Short Stature in Children

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A consideration of all of the causes of short stature would approach the scope of a general pediatric textbook. Therefore, this discussion will focus on the most common endocrine abnormalities that cause growth failure and their differential diagnosis.

GENERAL CONSIDERATIONS

Growth Standards

Accurate serial measurements of height and weight and an accurate record of growth are essential components of the clinical evaluation of all children. Maintenance of a growth chart allows comparison of an individual child with a large population in terms of both percentile ranking and the determination of "height age": the chronologic age at which the patient's height falls on the 50th percentile. The growth chart also facilitates observations of the pattern of growth and provides the basis for calculation of growth velocity.

Until recently, growth standards used in the United States were based on data accumulated more than 30 years ago. Newer standards, compiled by the National Center for Health Statistics of the United States Public Health Service, and growth charts based on these data are now generally available.

The pattern of growth is of great help in the assignment of a patient to a general diagnostic category. As shown in Fig 1, children with a congenital condition interfering with growth show persistent deviation away from the normal curve from a very early age. At times this occurs before 3 to 6 months of age, and it is almost always apparent within the first 12 to 18 months of life. Children with an acquired abnormality affecting growth follow a normal curve for a variable period of time and then begin to deviate away from the norm.

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In contrast, the child with constitutional delay in growth and adolescence may show transient deceleration of growth from late infancy through the third year of life, but subsequently will grow at a normal rate. Although the height of children with familial short stature is well below average, their growth curve parallels the standard curve.

The growth rate or height velocity can also be calculated from serial measurements plotted on the growth curve. In general, an abnormal growth rate suggests that a significant problem may be present and is an indication for carrying out diagnostic studies. On the other hand, a normal growth rate is reassuring to the patient, parents, and physician and suggests that extensive diagnostic studies can be postponed or need not be pursued.

The definition of normal growth velocity varies with age and sex. For practical purposes, a growth rate below 5 cm/yr in both boys and girls between 5 years of age and the beginning of rapid adolescent growth is subnormal. Because younger children normally grow more rapidly, the lower limit of normal for height velocity must be raised with decreasing age. A growth rate between birth and 6 months of age below 16 cm in girls and 17 cm in boys should be evaluated. Between 6 to 12 months, both boys and girls should grow at least 8 cm. A growth rate between 1 and 2 years of age below 11 cm for girls and 10 cm for boys is less than expected for this age. Between 2 to 5 years of age both boys and girls should grow 6 cm/yr.

The determination of body proportions provides additional useful clinical information. The proportions that have been most widely used are the ratio of upper body segment to lower body segment and the relationship between arm span and height. The average measurements for these two proportions as a function of age and sex are shown in Table 1. The lower segment is the distance from the top of the symphysis pubis to the heel, with the ankle at 90 degrees. In practice, the upper segment measurement is obtained by subtracting the lower segment measurement from the total height. Arm span is measured with the arms fully extended. Short patients with primary disorders of bone and cartilage, or with long standing hypothyroidism, have relatively short extremities. Their arm span is shorter than their height, and their upper/lower segment ratio is greater than expected. Other short children are normally proportioned.

EDUCATIONAL OBJECTIVE

145. Appropriate understanding of the role of measurements of growth hormone in the evaluation of the child with short stature (81/82).

Bone Age Determination

Determination of the level of epiphyseal maturation is often helpful in evaluating children with abnormal growth. The standards published by Greulich and Pyle, which are based on the left hand and wrist, have found the most general use in the United States. These standards are not useful before 6 months of age because normal infants may not have calcified carpal centers until that time.

A delayed bone age does not provide specific diagnostic information inasmuch as epiphyseal maturation is delayed in all of the disorders that cause short stature and in constitutional delay in growth and adolescence as well. The bone age tends to be normal in genetic or familial short stature.

The major value of determining bone age is prognostic. Short children whose bone age is delayed have a much better prognosis for further growth and ultimate height than do children whose level of epi-

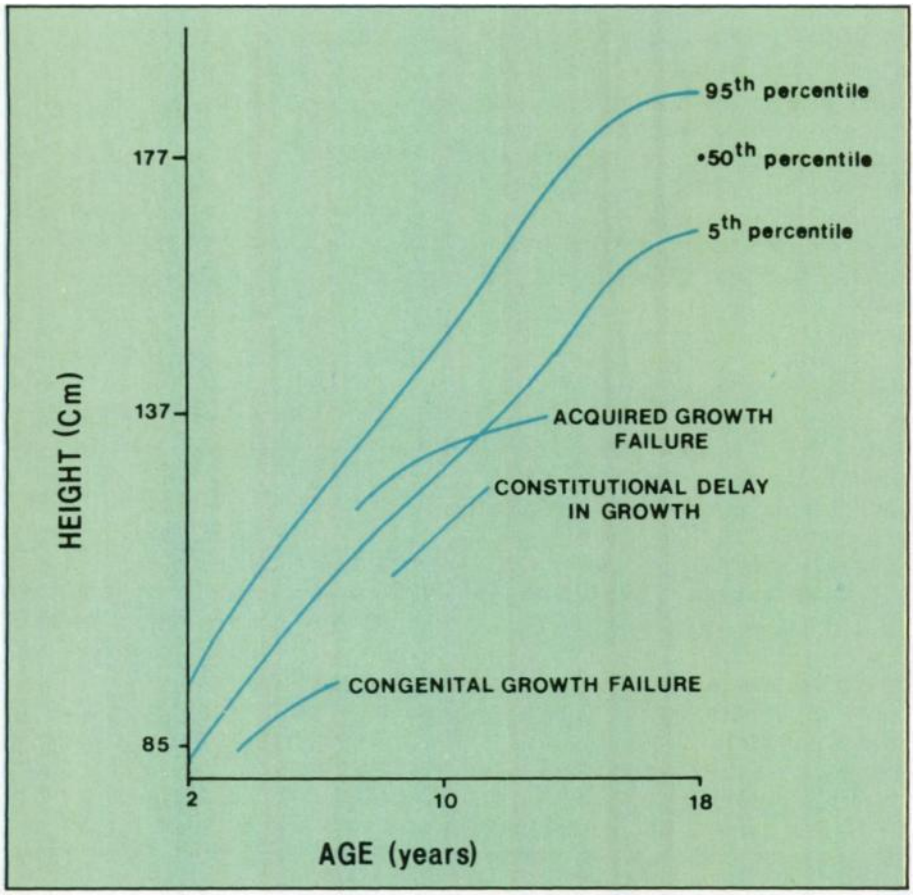

Fig 1. Characteristic growth patterns plotted against growth curve based on current National Center for Health Statistics Standards. (Reprinted with permission from Frasier SD: Abnormalities of growth, in Pediatric Endocrinology. New York, Grune & Stratton, 1980.)

TABLE 1. Body Proportions: 50th Percentile Standards for Upper/Lower Segment Ratio and Arm Span Compared to Height

Age	Upper/Lower Segment Ratio		Arm Span Minus Height (cm)	
	Female	Male	Female	Male
Birth	1.70	1.70	−2.5	−2.5
6 mo	1.60	1.62	−3.0	−2.5
12 mo	1.52	1.54	−3.3	−2.5
18 mo	1.46	1.50	−3.3	−2.7
24 mo	1.41	1.42	−3.5	−3.0
3 yr	1.30	1.35	−4.0	−2.7
4 yr	1.22	1.24	−3.8	−3.0
5 yr	1.15	1.19	−3.5	−3.3
6 yr	1.10	1.12	−3.3	−2.5
7 yr	1.06	1.07	−2.0	−2.5
8 yr	1.02	1.03	−1.8	−1.2
9 yr	1.01	1.02	−1.2	0
10 yr	1.00	0.99	−1.0	0
11 yr	0.99	0.98	0	0
12 yr	0.99	0.98	0	+2.0
13 yr	1.00	0.97	0	+3.3
14 yr	1.01	0.97	0	+3.3
15 yr	1.01	0.98	+1.2	+4.3

physeal maturation is consistent with their chronologic age. The simplest method of height prediction is the use of the Bailey-Pinneau tables as published in the Greulich and Pyle's *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. This predication is based on the patient's chronologic age, bone age, and current height. The accuracy is relatively poor when the bone age is less than 10 years. At best, the Bailey-Pinneau predication is reliable to ±4 to 6 cm (±1.5 to 2 inches). The equation of Roche, Wainer, and Thissen (RWT method) is more complicated to apply than the Bailey-Pinneau tables and utilizes the patient's chronologic age, recumbent length, weight, and parental heights in arriving at a predication. This method is gaining in popularity because of its somewhat greater accuracy. It must be borne in mind that the accuracy of both methods depends on the validity of the bone age determination.

CAUSES OF SHORT STATURE

Chronic Disease of a Nonendocrine Organ System

Chronic disease of any major organ system may interfere with growth and lead to short stature. The history, physical examination, and routine laboratory evaluation will uncover the clues that allow the diagnostic search to be narrowed to a particular system and eventually to a specific disorder. The growth pattern in children with nonendocrine chronic illness is that of acquired growth failure. Body proportions are normal except in disorders primarily affecting bone and cartilage; in such disorders the limbs are shorter than expected.

Short patients growing at a subnormal rate for their age should have a screening hematologic evaluation and routine urinalysis with particular attention to the presence of reducing substances and protein, as well as urine specific gravity and pH. A screening chemistry panel should be performed to evaluate electrolyte and acid-base status, as well as kidney and liver function.

Common Nonendocrine Conditions

In Table 2 are listed several nonendocrine conditions that require consideration in a differential diagnosis of short stature. These are not really disorders, but rather are variations of normal which show more or less characteristic clinical pictures and patterns of growth.

Children with constitutional delay in growth and adolescence are normal in height and length at birth. They grow normally for several months or longer and usually deviate away from a normal growth pattern for some period of time between 6 and 36 months of age. After that time, the growth rate is normal and their growth pattern parallels the normal growth curve. When seen for evaluation, these children are usually growing at a normal rate for age. Puberty is delayed, and there is a later than average adolescent acceleration of growth. However, normal adult height is attained and normal sexual development occurs. There is usually a family history of a similar pattern of childhood and adolescent growth in one parent or other first degree relative. The great majority of children who fall into this category are short, but otherwise normal, boys.

The general screening studies previously described are not necessary in short children who are growing at a normal rate. However, a bone age x-ray should be obtained for prognostic purposes. Their bone age is delayed and is more consistent with height age than with chronologic age. Tests of thyroid function are often performed but only sometimes indicated, and the diagnosis of hypothyroidism can usually be eliminated by history and physical examination. The short child who is active, alert, and clearly euthyroid in the examining room, does not need laboratory confirmation of his normality.

The question of treatment is controversial as ultimate height is normal without therapy. There is very little evidence that children who are treated are any taller than they would have been without treatment. Normal short children do not respond with any consistency to thyroxine or physiologic amounts of human growth hormone. Potent androgens or human chorionic gonadotropin should not be administered because these agents cause virilization and accelerate epiphyseal development. A large number of synthetic steroids, designed to have an increased anabolic/androgenic ratio, have been used to accelerate the growth of normal short children, and such agents do increase the rate of linear growth in the short run. However, in no instance has there been a complete separation of anabolic from androgenic activity, and the effect of these agents on epiphyseal maturation cannot be predicted in an individual child.

If possible, it is preferable to help these patients and their families work through the problems of short stature rather than to alter growth and development with a pharmacologic agent. The cautious administration of an anabolic agent is indicated only when short stature creates psychologic problems that cannot be solved in other ways. I recommend treating only prepubertal patients who are at least 12 years old and whose bone age is at least 2 years behind their chronologic age. This recommendation is based on the observation that bone age is more likely to be unduly accelerated by treatment in younger children. Because the aim of treatment at this age is acceleration of growth and not the induction of sexual maturation, an agent with a maximum anabolic/androgenic ratio is preferable. I use oxandrolone in a dose of 0.1 to 0.25 mg/kg of body weight in one or two doses each day. Treated patients must be seen at frequent intervals to monitor the clinical effects of therapy. Bone age x-rays should be obtained every six months. Therapy should be discontinued if epiphyseal maturation advances out of proportion to the change in chronologic age or if unacceptable virilization is induced.

Anabolic/androgenic steroids are occasionally hepatotoxic and base line tests of liver function, as well as periodic follow-up evaluation, must be carried out. High-dose androgen therapy has been associated with the development of hepatic tumors and, although such tumors have not developed in patients receiving anabolic/androgenic therapy for the acceleration of growth, the physician who treats short children with these agents must be aware of this potential complication.

TABLE 2. Common Nonendocrine conditions

I. Constitutional delay in growth and adolescence
II. Familial (genetic) short stature
III. Intrauterine growth retardation

Patients with familial or genetic short stature tend to be short at birth. They grow parallel to the normal curve but below the fifth percentile from early infancy. Adolescent development and the adolescent acceleration of growth occurs at the usual time. Ultimate height is short for the patient's racial and ethnic background but is consistent with family height. All laboratory studies are normal, including bone age. There is no therapy to modify either growth rate or ultimate height.

Intrauterine growth retardation (IUGR), which occurs as both an isolated abnormality and in a number of conditions in which short stature is associated with multiple congenital malformations, is usually sporadic. There is no family history of a similar pattern of growth. As this condition has multiple causes, the clinical course is highly variable. Many affected children rapidly catch up to a length that is within the range of normal for their age. A subgroup of children with IUGR remain small during infancy and early childhood, but show later catch-up growth and ultimately reach a normal height. However, a significant number of children with IUGR remain small and do not experience a period of accelerated growth in infancy or later childhood.

The diagnosis of IUGR depends on the history of the length of gestation and the measurement of weight and length at birth. As the determination of birth length and the history of the length of the pregnancy are notoriously inaccurate,

TABLE 3. Endocrine Disorders

I. Hypothyroidism
II. Abnormalities of the X chromosome
III. Growth hormone deficiency
IV. Deprivation (psychosocial) dwarfism
V. Cortisol excess

the diagnosis is frequently based on birth weight and the best estimate of the length of pregnancy. All laboratory studies of endocrine function are normal. The bone age of patients with IUGR is variable when compared to both height age and chronologic age. In general, the bone age of patients who catch up to normal height is normal. Patients who remain short generally have delayed epiphyseal maturation.

The same considerations apply to the treatment of short children with a history of IUGR as those discussed for children with constitutional delay in growth and adolescence. Anabolic/androgenic steroid therapy may benefit children with IUGR who are significantly below average height and whose bone age is delayed. The possibility of side effects including undue acceleration of epiphyseal maturation and abnormalities in liver function, must be kept in mind.

General statements cannot be made regarding the long-term prognosis for ultimate height in IUGR. Although many patients who are small at birth achieve a normal adult height, there are a significant number who may be short at maturity. Unfortunately, there is no satisfactory way of predicting which children fall into the group with an unfavorable prognosis.

Endocrine Disorders

The major endocrine disorders that must be considered in the differential diagnosis of short stature are listed in Table 3.

Hypothyroidism. Children with congenital or acquired primary hypothyroidism often are first seen with the complaint of growth failure. As the diagnosis of congenital hypothyroidism should be made by neonatal screening, this discussion will focus on acquired disease.

By far the most common cause of acquired hypothyroidism is autoimmune or Hashimoto's thyroiditis. Females are affected four or five times more often than are males, and often there is a strong family history of thyroid disease.

If short stature is due to hypothyroidism, associated symptoms can usually be elicited. These include cold intolerance, increased need for sleep, constipation, muscle aches and weakness, decreased activity, and mental dullness. Hypothyroid children are both short and growing at a subnormal rate. Their growth curve is that of acquired growth failure. If growth is impaired from an early age, body proportions may be relatively infantile with a greater than expected upper/lower segment ratio and short arm span in relation to height.

When hypothyroidism has been present for more than 6 to 12 months, patients may appear pale and puffy. Speech may be slow and the voice may be hoarse and low-pitched. The skin is usually thickened, dry, coarse, and cool. Scalp hair may be dry and brittle. Some patients show an unusual type of hirsutism in which there is an increase in fine, dark lanugo-like hair over the back, shoulders, and upper arms. Dental development is frequently delayed. There may be bradycardia and an elevation in diastolic blood pressure. Although there is muscle weakness, the muscles of the extremities may be hypertrophied. There is characteristic delay in the relaxation phase of the deep tendon reflexes which is most easily demonstrated at the ankle. Goiter is frequently present, and the thyroid is two or three times the normal size. The surface is generally irregular but not nodular, and the consistency of the gland is firm and rubbery.

The diagnosis of acquired primary hypothyroidism is confirmed by the demonstration of a decreased serum concentration of thyroxine and an elevated serum concentration of thyroid-stimulating hormone (TSH). After chronic disease of a nonendocrine organ system has been eliminated from consideration, these two tests of thyroid function should be performed in all short children who are growing at a subnormal rate. Antibodies to thyroglobulin and thyroid microsomes should be sought in all hypothyroid patients.

Epiphyseal maturation is usually significantly delayed in acquired hypothyroidism. At times characteristic epiphyseal stipling (epiphyseal dysgenesis) is seen. This abnormality may not become evident until therapy is begun, but it is frequently present during the resolving phase of hypothyroidism.

The therapy for acquired hypothyroidism is sodium-L-thyroxine. The dose is 4 to 6 μg/kg/day between 1 and 5 years of age, and 3 to 5 μg/kg/day, up to a maximum of 150 μg in older patients. Therapy should be monitored with determinations of serum thyroxine and TSH, and treatment should lead to normalization of both serum thyroxine and TSH concentrations.

All abnormalities associated with acquired hypothyroidism, including growth failure, should resolve completely with appropriate replacement therapy.

Abnormalities of X Chromosome (Gonadal Dysgenesis). It is now clear that there are a wide variety of X chromosome abnormalities that may be associated with a broad spectrum of phenotypic abnormalities (Table 4). The unifying expressions are short stature and gonadal dysgenesis, but even these features are not uniformly present. Abnormalities of the X chromosome occur with an incidence of 1 to 1.5/2,000 term births, and they must be considered in the evaluation of any short girl whether or not associated abnormalities and/or sexual immaturity are present.

The pathogenesis of the short stature seen with X chromosome abnormalities is not well understood. Linear growth in females depends, at least in part, on homozygosity for genes that are carried on the X chromosome. When these height-determining genes are not present in the homozygous state, growth failure and ultimate short stature result. Deficient hormone production or responsiveness has not been demon-

strated. Growth hormone secretion and somatomedin generation are normal. Although the incidence of autoimmune thyroiditis is increased, hypothyroidism does not account for the growth failure.

Short stature is present from birth in up to half of the patients. In almost all patients height is below that expected by age 4 or 5 years. The growth rate is subnormal and there is no pubertal acceleration of growth.

Patients with gonadal failure usually show no estrogen effect at the time of expected puberty. However, the increase in adrenal androgen production, which is part of normal pubertal development, does occur, and girls with gonadal failure develop pubic and axillary hair. In a few patients in whom sufficient gonadal tissue is present, pubertal development may advance and menarche may occur. Regular menstruation and pregnancy are possible but extremely rare.

If no chronic illness is present, all euthyroid girls being evaluated for short stature should have chromosome analysis of peripheral lymphocytes. As no more than half of the patients with abnormalities of the X chromosome are chromatin-negative, the buccal smear is not a satisfactory method of diagnosis. The presence of primary gonadal failure can be confirmed by demonstrating elevated concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Because of the association between abnormalities of the X chromosome and autoimmune thyroiditis, thyroid function should be evaluated and antithyroid antibodies should be measured at regular intervals. Epiphyseal development is delayed in most patients with short stature due to an abnormality of the X chromosome.

The treatment of girls with an abnormality of the X chromosome is directed at promoting linear growth, inducing secondary sexual maturation, and, when necessary, correcting associated anomalies. Only the management of short stature will be considered here. Therapy with androgen/anabolic steroids accelerates linear growth in the majority of patients. There is some, but still only minimal, evidence that such treatment increases ultimate height in this group of children. It has been suggested that the combination of human growth hormone and an anabolic agent is preferable to an anabolic steroid used alone. Growth hormone alone is without effect as is thyroxine.

Patients should be treated with anabolic steroid therapy at age 8 to 10 years with 0.1 to 0.2 mg of oxandrolone per kilogram of body weight per day given in two doses. Patients are checked for their response and the presence of side effects at three-month intervals, and bone age is monitored every six months. Therapy is continued as long as there is an increase in growth rate without an undue advance in bone age or unacceptable virilizing side effects. When older patients wish to be feminized, anabolic steroid therapy is continued if it is still having a positive effect.

The ultimate height of girls with abnormalities of the X chromosome is much less than that of normal adult women. The average adult height of patients treated with estrogens alone is 142 to 145 cm (56 to 58 inches), and the range extends from 132 to 163 cm (52 to 65 inches).

Growth Hormone Deficiency. Although growth hormone (GH) deficiency is a relatively rare cause of short stature, it should be looked for after chronic nonendocrine disease, hypothyroidism, and abnormalities of the X chromosome have been eliminated as diagnostic possibilities.

GH deficiency may result from an intracranial lesion or may occur in the absence of any anatomic abnormality. Table 5 shows the major categories of intracranial lesion that may lead to a deficiency of GH. Congenital midline defects range from anencephaly at one extreme through septo-optic dysplasia, to cleft lip and/or palate, and the single upper central incisor syndrome at the other. There may be defects in pituitary development; these include pituitary agenesis, pituitary hypoplasia, and ectopic pituitary. By far the most common associated neoplasm is craniopharyngioma. Hand-Schuller-Christian disease, basilar skull fracture, and several infections, particularly tuberculous meningitis may lead to abnormalities in GH synthesis and/or secretion. Intracranial radiation of patients with neoplasms or leukemia may lead to GH deficiency, which complicates their prolonged survival.

TABLE 4. Abnormalities Found in Patients with X Chromosome Disorder

Abnormality	Patients (%)
Short stature	95–100
Gonadal failure	95–100
Skin: pigmented nevi	60–70
Face:	
Prominent ears	60–90
Small mandible	60–90
Narrow, arched palate	60–90
Ptosis	30–60
Epicanthal folds	20–50
Neck:	
Short neck	60–90
Low hairline	50–80
Webbed neck	40–60
Chest:	
Shield chest	80–90
Pectus excavatum	40–50
Abnormal nipples	30–80
Extremities:	
Congenital lymphedema	50–80
Abnormal nails	80–90
Puffiness of toes	30–50
Clinodactyly	20–40
Cubitus valgus	60–80
Heart:	
Coarctation of aorta	10–30
Other anomalies	5–15
Kidney: renal anomalies	50–70

TABLE 5. Growth Hormone Deficiency Due to Intracranial Lesion

I. Congenital
   A. Midline defect
   B. Pituitary dysgenesis
II. Acquired
   A. Neoplasms
   B. Reticuloendotheliosis
   C. Trauma
   D. Infection
   E. Radiation therapy

TABLE 6. Pathogenesis of Idiopathic Growth hormone Deficiency

I. Neurotransmitter defect
II. Releasing hormone deficiency
III. Pituitary growth hormone deficiency
IV. Biologically inactive growth hormone
V. Unresponsiveness to growth hormone
VI. Unresponsiveness to somatomedin

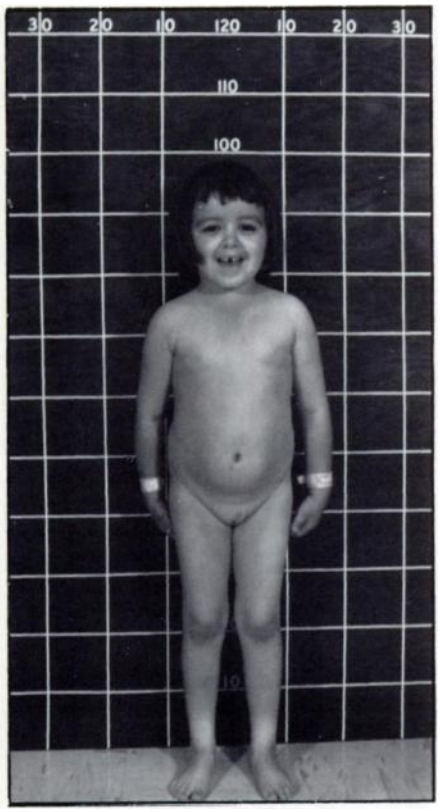

Fig 2. Eight-year-old girl with growth hormone deficiency. Height age is 3 5/12 years, and weight age is 3 9/12 years. Note normal body proportions and missing deciduous single central incisor. (Reprinted with permission from Frasier SD: Growth disorders in children. Ped Clin North Am 26:1, 1979.)

The physiologic system that is responsible for GH secretion and action involves several different levels. These include the central nervous system outside of the hypothalamus, the hypothalamus itself, the pituitary gonadotroph, and the mechanisms through which GH generates its end-organ hormones, the somatomedins. As shown in Table 6, functional defects may exist at any of these levels and lead to the clinical syndrome of GH deficiency. Defective neurotransmitter metabolism mediating input to the hypothalamus may be involved in the transient GH deficiency of psychosocial dwarfism. Growth hormone releasing factor deficiency may exist as part of a syndrome of multiple hypothalamic releasing hormone deficiencies or may occur as an isolated abnormality. Pituitary GH deficiency may also occur as an isolated problem or in association with deficiencies of other pituitary hormones. Recently a syndrome in which growth hormone is detectable by standard immunologic techniques but is biologically inactive has been described. Patients with this syndrome have low levels of somatomedin which can be increased by the administration of exogenous growth hormone. Patients may have a biologically active growth hormone which fails to generate somatomedin because of a defect in the GH receptor mechanism. This syndrome, described by Laron, is a recessively inherited genetic abnormality. Patients with peripheral unresponsiveness to somatomedin have also been described.

If growth hormone deficiency is congenital, growth failure is usually noted by 12 to 18 months of age. Children with acquired GH deficiency have the growth curve of acquired growth failure. GH deficient children are normally proportioned and their upper/lower segment ratio and the relationship between arm span and height are normal. Many patients share a number of physical features regardless of the underlying etiology which, when taken together, produce a common appearance (Fig 2). Patients tend to be overweight for their height, and their height age is less than their weight age. Although the excess fat deposition does not spare the extremities, it is frequently concentrated over the chest and abdomen. Head size may also be more consistent with chronologic age than height. This overall appearance has been described as "doll-like" or "cherubic." The voice may be high-pitched and squeaky due to immaturity of the facial bones. Congenital GH deficiency may first become manifest in early infancy as hypoglycemia with convulsions, cyanosis, and shock. In the male, associated congenital gonadotropin deficiency may lead to micropenis, and the combination of microgenitalia and hypoglycemia is usually due to multiple pituitary hormone deficiencies which include growth hormone.

Associated endocrine abnormalities are also frequently present in acquired GH deficiency. The most common of these is diabetes insipidus in patients with chronic reticuloendotheliosis. Intracranial lesions may also lead to impaired gonadotropin secretion and failure of adolescent development to begin or to progress may be an associated presenting problem. Hypoglycemia is also commonly seen in GH deficient children with organic pituitary dysfunction.

As growth hormone is often undetectable in the serum of healthy persons, a random determination of the concentration of growth hormone is of no value. Children in whom the diagnosis is suspected on clinical grounds should be screened for GH deficiency and, if the child is old enough to cooperate, an exercise test should be performed. Patients are instructed to have nothing by mouth for three or four hours and to rest quietly for 30 minutes after coming to the office or are studied between 8 and 9 AM after an overnight fast without a rest period. A control blood sample is drawn and the patient either walks on a level surface for 15 minutes and then runs up and down one flight of stairs for five minutes or performs 20 minutes of parent-supervised vigorous exercise consisting of jumping jacks, running, or whatever is preferable for the patient. A postexercise blood sample is then obtained. Between 80% and 90% of normal children will respond to exercise with an increase in the serum concentration of growth hormone to ≥6 ng/ml. Pretreatment with propranolol (20 mg to children weighing less than 20 kg and 40 mg to heavier children) enhances the response. A propranolol-primed test should be performed in children who fail to respond to exercise alone prior to proceeding to definitive test-

ing. Children who are too young to perform standardized exercise should be given L-dopa, as described for definitive testing, with samples obtained at 0, 30, and 60 minutes.

Children who fail to respond to a screening test need definitive testing with two stimuli. The tests that have been standardized for this purpose are insulin-induced hypoglycemia, intravenous arginine, oral L-dopa, and intramuscular or subcutaneous glucagon.

Hypoglycemia is induced by the intravenous injection of regular insulin in a dose of 0.05 to 0.1 unit/kg of body weight. Blood samples are obtained for the determination of both blood glucose and growth hormone concentrations at 10- or 15-minute intervals over an initial hour, and at 20- or 30-minute intervals over a second hour. A 50% decrease in the concentration of blood glucose results in an increase in the concentration of growth hormone in serum to ≥8 ng/ml in more than 85% to 90% of normal children. The peak serum concentration of growth hormone is usually observed at 30 to 60 minutes after the administration of insulin. Symptoms of hypoglycemia may be seen between 15 and 45 minutes. The person performing the test must be prepared to administer 50% glucose intravenously and/or 1 mg of glucagon intramuscularly if termination of the test is indicated.

Arginine HCl, which is available as a 10% solution for use as a diagnostic reagent, is administered as an intravenous infusion over 30 minutes. The dose is 0.5 gm/kg of body weight up to a maximum of 30 gm. Blood samples are obtained every 15 minutes for the first hour and at 30-minute intervals over a second hour. Between 80% and 85% of healthy children will respond with a peak serum growth hormone level ≥8 ng/ml, usually at 30 to 60 minutes. Girls are somewhat more likely to respond than are boys. The intravenous infusion of arginine is essentially without side effects.

When L-dopa is administered by mouth there is a prompt release of GH from the pituitary. The dose of L-dopa is 25 mg for children weighing less than 15 kg, 250 mg for children weighing 15 to 30 kg, and 500 mg for children weighing more than 30 kg. Blood samples are obtained every 30 minutes over a two-hour period. A peak serum growth concentration of ≥8 mg/ml is seen in 85% to 90% of healthy children in the 30- or 60-minute sample. Unpleasant side effects, particularly nausea and/or vomiting, are induced by L-dopa in a significant number of children.

The intramuscular or subcutaneous administration of glucagon in a dose of 0.03 μg/kg up to 1.0 mg results in a significant increase in the serum concentration of GH as a relatively late response. Blood samples are obtained at 30-minute intervals over a three-hour period following glucagon injection, and a maximum GH concentration of ≥8 ng/ml is observed between 120 and 150 minutes in 75% to 80% of normal children. No significant side effects have been reported following glucagon administration.

Patients with growth hormone deficiency respond dramatically to the administration of human growth hormone (hGH). At present, the source of hGH, available from the National Pituitary Association (NPA) or commercial sources, is human pituitary glands. Recombinant DNA technology should provide another source of hGH in the near future. Human growth hormone is administered intramuscularly in an initial dose of 0.05 to 0.1 unit/kg of body weight, three times a week. Catch-up growth, without an undue acceleration of bone age, is seen in about 80% to 90% of patients. The response is greatest during the first 6 to 12 months of therapy and subsequently declines. The dose of hGH may be increased in increments of 0.05 unit/kg at 6- to 12-month intervals up to 0.2 to 0.25 unit/kg three times a week. The concomitant administration of oxandrolone in a dose of 0.1 to 0.25 mg/kg/day or fluoxymesterone, 4 to 10 mg/day may ameliorate the declining effect.

There are surprisingly few side-effects when hGH is administered to growth hormone deficient patients. Local tenderness at the site of injection is an occasional complaint. Allergic reactions have not been noted. A significant proportion of treated patients have developed antibodies to hGH, but in all but a few patients the antibodies have not interfered with the biologic activity of hGH.

Because of limitations in the supply of hGH, insufficient numbers of patients have been treated from an early age until maturity to allow any definitive statements regarding the effect on their ultimate height. Without therapy, affected children would not be expected to reach a height of 152 cm (60 inches), and many would be less than 137 cm (54 inches) tall. Theoretically, treated patients should attain a normal adult height.

Deprivation (Psychosocial) Dwarfism. The syndrome of deprivation or psychosocial dwarfism is characterized by emotional disturbances and abnormalities in behavior that are associated with reversible growth failure and transient impairment of pituitary function.

Although there is no doubt that environmental deprivation can lead to abnormalities in growth, the pathogenic link between the resulting emotional disturbances and growth hormone deficiency remains obscure. Preliminary data suggest that neurotransmitter function may be impaired in this syndrome. However, no definite conclusions can be reached regarding the pathogenic significance of this finding. There are also fragmentary data that suggest that the growth retardation of affected patients may be related to their sleep disturbances, but these observations also await confirmation. The etiologic role of malnutrition is controversial. Present data indicate that although impaired food intake may contribute to the growth failure of some patients, it is usually not the only causative factor.

The age of onset of growth failure is highly variable. At the time of initial evaluation patients are well below average height for their age and are growing at a subnormal rate. Their growth curve cannot be distinguished from that seen in acquired growth hormone deficiency. The growth retardation is proportional. The relationship between span and height is normal and the upper/

lower segment ratio is appropriate for the patient's height. Although there is a tendency for the patients to be underweight for height, this is a variable finding and some patients are mildly or even moderately obese. There may be a protuberant abdomen and thin extremities, both of which suggest the possibility of intestinal malabsorption.

In most patients, the characteristic behavior abnormalities begin before age 2 years. Disturbed behavior is centered around drinking, eating, and sleeping. Almost all patients show bizarre polydipsia. It is not unusual for them to drink from toilet bowls, sprinkler heads, gutters, or fish tanks. Water is frequently requested throughout the night. Most affected children have a voracious appetite. They frequently eat from garbage cans, and they beg or steal food from friends, neighbors, or food stores. Rumination and cyclic vomiting are sometimes seen. Insomnia and roving nighttime behavior are common. Many patients have difficulty with bladder and bowel training. Apparent retardation of intellectual development and speech is frequent.

These patients usually have disrupted families. The incidence of divorce and separation is higher than expected, and the father is frequently out of the home. One or both parents are often alcoholic. There may be clear evidence of estrangement between the parents, particularly the mother, and the patient. A past history or current physical evidence of child abuse is often found. The child with psychosocial dwarfism tends to be isolated and does not participate in family activities.

The diagnosis depends primarily on past history and subsequent clinical course. When tests of pituitary function are performed during the time that growth is impaired, there is usually evidence of growth hormone deficiency. Many patients also have adrenocorticotropin (ACTH) deficiency. Thyroid function is normal. If pituitary function is studied during the recovery phase when growth is accelerated, growth hormone and ACTH secretion are found to be normal. The bone age is markedly retarded during the period of growth failure, and epiphyseal maturation normalizes during the phase of catch-up growth.

The therapy of deprivation dwarfism is modification of the patient's environment. This most often takes the form of hospitalization for initial diagnostic evaluation and subsequent placement in a foster home. Removal of the patient from the depriving environment is usually followed by remarkable changes in weight gain and linear growth. When patients are removed from their home, their abnormal pattern of behavior is also modified. Appetite becomes more normal and bizarre eating and drinking habits lessen. There is frequently a marked increase in verbal behavior and intellectual retardation is no longer apparent. It is not unusual for patients to become much more extroverted and social. Sleep disturbances decrease and bowel and bladder control are better established.

The ultimate prognosis for weight gain, growth, and adolescent development is good, provided the patient can remain in a supportive environment. The long-term psychological prognosis is guarded and very little has been written about the ultimate psychological and social function of patients with deprivation dwarfism.

Glucocorticoid Excess. Glucocorticoid excess in infancy and childhood almost always leads to a subnormal growth rate, short stature, and delayed epiphyseal maturation. Occasionally growth failure is the primary or only clinical manifestation. This diagnosis should be considered, and appropriate tests for cortisol excess should be performed whenever the cause of growth failure is obscure as well as when there are more classic symptoms and signs of increased glucocorticoid secretion.

SUMMARY

Short stature in childhood has many possible causes, only the minority of which are endocrine disorders. In addition to a complete history and physical examination, the most important information that can be brought to bear on the differential diagnosis of short stature is accurate serial measurements of length and/or height. When these data are used to calculate growth velocity and are plotted on a standard growth curve, short children can be quickly classified into those growing at a subnormal rate and likely to have a significant underlying problem and those whose growth rate is normal and who are very unlikely to have any problem. In general, diagnostic studies may be limited to short children who are growing at a subnormal rate. Endocrine disease should only be considered after chronic illness of a nonendocrine organ system has been eliminated from consideration. The possibilities of hypothyroidism, an abnormality of the X chromosome in short girls, and growth hormone deficiency should be sequentially evaluated. The unusual diagnoses of deprivation dwarfism and glucocorticoid excess must be kept in mind. If a specific diagnosis is confirmed, appropriate therapy can be instituted. The vast majority of short children are growing at a normal rate and are boys with constitutional delay. A bone age x-ray is extremely helpful in arriving at a prediction of their mature height which is almost always within the range expected in their family. The reassurance provided by this maneuver usually makes any pharmacologic therapy unnecessary.

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Short Stature

Short Stature as the Primary Manifestation of Coeliac Disease. Groll A, et al: *Lancet* 2:1097, 1980.

Thirty-four patients aged 2½ to 17 years with short stature of undetermined cause and no gastrointestinal symptoms underwent jejunal biopsy for exclusion of coeliac disease. Eight patients had subtotal or severe partial villous atrophy; seven of these showed a significant acceleration in growth velocity after the introduction of a gluten-free diet. The authors conclude that short stature by itself, in the complete absence of gastrointestinal symptoms, is an indication for jejunal biopsy, particularly if bone age is delayed by more than four years and/or there are associated hematologic abnormalities.

Comment: In this study 21% of children with short stature, in whom dysmorphic or primary endocrinopathy had been ruled out, proved to have coeliac disease. It is well known that some patients with coeliac disease may have only short stature and failure to thrive; however, most do have gastrointestinal manifestations such as abdominal distention, abdominal distress, or foul-smelling stools. What is surprising is that such a large percentage of this group of 34 patients had coeliac disease. This may be a reflection of the fact that the study was carried out in England, where coeliac disease is probably more common than in the United States. Despite the fact that coeliac disease is less commonly diagnosed in this country than it previously had been, physicians must maintain a high index of suspicion. Screening tests are unreliable and when the diagnosis is suspected, jejunal biopsy should be performed. Blind trials of a gluten-free diet frequently cause confusion and should be avoided. Patients who are true coeliacs should be on a strict gluten-free diet for life. (*K. Nord*)

EDUCATIONAL OBJECTIVE

131. Appropriate familiarity with the clinical picture of heatstroke and of its prevention and treatment (81/82).

Heatstroke

Exertional Heatstroke in Novice Runners. Hanson PG, et al. *JAMA* 242:154, 1979.

As former President Carter demonstrated, heatstroke can develop in presumably trained people who are running in hot weather. Heat production in steady-state exercise in adults can produce 1,000 kcal/hr or more, and rectal temperatures can reach 41° C. A critical thermal maximum of 42° C, when reached, can lead to heatstroke. Runners, especially novices, need data about temperature and humidity and need to be reminded to drink adequate volumes of hypotonic fluids during exercise. They also need to recognize the early symptoms of evolving hyperthermia including increasing fatigue, hyperventilation, nausea, disorientation, and eventual staggering gait. Other clinical features of heatstroke include hyperpyrexia and incoherence of speech with eventual loss of consciousness. Although anhidrosis and tachycardia may be seen, active sweating and relative bradycardia may occur in conditioned athletes. Treatment of heatstroke includes rapid vigorous cooling, rehydration, and maintenance of adequate circulation.

Comment: Heatstroke is the second most common cause of athletic death (CNS injuries is the number 1 cause of death). It is preventable by avoidance of excessive exercise in hot weather, acclimatization, and education. During hot weather the athlete needs frequent rest and adequate intake of hypotonic fluids. (*R.H.R.*)

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