MONOGRAPHS OF THE SOCIETY FOR RESEARCH IN CHILD DEVELOPMENT

IV. GROWTH FAILURE IN INSTITUTIONALIZED CHILDREN

Dana E. Johnson and Megan R. Gunnar

Children within institutional care settings experience significant global growth suppression, which is more profound in children with a higher baseline risk of growth impairment (e.g., low birth weight [LBW] infants and children exposed to alcohol in utero). Nutritional insufficiencies as well as suppression of the growth hormone–insulin-like growth factor axis (GH-IGF-1) caused by social deprivation likely both contribute to the etiology of psychosocial growth failure within these settings. Their relative importance and the consequent clinical presentations probably relate to the age of the child. While catch-up growth in height and weight are rapid when children are placed in a more nurturing environment, many factors, particularly early progression through puberty, compromise final height. Potential for growth recovery is greatest in younger children and within more nurturing environments where catch-up in height and weight is positively correlated with caregiver sensitivity and positive regard. Growth recovery has wider implications for child well-being than size alone, because catch-up in height is a positive predictor of cognitive recovery as well. Even with growth recovery, persistent abnormalities of the hypothalamic-pituitary-adrenal system or the exacerbation of micronutrient deficiencies associated with robust catch-up growth during critical periods of development could potentially influence or be responsible for the cognitive, behavioral, and emotional sequelae of early childhood deprivation. Findings in growth-restricted infants and those children with psychosocial growth are similar, suggesting that children experiencing growth restriction within institutional settings may also share the risk of developing the metabolic syndrome in adulthood (obesity, Type 2 diabetes mellitus, hypertension, heart disease). Psychosocial deprivation within any caregiving environment during early life must be viewed with as much concern as any severely debilitating childhood disease.

A syndrome of poor growth in socially deprived children has been recognized since the eponymous Kasper Hauser was discovered stunted and developmentally delayed at the Haller Gate of the city of Nuremberg on the morning of May 26, 1828. At the time of his abandonment at 16 years of age,

MRG was supported by grants from the U.S. National Institute of Mental Health: 080905, 078105, and 079513.

Corresponding author: Dana E. Johnson, UMMC, Fairview, 2450 Riverside Ave., East Bldg. MB622, Minneapolis, MN 55454, email: johns008@umn.edu

his pubertal development was delayed and he was only 145 cm (4 ft, 9 inches) tall. Profoundly impaired in all developmental areas and exhibiting a number of extremely odd behavioral and emotional characteristics, he eventually conveyed that he had spent most of his life on a diet of bread and water, living in a tiny "cage" 6- to 7-ft long, 4-ft wide, and 5-ft tall, virtually devoid of light, with a dirt floor, a straw bed, a woolen blanket, and a bucket in which to relieve himself (Money, 1992). During the late 19th and first half of the 20th century, psychosocial growth failure evolved from a curiosity to a well-recognized syndrome associated with neglect/abuse in both institutional and family settings (Blizzard & Bulatovic, 1996; Chapin, 1908, 1915; English, 1984; Gardner, 1972; Money, Annecillo, & Kelley, 1983; Spitz, 1945, 1946). As growth is arguably the key parameter for assessing health and well-being in children, the appalling global suppression of normal physical development was a harbinger of the pervasive developmental and medical problems documented in institutionalized children during the past 60 years (Beckett et al., 2002, 2007; Bruce, Tarullo, & Gunnar, 2009; Castle et al., 1999; Cermak & Daunhauer, 1997; Colvert et al., 2008; Croft et al., 2007; Geoffroy et al., 2007; Gunnar & Van Dulmen, 2007; Johnson, 2000; Kreppner et al., 2007; Marshall, Reeb, Fox, Nelson, & Zeanah, 2008; Nelson, 2007; Nelson, Furtado, Fox, & Zeanah, 2009; Nelson et al., 2007; O'Connor & Rutter, 2000; O'Connor, Rutter, Beckett, Keaveney, & Kreppner, 2000; Roy & Rutter, 2006; Rutter, 1998, 2008; Rutter, Colvert et al., 2007; Rutter & O'Connor, 2004; Rutter, Kreppner, & O'Connor, 2001; Sonuga-Barke et al., 2008; Stevens et al., 2008; Windsor, Glaze, & Koga, 2007; Zeanah et al., 2009; Zeanah, Smyke, Koga, & Carlson, 2005).

Contemporary work in this field can be traced to the descriptive report of Talbot and Sobel in 1947, who described patients with short stature they believed was caused by emotional disturbances (Talbot, Sobel, Burk, Lindemann, & Kaufman, 1947). For these 21 children who failed to grow and had poor appetites, psychiatric workup revealed a variety of diagnoses including chronic bereavement, maternal psychopathology, chronic poverty, and parental rejection. In three cases, psychiatric intervention led to improvement in appetite and enhanced growth.

Perhaps the most convincing early demonstration of how an adverse emotional environment affects growth took place after World War II in Germany, when British nutritionist Elsie Widdowson studied 50 children between the ages of 4 and 14 years in two small municipal orphanages within the British Zone of Occupation (Widdowson, 1951). A young, cheerful woman who was fond of children cared for one group of children and an older, stern woman who was a strict disciplinarian to all children except for a small group of favorites cared for the second group. During the first 6 months of observation, the children cared for by the younger woman gained weight and height far better than those in the orphanage governed by the strict matron, with the exception of her favorites who did quite well. During the second 6

TABLE 3

Classification of Types and Subtypes of Psychosocial Short Stature

Classification	Type I: Infantile	Type IIa: Hyperphagic Short Stature	Type IIb: Nonhyperphagic Short Stature	Type III: Anorexic
Age	Infancy	≥3 years	≥3 years	Infancy or later
Failure to thrive	Yes	Variable	Variable	Not usual
Bizarre behaviors (see Table 6)	No	Usual (particularly hyperphagia)	Variable	No
Depression	Yes	Yes	Yes	Yes
Growth hormone secretion	Normal	Decreased	Variable	Normal
Growth hormone responsiveness	Unknown	Variable	Variable	Variable

months, arrangements were made to provide additional rations to one of the orphanages and, concurrent with the improvement in daily calories, the caretakers shifted as well. During the second 6 months, despite receiving additional calories, the children in the orphanage managed by the stern matron grew poorly. Her favorites, who accompanied her to the other institution, again were the exceptions and gained weight and height better than either of the other two groups in the study. The children previously cared for by the strict matron and now cared for by the cheerful woman during the second 6 months rapidly gained weight and height despite no increase in calories.

These early observations of growth failure in children raised under adverse conditions spawned a considerable body of literature during the ensuing decades categorizing three types (I, II, and III) and two subtypes (IIa and IIb) of growth failure (Table 3) based on age of onset, growth hormone (GH) kinetics/response, and behaviors exhibited by affected children (Blizzard & Bulatovic, 1996; Gardner, 1972; Gohlke, Frazer, & Stanhope, 2002; Gohlke, Khadilkar, Skuse, & Stanhope, 1998; Skuse, Albanese, Stanhope, Gilmour, & Voss, 1996). More than a dozen terms have been utilized (Table 4) in the pediatric endocrinology literature, but since the clinical presentation includes proportional short stature in most cases, psychosocial short stature emerged as the name most commonly used in recent years. However, although short stature may be a meaningful nomenclature for many children in the clinical literature, it does not seem appropriate for institutionalized children, because, in addition to short stature, these children frequently exhibit growth failure in weight and head circumference. Thus, a more inclusive term, *psychosocial growth failure* will be utilized in this report. Likewise, the term catch-up growth will refer not only to length/stature but weight and head circumference as well.

TABLE 4

Synonyms for Psychosocial Growth Failure

Abuse dwarfism
Deprivation dwarfism
Deprivation syndrome dwarfism
Emotional deprivation
Nonorganic failure to thrive
Psychosocial deprivation dwarfism
Psychosocial dwarfism
Psychosomatic dwarfism
Psychosocial short stature
Reversible hyposomatotrophism
Reversible somatotropin deficiency
The "garbage can" syndrome
Transient hypopituitarism

GROWTH DURING AND AFTER INSTITUTIONAL CARE

Growth Suppression

A high incidence of growth failure in institutionalized children is a universal finding with every cohort reported to date showing moderate to severe suppression of height, weight, and head circumference (Johnson et al., 2010; Miller et al., 2009; Rutter, 1998; Smyke et al., 2007; The St. Petersburg-USA Orphanage Research Team, 2005; Van Ijzendoorn, Bakermans-Kranenburg, & Juffer, 2007). An exhaustive meta-analysis of 122 study outcomes in 33 papers on children placed for international adoption, most of whom had been institutionalized, documented large growth lags in all three parameters at the time of placement (Van IJzendoorn et al., 2007). These findings were similar though quantitatively greater than the degree of growth suppression observed in children removed from their families due to neglect or abuse in Western Europe and the United States (King & Taitz, 1985; Olivan, 2003; Pears & Fisher, 2005; Wyatt, Simms, & Horwitz, 1997).

The desire of parents to adopt as young a child as possible has skewed the mean age of children generally included in growth studies of postinstitutionalized adoptees toward infancy and early childhood (6–44 months; Van IJzendoorn et al., 2007). Only one study examined the effects of lifelong institutionalization into late childhood and adolescence (Himes et al., 2008). Growth data were collected between 1997 and 2001 in 255 children (5.00–18.99 years) housed in six Romanian neuropsychiatric institutions. All children had been institutionalized since birth under extreme circumstances of psychosocial deprivation. These children showed profound retardation in height, weight, and head circumference, with median *z* scores for height and weight ranging between −5.00 and −3.00 across the age range.

Two recent studies have expanded our knowledge of the biologic and environmental factors contributing to psychosocial growth failure and recovery in infancy and early childhood. The Bucharest Early Intervention Project (BEIP), the first randomized controlled study of foster versus institutional care, offered a unique opportunity to study growth in 124 otherwise healthy institutionalized (63 males) and 72 never institutionalized (31 males) Romanian children (Ghera et al., 2009; Johnson et al., 2010; Marshall & Fox, 2004; Marshall et al., 2008; Moulson, Fox, Zeanah, & Nelson, 2009; Nelson, 2007; Nelson, Parker, & Guthrie, 2006; Nelson et al., 2007; Parker & Nelson, 2005a, 2005b; Smyke et al., 2007; Windsor et al., 2007; Zeanah et al., 2003; Zeanah et al., 2005). These subjects, first assessed at 21 months (range 5.4–32 months), had measures of growth, caregiving environment, and cognitive development assessed before and at intervals following randomization of those to foster care versus institutional care as usual (Johnson et al., 2010). The Eastern European Growth Study (EEGS) followed a convenience sample of 138 children adopted at an average age of 20.4 months (range 7.3–58.9) who were first evaluated at an average of 17 days (range 5–37) after arrival in the United States. These subjects had measures of growth, dietary intake, and serum growth factors at intervals throughout the first 6 months in their adoptive homes (Miller et al., 2009). In both studies, gestational age was either not available or deemed unreliable. Therefore, it was impossible to say whether children were appropriate- or small-for-gestational age (SGA).

In BEIP and EEGS, baseline measures were significantly smaller and *z* scores <-2.00 more frequent in institutionalized versus noninstitutionalized children. In multiple regression models, significant independent predictors of lower height *z* scores in BEIP and EEGS included increasing age and lower birth weight (<2,500 g; Table 5). Low birth weight (LBW) also independently predicted lower weight and head circumference in both studies. Children with probable prenatal alcohol exposure, a category with a significantly lower mean birth weight, was an independent predictor of lower height *z* scores and approached significance as an independent predictor of head circumference in EEGS.

Catch-Up Growth

Most children with psychosocial short stature have an immediate and dramatic surge in growth when removed from their hostile environment. This pathonomonic finding has been observed in postinstitutionalized children within adoptive families (Van IJzendoorn et al., 2007), institutionalized children for which the orphanage caregiving environment has been improved (The St. Petersburg-USA Orphanage Research Team, 2008), and in children in European and American child welfare systems placed within foster homes (King & Taitz, 1985; Olivan, 2003; Wyatt et al., 1997). Meta-analysis of growth

TABLE 5

PREDICTORS OF *z* SCORES AT BASELINE AND Δ*z* SCORES AFTER ADOPTION OR FOSTER CARE INTERVENTION IN INSTITUTIONALIZED CHILDREN FROM THE BUCHAREST EARLY INTERVENTION STUDY (BEIP[1]) AND EASTERN EUROPEAN ADOPTION STUDY (EEGS[2]) USING MULTIPLE REGRESSION AND IN THE META-ANALYSIS OF GROWTH IN INTERNATIONAL ADOPTEES REPORTED BY VAN IJZENDOORN ET AL. (2007; META[3])

	Baseline Measures								
	Height *z* Score			Weight *z* Score			OFC *z* Score		
Predictors	BEIP	EEGS	META	BEIP	EEGS	META	BEIP	EEGS	META
Gender	*ns*	*ns*		*ns*	*ns*		*ns*	*ns*	
Birth weight	↑	↑		↑	↑		↑	↑	
High risk for fetal alcohol syndrome		↓						↓*	
Age[1,2] or duration institutionalization[3]	↓	↓	↓	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
Caregiving quality	*ns*			*ns*			*ns*		

	Catch-Up Growth					
	ΔHeight *z* Score		ΔWeight *z* Score		ΔOFC *z* Score	
Predictors	BEIP	META	BEIP	META	BEIP	META
Gender	*ns*		*ns*		*ns*	
Low birth weight	*ns*		*ns*		*ns*	
Age < 12 months	↑	↑	↑	*ns**	↑	*ns*
Baseline *z* score	↓		↓		↓	
Postplacement caregiving quality	↑		↑		*ns*	

Note. —↑ = a positive and ↓ = a negative relationship between the dependent variable and the predictor ($p < .05$), *ns* = not significant.

*Trend for children ≤ 24 months to have more catch-up than children placed at >24 months.

after adoption revealed almost complete catch-up in height and weight during childhood but less robust improvement in head size (Van IJzendoorn et al., 2007). Earlier arrival in the adoptive family (<12 months of age) was significantly related to more complete catch-up in height. Catch-up growth in weight was somewhat better prior to 24 months but the results were not statistically significant. Age effect on head size (occipital frontal circumference, OFC) could not be determined due to the small number of published studies reporting sequential OFC measurements following adoption (Table 5).

In BEIP, growth within the group of institutionalized children randomized to foster care was compared to those randomized to ongoing institutional care as usual (Johnson et al., 2010). When growth was plotted at 6-month intervals during the first 18 months following randomization, the foster care group showed rapid increases in height and weight *z* scores during the first

12 months while those in the institutional care-as-usual group showed no improvement. Catch-up growth ceased as height and weight *z* scores approached the normal population mean following which significant changes did not occur between 12 and 18 months postrandomization. By 12 months postrandomization, the percentage of the foster care group in the normal range (≥ -2) had improved from 91% to 100% for height, 75% to 90% for weight, and 84% to 94% for weight-for-height. Multiple regression models accounted for significant variance in improvements in *z* for height, weight, and OFC. Significant unique predictors of greater improvement for all three included lower baseline *z* scores and younger age (<12 months) at randomization (Table 5). Neither gender nor LBW influenced catch-up growth. While LBW infants remained somewhat smaller at 42 months of age in BEIP, the difference was only significant for OFC.

Growth and Environment

BEIP is the only study that has been able to correlate growth in children living under adverse social circumstances with standardized measures of the caregiving environments. The Observational Record of the Caregiving Environment (NICHD Early Child Care Research Network, 1996) was adapted and used to assess caregiver-child interactions in both institutions and foster families (Smyke et al., 2007). The caregiving quality scores (CQS; range 1–4) were obtained by averaging five qualitative scores (i.e., detachment [reversed], flat affect [reversed], positive regard for child, sensitivity, and stimulation of development), each of which received a rating from 1 (*not at all characteristic*) to 4 (*highly characteristic*). CQS were significantly lower at baseline in the institutionalized versus noninstitutionalized group and were lowest for the youngest ages.

Two previous studies using parent perceptions of their child's preadoption caregiving environment confirmed lower height in children experiencing parent-reported deprivation. Whereas one study showed a dose-dependent relationship between deprivation and lower linear growth at adoption (Kertes, Gunnar, Madsen, & Long, 2008), the other failed to confirm that finding (Johnson & Adoption Project Team, 2006). Within the range measured within the institutional environments in BEIP, caregiving quality was not a significant independent predictor of baseline growth; however, this may only indicate that even the best caregiving observed was below the threshold needed to support normal growth (Table 5).

Although growth clearly improves after children are removed from an adverse environment, whether variations in the improved caregiving environment affect catch-up growth, has never been directly explored. Previous work has indirectly addressed this issue. Taitz and King (1988) found that children

removed and placed in long-term foster care versus ongoing monitoring in their original home had the most marked improvement in height with 55% of these children increasing by more than 1.00 *z* score versus only 11% of those with ongoing exposure to their initial environment. Gohlke and colleagues found that 29 of 30 patients (97%) with psychosocial short stature treated with a long-term change in environment increased their height velocity versus 14 of 30 (47%) treated with social service intervention in their original home (Gohlke, Frazer, & Stanhope, 2004).

The hypothesis that catch-up growth is directly related to a child's individual caregiving environment was tested in BEIP (Johnson et al., 2010). Following randomization, CQS in the foster care group improved substantially and did not differ significantly from the noninstitutionalized group. Individual CQS in the foster care group were positively related to change in height and weight but not head circumference *z* scores from baseline to 42 months of age. Components of CQS that correlated positively with catch-up in height and weight included sensitivity and positive regard for the child but not stimulation of cognitive development. Caregiver detachment was negatively correlated with height catch-up.

Catch-Up Growth and Cognitive Outcome

Based on reports of improved stature correlating with cognitive gains in stunted, cognitively impaired children treated with exogenous GH, the relationship between catch-up growth and cognition was investigated in BEIP (Johnson et al., 2010). Baseline developmental quotient, birth weight, and height catch-up were significant independent predictors of cognitive abilities at follow-up. Each incremental increase of 1.00 in standardized height scores between baseline and 42 months was associated with a mean increase of 12.6 points in verbal IQ.

Summary

Children within institutional care settings experience significant global growth suppression, which is more profound in individuals with a higher baseline risk of postnatal growth impairment (e.g., LBW infants and children exposed to alcohol in utero). Catch-up growth in height and weight are rapid when children are placed in a more nurturing environment. Potential for growth recovery is greater in children who are the most growth impaired, who are younger, and who are placed in more nurturing environments. Catch-up growth in height is an independent predictor of cognitive recovery.

MECHANISM INVOLVED IN GROWTH SUPPRESSION AND RECOVERY IN INSTITUTIONALIZED CHILDREN

Normal growth is a complex, multifactorial process dependent on adequate nutrition and appropriate production of endogenous growth factors. Both are likely to be affected by an institutional environment.

Malnutrition

Access to sufficient macro- and micronutrients to support growth is critically important and, worldwide, the most common cause of growth failure during childhood (Boersma & Wit, 1997). Nutritional demands will vary depending on growth rates at particular stages of development and whether preexisting deficits due to pre- or postnatal malnutrition exist. During the most rapid growth phase between birth and 18 months, the effects of even modest nutritional deficits become magnified particularly in LBW infants who are represented in disproportionately high numbers within institutional care settings (Johnson, 2000; Landgren et al., 2006; Miller et al., 2009; Smyke et al., 2007). With the time and fiscal constraints experienced by virtually all orphanages worldwide, it is highly unlikely that each child's unique nutritional needs can be individualized within an environment where dietary plans and feeding protocols are strictly regimented.

Children also need the ability, desire, and opportunity to consume a diet sufficient to permit normal growth. Children with disabilities make up a high percentage of orphanage residents and many have significant neuromotor problems (cerebral palsy) or orofacial malformations (cleft lip/palate) that interfere functionally or anatomically with a child's ability to eat (Johnson, 2000; Landgren et al., 2006; Rosenberg, Pajer, & Rancurello, 1992; The St. Petersburg-USA Orphanage Research Team, 2005). Many children are apathetic with no desire to eat. This phenomenon, part of a syndrome termed "hospitalism" by Spitz, was originally described in infants deprived of attention who showed evidence of anxiety, sadness, and retarded physical development. Mortality in these early descriptive studies was very high despite adequate food and meticulous care (Spitz, 1945, 1946).

Even when an appropriate diet is available and the child has the ability and desire to eat, they may lack the opportunity to consume adequate nutrition. In most institutions child-to-caregiver ratios are so high, it is difficult to adequately attend to even a child's most basic needs (Muhamedrahimov, 1999). This problem is particularly acute in infants and young toddlers who are completely incapable of assisting with their care. In these situations, caregiver actions are based on efficiency and expediency rather than being responsive to child-based cues. Bottles are propped on pillows or the time spent feeding a child is abbreviated simply due to the volume of work. Various techniques

used to decrease feeding times such as enlarging the hole in the tip of the nipple, rapidly shoveling food into a child's mouth while the child is prone, or the caregiver stands behind the child, can cause gagging, increasing the risk of oral aversion, which further complicates the feeding process (Cermak & Daunhauer, 1997).

Considering that institutionalized infants are highly vulnerable to insufficient intake, it is not surprising that subnutrition is felt to be the principal cause of deprivation-associated growth failure within this age group. Infants with this condition (Type I or the infantile form; Table 3) present with a generalized failure to thrive affecting all growth parameters, are described as depressed with a poor appetite, do not usually exhibit bizarre behaviors as is common in other types of deprivation-associated growth failure, and reportedly have normal GH secretion (Bakwin, 1949; Blizzard & Bulatovic, 1996; Rutter, 1981). A 30% incidence of wasting (weight-for-height *z* scores <-2.00) in institutionalized children below 12 months of age in BEIP appears to support the hypothesis that subnutrition is a major determinant in psychosocial growth failure at least in the youngest age group (Johnson et al., 2010). While nutrition remains important for children of all ages, outside of infancy and early childhood, there is less evidence that caloric deprivation is the primary factor in the etiology of psychosocial growth failure, because weight-for-height has generally been reported to be within the normal range (Blizzard & Bulatovic, 1996; Gohlke et al., 2002; Gohlke et al., 1998). Even in profoundly deprived Romanian children with markedly impaired growth in height and weight, body mass index (BMI) was generally in the low normal range (Himes et al., 2008).

Hypothalamic–Pituitary-End-Organ Suppression

Adequate substrate alone is insufficient for normal growth. Careful studies in the 1940s in hospitals and orphanages in New York by pioneers in this field, such as Harry Bakwin, Margaret Ribble, René Spitz, and Katherine Wolf, documented poor weight gain in institutionalized children receiving adequate calories (Bakwin, 1949; Gardner, 1972; Spitz, 1945, 1946). Production of a highly choreographed sequence of endocrine growth factors is required for optimal growth from fetal life through adolescence. While thyroxin, androgens, estrogens, and glucocorticoids all play important roles at various points in development, components of the growth hormone–insulin-like growth factor axis (GH-IGF-1) are requisite for optimal linear growth from fetal life through adolescence (Rosenfeld, 2003) and have been the subject of intense investigation over the past four decades in regard to psychosocial growth failure.

A full description of the role of the GH-IGF-1 axis in growth promotion is outside the scope of this discussion; however, basic information is helpful in

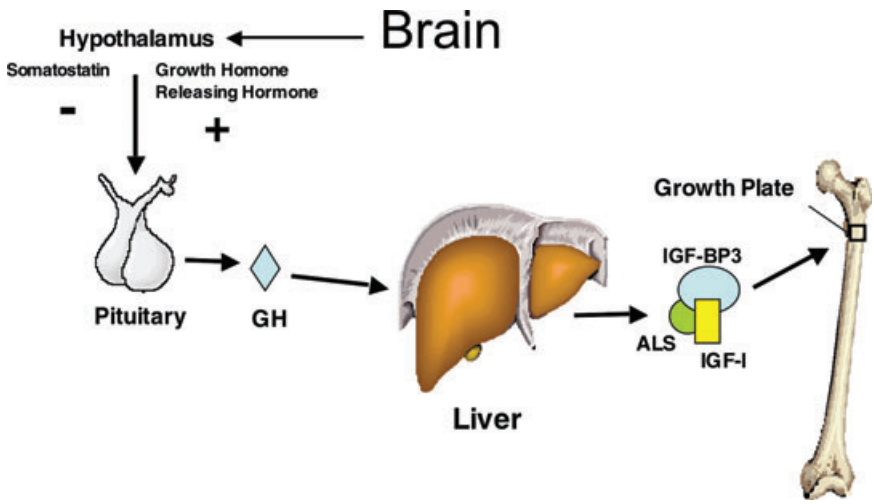

FIGURE 1.—Simplified diagram of the growth hormone–insulin-like growth factor axis. GH = growth hormone, IGF-1 = insulin-like growth factor 1, IGF-BP3 = insulin-like growth factor binding protein-3, ALS = acid labile subunit.

understanding what role the GH-IGF-1 axis may play in growth failure in institutionalized children (Figure 1). For further details, the reader is referred to the comprehensive review by Kemp and Frindik (2008). In brief, the release of GH from the pituitary is under the control of three peptides, two from the hypothalamus and one from the gastrointestinal tract. The hypothalamic peptides include GH-releasing factor that stimulates GH secretion and is under the control of the dopamanergic pathways, and somatostatin that inhibits GH release. Ghrelin, produced predominately in the stomach, also stimulates GH release, but the role of this peptide in normal physiology has not yet been elucidated. Following GH release, binding to the GH receptor in the liver stimulates production of insulin-like growth factor I (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and a glycoprotein termed acid labile subunit (ALS). All three components are low in GH deficiency and are restored when GH levels are normalized. IGF-1, tightly bound in a complex with IGFBP-3, and ALS is then transported to IGF-1 receptors in peripheral tissues. Binding of unbound IGF-1 to receptors on cartilage cells within the bone growth plate is probably responsible for stimulating the majority linear growth. Until the last few weeks of gestation, GH does not influence the hepatic production of IGF-1; hence, GH insufficiency has little effect on birth size but significant effects on postnatal growth (Gluckman et al., 1992; Mehta et al., 2005; Rosenfeld, 2003; Wit & Van Unen, 1992).

Definitive proof that the GH-IGF axis is altered in psychosocial growth failure dates from the reports of Powell and associates who documented

TABLE 6

Behavioral Findings Reported in Childhood Psychosocial Short Stature

Polydypsia
Polyphagia
Stealing of food
Eating from garbage cans
Retarded speech
Solitary play
Temper tantrums
Enuresis
Shyness
Drinking from toilet bowls
Encopresis
Gorging to the point of vomiting
Prowling at night
Sleep cycle disruption
Anxiety
Aggression
Pain agnosia

the association between emotional deprivation and abnormal GH kinetics in stunted, neglected children (Powell, Brasel, & Blizzard, 1967; Powell, Brasel, Raiti, & Blizzard, 1967). Unlike the infantile variety (Type I), which affects height, weight, and head circumference, Type II or the childhood variety (Table 3) affects primarily stature. In this syndrome, "failure to thrive" as classically defined by weight-for-height or BMI is often not present and some children are overweight. Children can be depressed and often exhibit bizarre behaviors such as hyperphagia, polydypsia, retarded speech, solitary play, temper tantrums, shyness, and enuresis (Table 6). GH secretion is reported to be decreased or absent. (Blizzard & Bulatovic, 1996). Data from EEGS are consistent with suppression of the GH-IGF-1 axis in institutionalized children, because levels of IGF-1 and IGFBP-3 were low in postinstitutionalized children at the time of adoption and IGFBP-3 was an independent predictor of height at the time of arrival (Table 5; Miller et al., 2009). While suppression of normal GH secretion is well documented in children with psychosocial short stature, treatment with exogenous GH has mixed results, particularly if a child's environment is not improved. Therefore, GH "resistance" at the level of the GH receptor or in production, transport, or action of IGF-1 may also be a component in the pathophysiology of psychosocial growth failure.

The GH-IGF-1 axis is not the only hypothalamic–pituitary-based endocrine system affected by deprivation. Thyroid stimulating hormone levels may be low (Blizzard & Bulatovic, 1996), and many of the behaviors described, particularly disrupted sleep cycles, abnormal control of appetite, polydipsia, and enuresis suggest global hypothalamic–pituitary dysregulation.

Gonadotropin secretion is also impaired, and delayed puberty has been reported in cohorts of older emotionally deprived children (Gohlke & Stanhope, 2002; Himes et al., 2008). In Romanian children institutionalized since birth, timing of puberty, estimated by probit analysis of stages of pubic hair and breast development in girls and of pubic hair stages and testicular volume in boys, was delayed by approximately 2.5 years in girls and 1.5 years in boys compared to healthy children (Himes et al., 2008).

Apart from the GH-IGF-1 axis, the hypothalamic–pituitary–adrenal axis (HPA axis) has received the most attention as abnormal levels of stress hormones have been shown to correlate with poor cognitive (Lupien & McEwen, 1997) and emotional functioning (de Haan, Gunnar, Tout, Hart, & Stansbury, 1998; Schmidt et al., 1997) and with poor growth. Experiments with rodents have demonstrated the ability of acute stressors to increase the HPA axis hormone levels with a concomitant decrease in GH levels (Armario, Castellanos, & Balasch, 1984; Armario, Lopez-Calderon, Jolin, & Castellanos, 1986; Barbarino et al., 1990; Barinaga, Bilezikjian, Vale, Rosenfeld, & Evans, 1985; Brown & Martin, 1974; Kokka, Garcia, George, & Elliot, 1972; Kuhn, Pauk, & Schanberg, 1990; Rivier & Vale, 1985; Smith, Coplan, Trost, Scharf, & Rosenblum, 1997).

Early childhood adversity is known to profoundly affect the development of the HPA axis (Gunnar & Donzella, 2002; Gunnar & Quevedo, 2007; Gunnar & Quevedo, 2008). Within the context of institutional care, Carlson and Earls (1997) demonstrated that children living in Romanian orphanages had lower baseline morning cortisol levels and slightly higher evening levels compared to children living in enriched environments. This suppressed, atypical diurnal patterns of cortisol production with lower cortisol levels in the morning compared with controls has been described in additional groups of children living in or recently adopted from institutional care in Russia and China (Tarullo & Gunnar, 2006) as well as foster care in the United States (Dozier et al., 2006; Fisher, Gunnar, Dozier, Bruce, & Pears, 2006; Fisher, Stoolmiller, Gunnar, & Burraston, 2007). Bruce and colleagues further refined this observation by showing that children in U.S. foster care with low morning cortisol levels experienced more severe physical neglect (parental failure to provide adequate food, clothing, shelter, or medical care), whereas children experiencing more emotional maltreatment had high morning cortisol levels (Bruce, Fisher, Pears, & Levine, 2009).

Blunted morning cortisol levels may be a consequence of chronic stress and chronic activation of the HPA system (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Gunnar & Vazquez, 2001; Heim et al., 2000). The postulated mechanism involves down-regulation of corticotropin-releasing factor (CRF) receptors in the pituitary in response to a persistent stress-induced elevation of CRF levels. Heightened CRF activity increases somatostatin production, which inhibits release of GH, while cortisol operates at the level of the liver

to reduce responsiveness of the liver to GH and thus to reduce IGF-1 production. Thus, chronic activation of this stress-sensitive neuroendocrine system may play a role in reducing growth in institutionalized children.

The 1990s brought attempts to subdivide the childhood variety of psychosocial growth failure into additional diagnostic groups. In 1996, Skuse and colleagues defined what they believed to be to be a distinctive subgroup of older children with a normal BMI, suppressed GH production, and characteristic behavior problems centered on eating. Blizzard and Bulatovic (1996) suggested that this "hyperphagic short stature" syndrome be termed Type IIA. In studies of clinical populations of children outside of infancy, this presentation appeared to be the most common and have the most consistent findings. Type IIB was used to define a heterogeneous subgroup of nonhyperphagic patients with variable findings in terms of GH kinetics, improvement with change in environment, and response to GH treatment (Blizzard & Bulatovic, 1996). Boulton and colleagues described an additional group of children, later termed Type III by Blizzard and Bulatovich (1996), with anorexic eating habits, depression and/or attachment problems, and normal GH levels who had a greater response to exogenous GH administration (Boulton, Smith, & Single, 1992).

Before attempting to determine whether institutionalized children fit into one of these four previously described diagnostic categories, it is prudent to consider that all classification studies have relied on convenience samples of children referred to specialists for evaluation of short stature prior to or after entering the child protection system. Under these circumstances, basic social and medical information is lacking and it is virtually impossible to ascertain the type, severity, or duration of adversity experienced by these children. This absence of randomized controlled studies examining environment and growth as well as failing to take into account the effects of important growth-impairing medical conditions likely prevalent in this population, for example, LBW and fetal alcohol exposure (Johnson, 2000; Landgren et al., 2006; Miller et al., 2009; Miller et al., 2006, 2007; Smyke et al., 2007), may account for observed variations in the response of children to adversity and social intervention as well as the variety of growth failure subtypes described. An attempt to define additional growth parameters that could help distinguish among Types IIA, IIB, and III found more commonalities than differences (Gohlke et al., 2002). Children in all three groups experienced significant improvement in growth velocity after intervention. Some children in each group received GH plus social service intervention, but the effect of GH was indistinguishable from social service intervention alone, although the small sample sizes precluded rigorous statistical analysis. The conclusion was that all three types of childhood psychosocial short stature had two characteristic findings in common; otherwise unexplained growth failure occurring in association with socially stressful conditions (e.g., abuse/neglect) followed by

significant catch-up growth when the child's environment is improved. It is important to note that these two pathonemonic findings are characteristic of Type I or infantile psychosocial growth failure as well. Hence, the unifying theme of growth suppression with adversity and recovery with nurture is found in all four categories of psychosocial growth failure.

Further complicating delineating both the etiology of growth failure during adversity and whether the described subtypes truly represent different entities is that caloric deprivation and abnormalities of the GH-IGF-1 axis can produce similar clinical and laboratory findings. The hypothesis that psychosocial growth failure in infancy is predominately a nutritional problem is based on the assumption that weight-for-height or BMI is predominately an indicator of caloric sufficiency. This premise was called into question by the study of Mehta and colleagues who found that infants with isolated congenital GH deficiency had significant decreases in weight and height *z* scores as well as low BMI *z* scores (−1.80 at 6 months to −0.90 at 24 months) during the first 2 years of life despite reportedly normal caloric intake (Mehta et al., 2005). A decrease in lean body mass, a parameter influenced more by the GH-IGF-1 axis than caloric intake, was postulated as one possible mechanism for this unexpected finding. Likewise, malnutrition can cause GH insensitivity (Thissen, Underwood, & Ketelslegers, 1999) leading to significantly lower levels of IGF-1 and IGFBP-3 than in healthy subjects (Haspolat et al., 2007; Palacio, Perez-Bravo, Santos, Schlesinger, & Monckeberg, 2002).

Recovery

While it appears clear that improvements in environment and growth parallel one another, it is much more difficult to assess the relative contributions of improved nutritional intake versus endocrine recovery in catch-up. In one sense, the question is moot because both are required for appropriate growth, but the question of nutrition versus nurture has important policy and budgeting implications for child welfare systems that are institution-based.

During infancy when caloric needs are highest, children are more dependent, and caregiving quality is lowest (Johnson et al., 2010), placement into a foster or adoptive home will likely improve diet as well as individual attention and feeding technique. However, within the context of psychosocial growth failure during infancy, the presumption that alterations in caloric intake are both cause and cure is so strong that few have actually tested this hypothesis. Whitten and colleagues reported the only study that demonstrated that growth recovery in infants diagnosed with psychosocial growth failure was directly related to increased caloric intake (Whitten, Pettit, & Fischhoff, 1969). However, more recent work emphasizes the additional contribution of nurture on growth during early life. The St. Petersburg-USA Orphanage Research Team (2008) found that a social-emotional relationship intervention

without change in nutrition within an institutional environment improved growth for infants and young children. Work with LBW infants within the arguably stressful environment of a newborn intensive care unit has demonstrated better short-term weight gain, serum levels of insulin and IGF-1 despite identical caloric intake when infants received massage therapy (nurture?) for three 15-min periods a day (Field et al., 2008). There is, however, ample evidence that increased caloric intake is not the principal factor in growth recovery in previously described clinical populations of older children with psychosocial growth failure. In the study comparing characteristics of the three types of childhood psychosocial short stature (Types IIa, IIb, and III), BMI at presentation was within normal limits and did not increase significantly after intervention in any of the three subgroups (Gohlke et al., 2002).

Since the initial reports of Powell and associates, qualitative improvements in the caregiving environment have been associated with normalization of GH kinetics within days or weeks, although some patients exhibited delayed recovery or continued suppression (Gohlke et al., 2004; Powell et al., 1967; Powell et al., 1967). Other pituitary systems also demonstrate recovery. Substantial reconstitution of the diurnal pattern of cortisol secretion occurred within several months after improvement in the caregiving environment in children who were institutionalized or in foster care (Dozier et al., 2006; Fisher et al., 2006; Tarullo & Gunnar, 2006).

The observation that catch-up growth in height was the only significant independent auxologic predictor of cognitive abilities at 42 and 54 months suggests that the GH-IGF-1 axis may also play a role in cognitive recovery. The role of this complex system in cognitive development is supported by substantial experimental (Rodriguez, Gaunt, & Day, 2007; Scheepens, Moderscheim, & Gluckman, 2005) and clinical evidence. In normal 8- to 9-year-old children, IGF-1 levels were shown to be positively related to IQ (Gunnell, Miller, Rogers, & Holly, 2005). Children with 18q deletions (Cody et al., 2005), Prader–Willi syndrome (Myers et al., 2007), or born SGA (Van Pareren, Duivenvoorden, Slijper, Koot, & Hokken-Koelega, 2004) conditions characterized by both short stature and cognitive delays, have shown significant improvement in height, IQ and brain structure following treatment with GH. Finally, children with defects in the GH receptor, have IQs and brain structural abnormalities that differ depending on which exon contains the point mutation or deletion (Shevah, Kornreich, Galatzer, & Laron, 2005).

Role of Genetics in Deprivation-Associated Growth Failure and Catch-Up

Whether genetics plays a role in either growth suppression during deprivation or catch-up following environmental improvement is essentially unexplored. Skuse et al. (1996) reported a hereditary predisposition in Type IIA or hyperphagic short stature. In this condition, a number of observations

including the description of a high rate of familial aggregation in full sibships of Type IIA-affected families led to the conclusion that this particular type of deprivation-associated growth failure is due to a highly influential gene inherited in a Mendelian pattern. Further investigation examined whether the genetic locus that predisposes to hyperphagic short stature coinherits with the Prader-Syndrome locus at 15q11–13. Although both conditions share the characteristics of GH insufficiency, hyperphagia, and mild learning deficits, no evidence was found in affected children of coinheritance of the Prader–Willi syndrome critical region (Gilmour, Skuse, & Pembrey, 2001).

Ongoing investigation on the role genetic factors play in the etiology and expression of both growth failure and recovery is clearly warranted, because recent work has identified a number of gene loci that are strongly associated with variations in human growth (Lettre et al., 2008; Sanna et al., 2008; Willer et al., 2009) and a number of mutations accounting for rare Mendelian disorders have been described in the GH-IGF-1 axis (Rodriguez et al., 2007; Rosenfeld, 2007; Rosenfeld et al., 2007; Savage et al., 2007). Perhaps most pertinent to this discussion is a GH receptor polymorphism in exon 3, consisting of the deletion (d3) or retention (fl) of the entire exon. More than half of healthy European subjects are either hetero- or homozygous for this isoform (Binder, Baur, Schweizer, & Ranke, 2006), which does not appear to influence final adult height (Audi et al., 2008; Kenth, Shao, Cole, & Goodyer, 2007) but may play a role in suboptimal fetal but enhanced postnatal growth (de Graaff, Meyer, Els, & Hokken-Koelega, 2008; Jensen et al., 2007; Tauber et al., 2007). Don Santos and colleagues (Raz et al., 2008) evaluated two cohorts of children of European descent with height z scores <-2.00 carrying the diagnosis of idiopathic short stature or SGA. Children carrying one or both of the d3 alleles grew approximately twice as well in response to GH treatment as those homozygous for the full-length isoform. Subsequent work with additional populations of children receiving GH have reported conflicting results, with some confirming the original findings and others showing minimal to no effect of the d3 isoform in response to exogenous GH (Audi et al., 2008; Buzi et al., 2007; de Graaff et al., 2008; Marchisotti et al., 2009; Raz et al., 2008).

Summary

Four different clinical types of growth failure in adverse social situations have been described in the clinical literature (Types I, IIa IIb, and III), although their similarities are more striking than their differences. All present with otherwise unexplained growth failure occurring in association with socially stressful conditions (e.g., abuse/neglect) followed by significant catch-up growth when the child's environment is improved. Nutritional insufficiency as well as social deprivation contribute to the etiology of psychosocial growth failure within institutional care settings and influence

recovery under more nurturing circumstances. Under more nurturing conditions the GH-IGF-1 and HPA axes functioning returns to normal in most children. Not only is GH-IGF-1 axis important in terms of improvements in size but it may also play a beneficial role in cognitive recovery as well. Chapter III outlines the problems of applying conventional attachment classifications in institutionalized children. Likewise, the three types and two subtypes of growth failure described in clinical populations are not particularly helpful or informative within the context of psychosocial growth failure in institutionalized children. Considering the possible role of genetics, the findings that medical conditions such as SGA and alcohol exposure worsen deprivation-associated growth failure and that caregiving environment and age significantly influence catch-up, all four types must be re-examined to determine if they are truly unique diagnostic entities or merely variations on the common theme of growth suppression during deprivation and recovery with nurture.

LONG-TERM EFFECTS OF MEDICAL EFFECTS OF EARLY ADVERSITY AND PSYCHOSOCIAL GROWTH FAILURE

Endocrine Dysregulation

The earlier onset of puberty in international adoptees, first reported in 1981 by Adolfsson and Westphal, was subsequently confirmed in a number of retrospective studies (Adolfsson & Westphal, 1981; Bourguignon et al., 1992; Mason & Narad, 2005; Proos, Hofvander, & Tuvemo, 1991a, 1991b; Teilmann, Pedersen, Skakkebaek, & Jensen, 2006). This phenomenon of early sexual maturation is of particular concern to adoptive parents, not only because early puberty compromises final height by shortening the childhood growth period, but those who mature earlier tend to suffer from mental health problems, especially depression, engage in earlier sexual exploratory behavior, and may exhibit more externalizing behaviors (Graber, Lewinsohn, Seeley, & Brooks-Gunn, 1997; Johansson & Ritzen, 2005; Michaud, Suris, & Deppen, 2006; Sonis et al., 1985; Sonis et al., 1986; Weissenberger, Leschek, & Zametkin, 2001). In addition, it is yet one more reason adopted children differ from their nonadopted peers. These vulnerabilities may contribute to the development of and/or aggravate emotional difficulties and conduct problems, which are more prevalent during early adolescence in postinstitutionalized children (Colvert et al., 2008; Graber et al., 1997; Johansson & Ritzen, 2005; Michaud et al., 2006; Rutter, Kreppner et al., 2007).

Four recent studies have significantly improved our knowledge on the incidence and relative risk, gender differences, changes in the timing of puberty, risk factors, and pathophysiology of this condition. Soriano-Guillén

and colleagues reported a national survey on central precocious puberty from 34 pediatric endocrinology clinics in Spain involving 250 patients (Soriano-Guillen et al., 2010). Teilmann and colleagues reported on two groups of international adoptees: one group with precocious puberty identified through a search of the Danish Civil Registration System (Teilmann, Pedersen, Skakkebaek, & Jensen, 2006) and a longitudinal cohort study of 276 randomly recruited internationally adopted girls (4–13 years of age) followed with biannual examinations over a period of 2 years (Teilmann et al., 2009). Proos (2009) retrospectively analyzed data from 107 Indian girls adopted to Sweden, and Sonuga-Barke and colleagues (Sonuga-Barke, Schlotz, & Rutter, 2010) longitudinally followed growth and development from early childhood through mid-adolescence in 144 postinstitutionalized children adopted from Romania.

In children born in Spain and not adopted, the overall incidence for the population at risk for central precocious puberty (onset of puberty <8 years for girls and <9 years for boys) was 5.39 (4.61–6.26) per million person-years at risk; 10.73 (9.1–12.56) for girls and 0.97 (0.57–1.5) for boys (Soriano-Guillen et al., 2010). The overall incidence in adoptees (international and domestic) was markedly higher at 150 (108.9–201.4); 265.8 (189–363.7) for girls; and 34.08 (19.99–38.77) for boys. The overall relative risk of central precocious puberty in internationally and domestically adopted children compared to those born in Spain was 27.82 (19.99–38.77). The findings were similar in the Danish national study where international adoptees had an overall relative risk of 10.62 (7.95–14.18), compared to children with Danish backgrounds (Teilmann, Pedersen, Jensen, Skakkebaek, & Juul, 2005). Additionally, the Spanish study was the first to confirm an increased relative risk of 18.28 (8.57–38.98) in domestic adoptees as well.

In the Danish cohort studied longitudinally, mean age of breast development was 9.5 years and mean age of menarche was 12.1 years, both significantly earlier compared to the reference group of Danish-born girls (Teilmann et al., 2009). The normal probability curves for pubertal changes as a function of age paralleled those for Danish girls but were displaced 1.3 years earlier for both breast development and menarche. Consequently, a large proportion of international adoptees (16%) entered puberty prior to 8 years of age and met the age criteria for the diagnosis of central precocious puberty. Proos (2009) found an earlier median age of menarche (11.6 years) in Indian adoptees to Sweden that was significantly lower than Swedish girls as well as privileged Indian girls residing in India. Puberty in the adopted cohort started 1.5 years earlier (Proos, 2009).

A reasonable question is whether this is true early puberty in adopted children or merely normal pubertal changes occurring on the timeline of children in the country of origin. However, scrutiny of the pediatric endocrinology literature leaves little doubt that sexual maturation in adopted girls is earlier

than expected when compared to children in their sending countries (Teilmann et al., 2009). Neither does this increased risk appear to be related to physical relocation of a child to a different environment or perhaps due to environmental exposures in their country of origin prior to immigration as suggested by Krstevska-Konstantinova et al. (2001), as the relative risk of precocious puberty is increased in domestic adoptees in Spain (Soriano-Buillen et al., 2010). In addition, the relative risk of precocious puberty in children immigrating with their parents was no different in Spain (1.55 [0.97–2.38]) (Soriano-Guillen et al., 2010) and only marginally increased in Denmark (1.56 [1.02–2.37]) (Teilmann et al., 2006).

The finding of an early but otherwise normal pubertal rise in pituitary and ovarian hormones that predate external signs of sexual maturation (Teilmann et al., 2009) suggests that puberty is centrally driven through the hypothalamic-pituitary axis, rather than being caused by exposure to environmental agents that mimic the actions of hormones (Krstevska-Konstantinova et al., 2001). Why central mechanisms are activated early is unknown, but two risk factors have been postulated. Growth restriction in early life followed by rapid weight gain during infancy and early childhood has been associated with early puberty (Dunger, Ahmed, & Ong, 2006; Hokken-Koelega, 2002; Ibanez, Potau, Francois, & de Zegher, 1998; Lazar, Pollak, Kalter-Leibovici, Pertzelan, & Phillip, 2003; Van Weissenbruch, Engelbregt, Veening, & Delemarre-Van de Waal, 2005). In Indian girls adopted to Sweden, those children most stunted at the time of arrival and experiencing the greatest catch-up growth had the earliest menarche (Proos, 2009). The other potential risk factor commonly shared by adopted children is a period of psychosocial deprivation prior to adoption. In the study of postinstitutionalized Romanian children, the group who had spent >6 months within institutional care prior to adoption had a significantly higher frequency of puberty indicators at age of 11 years than the comparison group consisting of within UK adoptees and Romanian adoptees spending <6 months within institutional care (Sonuga-Barke et al., 2010). In both Danish studies, the relative risk of early puberty was significantly increased in international adoptees from all areas of the world with the exception of Korea, a country where children are placed in foster rather than institutional care while awaiting adoption (Teilmann et al., 2006; Teilmann et al., 2009).

Long-term dysregulation of the posterior pituitary has been described as well. Fries and colleagues reported lower baseline arginine vasopressin levels in the urine of postinstitutionalized children versus controls approximately 3 years after placement (Wismer Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005). After a short period of interaction with their own mothers, postinstitutionalized children failed to show elevation in oxytocin levels, which is expected in control children in response to social stimulation. The authors speculated that alterations in the oxytocin and vasopressin neuropeptide systems,

which are critical in establishing social bonds and the regulation of emotional behaviors, are adversely affected by deprivation and may contribute to the social and emotional problems seen in this population of children.

Metabolic Syndrome

Striking parallels exist in children with psychosocial growth failure and SGA infants, another growth-impaired pediatric population experiencing early growth impairment (nutritional) followed by recovery. Both groups share a higher incidence of disturbed GH secretion with lower levels of IGF-1 and IGFBP-3 (Albertsson-Wikland, Boguszewski, & Karlberg, 1998) as well as earlier and accelerated pubertal development particularly in girls (Hokken-Koelega, 2002; Ibanez et al., 1998; Lazar et al., 2003; Van Weissenbruch et al., 2005). Programing of the HPA axis in association with an adverse environment in early life for SGA infants is felt to be a key component in the cascade of changes that ultimately increases the risk for developing the metabolic syndrome (obesity, Type 2 diabetes mellitus, hypertension, heart disease, and polycystic ovary syndrome) (Clark, 1998; Jones et al., 2006). Reduced size at birth (SGA) has been shown to be associated with an enhanced biological response to stress in adults (Jones et al., 2006). In Romanian adoptees evaluated 6.5 years after adoption, children reared in orphanages for more than 8 months in their first years of life had higher cortisol levels over the daytime hours than did early adopted ($\leq$4 months) or Canadian-born children. The longer beyond 8 months that these children remained institutionalized the higher their cortisol levels (Gunnar, Morison, Chisholm, & Schuder, 2001). In international adoptees from multiple countries evaluated from 3.3 to 11.6 years after arrival, preadoption deprivation predicted growth delay at adoption, which, in turn, predicted higher morning cortisol levels and a larger diurnal cortisol decrease (Kertes et al., 2008). Even in children who remained institutionalized, those who demonstrated growth recovery within the orphanage had normal diurnal variation in cortisol levels but higher daily cortisol production than both chronically stunted institution-reared or family-reared children (Dobrova-Krol, Van Ijzendoorn, Bakermans-Kranenburg, Cyr, & Juffer, 2008). In the only longitudinal follow-up of postinstitutionalized children into adolescence, by 15 years of age, the group of postinstitutionalized Romanian adoptees who had spent >6 months within institutional care prior to adoption were beginning to trend higher in weight than in height suggesting a tendency toward obesity (Sonuga-Barke et al., 2010). Whether growth failure associated with social deprivation during early life places affected children at the same risk for developing the metabolic syndrome as those born SGA (Fernandez-Twinn & Ozanne, 2006; McMillen & Robinson, 2005; Silveira, Portella, Goldani, & Barbieri, 2007; Wells, 2007) is unknown, but clearly close

medical follow-up is warranted to identify conditions associated with significant long-term morbidity and mortality.

Final Height

Although robust catch-up growth postadoption is encouraging, the odds for achieving full, innate growth potential may be diminished in children within institutional care because of a combination of risk factors including earlier puberty, prenatal growth deficiency, and growth retardation within the institutional care environment. The meta-analysis of postadoption growth in younger children confirmed this risk by demonstrating good catch-up during early and middle childhood but significant lag in height during adolescence and young adulthood compared to the reference population (Van IJzendoorn et al., 2007). Gohlke and Stanhope (2002) examined final adult height in 18 individuals with psychosocial growth failure diagnosed in late childhood and early adolescence (mean age 10.7 years, range 5.7–14.0 years) who benefited from placement in foster care or experienced an improved home environment through social service intervention. While children experienced catch-up growth and most (78%) had a near final height within the normal mid-parental target range (±2 *SD*) of their biological parents, mean final height was significantly shorter (z score = −2.40) than the mean of the mid-parental target height (−1.50). In postinstitutionalized Romania adoptees spending longer than 6 months within institutional care, by 15 years of age, height was −1.07 *SD* and weight −0.82 *SD*, both significantly different from the pooled comparison group (Sonuga-Barke et al., 2010). In Indian girls adopted to Sweden, final height for age was −1.4 *SD* and final weight for age was −1.1 *SD*. LBW, stunting prior to adoption, and early puberty all appeared to contribute to compromised adult height (Proos, 2009).

Since psychosocial growth failure appears, in large part, to be mediated through the GH-IGF-1 axis, it is instructive to compare adult heights in nontreated and treated GH-deficient children. Untreated children had a mean adult height z score of −4.70 (range −6.10 to −3.90). Those children with GH deficiency treated with recombinant GH had final adult height z scores of −1.40 to −0.50 in women and −1.30 to 0.07 in men (Frindik & Baptista, 1999) similar to those reported in preadoption psychosocial growth failure. Positive correlates of height outcome in GH-deficient children treated with exogenous GH included duration and continuity of GH administration, age of initiation of treatment, GH dose, and the growth rate during the first year of treatment. Delayed onset of puberty also appeared to enhance adult height in some studies (Bourguignon et al., 1986; Price & Ranke, 1994). Based on these observations, correlates for a more normal adult height in children with psychosocial growth failure would likely include an earlier age at placement,

a more rapid normalization of the GH-IGF-BP3 axis (nurture and nutritional environment), and a normal or late onset of puberty.

Catch-Up Growth and Micronutrient Insufficiency

Iron, a micronutrient critical for both erythropoiesis and brain development, is particularly vital in the first few years of life when rapid growth and development are occurring. Iron deficiency, not limited only to iron deficiency anemia but also to deficiency of lesser severity, may have long-term effects on brain development and subsequent cognitive and behavioral development (Georgieff, 2006, 2007, 2008; Lozoff & Georgieff, 2006). Iron status and dietary intake was studied in a subgroup of EEGS participants (Fuglestad et al., 2008). At adoption, mean percent transferring saturation and mean corpuscular volume were low compared with the U.S. population. Participants with Giardia lamblia at baseline, an intestinal parasite that interferes with iron absorption, had more compromised iron status at arrival.

Despite improvement in the caregiving and dietary environment, compromised iron status persisted 6 months after adoption. Mean serum ferritin concentration became lower than the U.S. population at follow-up, although the mean daily iron intake was more than the Recommended Dietary Allowance. During periods of rapid catch-up growth after growth restriction, iron is preferentially shunted away from storage (e.g., liver) and nonstorage (e.g., heart and brain) tissues in the service of increased requirements for erythropoiesis that accompanies the growth spurt (Georgieff, 2006). In this study, iron intake was related to slight improvements in red blood cell functional indices, indicating that dietary iron was likely being used for erythropoiesis. However, growth rate (change in height *z* scores) was negatively correlated with change in serum ferritin concentrations between baseline and follow-up ($r = -.34$; $p < .05$).

Previous studies that have shown rapid growth to increased iron demand (Georgieff, Wewerka, Nelson, & Deregnier, 2002). Within the context of a significant degree of iron deficiency at adoption, preferential shunting of iron into erythropoiesis during catch-up growth, and initial and perhaps ongoing Giardia lamblia infection, dietary intake was insufficient to replenish iron stores during the 6-month follow-up period. Therefore, among the many risk factors that predispose institutionalized children to abnormal brain development, robust catch-up growth adds the additional risk of persistence or even development of brain iron insufficiency. These data suggest that other micronutrients critical for brain development (e.g., zinc, copper, selenium, iodine) may be affected as well (Georgieff, 2007).

Summary

Although catch-up in height and weight is rapid and postinstitutionalized children are well within the normal range during childhood, many factors, particularly early and more rapid progression through puberty in girls, compromise final height. There is also reason for concern that children with psychosocial growth failure may share the risks with SGA infants of developing the metabolic syndrome (obesity, Type 2 diabetes mellitus, hypertension, heart disease). Even if growth recovers, persistent abnormalities of the hypothalamic-pituitary-adrenal system or the presence of micronutrient deficiencies during critical periods of development could potentially influence or be responsible for the cognitive, behavioral, and emotional sequelae of early childhood deprivation.

CONCLUSIONS

From this review, three significant themes emerge with relevance to the care of institutionalized children in regards to children's growth. Infants who are LBW are particularly vulnerable to the effects of social deprivation and should be the first triaged to family care. The unique nutritional needs of LBW infants are unlikely to be appreciated, and even if they were, dependence on conformity in orphanages makes it unlikely that these children will receive the individualized nutritional interventions needed to optimize growth. Growth at baseline in institutionalized LBW infants is particularly impaired, consistent with the global growth failure described in LBW infants who experienced social deprivation in birth families (Elgen, Johansson, Markestad, & Sommerfelt, 2005; Emond, Lira, Lima, Grantham-McGregor, & Ashworth, 2006; Kelleher et al., 1993). LBW infants also have a higher risk for smaller head (brain) size even after placement in a more nurturing environment, a finding that has also been observed in LBW infants exposed to social deprivation within the family (Emond et al., 2006; Escalona, 1982; Kelleher et al., 1993). Second, the early sensitive period for growth recovery (<12 months) similar to the early sensitive period for cognitive recovery previously described (Nelson et al., 2007) necessitates placement within family care as quickly as possible. Third, although family care is important, higher quality caregiving within the institutional environment would help to ensure the best outcomes. In situations where family care is not an option, any improvement in the diet and/or caregiving environment within institutions would improve outcome. However, the inertia of tradition as well as limited human and financial resources hinders accomplishing this goal in most situations.

Growth, particularly in stature, proves not only to be a useful biologic measure of caregiving environment but also an informative indicator of cognitive

improvement in at-risk children. As countries heed the call to eliminate institutions by developing kinship and foster care, postplacement growth could be used as a cost-effective marker of caregiving quality and child well-being pending sufficient staffing and funding of more comprehensive social services programs.

The significance of the findings in psychosocial growth failure extends beyond the millions of institutionalized children worldwide to the impoverished hundreds of millions that are stunted and/or do not meet their developmental potential. Institutions may provide a greater likelihood of exposure to toxic levels of stress, but these observations on the interaction of deprivation and growth are almost certainly valid in populations of children stressed by other factors such as poverty and conflict. The interdependence of nutrition and social environment on child outcomes has recently received attention in regard to achieving UN Millennium Development Goals (Black et al., 2008). The study of growth in institutionalized children adds strong experimental support to the conclusion of Black et al. that strategies that fail to address nurture along with health and nutrition will likely fail to achieve significant improvements in overall child well-being (Black et al., 2008). Psychosocial deprivation within any caregiving environment during early life must be viewed with as much concern as any severely debilitating childhood disease.

REFERENCES

Adolfsson, S., & Westphal, O. (1981). Early pubertal development in girls adopted from far-eastern countries. *Pediatric Research*, **15**(1), 82.

Albertsson-Wikland, K., Boguszewski, M., & Karlberg, J. (1998). Children born small-for-gestational age: Postnatal growth and hormonal status. *Hormone Research in Paediatrics*, **49**(# Suppl 2), 7–13.

Armario, A., Castellanos, J. M., & Balasch, J. (1984). Adaptation of anterior pituitary hormones to chronic noise stress in male rats. *Behavioral and Neural Biology*, **41**(1), 71–76.

Armario, A., Lopez-Calderon, A., Jolin, T., & Castellanos, J. M. (1986). Sensitivity of anterior pituitary hormones to graded levels of psychological stress. *Life Sciences*, **39**(5), 471–475.

Audi, L., Carrascosa, A., Esteban, C., Fernandez-Cancio, M., Andaluz, P., et al. (2008). The exon 3-deleted/full-length growth hormone receptor polymorphism does not influence the effect of puberty or growth hormone therapy on glucose homeostasis in short non-growth hormone-deficient small-for-gestational-age children: Results from a two-year controlled prospective study. *Journal of Clinical Endocrinology and Metabolism*, **93**(7), 2709–2715.

Bakwin, H. (1949). Emotional deprivation in infants. *Journal of Pediatrics*, **35**, 512–521.

Barbarino, A., Corsello, S. M., Della Casa, S., Tofani, A., Sciuto, R., Rota, C. A., et al. (1990). Corticotropin-releasing hormone inhibition of growth hormone-releasing hormone-induced growth hormone release in man. *Journal of Clinical Endocrinology and Metabolism*, **71**(5), 1368–1374.

Barinaga, M., Bilezikjian, L. M., Vale, W. W., Rosenfeld, M. G., & Evans, R. M. (1985). Independent effects of growth hormone releasing factor on growth hormone release and gene transcription. *Nature*, **314**(6008), 279–281.

Beckett, C., Bredenkamp, D., Castle, J., Groothues, C., O'Connor, T. G., & Rutter, M. (2002). Behavior patterns associated with institutional deprivation: A study of children adopted from Romania. *Journal of Developmental and Behavioral Pediatrics*, **23**(5), 297–303.

Beckett, C., Maughan, B., Rutter, M., Castle, J., Colvert, E., Groothues, C., et al. (2007). Scholastic attainment following severe early institutional deprivation: A study of children adopted from Romania. *Journal of Abnormal Child Psychology*, **35**(6), 1063–1073.

Binder, G., Baur, F., Schweizer, R., & Ranke, M. B. (2006). The d3-growth hormone (GH) receptor polymorphism is associated with increased responsiveness to GH in Turner syndrome and short small-for-gestational-age children. *Journal of Clinical Endocrinology and Metabolism*, **91**(2), 659–664.

Black, M. M., Walker, S. P., Wachs, T. D., Ulkuer, N., Gardner, J. M., Grantham-McGregor, S., et al. (2008). Policies to reduce undernutrition include child development. *Lancet*, **371**(9611), 454–455.

Blizzard, R. M., & Bulatovic, A. (1996). Syndromes of psychosocial short stature. In F. Lifshitz (Ed.), *Pediatric Endocrinology* (3rd ed., pp. 83–93). New York: Marcel Dekker.

Boersma, B., & Wit, J. M. (1997). Catch-up growth. *Endocrine Reviews*, **18**(5), 646–661.

Boulton, T. J., Smith, R., & Single, T. (1992). Psychosocial growth failure: A positive response to growth hormone and placebo. *Acta Paediatrica*, **81**(4), 322–325.

Bourguignon, J. P., Gerard, A., Alvarez Gonzalez, M. L., Fawe, L., & Franchimont, P. (1992). Effects of changes in nutritional conditions on timing of puberty: Clinical evidence from adopted children and experimental studies in the male rat. *Hormone Research in Paediatrics*, **38**(Suppl 1), 97–105.

Bourguignon, J. P., Vandeweghe, M., Vanderschueren-Lodeweyckx, M., Malvaux, P., Wolter, R., Du Caju, M., et al. (1986). Pubertal growth and final height in hypopituitary boys: A minor role of bone age at onset of puberty. *Journal of Clinical Endocrinology and Metabolism*, **63**(2), 376–382.

Brown, G. M., & Martin, J. B. (1974). Corticosterone, prolactin, and growth hormone responses to handling and new environment in the rat. *Psychosomatic Medicine*, **36**(3), 241–247.

Bruce, J., Fisher, P. A., Pears, K. C., & Levine, S. (2009). Morning cortisol levels in preschool-aged foster children: Differential effects of maltreatment type. *Developmental Psychobiology*, **51**(1), 14–23.

Bruce, J., Tarullo, A. R., & Gunnar, M. R. (2009). Disinhibited social behavior among internationally adopted children. *Development and Psychopathology*, **21**(1), 157–171.

Buzi, F., Mella, P., Pilotta, A., Prandi, E., Lanfranchi, F., & Carapella, T. (2007). Growth hormone receptor polymorphisms. *Endocrine Development*, **11**, 28–35.

Carlson, M., & Earls, F. (1997). Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in Romania. *Annals of the New York Academy of Sciences*, **807**, 419–428.

Castle, J., Groothues, C., Bredenkamp, D., Beckett, C., O'Connor, T., & Rutter, M. (1999). Effects of qualities of early institutional care on cognitive attainment. E.R.A. Study Team. English and Romanian adoptees. *American Journal of Orthopsychiatry*, **69**(4), 424–437.

Cermak, S. A., & Daunhauer, L. A. (1997). Sensory processing in the postinstitutionalized child. *American Journal of Occupational Therapy*, **51**(7), 500–507.

Chapin, H. D. (1908). A plan of dealing with atrophic infants and children. *Archives of Pediatrics*, **25**, 491–496.

Chapin, H. D. (1915). Are institutions for infants necessary? *JAMA*, **64**, 1–3.

Clark, P. M. (1998). Programming of the hypothalamo-pituitary-adrenal axis and the fetal origins of adult disease hypothesis. *European Journal of Pediatrics*, **157**(Suppl 1), S7–S10.

Cody, J. D., Semrud-Clikeman, M., Hardies, L. J., Lancaster, J., Ghidoni, P. D., Schaub, R. L., et al. (2005). Growth hormone benefits children with 18q deletions. *American Journal of Medical Genetics Part A*, **137**(1), 9–15.

Colvert, E., Rutter, M., Beckett, C., Castle, J., Groothues, C., Hawkins, A., et al. (2008). Emotional difficulties in early adolescence following severe early deprivation: Findings from the English and Romanian adoptees study. *Development and Psychopathology*, **20**(2), 547–567.

Croft, C., Beckett, C., Rutter, M., Castle, J., Colvert, E., Groothues, C., et al. (2007). Early adolescent outcomes of institutionally-deprived and non-deprived adoptees. II: Language as a protective factor and a vulnerable outcome. *Journal of Child Psychology and Psychiatry*, **48**(1), 31–44.

de Graaff, L. C., Meyer, S., Els, C., & Hokken-Koelega, A. C. (2008). GH receptor d3 polymorphism in Dutch patients with MPHD and IGHD born small or appropriate for gestational age. *Clinical Endocrinology (Oxford)*, **68**(6), 930–934.

de Haan, M., Gunnar, M. R., Tout, K., Hart, J., & Stansbury, K. (1998). Familiar and novel contexts yield different associations between cortisol and behavior among 2-year-old children. *Development and Psychobiology*, **33**(1), 93–101.

Dobrova-Krol, N. A., Van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., Cyr, C., & Juffer, F. (2008). Physical growth delays and stress dysregulation in stunted and non-stunted Ukrainian institution-reared children. *Infant Behavior and Development*, **31**(3), 539–553.

Dozier, M., Manni, M., Gordon, M. K., Peloso, E., Gunnar, M. R., Stovall-McClough, K. C., et al. (2006). Foster children's diurnal production of cortisol: An exploratory study. *Child Maltreatment*, **11**(2), 189–197.

Dunger, D. B., Ahmed, M. L., & Ong, K. K. (2006). Early and late weight gain and the timing of puberty. *Molecular and Cellular Endocrinology*, **254–255**, 140–145.

Elgen, I., Johansson, K. A., Markestad, T., & Sommerfelt, K. (2005). A non-handicapped cohort of low-birthweight children: Growth and general health status at 11 years of age. *Acta Paediatrica*, **94**(9), 1203–1207.

Emond, A. M., Lira, P. I., Lima, M. C., Grantham-McGregor, S. M., & Ashworth, A. (2006). Development and behaviour of low-birthweight term infants at 8 years in northeast Brazil: A longitudinal study. *Acta Paediatrica*, **95**(10), 1249–1257.

English, P. C. (1984). Pediatrics and the unwanted child in history: Founding homes disease and the origins of foster care in New York City, 1860–1920. *Pediatrics*, **75**, 699–711.

Escalona, S. K. (1982). Babies at double hazard: Early development of infants at biologic and social risk. *Pediatrics*, **70**(5), 670–676.

Fernandez-Twinn, D. S., & Ozanne, S. E. (2006). Mechanisms by which poor early growth programs Type 2 diabetes, obesity and the metabolic syndrome. *Physiology and Behavior*, **88**(3), 234–243.

Field, T., Diego, M., Hernandez-Reif, M., Dieter, J. N., Kumar, A. M., Schanberg, S., et al. (2008). Insulin and insulin-like growth factor-1 increased in preterm neonates following massage therapy. *Journal of Developmental and Behavioral Pediatrics*, **29**(6), 463–466.

Fisher, P. A., Gunnar, M. R., Dozier, M., Bruce, J., & Pears, K. C. (2006). Effects of therapeutic interventions for foster children on behavioral problems, caregiver attachment, and stress regulatory neural systems. *Annals of the New York Academy of Science*, **1094**, 215–225.

Fisher, P. A., Stoolmiller, M., Gunnar, M. R., & Burraston, B. O. (2007). Effects of a therapeutic intervention for foster preschoolers on diurnal cortisol activity. *Psychoneuroendocrinology*, **32**(8–10), 892–905.

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology*, **30**(10), 1010–1016.

Frindik, J. P., & Baptista, J. (1999). Adult height in growth hormone deficiency: Historical perspective and examples from the national cooperative growth study. *Pediatrics*, **104**(4 Pt 2), 1000–1004.

Fuglestad, A. J., Lehmann, A. E., Kroupina, M. G., Petryk, A., Miller, B. S., Iverson, S. L., et al. (2008). Iron deficiency in international adoptees from Eastern Europe. *Journal of Pediatrics*, **153**, 272–277.

Gardner, L. I. (1972). Deprivation dwarfism. *Scientific American*, **227**(1), 76–82.

Geoffroy, M. C., Cote, S. M., Borge, A. I., Larouche, F., Seguin, J. R., & Rutter, M. (2007). Association between nonmaternal care in the first year of life and children's receptive language skills prior to school entry: The moderating role of socioeconomic status. *Journal of Child Psychology and Psychiatry*, **48**(5), 490–497.

Georgieff, M. K. (2006). Iron. In W. H. Hay and P. J. Thureen (Eds.), *Neonatal nutrition and metabolism* (2nd ed., pp. 291–298). Cambridge, UK: Cambridge University Press.

Georgieff, M. K. (2007). Nutrition and the developing brain: Nutrient priorities and measurement. *American Journal of Clinical Nutrition*, **85**(2), 614S-620S.

Georgieff, M. K. (2008). The role of iron in neurodevelopment: Fetal iron deficiency and the developing hippocampus. *Biochemical Society Transactions*, **36**(Pt 6), 1267–1271.

Georgieff, M. K., Wewerka, S. W., Nelson, C. A., & Deregnier, R. A. (2002). Iron status at 9 months of infants with low iron stores at birth. *Journal of Pediatrics*, **141**(3), 405–409.

Ghera, M. M., Marshall, P. J., Fox, N. A., Zeanah, C. H., Nelson, C. A., Smyke, A. T., et al. (2009). The effects of foster care intervention on socially deprived institutionalized children's attention and positive affect: Results from the BEIP study. *Journal of Child Psychology and Psychiatry*, **50**(3), 246–253.

Gilmour, J., Skuse, D., & Pembrey, M. (2001). Hyperphagic short stature and Prader–Willi syndrome: A comparison of behavioural phenotypes, genotypes and indices of stress. *British Journal of Psychiatry*, **179**, 129–137.

Gluckman, P. D., Gunn, A. J., Wray, A., Cutfield, W. S., Chatelain, P. G., Guilbaud, O., et al. (1992). Congenital idiopathic growth hormone deficiency associated with prenatal and early postnatal growth failure. The International Board of the Kabi Pharmacia International Growth Study. *Journal of Pediatrics*, **121**(6), 920–923.

Gohlke, B. C., Frazer, F. L., & Stanhope, R. (2002). Body mass index and segmental proportion in children with different subtypes of psychosocial short stature. *European Journal of Pediatrics*, **161**(5), 250–254.

Gohlke, B. C., Frazer, F. L., & Stanhope, R. (2004). Growth hormone secretion and long-term growth data in children with psychosocial short stature treated by different changes in environment. *Journal of Pediatric Endocrinology and Metabolism*, **17**(4), 637–643.

Gohlke, B. C., Khadilkar, V. V., Skuse, D., & Stanhope, R. (1998). Recognition of children with psychosocial short stature: A spectrum of presentation. *Journal of Pediatric Endocrinology and Metabolism*, **11**(4), 509–517.

Gohlke, B. C., & Stanhope, R. (2002). Final height in psychosocial short stature: As there complete catch-up? *Acta Paediatrica*, **91**(9), 961–965.

Graber, J. A., Lewinsohn, P. M., Seeley, J. R., & Brooks-Gunn, J. (1997). Is psychopathology associated with the timing of pubertal development? *Journal of the American Academy of Child and Adolescent Psychiatry*, **36**(12), 1768–1776.

Gunnar, M. R., & Donzella, B. (2002). Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology*, **27**(1–2), 199–220.

Gunnar, M. R., Morison, S. J., Chisholm, K., & Schuder, M. (2001). Salivary cortisol levels in children adopted from romanian orphanages. *Development and Psychopathology*, **13**(3), 611–628.

Gunnar, M. R., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology*, **58**, 145–173.

Gunnar, M. R., & Quevedo, K. M. (2008). Early care experiences and HPA axis regulation in children: A mechanism for later trauma vulnerability. *Progress in Brain Research*, **167**, 137–149.

Gunnar, M. R., & Van Dulmen, M. H. (2007). Behavior problems in postinstitutionalized internationally adopted children. *Development and Psychopathology*, **19**(1), 129–148.

Gunnar, M. R., & Vazquez, D. M. (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. *Development and Psychopathology*, **13**(3), 515–538.

Gunnell, D., Miller, L. L., Rogers, I., & Holly, J. M. (2005). Association of insulin-like growth factor I and insulin-like growth factor-binding protein-3 with intelligence quotient among 8- to 9-year-old children in the Avon Longitudinal Study of Parents and Children. *Pediatrics*, **116**(5), e681–e686.

Haspolat, K., Ece, A., Gurkan, F., Atamer, Y., Tutanc, M., & Yolbas, I. (2007). Relationships between leptin, insulin, IGF-1 and IGFBP-3 in children with energy malnutrition. *Clinical Biochemistry*, **40**(3–4), 201–205.

Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., et al. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA*, **284**(5), 592–597.

Himes, J. H., Park, K., Iverson, S. L., Mason, P., Federici, R., & Johnson, D. E. (2008). Physical growth and sexual maturation of severely deprived children reared in Romanian orphanages. In K. Ashizawa & C. N. (Eds.), *Advances in the study of human growth and development* (pp. 93–98). London: Smith-Gordon.

Hokken-Koelega, A. C. (2002). Timing of puberty and fetal growth. *Best Practice and Research Clinical Endocrinology and Metabolism*, **16**(1), 65–71.

Ibanez, L., Potau, N., Francois, I., & de Zegher, F. (1998). Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: Relation to reduced fetal growth. *Journal of Clinical Endocrinology and Metabolism*, **83**(10), 3558–3562.

Jensen, R. B., Vielwerth, S., Larsen, T., Greisen, G., Leffers, H., & Juul, A. (2007). The presence of the d3-growth hormone receptor polymorphism is negatively associated with fetal growth but positively associated with postnatal growth in healthy subjects. *Journal of Clinical Endocrinology and Metabolism*, **92**(7), 2758–2763.

Johansson, T., & Ritzen, E. M. (2005). Very long-term follow-up of girls with early and late menarche. *Endocrrine Development*, **8**, 126–136.

Johnson, D. E. (2000). Medical and developmental sequelae of early childhood institutionalization in Eastern European adoptees. In C. A. Nelson (Ed.), *The effects of early adversity on neurobehavioral development: The Minnesota Symposia on Child Psychology* (pp. 113–162). Mahwaw, NJ: Lawrence Erlbaum Associates.

Johnson, D. E., & Adoptionsproject-Team, I. (2006). Zusammenhange zwischen dem Wachstum von psychisch belasteten Kindern und kognitiver sowie emotionaler Entwicklung. In K. H. Brisch & T. Hellbrugge (Eds.), *Kinder ohne Bindung: Deprivation, Adoption und Psycholtherapie* (pp. 138–160). Stuttgart: Klett-Cotta.

Johnson, D. E., Guthrie, D., Smyke, A. T., Koga, S. F., Fox, N. A., Zeanah, C. H., et al. (2010). Growth and associations between auxology, caregiving environment, and cognition in socially deprived Romanian children randomized to foster vs ongoing institutional care. *Archives of Pediatrrics and Adolescent Medicine*, **164**(6), 507–516.

Jones, A., Godfrey, K. M., Wood, P., Osmond, C., Goulden, P., & Phillips, D. I. (2006). Fetal growth and the adrenocortical response to psychological stress. *Journal of Clinical Endocrinology and Metabolism*, **91**(5), 1868–1871.

Kelleher, K. J., Casey, P. H., Bradley, R. H., Pope, S. K., Whiteside, L., Barrett, K. W., et al. (1993). Risk factors and outcomes for failure to thrive in low birth weight preterm infants. *Pediatrics*, **91**(5), 941–948.

Kemp, S. F., & Frindik, P. J. (2008). Disorders of growth. In K. Sarafoglou, G. F. Hoffman and K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (1st ed., pp. 441–476). New York: McGraw-Hill.

Kenth, G., Shao, Z., Cole, D. E., & Goodyer, C. G. (2007). Relationship of the human growth hormone receptor exon 3 genotype with final adult height and bone mineral density. *Journal of Clinical Endocrinology and Metabolism*, **92**(2), 725–728.

Kertes, D. A., Gunnar, M. R., Madsen, N. J., & Long, J. D. (2008). Early deprivation and home basal cortisol levels: A study of internationally adopted children. *Development and Psychopathology*, **20**(2), 473–491.

King, J. M., & Taitz, L. S. (1985). Catch up growth following abuse. *Archives of Disease in Childhood*, **60**(12), 1152–1154.

Kokka, N., Garcia, J. F., George, R., & Elliot, H. W. (1972). Growth hormone and ACTH secretion: Evidence for an inverse relationship in rats. *Endocrinology*, **90**(3), 735–743.

Kreppner, J. M., Rutter, M., Beckett, C., Castle, J., Colvert, E., Groothues, C., et al. (2007). Normality and impairment following profound early institutional deprivation: A longitudinal follow-up into early adolescence. *Developmental Psychology*, **43**(4), 931–946.

Krstevska-Konstantinova, M., Charlier, C., Craen, M., Du Caju, M., Heinrichs, C., de Beaufort, C., et al. (2001). Sexual precocity after immigration from developing countries to Belgium: Evidence of previous exposure to organochlorine pesticides. *Human Reproduction*, **16**(5), 1020–1026.

Kuhn, C. M., Pauk, J., & Schanberg, S. M. (1990). Endocrine responses to mother-infant separation in developing rats. *Developmental Psychobiology*, **23**(5), 395–410.

Landgren, M., Andersson Gronlund, M., Elfstrand, P. O., Simonsson, J. E., Svensson, L., & Stromland, K. (2006). Health before and after adoption from Eastern Europe. *Acta Paediatrica*, **95**(6), 720–725.

Lazar, L., Pollak, U., Kalter-Leibovici, O., Pertzelan, A., & Phillip, M. (2003). Pubertal course of persistently short children born small for gestational age (SGA) compared with idiopathic short children born appropriate for gestational age (AGA). *European Journal of Endocrinology*, **149**(5), 425–432.

Lettre, G., Jackson, A. U., Gieger, C., Schumacher, F. R., Berndt, S. I., Sanna, S., et al. (2008). Identification of ten loci associated with height highlights new biological pathways in human growth. *Nature Genetics*, **40**(5), 584–591.

Lozoff, B., & Georgieff, M. K. (2006). Iron deficiency and brain development. *Seminars in Pediatric Neurology*, **13**(3), 158–165.

Lupien, S. J., & McEwen, B. S. (1997). The acute effects of corticosteroids on cognition: Integration of animal and human model studies. *Brain Research Reviews*, **24**(1), 1–27.

Marchisotti, F. G., Jorge, A. A., Montenegro, L. R., Berger, K., de Carvalho, L. R., Mendonca, B. B., et al. (2009). Comparison between weight-based and IGF-I-based growth hormone (GH) dosing in the treatment of children with GH deficiency and influence of exon 3 deleted GH receptor variant. *Growth Hormone and IGF Research*, **19**(2), 179–186.

Marshall, P. J., & Fox, N. A. (2004). A comparison of the electroencephalogram between institutionalized and community children in Romania. *Journal of Cognitive Neuroscience*, **16**(8), 1327–1338.

Marshall, P. J., Reeb, B. C., Fox, N. A., Nelson, C. A., & Zeanah, C. H. (2008). Effects of early intervention on EEG power and coherence in previously institutionalized children in Romania. *Development and Psychopathology*, **20**(3), 861–880.

Mason, P., & Narad, C. (2005). Long-term growth and puberty concerns in international adoptees. *Pediatric Clinics of North America*, **52**(5), 1351–1368.

McMillen, I. C., & Robinson, J. S. (2005). Developmental origins of the metabolic syndrome: Prediction, plasticity, and programming. *Physiological Reviews*, **85**(2), 571–633.

Mehta, A., Hindmarsh, P. C., Stanhope, R. G., Turton, J. P., Cole, T. J., Preece, M. A., et al. (2005). The role of growth hormone in determining birth size and early postnatal growth, using congenital growth hormone deficiency (GHD) as a model. *Clinical Endocrinology (Oxford)*, **63**(2), 223–231.

Michaud, P. A., Suris, J. C., & Deppen, A. (2006). Gender-related psychological and behavioural correlates of pubertal timing in a national sample of Swiss adolescents. *Molecular and Cellular Endocrinology*, **254–255**, 172–178.

Miller, L. C., Chan, W., Litvinova, A., Rubin, A., Comfort, K., Tirella, L., et al. (2006). Fetal alcohol spectrum disorders in children residing in Russian orphanages: A phenotypic survey. *Alcoholism: Clinical and Experimental Research*, **30**(3), 531–538.

Miller, L. C., Chan, W., Litvinova, A., Rubin, A., Tirella, L., & Cermak, S. (2007). Medical diagnoses and growth of children residing in Russian orphanages. *Acta Paediatrica*, **96**(12), 1765–1769.

Miller, B. S., Kroupina, M. G., Iverson, S. L., Mason, P., Narad, C., Himes, J. H., et al. (2009). Auxological evaluation and determinants of growth failure at the time of adoption in Eastern European adoptees. *Journal of Pediatric Endocrinology and Metabolism*, **22**(1), 31–39.

Money, J. (1992). *The Kaspar Hauser syndrome of "psychosocial dwarfism"* (1st ed.). Amherst, NY: Prometheus Books.

Money, J., Annecillo, C., & Kelley, J. F. (1983). Growth of intelligence: Failure and catch-up associated respectively with abuse and rescue in the syndrome of abuse dwarfism. *Psychoneuroendocrinology*, **8**(3), 309–319.

Moulson, M. C., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2009). Early adverse experiences and the neurobiology of facial emotion processing. *Developmental Psychology*, **45**(1), 17–30.

Muhamedrahimov, R. J. (1999). New attitudes: Infant care facilities in St. Petersburg, Russia. In J. D. Osofsky and H. E. Fitzgerald (Eds.), *WAIMH handbook of infant mental health* (Vol. **1**, pp. 245–294). New York, NY: Wiley.

Myers, S. E., Whitman, B. Y., Carrel, A. L., Moerchen, V., Bekx, M. T., & Allen, D. B. (2007). Two years of growth hormone therapy in young children with Prader-Willi syndrome: Physical and neurodevelopmental benefits. *American Journal of Medical Genetics (Part A)*, **143**(5), 443–448.

Nelson, C. A. (2007). A neurobiological perspective on early human development. *Child Development Perspectives*, **1**(1), 13–18.

Nelson, C. A., Furtado, E. A., Fox, N. A., & Zeanah, C. H. (2009). The deprived human brain. *American Scientist*, **97**, 222–229.

Nelson, C. A., Parker, S. W., & Guthrie, D. (2006). The discrimination of facial expressions by typically developing infants and toddlers and those experiencing early institutional care. *Infant Behavior and Development*, **29**(2), 210–219.

Nelson, C. A., Zeanah, C. H., Fox, N. A., Marshall, P. J., Smyke, A. T., & Guthrie, D. (2007). Cognitive recovery in socially deprived young children: The Bucharest Early Intervention Project. *Science*, **318**(5858), 1937–1940.

NICHD Early Child Care Research Network. (1996). Characteristics of infant child care: Factors contributing to positive caregiving. *Early Childhood Research Quarterly*, **11**, 269–306.

O'Connor, T. G., & Rutter, M. (2000). Attachment disorder behavior following early severe deprivation: Extension and longitudinal follow-up. English and Romanian Adoptees Study Team. *Journal of the American Academy of Child and Adolescent Psychiatry*, **39**(6), 703–712.

O'Connor, T. G., Rutter, M., Beckett, C., Keaveney, L., & Kreppner, J. M. (2000). The effects of global severe privation on cognitive competence: Extension and longitudinal follow-up. English and Romanian Adoptees Study Team. *Child Development*, **71**(2), 376–390.

Olivan, G. (2003). Catch-up growth assessment in long-term physically neglected and emotionally abused preschool age male children. *Child Abuse and Neglect*, **27**(1), 103–108.

Palacio, A. C., Perez-Bravo, F., Santos, J. L., Schlesinger, L., & Monckeberg, F. (2002). Leptin levels and IgF-binding proteins in malnourished children: Effect of weight gain. *Nutrition*, **18**(1), 17–19.

Parker, S. W., & Nelson, C. A. (2005a). An event-related potential study of the impact of institutional rearing on face recognition. *Development and Psychopathology*, **17**(3), 621–639.

Parker, S. W., & Nelson, C. A. (2005b). The impact of early institutional rearing on the ability to discriminate facial expressions of emotion: An event-related potential study. *Child Development*, **76**(1), 54–72.

Pears, K., & Fisher, P. A. (2005). Developmental, cognitive, and neuropsychological functioning in preschool-aged foster children: Associations with prior maltreatment and placement history. *Journal of Developmental and Behavioral Pediatrics*, **26**(2), 112–122.

Powell, G. F., Brasel, J. A., & Blizzard, R. M. (1967). Emotional deprivation and growth retardation simulating idiopathic hypopituitarism. I. Clinical evaluation of the syndrome. *New England Journal of Medicine*, **276**(23), 1271–1278.

Powell, G. F., Brasel, J. A., Raiti, S., & Blizzard, R. M. (1967). Emotional deprivation and growth retardation simulating idiopathic hypopituitarism. II. Endocrinologic evaluation of the syndrome. *Child Abuse Neglect*, **276**(23), 1279–1283.

Price, D. A., & Ranke, M. B. (1994). Final height following growth hormone treatment. In M. B. Ranke & R. Gunnarsson (Eds.), *Progress in growth hormone therapy—5 years of KIGS* (pp. 129–144). Mannheim, Germany: J&J Verlag.

Proos, L. A. (2009). Growth & development of Indian children adopted in Sweden. *Indian Journal of Medical Research*, **130**(5), 646–650.

Proos, L. A., Hofvander, Y., & Tuvemo, T. (1991a). Menarcheal age and growth pattern of Indian girls adopted in Sweden. I. Menarcheal age. *Acta Paediatrica Scandinavia*, **80**(8–9), 852–858.

Proos, L. A., Hofvander, Y., & Tuvemo, T. (1991b). Menarcheal age and growth pattern of Indian girls adopted in Sweden. II. Catch-up growth and final height. *Indian Journal of Pediatrics*, **58**(1), 105–114.

Raz, B., Janner, M., Petkovic, V., Lochmatter, D., Eble, A., Dattani, M. T., et al. (2008). Influence of growth hormone (GH) receptor deletion of exon 3 and full-length isoforms on GH response and final height in patients with severe GH deficiency. *Journal of Clinical Endocrinology and Metabolism*, **93**(3), 974–980.

Rivier, C. V., & Vale, W. W. (1985). Involvement of corticotropin-releasing factor and somatostatin in stress-induced inhibition of growth hormone secretion in the rat. *Endocrinology*, **117**(6), 2478–2482.

Rodriguez, S., Gaunt, T. R., & Day, I. N. (2007). Molecular genetics of human growth hormone, insulin-like growth factors and their pathways in common disease. *Human Genetics*, **122**(1), 1–21.

Rosenberg, D. R., Pajer, K., & Rancurello, M. (1992). Neuropsychiatric assessment of orphans in one Romanian orphanage for "unsalvageables." *JAMA*, **268**(24), 3489–3490.

Rosenfeld, R. G. (2003). Insulin-like growth factors and the basis of growth. *New England Journal of Medicine*, **349**(23), 2184–2186.

Rosenfeld, R. G. (2007). Pharmacogenomics and pharmacoproteomics in the evaluation and management of short stature. *European Journal of Endocrinlogy*, **157**(Suppl 1), S27–S31.

Rosenfeld, R. G., Belgorosky, A., Camacho-Hubner, C., Savage, M. O., Wit, J. M., & Hwa, V. (2007). Defects in growth hormone receptor signaling. *Trends in Endocrinology and Metabolism*, **18**(4), 134–141.

Roy, P., & Rutter, M. (2006). Institutional care: Associations between inattention and early reading performance. *Journal of Child Psychology and Psychiatry*, **47**(5), 480–487.

Rutter, M. (1981). *Maternal deprivation reassessed*. New York: Penguin.

Rutter, M. (1998). Developmental catch-up, and deficit, following adoption after severe global early privation. English and Romanian Adoptees (ERA) Study Team. *Journal of Child Psychology and Psychiatry*, **39**(4), 465–476.

Rutter, M. (2008). Institutional effects on children: Design issues and substantive findings. *Monographs of the Society for Research in Child Development*, **73**(3), 271–278.

Rutter, M., Colvert, E., Kreppner, J., Beckett, C., Castle, J., Groothues, C., et al. (2007). Early adolescent outcomes for institutionally deprived and non-deprived adoptees. I: Disinhibited attachment. *Journal of Child Psychology and Psychiatry*, **48**(1), 17–30.

Rutter, M., Kreppner, J., Croft, C., Murin, M., Colvert, E., Beckett, C., et al. (2007). Early adolescent outcomes of institutionally deprived and non-deprived adoptees. III. Quasi-autism. *Child Psychology and Psychiatry*, **48**(12), 1200–1207.

Rutter, M. L., Kreppner, J. M., & O'Connor, T. G. (2001). Specificity and heterogeneity in children's responses to profound institutional privation. *British Journal of Psychiatry*, **179**, 97–103.

Rutter, M., & O'Connor, T. G. (2004). Are there biological programming effects for psychological development? Findings from a study of Romanian adoptees. *Developmental Psychology*, **40**(1), 81–94.

Sanna, S., Jackson, A. U., Nagaraja, R., Willer, C. J., Chen, W. M., Bonnycastle, L. L., et al. (2008). Common variants in the GDF5-UQCC region are associated with variation in human height. *Nature Genetics*, **40**(2), 198–203.

Savage, M. O., Camacho-Hubner, C., David, A., Metherell, L. A., Hwa, V., Rosenfeld, R. G., et al. (2007). Idiopathic short stature: Will genetics influence the choice between GH and IGF-I therapy? *European Journal of Endocrinology*, **157**(Suppl 1), S33–S37.

Scheepens, A., Moderscheim, T. A., & Gluckman, P. D. (2005). The role of growth hormone in neural development. *Hormone Research in Paediatrics*, **64**(Suppl 3), 66–72.

Schmidt, L. A., Fox, N. A., Rubin, K. H., Sternberg, E. M., Gold, P. W., Smith, C. C., et al. (1997). Behavioral and neuroendocrine responses in shy children. *Developmental Psychobiology*, **30**(2), 127–140.

Shevah, O., Kornreich, L., Galatzer, A., & Laron, Z. (2005). The intellectual capacity of patients with Laron syndrome (LS) differs with various molecular defects of the growth hormone receptor gene. Correlation with CNS abnormalities. *Hormone and Metabolic Research*, **37**(12), 757–760.

Silveira, P. P., Portella, A. K., Goldani, M. Z., & Barbieri, M. A. (2007). Developmental origins of health and disease (DOHaD). *Jornal de Pediatria*, **83**(6), 494–504.

Skuse, D., Albanese, A., Stanhope, R., Gilmour, J., & Voss, L. (1996). A new stress-related syndrome of growth failure and hyperphagia in children, associated with reversibility of growth-hormone insufficiency. *Lancet*, **348**(9024), 353–358.

Smith, E. L., Coplan, J. D., Trost, R. C., Scharf, B. A., & Rosenblum, L. A. (1997). Neurobiological alterations in adult nonhuman primates exposed to unpredictable early rearing.

Relevance to posttraumatic stress disorder. *Annals of the New York Academy of Science*, **821**, 545–548.

Smyke, A. T., Koga, S. F., Johnson, D. E., Fox, N. A., Marshall, P. J., Nelson, C. A., et al. (2007). The caregiving context in institution-reared and family-reared infants and toddlers in Romania. *Journal of Child Psychology and Psychiatry*, **48**(2), 210–218.

Sonis, W. A., Comite, F., Blue, J., Pescovitz, O. H., Rahn, C. W., Hench, K. D., et al. (1985). Behavior problems and social competence in girls with true precocious puberty. *Journal of Pediatrics*, **106**(1), 156–160.

Sonis, W. A., Comite, F., Pescovitz, O. H., Hench, K., Rahn, C. W., Cutler, G. B., Jr., et al. (1986). Biobehavioral aspects of precocious puberty. *Journal of the American Academy of Child and Adolescent Psychiatry*, **25**(5), 674–679.

Sonuga-Barke, E. J., Beckett, C., Kreppner, J., Castle, J., Colvert, E., Stevens, S., et al. (2008). Is sub-nutrition necessary for a poor outcome following early institutional deprivation? *Developmental Medicine and Child Neurology*, **50**(9), 664–671.

Sonuga-Barke, E. J., Schlotz, W., & Rutter, M. (2010). VII. Physical growth and maturation following early severe institutional deprivation: Do they mediate specific psychopathological effects? In M. Rutter, E. J. Sonuga-Barke, C. Beckett, J. Kreppner, R. Kumsta, W. Schlotz, et al. (Eds.), *Monographs of the Society for Research in Child Development*, **75**(1), 143–166.

Soriano-Guillen, L., Corripio, R., Labarta, J. I., Canete, R., Castro-Feijoo, L., Espino, R., et al. (2010). Central precocious puberty in children living in Spain: Incidence, prevalence, and influence of adoption and immigration. *Journal of Clinical Endocrinology and Metabolism*.

Spitz, R. (1945). Hospitalism: An inquiry into the genesis of psychiatric conditions in early childhood. In A. Freud, H. Hartman, & K. E. (Eds.), *The psychoanalytic study of the child* (pp. 53–74). New York: International Universities Press.

Spitz, R. (1946). Hospitalism, a follow-up report. In A. Freud & E. K. Hartman (Eds.), *The psychoanalytic study of the child* (Vol. **2**). New York: International Universities Press.

Stevens, S. E., Sonuga-Barke, E. J., Kreppner, J. M., Beckett, C., Castle, J., Colvert, E., et al. (2008). Inattention/overactivity following early severe institutional deprivation: Presentation and associations in early adolescence. *Journal of Abnormal Child Psychology*, **36**(3), 385–398.

Taitz, L. S., & King, J. M. (1988). Growth patterns in child abuse. *Acta Paediatrica Scandinavia Suppl*, **343**, 62–72.

Talbot, N. B., Sobel, E. H., Burk, B. S., Lindemann, E., & Kaufman, S. B. (1947). Dwarfism in healthy children: It's possible relation to emotional, nutritional and endocrine disturbances. *New England Journal of Medicine*, **236**, 783–789.

Tarullo, A. R., & Gunnar, M. R. (2006). Child maltreatment and the developing HPA axis. *Hormones and Behavior*, **50**(4), 632–639.

Tauber, M., Ester, W., Auriol, F., Molinas, C., Fauvel, J., Caliebe, J., et al. (2007). GH responsiveness in a large multinational cohort of SGA children with short stature (NESTEGG) is related to the exon 3 GHR polymorphism. *Clinical Endocrinology (Oxford)*, **67**(3), 457–461.

Teilmann, G., Pedersen, C. B., Jensen, T. K., Skakkebaek, N. E., & Juul, A. (2005). Prevalence and incidence of precocious pubertal development in Denmark: An epidemiologic study based on national registries. *Pediatrics*, **116**(6), 1323–1328.

Teilmann, G., Pedersen, C. B., Skakkebaek, N. E., & Jensen, T. K. (2006). Increased risk of precocious puberty in internationally adopted children in Denmark. *Pediatrics*, **118**(2), e391–e399.

Teilmann, G., Petersen, J. H., Gormsen, M., Damgaard, K., Skakkebaek, N. E., & Jensen, T. K. (2009). Early puberty in internationally adopted girls: Hormonal and clinical markers of

puberty in 276 girls examined biannually over two years. *Hormone Research in Paediatrics*, **72**(4), 236–246.

The St. Petersburg-USA Orphanage Research Team. (2005). Characteristics of children, caregivers, and orphanages for young children in St. Petersburg, Russian Federation. *Applied Developmental Psychology*, **26**, 477–506.

The St. Petersburg-USA Orphanage Research Team. (2008). The effects of early social-emotional and relationship experience on the development of young orphanage children. *Monographs of the Society for Research on Child Development*, Serial No. 291, **73**(3).

Thissen, J. P., Underwood, L. E., & Ketelslegers, J. M. (1999). Regulation of insulin-like growth factor-I in starvation and injury. *Nutrition Reviews*, **57**(6), 167–176.

Van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., & Juffer, F. (2007). Plasticity of growth in height, weight, and head circumference: Meta-analytic evidence of massive catch-up after international adoption. *Journal of Developmental and Behavioral Pediatrrics*, **28**(4), 334–343.

Van Pareren, Y. K., Duivenvoorden, H. J., Slijper, F. S., Koot, H. M., & Hokken-Koelega, A. C. (2004). Intelligence and psychosocial functioning during long-term growth hormone therapy in children born small for gestational age. *Journal of Clinical Endocrinology and Metabolism*, **89**(11), 5295–5302.

Van Weissenbruch, M. M., Engelbregt, M. J., Veening, M. A., & Delemarre-Van de Waal, H. A. (2005). Fetal nutrition and timing of puberty. *Endocrine Development*, **8**, 15–33.

Weissenberger, A. A., Leschek, E. W., & Zametkin, A. J. (2001). Case study: Sexual hyperactivity treated with psychostimulants in familial male precocious puberty. *Journal of the American Academy of Child and Adolescent Psychiatry*, **40**(3), 373–376.

Wells, J. C. (2007). The programming effects of early growth. *Early Human Development*, **83**(12), 743–748.

Whitten, C. F., Pettit, M. G., & Fischhoff, J. (1969). Evidence that growth failure from maternal deprivation is secondary to undereating. *JAMA*, **209**(11), 1675–1682.

Widdowson, E. M. (1951). Mental contentment and physical growth. *Lancet*, **1**, 1316–1318.

Willer, C. J., Speliotes, E. K., Loos, R. J., Li, S., Lindgren, C. M., Heid, I. M., et al. (2009). Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nature Genetics*, **41**(1), 25–34.

Windsor, J., Glaze, L. E., & Koga, S. F. (2007). Language acquisition with limited input: Romanian institution and foster care. *Journal of Speech, Language and Hearing Research*, **50**(5), 1365–1381.

Wismer Fries, A. B., Ziegler, T. E., Kurian, J. R., Jacoris, S., & Pollak, S. D. (2005). Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. *Proceedings of the National Academy of Sciences USA*, **102**(47), 17237–17240.

Wit, J. M., & Van Unen, H. (1992). Growth of infants with neonatal growth hormone deficiency. *Archives of Disease in Childhood*, **67**(7), 920–924.

Wyatt, D. T., Simms, M. D., & Horwitz, S. M. (1997). Widespread growth retardation and variable growth recovery in foster children in the first year after initial placement. *Archives of Pediatrics and Adolescent Medicine*, **151**(8), 813–816.

Zeanah, C. H., Egger, H. L., Smyke, A. T., Nelson, C. A., Fox, N. A., Marshall, P. J., et al. (2009). Institutional rearing and psychiatric disorders in Romanian preschool children. *American Journal of Psychiatry*, **166**(7), 777–785.

Zeanah, C. H., Nelson, C. A., Fox, N. A., Smyke, A. T., Marshall, P., Parker, S. W., et al. (2003). Designing research to study the effects of institutionalization on brain and behavioral development: The Bucharest Early Intervention Project. *Development and Psychopathology*, **15**(4), 885–907.

Zeanah, C. H., Smyke, A. T., Koga, S. F., & Carlson, E. (2005). Attachment in institutionalized and community children in Romania. *Child Development*, **76**(5), 1015–1028.