Growth of adolescents who were born at extremely low birth weight without major disability

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**Objective:** To compare growth between adolescents who were born at extremely low birth weight (ELBW, ≤1000 g) and adolescents who were born at normal birth weight (NBW, ≥2500 g).

**Design/Methods:** Cross-sectional design. Fifty-three ELBW and 53 NBW adolescents without a major neurodevelopmental disability were matched by sex, race, age, and socioeconomic status. Anthropometrics (z scores), bone age, body composition (Lunar DPX-L densitometry), and sexual maturity were assessed. ELBW adolescents were classified as being born small for gestational age (SGA) or not (NSGA).

**Results:** Subjects were 58.5% female, 43.4% black, and 56.6% white. The mean birth weight for ELBW subjects was 849 g and 3355 g for NBW subjects. The mean age was 14.85 years. On average, ELBW adolescents were 4.8 cm shorter and 9.1 kg lighter than NBW adolescents. ELBW adolescents had lower mean z scores for height (P < .0001), weight (P < .0001), and head circumference (P < .0001) than NBW adolescents. ELBW/SGA subjects had lower mean z scores for height (P < .0001) and weight (P = .001) than NBW subjects. Head circumference z scores were lower for the ELBW/SGA group than the ELBW/NSGA group or the NBW group (P = .003). Sexual maturity and relative body composition were similar between groups. Bone age, measured in SD units, was more advanced in the ELBW group (0.86 vs. 0.42, P = .039).

**Conclusions:** ELBW adolescents who survive without a major neurodevelopmental disability attain lower growth measurements compared with NBW adolescents but have similar sexual maturation and relative body composition. (J Pediatr 2000;136:633-40)
maturity. To our knowledge data on body composition and bone maturation during ELBW adolescent years are lacking.

Studies performed on adolescents who were born at low birth weight (<2500 g) before major advances in neonatology suggested that their anthropometric measurements were lower than those of adolescents born at normal birth weight. The findings were more definitive for low birth weight adolescents who were also born small for gestational age. However, very few adolescents who were born <1000 g were included in these studies. We hypothesized that ELBW adolescents would attain lower growth (by anthropometric measurements) and different body composition than an NBW control group and that these parameters would be lowest for ELBW adolescents who were SGA. Bone age and sexual maturation measurements were also expected to be lower in the ELBW adolescents.

METHODS

Subjects

The subjects included adolescents born between 1978 and 1984 at term (>37 weeks' gestation), of normal birth weight (>2500 g), and with no major neurodevelopmental impairment (as defined previously for the ELBW group) served as our comparison group. This control group was matched to the case subjects by age, sex, race, and socioeconomic status (with the Hollingshead Scale). The University of Alabama Adolescent Clinic and Primary Care Clinic, the Children's Hospital of Alabama Youth Volunteer Program, and Camp Birmingham Summer Program were the primary targets of the NBW adolescent recruitment efforts. In addition, announcements of the study were posted in several locations in the Birmingham area. A catalogue of information forms was kept of all potential members of the control group for each case. A research assistant randomly selected one member of the control group by picking one name at random from a list.

Assessments

Each subject underwent anthropometric measurement including standing height, weight, and head circumference. A nutritionist blinded to birth weight status obtained all measurements in a standardized manner. Each measurement was performed at least 3 times with the data recorded when 2 equal measurements were obtained. Raw anthropometric measurements were converted to standard z scores to allow calculation of sample means for comparison of both male and female subjects across the range of ages. The z scores were calculated for height and weight measurements with ANTHRO software from the Centers for Disease Control and Prevention (ANTHRO: Software for calculating pediatric anthropometry 1.01 ed). The reference population was provided by National Center for Health Statistics growth charts (NCHS growth curves for children birth to 18 years United States). Height and weight percentiles were obtained with this same software. ANTHRO software does not include head circumference data; therefore those z scores were calculated with the formula (z score = [actual measurement - median reference value]/[SD value of reference]). The reference population for head circumference data included participants of the Fels Longitudinal Study.

Body composition was assessed by dual energy x-ray absorptiometry with a Lunar DPX-L densitometer (Lunar Radiation, Madison, WI). The total dose of radiation for a scan is less than 0.02 mrem. The DEXA scans provided direct measurement of body fat, lean soft tissue mass, and bone mineral mass (in grams). In addition, bone mineral density (grams per square centimeters) was recorded. Scans were analyzed with the adult medium mode (DPX-L version 1.3z).

A physician who was blinded to birth weight status performed assessments of sexual maturity with Tanner
Stages. Stages of breast development and pubic hair were characterized for female subjects. For male subjects Tanner stages were determined for pubic hair and testicular size; in addition, testicular size was characterized by measurement with an Orchiodometer (Test-Size orchiodometer, Accurate Surgical & Scientific Instruments Corporation). A pediatric radiologist blinded to the patient’s birth weight status calculated bone ages in SD units of a reference population according to the standards of Greulich and Pyle.

All parental heights and weights and birth weights of members of the control group were obtained from parental report. Birth weight and gestational age data for adolescents in the ELBW group were extracted from the Newborn Follow-up Program database. In this database the best estimate of gestational age was derived from maternal last menstrual period, clinical history, physical examination, and ultrasonographic fetal measurements. ELBW adolescents were categorized as SGA if birth weight was ≤10th percentile according to Brenner standards and as not being SGA if birth weight was >10th percentile. These standards have been used previously in our institution for comparisons. Because of our exclusion criteria, no one in the control group was SGA.

Informed consent was obtained from all participants. In addition, parental informed consent was obtained for participants younger than 14 years of age. Each participant completed the entire battery of evaluations during a single outpatient visit. The study design and methods were approved by both the Institutional Review Board for Human Use at the University of Alabama Birmingham and the Scientific Advisory Board of the General Clinical Research Center.

Data analysis was performed with SAS and SPSS statistical packages. Comparisons on continuous outcomes between NBW and ELBW adolescents were performed with the t test and summarized by univariate analyses. General linear models were run to compare differences among ELBW/SGA, ELBW/NSGA, and NBW adolescents with and without covariate adjustments. Where significant differences existed, multiple comparison procedures were used with Tukey’s LSD with a Bonferroni adjustment on the overall type I error rate. For exploratory purposes multiple stepwise regression was used to find predictors of z scores.

**RESULTS**

In each group of 53 ELBW adolescents and 53 NBW adolescents, 31 (58.5%) were female. 22 (41.5%) were male. 23 (43.4%) were black, and 30 (56.6%) were white. The mean age at assessment was similar between groups (Table I). The mean gestational age was 28.2 weeks for the ELBW group, and the NBW group gestational age was >37 weeks by inclusion criteria. There were 22 (41.5%) ELBW adolescents who were also SGA. Mean Hollingshead socioeconomic scores were similar between groups. The percent of adolescents who had private insurance or Medicaid or who were recipients of Social Security Income was not significantly different between the groups. The percent of mothers with less than a twelfth grade education was similar between the groups. No significant difference was seen in the level of paternal education among the subjects for whom this information was available.

Adolescents who were born at ELBW had lower mean height (160.5 cm vs 165.3 cm) than NBW adolescents (P = .006) (Table II). Height by age z scores were also lower in the ELBW group compared with NBW adolescents (-0.37 vs 0.28, P < .0001). The percent of ELBW adolescents with height for age z scores below -2 (which corresponds closely to ≤2nd percentile) was 5.7% (n = 3) compared with none of the NBW adolescents; 21% (n = 11) of ELBW adolescents had height for age z scores below -1 compared with 7.5% (n = 4) of the NBW adolescents. In addition to z scores, we compared the frequency distribution of percentiles for heights by age (Fig 1); 56% of the ELBW adolescents were below the 25th percentile compared with 11% of the NBW adolescents.

**Table I. Sociodemographic characteristics**

<table>
<thead>
<tr>
<th></th>
<th>ELBW (n = 53)</th>
<th>NBW (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y, mean [SD])</td>
<td>14.8 (1.8)</td>
<td>14.9 (1.7)</td>
</tr>
<tr>
<td>Birth weight (g, mean [SD])</td>
<td>849 (109)</td>
<td>3355 (626)</td>
</tr>
<tr>
<td>Gestational age (weeks, mean [SD])</td>
<td>28.2 (2.3)</td>
<td>&gt;37</td>
</tr>
<tr>
<td>Small for gestational age (n [%])</td>
<td>22 (41.5)</td>
<td>0</td>
</tr>
<tr>
<td>Socioeconomic score (mean [SD])</td>
<td>40.8 (11.8)</td>
<td>40.3 (13.1)</td>
</tr>
<tr>
<td>Maternal education &lt;12th grade (n [%])</td>
<td>8 (15.1)</td>
<td>8 (15.1)</td>
</tr>
<tr>
<td>Private medical insurance (n [%])</td>
<td>43 (81.1)</td>
<td>46 (86.8)</td>
</tr>
<tr>
<td>Medicaid (n [%])</td>
<td>6 (11.3)</td>
<td>4 (7.5)</td>
</tr>
</tbody>
</table>

*P = not significant.
*With Hollingshead scale.
by age by group is presented in Fig 2; 54% of the ELBW adolescents were <25th percentile compared with 15% of the NBW adolescents.

The mean head circumference measurements were lower for the ELBW group compared with those for the NBW group (54.7 cm vs 56.6 cm, P < .0001). Head circumference by age $z$ scores were lower in the ELBW group than the NBW group (0.01 vs 1.26, P < .0001). The percent of ELBW adolescents with head circumference for age $z$ scores below $-2$ was 7.7% ($n = 4$) and below $-1$ was 23.1% ($n = 12$). None of the NBW adolescents had head circumference $z$ scores $<-1$.

We also compared the ELBW adolescents who were SGA with those who were NSGA and with the NBW control group (Table II). ELBW adolescents who were born SGA had lower mean $z$ scores for height by age than the NBW group at a significant level ($P < .0001$). For weight by age, the ELBW SGA and ELBW NSGA groups had lower measurements than NBW adolescents ($P < .05$). NBW adolescents had higher head circumference $z$ scores than ELBW SGA ($P < .0001$) and ELBW NSGA ($P = .003$) adolescents; in addition, ELBW NSGA adolescents had larger head circumferences than ELBW SGA adolescents ($P = .018$).

Mean total body fat, total lean tissue mass, total bone mineral content, and total muscle mass were lower in the ELBW group compared with the NBW group (Table III). Bone mineral density was not significantly different between the groups. We compared the proportions of each compartment to total body weight (lean tissue mass plus body fat plus bone mineral content) as measured by DEXA between the groups. We found no statistically significant difference between the proportions obtained for body fat/total weight, lean tissue mass/body weight, bone mineral content/body weight, or muscle mass/body weight with multivariate analysis of variance. We further compared ELBW adolescents who were born SGA or NSGA with the NBW adolescents. ELBW/SGA adolescents had lower lean tissue mass, lower muscle mass, and lower bone mineral content than NBW adolescents at a significant level. However, the proportions of these compartments to total weight were not significantly different between the groups. Therefore the relative body composition of the 3 groups was not significantly different.

Bone age measured in SD units was more advanced in the ELBW group (mean = 0.86) than in the NBW group (mean = 0.42) at a significant level ($P = .059$) after controlling was done for co-variates such as height, sexual maturity rating, sex, and race. When we analyzed separately the ELBW adolescent group, we found that the ELBW NSGA group had the more advanced bone age measured in SD units (Table II).

ELBW adolescents had similar sexual maturity rating distribution compared with NBW adolescents. All female subjects had entered puberty, and most were at SMR 4 or 5 for breast development (27 of 31 ELBW adolescents and 30 of 31 NBW adolescents) and for pubic hair (27 of 31 ELBW adolescents and 27 of 31 NBW adolescents). All except one male subject in the ELBW group and all male subjects in the NBW group had entered puberty. Most male adolescents were SMR 4 or 5 in each group for testicular development (18 of 22 ELBW adolescents and 18 of 22 NBW adolescents) and for pubic hair (18 of 22 ELBW adolescents and 17 of 22 NBW adolescents).
Table II. Mean height, weight, and head circumference and z scores with NCHS growth curves

<table>
<thead>
<tr>
<th>Growth parameters</th>
<th>ELBW (n = 53)</th>
<th>ELBW, NSGA (n = 31)</th>
<th>ELBW, SGA (n = 22)</th>
<th>NBW (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm, mean [SD])</td>
<td>160.5 (9.3)*</td>
<td>161.7 (9.7)</td>
<td>158.9 (8.7)</td>
<td>165.3 (8.2)</td>
</tr>
<tr>
<td>z score, mean (SD)</td>
<td>-0.37 (0.94)*</td>
<td>-0.20 (0.88)</td>
<td>-0.62 (0.99)*</td>
<td>0.28 (0.88)</td>
</tr>
<tr>
<td>Weight (kg, mean [SD])</td>
<td>55.3 (15.0)*</td>
<td>57.0 (14.7)</td>
<td>52.9 (15.5)</td>
<td>64.4 (16.1)</td>
</tr>
<tr>
<td>z score, mean (SD)</td>
<td>-0.01 (1.29)*</td>
<td>0.19 (1.19)</td>
<td>-0.30 (1.40)*</td>
<td>0.84 (1.09)</td>
</tr>
<tr>
<td>Head circumference (cm, mean [SD])</td>
<td>54.7 (2.1)*</td>
<td>55.2 (1.7)</td>
<td>54.0 (2.4)</td>
<td>56.6 (1.8)</td>
</tr>
<tr>
<td>z score, mean (SD)</td>
<td>0.01 (1.21)*</td>
<td>0.38 (0.94)†</td>
<td>-0.53 (1.52)†</td>
<td>1.26 (1.10)</td>
</tr>
<tr>
<td>Bone age (mean [SD])</td>
<td>0.86 (1.18)*</td>
<td>1.06 (0.98)†</td>
<td>0.58 (1.39)†</td>
<td>0.42 (0.99)</td>
</tr>
</tbody>
</table>

*Significantly different from NBW control group P < .05 after controlling was done for covariates (ie, sexual maturation rating, parental height, parental weight, sex, race).
†Significantly different from NBW control group by GLM procedure.
*Significantly different from ELBW NSGA group by post hoc Tukey's test with Bonferroni correction.

Table III. Dual-energy x-ray absorptiometry measurements by groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>ELBW (n = 53)</th>
<th>ELBW, NSGA (n = 31)</th>
<th>ELBW, SGA (n = 22)</th>
<th>NBW (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body fat (kg)</td>
<td>13.09 (8.82)†</td>
<td>13.28 (9.11)</td>
<td>12.81 (8.61)</td>
<td>17.20 (9.58)</td>
</tr>
<tr>
<td>% Total body mass</td>
<td>23.09 (10.99)</td>
<td>23.18 (10.88)</td>
<td>22.95 (11.38)</td>
<td>25.99 (10.74)</td>
</tr>
<tr>
<td>Lean tissue mass (kg)</td>
<td>38.81 (10.19)†</td>
<td>40.17 (10.72)</td>
<td>36.89 (9.30)‡</td>
<td>43.40 (9.72)</td>
</tr>
<tr>
<td>% Total body mass</td>
<td>72.72 (10.62)</td>
<td>72.59 (10.50)</td>
<td>72.91 (11.05)</td>
<td>69.93 (10.40)</td>
</tr>
<tr>
<td>Muscle mass (kg)</td>
<td>17.85 (5.53)†</td>
<td>18.45 (5.60)</td>
<td>16.98 (4.93)‡</td>
<td>20.46 (5.01)</td>
</tr>
<tr>
<td>% Total body mass</td>
<td>33.11 (5.19)†</td>
<td>33.04 (5.36)</td>
<td>33.21 (5.07)</td>
<td>32.79 (4.78)</td>
</tr>
<tr>
<td>Bone mineral content (kg)</td>
<td>2.25 (0.62)†</td>
<td>2.35 (0.62)</td>
<td>2.11 (0.61)‡</td>
<td>2.52 (0.51)</td>
</tr>
<tr>
<td>% Total body mass</td>
<td>4.19 (0.55)</td>
<td>4.25 (0.55)</td>
<td>4.14 (0.56)</td>
<td>4.07 (0.54)</td>
</tr>
<tr>
<td>Bone mineral density (g/cm²)</td>
<td>1.09 (0.13)</td>
<td>1.11 (0.12)</td>
<td>1.07 (0.15)</td>
<td>1.15 (0.10)</td>
</tr>
</tbody>
</table>

*Totals mean (±SD).
†P < .01 between ELBW and NBW with multivariate analysis of variance and least square means (after controlling for sex, race, and sexual maturation rating).
‡P < .05 between ELBW SGA and NBW with GLM procedure with Tukey's test and Bonferroni correction.

Stepwise regression analyses were used to explore which factors played a role in determining height by age, weight by age, and head circumference z scores by group. Height by age z scores continued to be significantly different between ELBW and NBW adolescents after controlling was done for mid-parental height, Tanner stage, bone age, and socioeconomic status (R² = .238, P < .0001). Parental height was a significant predictor of height z scores (beta = .152, P < .001). Mid-parental height and weight were not significantly different between the groups. Weight by age z scores were higher for NBW than ELBW adolescents after controlling was done for sex, race, SMR, parental weight, and percent of body fat with regression analysis (R² = .621, P < .0001). Head circumference z scores also continued to be significantly different between the groups after controlling was done for sex, race, socioeconomic status, and height (R² = .259, P < .0001).

**Discussion**

Our results demonstrate that ELBW adolescents who survive without a major neurodevelopmental disability attain lower growth parameters than adolescents. Testicular size in boys as measured by the orchiodometer was not significantly different between the groups. Female subjects had similar age of menarche (11.15 years for ELBW vs 11.45 years for NBW) in both groups. No differences were seen in sexual maturation by race.

Although none of the adolescents in the ELBW or NBW group had any major chronic illness, 5 adolescents in the ELBW group and 6 adolescents in the NBW group reported having a history of asthma. One adolescent in the ELBW group had a history of mild scoliosis, and one adolescent in the NBW group had a history of rheumatic fever.
their normal birth weight peers. However, most ELBW children will attain measurements within 2 SD of the mean on NCHS growth charts. ELBW adolescents who were born SGA have the lowest anthropometric measurements. Previous studies of very low birth weight children had documented catch-up growth up to 8 years of age with poorer growth attainment among SGA compared with appropriate for gestational age children. Hack et al described 249 very low birth weight children born in 1977 to 1979 who were monitored at several ages. They reported that at 40 weeks, 54% were subnormal in weight and 60% were subnormal in height; at 8 months of age, 33% and 22% were subnormal in height and weight, respectively, and at 8 years 8% were subnormal in height and weight. SGA children had lower rates of catch-up growth.

Hirata and Bosque reported a normal growth attainment for adolescents who weighed <1000 g at birth; however, this study had no control group. The importance of having an NBW control group of children matched for race, sex, and socioeconomic status has been previously emphasized. Similar to our results, Hack et al reported that their very low birth weight population had approached the 50th percentile for age according to the NCHS data, but the mean growth measures of the NBW control group were higher. Because current NCHS percentiles were developed 20 years ago, it is likely that secular growth changes have made them inappropriate for current use; however, no superior standard currently exists. A data collection and analysis is now in progress to establish updated norms. In our study, all mean growth parameters were >50th percentile for NBW adolescents. Although it is possible that adolescents with increased weight may desire medical advice and be more likely to volunteer for the study, the percent of body fat was similar between case and control groups as measured by DEXA.

Body composition as measured by DEXA does not appear to be significantly different between ELBW and NBW adolescents, because all compartments measured were proportionally lower. Therefore according to this study, it appears that ELBW adolescents are symmetrically smaller compared with NBW adolescents. Whether their body composition was different at earlier points in development is not clear; however, this is likely given that intrauterine growth retardation has been compared to malnutrition, and several of our subjects were characterized as being SGA. Bone mineral density did not differ significantly between the groups.

Sexual maturation as measured by Tanner staging did not differ significantly between the groups despite ELBW children having lower anthropometric measurements. Similar findings have been reported for low birth weight infants born <2500 g. Premature thelarche has also been reported in ELBW children, which may lead to the belief that sexual maturation is advanced for these children. Early sexual maturity was not demonstrated in our study. We collected sexual maturation data in a cross-sectional sample of adolescents, and we did not obtain sex hormone measurements. However, our sample included children in both early and late adolescence, with no difference found between the groups. In addition, no difference was seen in age at onset of menarche among the female subjects studied.

Perhaps most concerning was our finding of advanced bone age among ELBW children; however, the difference was fairly small (0.44 SD units), and the sample mean remained within 2 SD of that expected for age. Fitzhardinge and Steven observed retarded bone maturity in a group of 4-year-old low birth weight children and suggested the possibility that retardation in bone age may account for shorter stature at that age. In contrast, Powls et al showed an advanced bone age in their very low birth weight children at a median age of 12; however, they did not obtain bone ages for their control group. In our study the bone age of our cohort of ELBW adolescents was advanced compared with that of the NBW group. This finding suggests that ELBW children may be shorter as adults than even their present heights suggest. Furthermore, this finding supports the previous suggestion that growth hormone may have little value for these children, because exogenous growth hormone therapy may advance bone age even more and thus compromise further the expected final stature. Our study assessed bone age at one point in time; therefore we do not know whether the bone ages of these ELBW children were advanced before their study visit. Further research on bone age at different age levels may help clarify this issue. None of the subjects in the study had taken growth hormone. It is possible that some adolescents in our study had received steroid therapy intermittently, which may have affected bone age; however, in a study on the effects of steroids on growth in children with asthma, Crowley et al did not demonstrate differences in bone age between their groups. In addition, in our sample the number of adolescents who reported asthma was similar between both groups.

Previous studies on growth have demonstrated that parental size is a significant predictor of anthropometric measurements of children. We observed similar results in our study. Parental height was a significant predictor of height z scores, and parental weight was also a significant predictor of weight z scores. It is important that growth differences observed between ELBW and NBW subjects persisted after controlling was done for parental measurements.

In our study ELBW adolescents who were born SGA had lower height by age measurements than NBW adolescents. This finding supports the find-
ings of other published studies, some of which included term infants who were born SGA. We did not demonstrate a statistically significant difference in height between ELBW adolescents who were SGA or not; this could be related to our sample size. However, being SGA did correlate with a lower weight and smaller head circumference within the ELBW adolescent group. The proportion of ELBW adolescents who were also SGA in our sample was fairly large (41.5%). This percentage may be related to the standard used. However, when the data were compared with other available standards, a similar percentage of SGA children was obtained. In addition, these children represent survivors of extreme prematurity during the late 1970s and the early 1980s, and it is likely that children who were SGA were more likely to survive.

Our sample consisted of children who were born between 1978 and 1984. Neonatal care has changed dramatically since that time; therefore it is possible that growth characteristics of children born more recently may be different. However, Hack reported that the rates of subnormal growth were similar between 2 groups of ELBW survivors born between 1993 to 1994 and 1977 to 1979 when they were studied at the age of 2 years. Only 57 of the 93 ELBW survivors without major disability participated in our study. However, the children studied did not differ in their neonatal characteristics (gestational age, sex, race, and birth weight) from children not included in the sample. In addition, the Newborn Follow-up Program monitors children cared for in hospitals within a single county in Alabama, which may preclude generalizability to other geographic areas.

There is increasing interest on the effects of diet and nutrition in early life and long-term consequences on health, growth, and functional outcome. It has been suggested that suboptimal early nutrition has an enhancing effect on long-term bone mineralization. A recent study found no effect of early diet on bone mass in preterm children at 8 to 12 years of age. However, poor nutrition during the neonatal period may result in higher bone formation rates during childhood. Future data collected on follow-up cohorts of children who were born at extreme prematurity should include information on their early diets.

The impact of lower growth attainment on adolescents must be explored. Do lower anthropometric measurements affect the function or self-image of ELBW children as they enter adolescent years? Previous research on school-age children and growth has shown that smaller head circumferences are related to poorer cognitive outcomes. Thus intervention to improve growth may be necessary.

In summary, in our sample, although ELBW adolescents without major neurodevelopmental impairment attained growth parameters within 2 SD of the mean, they were smaller in stature, weight, and head circumference compared with NBW adolescents. Body composition and sexual maturation were similar for ELBW and NBW adolescents; therefore ELBW adolescents were symmetrically smaller than their NBW peers. ELBW adolescents who were also SGA had greater differences in growth parameters compared with NBW adolescents. The implication of advanced bone age must be assessed further. This study emphasizes the need for careful follow-up through the adolescent years of ELBW children. Further research on the effects of nutritional intervention is needed.

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