GROWTH/GROWTH DISORDER

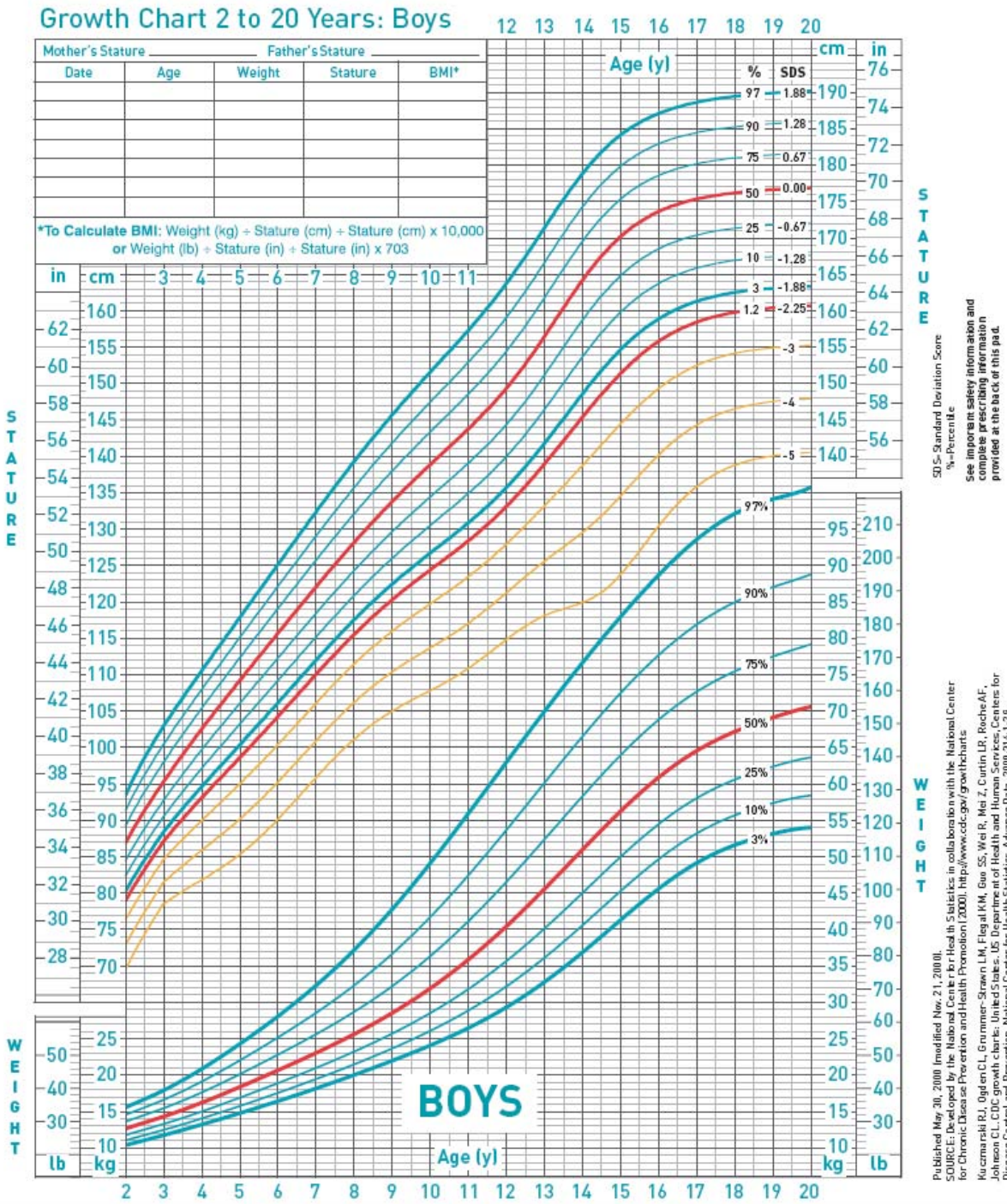## Dr. Sharon Oberfield
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Auxology is the scientific study of the growth and development of children on both a societal and an individual level. On a societal level, the stature achieved by the general population of children and adults reflects the socioeconomic status of that society. On an individual level, a multitude of endocrine, nutritional, metabolic, genetic, and psychological factors are involved in the pattern of an individual child's growth, which therefore provides a physician with a very useful marker of that child's state of health.

GROWTH PATTERNS

The standard so-called longitudinal, or "distance," growth charts currently used in the U.S. to track an individual's linear growth at various ages are based on nation-wide data involving a heterogeneous population of children gathered by the National Center for Health Statistics in 1979, updated in 2000. Using the charts, a child's growth pattern can be tracked from birth to age 18. The charts show the mean and 5th percentile and 95th percentile limits (**Figure 1**).

Because of subtle differences between the sexes, separate charts are used for boys and girls. Boys grow slightly more than girls in utero and are born slightly longer than girls (mean 50.4 cm, 19.9", compared to 49.7 cm, 19.6"). The prenatal differential in growth rate is lost soon after birth, and although boys remain on average very slightly taller than girls for most of childhood, the two sexes' growth rates are identical. The growth rate in both sexes is most rapid in the first year (average, 10"), then decelerates over the next few years to an average rate of 2–2.5", which is maintained from about 3–4 years on until the onset of puberty. During this childhood period the two hormones most important for growth are growth hormone and thyroid hormone. At puberty, under the influence of estrogen and testosterone, the growth rate increases once more, although never reaching the rapid rate of infancy. The mean peak growth rate, in mid-puberty, is 8.3 cm/year (3.25") for girls, 9.5 cm (3.75") for boys. The two sexes diverge at puberty: pubertal growth starts earlier in girls, at an average age of 10.5 and continues until the epiphyses of the bones fuse and growth ceases at an average age of 16. Boys start their growth spurt on average 2 years later than girls, at about 12.5, at which point they are about 8 cm taller than girls were when their sexual development started. Boys have a more extended growth spurt, stop growing at an average age of 18, and are about 12.5 cm (5") taller as adults than women are.

It requires the action of the sex hormones, in particular, estrogen in both sexes, for the cartilaginous growth plates of the bones to disappear, the epiphyses to fuse to the metaphyses, and further growth to cease.

Figure 1: Growth Curve
Eli Lilly

In girls the average age at which breast development (thelarche) begins is 10.5 although there is great variability and the normal age at thelarche ranges from 8 to 13. Age at menarche in the U.S. is on average 12 years, 3 months and can occur over a range of 10 to 16.5. Menarche occurs as growth is decelerating and bone fusion has started. After menarche, a girl grows about 2–3" more.

In boys the first visible sign of puberty is usually testicular enlargement, at an average age of 12.5, with a range in age of 10 to 13.5. Peak growth rate occurs at about 15. Thereafter, growth decelerates and ceases at about 18 years.

SECULAR TREND

The so-called secular trend is the name given to the observation that in the economically developed countries over the past 100–200 years there has been a general trend to earlier sexual maturation and, to a lesser extent, to an increase in the average adult size of men and women. The age at menarche in Western countries has advanced an average of 3–4 months every decade since the 1850's. The major factors responsible for this secular trend are better nutrition and a lessening of disease. Once the optimal state of general nutrition in a society has been reached and stabilizes, the secular trend levels off. This has happened in the U.S., and the age at menarche has not changed significantly in a few decades.

BODY MATURATION

In addition to linear growth, children's body proportions change as they age and mature. This maturation is primarily under the influence of thyroid hormones. Comparing the body's upper segment (measurement from the top of the head to the top of the symphysis pubis) with the lower segment (measured from the top of the symphysis pubis to the bottom of the feet), an infant is born with an upper/lower (U/L) segment ratio of 1.7, the head and trunk being almost twice as long as the lower extremities. As the child matures, the legs grow faster than the trunk so that as the child approaches puberty, the U/L segment ratio is 1. Under the influence of the sex hormones, the extremities continue to grow faster than the trunk (U/L segment ratio about 0.9). However, the legs stop growing earlier than the trunk, and the adult U/L segment ratio is again 1.

BONE AGE

Growth can be assessed by measuring serially the height and weight of a child. A child's body maturation is more difficult to assess. It can sometimes be quite different from the chronological age of the child. The most sensitive measurement of body maturation is a radiologic estimation of the bone age: The epiphyses of the bones are mostly cartilaginous at birth. As a child matures, the epiphyses calcify and the amount and configuration of that calcification change in relation to the shafts of the bones, having a characteristic appearance at each age. Eventually the calcified epiphyses fuse with the shafts, the growth zones disappear, and growth ceases at the end of puberty. The best-studied progression of bone maturation has been in the hands, and an x-ray of the child's wrist and hand for a "bone age" is the best objective marker we have for assessing the actual maturation of a child's body. From this we can estimate a child's growth potential. For example a boy of 14 with a bone age of 12 (epiphyses which resemble best the stage of calcification of a 12 year old) has completed about 84% of his growth; a boy of 14

with a bone age of 14 has completed 92% of his growth. Knowing this and the boy's height at the time the x-ray was taken, one can get an estimate of his growth potential and his projected adult height.

ORGAN GROWTH

Linear growth is primarily skeletal and muscular growth. Each organ system in the body has its own inherent rhythm of growth, which may be quite different from the pattern of general body size increase. For example, the brain has achieved 80% of its adult size by the age of 2 and in general stops increasing in size by age 11–12. A 10 year old may have almost twice as much lymphoid tissue as he or she will have as an adult. The ovaries and testes hardly change in size until the second decade of life. Such disparate patterns of growth have significance when evaluating diseases of the various organ systems.

GROWTH; CLINICAL CONSIDERATIONS

SHORT STATURE

Since the pattern of a child's growth not only reflects his or her genetically determined potential but also can be influenced by the child's general state of physical and mental well-being, it is necessary in considering the unusually short child to decide first of all whether the child's stature is normal or abnormal for that child. Fortunately, the vast number of short children are healthy and are only reflecting genetic variations in size. Their normal pattern of growth separates them from those children who have organic conditions that must be addressed.

Definitions
Short stature: height > 2.0 standard deviations below the mean height for age and sex (at or below the 3rd percentile) (see curve, Figure 1)
Slow normal growth: normal pattern paralleling the normal growth curve, unchanging deviation from the mean
Growth failure: progressive fall-off in rate of growth, increasing deviation from the mean and from the normal curve.

The myriad causes of short stature fall into four broad categories: genetic, endocrine, metabolic/nutritional, and end-organ abnormalities.

Genetic
Familial short stature
Constitutional growth delay

These two categories of genetically based short stature account for the vast majority of short children. Children in both these categories are born with normal length and weight, but by the end of the first two years of life have dropped to the 5th percentile or below in height. They then grow consistently throughout childhood at the level they have established. Their growth rate is, and stays, at the lower limit of normal. There is no true growth failure. The pattern of growth before puberty is the same for both familial short stature and constitutional growth delay, which cannot be distinguished from each other by their growth charts. They can be separated from one

another only by their different body maturations. The child with familial short stature has a body maturation normal for his or her age. The bone age is normal. The child will go into puberty and stop growing at the usual age and will be a short adult with a height in the same percentile as an adult that it was in when a child.

The child with constitutional growth delay, on the other hand, has an immature body maturation as measured by a delayed bone age and therefore more growth potential for his or her chronological age. Such a child will be a "late bloomer," will grow longer, go into puberty later, and stop growing at a later age than the child with familial shortness. He or she will be taller as an adult, will have achieved a higher percentile, and be closer to the average than as a child.

There is usually a family history of similar patterns of growth in childhood.

These two categories comprise over 90% of short children. Thus, over 90% of short children can be identified as normal by their normal birth size and normal growth pattern.

Intrauterine growth retardation

Unlike the previous two categories of genetic shortness, these children are identified as small for gestational age in utero and are abnormally small in both length and weight at birth. Such children are also known as primordial ("from the germ cell") dwarfs. An infant with IUGR might be born at term weighing, for example, 3 lb (normal lower limit, 5 lb 8 oz) and being 16" long (normal average, 20"). Several syndromes have been identified, all characterized by prenatal growth failure. Among these are:

Russell dwarfism—triangular face, gracile limbs, normal IQ
Silver dwarfism—hemihypertrophy and tendency to early puberty
Seckel's "bird-headed" dwarfism—high cheek bones, small chin, severe mental
    retardation, hypoparathyroidism
Bloom's syndrome—facial telangiectasia, marked chromosome breakage, tendency to
    develop early malignancies.

All are characterized by IUGR, prenatal and postnatal growth failure, and very short adult height. Men with the Russell-Silver syndrome average 152 cm (about 5'), women 144.7 cm (4'9").

X chromosome abnormalities (Turner's syndrome or XO gonadal dysgenesis)

Although many genes determine stature, important ones reside on the short arm of the X chromosome. Girls with deletions of all (X,) or part of the X chromosome have growth failure, with or without other characteristic physical features such as extra skin folds of the neck (pterygium colli), increased carrying angles of the elbows (cubitus valgus), and lymphedema of fingers and legs. More significant is the absence of functioning gonadal tissue ("streak gonads"), with consequent failure to enter puberty, and infertility. Associated cardiac abnormalities include bicuspid aortic valves and coarctation of the aorta. Structural abnormalities of the kidneys are often present. Girls with Turner's Syndrome are prone to thyroiditis and may have sensoneural hearing loss.

The growth pattern shows increasing deviation from the mean. Adult height without treatment averages 4'8".

Endocrine causes of short stature

The hormones most directly involved in prepubertal growth are growth hormone and thyroid hormone. Growth hormone is responsible for linear growth, primarily through the action of GH and even more important, the GH-dependent factor, IGF l, on the cartilaginous growth plates of the bones. Thyroid hormone, in addition, is responsible for proper body maturation.

Once GH is secreted from the somatotroph, it is bound to a specific peptide (GHBP) and transported to hepatic target sites. The GHBP is the extracellular domain of the GH receptor. When GH binds to its receptor, it initiates the signaling pathway through the transmembrane elements of the GH receptor and via the intracellular domain, activating the Janus Kinase (JAK 2) system, which in turn activates the signal transducers and activators of transcription (STATs). Docking sites on genomic DNA allow binding of the specific STAT5b, leading to initiation of transcriptional sequences for components of a ternary complex: IGF-1, IGFBP-3, and acid labile subunit (ALS). The ternary complex forms a stable unit allowing the transport of IGF-1 to its target site, the type 1 IGF-1 receptor on epiphyseal chondrocytes, leading to their proliferation and resulting in linear growth.

Several studies have recently confirmed that the GHR is already constitutively dimerized prior to growth hormone binding. The binding of growth hormone appears to cause a conformational shift in this dimer with rotation in the intracellular domain. This aligns the JAK2 on each dimer allowing tyrosine phosphorylation to begin. It also appears that usually the JAK2 domains are too close together and inhibition of kinase activity occurs via a pseudo-binding inhibitory domain. As growth hormone binds to the GH receptor, not only is there rotation of the GHR dimer complex but there is also a widening of the gap between individual intracellular GHR domains. This appears essential for activation of JAK 2 (Data originally presented by Dr. Michael Waters at LWPES/ESPE meeting in September 2009).

The discrete steps by which STAT5b is initiated, binds to DNA sites, activates DNA polymerase, which then transcribe for IGF-1, IGFBP-3, and ALS, are being elucidated. Recently, growth failure due to the abnormalities of the GH signal pathway, such as mutations of STAT5b, has been identified in pediatric patients, whose short stature was previously termed idiopathic. **Table 1** denotes a simplified scheme of our current knowledge of the growth system cascade. **Figure 2** is a pictorial representation.

TISSUE	GROWTH FACTOR	GENOMIC ORGANIZATION	CLINICAL/LAB PRESENTATIONS
Hypothalamus	GHRH	• PTX 1, HESX 1	• Hypothalamic (idiopathic GH deficiency) • Hypothalamic infiltrative disease
	↓		
Pituitary	GH	• PROP 1, PIT 1, LHX 3, GH 1, POU1F1	• Pituitary tumors • Hypoplasia
	↓		
Hepatocytes, Osteoblasts	GH Receptor	• GHR 1	• Growth hormone resistance
	↓		
	J2K, Stat 5b		
	↓		
	IGF1, IGFBPs, ALS		
	↓		
Chondrocytes	IGF1 Receptor	• IGF1 mRNA gene, IGF1 receptor gene	• IGF1 resistance

Table 1: Growth Failure Resulting from Reduced GH Secretion or Action.
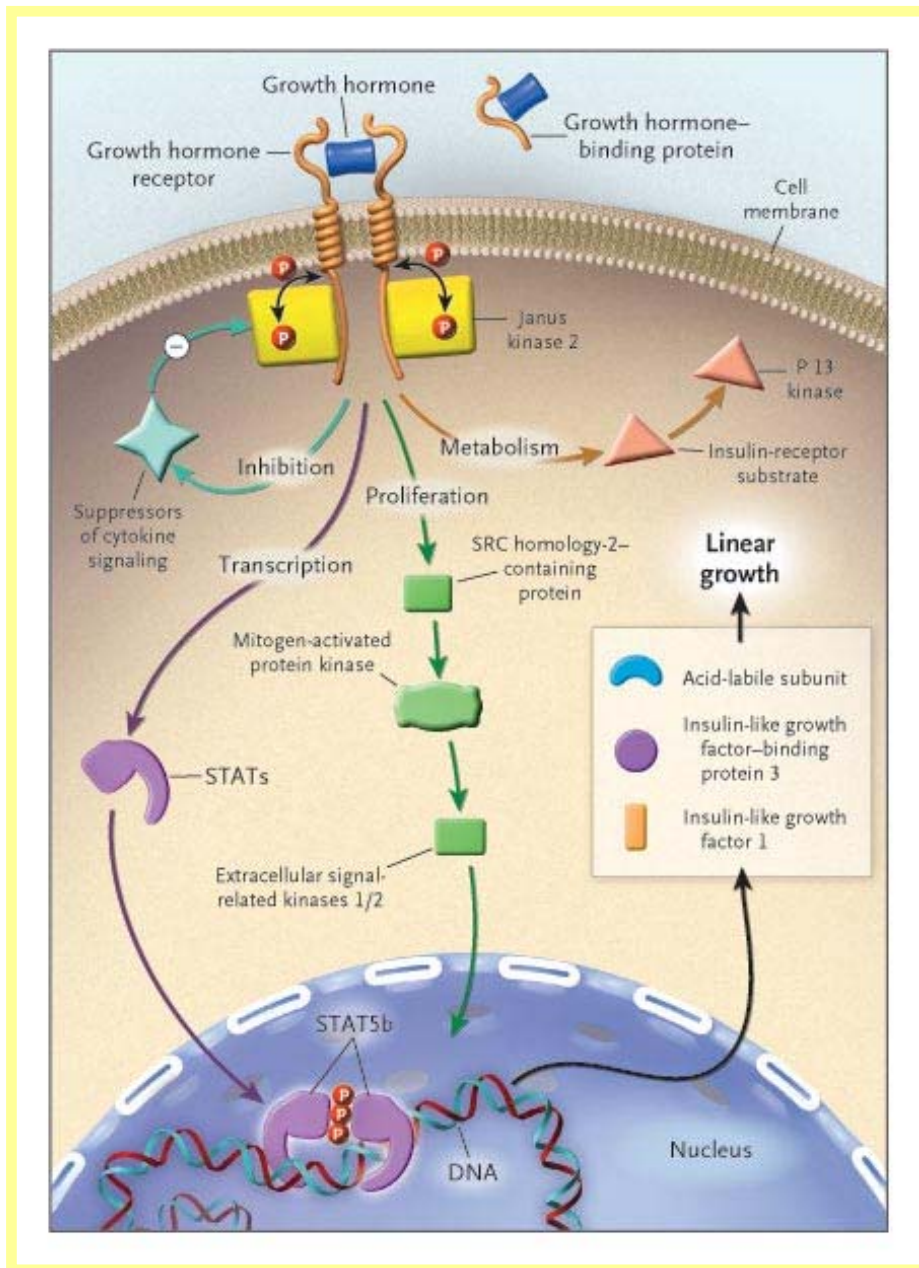
Figure 2: Growth Hormone-Activating Intracellular Signaling
Eugster, E. A. et. al. N Engl J Med 2003;349:1110-1112

Panhypopituitarism

Idiopathic:

characterized by small or absent anterior pituitaries with deficiencies of GH, TSH, ACTH, FSH and LH. Profound growth failure from early childhood with characteristic chubby and immature appearance.

Organic:

hypopituitarism due to destruction of the pituitary gland by tumor, usually a craniopharyngioma, granulomas, or other masses. Growth failure dates from the age at which the pituitary damage occurs. Other causes of panhypopituitarism which cause growth failure include congenital structural abnormalities of the brain affecting the area of the hypothalamus. For example, septo-optic dysplasia (absent septum pellucidum and hypoplastic optic nerves) is associated with deficiencies of hypothalamic releasing hormones such as GH releasing hormone and of the supraoptic and paraventricular nuclei where vasopressin is synthesized. Unlike idiopathic hypopituitarism which involves deficiency only of the hormones of the anterior pituitary, organic hypopituitarism may be associated with deficiency of the posterior pituitary hormone, vasopressin, also.

Functional:

Psychosocial dwarfism (emotional deprivation or maternal deprivation syndrome) is a form of reversible growth hormone deficiency which develops secondary to psychological stresses caused by a hostile psychosocial environment. In addition to significant growth failure, children with this syndrome have a set of bizarre behavioral disturbances, including hyperactivity, drinking out of toilet bowls, and eating garbage. The majority of these children will be growth hormone–deficient when tested but will grow dramatically when removed from the emotionally hostile environment, and when retested will have a normal GH response.

The profound malnutrition associated with anorexia nervosa can be associated with growth failure and pubertal arrest. In the majority of patients with anorexia, GH levels are increased and IGF 1 and IGFBP 3 levels are significantly reduced, suggestive of GH resistance. Furthermore, FSH and LH are low. Most hormone levels will return spontaneously to normal when weight gain occurs.

Isolated growth hormone deficiency

This is probably the most common pituitary deficiency of childhood, believed in the majority of cases to be due to an absence of hypothalamic growth hormone-releasing hormone. It usually presents with growth failure as an isolated finding. Although affected children may be pudgy and look immature for their age, their body proportions are normal and bone age is appropriate or advanced for the child's "height age" (the age at which the child's height would be in the 50th percentile), although the bone age is retarded below the child's chronological age. **(GH levels are low. IGF-1 levels are low.)**

Peripheral resistance to growth hormone

In 1984 Zvi Laron described children with growth failure and the physical appearance of growth hormone deficiency, but with elevated levels of GH in their blood. However, the growth hormone–dependent factors, IGF 1 and IGF binding protein 3, were very deficient, and serum growth hormone binding protein (GHBP), which is believed to be a protein derived from the extracellular part of the GH receptor, was decreased in amount, suggesting that the primary defect is an absence of or decrease in tissue GH receptors. Laron dwarfism is an autosomal

recessive disorder identified primarily in families in the Mideast and Ecuador. In addition to a characteristic appearance, with frontal bossing of the forehead, a depressed nasal bridge, and relatively short extremities, the children have the growth failure of severe growth hormone resistance. The heights of adult men with this condition range from 119 cm to 143 cm (3'11" – 4'8.5"), of women, from 100 cm to 136 cm (3' 3.5" - 4' 5.5".) **(GH levels are high. IGF-1 levels are low.)**

Stat 5b mutations

Several papers have examined a mutation in the STAT system, specifically of the STAT5b gene. Koefed and colleagues examined a child with consanguineous parents; the child had growth failure and failure-to-thrive almost immediately following birth, but she did not have intrauterine growth retardation (IUGR). The child had a broad forehead and saddle nose, and she had a normal basal GH level. IGF-1, IGFBP-3, and the ALS were markedly low, and she showed no significant growth response to one year of GH therapy. Patients with this defect will continue to drop further below the third percentile for height over time. Because the defect lies in the pathway that ultimately leads to IGF-1, patients with STAT5b mutations will not respond to GH treatment but might be candidates for IGF-1 replacement therapy. **(GH levels are high. IGF-1 levels are low.)**

Type 1 IGF receptor defects

Patients with type 1 IGF receptor defects have unexplained IUGR, short stature more than two standard deviations below the mean and IGF-1 levels more than two standard deviations above the mean. Also, these patients will be well below the third percentile for height, but unlike those with the STAT5b mutation, their growth may be parallel to the third percentile. These characteristics may indicate a loss of function of type 1 IGF receptors.

There can also be a deletion of the IGF-1 gene itself. One case study of a boy born with IUGR is different from the previous example because his height continued to distance itself from the third percentile as he aged. **(GH levels are high. IGF-1 levels are high.)**

Primary hypothyroidism

In addition to growth failure, the child with thyroid hormone deficiency will have immature body proportions and features and a bone age retarded to even younger than the "height age"; that is, body maturation is more affected than linear growth. Associated physical findings are dry yellowish skin, pudginess, immature facial features, constipation, and mental slowness.

Delayed puberty

Since children who do not enter puberty at the expected time fail to show rapid pubertal growth at the same time as their peers, their growth pattern appears to deviate downward from the percentile along which they had been growing. This apparent growth failure is an illusion of the growth charts, since the child with delayed puberty continues to grow steadily at a normal prepubertal growth rate. Such a picture can be seen with the delayed puberty associated with constitutional growth delay. It is also seen in children with failure of sexual development due to gonadotropin deficiency or gonadal failure.

Cushing's syndrome

Spontaneous Cushing's syndrome is seen relatively infrequently in the pediatric age group although iatrogenic Cushing's syndrome can be seen in children treated with high-dose glucocorticoid therapy for malignancy, nephrotic syndrome, and other conditions. ACTH-producing pituitary adenomas or glucocorticoid-secreting adrenal tumors are infrequent, and

ectopic ACTH production very rare in pediatrics. In addition to the typical features of the syndrome (a round, plethoric face, central obesity, prominent striae, and so on) there is a striking and profound cessation of linear growth. This growth failure is due to derangements in GH metabolism: the release of GH from the pituitary, the synthesis and release of IGF 1 from the liver, and the action of IGF 1 on the chondrocytes of the growth plate are all inhibited by the presence of excess glucocorticoids.

Metabolic and nutritional disturbances

In addition to an intact genetic and hormonal milieu, normal growth requires a normal metabolism and adequate nutrition.

Chronic anoxia: Conditions associated with chronic anoxia such as cyanotic congenital heart disease are associated with impaired growth, possibly as a result of the fact that the supply of oxygen needed for normal energy metabolism is compromised but also in large part as a result of the poor nutritional status of these compromised children

Acidosis/uremia: When renal function falls below 30% of normal and acidosis and uremia are present, chronic renal disease is accompanied by a significant growth failure. Although anorexia, urinary protein wasting, and bone abnormalities (renal rickets) associated with renal failure play a part, the growth failure is primarily due to abnormal GH metabolism. Although growth hormone levels in the blood are normal, hepatic synthesis of IGF 1 is deficient. In addition, there is an increase in the serum IGF binding protein (IGFBP 3), and thus there is less free IGF 1 available for local action on the growth plates.

Malnutrition and malabsorption:

Caloric deprivation causes growth failure. In profound malnutrition an inhibitor of IGF 1 activity is found in the serum. But much more subtle forms of malabsorption and malnutrition exist which may often be unsuspected until they present as growth failure. Regional ileitis (Crohn's disease) is an often unsuspected cause of growth failure as GI symptoms can be mild or absent. The mechanism for the growth failure is a significant leakage of proteins into the stool from the inflamed small intestine ("protein-losing enteropathy"). Untreated celiac disease and chronic diarrhea secondary to parasitic infestation may also present as growth failure.

End organ (skeletal) disorders

Genetic abnormalities in the formation of cartilage and bone result in profound compromise of stature, with disproportionate body measurements, as is seen in achondroplasia and other chondrodystrophies. Although the disproportion is readily apparent on physical examination, identification of the particular type of chondrodystrophy causing the growth failure is based on radiologic criteria.

TALL STATURE

The same considerations relevant to the short child apply also to the unusually tall child, that is, 2 standard deviations or more above the mean for age and sex (>97%.) As in the case of short stature, the great majority of such children are expressing a normal pattern of growth which should be differentiated from pathological overgrowth. The normally tall child's growth will

parallel the normal growth curve; the pathologically tall child will accelerate further from it, with increasing deviation upward from the mean.

Genetic
Familial tall stature
Constitutional acceleration of growth and development

Most of the tall children brought to the attention of the endocrinologist are expressing one of these two benign growth patterns. The children in both categories are of normal height at birth, rise to or above the 90th–95th percentile by about 18 months of age, and grow consistently along their curve throughout childhood. The two conditions can only be differentiated on the basis of differences in body maturation. In familial tall stature, the bone age is appropriate for the chronological age, puberty will occur at the average age, and the adult height will be in the same percentile as in childhood. The child with constitutional acceleration of growth and development will have a body maturation advanced for his or her age, the child will go into puberty in the early range of normal, and will stop growing at a younger age. The adult height will be at a lower percentile, more toward average, than it was during childhood.

Prenatal overgrowth syndromes
There are several genetic syndromes associated with pre- and postnatal overgrowth. Associated physical findings are diagnostic. Among them are:

Soto's syndrome (cerebral gigantism): large birth size with excessively rapid growth in the first 2–4 years of life. Thereafter, growth rate decelerates so that growth parallels the 95th percentile. The face characteristically has hypertelorism, high-arched palate, and prominent jaw. Neuroradiologic studies show large cerebral ventricles without increased pressure. In more than 90% of patients, Soto Syndrome is due to haploid insufficiency of NSD1- Nuclear Receptor Su-var Enhancer of Zeste and Trithorax Domain Protein 1, chromosome 5q35, OMIM 606681. Cerebral gigantism is thus a genetic condition due to heterozygous microdeletion and loss of function mutations of NSD1. Tumors occur in 2-4% of patients with cerebral gigantism and surveillance after age 8-10 years is suggested.

Beckwith-Wiedemann syndrome: fetal and neonatal gigantism associated with omphalocoele, hemihypertrophy, macroglossia, and neonatal hypoglycemia. Affected children and adults are at or beyond the 90th percentile. In many cases, overexpression of the paternally imprinted gene for IGF 2, a fetal growth factor, due to an excess of paternal over maternal alleles of chromosome 11 p 15.5 region, has been implicated.

Weaver's syndrome: pre- and postnatal overgrowth with lengths >97th percentile, but, in contrast to Soto's syndrome, growth parallels the curve without abnormal acceleration. The face is round in infancy with a large head, broad forehead, small recessed chin, and large ears. Finger pads are prominent. The syndrome involves a mutation on chromosome 5q35, OMIM #277590, with some patients having a mutation in the NSD1 gene.

Endocrine causes of tall stature
Pituitary gigantism
This is a rare condition in childhood, caused by the secretion of excessive growth hormone by a pituitary adenoma, or because of hyperplasia of GH-producing cells of the pituitary. The growth pattern is one of rapidly accelerated growth with increasing deviation above the mean

height for the child's age and sex. Adult heights, without intervention, have been well over 7 feet. Acromegaloid features are present even in childhood: frontal bossing, broad hands and feet with thickened heel pads, and coarsely trabeculated distal phalangeal bones on X-ray.

Precocious puberty

The occurrence of sexual development at an inappropriately early age (<8 yo in girls, <10 yo in boys) is accompanied by the accelerated growth characteristic of the pubertal growth spurt. The growth pattern deviates upward from the mean and percentiles are crossed. But since the bone age advances more rapidly than height as the body matures, the epiphyses fuse too soon and growth ceases early. There is a net loss of growth potential. The adult height may be significantly shorter than normal.

Thyrotoxicosis

In addition to the hyperactivity, weight loss, hyperphagia, tachycardia, and other usual signs and symptoms of excess thyroid hormone, childhood thyrotoxicosis results in a characteristic disturbance of the growth pattern in which linear growth is accelerated abnormally with increasing deviation upward, crossing percentiles. Since the bone age advances at the same pace as height (in contrast to precocious puberty), there is neither a gain nor loss in growth potential and the adult height is not affected.

Metabolic/nutritional factors

Childhood exogenous obesity is often associated with tall stature and advanced skeletal maturation in a pattern identical to constitutional acceleration of growth and development. Puberty is early and adult height at a lower percentile than the percentile the child was following.

END ORGAN ABNORMALITIES

Marfan's syndrome:

This is a hereditable disorder of connective tissue believed to involve a mutation in the fibrillin-1 gene on chromosome 15. Affected children are of normal size at birth. As the child grows, the child becomes remarkably tall and thin, with elongated limbs, fingers and toes (arachnodactyly), lax joints, and ocular abnormalities (ectopia lentis, severe myopia). Important cardiovascular abnormalities include prolapse and regurgitation of cardiac valves and progressive aortic root dilatation, which may lead to early death due to aortic rupture or dissection. Adult women may be well over 6', and men with this disorder over 7' tall.

Summary

1. Normal growth depends on a normal genetic, hormonal, metabolic, nutritional, and psychological milieu. Charting a child's growth provides a quick and easy way to monitor her or his well-being.

2. Short stature per se is not a disease. Over 90% of short children have a normal growth pattern. Similarly, most tall children are expressing a normal genetic potential.

3. Normally a child grows consistently along a particular percentile curve established in the first 2–3 years of life. A pattern of growth that deviates downward or upward, crossing percentiles, is abnormal and warrants investigation.

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