Growth Retardation Is Associated with Changes in the Stress Response System and Behavior in School-Aged Jamaican Children

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ABSTRACT In the developing world, 39% of children <5 y old are short for their age (stunted, defined as height-for-age less than –2 SD of National Center for Health Statistics references), and many have poor levels of mental development along with behavioral problems. We showed previously that 8- to 10-y-old children from a longitudinal cohort who experienced early childhood stunting had altered hypothalamic-pituitary-adrenocortical (HPA) and sympathetic-adrenomedullary (SAM) system activity. We repeated the study with 31 newly recruited, stunted Jamaican school children (less than –2.0 SD height-for-age) and 31 nonstunted controls (P < 0.05). Children were matched for sex, age, and school. All children were tested in a 1.5-h session, including psychological and physiologic stressors, in which their behaviors, salivary cortisol concentrations and heart rates were measured. In addition, we measured urinary catecholamine (epinephrine, norepinephrine, dopamine) concentrations, which were not reported for the children in the longitudinal cohort. After controlling for covariates that differed between groups (child intelligence quotient, body mass index and birth weight), stunted children had faster resting heart rates while lying and sitting (P < 0.05) and also during psychological testing (P < 0.05), as well as higher concentrations of urinary epinephrine (P < 0.05) and norepinephrine (P < 0.05), compared with nonstunted children. In addition, the stunted children were less happy (P < 0.01), more inhibited (P < 0.01) and more frustrated (P < 0.05) during the psychological tests than nonstunted children. These results suggest that growth retardation is associated with alterations in stress-sensitive systems, particularly the SAM system, and that this connection may contribute to the poor levels of development observed in stunted children. J. Nutr. 132: 3674–3679, 2002.

KEY WORDS: • stunting • linear growth retardation • stress sensitive systems • malnutrition
• school age children

In the developing world, 39% of children <5 y old are short for their age (stunted, less than –2 SD of the National Center for Health Statistics references) (1), and stunting is usually associated with delayed mental and behavioral development (2,3). Although the associations between growth retardation and poor developmental outcomes are familiar, the mechanisms that produce these connections are still not fully understood. There is considerable evidence in the animal literature that early conditions of adversity shape reactivity and regulation of stress-sensitive systems and influence later outcomes (4), and that early undernutrition may be a contributing factor (5). Changes in how the body deals with stress, in turn, may then increase vulnerability to a wide range of health and behavioral problems.

When the brain perceives a stressor, two major pathways are activated (6) as follows: 1) the hypothalamic-pituitary-adrenal (HPA) axis, a hormone system that produces cortisol; and 2) the sympathetic-adrenomedullary (SAM) system, a system producing catecholamines [epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine], which have strong effects on heart rate. In the short term, these systems recruit attention (vigilance to threat), metabolic resources and modify neural activity to promote immediate survival needs.

Initial input to the hypothalamus induces secretion of corticotropin-releasing hormone (CRH), which eventually stimulates adrenocorticotropic hormone, and then cortisol a few minutes later. After exposure to a stressor, it typically takes 20–30 min for cortisol levels to reach their peak, and it may take several hours for the cortisol to be cleared from the plasma (7). Cortisol rises (in response to CRH release) in situations associated with physical or mental exertion, novelty or uncertainty, social conflict, negative emotions and feelings of threat or loss of control (8), and can be measured in plasma, urine and saliva. Even short-term exposure to high cortisol levels, however, appears to impede declarative memory, most likely mediated by effects on the hippocampus and parahip-
pocampal regions of the brain (9). Similar negative effects on sustained attention have also been noted (10). More prolonged exposure to elevated levels of cortisol and other glucocorticoids promotes negative affect, depression and problems with reasoning and attentional systems (11).

The SAM system produces catecholamines [epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine], which play a variety of roles in the body, and are primarily signaling molecules. Epinephrine is produced by the adrenal medulla and influences metabolic processes such as carbohydrate metabolism, whereas norepinephrine is produced by the postganglionic sympathetic nerves and affects the vascular system (heart rate) (12). Brief psychological stressors have been shown to increase heart rate and plasma catecholamine (epinephrine and norepinephrine) concentrations, and result in increased vigilance, arousal and anxiety (13). It has been determined that exaggerated psychophysiological responses to behavioral challenges are risk factors for cardiovascular disease (14–17), and some investigators have suggested that recurring and excessive cardiovascular responses during periods of stress can lead to the development of a high blood pressure (18,19).

We previously reported (20) that Jamaican children who were stunted in early childhood and participated in a longitudinal study of growth and development (21) had higher cortisol levels and heart rates than nonstunted children at 8–10 y of age. We now report the findings from a second study of newly recruited stunted and nonstunted children, 8–10 y of age in schools in poor areas of Kingston, Jamaica. The objectives of this study were to compare the stunted and nonstunted groups in their response to a series of psychological and physiologic stressors in measures of salivary cortisol levels, heart rate, urinary catecholamine (epinephrine, norepinephrine, dopamine) concentrations and behavior. A further objective was to compare the findings from the present study with those from the previous study.

SUBJECTS AND METHODS

Subjects and anthropometry. All children aged 102–120 mo in grades 2, 3 and 4 from the fifteen government schools in downtown Kingston were measured using a portable stadiometer and standard anthropometric techniques (22). All stunted children (n = 31, less than −2.0 SD height/age) were identified, and then matched individually to nonstunted children (n = 31, more than −1.0 SD height/age) of the same age (±4 mo) and sex, and in the same class (23). The reported prevalence of stunting in Jamaica, based on data from 1995 to 2000, is 6% of children 0–5 y old (1). As a proportion of children screened (n = ~350) the prevalence of stunting was ~8%. The children came from very poor homes and it is likely that most of them were short secondary to undernutrition. However, a few would have been short due to their genetic potential. Age was obtained from teachers’ records. If there was no child in the same class as the index child who was the same sex and age as the index child, then a child in the grade below was selected. Children in Jamaican schools are organized into “streams” or classes according to their ability from A (high level of academic achievement) to E (low level of academic achievement). To avoid biasing the control group to include higher achieving children, we matched by stream when two children of different grade levels were compared. This study was conducted with the approval of the Human Subjects Review Board of the University of the West Indies; written, informed consent was obtained from parents, and verbal assent was obtained from children before their participation.

Test session. Children were collected from school and brought to the Tropical Metabolism Research Unit of the University of the West Indies for testing (~25 min by car). Testing began between 0830 and 1330 h, and there were no significant differences between groups for timing of testing. Because the test session was identical to that used previously and has been described in detail (20), only a brief description will be given here. The session lasted ~1.5 h, and included three testing baseline periods (lying and sitting before psychological testing, lying after testing) during which heart rate was measured. Heart rate was also measured while the child moved from lying to sitting. The psychological test session included an interview with an unfamiliar adult who asked 12 standardized questions; this was followed by three cognitive tests, mental arithmetic, a paired-associate memory test and a test for fine motor skills (pegboard). After these tests were two frustrating tasks including threading clogged beads and drawing a circle with an extremely difficult apparatus (Etch a Sketch: Ohio Art Company, Byran, OH). The session finished with an isometric hand grip test. Immediately before the first measurement of baseline heart rate (lying), all children were given 250 mL of a chocolate drink containing 958 kJ (229 kcal), 13 g protein, 6 g fat and 34 g carbohydrate to ensure that they were not hungry during testing, and to equalize potential postprandial effects. During the test session, three samples of salivary cortisol and two urine samples were obtained. Heart rate was recorded throughout the session. Care was taken to ensure that no child was obviously distressed by the testing procedure. The testing environment was highly standardized. The children were tested in the same room by one of two unfamiliar female testers who were unaware of the children’s group. The large age range of the children involved in the study masked any obvious height differences among children. The only difference in testing experience among subjects was that some were tested immediately upon arrival and others had to wait for ~1 h before testing. However, equal numbers from both groups were tested first and second, which minimized the effects of order. The two testers tested equal numbers from each group, and there were no significant differences between the testers in any outcome measures.

Behavioral ratings. Behaviors were rated twice during the interview on 5-point rating scales and included the following: responsive vocalizations (1 = no response, 5 = 5 or more long sentences), affect (1 = clearly unhappy most of the time (furrowed brow or grimacing), 5 = clearly happy most of the time (smiling, grinning or laughing)), inhibition (1 = visibly withdrawn most of the time (limited eye contact with tester, uncomfortable), 5 = very outgoing most of the time (much eye contact with tester, clearly comfortable)), and movement (1 = fidgeting or movement 0–25% of time (fiddling with clothes or face, pulling hair, touching face, sucking fingers, shuffling feet, chewing on pencil), 5 = lots of fidgeting, 75–100% of time). Behaviors were also rated once during each frustrating task and included affect and movement, which were the same as in the initial interview, and frustration (1 = no signs of frustration (looking up at tester, grimacing, sighing or shrugging) 5 = many signs of frustration, >75% of time)), attention (1 = engaged in task very little of the time (easily distracted, looks up at any provocation), 5 = intensely engaged most of the time (absorbed, concentrating)), and spontaneous vocalizations (number made). All behavior ratings were developed during extensive pilot testing, and interobserver reliabilities were high before and during the study for all measures (mean Cohen’s κ, 0.94; range, 0.80–1.00). The ratings have been used previously (20), and correlated among themselves in a theoretically sensible way.

Cortisol. Cortisol concentration was assessed because it is a well-established measure of short-term psychological stress and is one of the critical outputs of the HPA axis (24). Salivary cortisol accurately reflects unbound free (and therefore active) hormone levels (25) and has been shown to be a better measure of HPA function than plasma measurements (26). Salivary cortisol levels are unaffected by salivary flow rate (27).

Three saliva samples of ~0.5 mL each were obtained from each child. The first sample was a baseline measure and was taken as soon as the child arrived at the University for testing. The second sample was linked to the first part of the psychological test session, and the third to 20 min after the psychological testing finished, based on an approximate time delay between cortisol secretion and resulting salivary levels (28). Saliva samples were collected in tubes designed specifically for saliva (Salivettes, Sarstedt, Newton, NC), briefly centrifuged (1000 × g, 2 min, 20°C), transferred to cryovials and frozen at −80°C. The cortisol samples were assayed using a modified 125I RIA kit (“Magic Cortisol,” Ciba-Corning, Medfield, MA) (29) in a laboratory at Stanford University regularly using this assay. The
intra-assay CV (±SD) of duplicate samples was 3.1 ± 2.1% and the interassay CV (±SD) of a standard saliva pool was 5.6 ± 3.9% (n = 7). To control for the known diurnal rhythm in cortisol levels in the study design, time of testing was balanced across children from all groups.

**Catecholamines and heart rate.** The catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) were assessed in urine samples using a development enzyme-linked immunosorbent assay (ELISA). Samples were obtained from each child; the first, which was not assayed, was obtained before the psychological testing to void the child’s bladder. The second, which was assayed, was obtained at the end of the entire test session and represented cumulative excretion of catecholamines throughout the entire 1.5 h of testing. According to standard procedure, the samples were acidified within 1–2 h of testing with 6 mol/L NaCl to a pH of 2, and then stored at −80°C (12). Samples were then assayed according to a standard method of ion-pair reversed-phase HPLC (30). Results were corrected for the recovery of the internal standard as well as for the volume of urine produced.

Heart rate has traditionally been used to measure short-term reactivity of the autonomic nervous system, particularly in response to speech stressors such as mental arithmetic, in which responses include increased systolic and diastolic blood pressure, heart rate, T-wave amplitude and blood volume pulse. Although it is not a direct measure of the SAM system, heart rate is a valuable outcome measure because it can be monitored noninvasively, continuously and accurately throughout the testing session. We recorded heart rate with a chest band heart rate monitor (Polar Vantage XL, Polar CIC, Port Washington, NY) that has been used frequently to assess heart rate (31–33). Polar Vantage XL heart rate monitors are designed with a recording belt and a watch in which the information is stored. For this study, the watches were set to record average heart rates every 5 s, which is the most accurate setting possible. After each test, the data for each child were downloaded into a portable computer, with a commercially available computer interface device (Polar CIC). Mean heart rate was calculated for each test event (including 3 resting levels and each test) and for the periods between each event (total of 20 events); the value for “mean value for psychological stressors” was calculated.

**Socioeconomic variables.** Socioeconomic information was obtained from each child through a home interview with the child’s primary caretaker. The mothers or guardians of all children were visited at home, and details of maternal characteristics, including education, occupation, standard of housing and household possessions were recorded. The level of stimulation in the home was also assessed. Two interviewers were used to collect the data; both were unaware of the child’s group, trained by the same people and not involved with any other part of the study. To quantify socioeconomic status (SES), economic and stimulation indices that have been frequently used in Jamaica were created (20,34,35); these are associated with certain household items, e.g., television, refrigerator and radio. The stimulation index included the number of people per room, and the possession of certain household items, e.g., television, refrigerator and radio. The stimulation index included measurements of the number of books, writing materials, toys, games, trips out of the area and verbal interaction with parents.

Mothers and children were given the Peabody Picture Vocabulary Test (PPVT) (36) as a proxy for intelligence quotient (IQ). Socioeconomic information and maternal and child PPVT scores were available for 60 of 62 children. The missing values resulted from difficulties in locating the children’s homes. To avoid losing those children (n = 2) from the analyses, means from the appropriate subgroups for the final two ratings were used to replace the missing values. Birth weight was obtained through birth records from mothers or guardians. Birth weight was available for only 48 of 62 children (77%), due to missing family records.

**Data analysis.** Required sample sizes were calculated using data from the literature and were adequate to detect differences > 0.5 SD between experimental and control groups for the major outcome measures (cortisol, heart rate, catecholamines and behavior ratings) as statistically significant at the 0.05 level and with a power of 90%. The necessary sample size would be at least 60 in each group. However, we had to use a sample size that was smaller than ideal due to the limited number of stunted children living in downtown Kingston.

The data were first examined for normality and transformed where necessary; log transformations were used to normalize cortisol and epinephrine, and the transformed variables were used in all analyses. The characteristics of the two groups were compared [e.g., economic rating, stimulation rating, maternal IQ, subject IQ, body mass index (BMI)]. Bivariate correlations were then calculated between each dependent variable and all socioeconomic variables, height for age, BMI, birth weight, and maternal and child IQ with groups separate, and there were no significant associations among the variables. However, due to the differences between groups in subject IQ, BMI and birth weight, all analyses of group differences were calculated including child IQ and BMI as covariates. Because birth weight was available for only 48 of the 62 children and to preserve power, the analyses were repeated with birth weight as the only covariate. Birth weight has been shown to be quadratically related to cortisol levels in childhood (37); therefore, birth weight squared was used in the analyses. We examined differences between the stunted and nonstunted groups in behaviors, mean heart rates during the three baselines and psychological and physiologic stressors and urinary catecholamines using t tests, and then analyses of covariance (ANCOVA) to allow for the covariates. The assumptions of homogeneity of variance, normal distribution and parallel slopes for the covariance analyses were satisfied. We used repeated-measures ANCOVA to examine group differences over time in responsive vocalizations (12 measurements), salivary cortisol level (3 measurements) and heart rate (18 measurements) during the psychological stress session.

**RESULTS**

**Sample characteristics.** The groups did not differ in age, economic or stimulation indices, or maternal IQ (Table 1). The stunted children were significantly shorter than nonstunted controls, and had lower BMI, lower PPVT scores and lower birth weights than the nonstunted children.

**Behavioral measures.** Stunted children differed from nonstunted children in several of the observed behaviors (Table 2). In the interview, stunted children were more inhibited (P = 0.003) and less happy (P = 0.0001), and in the two frustrating tasks they were more frustrated (P = 0.002). All differences remained significant with the inclusion of child IQ and BMI, in which inhibition and happy affect (P < 0.01), frustration (P < 0.05). The inhibition and happy affect remained significant with the inclusion of birth weight. Frustration bordered on significance (P = 0.07) with the inclusion of birth weight. The loss of significance was likely a result of the substantial loss of power due to the small number of children who had birth weight data. None of the three covariates was significant associations among the

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Characteristics of the stunted and nonstunted children¹,²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stunted</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>Height for age, z-score</td>
<td>−2.3 ± 0.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>14.9 ± 1.3</td>
</tr>
<tr>
<td>Economic index</td>
<td>0.4 ± 1.4</td>
</tr>
<tr>
<td>Stimulation index</td>
<td>6.5 ± 2.5</td>
</tr>
<tr>
<td>Subject PPVT, raw score</td>
<td>49.5 ± 11.0</td>
</tr>
<tr>
<td>Maternal PPVT, raw score</td>
<td>85.3 ± 25.0</td>
</tr>
</tbody>
</table>

¹ Values are means ± SD, n = 31 except for birthweight where n = 25 stunted, n = 23 non-stunted and maternal Peabody Picture Vocabulary Test (PPVT), where n = 31 stunted, n = 29 nonstunted.  
² Different from the stunted group, P < 0.05.

* P values were calculated by the Pearson chi-square test for sex, and by the two-sample Student’s t test for all other variables.
in any of the analyses. During the interview, stunted children tended (\(P = 0.08\)) to talk less (“vocalization”) than the nonstunted children. In the frustrating tasks, stunted children had a tendency to be less happy (\(P = 0.08\)) than nonstunted children, they tended (\(P = 0.08\)) to use fewer strategies when trying to figure out how to thread the beads and they tended (\(P = 0.06\)) to be less persistent (fewer restarts) when trying to draw a circle on the Etch-A-Sketch.

**Salivary cortisol.** Stunted children did not differ from nonstunted children in their salivary cortisol concentrations (Table 3), compared using repeated-measures ANCOVA over the three time points (group effect, \(P = 0.19\); test effect, \(P < 0.0001\)). Cortisol concentrations declined over the test period in stunted children, and peaked at the mid-test point for the nonstunted children, suggesting that the groups may have differed in their reactivity. However, the interaction between group and test was not significant. In a regression predicting the mid-test point from baseline and group, group was not significant. There were no significant correlations between cortisol levels and interview vocalizations or any other behaviors.

**Heart rate.** Stunted children had faster heart rates than nonstunted children at every point in the testing sequence, and both groups had very similar overall response patterns of heart rate change over time. Stunted children had faster initial resting lying (\(P = 0.005\)) and sitting (\(P = 0.04\)) heart rates than nonstunted children (Table 4). The differences for the lying resting levels remained significant with the inclusion of child IQ and BMI as covariates (\(P = 0.007\)), and with the inclusion of birth weight (\(P = 0.03\)). The difference at sitting resting levels also remained significant with inclusion of the covariates (\(P = 0.03\)) and birth weight (\(P = 0.05\)). The stunted group had faster heart rates during the psychological tests using repeated-measures ANCOVA (\(P = 0.05\)) and tended (\(P = 0.06\)) to have faster final lying resting rates. No cardiovascular response to the isometric hand grip or to postural change was evident in either group.

**Urinary catecholamines.** Stunted children had higher concentrations of urinary epinephrine (\(P = 0.009\)) and norepinephrine (\(P = 0.02\)) than nonstunted children (Table 5). Dopamine levels did not differ. After inclusion of child IQ or birth weight into the analysis, the differences remained significant for epinephrine and norepinephrine.

## DISCUSSION

**Behavior, salivary cortisol, heart rate and urinary catecholamines.** We showed that Jamaican children who had experienced childhood growth retardation had faster heart rates, and higher urinary epinephrine and norepinephrine concentrations than school-, sex- and age-matched controls during a test session of psychological and physiologic stressors. The stunted children were also more inhibited, more easily frustrated and less happy than the nonstunted children. These findings replicate most of our previously reported findings from a longitudinal cohort of stunted and nonstunted children, in which stunted children also showed higher heart rates and thyroid hormones.

### TABLE 2

**Behavioral observations of the stunted and nonstunted children (on a scale of 1 to 5) during psychological testing**

<table>
<thead>
<tr>
<th>Measure of Persistence</th>
<th>Stunted</th>
<th>Nonstunted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Values are median (interquartile range), (n = 31). * Different from the stunted group, (P &lt; 0.05). **</td>
<td>3.5 (2.0)</td>
<td>4.5 (2.1)</td>
</tr>
<tr>
<td>Happy affect rating3</td>
<td>3.6 (1.1)</td>
<td>4.0 (0.9)</td>
</tr>
<tr>
<td>Frustration</td>
<td>3.8 (1.0)</td>
<td>2.9 (1.2)*</td>
</tr>
<tr>
<td>Attention</td>
<td>3.6 (1.1)</td>
<td>4.0 (0.9)</td>
</tr>
<tr>
<td>Nonstunted</td>
<td>3.4 (0.9)</td>
<td>3.1 (1.2)*</td>
</tr>
<tr>
<td>Frustrating tasks</td>
<td>2.6 (1.1)</td>
<td>3.5 (0.7)*</td>
</tr>
</tbody>
</table>

**TABLE 3**

**Salivary cortisol concentrations in stunted and nonstunted children before, during and after psychological testing**

<table>
<thead>
<tr>
<th>Time</th>
<th>Stunted</th>
<th>Nonstunted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.55 (8.83)</td>
<td>7.73 (4.97)</td>
</tr>
<tr>
<td>Mid-test</td>
<td>8.28 (5.79)</td>
<td>9.38 (3.59)</td>
</tr>
<tr>
<td>Post-test</td>
<td>6.07 (5.52)</td>
<td>5.72 (4.41)</td>
</tr>
</tbody>
</table>

**TABLE 4**

**Heart rates of stunted and nonstunted children during a psychological testing sequence**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Stunted</th>
<th>Nonstunted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting (lying)</td>
<td>90.8 ± 10.8</td>
<td>83.4 ± 8.8*</td>
</tr>
<tr>
<td>Physiologic stressor (postural change)</td>
<td>97.5 ± 10.4</td>
<td>93.1 ± 8.5</td>
</tr>
<tr>
<td>Resting (sitting)</td>
<td>94.7 ± 10.6</td>
<td>89.3 ± 9.6*</td>
</tr>
<tr>
<td>Psychological stressors</td>
<td>98.0 ± 9.1</td>
<td>92.1 ± 8.9*</td>
</tr>
<tr>
<td>Resting (lyying)</td>
<td>88.0 ± 12.6</td>
<td>82.7 ± 8.1</td>
</tr>
</tbody>
</table>

**TABLE 5**

**Urinary catecholamines in stunted and nonstunted children during psychological testing**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Stunted</th>
<th>Nonstunted</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Dopamine, (\mu)mol/mmol creatinine</td>
<td>0.425 ± 0.119</td>
<td>0.412 ± 0.377</td>
</tr>
<tr>
<td>Epinephrine, (\mu)mol/mmol creatinine</td>
<td>0.018 (0.01)</td>
<td>0.013 (0.007)*</td>
</tr>
<tr>
<td>Norepinephrine, (\mu)mol/mmol creatinine</td>
<td>0.029 ± 0.007</td>
<td>0.024 ± 0.007*</td>
</tr>
</tbody>
</table>

**1 Values are means ± SD for dopamine and norepinephrine, and median (interquartile range) for epinephrine. * Different from stunted group, \(P < 0.05\).**
altered behavior in response to the same test session (20). The children from the previous study also had significantly higher urinary epinephrine and norepinephrine (unpublished data). However, in the previous study (20) stunted children had higher salivary cortisol concentrations, a finding we were unable to replicate in the present study. Unfortunately, we were limited to a small sample size because of the limited numbers of available stunted children in downtown Kingston schools; thus, the sample sizes may have been too small to detect differences. However, given that the previous study had similarly small numbers, it may be relevant that salivary cortisol concentrations, urinary epinephrine concentrations and mean heart rates in both the stunted and nonstunted groups were all higher than in the previous study (20). These findings cannot be explained simply by techniques of analysis because cortisol and catecholamine analyses in both studies were conducted at the same time in the same laboratories. The findings also cannot be explained by methodological considerations because the testing procedures, time of day and testers were identical in both studies. Thus, this consistent finding suggests that a substantial “novelty” effect was evident in this newly recruited group of stunted and nonstunted children. In the previous study, all children had visited the University of the West Indies six different times between ages 1 and 8 years and may have become habituated to the experience of being picked up by a driver and transported to the University. Habituation to a stressor (such as being handled at a young age) has been shown to occur in both animals (38) and humans (39). It is possible that the difference in HPA activity between the groups may be apparent only with moderate and not severe stressors, as has been found in some animal models (40).

Effect of social background. There is usually a relationship between undernutrition and poor environmental conditions (41), and there is some evidence that the environment is associated with physiologic stress levels in children (42–44). In both nonhuman primates (45) and in human populations, (42,46) there appears to be a strong correlation between lower social status (either in terms of social hierarchy or in terms of SES) and physiologic outcome measures that reflect aberrant stress system activity. It is therefore possible that environmental factors could contribute to differences between the groups reported in these studies. However, stunted and nonstunted groups had very similar home backgrounds; they were matched for age, sex, and school, and their maternal IQ, economic and stimulation indices were not different. In fact, the stunted children actually had slightly higher values for the latter two indices. We included covariates that differed between the groups (child's BMI, IQ and birth weight) in the analyses, even though none was significantly related to any of the outcome measures. Most group differences, including resting level and response heart rates, urinary epinephrine, norepinephrine, and the inhibition and happy ratings remained significant after the inclusion of covariates. Thus, these findings suggest that the physiologic differences in stress-sensitive systems that we report here were linked directly to growth retardation. The changes to the stress systems may be associated with concurrent stunting, but because stunting usually occurs in the first 5 years of life (47), it is likely that the insult probably occurred in early childhood and persisted. Researchers have shown that there are differences in anthropometry and neuromuscular reaction time between children who are short and from areas of high SES (suggesting genetic shortness), and children who are the same height for age from areas of low SES (suggesting environmental factors) (48); stunted children from areas of low SES have shorter limbs, narrower shoulders, thinner skinfolds and poorer neuromuscular reaction time than the genetically short children. These findings suggest that there are several socioeconomic factors that could relate to the anthropometric and physiologic correlates of growth retardation, which could then independently contribute to outcomes.

Birth weight. Birth weight has been shown to be quadratically related to cortisol (37), and extensive literature addresses the relation between fetal experience and later outcomes (49). The stunted group in this study had slightly lower birth weights; however, birth weight had no significant effect on any outcome measure. Furthermore, most associations between stunting and the outcomes remained significant after controlling for birth weight. Thus, in this population, we can assume that the significant relationship between stunting and the outcome measures was due mainly to postnatal growth. In a recent study, cortisol levels were shown to be inversely related to birth weight and birth length in children who had experienced intrauterine growth retardation (IUGR) (50). The authors concluded that IUGR children might be affected by intrauterine reprogramming of hypothalamic-pituitary-adrenal axis, which could then result in a permanent modification of the neuroendocrine response to stress. Thus, children with increased cortisol secretion may be at higher risk of growth failure. Future work should address the issue of pre- and postnatal growth retardation, thus allowing better differentiation and thereby disentanglement of the specific consequences of stunting during various phases of life.

Mechanisms and implications. It is becoming increasingly apparent that in humans and higher primates, both activation and negative feedback regulation of the HPA and SAM systems are heavily associated with regions in the prefrontal cortex that are involved in attention and emotion regulation (51). These regions are rich in receptors for cortisol and have a protracted period of development in humans, i.e., they are not fully mature until near the end of adolescence. Although not well understood, disturbances in stress system function during development are likely to alter the development of prefrontal circuits involved in emotion regulation and executive functions such as working memory, control of attention and inhibition of behavior. In children, both shy, anxious, internalizing behavior and underregulated, reckless, externalizing behavior patterns have been associated with increased stress-reactivity and poorer stress system regulation (52). Disordered stress system functioning has been noted for animals that are extremely fearful of novel situations and highly reactive to stressors such as restraint (53). Rats that were undernourished as pups and then rehabilitated showed increased emotionality and increased response to stressors (54), suggesting that protein-energy malnutrition may be a factor resulting in disordered stress response. Analogously, several studies including the present one have shown that undernourished children are inhibited or anxious (55), suggesting that these same mechanisms may be operating in humans. Given the small sample sizes reported in this study, we cannot make strong claims about the mechanisms at work here, and further work is clearly necessary to understand the complexities of these mechanisms.

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LITERATURE CITED


