The ketogenic diet is a high-fat, low-carbohydrate, adequate-protein diet first developed 80 decades ago for the management of difficult-to-control seizures in children. Recent studies have documented the short-term and long-term benefits of this diet in improving seizure control. An evaluation by the Blue Cross/Blue Shield Technology Center reported that the diet's effectiveness in providing seizure control for children with difficult-to-control seizures has remained as good, or better than any of the newer medications. Although the mechanisms by which the diet decreases seizures remain unknown, the level of ketosis produced by the incomplete oxidation of fats when carbohydrates are in short supply appears to play a critical role in the effectiveness of this diet.

The classic ketogenic diet consists of a 4:1 ratio of fat to carbohydrate and protein combined. Because there are 9 calories/g of fat compared with 4 calories/g of either carbohydrate or protein, the fat content of such a ketogenic diet provides 90% of the child's calorie intake. Carbohydrates are severely restricted and are usually less than 10 g/d. Younger rapidly growing children and adolescents are often started in treatment by receiving a less stringent 3:1 ratio of fat to carbohydrate plus protein to allow sufficient protein (1.5 g/kg per day) for growth. Growth while receiving the ketogenic diet remains within the normal range.

Context Little prospective long-term information is available on the effect of a ketogenic diet on plasma lipoproteins in children with difficult-to-control seizures.

Objective To determine the effect in children with intractable seizures of a high-fat ketogenic diet on plasma levels of the major apolipoprotein B (apoB)-containing lipoproteins, low-density lipoprotein (LDL) and very LDL (VLDL); and the major apolipoprotein A-I (apoA-I)-containing lipoprotein, high-density lipoprotein (HDL).

Design, Setting, and Patients A 6-month prospective cohort study of 141 children (mean [SD] age, 5.2 [3.8] years for 70 boys and 6.1 [4.4] years for 71 girls) with difficult-to-treat seizures who were hospitalized for initiation of a high-fat ketogenic diet and followed up as outpatients. This cohort constituted a subgroup of the 371 patients accepted into the ketogenic diet program between 1994 and 2001. A subset of the cohort was also studied after 12 (n=59) and 24 (n=27) months.

Intervention A ketogenic diet consisting of a high ratio of fat to carbohydrate and protein combined (4:1 [n=102], 3.5:1 [n=7], or 3:1 [n=32]). After diet initiation, the calories and ratio were adjusted to maintain ideal body weight for height and maximal urinary ketosis for seizure control.

Main Outcome Measures Differences at baseline and 6-month follow-up for levels of total, VLDL, LDL, HDL, and non-HDL cholesterol; triglycerides; total apoB; and apoA-I.

Results At 6 months, the high-fat ketogenic diet significantly increased the mean plasma levels of total (58 mg/dL [1.50 mmol/L]), LDL (50 mg/dL [1.30 mmol/L]), VLDL (8 mg/dL [0.21 mmol/L]), and non-HDL cholesterol (63 mg/dL [1.63 mmol/L]) (P<.001 vs baseline for each); triglycerides (58 mg/dL [0.66 mmol/L]) (P<.001); and total apoB (49 mg/dL) (P<.001). Mean HDL cholesterol decreased significantly (P<.001), although apoA-I increased (4 mg/dL) (P=.23). Significant but less marked changes persisted in children observed after 12 and 24 months.

Conclusions A high-fat ketogenic diet produced significant increases in the atherogenic apoB-containing lipoproteins and a decrease in the antiatherogenic HDL cholesterol. Further studies are necessary to determine if such a diet adversely affects endothelial vascular function and promotes inflammation and formation of atherosclerotic lesions.
Calories are calculated at about 80% of estimated dietary requirements. After diet initiation, the calories and ratio are adjusted to maintain the child’s ideal body weight for height and maximal urinary ketosis for seizure control.9

Some10,11 but not all12,13 previous studies indicated that a ketogenic diet produced significant increases in the plasma levels of total cholesterol and triglycerides. Few data are available concerning the effects of a ketogenic diet on the plasma levels of the major apolipoprotein B (apoB)–containing lipoproteins, low-density lipoprotein (LDL) and very LDL (VLDL); and the major apolipoprotein A-I (apoA-I)–containing lipoprotein, high-density lipoprotein (HDL). In 1 report, no significant effect on the plasma VLDL, LDL, and HDL cholesterol levels was found in 24 children treated with the classic 4:1 ketogenic diet for 3 weeks.12 Whether a very high-fat diet can induce elevated levels of the triglyceride-rich VLDL and the cholesterol-rich LDL but lower levels of HDL cholesterol is an important question, because each of these effects predicts the development of early atherosclerotic lesions, fatty streaks, and fibrous plaques in the aorta and coronary arteries in adolescents and young adults.14,15

This prospective study evaluated the effects of a ketogenic diet on plasma lipoproteins in children treated with a ketogenic diet for intractable seizures. The objectives were to determine the effect of a ketogenic diet on the plasma levels of VLDL, LDL, and HDL cholesterol, and their major apolipoproteins, apoB and apoA-I; and the proportion of children who developed either elevated total and LDL cholesterol or increased triglyceride levels, or low HDL cholesterol by using guidelines from the National Cholesterol Education Program (NCEP) Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents.16

**METHODS**

**Patient Population**

A cohort of 371 patients who initiated the ketogenic diet in an attempt to control their seizures between 1994 and 2001 comprised the study population.2 Of the 230 patients in this study, 86 discontinued the ketogenic diet because of ineffective seizure control (n=37), intercurrent illness (n=12), diet too restrictive (n=25), planned discontinuation (n=4), and other (n=8). An additional 144 patients were not included because of missing samples at baseline or at 6 months (plus or minus 1 month). Thus, 141 (38%) of 371 patients were included in this study. There were no other sources of potential bias in the selection among the patients receiving a ketogenic diet.

The 141 children (boys, n=70; girls, n=71) were between the ages of 4 months and 20 years (Table 1) and met the following criteria for entry into this study: (1) satisfied the requirements for inpatient admission to the Johns Hopkins ketogenic diet program, as previously published;2 (briefly, infants, children, or adolescents had to have a minimum of 2 seizures per week and must have not responded to at least 2 medications); (2) admitted to the Johns Hopkins Hospital for initiation of the ketogenic diet and managed according to a preset protocol; and (3) blood sample obtained after an overnight fast for a lipid and lipoprotein profile, both at the time of initiation in the ketogenic diet, and 6 months (plus or minus 1 month) after starting the diet. The mean (SD) age was 5.2 (3.8) years for the 70 boys and 6.1 (4.4) years for the 71 girls.

Of the 141 patients who met the above criteria, follow-up fasting blood specimens were also obtained for 59 patients at 1 year of follow-up (12 months plus or minus 1 month) and for 27 patients at 2 years of follow-up (24 months plus or minus 1 month). The Johns Hopkins Joint Committee on Clinical Investigation approved the project. Parents of all children who initiated the ketogenic diet program signed an approved informed consent to collect, analyze, and report the data.

**Dietary Protocol**

The patients fasted for 48 hours and then the diet was introduced with one third of the calculated diet as egg nog for 3 meals, followed up by two thirds of the calories as egg nog for the next 3 meals. The full calculated diet was then begun, and the child was discharged to home. At the onset of the diet, 102 of the patients received a 4:1 ratio of fat to carbohydrate plus protein, 7 received a 3.5:1 ratio, and 32 received a 3:1 ratio (Table 1). Patients were followed up by telephone and the diet adjusted depending on the level of ketosis and the degree of seizure control. The caloric intake was adjusted based on the child’s weight gain or loss to achieve and maintain an ideal body weight for height. Dietary compliance was assessed by using a standardized Ketogenic Diet Nutrition Consult form developed by the Johns Hopkins Pediatric Epilepsy Center. This was used to monitor medical/nutritional status and seizure control, and to adjust the diet appropriately.

**Measurement of Plasma Lipids, Lipoproteins, and Apolipoproteins**

Plasma cholesterol and triglyceride levels were measured by enzymatic/colorimetric methods as previously described.17 The plasma level of HDL cholesterol was determined in the supernatant following precipitation of the apoB-containing lipoproteins with heparin manganese.17 The LDL cholesterol level was calculated by using the Friedewald equation18 in samples with a triglyceride level of less than 400

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>41 (29.1)</td>
</tr>
<tr>
<td>&gt;3-10</td>
<td>52 (36.9)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>52 (36.9)</td>
</tr>
<tr>
<td>Sex, male</td>
<td></td>
</tr>
<tr>
<td>70 (49.7)</td>
<td></td>
</tr>
<tr>
<td>Weight percentile*</td>
<td></td>
</tr>
<tr>
<td>&lt;50th</td>
<td>70 (49.7)</td>
</tr>
<tr>
<td>50th</td>
<td>11 (7.8 )</td>
</tr>
<tr>
<td>&gt;50th</td>
<td>60 (42.5)</td>
</tr>
</tbody>
</table>

*The categorization of weight is presented as adjusted for age and sex based on normative data.3

©2003 American Medical Association. All rights reserved.
mg/dL (<4.52 mmol/L). The VLDL cholesterol level was calculated by dividing the total triglyceride level by 5.18 The non-HDL cholesterol level was calculated by subtracting the HDL cholesterol from the total cholesterol. Plasma levels of total apoB and apoA-I were measured by using immunoturbidimetric methods as previously described.19 The procedures used to ensure laboratory quality control have been reported previously in detail.19

Statistical Methods
Differences between baseline and the 6-month follow-up were assessed by using a general linear model to fit each outcome variable as a function of the independent variable. This regression technique uses the general estimating equation method developed to account for multiple observations from the same subject.20 Through an adjustment of the variance-covariance matrix, the correlation that is inherent among repeated measures is controlled.21 The analytic plan focused on first modeling changes in plasma levels of lipids, lipoproteins, and apolipoproteins by using a univariate approach whereby the individual contributions of each independent variable could be assessed. In accomplishing this step, the most parsimonious model could be constructed to account for the contribution of each factor. Given the exploratory nature of this step in the analysis, overall type I error was not adjusted for multiple comparisons; however, within each independent variable, comparisons across strata and time were adjusted by using Bonferroni correction to account for multiple comparisons.

The independent variables included in the univariate analysis were sex, age (4 months to 3 years, >3 years to 7 years, >7 years to 10 years, and >10 years), weight (by age- and sex-specific percentiles: <50th, 50th, and >50th), and the ratio of fat to protein plus carbohydrate in the ketogenic diet (3:1, 3.5:1, and 4:1). The dependent variables included the plasma levels of total cholesterol, VLDL cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides, total apoB, apoA-I, and the ratios of total cholesterol to HDL cholesterol, LDL to HDL cholesterol, LDL cholesterol to apoB, HDL cholesterol to apoA-I, and apoB to apoA-I.

Once the influence of each independent variable was ascertained, the second step of the analytic plan focused on the construction of a multivariate model that could best explain changes in plasma measures from baseline to 6 months of receiving the ketogenic diet. To accomplish this, the general linear model was then extended to a multivariate model where the effect of multiple independent variables on the outcome variable of interest was assessed simultaneously. The use of multivariate regression techniques allows for an experiment-wise type I error level of .05. The outcome of interest was the change between these 2 points (baseline and 6 months receiving the diet) with adjustment made for the baseline plasma measure. The distributions of all dependent variables were assessed for normality based on tests of the coefficient of skewness and of kurtosis.22 When appropriate, data transformations were made to approximate normality. Ratio data, such as total cholesterol and HDL cholesterol, were transformed by using log-transformation to approximate normality.

Statistical analyses were performed by using SAS version 8.02 (SAS Institute, Cary, NC). Estimates of statistical power based on the available sample size were made by using PASS 2002 (NCSS Statistical Software, Kaysville, Utah). P < .05 was considered statistically significant.

RESULTS
Characteristics of the Study Population
The clinical characteristics of the study population are summarized in Table 1. The patients ranged in age from 4 months to 20 years. The number of boys and girls was almost identical (n = 70 and n = 71, respectively). Sixty-six percent of the study population was 4 months to 7 years of age. The percentages of those patients below, at, or above the median weight for age were as expected.

The percentage distribution of the ratios of fat to carbohydrate plus protein in the ketogenic diet in the study population is also summarized in Table 1. Most patients (72.3%) received a treatment ratio of 4:1. The infant/children and adolescent groups had the greatest numbers receiving a 3:1 or 3.5:1 treatment ratio, consistent with the requirements of more protein during these periods of more rapid growth.

The seizure types at the onset of the ketogenic diet were myoclonic/atonic or infantile spasms (n = 68), absence/atypical absence (n = 23), tonic/clonic/tonic-clonic (n = 22), complex/simple partial (n = 21), unclassified (n = 4), and no seizures at diet onset (n = 3). After 6 months of receiving a ketogenic diet, 93 patients (66%) were at least 50% improved with 17 seizure-free, 39 were less than 50% improved, and 9 patients were missing the seizure control data.

Influence of Independent Variables on Dependent Variables
There were no significant differences at baseline or 6-month follow-up for sex, age, weight for age, or ratio of fat to carbohydrate plus protein in the 3 dietary groups for the plasma levels of total cholesterol, LDL cholesterol, non-HDL cholesterol, or total apoB.

There were no significant differences at baseline or follow-up for sex, age, weight for age, or ratio of fat to carbohydrate plus protein in the 3 dietary groups for the plasma levels of total cholesterol, LDL cholesterol, and apoB.
EFFECT OF KETOGENIC DIET ON LIPID LEVELS IN CHILDREN

The baseline mean levels for the ratios of total cholesterol to HDL cholesterol, LDL to HDL cholesterol, LDL cholesterol to apoA-I, and apoB to apoA-I are shown in Table 3. These ratios are similar to those reported in healthy pediatric populations, with the exception of the mean ratio of LDL cholesterol to apoB, which was lower at baseline in this study population than in the reference populations. A low ratio of LDL cholesterol to apoB suggests the presence of small dense LDL particles, a feature of small dense LDL particles, a feature of atherogenic risk.

There were no significant differences between the various age, sex, weight, and ketogenic diet groups at baseline or 6-month follow-up for the ratios of total cholesterol to HDL cholesterol or LDL to HDL cholesterol, except that at baseline those patients in the 4:1 ketogenic diet group had a higher ratio of LDL to HDL cholesterol (2.19 [0.22] vs 1.82 [0.07], P = .008) than those patients in a 3.5:1 or 3:1 diet group. The ratio of LDL cholesterol to apoB was significantly higher at baseline in the 7- to 10-year-old age group (1.82 [0.07] vs 1.69 [0.03], P = .03) than those children in the less than 3-year-old group but this difference was not present at the 6-month follow-up. At baseline, the ratio of HDL cholesterol to apoA-I was significantly higher in the 3- to 7-year-old age group (0.39 [0.01] vs 0.36 [0.01], P = .03) vs the less than 3-year-old group but significantly lower in those patients with a weight of more than 95 percentile (0.37 [0.01] vs 0.41 [0.02], P = .03) vs those with a weight of 95 percentile or less; neither of these differences was present at the 6-month follow-up. At the 6-month follow-up, the youngest group had a significantly lower ratio of LDL cholesterol to apoA-I (0.28 [0.01] vs 0.32 [0.01], P = .007) than in the 10-year-old or higher group. The ratio of apoB to apoA-I was significantly higher at baseline in the girls than in the boys (0.65 [0.02] vs 0.57 [0.02], P = .01) but was significantly lower in the 7- to 10-year-old group (0.55 [0.03] vs 0.69 [0.03], P = .049) vs the less than 3-year-old group. These differences were not present after 6 months of the ketogenic diet.

### Baseline Levels of Plasma Lipid, Lipoprotein, and Apolipoprotein Levels

The baseline levels of plasma lipids, lipoproteins, and apolipoproteins for the study population are shown in Table 2.

<table>
<thead>
<tr>
<th>Plasma Level</th>
<th>Baseline, Mean (SD), mg/dL</th>
<th>6 Months, Mean (SD), mg/dL</th>
<th>Adjusted Mean Difference (95% CI), mg/dL*</th>
<th>t†</th>
<th>df</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>174 (46)</td>
<td>232 (94)</td>
<td>58 (44-72)</td>
<td>7.8</td>
<td>236</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>99 (30)</td>
<td>148 (70)</td>
<td>50 (38-62)</td>
<td>8.9</td>
<td>225</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>56 (15)</td>
<td>49 (18)</td>
<td>−7 (−11 to −3)</td>
<td>−4.0</td>
<td>228</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>17 (7)</td>
<td>25 (13)</td>
<td>8 (6-10)</td>
<td>6.7</td>
<td>228</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>118 (46)</td>
<td>181 (88)</td>
<td>63 (49-77)</td>
<td>8.9</td>
<td>228</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>96 (110)</td>
<td>154 (179)</td>
<td>58 (44-72)</td>
<td>7.8</td>
<td>236</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>149 (29)</td>
<td>152 (31)</td>
<td>−4 (−2 to 0)</td>
<td>1.2</td>
<td>214</td>
<td>.23</td>
</tr>
<tr>
<td>ApoB</td>
<td>89 (23)</td>
<td>140 (59)</td>
<td>49 (39-59)</td>
<td>10.1</td>
<td>213</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Multivariate repeated measures linear regression model, adjusting for sex, age, weight (age-adjusted percentile), and fat/protein plus carbohydrate ratio of ketogenic diet.†Statistics are based on the multivariate regression model and test whether the mean difference is different from zero.

### Table 2. Mean Plasma Levels of Lipids, Lipoproteins, and Apolipoproteins at Baseline and 6 Months in Patients Receiving the Ketogenic Diet

©2003 American Medical Association. All rights reserved.
finding consistent with the higher baseline triglyceride and VLDL cholesterol levels in this study population.

Effect of a Ketogenic Diet on the Plasma Levels of Lipids, Lipoproteins, and Apolipoproteins

After 6 months of receiving the ketogenic diet, the mean LDL cholesterol level increased 50 mg/dL (1.30 mmol/L), reflecting a mean shift of almost 2 SDs (Table 2). The mean LDL cholesterol level of 148 mg/dL (3.83 mmol/L) after the ketogenic diet reflects a value that is considerably higher than the 95th percentile (130 mg/dL [3.79 mmol/L]) for this age group. The mean total cholesterol level also increased markedly to 232 mg/dL (6.01 mmol/L), 2 SDs higher than the mean for a reference healthy population, and notably higher than the 95th percentile of approximately 200 mg/dL (5.18 mmol/L), a level considered to be high by the NCEP pediatric panel.16

The difference in the mean triglyceride level after 6 months of receiving the ketogenic diet was also significantly higher compared with baseline. The mean value of 154 mg/dL (1.74 mmol/L) well exceeded the approximate 95th percentile for triglycerides in the first decade (100 mg/dL [1.13 mmol/L]) and the second decade (130 mg/dL [1.47 mmol/L]) of life. The mean difference between the baseline and follow-up VLDL levels was also significant and in proportion to that expected by the increase in the triglyceride levels. Measuring the non-HDL cholesterol and the apoB levels also assessed the change in the apoB-containing lipoproteins. Both of these parameters also increased significantly to mean levels that exceeded the 95th percentiles reported in reference healthy pediatric populations.19,20 A sizable proportion of the study population was now both hypertriglyceridemic and hypercholesterolemic.

The difference in the mean level of HDL cholesterol between baseline and 6 months in patients receiving the ketogenic diet was –7 mg/dL (–0.18 mmol/L) (Table 2). This significant shift toward lower HDL cholesterol values increased notably the number of children with low (<35 mg/dL [0.91 mmol/L]) or borderline low (35 to 45 mg/dL [0.91 to 1.17 mmol/L]) levels. However, apoA-I, the major protein of HDL cholesterol, did not change significantly between baseline and after 6 months, indicating that the number of HDL particles did not decrease on the ketogenic diet but that the composition of HDL had, containing less cholesterol in its core.

| Table 3. Mean Ratios of Plasma Levels of Lipids, Lipoproteins, and Apolipoproteins at Baseline and 6 Months With the Ketogenic Diet |
|-----------------|---------------------|-----------------|-----------------|----------------|-----------------|
|                 | Baseline, Mean (SD) | 6 Months, Mean (SD) | Adjusted Mean Difference (95% CI) t df Value
| Total cholesterol/HDL | 3.36 (1.15) | 5.20 (2.09) | 1.84 (1.35-2.33) | 7.42 | 240 | <.001
| LDL/HDL          | 1.92 (0.85) | 3.24 (1.86) | 1.32 (0.99-1.65) | 8.52 | 224 | <.001
| LDL/ApoB         | 1.10 (0.19) | 1.11 (0.28) | 0.01 (–0.05 to 0.07) | 0.18 | 208 | .85
| HDL/ApoA-I       | 0.39 (0.08) | 0.34 (0.10) | –0.06 (–0.08 to –0.04) | –5.94 | 212 | <.001
| ApoB/ApoA-I      | 0.61 (0.17) | 0.96 (0.46) | 0.34 (0.26-0.42) | 8.65 | 212 | <.001

Abbreviations: ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Effect of a Ketogenic Diet on Lipid Ratios

Compared with baseline, the ratios of total to HDL cholesterol, LDL to HDL cholesterol, and apoB to apoA-I all increased significantly after 6 months of receiving a ketogenic diet (Table 3). Each of these ratios provides an assessment of the relative amounts of the apoB-containing lipoproteins to the apoA-I–containing lipoproteins. The greatest increase occurred in the ratio of apoB to apoA-I, which increased 2 SDs from the mean at baseline. The increase in the ratio of total to HDL cholesterol and LDL to HDL cholesterol were between 1 and 2 SDs higher than the means at baseline. Conversely, the ratio of HDL cholesterol to apoA-I decreased significantly, indicating that the HDL particles contained less cholesterol relative to apoA-I, a change that is likely to reflect an exchange of cholesterol esters from the core of HDL cholesterol for triglycerides from VLDL cholesterol. The ratio of LDL cholesterol to apoB did not change significantly after receiving the ketogenic diet; this might reflect the already low ratio present at baseline.

Effect of Ketogenic Diet on the Development of Dyslipidemia in Children

We next determined the proportion of patients who developed high or borderline high levels of total cholesterol and LDL cholesterol (Figure 1), total triglyceride levels (Figure 2), or low or borderline low levels of HDL cholesterol (Figure 1) after 6 months by using the definitions of the NCEP pediatric panel.16

At baseline, 75% of the children had acceptable levels of LDL cholesterol (<110 mg/dL [<2.85 mmol/L]), a proportion similar to a reference healthy population (Figure 1). However, 11% had borderline elevated LDL cholesterol levels (110 to 129 mg/dL [2.85 to 3.44 mmol/L]) and 14% had elevated levels; therefore, a higher proportion had elevated levels at baseline compared with approximately 5% that were expected to be elevated in a healthy pediatric population. After 6 months of receiving the ketogenic diet, 53% had elevated LDL cholesterol levels and only 28% were in the acceptable range.

For total cholesterol, 22% had elevated levels (≥200 mg/dL [≥5.18 mmol/L]) at baseline, 27% had borderline elevated levels (170-199 mg/dL [4.40-5.15 mmol/L]), and only 51% were in the acceptable range (Figure 1). The greater shift toward higher total cholesterol levels than LDL cholesterol levels at baseline was because of the higher levels of VLDL cholesterol. After 6 months of the ketogenic diet,
61% of the study population had high cholesterol levels, 17% were borderline high, and only 22% remained in the acceptable range.

At baseline, 75% of the study population had acceptable (>45 mg/dL [>1.17 mmol/L]) HDL cholesterol levels, a proportion similar to that found in reference populations, 18% had borderline low (35-45 mg/dL [0.91-1.17 mmol/L]) levels, and approximately 6% had low (<35 mg/dL [<0.91 mmol/L]) HDL cholesterol levels (Figure 1). After 6 months receiving a ketogenic diet, 16% developed low HDL cholesterol levels, 33% were borderline low, and only 51% were in the acceptable range.

The cut points for total triglyceride levels recommended by the NCEP pediatric panel differ between the first and second decades (Figure 2). For the younger children, 21% had high (≥100 mg/dL [1.13 mmol/L]) triglyceride levels at baseline, 33% had borderline high levels, and 46% had acceptable levels. After 6 months of the ketogenic diet, 65% were hypertriglyceridemic, 21% had borderline high triglyceride levels, and only 14% had acceptable levels. In the older children aged 10 to 19 years, 22% had elevated (≥130 mg/dL [1.47 mmol/L]) triglyceride levels at baseline, a proportion similar to the younger children. However, a higher proportion (62%) of the older children had acceptable levels at baseline, and fewer (16%) had borderline high elevated levels. There was only a small increase in the number of older children with hypertriglyceridemia, but the proportion (27%) of those with borderline high levels increased, while those (46%) with acceptable levels decreased.

### Long-term Effect of the Ketogenic Diet on Plasma Lipid and Lipoprotein Levels

We next examined whether the effects of the ketogenic diet persisted on follow-up of the patients receiving this diet for up to 24 months (Figure 3). The significantly higher mean plasma levels of total cholesterol and LDL cholesterol observed after 6 months remained significantly higher at both 12 and 24 months of follow-up. The mean levels of total and LDL cholesterol were lower after 12 and 24 months of the ketogenic diet than after 6 months but remained higher than the cut points used for high values. A similar pattern was observed for plasma triglyceride levels, although the higher value at 24 months compared with baseline was not statistically significant. The lower mean level of HDL cholesterol observed after 6 months remained significantly lower at both 12 and 24 months of follow-up.

### COMMENT

The major finding of this study was the marked increase in the apoB-contain-
lipoproteins, VLDL and LDL cholesterol, after 6 months of the ketogenic diet. This was accompanied by both hypercholesterolemia and hypertriglyceridemia, which were so extensive that only about 1 in 6 of the study population had either a cholesterol or triglyceride level in the acceptable range for a pediatric population. Although the influence of age, sex, weight, and ratio of fat to carbohydrate plus protein in the diet was controlled for in the analyses, the results of this study cannot be extrapolated to the general pediatric population.

Our study group was also receiving a number of medications for seizure control so diverse that it is not possible to determine the influence of each drug and dosage combination with the baseline levels of plasma lipids, lipoproteins, and apolipoproteins. Although it is possible that these seizure medications may have produced higher baseline VLDL cholesterol and triglyceride levels in this population, the mean LDL cholesterol level was similar to that found in reference healthy populations. Also, the liver function tests in this study population had no relationship to the baseline lipid and lipoprotein levels (data not shown). The effect of the ketogenic diet on the LDL cholesterol level (and other lipid and lipoprotein parameters) was so marked that it is highly unlikely that such an effect is simply explained by the special nature of this study population.

The magnitude of the changes also considerably exceeds those that might be expected to occur with any laboratory drift with time. The elevation in the LDL cholesterol level in response to the ketogenic diet was a general characteristic of this study population and occurred independently of the baseline LDL cholesterol level or of the degree of seizure control (data not shown). Only 10 boys and 15 girls did not manifest any increase in their LDL cholesterol levels. The dramatic increase in the mean total cholesterol level found empirically was close to that of 57.1 mg/dL (1.48 mmol/L), predicted from a computer analysis by using Keys’ and Hegsted’s formulas of healthy adults on a high-fat low-carbohydrate weight-maintaining energy intake.

The ketogenic diet also had a marked effect on the HDL cholesterol level in this population. At baseline, the distribution of the HDL cholesterol level was similar to that expected for a pediatric population. After 6 months of the ketogenic diet, only about half the study group had an HDL cholesterol level in the acceptable range. It is not unusual for the HDL cholesterol level to decrease when accompanied by an increase in VLDL and triglyceride levels, an effect often related to an enhanced exchange of triglyceride from VLDL cholesterol for cholesteryl esters on HDL cholesterol by the cholesteryl ester transfer protein. The resultant HDL particles and its apoA-I component appear to be removed more avidly by the kidney, resulting in lower plasma levels of both HDL cholesterol and apoA-I, and a decreased number of HDL particles. However, we found that the apoA-I levels did not decrease with the ketogenic diet, suggesting another effect of this diet on HDL cholesterol metabolism. For example, the ketogenic diet may have increased the biosynthesis of apoA-I or decreased the catabolism of the HDL particle, by mechanisms that are not completely understood at this time.

The ratios of total to HDL cholesterol, LDL to HDL cholesterol, and apoB to apoA-I have been used to assess the relative proportions of the apoB-containing and apoA-I-containing lipoproteins. Higher ratios indicate an increase in the risk of developing coronary artery disease in adults, of early lesions of atherosclerosis in children and young adults, and of parental history of myocardial infarction. Each of these ratios increased significantly after the ketogenic diet primarily because of the increased increase in the non-HDL cholesterol, another indicator of the concentrations of the apoB-containing lipoproteins.

We used the ratio of LDL cholesterol to apoB to estimate the particle composition of LDL. The increase in the apoB-containing particles observed after the ketogenic diet might be because of increased hepatic biosynthesis and secretion of VLDL cholesterol, leading to an enhanced exchange of triglycerides in VLDL cholesterol for cholesteryl esters in the core of LDL cholesterol by cholesteryl ester transfer protein, followed up by hydrolysis of triglyceride in LDL cholesterol by hepatic lipase and lipoprotein lipase, which produces a cholesterol-depleted small dense LDL cholesterol. This may be related to the known effect of ketone bodies to stimulate the biosynthesis of fatty acids and triglycerides in the liver. Overproduction of VLDL cholesterol and consequently of small dense LDL cholesterol is thus accompanied by a low ratio of LDL cholesterol to apoB.

After 6 months of the ketogenic diet, the ratio of LDL cholesterol to apoB did not change significantly. There are several possible explanations for this observation. First, small dense LDL, as judged by a lower mean ratio (1.1) of LDL cholesterol to apoB than that (1.2) found in healthy pediatric populations, was present at baseline consistent with the higher than average baseline VLDL cholesterol and triglyceride levels. Second, it is possible that...
the ketogenic diet influenced the activity of cholesterol ester transfer protein or of lipoprotein lipase and/or hepatic lipase, impeding the formation of the small dense LDL particles. Further studies of both the complete chemical composition of the apoB-containing lipoproteins and of their metabolism will be necessary to understand the mechanisms of action of the ketogenic diet in this population.

Our findings of the induction of marked dyslipidemia in children treated with a ketogenic diet cannot be directly extrapolated to the use of a ketogenic diet in children or adults for the purposes of weight reduction. In fact, a major difference in our pediatric population is that the ketogenic diet was designed to have sufficient calories to promote healthy growth and development. Measurement of lipids and lipoproteins in healthy adults receiving a ketogenic diet has usually been obtained while the patients are actively losing weight, and more information is needed to determine what effect such a diet might have in adults who are consuming sufficient calories to maintain their weight. A high-protein but low-fat ketogenic diet has been used to treat adolescents with morbid obesity. Such children lose weight successfully during which time the plasma cholesterol, LDL cholesterol, and HDL cholesterol levels fall significantly. Thus, it appears possible to use a high-protein diet that is also low in fat to induce weight reduction. Further studies are clearly indicated in both children and adults on the influence of both high-fat and low-fat ketogenic diets on lipoprotein metabolism. Finally, it is possible to use a high-fat ketogenic diet to treat intractable seizures that uses medium-chain triglycerides rather than the classical long-chain triglycerides. The use of medium-chain triglycerides as the source of fat in such a ketogenic diet appears to produce less of a dyslipidemia than the classic ketogenic diet.

Few serious complications because of the classic or modified ketogenic diet have been reported. During the initial hospitalizations, short-term complications include hypoglycemia, vomiting, diarrhea, dehydration, and refusal to eat. Longer-term complications include irritable bowel syndrome, kidney stones, acidosis, hyperuricemia, hypocalcemia, decreased amino acids, growth, and hypercholesterolemia. In this study, we did not assess the influence of the ketogenic diet on the development of early lesions of atherosclerosis in this population. It remains to be determined whether such a ketogenic diet might induce thickening of the intima of the carotid arteries or endothelial dysfunction, both of which appear to be accentuated in young populations with elevated LDL cholesterol levels. The marked dyslipidemia such as that induced by the ketogenic diet might also produce an inflammatory response, as judged by highly sensitive C-reactive protein, IL-8, and other inflammatory markers.

Even if the ketogenic diet in this group is inflammatory and atherogenic, this will most likely not preclude its use in intractable seizures in children. Such treatment is highly effective and its anti-epileptic action may persist long after the diet is discontinued. Most patients have stopped the ketogenic diet after 2 years and the temporary use in childhood is unlikely to be associated with a long-term increase in risk for coronary artery disease in adulthood. Conversely, prolonged use of a hypercholesterolemic diet throughout childhood and adolescence is likely to be atherogenic. For example, healthy young men aged 20 to 25 years who had a cholesterol level of more than 210 mg/dL (5.44 mmol/L) had 5 times the rate of coronary artery disease 30 to 40 years later than those who had a cholesterol level of less than 170 mg/dL (4.40 mmol/L).

Obtained funding: Freeman. Administrative, technical, or material support: Kwiterovich, Vining, Pyzik. Study supervision: Vining.

Funding/Support: This study was supported in part by grant NO1-HD-7-3268 from the National Institutes of Health, the Johns Hopkins University School of Medicine, General Clinical Research Center, MO1-RR-00052 from the National Center For Research Resources-National Institutes of Health, the Roxanne Fellowship Funds, and the Vaswani Family.

REFERENCES
18. Friedewald WT, Levy RI, Fredrickson DS. Estima-


The law of things is that they who tamper with veracity, from whatever motive, are tampering with the vital force of human progress.
—John Morley (1838-1923)