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13.7.1 Normal growth and its disorders 2417 Fig. 13.7.1.1 UK-WHO growth standards 0–4 years in boys. © 2009 Department of Health.

section 13 Endocrine disorders 2418 Fig. 13.7.1.2 UK-WHO growth standards 0–4 years in girls. © 2009 Department of Health.

13.7.1 Normal growth and its disorders 2419 Before considering the problems of growth (summarized in Table 13.7.1.1), it is helpful to understand the three phases of postnatal growth separately: infancy, childhood, and adolescence. Infancy Growth is most rapid in the first year of life. Despite a normal weight loss of up to 10% in the first two weeks of life, weight will triple from a mean of 3.3 kg at birth to 10 kg and length increases by 50% from 50 cm to 75 cm, with a height velocity of 25 cm per year. Head cir- cumference, which reflects brain growth, increases by one-third over the year, two-thirds of this occurring within the first 6 months. Much tracking of growth measurements (movement upwards or downwards across centile bands) takes place over this first 6 months. Weight, length, and head circumference may each shift as much as one centile band which, if in a downwards move, may pose difficul- ties in the differential diagnosis of failure to thrive, but in normal growth variants this will cease once the genetic or preprogrammed centile has been attained. There are several reasons for this. First, size at birth principally tends to reflect maternal height and also pla- cental function. Second, in the absence of disease, growth will follow a genetically determined trajectory. Adequate nutrition is a highly important factor in determining normal growth and has a funda- mental influence during infancy. A good example of shifts in growth centiles is catch-up growth exhibited by infants who have been subject to intrauterine growth retardation. Unless there are other constraints, more than 95% will show full catch-up of length and weight by the end of the first year and 98% by 2 years of age. This should not be confused with in- fants of preterm birth whose relative size may be attributed to their prematurity. Here, by convention, measurements are adjusted for gestational age up until their first birthday for those born after 32 weeks' gestation and their second birthday for those below 32 weeks' gestation. Childhood The childhood phase of growth lasts from the second year of life until the clinical onset of puberty. The rate of height and weight gain is less rapid than in infancy and is similar between boys and girls until the onset of puberty. This phase of growth is largely under the control of hormonal factors most notably growth hormone (GH) and insulin-like growth factor 1 (IGF-1). There are also environ- mental influences such as the seasons and health and endogenous rhythms which produce spurts of growth, the largest of which at around about 6 years of age is known as the mid-childhood growth spurt. This is one of a series of prepubertal growth spurts occurring approximately every 2 years. Although there is a temporal associ- ation with adrenarche, which is the maturation of the adrenal cortex to produce adrenal androgens, there is no direct link between this phase of adrenal physiology and growth as the prepubertal growth spurts are multiple and the mid-childhood spurt, although the most consistent, is not necessarily the largest prepubertal growth spurt. Adolescence The most marked difference in growth between the sexes starts during puberty. The total height gain in the male during this period is 25 to 30 cm, greater than in the female which is 20 to 25 cm. However, most of the 14 cm average difference between men and women occurs before the onset of the adolescent growth spurt. Approximately 11 to 12 cm is accounted for by boys continuing to grow at the prepubertal growth rate for a further 2 years until the onset of the faster pubertal growth spurt, which contributes 2 to 3 cm more height than in girls. Although the rapid acceleration in growth is coincident with the clinical and hormonal onset of puberty in both sexes, it is much more intense and hence more immediately noticeable in girls and they will attain the maximum growth rate (peak height velocity) 1 year after starting puberty, whereas in boys the acceleration is far more gradual and peak growth occurs 2 years after the onset of puberty. Disorders of growth Simple errors Quite often children who are thought to have a growth disorder turn out not to; the apparent problem is due to an error in measurement or in plotting on a growth chart. Simply repeating these procedures if an odd pattern of growth is seen will usually reveal the problem. Genuine growth disorders demonstrate a continued trend, whether this is acceleration or deceleration of growth at inappropriate times or weight loss or gain when unexpected or at an unusual age. Table 13.7.1.1 Principal causes of abnormalities in growth and stature Short stature Tall stature Familial short stature Familial tall stature Constitutional delay of growth and/or puberty Constitutionally advanced growth and/or puberty (constitutional tall stature) Idiopathic short stature Obesity Small for gestational age/intrauterine growth retardation Precocious sexual maturation Psychosocial short stature Supernumerary sex chromosomes, e.g. Klinefelter's, XYY, XXX Chronic disease: recognized and unrecognized Genetic/dysmorphic tall stature syndromes, e.g. Marfan's, Sotos, Beckwith–Wiedemann Endocrine gland disorders including GH deficiency Genetic abnormalities of the GH axis Chromosomal variations including SHOX deletions Genetic/dysmorphic short stature syndromes, e.g. Turner's, Russell–Silver, Noonan's Skeletal dysplasias

Growth standards Current UK-WHO charts aged 0–4 years are based on the WHO growth standards which are derived from prospectively collected data from over 8000 infants in six countries around the world until 5 years of age (see Figs. 13.7.1.1 and 13.7.1.2). These infants were breast fed and reared in optimal socioeconomic circumstances. They represent the ideal pattern of growth in health and are suitable for all ethnic groups. Charts are available in centile format (commonly used in the United Kingdom and United States) and in standard deviation format preferred in many European countries. Beyond age 4 years, the UK 1990 growth data (see Figs. 13.7.1.3 and 13.7.1.4) continues to be used. Familial short stature The term 'genetic short stature' should be avoided in this situation as it is imprecise, and the meaning can be confused with small size from a chromosomal or single gene abnormality. From short parents generally come short children. The target centile range can generally be estimated from the information pro- vided on national growth standards. In the United Kingdom a rela- tively simple formula is applied. The target or mid-parental height is a simple mean of the parents' height adjusted for the 14 cm mean male–female difference. Thus, target height for a boy is the parental mean plus 7 cm, and for a girl the target height is the parental mean minus 7 cm. The centile range within which most children of these biological parents will fall is 10 cm either side of the target height for boys and 8.5 cm for girls. A simpler method is the graphical Parent Height Comparator (see Figs. 13.7.1.3 and 13.7.1.4; top right). To estimate the mid-parental centile, plot the mother's and father's heights on their respective scales and join the two points with a line. The mid-parental centile is where this line crosses the centile line in the middle. Then compare the mid-parental centile to the child's current height centile, plotted on the adult height predictor scale (Figs. 13.7.1.3 and 13.7.1.4; bottom right). Nine out of ten children's height centiles are within plus or minus two centile spaces of the mid-parental centile. Children with short stature of familial origin grow normally with no deviation from their centile position. Assessment of height velocity over 1 year can confirm this. Clinical examination is un- remarkable, children having normal body proportions, and patho- logical estimations are also normal. However, in real life situations, several causes of short stature may coexist or overlap (e.g. familial short stature and constitutional growth delay, causing a greater than expected slowing of growth). Experienced clinical judgement is often necessary in situations like this and investigations may need to be performed for reassurance purposes. Once a familial cause of short stature is confirmed, the prin- cipal approach to management is reassurance of the child and their family. Some parents may wish to seek advantage for their child by requesting growth-promoting treatments such as GH but evidence suggests that there is no significant height gain in either the short or the long term in these children. Constitutional delay of growth and puberty Although a delayed process of growth and maturation may present with short stature and delayed puberty, most often in boys, the pro- cess of slowing of growth starts much earlier and generally has a predictable pattern. Infants are of normal size at birth, but weight and length may begin decelerating in the first year, and can cause significant cause for concern as nonorganic failure to thrive may be considered. The rate of growth is low normal, rarely subnormal, but height and weight may show only barely acceptable gains, with the children remaining below the normal centile range until catch-up growth occurs during puberty. These children are phenotypically normal and in very good health, and the only usual finding on in- vestigation is a moderately delayed bone age (1 to 3 years). When the height for bone age is plotted on the centile chart this often falls within the target centile range. Once identified, reassurance is all that is required, but a boost to growth and sexual development may be given with low-dose sex steroids if there is anxiety related to slow sexual development and growth in the mid-teenage years. Idiopathic short stature This term, more precisely defined as nonfamilial, non-GH defi- cient short stature, is inclusive of many pathologies. Children whose height lies 2.5 standard deviations below the mean and whose height falls below their target centile range are considered to have idiopathic short stature. Some children exhibit an appropriate height velocity and maintain their growth centile position, whereas others may grow slowly on the borderline of abnormal (c.4 cm/year). General investigations are unremarkable, and bone age may only be slightly delayed (<2 years). The GH response to stimulation tests is normal. The disparity between this normal response to GH provocation and an abnormal disorganized pattern of physiological secretion has been described as neurosecretory dysfunction, but in reality there may be many causes. One possibility is polymorphisms in the GH receptor with various alleles showing a different GH responsiveness. If GH treatment is given to children whose abnormal growth pattern falls tightly within this definition, a good growth response to GH can be seen almost equivalent to that of true GH deficiency itself. Given diagnostic uncertainties in any case, there may be a case for GH treatment using the same dosage regimen, and this is an approved indication in the United States of America, but not in Europe. However, there are inevitable accusations of advantage manipulation and social engineering which could be true if the precise definitions are not adhered to.

Small for gestational age Infants born with weight and/or length two standard deviations below the mean (2nd centile) are stated to be small for gestational age. This usually arises by a process of intrauterine growth retard- ation, but the terms are not interchangeable and indeed definitions differ. Obstetric practice will usually refer to intrauterine growth re- tardation as fetal measurements falling below the 10th centile for gestational age and maternal size. The causes of intrauterine growth retardation may be extrinsic to the fetus such as placental dysfunc- tion or twin–twin placental steal syndrome, or intrinsic such as in- sulin resistance or genetic reasons such as deletion of a paternally imprinted growth gene or the equivalent maternal uniparental di- somy. This latter cause may account for approximately 10% of those children with clinical Russell–Silver syndrome (see next). The diagnosis is reached from the obstetric history and subsequent postnatal growth pattern. In addition to intrauterine growth retard- ation there is often a sustained period of feeding difficulties and poor growth, often provoking much anxiety as general pathology

13.7.1 Normal growth and its disorders 2421 Fig. 13.7.1.3 United Kingdom 2013 childhood and puberty close monitoring chart for height, weight in boys 2–20 years. © Royal College of Paediatrics and Child Health 2013.

section 13 Endocrine disorders 2422 Fig. 13.7.1.3 Continued

13.7.1 Normal growth and its disorders 2423 Fig. 13.7.1.4 United Kingdom 2013 childhood and puberty close monitoring chart for height, weight in girls 2–20 years. © Royal College of Paediatrics and Child Health 2013.

section 13 Endocrine disorders 2424 Fig. 13.7.1.4 Continued

13.7.1 Normal growth and its disorders 2425 investigations are normal and fears of child protection issues are often raised. The infants are usually thin with little adipose tissue and may have a disproportionately large head, head circumference being within the normal centile range, length, and weight two standard deviations below the mean. In some cases, Russell–Silver syndrome may be defined clinically. These children show a typical triangular facies with frontal bossing, a pointed chin, clinodactyly of the fifth fingers and toes, and in about 50% there is some hemihypertrophy which may be quite subtle. In about 7 to 10% of suspected cases, uniparental disomy of the maternal chromosome 7 can be identified, suggesting that it is an imprinted paternal gene which is required for normal growth. Recent studies have also suggested that imprinting defects within the 11p15 region play a role. Bone age is often isochronological in children who do not show any catch-up growth, and consequently height prognosis is below the target centile range and often more than two standard deviations below the mean. For children over 4 years of age, GH treatment at 35 μg/kg per day (1.0 mg/m2 per day) has shown an initial catch-up and gradual acceleration to adult heights within the normal range. Overall growth gain may be predicted from the first-year response. Although some slight increase in insulin sensitivity and baseline glucose may be found, this is nonprogressive and reversible on stopping GH and long-term studies show continued benefits of having had GH treat- ment with lower blood pressure and an improved metabolic profile. Pathological causes of growth failure Recognized and unrecognized chronic disease Part of the assessment process of any child presenting with an ab- normality of growth is exclusion of other chronic conditions which may manifest initially as a variant of growth. Excess growth can result from overactivity of the thyroid gland as well as other non- endocrine causes of early puberty such as obesity. Slow growth is the more common, but usually less marked than it used to be in child- hood diseases such as chronic renal insufficiency, cystic fibrosis, type 1 diabetes, and inflammatory bowel disease as a result of much improved nutrition and clinical management of these conditions. Growth failure maybe the only presenting feature of conditions such as hypothyroidism, coeliac disease, inflammatory bowel dis- ease, or chronic renal insufficiency, so an initial screen should always include a full biochemical profile including vitamin D levels, a full blood count, iron status, inflammatory markers, thyroid function, and coeliac antibodies. Juvenile arthritis may, in its own right, and as a result of steroid treatment cause significant retardation of growth which may not be amenable to full catch-up if this is longstanding. However, GH treatment at standard doses may help restore growth in some chil- dren. Chronic eczema and other atopic manifestations may subtly slow the tempo of growth, resulting in short stature and delayed puberty, but height usually catches up completely although this may not occur until the late teens or early twenties. Excess endogenous glucocorticoid secretion in Cushing’s syn- drome (adrenal pathology) or Cushing’s disease (ACTH-secreting pituitary tumour) may present with slow or absent growth as well as other clinical signs such as central obesity, malar flushing, and striae. This can almost always be differentiated from children with exogenous obesity who usually grow faster than the norm and are taller than expected for their age. GH treatment is indicated in children with chronic renal insuf- ficiency in a high-dose regimen of 50 μg/kg per day (1.4 mg/m2 per day) as soon as growth failure occurs, as long as nutrition is opti- mized. The main benefit is abolishing or slowing the decline in height velocity resulting from the uraemia. Juvenile hypothyroidism Bone age is often markedly delayed in juvenile acquired hypo thyroidism. This is usually due to autoimmune thyroiditis and may often present insidiously with growth failure alone. Early recogni- tion and treatment with levothyroxine at an initial dose of 100 μg/m2 per day, titrated consequently to normalize thyroid function, will usually result in complete catch-up of growth. Psychosocial short stature Psychosocial short stature occurs in children and adolescents in association with psychological harassment and/or emotional de- privation and may be associated with transient abnormalities of the GH–IGF-1 axis. The clinical features can be very similar to those of GH deficiency, but children suffering from this syndrome usually have a disturbed family environment with a history or current evi- dence of child abuse, most commonly occult sexual abuse. A child with psychosocial growth failure tends to be isolated and may not participate in family activities. Behavioural disturbance and bizarre eating habits are common, with a tendency to hyperphagia rather than undernourishment. Two main subtypes of psychosocial short stature have been identified. Early-onset growth failure (type I or infantile psychosocial short stature) occurs during the first 2 years of life, is very common, and the cause is thought to be undernutrition. This manifests clinic- ally as failure to thrive. If sufficient nutrition is given, these children usually begin to grow normally again. Type II or childhood psychosocial short stature occurs in chil- dren older than 3 years. There is often a greater psychological com- ponent compared with type I psychosocial short stature. Failure to thrive is not such a marked feature and there may be a component of this in some patients diagnosed with constitutional growth delay. Abnormalities of GH secretion can be demonstrated, and these often resolve when the child is removed from the home environment. The clinical presentation is often a short child with growth failure and a normal body mass index, but paradoxical hyperphagia. In some situations, growth may not recover. In such children, full investiga- tion into the abnormality is needed and if inadequate GH secretion remains, replacement will be needed. Turner’s syndrome Turner’s syndrome should be suspected in all girls presenting with short stature and/or poor growth. The incidence of all karyotypes together with complete or partial absence of one X chromosome, or a structurally abnormal X is approximately 1 in 2500.

Girls with karyotype 45,X are more likely to show more features of the syn- drome, including peripheral oedema in infancy, webbed neck, low ears, low posterior hairline, cubitus valgus (increased carrying angle at the elbow), widely spaced nipples, a high arched palate, multiple small pigmented naevi, small convex nails, recurrent ot- itis media and deafness, delayed puberty, amenorrhea, and infer- tility due to ovarian dysgenesis, a higher prevalence of autoimmune hypothyroidism, and congenital heart disease of which coarctation of the aorta is the most common form.

section 13 Endocrine disorders 2426 Growth is decreased in utero resulting in a slightly reduced size at birth, and remains slow during infancy. The height velocity is subnormal during childhood and there is no pubertal acceleration of growth due to the absence of spontaneous oestrogen secretion. In untreated individuals with Turner’s syndrome, mean final height is approximately 143 cm. The short stature may be partly associated with haploinsufficiency of a homeobox-containing gene SHOX lo- cated on the pseudoautosomal region of the X and Y chromosomes. Treatment with GH is now the norm, starting as soon as possible after diagnosis, even in infancy. Most benefit is gained with an early initiation of treatment, and predicted when there is a good first year response. The target GH dose is 45 to 50 µg/kg per day (1.4 mg/m2 per day). Significant height gain may thus occur, with some girls at- taining adult heights within the predicted normal range. The link with family height is retained. Puberty may be induced with low-dose oestrogen (ethinyloestradiol), starting at 1 to 2 µg daily, increasing over approximately 2 years to 20 µg daily, at which time a cyclical pro- gestogen should be added often using the combined oral contracep- tive pill for convenience, but the timing should be as close to normal as possible as delaying this does not bring additional height gains. Cotreatment of the short stature with oxandrolone (a mild ana- bolic steroid) in Turner’s syndrome at a dose of 0.05 mg/kg per day (maximum 2.5 mg) from 9 years of age has been shown in random- ized controlled trials (RCTs) to improve final height by 4.6–7.1 cm. This is a similar result to that achieved by delaying the exogenous induction of puberty with low-dose oestrogen until 14 years of age. Another RCT has confirmed a very similar growth-promoting effect of early introduction of ultra-low-dose oestrogen treatment. SHOX deficiency Deletions or mutations of a homeobox-containing gene SHOX lo- cated on the pseudoautosomal region of the X and Y chromosomes are a rare cause of short stature which may respond to GH treatment. This gene also has a role in the aetiology of abnormal bone morph- ology (such as the radio-ulnar synostosis in Leri-Weill syndrome) and sensorineural hearing loss. Prader–Willi syndrome This condition is caused by either a deletion of the paternally im- printed genes on 15q or maternal uniparental disomy of chromo- some 15. Although often presenting at birth with extreme hypotonia and feeding difficulties, it is more often known for its association with obesity and hyperphagia and other hypothalamic dysfunc- tion such as delayed or absent puberty and slow growth due to a reduction in the numbers of gonadotropin releasing hormone and GH-releasing hormone secretory neurons. Although adult stature is only modestly reduced (155 cm in men, 147 cm in women), GH replacement at 35 µg/kg per day (1.0 mg/m2 per day) may reverse the slowdown in growth, but additionally improves body composition with increased lean body mass and may enhance motor develop- ment. Caution should be exercised in treating children with extreme obesity as sudden death within the first 6 months of GH therapy due to obstructive sleep apnoea has been reported. Skeletal dysplasia Skeletal dysplasia may be suspected when a child is either short for their family or has one parent of significant short stature also. Body disproportion may exist, such as discrepancy between upper and lower segment measurements, short arms (span less than height) or a disproportionately large head circumference. Most of the skel- etal dysplasias are monogenic.

The most common of the nonlethal genetic defects is achondroplasia, which is caused by mutations in the FGFR3 gene in the region 4p16.3. Several skeletal dysplasias are caused by mutations in genes that encode the family of fibroblast growth factor receptors which are tyrosine kinases and mutations within these proteins are thought to slow the rate of endochondral bone growth. Approximately 90% of cases of this disorder arise from de novo mutations. GH treatment may slow deceleration in some conditions, and may produce height gains in milder phenotypes, but is less effective than surgical limb-lengthening procedures. Individual evaluation should be performed. GH deficiency (secondary IGF-1 deficiency) The prevalence of GH deficiency has been variously reported as from 1 in 4000 to 1 in 9000 live births. Childhood-onset GH defi- ciency may be congenital or acquired, and may occur in isolation (isolated GH deficiency) or in association with one or more add- itional pituitary hormone deficiencies (multiple pituitary hormone deficiency), male–female ratio 2.2:1. Congenital GH deficiency may be caused by an inherited mutation or by a developmental abnor- mality. Acquired GH deficiency most frequently results from an intracranial tumour (craniopharyngioma, pituitary adenomas, or destructive lesions arising close to the hypothalamo-pituitary axis such as optic glioma associated with neurofibromatosis or sec- ondary to treatment with surgery or irradiation (doses >2400 cGy) which can damage the hypothalamus, or following traumatic brain injury. Neurofibromatosis type 1 may directly affect pituitary func- tion, leading to growth failure and/or precocious puberty. Genetic causes of GH deficiency Four distinct familial types of isolated GH deficiency are caused by mutations in the GH1 gene: type IA is inherited in an autosomal recessive manner and results in a complete absence of endogenous GH; type IB is also inherited in an autosomal recessive manner; type II is inherited in an autosomal dominant manner; and type III is X-linked. Endogenous GH levels are diminished compared with normal in types IB, II, and III. The development of the pituitary gland is controlled by a large number of genes and transcription factors. Several mutations in the gene encoding POU1F1, a pituitary-specific transcription factor responsible for pituitary development and hormone expression, have been shown to result in combined pituitary hormone deficiencies often of delayed onset. Other mutations in genes encoding pituitary transcription fac- tors, such as PROP1, LHX3, LHX4, HESX1, OTX2, SOX2, SOX3, GLI2, GLI3, FGFR1, FGF8, and PROKR have also been described. Clinical features The severity and duration of GH deficiency is usually reflected by the height deficit and the clinical appearance. Although GH has effects on fetal growth, manifested by a slightly reduced birth length and size, children with congenital GH deficiency may not present with growth failure until after the second year of life. Children with GH deficiency have skeletal proportions that are normal for their age and some are overweight for their height. Central adiposity if it occurs has a classical marbled appearance. Head circumference is within the normal range for age, but growth of the facial bones may be delayed, with a tendency for crowding of the facial features in the centre of the face, giving a doll-like facies.

13.7.1 Normal growth and its disorders 2427 Dentition and skeletal maturity are also delayed. The voice may be high pitched due to the small size of the larynx. Significant hypoglycaemia only occurs in infants with severe iso- lated GH deficiency, and this tendency to hypoglycaemia usually wanes beyond the age of 5 years. However, if there is concurrent defi- ciency of ACTH (i.e. multiple pituitary hormone deficiency), hypo- glycaemia will be exaggerated. In these cases, treatment with both GH and glucocorticoids is required. The clinical features are less marked in children with milder or partial forms of GH deficiency. If a child’s height velocity over 1 year is low and other causes of growth failure have been excluded, the GH status should be assessed, along with other aspects of hypothalamo- pituitary function. Biochemical diagnosis Measurements of random serum GH concentrations are not helpful in diagnosing GH deficiency, as GH is secreted in a pulsatile

manner. Subnormal IGF-1 and IGFBP3 levels are only confirmatory of the diag- nosis, as low levels are often found in short slowly growing children. The diagnosis is made on the basis of a provocation test, which assesses GH secretory reserve, in combination with an IGF-1 level which, if low, confirms an IGF-1 deficiency secondary to the GH deficiency. Various stimuli may be used, including insulin, glucagon, ar- ginine, clonidine, and levodopa. The tests should be done using a standardized protocol after a prescribed fast dependent on the child's age and only where there are experienced medical and nursing staff supervising the child constantly, and where full resuscitation facil- ities are immediately available. A peak GH concentration of less than 6.7 µg/litre has tradition- ally been used to support the diagnosis of GH deficiency. This value depends on the assay used and the recombinant GH refer- ence preparation, and when there are different conversion factors between international reference units and mass-based units. Lower spontaneous levels are seen prior to puberty and in obesity, both of which can give false positive results if not correctly interpreted. Peripubertal patients should have sex steroid treatment to 'prime' the somatotrophs to release GH prior to the stimulation test. It is clear, therefore, that diagnosing GH deficiency can be impre- cise due to an overlap with the spectrum of normality. The growth re- sponse to a trial of GH therapy is ultimately the best diagnostic test. Treatment with GH GH treatment in the standard regimen of 25 to 35 µg/kg per day given by subcutaneous injection starting as soon as possible after diagnosis may allow complete catch-up of growth, with final heights in both idiopathic GH deficiency and multiple pituitary hormone deficiency falling between –1.0 and –1.6 standard deviations (–0.1 to –0.3 standard deviations below mid-parental height). Although physiological GH secretion increases during puberty, there are no current recommendations for altering the GH dose during adoles- cence. Recommendations for the diagnosis and treatment of growth hormone deficiency and other licensed indications reflect modifica- tions of the UK National Institute of Health and Clinical Excellence (NICE) clinical guideline. Primary IGF-1 deficiency (GH insensitivity,
Laron's syndrome) This is a very rare disorder which phenotypically may be similar to the much more common severe GH insufficiency, but the growth retardation is much more severe. In primary IGF-1 de- ficiency there is excessive secretion of GH by the pituitary gland; the fault lies in the GH receptor, which is either absent or non functioning, leading to undetectable levels of IGF-1 and its acid- labile subunit before and after a brief course of GH (the IGF-1 generation test). The abnormality is due to one of several mu- tations in the receptor gene, which is inherited according to an autosomal recessive pattern. Recombinant IGF-1 is licensed in Europe and in the United States of America, following successful clinical trials. Tall stature Given our 'heightist' society, which values tallness over shortness, and the tendency for a secular trend in increasing stature from one generation to the next (by c.1 cm per decade), referrals for concern about tall stature are far fewer than for short stature. By definition, the extremes of stature in men and women (i.e. the 99.6th centile) of 196 cm and 180 cm respectively, seem shorter than those actually tolerated and accommodated in society. As with short stature, diag- nosis of a disorder depends on whether there is rapid growth for chronological age or not. Causes of tall stature with rapid growth Genetically identifiable syndromes will cause rapid growth from infancy, but the clue to diagnosis is in the phenotype (e.g. large head circumference, classic elongated facies, and mild developmental delay in Sotos syndrome; hemihypertrophy, hyperinsulinism, and Wilms' tumour (nephroblastoma) in Beckwith–Wiedemann syndrome). Marfan's syndrome is an autosomal dominant condition affecting connective tissue where tall stature may be associated with scoliosis, chest deformities, high arched palate and arachnodactyly, disloca- tion of the lenses, and dissection of the aorta. Tall stature is noticed from infancy with general accelerated growth. Cardiac assessment and follow-up are essential in all suspected cases. Klinefelter's syndrome (47,XXY) males are of normal size in in-

fancy, but height acceleration throughout childhood is more rapid than usual. Extreme adult tall stature can be predicted early on as all the excess growth occurs in the prepubertal years, the adoles- cent growth spurt being of normal size and duration, which is in contrast with 47,XYY males who may exhibit tall stature during infancy and childhood, but in whom the adolescent growth spurt is exaggerated. Precocious sexual maturation Rapid growth may occur as a result of premature sexual matur- ation resulting from any cause, and it is essential that this is ex- cluded in a child with tall stature and increased height velocity (see Chapter 13.7.2). Familial tall stature Children coming from tall parents are expected to be tall, and are often long at birth; the same approach to diagnosis and predicting adult height can be followed as for familial short stature (see earlier). Height velocities are not excessive for their age, but in general tall children grow more quickly than short children and secrete larger amounts of GH and IGF-1.

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