Disorders of Growth

Across the Lifespan

Learning Objectives

- Be comfortable reviewing weight and height growth curves during childhood and calculating the mid-parental height.
- Be able to identify abnormal and normal trends in growth based on growth curves and clinical presentations.
- Be able to identify genetic, hormonal, psychosocial, environmental, and nutritional causes of abnormal growth during childhood.

Pre-Session Reading and In-Class Material

http://medcell.org/tbl/disorders_of_growth

Optional Reading: http://medcell.org/tbl/files/disorders_of_growth/short_stature_review.pdf

Normal Human Growth

Human growth proceeds in several well-defined stages:

- Dramatic fetal grown (the most rapid phase of human growth)
- Deceleration of growth immediately after birth
- Prolonged growth phase during childhood
- Prepubertal deceleration of growth
- Pronounced growth spurt during puberty
- Cessation of growth after growth plates fuse

Factors Affecting Growth

Genetics plays a key role in growth. Also, genetic mutations can significantly affect someone's growth trajectory. Additionally, several factors may affect a child's genetic potential for height. These include nutritional (calories, protein, calcium, minerals, vitamins), hormonal, environmental (oxygen, toxins, medication use, sleep, activity), and psychosocial (positive attitude, self-esteem, sense of security, sense of being loved). With respect to hormones, the amount and the time of production will also play a role in growth. Hormones including growth hormone, thyroid hormone, insulin, sex steroids, and glucocorticoids can all affect growth.

Risks of Short Stature

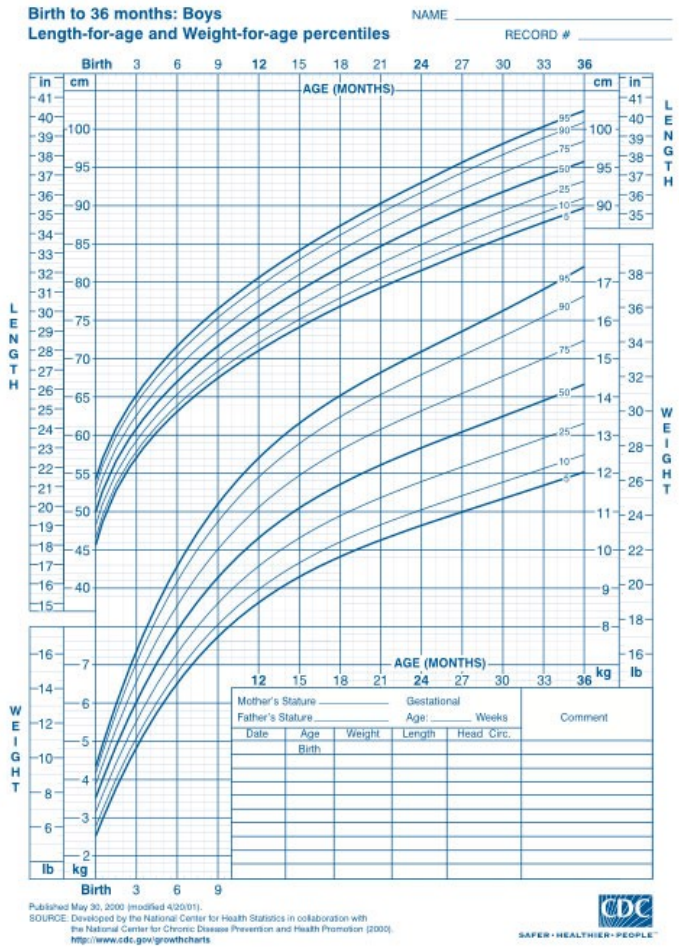
Safety features in cars (e.g. airbags, seatbelts) are designed for people over 5 feet tall. Drivers under 5 feet tall are more likely to be injured or killed by airbags that taller drivers because they pull their seats forward, putting them too close to the airbags.

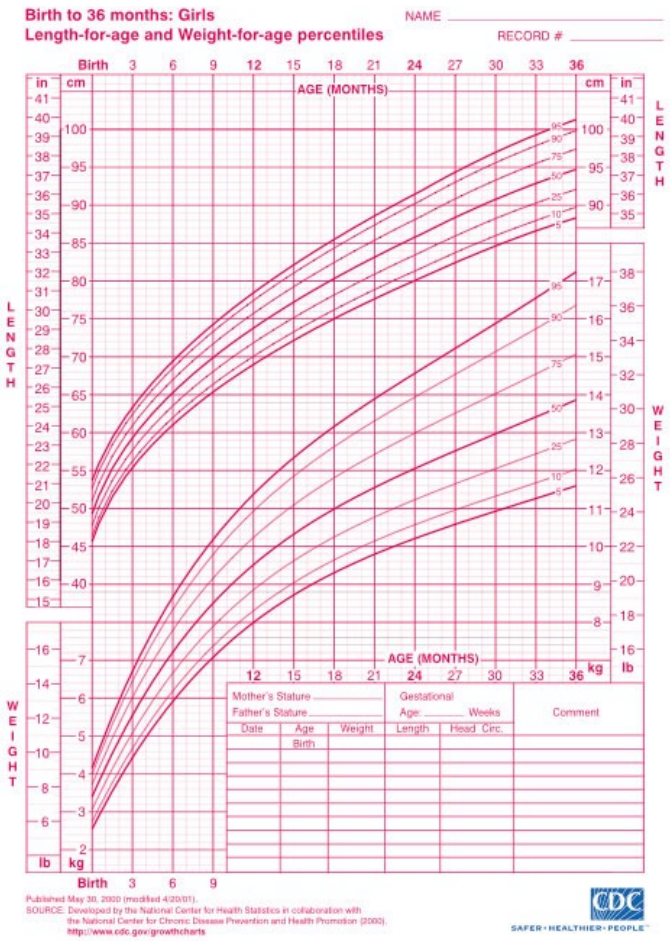
Growth Charts and Normal Growth

Children can have an innocent shift upward or downward along the growth curve. Children may cross percentiles to find their growth percentile based on genetic potential for height between 0 - 3 years of life. Peri-pubertal slowing occurs normally just prior to puberty. Timing of puberty (early or late) can cause a shift in the growth curve that may look like abnormal growth.

Birth to 36 Months

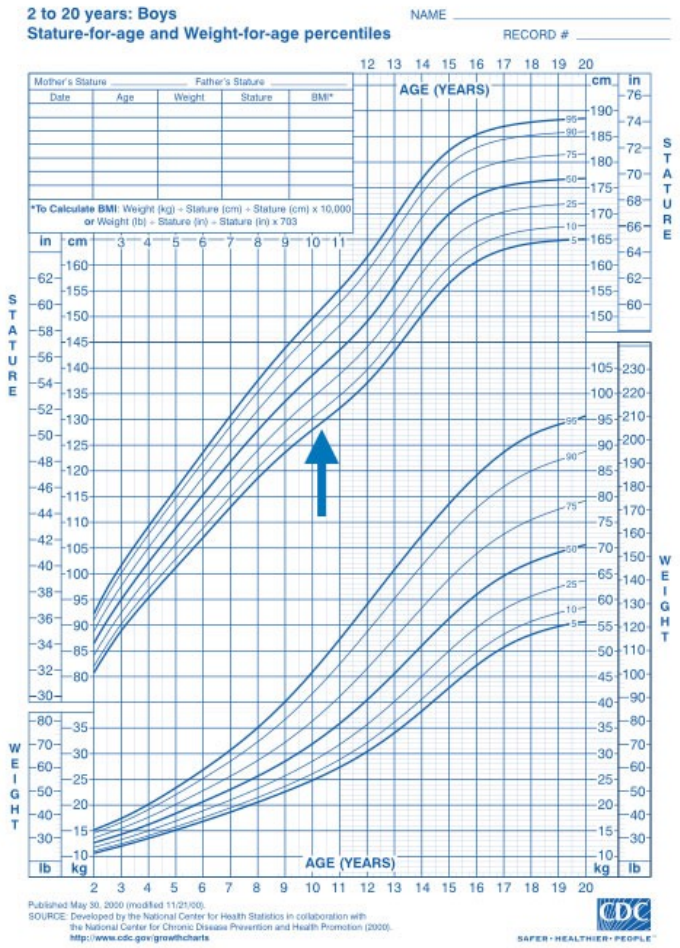
Between birth and 36 months, children may be changing height and weight percentiles as they find a percentile that they will grow along after 3 years of age. Their percentiles are likely changing to get closer to their mid-parental height percentile.

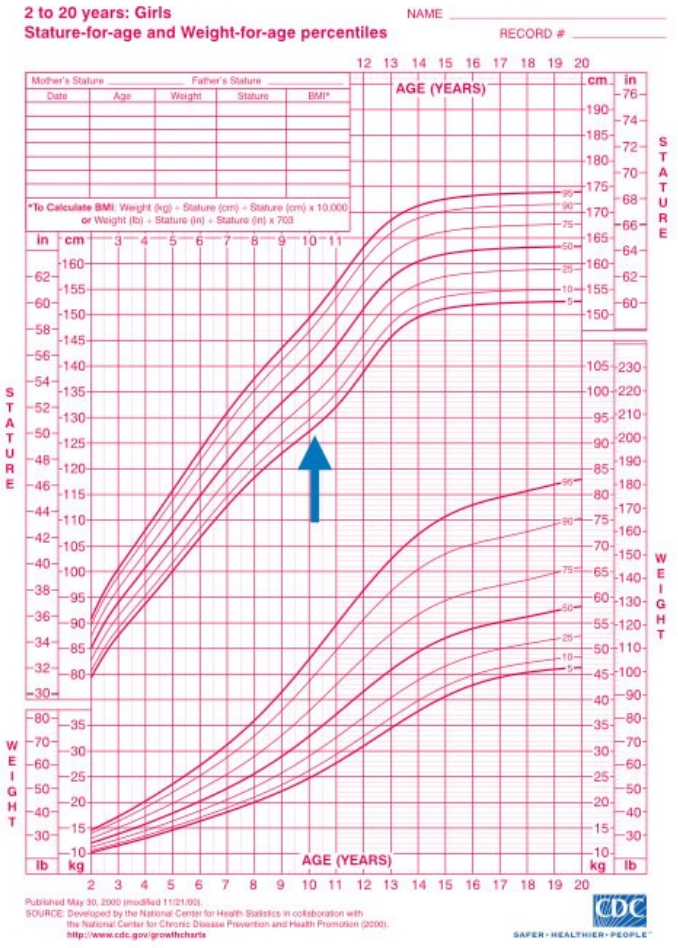




Two to 20 Years

The arrows in the charts below denote time of peripubertal slowing. This means that the growth velocity decreases slightly, prior to increasing during the pubertal growth spurt. This is common and normal.





Mid-Parental Height - Genetic Potential

We typically think of the mid-parental height (MPH) as the genetic potential for height or the “target height.”

Mid-parental height is the average of the mother’s and father’s heights, then correcting for the sex of the child. When you calculate the mid-parental height (MPH), you add 5 inches or subtract 5 inches depending on whether or not you are adjusting for male or female sex.

If you have a patient of female sex, you would calculate the mid-parental height by subtracting 5 inches (13 cm) from dad’s height and averaging with mom’s height. If you have a patient of male sex, you would calculate the mid-parental height by adding 5 inches (13 cm) to mom’s height and averaging with dad’s height. MPH has a standard deviation of about 4 inches (10 cm).

For boys: MPH = father’s height + mother’s height + 5 inches/2

For girls : MPH = father’s height + mother’s height - 5 inches/2

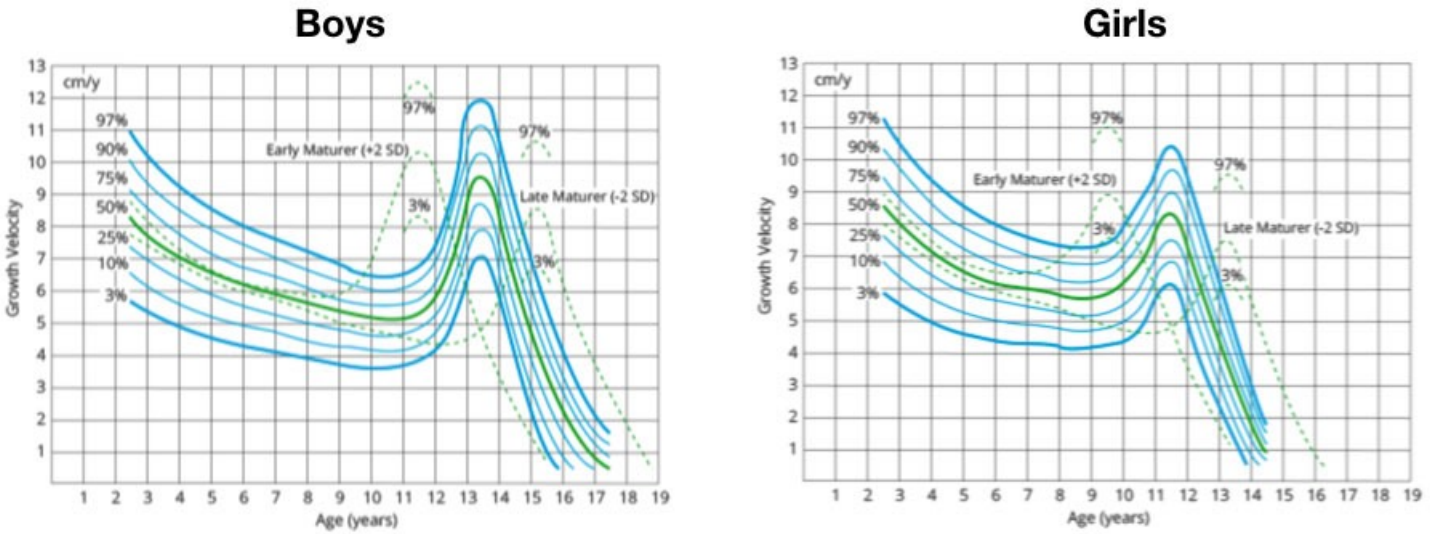
Target Height = MPH +/- 4 inches

The interpretation of MPH is only valid for normal pregnancy, normal birth weight, normal growth and puberty. Also, if there is a significant difference between parents' heights, MPH may not be accurate.

Growth Velocity

Growth velocity is arguably one of the most important assessments of a child's growth. Linear growth occurs in small increments rather than steadily and continuously. Because of this and inherent inaccuracies in measurements of linear growth when using conventional equipment, growth velocity should be calculated with at least 3 values over at least a 6 month period. Note that growth velocity decreases prior to the pubertal growth spurt.

Growth Velocity Charts



For girls, maximum growth velocity occurs a year before menarche around tanner stage III. For boys, maximum growth velocity occurs around tanner stage IV. Peak growth velocity varies depending upon if puberty occurs earlier in life or later in life (early and late bloomers) but total area under curve should be similar.

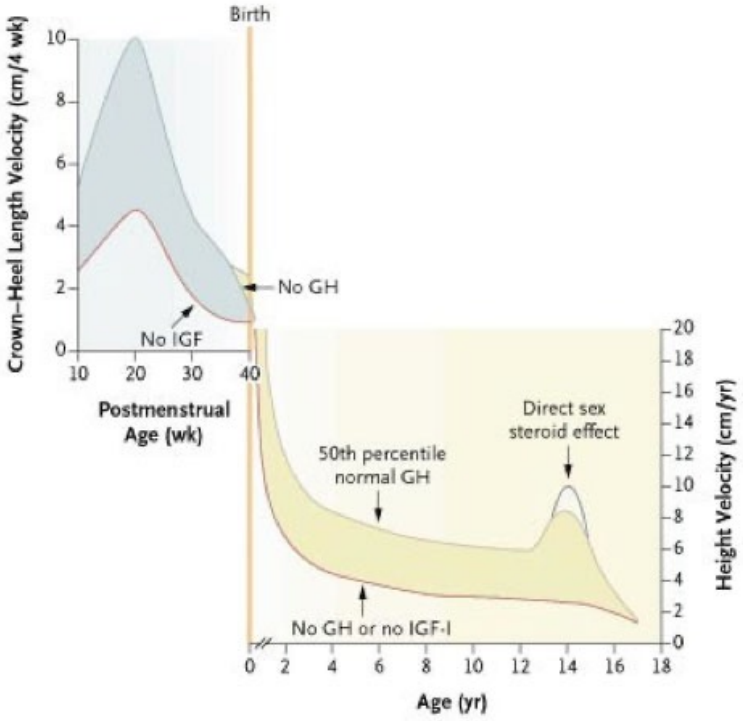
Normal Growth Velocity

Age	Inches/year	cm/year
0 - 12 months	10	25
12 - 24 months	5	12
24 - 36 months	3	8
3 years to puberty	1.75 - 2.75	3 - 7

Hormones and Growth Velocity

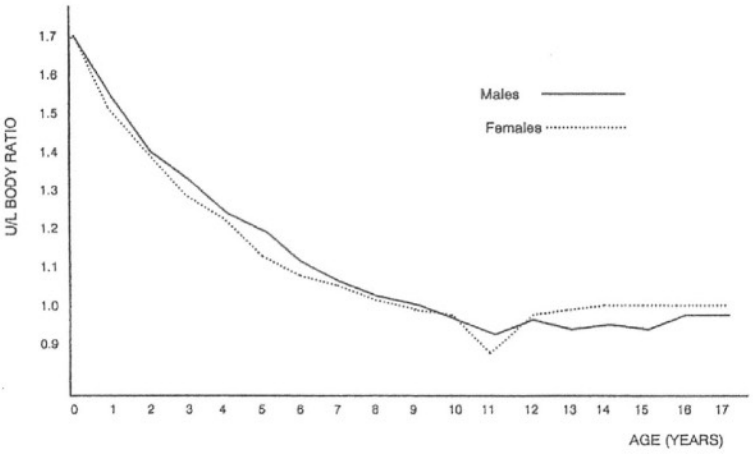
The graph below shows the effect of insulin-like growth factor (IGF) and growth hormone (GH) in prenatal and postnatal growth. The upper gray line in both panels approximates the 50th percentile for boys. In the prenatal panel, the lower red line charts growth in the absence of IGF, demonstrating the central role of IGF in prenatal growth. In contrast, growth is largely independent of GH, except for a small effect before birth.

Postnatal growth depends on both GH and IGF as shown by the red line that tracks growth in the absence of either GH or IGF. Our current understanding is that growth hormone initiates a signaling pathway that leads to the production of IGF. Thus, the shaded area in postnatal growth indicates the direct effect of IGF on growth velocity.



Body Proportions

Measuring body proportions can indicate whether short stature is proportionate (i.e. involves both the trunk and lower extremities) or disproportionate (i.e. involves one segment more than the other). The length of the lower segment is the measure of the distance between the upper border of the symphysis and the floor in the standing patient (not wearing shoes). The upper segment is determined by subtracting the length of the lower segment from the standing height.



The ratio of the lengths of upper segment (US) to lower segment (LS) changes during childhood. At birth the US:LS ratio is about 1.7. By 11 years of age the ratio is near 1.0 and remain there through adulthood.

Several pathological conditions can alter the ratio of upper segment to lower segment. An increase in US:LS is seen when the trunk is abnormally long or limbs abnormally short and can be caused by achondroplasia, rickets and untreated hypothyroidism. A decrease in US:LS is seen when the trunk is abnormally short or the limbs are abnormally long. Several conditions can decrease US:LS including spondyloepiphyseal dysplasia, vertebral anomalies, scoliosis, short neck (Klippel-Feil syndrome, Turner's) and arachnodactyly (Marfan's, homocystinuria).

Arm span measurement can also indicate disproportionate stature. Arm span is the distance between finger tips on opposite hands when arms are extended perpendicular to the body. In

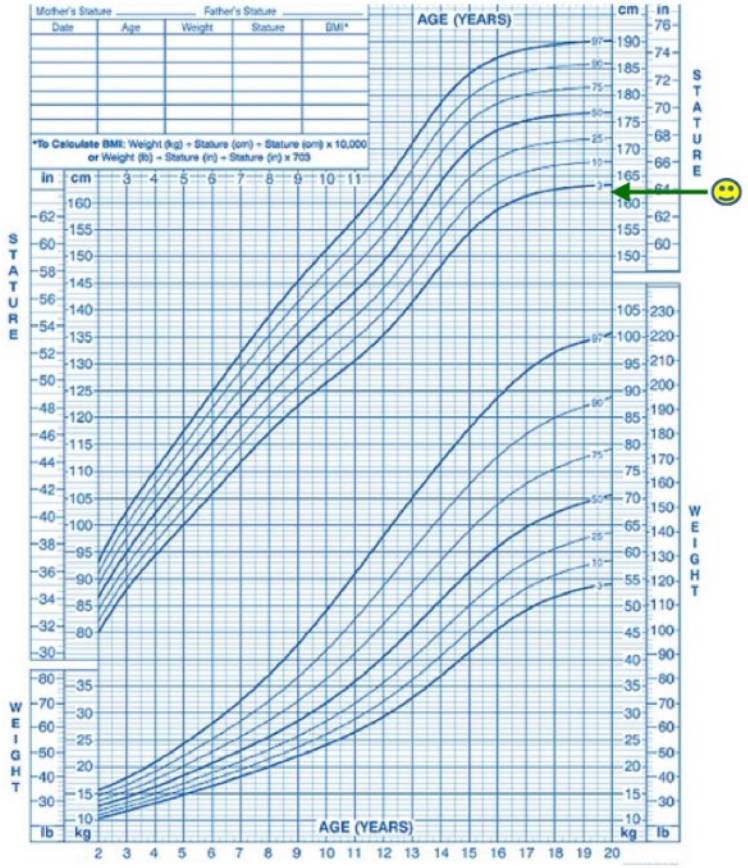
childhood, arm span is about 1 cm less than height, and in teenagers, arm span is about equal to height. Of note, disproportionate trunk dysplasia would present with US < LS and arm span > height. Disproportionate limb dysplasia would present with US > LS and arm span < height.

Short Stature

Short stature can has population-based and biological-based definitions. The population-based definition is based on normative data and marks short stature as shorter than the 5th percentile or shorter than two standard deviations below the mean (about the 2.5% percentile). The biological definition of short stature is obtained from analysis of the child's height in the context of the genetic potential for height of mid-parental height (MPH).

Example

A boy is at the 5th percentile for height and is the shortest child in his class. His parents' heights are



5 feet 4 inches for his father and 4 feet 11 inches for his mother. Is his height abnormal?

First calculate the boy's MPH which is 5 feet 4 inches. Then, in the chart below find the percentile of his MPH at 20 years of age which is a little below the 3rd percentile. Thus, his current 5th percentile for height would not be considered abnormal based on his genetic potential for height.

Patient History

The following factors are important to consider in a patient's history.

- Prenatal history
- Birth weight, length and head circumference
- Timing of dental eruption
- Chronic illness and hospitalizations
- Evidence of thyroid, pituitary or bone disorders
- Medications: glucocorticoids, stimulants
- Psychosocial or nutritional deprivation
- Family history: heights and ages at puberty,
- Evaluation of growth chart and growth velocity
- Anyone in the family shorter than 5 feet tall
- Anyone in the family taller than six feet six inches
- Nutrition: caloric intake versus calories burned and special diets
- Patient or family history of developmental delays, IEP, genetic conditions
- Family history of early or late puberty

Questions to ask the patient include ages at which men in the family (father and brothers) voices changed of if they continued to grow after high school and when women in the family had menarche.

Physical Exam

Below is a general and incomplete list of items to look for on a physical exam. While performing the exam, keep in mind the potential causes of short stature and growth failure. For example, midline abnormalities (including central incisor) suggest a problem with the pituitary gland.
Hyperpigmentation of neck, axillae and intertriginous areas.

Etiology

Short stature may or may not be pathologic. Keep in mind the general broad categories into which short stature could fall:

- Syndromic short stature – Turner's syndrome, Noonan syndrome, Down's syndrome, chromosomal abnormalities can all prevent normal growth
- Familial short stature (FSS) – your family members are short, and so are you!
- Constitutional delay of growth and puberty – they are going to grow, but they are behind other children their age
- Chronic medical problems
- Endocrine – hypo/hyperthyroidism, adrenal insufficiency, Cushing's syndrome

- Idiopathic Short Stature (ISS) – you are short, and we're not sure why, but your growth velocity is fine and we've ruled out other pathologic causes of short stature
- Psychosocial stressors – children in an abusive household may not grow. It is good to have a high index of suspicion.
- Malnutrition – if you don't ingest/absorb enough calories for your body to function, you may see a decline in stature after a decline in weight. This could be a sign of an underlying problem with absorbing nutrients or it could be poor intake
- Chronic disease – if your body is using up all of its energy because of the stressors of a chronic illness, growth may be impaired.

Urgent Referral

Intracranial tumors often present with growth failure and it is important to rule out potential life-threatening causes of growth failure. Patients with poor height velocity in the setting of worrisome clinical symptoms, such as severe headaches or vision changes, may need an urgent MRI of the brain and/or pituitary, specifically thin cuts of the pituitary.

Summary of Clues to a Growth Disorder

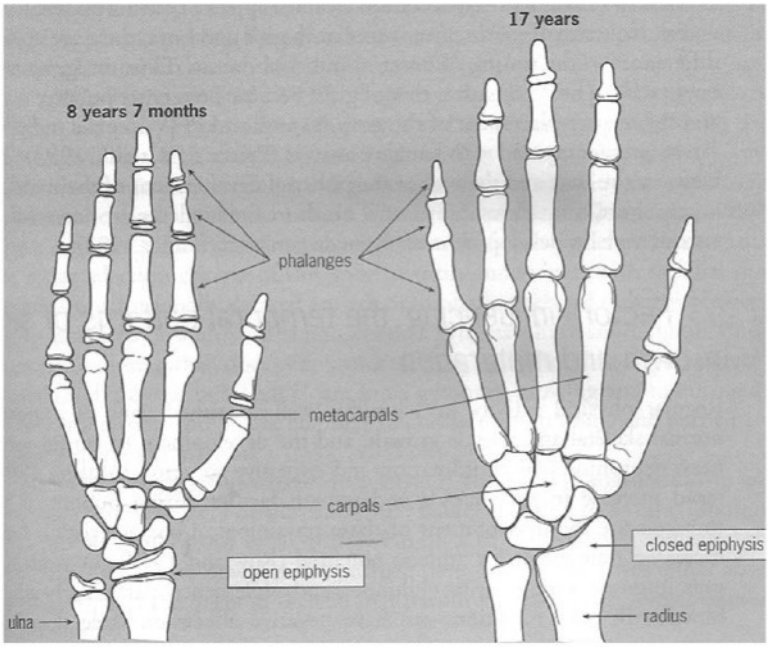
- Abnormal growth velocity for chronological and pubertal stage
- Height that is more than 2 - 2.5 standard deviations below the mean
- Growth that crosses 2 or more percentile lines
- Child consistently growing along a percentile significantly different from his or her MPH percentile
- Abnormally delayed or advanced bone age (> 2 standard deviations from chronological age)
- Physical features suggestive of genetic syndromes
- Disproportionate short stature

Bone Age

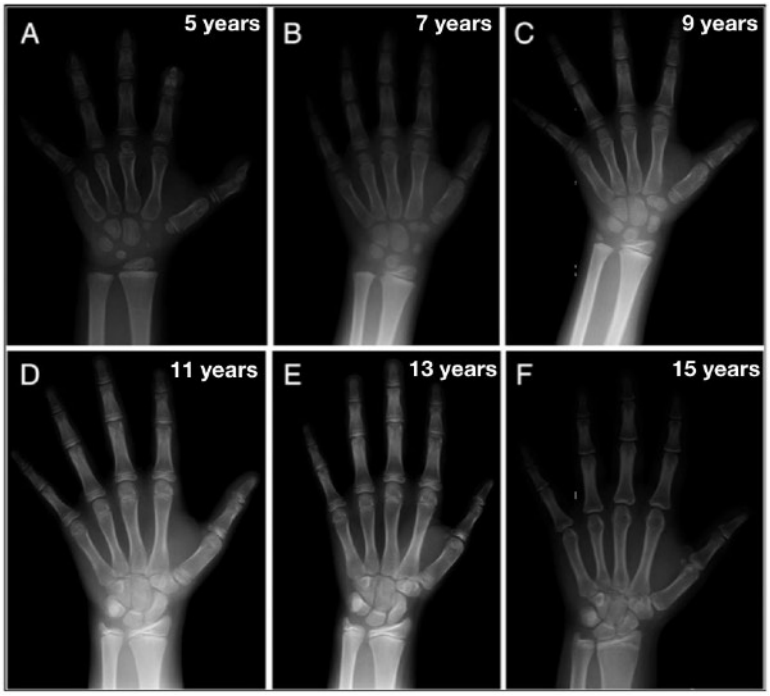
Pediatricians have used skeletal maturation as a tool for assessing children's health for over 75 years. Bone age is an interpretation of skeletal maturity, based on radiographs of the left hand and wrist. Although widely used, the ability to predict age based on skeletal maturity varies widely across ethnicities.

> "Current methods of assessing skeletal maturation are derived from primarily white populations. In modern studies, researchers have explored the accuracy of bone age across various ethnicities in the United States. Researchers suggest there is evidence that indicates the bone ages obtained from current methods are less generalizable to children of other ethnicities, particularly children with African and certain Asian backgrounds."
>
> - Creo et al., Pediatrics 2017

The diagram below shows skeletal maturity between ages 8 and 17 years old. Note the closing of the growth plate (closed epiphysis) in both the ulna and radius at 17 years of age.



Shown below are radiographs showing skeletal maturation from 3 years to 15 years of age.

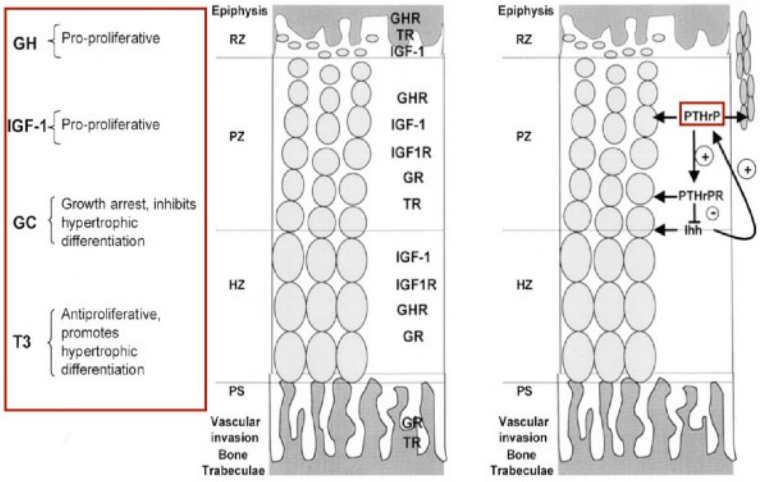


Hormones and Bone Growth

Recall that the growth plate can be divided into different zones based on the status of the chondrocytes.

- Resting Zone (RZ) - Slow growing region
- Proliferative Zone (PZ) - Rapid cell division of chondrocytes
- Hypertrophic Zone (HZ) - Chondrocytes increase in size
- Primary spongiosum (PS) - Calcification of cartilage

As shown in the image below, hormones affect the growth and activity of chondrocytes in each of the zones and chondrocytes in each zone express receptors that bind specific hormones.



GH = Growth Hormone

IGF-1 = insulin-like growth factor 1

GC = Glucocorticoids

T3 = active thyroid hormone

GHR = growth hormone receptor

TR = thyroid hormone receptor

IGF-1R = IGF-1 receptor

GR = glucocorticoid receptors

PTHrP = Parathyroid hormone related peptide

Estrogen is the primary hormone that causes fusion of the bones, and thus, bone age advancement.

Causes of Advanced and Delayed Bone Age

Advanced Bone Age

- Early puberty
- Early adrenarche
- Hyperthyroidism
- Obesity
- Overproduction of hormones from tumors (ovarian, testicular, germ cell, etc.)
- Estrogen exposure

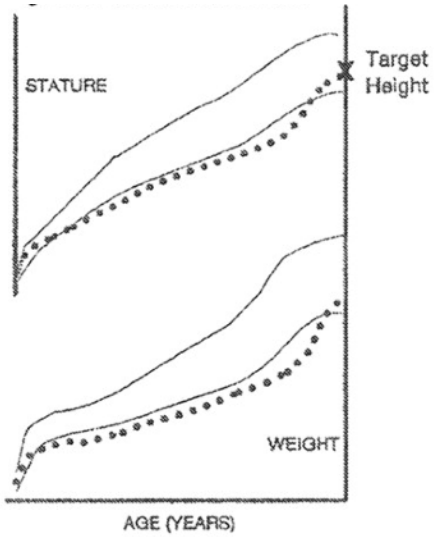
Delayed Bone Age

- Delayed puberty
- Hypothyroidism
- Growth Hormone deficiency
- Malnutrition, anorexia
- Chronic illness
- Turner syndroms, Trisomy 21
- Neglect/abuse
- ADHD medications

Quiz

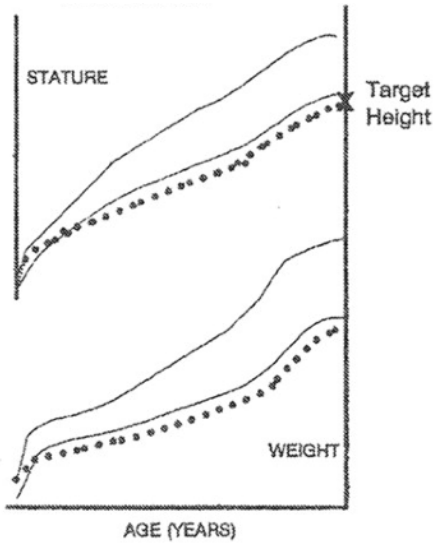
Case 1

The patient has had short stature tracking below the growth curve (but largely parallel to the curve) since 3-4 years of age. They had some peripubertal slowing where they appeared to be tracking further away from the curve as they got into their late teen years and seemed to be tracking far from their target height. Once they go through puberty, however, they are able to reach his final adult target height. What is the diagnosis?



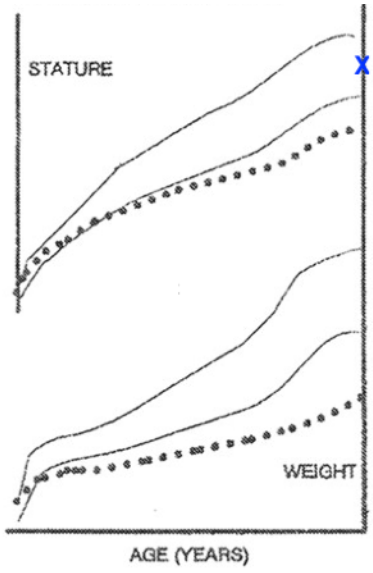
Case 2

The patient has been tracking below the curve for much of their life. They initially crossed percentiles early on in life around age 4-6 years. Weight and height seem to be proportional. However, even though he is tracking below the curve and has crossed percentiles, he is still on track to meet his genetic potential for height. What is the diagnosis?



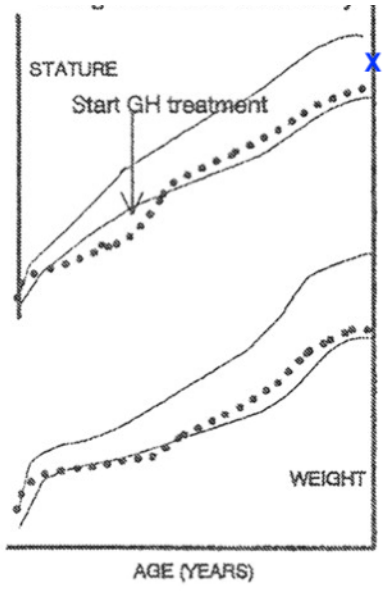
Case 3

The patient appears to have had a decline in weight prior to a decline in height. The decline in weight is also more severe than the decline in height. Unfortunately, their weight tracks further and further away from the growth curve over time, as does their height. X marks their target adult height based on genetic potential



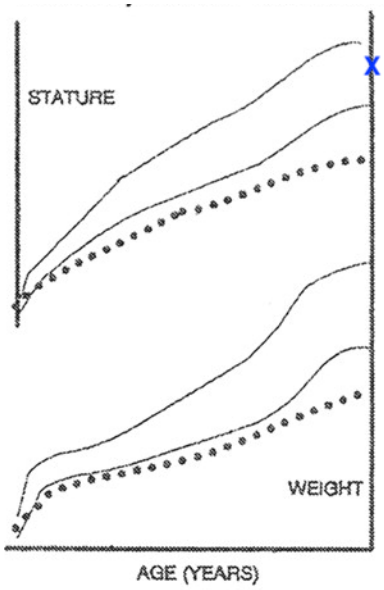
Case 4

For this patient, their height was tracking away from the curve more than their weight was, and thus their pediatrician suspected an endocrine problem. Once they were started on GH treatment, they were able to get closer to their genetic potential for target height. X marks target height. It was not reached because of the delay in diagnosis.



Case 5

This patient has been tracking further from the curve in both height and weight over their lifetime. However, height has tracked further away from the curve than weight, and the growth velocity has been lower than expected. The final adult height is much lower than would be anticipated based on the genetic potential for their target height. They appear to have been growing poorly for most of their life with a low growth velocity.



Answers

1. Constitutional delay of growth and puberty
2. Familial short stature
3. Primary nutritional deficiency, severe chronic illness, or psychosocial distress
4. Congenital growth hormone deficiency
5. Genetic disorder of short stature (turner syndrome, noonan syndrome); other endocrine disorders would also look like this if they went untreated.