

## SUPPLEMENT ARTICLE

# Growth at Puberty

ALAN D. ROGOL, M.D., Ph.D., JAMES N. ROEMMICH, Ph.D., AND PAMELA A. CLARK, M.D.

**Abstract:** Somatic growth and maturation are influenced by a number of factors that act independently or in concert to modify an individual's genetic potential. The secular trend in height and adolescent development is further evidence for the significant influence of environmental factors on an individual's genetic potential for linear growth. Nutrition, including energy and specific nutrient intake, is a major determinant of growth. Paramount to normal growth is the general health and well-being of an individual; in fact, normal growth is a strong testament to the overall good health of a child. More recently the effect of physical activity and fitness on linear growth, especially among teenage athletes, has become a topic of interest.

Puberty is a dynamic period of development marked by rapid changes in body size, shape, and composition, all of which are sexually dimorphic. One of the hallmarks of puberty is the adolescent growth spurt. Body compositional changes, including the regional distribution of body fat, are especially large during the pubertal transition and markedly sexually dimorphic. The hormonal regulation of the growth spurt and the alterations in body composition depend on the release of the gonadotropins, leptin, the sex-steroids, and growth hormone. It is very likely that *interactions* among these hormonal axes are more important than their main effects, and that alterations in body composition and the regional distribution of body fat actually are signals to alter the neuroendocrine and peripheral hormone axes. These processes are merely magnified during pubertal development but likely are pivotal all along the way from fetal

growth to the aging process. © Society for Adolescent Medicine, 2002

## KEY WORDS:

Adipose tissue  
Body composition  
Bone mineral  
Growth hormone  
Growth  
Insulin-like growth factor-1  
Leptin  
Nutrition  
Puberty  
Sex-steroid hormones

Growth and physical maturation are dynamic processes encompassing a broad spectrum of cellular and somatic changes. Traditionally, the assessment of growth has placed its primary focus on stature, but changes in body proportions and body composition are essential elements of the growth process. Growth standards have been developed for each of these parameters and aid in the identification of children with normal growth, variations of normal growth and development, and the broad spectrum of abnormal growth states.

## Factors Influencing Somatic Growth

Somatic growth and maturation are influenced by a number of factors that act independently or in concert to modify an individual's genetic potential. These may be broadly defined as nutritional, genetic, and hormonal. At birth an infant's size is determined more by maternal nutrition and intrauterine and placental factors than by genetic makeup. Birth length and ultimate adult height have a correlation coefficient of only 0.25, compared with 0.80 by 2 years of age [1]. There is also evidence that not all

From the Departments of Pediatrics (A.D.R., J.N.R., P.A.C.) and Pharmacology (A.D.R.), University of Virginia, Charlottesville, Virginia.

Address correspondence to: Alan D. Rogol, M.D., Ph.D., 685 Explorers Road, Charlottesville, VA 22911-8441. E-mail: arogol@cstone.net.

This work was supported in part by grants HD 32631 (to A.D.R.), RR 00847 (to the University of Virginia General Clinical Research Center), the Department of Pediatrics (J.N.R.) and the Genentech Foundation (to P.A.C.)

Manuscript accepted August 22, 2002.

genes are actively expressed at the time of birth. This likely accounts for the observation that the correlation between the size of the parents and child is weak during the first year of life, but rises to the adult value of 0.5 by about 18 months of age [2].

Growth in a number of dimensions shows a significant familial resemblance. Adult stature, *tempo* of growth, timing and rate of sexual development, skeletal maturation, and dental development are all significantly influenced by genetic factors [3], with estimates of genetic transmissibility ranging from 41% to 71% [2]. Twin studies have shown that the average difference in height between monozygotic twins is only 2.8 cm, compared with 12 cm for dizygotic twins of the same sex. Adult stature is best correlated with mid-parental height calculations, but the polygenic model of inheritance results in greater variation in size of children born to parents of disparate heights compared with those born to parents both of average height [4].

The overall contribution of heredity to adult size and shape varies with environmental circumstances, and the two continuously interact throughout the entire period of growth. Children with similar genotypes, who would reach the same adult height under optimal conditions, may be differently affected by adverse circumstances. Thus, the interaction between genetic makeup and the environment is complex and nonadditive [5]. The genetic control of the tempo of growth appears to be independent of that for body size and shape, and environmentally induced changes in tempo do not seem to significantly alter adult height or shape (somatotype) [2].

The secular trend in height and adolescent development is further evidence for the significant influence of environmental factors on an individual's genetic potential for linear growth. Since the turn of the century, children in average economic conditions have increased in height approximately 1 to 2 cm per decade [2]. The gain in adult stature, however, has been less, indicating that, in part, the trend toward greater size during childhood is the result of earlier maturation and adult height achievement.

In industrialized countries, the change in tempo of growth and adolescent maturation is stabilizing but continues in underdeveloped areas. The trend toward earlier sexual maturation is evident in a study comparing skeletal ages of boys in the United Kingdom in the 1960s (UK60) with two populations of boys in the United States in the 1990s (US90). The US90 boys matured considerably earlier than the UK60 children, and the two U.S. populations were not significantly different, validating the new refer-

ence values for use in North America [6,7]. Herman-Giddens and coworkers [8] have also indicated earlier maturation in girls. They have reported earlier onset of pubic hair (8.9 and 10.5 years) in African-American and white girls, respectively, than had previously been reported. In addition, breast development began by 8.9 and 10 years in these two groups of children, although palpation (to distinguish breast tissue from fatty tissue) was not permitted. Despite these findings the age at menarche has not decreased over the past few decades.

Nutrition, including energy and specific nutrient intake, is a major determinant of growth. Undernutrition is the single most important cause of growth retardation worldwide, although in the United States the causes are typically self-induced food restriction or systemic disease, rather than poverty-related. In addition to effects on overall growth, malnutrition secondary to avoidance of certain foods or malabsorption can lead to serious disorders such as osteopenia, anemia, and syndromes related to deficiencies of vitamins, minerals, essential fatty acids and amino acids, and trace elements. Undernutrition affects the most vital growth first and most intensely. Growth and development of muscle are affected more than bones, which in turn are influenced to a greater degree than teeth. Brain cell hyperplasia is affected more than myelination, and during puberty vital tissues and organs are affected to a greater degree than are the gonads [3]. Nutritional status also has a significant modulating effect on the timing of adolescent sexual development. Undernutrition is associated with later age of menarche (as well as secondary amenorrhea), whereas a moderate degree of obesity is associated with early sexual maturation [9,10].

Paramount to normal growth is the general health and well-being of an individual; in fact, normal growth is a strong testament to the overall good health of a child. Studies of short-term linear growth in children have shown that shrinkage may even occur during periods of catabolic stress, presumably owing to compression of nongrowing bone and cartilage and a possible shift in the balance between bone deposition and resorption during illness [11]. In general, such illnesses have self-limited effects and catch-up growth is typically observed after resolution of symptoms. The term "well-being" also encompasses the realm of mental health. Psychosocial dwarfism secondary to abuse or neglect, despite good physical health and adequate nutrition, has profound consequences on growth.

More recently the effect of physical activity and fitness on linear growth, especially among teenage athletes, has become a topic of interest. Although moderate activity is associated with cardiovascular benefits and favorable changes in body composition, excessive physical activity during childhood and adolescence may negatively affect growth and adolescent development. Sports that emphasize strict weight control in the setting of high-energy output are of particular concern. Studies of male scholastic wrestlers have shown decreased linear growth during the sport season with catch-up growth during the postseason [12]. Studies of elite female gymnasts and dancers have likewise demonstrated delayed growth and pubertal maturation during periods of intense training [13,14]. These sports, however, favor the success of certain body types, making selection bias a confounding variable in the assessment of the affect of training on growth and adolescent development. Most investigators would agree that physical training, when it does not result in severe restriction of energy and nutrient intake, does not have significant or permanent consequences on growth and adolescent development.

Essential to normal growth and development are adequate levels of several hormones, although deficiencies of these are a much less common cause of growth disturbances than the factors discussed above. Prepubertally, growth hormone (GH) and thyroid hormone are the primary hormones essential to growth. GH promotes the synthesis of protein, inhibits the formation of fat and carbohydrate, and is necessary for the proliferation of cartilage cells at the epiphyseal plate permitting linear growth. Thyroid hormone is essential to normal growth and development of the central nervous system and works in concert with GH to promote cartilage and bone formation. In addition, insulin plays an important role in the regulation of growth through the supply of metabolic substrate to cells and interaction with other growth factors to influence fetal growth. Rarely, excess levels of certain hormones such as cortisol (e.g., in Cushing disease or syndrome, or secondary to high doses of exogenous glucocorticoids) can result in growth failure. Although hormones exert independent effects during puberty, the *interaction* of gonadal and adrenal steroid hormones with GH becomes essential for the normal adolescent growth spurt and sexual maturation.

Differences in growth and development also vary as a function of gender and ethnic origin. Gender-specific patterns in the tempo of growth, timing of adolescent growth spurt, overall size, and the age of

skeletal maturity are well-known, but differences between the sexes are apparent from the time of fetal life. At birth, skeletal maturation of females is 4 to 6 weeks more advanced than that in males, and this trend continues throughout childhood and adolescence [2]. Growth velocity is slightly slower in females at birth, becomes equal around 7 months of age, and is then somewhat faster until age 4 years. Children of both genders then progress at the same rate until the adolescent growth spurt. On average, females enter puberty somewhat earlier than males but have a lower peak height velocity (9 cm versus 10.3 cm) and adult stature [15,16]. Overall size and the rate of development vary significantly among ethnic populations. African-American infants tend to be smaller at birth, followed by an acceleration of linear growth resulting in greater height attainment than Caucasian children during the first few years of life [17]. Skeletal maturity in African-American children, especially girls, also tends to be more advanced and the age at peak height velocity earlier [18,19]. African-American girls also tend to be taller and heavier than Caucasian girls during puberty, with a trend toward greater body mass index and higher skin fold measurements found in some studies [19]. Growth curves based on longitudinal data for defined ethnic populations are important for the differentiation of physiologic from pathologic patterns of growth and sexual maturation.

### Prepubertal Growth

Growth during childhood is a relatively stable process. The infancy shifts in the channel of growth are complete, and the child follows the trajectory previously attained. Until about age 4 years, girls grow slightly faster than boys and then both genders average a rate of 5 to 6 cm/year and 2.5 kg/year until the onset of puberty [2]. A general rule of thumb is that a child grows 10 in (25 cm) in the first year of life, half that (5 in or 12 to 13 cm) in the second year, and then 2.5 in (5 to 6 cm) until puberty. Assuming an average birth length of 20 in (51 cm) results in an average 1-year-old being 30 in (76 cm), a 2-year-old 35 in (89 cm), a 4-year-old 40 in (102 cm), and an 8-year-old 50 in (127 cm).

A wide range of normal exists for the growth velocity, however, and it depends on which percentile a child is growing. Those children growing along the 3rd percentile average 5.1 cm/year, whereas boys growing along the 97th percentile grow 6.4 cm/year and girls 7.1 cm/year during childhood to maintain the ambient trajectory [20]. To maintain

growth along the 10th percentile height, a child must grow at the 40th percentile for velocity; to grow along the 90th percentile for height, a velocity at the 60th percentile is required. This implies that a child who persistently grows at the 10th percentile for velocity will progressively cross percentiles downward on the standard height curve. Some children have a small increase in the growth velocity around 6 to 7 years of age ("mid-growth spurt"), but this is not a consistent finding, and the gain in height is generally of small magnitude. Seasonal variations in growth have been noted in some children. Linear growth tends to be greater in spring than in fall, but weight gain is greater in the fall months. This emphasizes the need for repeated measurements over the course of a year to accurately assess a child's growth pattern.

Hormonal control of growth continues to depend primarily on the thyroid hormones and the GH/insulin-like growth factor (IGF)-1 axis. During childhood, GH secretion patterns are similar in girls and boys and have a marked day-night rhythm [21]. GH secretion is maximal during the early hours of sleep and pulses of hormonal release occur during the day, but at a much lower level. GH secretory activity between bursts is typically low, and serum concentrations often fall to undetectable levels. IGF-1 plays an important role in muscle tissue growth through the stimulation of glycogen accumulation and the transfer of amino acids into cells for protein synthesis. It also promotes the growth of connective tissue, cartilage, and bone through the stimulation of cartilage growth and the formation of collagen. Adequate nutrition is necessary for growth during childhood, in part through its effects on the GH/IGF-1 axis. Both proper nutrition and insulin appear necessary for GH-stimulated IGF-1 production [22], and IGF-1 activity is blunted in cases of starvation, including anorexia nervosa, and in children with poorly controlled diabetes mellitus (i.e., intracellular starvation) [23].

### Pubertal Growth

Puberty is a dynamic period of development marked by rapid changes in body size, shape, and composition, all of which are sexually dimorphic. It is characterized by the greatest sexual differentiation since fetal life and the most rapid rate of linear growth since infancy. The onset of puberty corresponds to a skeletal (biological) age of approximately 11 years in girls and 13 years in boys [24]. On average, girls enter and complete each stage of puberty earlier than boys,

but there is significant intraindividual variation in the timing and tempo of puberty, even among children of the same gender and ethnic background.

One of the hallmarks of puberty is the adolescent growth spurt. As puberty approaches, the growth velocity slows to a nadir ("preadolescent dip") before its sudden acceleration during mid-puberty. The timing of the pubertal growth spurt occurs earlier in girls, typically at Tanner breast stage 3, and does not reach the magnitude of that of boys. Girls average a peak height velocity of 9 cm/year at age 12 and a total gain in height of 25 cm during the pubertal growth period [15]. Boys attain a peak height velocity of 10.3 cm/year, on average, 2 years later than girls, during Tanner genital stage 4, and gain 28 cm in height [16]. The longer duration of prepubertal growth in combination with a greater peak height velocity results in the average adult height difference of 13 cm between men and women [2].

Puberty is also a time of significant weight gain; 50% of adult body weight is gained during adolescence. In boys, peak weight velocity occurs at about the same time as peak height velocity (age 14) and averages 9 kg/year. In girls, peak weight gain lags behind peak height velocity by approximately 6 months and reaches 8.3 kg/year at about 12.5 [25,26]. The rate of weight gain decelerates in a manner similar to that of height velocity during the latter stages of pubertal development.

Sexual maturation occurs during puberty under the influence of gonadal steroid hormones (predominantly testosterone in males and estradiol in females) and the adrenal androgens, primarily dehydroepiandrosterone sulfate (DHEAS). Development usually occurs in a defined sequence within each gender, but individual variation does occur normally. Adrenarche, the production of adrenal androgens, generally occurs 1 to 2 years before the other hormonal changes of puberty, although visible evidence is generally not apparent until after thelarche in girls or testicular enlargement in boys. In both genders, adrenarche results in the appearance of sexual hair, adult-type body odor, and occasionally acne, and is a separate process from that of the centrally mediated gonadarche.

In boys, testicular enlargement and a thinning and reddening of the scrotum herald gonadarche. On average, this occurs between ages 11.5 and 12 years, but a broad range of normal exists. The onset of these changes before age 9 is considered precocious and later than age 14, delayed. The testes undergo enlargement from the prepubertal volume of 3 ml or less to 4 ml at the onset of puberty and undergo a

10-fold increase in size by the end of pubertal development [27]. Approximately 75% of boys will reach their peak height velocity during Tanner genital stage 4 and the remainder during stage 5. Sperm production and ejaculatory capability are present early during sexual development (biological age of 13.5 to 13.7 years) and do not correlate well with testicular size or other physical signs of sexual maturation.

The first evidence of gonadarche in girls is the appearance of breast buds (thelarche). This sign typically occurs between age 8 and 13 years, with an average of 11 years. Development before age 8 is considered precocious and later than age 13 delayed [2], although more recent data suggest that normal development may begin months earlier [8]. The pace of pubertal development correlates with the levels of sex steroid hormones during early puberty [28]. In girls, the duration of pubertal development is usually 3 to 3.5 years but may be completed within 2 years or take up to 5 to 6 years. Menarche usually follows the onset of breast development by about 2.5 years. In North America, the average age of menarche in girls of European descent is 12.8 to 13.3 years but slightly earlier in girls of African origin (12.5 years) [29,30]. Menstrual cycles tend to be anovulatory in more than half of girls up to 2 years beyond menarche, resulting in irregular intermenstrual intervals.

### Body Composition

The measurement of body composition has assumed an important role in endocrine and metabolic research studies as well as in the clinical practice of endocrinology. Physiologic growth occurs in all tissues at all times (fetal to adult). Body compositional changes, including the regional distribution of body fat, are especially large during the pubertal transition and markedly sexually dimorphic. It is important to understand the assumptions that are involved with each method of measurement because all human body composition methods are based on models that *indirectly estimate* the body composition. The major issue at puberty is the *changing* state of hydration of the fat-free mass (major source of metabolically active tissue) and thus methods that use a fixed value, usually that of the adult, lead to systematic overestimation of body fat. A detailed critique of the methods (two, three, and the criterion, 4 compartment models) has been published [31].

In general, from age 5 to 10 years, boys have 1 to 3 kilograms more fat-free mass (FFM) than girls, but

both accrue FFM at similar rates. They have similar amounts of fat mass from age 5 until about 10 years; however, the percentage of body fat is greater in the girls, who have approximately 1% more fat at age 5 years but about 6% by 10 years. During puberty, boys accrue FFM at a much greater rate and for a longer time so that the young adult amount of FFM is attained at age 15 to 16 years for girls, but 19 to 20 years for boys [32]. Pubertal girls increase the percentage of body fat and accrue fat mass at a rate of 1.14 kg/year. Pubertal boys decrease the percentage of body fat by 1.15 kg/year, but the fat mass remains relatively constant.

As noted above, marked changes in body composition, including alterations in the relative proportions of water, muscle, fat, and bone, are hallmarks of pubertal maturation and the result of typical female-male differences. Under the influence of the gonadal steroid hormones and the growth hormone, increases in bone mineral content and muscle mass occur, and the deposition of fat is maximally sexually dimorphic. The changes in the distribution of body fat (central vs. peripheral, subcutaneous vs. visceral, upper vs. lower body) result in the typical android and gynoid patterns of fat distribution of the older adolescent and adult [33]. Differential growth of the shoulders and hips and differences in lean tissue accrual between males and females are also evident.

Under the influence of testosterone, boys have a significant increase in the growth of bone and muscle with a simultaneous loss of fat in the limbs [26]. The maximal loss of fat and increase in muscle mass in the upper arms correspond to the time of peak height velocity. In boys, the significant increase in the amount of lean body mass exceeds the total gain in weight caused by the concomitant loss of adipose tissue. As height velocity declines, fat accumulation resumes in both genders but is twice as rapid in girls. As adults, males have 150% of the lean body mass of the average female and twice the number of muscle cells [34]. The increase in skeletal size and muscle mass leads to increased strength in males. Both androgens and estrogens promote deposition of bone mineral, and more than 90% of peak skeletal mass is present by age 18 in adolescents, who have undergone normal pubertal development at the usual time. In girls, nearly one-third of total skeletal mineral is accumulated in the 3- to 4-year period immediately after the onset of puberty [35,36]. Increases in both height and weight (to limits) are the strongest correlates of skeletal mineralization during childhood and adolescence. Boys have a marked age-related delay in skeletal mineralization com-

pared with girls. The former continue to accrue substantial bone mineral between the ages of 15 and 18 years. Increases in bone mineral density continue after the pubertal growth spurt. Adolescents with delayed puberty or secondary amenorrhea may fail to accrue bone mineral normally and have reduced bone mineral density as adults [37–42]. The pubertal accretion of bone mineral may account for more than one-half of the variability in bone mass in the elderly [43]).

The hormonal regulation of growth becomes increasingly complex with the onset of puberty. Adequate levels of thyroid hormone and cortisol continue to be prerequisites for normal growth, but the gonadal steroid hormones now play a major role. In addition, there is a dramatic activation of the GH/IGF-1 axis. During adolescence, the gonadal steroid hormones and the GH/IGF-1 axis continue to exert independent effects on growth, but of greater importance is the *interaction* between them, which subserves the dramatic alterations in linear growth and body composition during puberty. Other factors influencing bone mineralization during puberty include adequate calcium intake, physical activity, and ethnic background. African-American children have greater bone mineral density than do Caucasian and Hispanic children after age 5 years.

Pulsatile gonadotropin secretion has been documented at all ages, especially since the more sensitive third-generation assays have become available [44]. Puberty is heralded by an increase in the amplitude of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, which is detectable even before the external signs of puberty are evident. Initially, biologically relevant surges of LH occur predominantly at night, resulting in elevations of gonadal steroid hormone levels early in the morning. These then wane throughout the day. With continuing maturation of the hypothalamic-pituitary-gonadal axis, enhanced pulsatile LH release occurs throughout the waking hours as well, resulting in more stable elevations of gonadal steroid hormones. The rising levels of these hormones promote the development of secondary sex characteristics and the changes in body composition noted at puberty. Gonadal steroid hormones (primarily estradiol in both genders) also enhance bone mineral accrual and affect adult height by promoting epiphyseal fusion through direct effects on the growth plate [45].

During puberty, the GH/IGF-1 axis undergoes a dramatic activation. The rise in mean 24-hour GH levels results from an increase in the maximal GH secretory rate (pulse amplitude) and in the mass of

GH per secretory burst [46]. The differential increase in GH secretion between boys and girls at puberty follows the pattern of change in growth velocity. Girls show a significant rise in circulating GH levels beginning at Tanner breast stage 2, with the highest levels found at Tanner breast stage 3–4. An increase occurs later in males, peaking at Tanner genital stage 4 [47]. During mid-puberty the day–night rhythm is obscured because of a greater rate of rise in secretory amplitude during the day than at night. By the time adolescent development is complete, the levels of GH and IGF-1 decrease to prepubertal values in both genders.

During pubertal development the *interactions* between GH and the sex steroid hormones are striking and pervasive. Numerous studies of adolescent boys have shown that the rising levels of testosterone during puberty play a pivotal role in augmenting spontaneous GH secretion and production [46,48]. The ability of testosterone to stimulate pituitary GH secretion, however, appears to be transient, expressed only peripubertally, because GH and IGF-1 levels decrease significantly during late puberty and into adulthood despite continued high concentrations of gonadal steroid hormones [21]. In contrast with testosterone, estrogen modulates GH secretory activity in a disparate manner; low doses of estrogen stimulate IGF-1 production through enhanced GH secretion, but higher doses inhibit IGF-1 production at the hepatic level [49].

Clinical observations have shown that both GH and sex steroid hormones must be present for normal pubertal growth to occur. Individuals with a selective deficiency of either hormone (e.g., hypogonadotropic hypogonadism or isolated GH deficiency) experience an attenuated growth spurt [50,51]. Priming with sex steroids before GH provocative testing can stimulate the GH/IGF-1 axis and differentiate children with delayed puberty from those with GH deficiency [48].

Many of the growth-promoting effects of the gonadal steroid hormones are mediated through estrogens rather than androgens, via either direct secretion of estrogen or conversion of androgens to estrogen by peripherally located aromatase. Individuals with complete androgen insensitivity (formerly denoted testicular feminization) demonstrate that androgens are not necessary to support normal adolescent growth or to achieve pubertal levels of GH and IGF-1 if sufficient levels of estrogen are present [52]. Estrogens are also responsible for skeletal maturation and ultimate fusion of epiphyseal plates. Men with inactivating mutations of the estrogen

receptor gene or the aromatase gene have been described. Despite high levels of testosterone and normal virilization, these men have marked delays in skeletal maturation and continue to grow well into adulthood [42,53–54]. Studies utilizing nonaromatizable androgens or the estrogen-receptor antagonist tamoxifen have shown decreased GH secretion and IGF-1 levels [55,56]. Conversely, use of the androgen-receptor antagonist flutamide is associated with increasing circulating GH concentrations and daily production rate [57].

Leptin, the protein product of the obesity (*ob*) gene, has been the focus of many recent studies in humans. Because this hormone has been implicated in energy expenditure, nutrition, and puberty, some emphasis has been placed on its changes at puberty [58,59]. The mechanisms by which leptin regulates body weight and integrates adiposity with other neuroendocrine axes remain unclear. Leptin may also affect the timing and tempo because of its involvement in energy balance. It may be one of the factors through which activity (e.g., exercise training) and reduced adiposity affect the neuroendocrine axes. In effect, leptin may be a molecular signal linking nutritional status to the pubertal activation of the hypothalamic-pituitary-gonadal axis.

The relationship between gender, leptin concentration, and body fat mass accumulation during puberty remains unclear. Roemmich and colleagues [60] have noted that the gender difference in leptin concentrations of boys and girls is related to differences in the amounts of subcutaneous fat and greater androgen concentrations in boys. The leptin concentrations were more highly related to the subcutaneous fat mass than to the total fat mass.

### Conclusion

The changes in growth and body composition are now reasonably well-described, as are the activation and deactivation of some of the central and peripheral hormonal axes. Many changes in body composition may be highly correlated with changes in individual hormone levels and mode of secretion, but causal relationships among these various hormonal axes have yet to be rigorously defined [61]. It is very likely that *interactions* among these axes [62] are more important than their main effects and that alterations in body composition and the regional distribution of body fat actually are signals to alter the neuroendocrine and peripheral hormonal axes, for example, hypothalamic-pituitary-hormone re-

lease and insulin secretion. These processes are merely magnified during pubertal development but likely are pivotal all the way from fetal growth to the aging process.

My long-term colleagues Drs. Robert M. Blizzard and Johannes D. Veldhuis are gratefully acknowledged for their insight and support into the longitudinal and hormonal secretory aspects of the multiple studies done at the University of Virginia over the past 20 years.

### References

1. Tanner JM, Healy MJR, Lockart RD, et al. Aberdeen growth study: I. The prediction of adult body measurement from measurements taken each year from birth to five years. *Arch Dis Child* 1956;31:372.
2. Tanner JM. *Fetus Into Man: Physical Growth from Conception to Maturity*. Cambridge, MA: Harvard University Press, 1989.
3. Sinclair D. *Human Growth After Birth*. London: Oxford University Press, 1978:1–15,140–159.
4. Smith DW. *Growth and Its Disorders*. Philadelphia: WB Saunders Co., 1977.
5. Tanner JM. Auxology. In: Kappy MS, Blizzard RM, Migeon CJ (eds). *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, 4th edition. Springfield, IL: Charles C. Thomas, 1994:137–92.
6. Roemmich JN, Blizzard RM, Peddada SD, et al. Longitudinal assessment of hormonal and physical alterations during normal puberty in boys. IV: Predictions of adult height by the Bayley-Pinneau, Roche-Wainer-Thissen, and Tanner-Whitehouse methods compared. *Am J Human Biol* 1997;9:371–80.
7. Tanner JM, Oshman D, Bahhage F, Healy M. Tanner-Whitehouse bone age reference values for North American children. *J Pediatr* 1997;131:34–40.
8. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: A study from the Pediatric Research in Office Settings Network. *Pediatrics* 1999;99:505–12.
9. Epstein LH, Wing RR, Valaski A. Childhood obesity. *Pediatr Clin North Am* 1985;32:363–79.
10. Forbes GB. Influence of nutrition. In: Forbes GB (ed). *Human Body Composition. Growth, Aging, Nutrition and Activity*. New York: Springer-Verlag, 1987:209.
11. Wales JKH, Gibson AT. Short term growth: Rhythms, chaos, or noise? *Arch Dis Child* 1994;71:84–9.
12. Roemmich JN, Sinning WE. Sport-seasonal changes in body composition, growth, power and strength of adolescent wrestlers. *Int J Sports Med* 1996;17:92–9.
13. Malina RM. Physical growth and biological maturation of young athletes. *Exerc Sport Sci Rev* 1994;22:389–433.
14. Baxter-Jones ADG, Helms P, Baines-Preece J, Preece M. Menarche in intensively trained gymnasts, swimmers and tennis players. *Ann Hum Biol* 1994;21:407–15.
15. Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. *Arch Dis Child* 1969;44:291–303.
16. Marshall WA, Tanner JM. Variations in patterns of pubertal changes in boys. *Arch Dis Child* 1970;45:13–23.
17. Robson JRK, Larkin FA, Bursick JH, Perri KP. Growth standards for infants and children: A cross-sectional study. *Pediatrics* 1975;56:1014–20.
18. Berkey CS, Wang X, Dockery DW, Ferris BG. Adolescent height growth of U.S. children. *Ann Hum Biol* 1994;21:435–42.

19. Biro FM, McMahon RP, Striegel-Moore R, et al. Impact of timing of pubertal maturation on growth in black and white female adolescents: The National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr* 2001;138:636-43.
20. Roche AF, Himes JH. Incremental growth charts. *Am J Clin Nutr* 1980;33:2042-52.
21. Martha PM Jr, Rogol AD, Veldhuis JD, et al. Alterations in the pulsatile properties of circulating growth hormone concentrations during puberty in boys. *J Clin Endocrinol Metab* 1989;69:563-70.
22. Thissen J, Ketelslegers J, Underwood LE. Nutritional regulation of the insulin-like growth factors. *Endocr Rev* 1994;15:80-101.
23. Smith WJ, Underwood LE, Clemmons DR. Effects of calorie or protein restriction on insulin-like growth factor-1 (IGF-1) and IGF-binding proteins in children and adults. *J Clin Endocrinol Metab* 1995;80:443-9.
24. Tanner JM, Whitehouse RH, Marshall WA, Carter BS. Prediction of adult height, bone age, and occurrence of menarche, at ages 4 to 16 with allowance for midparental height. *Arch Dis Child* 1975;50:14-26.
25. Barnes HV. Physical growth and development during puberty. *Med Clin North Am* 1975;59:1305-17.
26. Tanner JM. The relationship of puberty to other maturity indicators and body composition in man. *Symp Soc Stud Hum Biol* 1965;6:211.
27. Marshall WA. Growth and sexual maturity in normal puberty. *Clin Endocrinol Metab* 1975;4:3-25.
28. DeRidder CM, Thissen JHH, Bruning PF, et al. Body fat mass, body fat distribution, and pubertal development: A longitudinal study of physical and hormonal sexual maturation in girls. *J Clin Endocrinol Metab* 1992;75:442-6.
29. Zacharias L, Wurtman RJ. Sexual maturation in contemporary American girls. *Am J Obstet Gynecol* 1970;108:833-46.
30. Finkelstein JW. The endocrinology of adolescence. *Pediatr Clin North Am* 1980;27:53-69.
31. Roemmich JN. Alterations in body composition during puberty. *Curr Opin Endocrinol Diabetes* 1998;5:11-8.
32. Malina RM, Bouchard C. Growth, Maturation, and Physical Activity. Champagne, IL: Human Kinetics Press, 1991.
33. Roemmich JN, Clark PA, Walter K, et al. Physical activity energy expenditure, body composition, and abdominal fat distribution during puberty. *Am J Physiol Endocrinol Metab* 2000;E1426-36.
34. Cheek DB, Grumbach MM, Grave GD, et al (eds). Control of Onset of Puberty. New York: John Wiley & Sons, 1974.
35. Bonjour J, Theintz G, Buchs B, et al. Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. *J Clin Endocrinol Metab* 1991;73:555-63.
36. Slemenda CW, Reister TK, Hui SL, et al. Influence on skeletal mineralization in children and adolescents: Evidence for varying effects of sexual maturation and physical activity. *J Pediatr* 1994;125:201-7.
37. Davies MC, Hall ML, Jacobs HS. Bone mineral loss in young women with amenorrhea. *Br Med J* 1990;301:790-3.
38. Drinkwater BL, Nilson K, Chestnut CH III, et al. Bone mineral content of amenorrheic and eumenorrheic athletes. *N Engl J Med* 1984;311:277-81.
39. Finkelstein JS, Klibanski A, Neer RM, et al. Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. *Ann Intern Med* 1987;106:354-61.
40. Finkelstein JS, Neer RM, Biller BMK, et al. Osteopenia in men with a history of delayed puberty. *N Engl J Med* 1992;326:600-4.
41. Mora S, Weber G, Guarneri M, et al. Effect of estrogen replacement therapy on bone mineral content in girls with Turner syndrome. *Obstet Gynecol* 1992;79:747-51.
42. Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N Engl J Med* 1994;331:1056-61.
43. Hui SL, Slemenda CW, Johnston CC. The contribution of bone loss to postmenopausal osteoporosis. *Osteoporosis Int* 1990;1:30-4.
44. Pandian MR, Odell WD, Carlton E, Fisher DA. Development of third-generation immunochemiluminometric assays of follitropin and lutropin and clinical application in determining pediatric reference ranges. *Clin Chem* 1993;39:1815-9.
45. Attie KM, Ramirez NR, Conte FA, et al. The pubertal growth spurt in eight patients with true precocious puberty and growth hormone deficiency: Evidence for a direct role of sex steroids. *J Clin Endocrinol Metab* 1990;71:975-83.
46. Martha PM Jr, Gorman KM, Blizzard RM, et al. Endogenous growth hormone secretion and clearance rates in normal boys, as determined by deconvolution analysis: Relationship to age, pubertal status, and body mass. *J Clin Endocrinol Metab* 1992;74:336-44.
47. Albertsson-Wikland K, Rosberg S, Karlberg J, Groth T. Analysis of 24-hour growth hormone profiles in healthy boys and girls of normal stature: Relation to puberty. *J Clin Endocrinol Metab* 1994;78:1195-1201.
48. Rose SR, Kibarian M, Gelatto M. Sex steroids increase spontaneous growth hormone secretion in short children. *J Pediatr Endocrinol* 1989;3:1-5.
49. Ho KY, Evans WS, Blizzard RM, et al. Effects of age and sex on the 24-hour profile of growth hormone secretion in man: Importance of endogenous estradiol concentrations. *J Clin Endocrinol Metab* 1987;64:51-8.
50. Aynsley-Green A, Zachman M, Prader A. Interrelation of the therapeutic effects of growth hormone and testosterone on growth in hypopituitarism. *J Pediatr* 1976;89:992-9.
51. Liu L, Merriam GR, Sherins RJ. Chronic sex steroid exposure increases mean plasma growth hormone concentration and pulse amplitude in men with isolated hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 1987;64:651-6.
52. Zachmann M, Prader A, Sobel EH, et al. Pubertal growth in patients with androgen insensitivity: Indirect evidence for the importance of estrogens in pubertal growth of girls. *J Pediatr* 1986;108:694-7.
53. Conte FA, Grumbach MM, Ito Y, et al. A syndrome of female pseudohermaphroditism, hypergonadotropic hypogonadism, and multicystic ovaries associated with missense mutations in the gene encoding aromatase (P450arom). *J Clin Endocrinol Metab* 1994;78:1287-92.
54. Morishima A, Grumbach MM, Simpson ER, et al. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiologic role of estrogens. *J Clin Endocrinol Metab* 1995;80:3689-98.
55. Metzger DL, Kerrigan JR. Estrogen receptor blockade with tamoxifen diminishes growth hormone secretion in boys: Evidence for a stimulatory role of endogenous estrogens during male adolescence. *J Clin Endocrinol Metab* 1994;79:513-8.
56. Veldhuis JD, Metzger DL, Martha PM Jr, et al. Estrogen and testosterone, but not a non-aromatizable androgen, direct network integration of the hypothalamo-somatotrope (GH)-IGF-I axis in the human: Evidence from pubertal pathophysiology and sex-steroid hormone replacement. *J Clin Endocrinol Metab* 1997;83:3414-20.
57. Metzger DL, Kerrigan JR. Androgen receptor blockade with flutamide enhances growth hormone secretion in late pubertal

- males: Evidence for independent actions of estrogen and androgen. *J Clin Endocrinol Metab* 1993;76:1147-52.
58. Apter D. Leptin in puberty. *Clin Endocrinol* 1997;47:175-6.
59. Rogol AD. Leptin and puberty. *J Clin Endocrinol Metab* 1998;83:1089-90.
60. Roemmich JN, Clark PA, Berr SS, et al. Alterations in growth and body composition during puberty: II. Relation of serum leptin concentrations to gender, maturation, body composition, fat distribution and energy expenditure. *Am J Physiol* 1998;275:E543-E551.
61. Roemmich JN, Clark PA, Mae V, et al. Alterations in growth and body composition during puberty: III. Influence of maturation, gender, body composition, fat distribution, aerobic fitness and energy expenditure on nocturnal growth hormone release. *J Clin Endocrinol Metab* 1998;83:1440-7.
62. Zhang J, Peddada SD, Malina RM, Rogol AD. A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. IV. Modeling of growth velocity, mean growth hormone (GH mean) and serum testosterone T concentrations. *Am J Human Biol* 2000;12:814-24.