One of the primary responsibilities of the general pediatrician is the identification of children with short stature and the determination of the possibility of an underlying cause. The primary responsibility of the pediatric endocrinologist is the identification of those children who have endocrine causes of growth failure. These include hypothyroidism, glucocorticoid excess, inborn errors of metabolism, or pituitary abnormalities. In any case, prompt diagnosis may allow early initiation of corrective therapy and ideally catch-up growth and normalization of stature can occur before epiphyseal fusion develops.

**Growth Hormone Deficiency**

The incidence of absolute growth hormone deficiency ranges from 1:4000 to 1:60,000, but cases of relative deficiency may be much more common. The diagnosis of growth hormone deficiency encompasses a wide spectrum of disorders, including structural defects of the hypothalamus or pituitary, abnormal synthesis or secretion of hypothalamic factors, deletions or mutations of the Pit-1 gene, abnormalities of the GHRH receptor, hereditary forms of isolated growth hormone deficiency, and acquired defects of growth hormone synthesis or secretion, most often secondary to tumors of the hypothalamus or pituitary gland. The basis of the diagnosis of growth hormone deficiency is primarily axiological, but may be associated with such clinical manifestations as hypoglycemia, micro phallus, cryptorchidism, nystagmus, or blindness.

**What Is Growth Hormone?**

In 1985, synthetic growth hormone was approved and was rapidly introduced into a patient population that had been proven to have growth hormone deficiency. This was fortunate because human pituitary growth hormone extracted from cadavers, occasionally resulted in Creutzfeldt–Jakob disease. This should not be the case for synthetic growth hormone.

Growth hormone is a 191 amino acid protein produced in the pituitary gland and released in a pulsatile fashion that reflects the interplay of multiple regulators, including two hypothalamic regulatory peptides, namely GH releasing hormone (GhRH) and somatostatin (SRIF). A third regulatory hormone, ghrelin is a peptide that is secreted in small amounts by the hypothalamus and in much larger amounts by the stomach. Ghrelin acts by way of a separate receptor, named the growth hormone secretagogue receptor (GHS-R).

Growth hormone has many anabolic and metabolic actions, including bone growth, muscle mass and lipolysis, but some of these effects are mediated through another set of hormones called the insulin growth factors (IGFs). IGFs are under growth hormone control and produced in the liver, as well as some other tissues and have growth-promoting actions on a wide variety of target tissues particularly cartilage and bone. The IGF peptides along with growth hormone itself, feedback on the hypothalamus and pituitary gland to control the release of growth hormone releasing hormone and somatostatin and the release of growth hormone from the pituitary somatotropes. Measurements of IGF-1 are a useful indicator of growth hormone action, but it should be kept in mind that other factors, such as nutritional status, can affect IGF-1. IGFBP-3 is often used as a surrogate measurement of growth hormone, but is not as useful as IGF-1, except in certain conditions, such as under 2 years of age.

**Normal Growth**

It is surprising to most that linear growth in prenatal life is relatively independent of growth hormone secretion and minimally affected by hypopituitarism. The size at birth is primarily regulated by maternal and placental factors. After birth newborns shift to a growth rate that is regulated by its own genetic potential and pituitary hormones. Between the ages of 3 years and the onset of puberty, the minimum annual growth rate is about 5-6 cm. per year and any child who grows less than 5 cm. per year deserves an evaluation.
Accurate measurement is essential in the workup of the short child. Measurements of arm span and sitting height can also be important in the evaluation of the short child. It is also helpful to mark the parents’ heights and the mid-parenteral height. (MPH -- calculated by adding the height of the parents, subtracting 13 cm. in girls and adding 13 cm. in boys, and then dividing by 2.)

This allows the child’s height to be compared to his/her genetic potential. Two standard deviations from the mid-parenteral height is about 9 cm. on either side of the MPH and 95% of children can be expected to fall within this range as adults. Children who are below the 3rd percentile on the growth chart or who are greater than 2 SD below the mid-parenteral height have short stature and deserve an evaluation. Disease-specific growth charts are also available for children with Down syndrome, Turner syndrome and achondroplasia.

Causes of Short Stature (Discussed in Part 1)
A. Normal Variance/Familial Short Stature
B. Constitutional Growth Delay
C. Nutritional Deprivation
D. Psychosocial Dwarfism
E. SGA - (Small for gestational age, also known as intrauterine growth retardation) Approximately 10% of children born SGA fail to reach normal growth percentiles by 2 years of age and recent studies show that growth hormone treatment can lead to improved growth velocity and ultimate target height. Growth hormone is FDA approved as a treatment for children born SGA who exhibit persistent growth failure. Treatment is typically started at age 3 years at a dose of 50-70 mcg/kg per day of growth hormone.
F. Systemic diseases were discussed in part 1 and include any underlying systemic illness resulting in short stature.
G. Genetic syndromes amenable to GH Treatment.
   1. Turner Syndrome: Short stature is a very common feature of Turner syndrome with a mean adult height ranging from 142-146 cm. These children are FDA-approved for growth hormone treatment and their ultimate target height is significantly improved. The cause of growth failure in Turner syndrome includes the loss of one copy of the homeobox gene, SHOX (short stature of homeobox-containing gene). Growth hormone therapy is capable of both accelerating short-term growth and increasing adult height in both Turner syndrome and any disorder in which there is a partial deficiency or haploinsufficiency of the SHOX gene.
   2. Prader-Willi Syndrome

Evaluation of the Short Child
A. Auxologic abnormalities, including:
   1. Severe Short Stature (-3 SD)
   2. Severe Growth Deceleration
B. Risk factors
   1. History of a brain tumor, cranial radiation or other disorders affecting the hypothalamic pituitary area
   2. Incidental finding of pituitary abnormalities on MRI
C. Screening for growth hormone/IGF-1 deficiency
   1. Order relevant laboratory studies, including a bone age, thyroid function, and chromosomes in a female, CBC, chem panel, sed rate and a celiac panel.
   2. Order an IGF-1 level and an IGFBP-3 if under 2 years of age. If the IGF-1 is low, proceed to the next set of testing, which includes two growth hormone stimulation tests. These include Clonidine, arginine, insulin, glucagon, levodopa, and Propranolol. If the peak growth hormone on both sets of tests is less than 10, then this child is a candidate for growth hormone replacement. Consider an MRI of the pituitary to rule out underlying pathology. If the growth hormone peak is over 10 but the height is less than 2.25 standard deviations below the mean, consider growth hormone treatment under the category of idiopathic short stature as noted above.
   3. Low levels of IGF-1 can provide presumptive evidence of reduced growth hormone secretion, but normal levels do not exclude the possibility of growth hormone deficiency.
   4. Patients, who have a deficiency of three or more pituitary hormones and an IGF-1 level of less than 84 ng/mL, can be considered to have growth hormone deficiency and may not require provocative testing. Insurance companies, however, may still require growth hormone stimulation before providing reimbursement for growth hormone therapy.

Conditions for Which Growth Hormone Is Now Approved
1. Growth Hormone Deficiency
2. Turner Syndrome
3. SGA
4. ISS (Idiopathic Short Stature) is defined as a condition in which the height of the child is more than 2.25 SD below the corresponding mean height for any given age and sex in a population group without evidence of systemic, endocrine, nutritional or chromosome abnormalities. This was FDA-approved in 2003 for growth hormone therapy.

5. Noonan Syndrome

6. Prader-Willi Syndrome

Concerns of Growth Tests

The pulsatile nature of growth hormone secretion renders assessment of random serum growth hormone concentrations virtually worthless in the diagnosis of growth hormone deficiency. Instead, growth hormone measurement follows pharmacological stimulation of the pituitary gland, which in essence measures growth hormone reserve or secretory capability. While such provocative testing is certainly of value, total reliance on these tests can be problematic for a variety of reasons:

1. Provocative testing is basically non-physiological.
2. No satisfactory mechanism has been developed for resolving conflicting data from two or more tests.
3. The definition of what constitutes an abnormal response to provocative testing is arbitrary. The availability of recombinant DNA-derived growth hormone in 1985 resulted in a loosening of the diagnostic cutoff to 10 ng/mL, on the basis of not totally convincing physiological data.
4. The reproducibility of provocative growth hormone testing has never been demonstrated convincingly.
5. The necessity of two growth hormone provocative tests has not been addressed adequately.
6. The potential effect of psychiatric disturbances, such as depression on growth hormone provocative testing, has not been assessed properly.
7. Provocative growth hormone testing is associated with significant costs, discomfort to the patient and some element of risks.
8. Demonstration of normal provocative testing does not exclude the possibility of various forms of growth hormone insensitivity.

Notwithstanding these concerns and criticisms, these evaluations have led to the discovery of many types of pituitary abnormalities, including brain tumors, which ultimately have saved many lives. Assessment of pituitary function may be important to the diagnosis of hereditary disorders of growth hormone synthesis or secretion, and, of course, attainment of a more reasonable target height has overwhelmingly satisfied many thousands of children (and of course, their parents).

Growth Hormone Therapy

Daily administration of growth hormone is recommended with injections administered in the evening since that mimics natural physiology. Growth hormone is routinely used in the range of 25-50 mcg/kg per day with the typical growth hormone deficient child accelerating growth from a pre-treatment rate of 3-4 cm. to 10-12 cm. per year in the first year of therapy with slowdowns in subsequent years. This progressive waning of growth hormone efficacy after the first year has been observed universally and is still not fully understood.

Risks of Growth Hormone Treatment

1. A small percent of patients complain of mild cramps in their legs and occasionally headache, which is most often transient.
2. Slipped capital femoral epiphysis (SCFE) causes hip pain due to separation of the head of the femur from the shaft. Although reported in the literature on growth hormone treated patients, the association is not clear and the occurrence is extremely rare. I have not witnessed any in my entire career.
3. Pseudotumor cerebri (benign intracranial hypertension) is manifested by severe headache, papilledema, nausea and visual changes. The incidence is approximately 1 in 1,000 and all cases have been reversed usually by temporary discontinuation or reducing the dose of growth hormone.
4. Fluid retention and edema in early months of treatment is rare in children, but more common in adults. It typically disappears with temporary interruption of treatment.
5. Pancreatitis has been reported in a few patients, but a causal relationship seems unlikely.
6. Carpal tunnel syndrome has also occurred in adults, but I have seen no reports in children.
7. Growth hormone does not cause diabetes, but high values may decrease insulin sensitivity. Therefore, monitoring is important.
8. There is always a concern about IGF-1 and its relationship to cancer, but there is no evidence that growth hormone treatment incites or initiates cancer formation.
9. Fifteen years ago there was a report of a link between growth hormone administration and leukemia in Japan, but this was found to be unrelated to growth hormone administration.
10. Approximately 3 months ago, an alert was sent out by the French government because of an increase in cardiovascular disease including intracranial bleed in a group of adults who had received growth hormone as children. Once again, this was not a warning or a published report, but it was an alert and at this publication date there are no data to substantiate this association. Further research is ongoing.

**Monitoring While on Growth Hormone**

Close follow-up with a pediatric endocrinologist is necessary to monitor growth velocity, IGF-1 levels, bone age progression and side effects. Periodic monitoring for scoliosis, tonsillar hypertrophy, papilledema and SCFE should be performed as part of the regular physical exam during follow-up visits.

**When to Stop Treatment**

Some endocrinologists feel that treatment should stop when an acceptable height is achieved or when the bone age is over 16 years in boys and over 14 years in girls. Alternatively, therapy can continue until the epiphyses fuse.

**The Role of Recombinant IGF-1 in a Selective Population of Short Children**

IGF-1 was approved by the U.S. Food and Drug Administration (FDA) in 2005 for use in short children with IGF-1 deficiency including patients with mutations in the growth hormone receptor, post-receptor signal abnormalities, transduction defects, growth hormone gene deletions with inhibitory growth hormone antibodies and those with IGF-1 gene deletion or defects. These patients are not growth hormone deficient and therefore will not generally respond adequately to exogenous growth hormone treatment.

**Diagnosis of IGF-1 Deficiency**

The diagnosis is made if the IGF-1 is low in a short child and the stimulation test reveals elevated growth hormone levels.

**Indications for IGF-1 Therapy**

IGF-1 deficiency is defined by a height standard deviation score of less than -3.0 and a basal IGF-1 standard deviation score of less than -3.0 with normal or elevated growth hormone response to a growth hormone stimulation test.

**Treatment of IGF-1 Deficiency**

IGF-1 was synthesized several years ago and is administered by injection similar to that of growth hormone.

**Conclusion/Author’s Experience**

I have administered IGF-1 to over 30 patients who have primary IGF-1 deficiency manifested by a height standard deviation of more than -3 and a basal IGF-1 standard deviation of more than -3 with elevated growth hormone response to growth hormone stimulation tests. In every case there has been improvement of growth velocity. In a small group of patients I utilized them combination of growth hormone and IGF-1 who had not responded significantly to either IGF-1 alone or growth hormone alone. The combination has improved their height velocity from an average of -3 standard deviations to -1 standard deviation. Clinical trials must be undertaken to investigate whether combination therapy should be initiated for these types of patients.