acidosis. Ketosis also produces a decrease in appetite and a decrease in thirst.

Anticonvulsant Mechanisms of the Ketogenic Diet

The mechanisms by which the ketogenic diet exerts its anticonvulsant effects are still unknown. Schwartzkroin [12] and Stafstrom [13] have recently been reviewing a proposed mechanism. It seems clear that neither the mild compensated acidosis associated with the diet, nor the initial dehydration appear to play a role in the diet’s anticonvulsant action (reviewed by Swink et al. [2]). The ketosis resulting from increased levels of β-OHB is thought to be critical, but that remains unproven. Traditionally the diet has been adjusted to maintain 3–4+ urinary ketosis. At least that urine concentration has been considered to be necessary, but not necessarily sufficient to achieve optimal seizure control. Recent studies have documented that urine ketones reach 4+ (160 mM) when blood β-OHB levels exceed 2 mM (range 2–12 mM) [14]. In that study, children with blood β-OHB levels >4 mM were significantly more likely to have a >50% or greater decrease in seizure frequency. Thus, 4+ urinary ketones may occur when blood levels are well below 4 mM. The precise correlation of blood level (if any) with seizure control remains to be determined. When home testing of blood ketones becomes available, which promises to be in the near future, the ketones of children on the diet may be monitored, just as blood glucose in diabetics is monitored. Then the correlation
of blood β-OHB and seizure control can be evaluated. Perhaps, more careful titration of blood β-OHB could improve seizure control.

How, or indeed if, β-OHB is the active anticonvulsant factor in the brain is a question also under active laboratory investigation. Proposed mechanisms for the antiepileptic efficacy of the ketogenic diet summarized from Schwartzkroin [12] include:

(1) changes in the energy metabolism within the brain resulting in higher ATP/ADP ratios, or lowering of the ATP level; such changes in the ATP/ADP ratios could result in changes in the K-ATP channels and hyperpolarization of the membrane;

(2) changes in the resting membrane potential with decreases in neuronal excitability, and/or changes in the properties of the membranes themselves;

(3) changes in transmitter function or in synaptic transmission, and/or

(4) changes in neuromodulatory systems such as the effects of insulin directly or on transmitter transport or on steroid synthesis or modulation.

The rapidity of response of some seizure types to fasting, and the slower response of others seizure types; the rapid recurrence of some seizures with glucose, and the permanent beneficial response of the diet in others, even with cortical abnormalities, suggests that the diet may work through multiple different mechanisms. The resurgence of interest in laboratory models of this alternative approach to anticonvulsant therapy shows promise of both understanding how the diet works, but also may lead to new understanding of the epilepsies and to the creation of novel antiepileptic treatments.

Complications and Side Effects of the Ketogenic Diet

The Complications of the Ketogenic Diet Include [11]:

Hypoglycemia although much feared is rarely seen during the initial 48 h of fasting, and then almost only in infants. Blood glucose is monitored on our protocol every 6 h during fasting and repeated every 2 h when <40 mg/dl. Monitoring is continued until the full diet is initiated. Hypoglycemia, if it occurs, is easily treated with small amounts of orange juice (30 cc). This is given if the glucose level is <25 mg/dl or if the child is symptomatic. Hypoglycemia is virtually never seen once the diet is commenced.

Acidosis is always present and rarely symptomatic. Once the diet is instituted it is not uncommon for children to thrive and to have a CO₂ of 12–16 mM. During the diet initiation, and occasionally during illness, children may become too acidic and even develop Kussmaul breathing. The administration of fluids, either orally or intravenously, or small amounts
of bicarbonate will usually correct the problem. At times small amounts of glucose may be needed. After the illness the diet is then resumed.

**Kidney stones**: Children on the ketogenic diet may have oxaluria and/or hypercalciuria, and may have increased urinary excretion of uric acid. Kidney stones (usually either urate or calcium oxalate have been reported in 5–8% of children on the diet [15]. Increasing the child’s fluid allotment and the addition of citrates to alkalinate the urine may decrease the incidence of stone formation and even permit the resolution of already formed stones.

**Growth**: Studies of growth during the first year of treatment with the diet Vining and Freeman [unpubl. data] show that linear growth of children on the diet continues within normal parameters. Small, rapidly growing children (<2 years of age) need close observation to assess that their growth is normal. They also require higher protein intake (1.2–1.4 g/kg) and frequent caloric adjustment as they grow. In all children weight gain is limited by the caloric limitations imposed and weight should remain near the child’s ideal body weight and increase only proportional to linear growth. There is no evidence that the diet, when supplemented with water-soluble vitamins, calcium and trace minerals provides inadequate nutrition. Despite the role of carnitine in fatty acid transport, there is no evidence that carnitine supplementation is needed for most children on the diet. On occasion, when children on the diet appear weak or are failing to thrive, a 1-month trial of carnitine supplementation (100 mg/kg) is utilized as a test of carnitine deficiency. None of our children have had dramatic improvements with this regimen.

**Lipid profiles**: It is widely believed that a diet high in fat will adversely affect plasma lipids and result in atherosclerosis. In an as yet unpublished study of 62 children on the diet for at least 1 year we found that the diet induced a ‘dyslipidemia’ (Fig. 3) with an increase in cholesterol and LDL from the 75th to the 99th percentile by the time children had been on the diet for 3 months. At that time the triglycerides were also increased but later normalized. The major carrier of cholesterol, apoB became significantly decreased. There were no substantial differences between age groups when the small numbers of children (<1 year, n = 8, 1–3 years, n = 24, 4–9 years, n = 30) were analyzed.

The longer term effects of the increase in cholesterol and LDL remain to be determined. The few children with dramatic increases in triglycerides have had their diet ratios reduced and continued on the diet with a decrease in the triglyceride levels.

**In summary**: The ketogenic diet is undergoing renewed clinical use and its success has stimulated renewed research interest. Even today it appears to be more effective than most new anticonvulsants. The diet is more effective, in a broader range of seizure types, and across a broader range of ages, than any anticonvulsant. Its mechanism(s) of action remains unknown but are under active investigation. As we understand more about this difficult-to-use alternative therapy for difficult-to-control seizures in childhood, we will,
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**Fig. 3.** Fatty acid catabolism and ketone body formation in the liver.

**Fig. 4.** Changes in the mean lipid levels (n = 62).
perhaps, develop new understanding of the mechanisms underlying epilepsy, and thereby develop less burdensome forms of anticonvulsant therapy.

References


Discussion

Dr. Fernstrom: The impression I get, then, is that these children could be on this diet for a year to stop the seizures and the seizures would remain in control. Would that be a typical of anticonvulsant drug treatment?

Dr. Freeman: No. These are children who have failed with anticonvulsants. It is dumbfounding that they respond at all. When they respond, we tell them that we will keep them on this treatment for 2 years but they are welcome to drop off at any point. In those who are 100% seizure-free, or more than 90%, when they stop the diet, seizures rarely recur. If they do recur they can always go back on the diet. Many of the children who have a 50–90% reduction will also drop off the diet in 2 years. These don’t seem to need a lot of anticonvulsant treatment, but I’m following them up right
now. But there are many parents of profoundly retarded children who say that they
don't want anticonvulsants any more as their children are more lively without, so they
prefer the diet.

Dr. Fernstrom: In the patients who are controlled on anticonvulsants, what is the
typical course of medication? Are they on it for ever or do you go for a few years and
then stop?

Dr. Freeman: I should say that most of those stay on medication. When you’ve had
as many seizures as these children have had, your chances of coming under control or
coming off medication are very low.

Dr. Pasquetti: Why is the protein intake kept at 1 g/kg. Can this be increased?

Dr. Freeman: Perhaps it’s witchcraft! It was 1 g/kg in the 1920s when the diet was
devised, and that’s what we still use. In the younger growing child we use 1.5 g/kg, but
you can’t give a lot more protein and still maintain that 4:1 ratio. I’m not sure why you
would want to give more though. They don’t seem to need it.

Dr. Pasquetti: Are there any changes in energy expenditure in the children on the
ketogenic diet? I suppose it is possible to increase energy expenditure.

Dr. Freeman: I don’t know anybody who’s studied that.

Dr. Holm: What about the free fatty acid levels? When fatty acid levels increase,
we should be concerned about possible complications including cardiac arrhythmias.

Dr. Freeman: We only measured the lipids that I showed you, not the free fatty
acids.

Dr. Holm: Ammonia would also be of interest because of the interference of fatty
acids with the urea cycle. You alluded to the cancer patients. May I briefly say that we
did studies on the substrate exchange across both human tumors in vivo and muscle.
We found that human colonic carcinomas take up virtually nothing but glucose and
 branched-chain amino acids. There’s no appreciable exchange of either fatty acids or
ketone bodies, and therefore such a diet would be very suitable for tumor patients,
especially when you consider that there is a profound disturbance of glucose utilization
in muscle at the start of tumor disease, but normal utilization of fatty acids and
especially of ketones. The uptake of ketones in muscle is proportionate to the supply.
This was published in Cancer Research [1]. We thought that cancer patients should
be supplied with a diet high in fat and low in carbohydrates. Up to now we have only
done one controlled study, which has not been published, but with such a diet there
was a gain in body cell mass.

Dr. Freeman: We have been looking for appropriate patients to do this in. There
are two children with treatment-unresponsive glioblastomas who were treated at the
Cleveland clinic with a ketogenic diet, and it is said anecdotally that their tumors
melted away. They had been expected to die within months but they were still alive
years later. I’m not aware of anybody who has repeated those experiments.

Dr. Abdul Rabbo: Is there any study of the bone turnover in those children? They
are chronically acidotic and have hypercalcuria. Is there any abnormality of bone
metabolism?

Dr. Freeman: We have not done bone density studies but other people have and
there is some osteoporosis in these children. We have not seen any fractures or
 clear-cut acute effects over the years that these children have been on the diet. Indeed,
we have a small number of children who have been on it as long as 15 years. So, yes, it
probably does affect bone metabolism but the significance is unclear.

Dr. Bunout: Dr. Freeman, I was concerned about your patient who died of an
arrhythmia. The reason why I’m concerned is because we use ketogenic diets on obese
patients, because they provide a marker of compliance. We have always feared the
possibility of cardiovascular complications. Do you think there was any causal relation
between your diet and what happened to that boy?
Dr. Freeman: That is a very important point. That is the only one of our children who has had a cardiac problem, and his problem predated the start of the diet. There are anecdotal reports of children treated with the ketogenic diet who have had cardiac arrhythmias. How this is related to the diet, I don't know. We are monitoring these children regularly now. It is certainly a concern.

Dr. Adnams: I'm interested in your definition of uncontrolled seizures. Did you go solely on clinically observable seizures or did you include children with subclinical seizures? In children with profound mental handicap we know that such seizures can contribute considerably to their decreased cognitive function.

Dr. Freeman: Our criterion for admission was that there had to be at least two clinical seizures a week. All our patients far exceeded that number. We did not count subclinical seizures. When we looked at the EEGs – and we haven't analyzed all the data yet – some of them normalized, but many of the children still have very abnormal EEGs even when they've have no seizures on the diet. When they come off the diet their EEGs continue to be abnormal, although they don't have seizures. How the diet controls these seizures long term, I don't have any idea, but when you go back to the original observations that 20 days of fasting might control seizures for a year, there must be something going on.

Dr. Holm: Is it really possible to administer so much fat without using artificial preparations?

Dr. Freeman: We use no artificial preparations. The diet contains 36% whipping cream, butter, mayonnaise, supplemented with various oils, olive oil, flaxseed oil, and so on. When we need a liquid formula for gastrostomy-fed children, we use the Ross carbohydrate-free formula to which we add microlipid and a little bit of polycose, so that is a made-up artificial formula and it's expensive. But most of the children who aren't tube-fed shop at the grocery store.

Dr. Uauy: I'm fascinated as we all are, but I think you need to consider some of the side effects and maybe you could optimize the fat composition with respect to the dyslipidemia. It looks as though your patients are responding like anyone else – if you give them a lot of saturated fatty acids, their LDL is going to go up and they're going to have higher triglycerides. Have you tried increasing the polyunsaturated fat intake? This might still be as ketogenic, because ketosis depends mainly on chain length. In fact if you give more MCTs, potentially they'll be more ketogenic. All the fatty acids are ketogenic as long as you keep the carbohydrate intake down, and you could improve the dyslipidemia in this way, as well as potentially cut down on the cholesterol load.

Dr. Freeman: That is one of the things that we hope to do. I appreciate your suggestion.

Dr. Uauy: My other question is that some of your patients have mental retardation, and seizures themselves can cause retardation to deteriorate with time. Have you been able to show a benefit in mental development and IQ before and after? That would also be a valuable asset, considering that one is always concerned that anticonvulsant drugs may be affecting mental development.

Dr. Freeman: We do not have as complete a set of data as I would like, but yes their intelligence does improve and their function improves. I think it is impossible for us to disentangle how much they improve by reducing their medication and how much by reducing their seizures or improving their EEG, but these children are by and large brighter and more alert. We have tackled this question with a sort of 'mini quality-of-life' scale, which I do on each of my children. It's very hard to do a full quality-of-life scale because I'm dealing with children from the age of 3 months on up to 20 years, children who have profound retardation and ones who are normal, children who have major motor deficits and ones with normal motor
function. So I compare each child to himself. My mini quality-of-life scale consists of four domains: mental function, motor function, impairment of quality of life by seizures, and impairment of quality of life by medicines. The score ranges from 0 to 4 in each category, so the maximum is 12. I am following the children after 6 months and 1 year.

_Dr. Uauy_: Does the diet work in children with focal seizures, and can you speculate on how it works?

_Dr. Freeman_: Yes, it sometimes works in children who clearly have focal seizures, and who have focal lesions, but those children are less likely to be controlled by diet than children with more generalized kinds of seizure disorders. How the diet works is a very interesting question. Whether it’s the level of β-hydroxybutyric acid _per se_, or an alteration in the energy metabolism in the brain, or a change in the ratio of ATP to ADP, which will have its own effects on the sodium channels in the brain, or whether the lipids change membrane properties is unclear. The rapidity with which many of these children respond to the ketogenic diet suggests that it’s more likely to be an effect on energy metabolism than an alteration in membrane properties.

_Dr. Rosenberg_: It seems to me that this is a fascinating therapeutic effect which cries out for some animal model experimentation. Clearly it would be possible to produce ketogenic diets in animals. There are also many ways in which one can induce seizures in animals – electroconvulsive, hypoglycemic, and so forth – so it would seem possible to look at whether all types of seizure activity are equally responsive to this kind of diet, and also then to look specifically at the changes occurring in cells and membranes, and to substitute factors in the diets that may or may not be critical. Is that a line of research that is going on?

_Dr. Freeman_: In 1997 there were two papers on the ketogenic diet at the American Epilepsy Society. In 1998 there were 10, and in 1999 there were 28. There are a lot of people working with rat models and beginning to ask these questions. I think that over the next few years we will begin to see good animal models and this is clearly the way forward.

_Dr. Fernstrom_: I was wondering about animal models, and it’s not obvious that any of them would be appropriate. You are treating a very unusual population, and you probably do not know the etiology of the seizures in many cases. How then could one be sure of the relevance of any animal model to what you see clinically?

_Dr. Freeman_: My population, as you say, is very diverse. They all have brain damage of one sort or another, but there are some children who are normal who just have lots of drop seizures. So I agree, I don’t know what is the exact appropriate model. But I would welcome information that the ketogenic diet raises the threshold for seizures in an animal model of any kind by modifying X or Y. That is the level of information we need at the moment.

**Reference**