Human growth hormone (hGH) or somatotropin is a single-chain 191-amino-acid polypeptide that circulates complexed to a binding protein (see below), or is unbound (‘free’). Multiple molecular forms of GH with various biological activities arise from post-translational processing. At all ages – from fetal through adult – GH is secreted in an intermittent, pulsatile pattern largely as a result of the reciprocal interactions of two hypothalamic peptides: growth hormone releasing hormone (GHRH) and somatostatin or somatropin release inhibiting factor (SRIF). As well as growth hormone itself there are a number of peptides, such as insulin-like growth factor (IGF-1), and neurotransmitters that control somatotropin release. Additionally novel compounds such as Ghrelin, released from the gut, and other GH-related peptides (GHRPs) may help to regulate GH release. During childhood there are apparently no differences between the sexes, although several investigators have noted significant correlations between height or height velocity and the amount of GH secreted throughout the day.

Growth hormone interacts with its receptor to generate IGF-I, the main mediator of GH action, in the liver and in most other tissues, including the epiphyses. This receptor, the extracellular domain of which is identical with the circulating GH binding protein, must link up with a second receptor molecule through a two-site GH bridge. This two receptors–one hGH molecular complex permits IGF-1 generation. In addition the circulating half-life of GH is virtually doubled by the presence of the binding protein.

Many of the effects of GH are mediated by IGF-1, which circulates in the plasma bound to one of a series of binding proteins called IGFBPs. These proteins circulate and modify IGF-1 action, either as stimulators or as inhibitors. Although there are at least six of these compounds, IGFBP-3 is the major circulating form.

This complex system subserves the process of growth. At puberty the pulsatile release of GH is increased 2–3-fold, predominantly by increased amounts of GH released at each secretory episode. Along with increasing amounts of sex steroid hormones, this accounts for the majority of the pubertal growth spurt following which the secretion of GH returns toward prepubertal values. As the levels of the GH binding protein do not increase as much as GH secretion, there is an apparent imbalance between the amounts of GH and its binding protein, permitting more GH to circulate in the active (‘free’) form. Theoretically, this increase also drives the local (e.g. epiphyseal) production of IGF-1 and its binding proteins and directly augments long bone growth.

Secretion of GH may be mediated by input from higher centers, allowing for modification of growth rate by environmental and emotional factors. The process of growth is also dependent on adequate nutrition, normal bone structure and biochemistry, normal thyroxine and other endocrine secretion as well as general health. Disruption of normal growth may therefore be an indication of many pathologies.

A number of genes, acting sequentially from the time of formation of the anterior neural ridge at 3–5 weeks of gestation, determine the development of the anterior pituitary gland. Some, such as Sonic (Shh), LHX3 and HESX1 which act early, help to determine the midline structure of the forebrain and often have a variable phenotype. Others, acting later, determine the development of specific cell lineages as straightforward single-gene defects, for instance Prop1 and Pit1 (presently called POU1F1) for lactotrophs, somatotrophs and thyrotrophs, Kal1 for gonadotrophs. Other gene defects may result in the absence of a specific hormone or its receptor (e.g. recessive or dominantly inherited growth hormone deficiency (GHD), Laron syndrome and GHRH receptor mutations).

Environmental influences account for about 25% of birth weight variance modulated through maternal nutrition, social factors and other mechanisms. Both placental and fetal genes can influence birth size, although subsequently genetic size is determined largely by inheritance from the parents. The mechanisms underlying this programming of stature are obscure.
ETIOLOGY

There are many classifications of short stature, all with their advantages and disadvantages. None is perfect, as any group of disorders can be viewed as a spectrum in which dividing lines are often difficult to establish. In this chapter the diagnostic classification is based on that of the European Society for Paediatric Endocrinology.

GROWTH HORMONE DEFICIENCY

GHD may be idiopathic and of hypothalamic or pituitary origin. Neurosecretory dysfunction is defined by the lack of bursts of GH secretion on an overnight profile. There are genetic defects of the GHRH gene and receptor, the GH gene and other, very rare, abnormalities of GH structure and function. The gene sequence required for the formation of the anterior pituitary gland may be disturbed (%Ptx1; %Hesx1; %P-Lim; %Prop1; %POU1F1/Pit1) and some of the central malformations producing GHD may be related to these abnormalities, such as septo-optic dysplasia (some Hesx1) (Fig. 2.1) and single central incisor (Sonic) (see Fig. 1.68). Any midline defect of the face, brain and head is of significance, for instance Rieger syndrome (hypodontia, mid-face hypoplasia and eye abnormalities), as it may imply malformation of the pituitary. Congenital infections may sometimes lead to GHD.

The growth-promoting actions of GH are mediated largely by the generation of local cartilage and possibly hepatic IGF-1. The various genetic mutations in the

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Fig. 2.1 Hypoplastic corpus callosum in septo-optic dysplasia associated with HESX1 mutation.

Fig. 2.2 Laron syndrome, facial view.

Fig. 2.3 Laron syndrome, whole body — note obesity and mid-face hypoplasia.
GH receptor that prevent generation of IGF-1 produce the rare Laron syndrome of GH resistance, in which there is clinical GHD in the presence of normal or high GH levels and low IGF-1 concentration (Figs 2.2 & 2.3). IGF-1 deficiency has been described.

GHD may be acquired as a result of tumors in the hypophyseal area (e.g. craniopharyngioma, germinoma, hamartoma) or may be secondary to effects from more distant CNS tumors or treatment of malignancy. The increasing number of survivors of childhood malignancy who have received cranial irradiation and have subsequently developed GHD means that this is a common cause of GHD (Fig. 2.4), although use of cranial irradiation in leukemia protocols is currently diminishing. Head trauma, meningitis, histiocytosis and hydrocephalus can damage the vulnerable pituitary stalk (Fig. 2.5).

GH deficiency may indeed be complete, for instance in familial gene deletion cases or after surgical removal of the pituitary gland with craniopharyngioma. It is more often a relative lack that may be defined in terms of response to various provocation tests or from the frequency and amplitude of overnight secretory episodes. The more minor degrees of deficiency merge...
with the lower end of the normal range and idiopathic short stature (Fig. 2.6).

Unequivocal GHD from an early age historically produced an adult height of between 130 and 140 cm (around 4 feet 5 inches, or approximately 5 standard deviations (SD) below the population mean) (Fig. 2.7) and was not uncommon (estimates vary between 1 in 4000 and 1 in 20 000 of the population depending on the definition of severity). It may still present late with markedly short stature (Fig. 2.8), but more commonly presents with relatively mild short stature and a slow rate of growth. There is relative obesity (Fig. 2.9).

IDIOPATHIC SHORT STATURE

Idiopathic short stature is defined by the absence of abnormalities in the history and physical examination. More specifically, birth weight and length are normal, as well as body proportions; there is no chronic ill health, no severe psychosocial disturbance, and a normal food intake.
If growth velocity is normal, there is no need to exclude GHD or other pathologies by formal testing. If the growth curve deviates clearly, for example more than 0.3 SD over 1 year, or more than 0.5 SD over 2 years, or if the calculated height velocity is below the 25th centile twice in a row (with an adequate measurement interval), then a GH provocation test or measurement of serum levels of IGF-1 and its binding protein (IGFBP-3) is undertaken, along with the screening tests described below. Idiopathic short stature can be subclassified into two groups, familial and non-familial short stature, each of which may be divided into a further two subgroups.

**Familial short stature**

This is characterized by:

- short stature (less than –2 SDS, where SDS is the standard deviation score; see Ch. 1) during the growth period and a reduced adult height compared with the normal mean.
- a height within the target range defined by parental size. (As a cut-off limit, the parent-specific lower limit of height SDS is given by: \[0.5 \times (\text{mother’s height SDS} + \text{father’s height SDS})/1.61\] – 1.73. A similar equation is also available as a simple chart for screening purposes.)

In many cases the following characteristics are also present (not obligatory):

- a normal height velocity (varying around the 25th centile). As the height centile lines diverge with increasing age, a short child on the 3rd height centile will show a velocity that varies around the 25th velocity centile. Similarly a tall child on the 97th centile will show variation around the 75th centile. The majority of children with ‘normal’ stature and an adequate gap between measurements will have a velocity that fluctuates within these limits.
- bone age consistent with (within ±2 SD) chronological age.

Familial short stature can further be subdivided into a group with a normal age at onset of puberty and a group with delayed puberty. (The cut-off limit for delayed puberty should ideally be based on recent population references. For the 1997 Dutch nationwide growth study, the 97th centile in girls for B2 is 12.7 years and for G2 in boys 13.4 years.)
Non-familial short stature

This is characterized by:

- short stature (height less than –2 SDS) during childhood.
- stature below the range defined by parental size (for cut-off limit, see equation above).

In many cases the following characteristics are also present (not obligatory):

- a retarded bone age (>2 SD below chronological age).
- a reduced height velocity (<25%) in the later childhood years (see familial short stature, above).

Again, this group can be further subdivided into a subgroup with normal onset of puberty and a subgroup with delayed puberty. The latter subgroup has usually been called constitutional delay of growth and adolescence. Adult height is generally in the normal range. Often there is a positive family history of delayed puberty in the same sex parent. Strictly speaking, this diagnosis can be made only after the normal, but late, onset of puberty. However, the combination of above four criteria strongly suggests this diagnosis (see Ch. 7).

Fig. 2.10 Combined familial short stature and delay of growth and puberty. Both parents are short but the 3-year delay in onset of puberty produces a fall from a height of —3.4 SDS at 12 years to —4 SDS at 15 years, with eventual recovery to within the genetic range for adult height (—2.2 SDS).
The condition presents much more commonly in boys.

In many cases a short child is short because of the genetic influence of its parents, in combination with delayed puberty (Fig. 2.10). Children with this combined form frequently present for medical assessment at a relatively young age and, because height can be markedly reduced in adolescence, give rise to much concern. Mistaken or concealed paternity may be present in some cases.

PRIMARY GROWTH FAILURE
Five groups of disorders are found in this broad category.

1. Clinically defined syndromes with chromosomal abnormalities

This group includes the Ullrich–Turner syndrome (see also Chs 5 & 7) and Down syndrome. As the Ullrich–Turner syndrome is relatively common (1 in 2500 female births) and is one of the few chromosomal or syndromic (see below) conditions in which the height deficit is potentially remediable, it will be described in detail.

The majority of fetuses with Ullrich–Turner syndrome do not survive to term, but chromosomal analysis is not performed routinely on all miscarriages. The exact chromosomal make-up is very variable with just over half being due to the classic 45X karyotype and the remainder to a variety of mosaics, chromosomal deletions and rings. Whatever the karyotype, the phenotypic features are similar, including a reduced adult height potential (see below), although the chances of spontaneous puberty may be greater in the mosaic forms.

Nuchal edema (also present in Down syndrome) may be seen on second-trimester ultrasonography and lead to diagnosis on amniocentesis.

Neonatal lymphedema (Fig. 2.11) and the related nail dysplasia (see Fig. 1.42) may allow an early diagnosis, which should be suspected in all females with coarctation of the aorta (Fig. 2.1). The major features of the condition are given in Table 2.1, but it is important to note that up to 40% of girls will show no external features apart from reduced height (Figs 2.13 & 2.14). Thus the diagnosis must be suspected in any girl presenting with short stature.

Adult height in the condition is reduced to a mean of around 145–147 cm (depending on the population), but is related to parental height in the same way as that of a normal child. Abnormalities of the SHOX gene (short stature on X chromosome) may be involved.
### Table 2.1 Features of, and dissimilarities between, the Noonan and Ullrich—Turner syndromes

<table>
<thead>
<tr>
<th></th>
<th>Noonan</th>
<th>Ullrich—Turner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Either</td>
<td>Female</td>
</tr>
<tr>
<td>Chromosomes</td>
<td>Normal. Dominant inheritance</td>
<td>45X, mosaic or abnormal X chromosome</td>
</tr>
<tr>
<td>Performance</td>
<td>Mild reduction in approx. 20%</td>
<td>Normal, some isolated performance deficits</td>
</tr>
<tr>
<td>Mean final height</td>
<td>Male 162 cm</td>
<td>146 cm</td>
</tr>
<tr>
<td></td>
<td>Female 152 cm</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Right-sided abnormalities (80%) and cardiomyopathy (10—20%)</td>
<td>Left-sided abnormalities, including coarctation and later aortic dissection</td>
</tr>
<tr>
<td>Gonads</td>
<td>Males sometimes cryptorchid, females normal</td>
<td>Streak ovaries</td>
</tr>
<tr>
<td>Eyes</td>
<td>Ptosis majority</td>
<td>Ptosis-minority</td>
</tr>
<tr>
<td>Other</td>
<td>Caf-au-lait spots, abnormal bleeding (70%)</td>
<td>Renal abnormalities</td>
</tr>
</tbody>
</table>

**Fig. 2.13** Broad chest, wide carrying angle and sexual infantilism in Ullrich—Turner syndrome, age 15.5 years.

**Fig. 2.14** Normal face and body phenotype (slightly broad chest) in Ullrich—Turner syndrome.
in the near universal growth failure seen in this condition. (SHOX is a transcription factor on the pseudoautosomal region of the X chromosome expressed in osteogenic cells of the mid-portion of the limbs and in the first and second pharyngeal arches. Leri–Weill dyschondrosteosis (see Fig. 1.146) results from complete deletion. In Ullrich–Turner syndrome there is haplo-insufficiency. A Y chromosome homolog is present to produce two functioning copies of the gene in the male. There are published centile charts for the condition, and so a predicted adult height may be obtained as described in Chapter 1, using the centile of both parents plotted on the adult centile position of the Ullrich–Turner centiles.

The main features of Prader–Willi–Labhart syndrome are given in Table 2.2 and Figs 2.15 & 2.16. It is due to deletion of the paternal component of chromosome 15q11 (or maternal uniparental isodisomy).

2. Clinically defined syndromes without known chromosomal abnormalities

There are literally thousands of clinically defined syndromes without currently known chromosomal abnormalities that are associated with short stature. Some of the features that may point to one of this multitude are given in Chapter 1.

Fig. 2.15
Prader–Labhart–Willi syndrome showing early moderate obesity.

Fig. 2.16
Prader–Labhart–Willi syndrome showing hypogonadism, age 14.5 years.

Fig. 2.17
Noonan syndrome.

An exact description of the majority of these disorders is beyond the scope of this text, but the reader may be aided by some of the commercially available computerized diagnostic databases or texts cited in the Foreword.

Amongst the commonest and most important of these syndromes presenting primarily with short stature are the Noonan (Fig. 2.17) and Russell–Silver (Fig. 2.18, Table 2.2) syndromes.
Noonan syndrome is common, with an incidence of around 1 in 2000 individuals. It is dominantly inherited (see Fig. 1.153) with variable expression, and recently the responsible gene mutation was identified. As the Noonan syndrome shares many phenotypic features of Ullrich–Turner syndrome, these are contrasted in Table 2.1. There is an overlap of some cases of the Noonan syndrome and neurofibromatosis, with some children showing multiple café-au-lait spots.

Some syndromes have no known cause, are associated with normal intelligence and only relatively mild dysmorphic features and yet can produce the most striking degrees of short stature (an example of which, geleophysic dwarfism, is given in Fig. 2.19).

### Table 2.2 Features of the Prader—Labhart—Willi and Russell—Silver syndromes, two of the more common short stature syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Characteristics</th>
</tr>
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| Prader—Labhart—Willi | Short stature, usually from birth, certainly from mid-childhood, with small feet and hands  
Early poor feeding and weight gain followed by overeating and obesity from early childhood  
Almond-shaped eyes and high forehead, squint  
Hypotonia  
Poor performance with behavior problems, especially related to food  
Hypogonadism, osteoporosis, premature adrenarche  
Diabetes mellitus (usually type 2, non-insulin-dependent)  
Partial deletion of the long arm of paternal chromosome 15 or evidence of maternal disomy |
| Russell—Silver  | Small from birth with delayed bone maturation  
Hemihypertrophy/atrophy  
Clinodactyly  
Small triangular lower face, the corners of the mouth may turn down  
Mild blue sclerae  
Thin or sparse head hair  
Café-au-lait spots  
Some cases associated with maternal uniparental isodisomy of chromosome 7 |

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height and weight in the normal centiles within the first 1 or 2 years of postnatal life. Asymmetric IUGR with low birth weight but normal length is often caused by events late in pregnancy and usually has a good outcome. Symmetric smallness (low weight and length) is less likely to recover (Fig. 2.20) and often hints at more severe, earlier or inherent problems, such as:

- genetic or metabolic disorders, e.g. chromosomal abnormalities and syndromes as described above, including Silver–Russell and Seckel syndrome (Fig. 2.21).
- damage in utero by environmental agents (infections, drugs, alcohol) (see Fig. 1.154).
- growth potential permanently restricted by severe placental dysfunction (Fig. 2.22).

The majority of premature infants born at less than 32 weeks will show growth failure with a severity related to the degree of prematurity and the presence of chronic lung disease. There is catch-up of length and weight in the majority by 5 years of age.

### 4. Skeletal dysplasias

In general, body dimensions are abnormal in these disorders, which mostly show relatively short limbs. There is a spectrum of severity of relatively common...
Fig. 2.19 Severe short stature as a result of a rare disorder, geleophysic nanism. Growth hormone was given between 6 and 7 years with no benefit. Death occurred at 13 years as a result of mitral valve involvement, height —10.2 SDS.

Fig. 2.20 IUGR untreated. Low birth length and weight with no evidence of catch-up and reduced adult height (—4.1 SDS); compare with Fig. 2.85.
short-limbed dwarfing disorders from the severe achondroplasia to the milder hypochondroplasia (Figs 2.23–2.27). The incidence of this group of disorders is around 1 in 15 000 live births. Achondroplasia is due to a single point mutation on chromosome 4p, which affects the fibroblast growth factor receptor 3, causing poor division of bone-forming fibroblasts. It is likely that many of the other conditions in this spectrum share quantitatively and qualitatively similar defects.

In the various types of spondyloepiphyseal dysplasia and spondylometaphyseal dysplasia (and the combined forms), the spine is affected along with specific areas of the long bones, producing variable shortening of the body segments and spinal deformity.

There are also many specific syndromes with bony dysplasia – some with dysmorphic features that overlap those described above. The growth retardation seen in the Ullrich–Turner syndrome is considered by some to be due to an underlying skeletal dysplasia, providing further overlap.

Fig. 2.21 Seckel syndrome — severe IUGR with later markedly reduced stature and bird-like facies (form of primordial short stature).

Fig. 2.22 Severe smallness for dates (540 g) and prematurity (29 weeks); 60-mL syringe and tape measure for comparison. This combination of events has a poor eventual size prognosis.

Fig. 2.23 Achondroplasia at birth.
The diagnosis of these disorders is often difficult and may require expert radiographic review (see below). In general, there is no medical therapy even with a more specific diagnosis, but a diagnosis can be important for prognosis and genetic counseling.

5. Disorders of bone metabolism

Disorders of bone metabolism are rare and include mucopolysaccharidoses, mucolipidoses and others that may have profound effects on the bony skeleton and other tissues. Of those that present primarily with short stature as opposed to their CNS or metabolic consequences, the most important are the Morquio syndrome (mucopolysaccharidosis type 4); mucolipidosis type 3, which often presents first to rheumatologists because of the claw hands (see Figs 1.23 & 1.24); and the juvenile form of Hunter syndrome (mucopolysaccharidosis type 2) (Fig. 2.28), in which short stature and a large jaw may be the only presenting feature before adult life, when more severe complications ensue.

These disorders characteristically all have a major impact on the individual and there are also genetic implications. They are almost all characterized by a back that is relatively short when compared with the legs (Figs 2.29 & 2.30).
Fig. 2.27 Achondroplasia growth chart — two episodes of femoral and tibial leg lengthening at 5 and 10.5 years. Height gain from —1 to +2.4 SDS on achondroplasia chart.
SECONDARY GROWTH FAILURE
In this category there are six subgroups.

1. Disorders in specific systems
The specific systems include cardiac, lung, liver, intestinal, renal, hematologic, CNS and generalized inflammatory disease. Often the diagnosis is made before the short stature is noted but, even in the asymptomatic child, it is important to rule out hidden organic pathology. The disorders that are most important to exclude are renal failure (Fig. 2.31); chronic anemia; chronic infections (HIV, tuberculosis) and chronic inflammatory bowel diseases (e.g. Crohn’s disease) (see Figs 1.85, 2.32 & 2.33). Chronic asthma produces short stature (Fig. 2.34) and delayed puberty, usually with later catch-up, but the treatment of asthma with inhaled steroids can also produce growth suppression in some individuals (see Fig. 2.53).

Gluten enteropathy (Figs 2.35–2.38), in susceptible populations, may present very late in childhood – although it is more usual to present in infancy with
Fig. 2.31 Short stature (—2.6 SDS) and poor growth rate as presenting feature of juvenile nephronophthisis causing renal failure, age 10.9 years. Treatment with estrogens was given to induce puberty at 14 years but the adult height is much reduced (—3.5 SDS).
anemia and failure to thrive – and have poor growth as its only feature. There may be abdominal distension and wasting of the buttocks, and hypocalcemia may be present; however, a high index of suspicion is required for the diagnosis.

All of the above will tend to produce thinness (see Ch. 4), which may be even more pronounced than the short stature or poor growth rate, documented as a weight ‘centile below the height ‘centile, no matter what the absolute height (or a reduced weight for height on a weight-for-height chart).

2. Endocrine disorders

The main endocrine disorders causing short stature in children are hypothyroidism, GH deficiency and Cushing syndrome. Patients with hypogonadism (see Ch. 7) can be short in the pubertal age range. Relative obesity is often a feature of all of these conditions.

### Hypothyroidism

Untreated congenital hypothyroidism (Fig. 2.39) (see Ch. 11), which is seen less commonly since the advent of neonatal screening, produces an adult height similar to that in severe GHD (see Fig. 11.7).

In the much more common acquired hypothyroidism (Fig. 2.40) there is growth retardation with obesity and delayed skeletal maturation and dentition. Usually puberty is delayed (see Ch. 7), but can be precocious with lactorrhea (see Ch. 6). The cause in iodine-sufficient areas is usually autoimmune thyroiditis, but the condition may occur in response to therapeutic irradiation. Isolated central hypothyroidism is rare (see Ch. 11).

### Cushing syndrome

Other than being caused by the administration of topical, oral, inhaled or injectable steroids, Cushing syndrome is rare in childhood. The causes are summarized in Table 2.3. Very little excess cortisol or other steroid is required to inhibit growth; hence growth failure is almost universal (except in rare cases of adrenal tumor where testosterone production predominates, causing a ‘pubertal’ growth pattern). The most striking feature of hyperadrenocorticism is a rapid increase in body fat (Figs 2.41–2.43), particularly the abdomen, cervical fat pad (‘buffalo hump’) (Fig. 2.44) and the face (‘moon face’) (Fig. 2.45).

**Table 2.3 Causes of Cushing syndrome in childhood and adolescence, in order of frequency**

<table>
<thead>
<tr>
<th>Etiology</th>
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<tbody>
<tr>
<td>Iatrogenic</td>
</tr>
<tr>
<td>Pituitary adenoma — commonest in late childhood</td>
</tr>
<tr>
<td>Adrenal adenoma — commonest in early childhood</td>
</tr>
<tr>
<td>Adrenal carcinoma</td>
</tr>
<tr>
<td>Bilateral nodular hyperplasia</td>
</tr>
<tr>
<td>Ectopic ACTH production</td>
</tr>
</tbody>
</table>

**Fig. 2.32** Ulcerative colitis — double-contrast barium enema showing extensive colonic ulceration.
Fig. 2.33 Crohn’s disease diagnosed at 6 years of age (—1 SDS). No growth response to hemicolecotomy, parenteral nutrition or elemental diet. Pubertal spurt, 16.5—18.5 years, induced by depot testosterone, but adult height —3.9 SDS.
A thinning of the skin causes striae, which are especially prominent in the iatrogenic syndrome (Fig. 2.46), and capillary friability leads to ecchymoses. There is weakness and a decreased muscle mass, but this appears less striking in children than in adults. Hypertension is usually, but not always, present. Demineralization of bones occurs, and may be demonstrated by dual-energy X-ray absorptiometry (DEXA) (Fig. 2.47). In non-iatrogenic forms of the syndrome, the secretion not only of glucocorticoids, but also of androgens, is increased, and signs of hyperandrogenization (excessive hair, acne and cliteromegaly) may be present.

In adulthood the differentiation of nutritional obesity from Cushing syndrome may be difficult, but in childhood, although some of the features may be similar (Fig. 2.48), the relatively tall stature that is almost always associated with overeating means that there is seldom diagnostic confusion.

Other endocrine disorders, such as poorly controlled diabetes, gonadal disorders, precocity with early
Fig. 2.37 Gluten enteropathy presenting as short stature (—4.8 SDS) at 13.2 years, with later catch-up growth to —2.4 SDS on gluten-free diet.

Fig. 2.38 Gluten enteropathy presenting at 5.5 years (—2.3 SDS) with later complete catch-up on gluten-free diet to within the target range.
Etiology

Fig. 2.39 Untreated congenital hypothyroidism — cretinism.

Fig. 2.40 Gross acquired hypothyroidism.

Fig. 2.41 Cushing disease due to pituitary adenoma — gross obesity.

Fig. 2.40 Gross acquired hypothyroidism.
Fig. 2.42 Cushing syndrome as a result of adrenal adenoma. There is almost complete cessation of growth in height at the same time as an increase in weight. Initial chemotherapy and surgery produce weight loss but a resumption of growth in height. There is almost complete normalization of height to target range (−0.4 SDS).

Fig. 2.43 Weight chart of patient in Fig. 2.42 shows persistent overweight (+1.5 SDS).
Fig. 2.44 Cushing syndrome with buffalo hump and hirsutism.

Fig. 2.45 Severe cushingoid facies in patient whose charts are shown in Figs 2.42 & 2.43.

Fig. 2.46 Iatrogenic Cushing syndrome secondary to treatment for dermatomyositis.
epiphyseal fusion, etc., can produce short stature and are described elsewhere in the text.

3. Metabolic disorders
Many inborn errors of metabolism are associated with short stature but present primarily with neurologic signs, or signs in other systems. Glycogen storage disease type Ia produces short stature with truncal obesity and thin limbs, a ‘doll-like’ face and hepatomegaly, and there may be macroscopic hyperlipidemia (Figs 2.49 & 2.50).

4. Disorders of calcium and phosphate metabolism, and disorders of bone

Pseudohypoparathyroidism
This is a rare heterogeneous disorder of post-receptor activation where variable hypocalcemia is associated with moderate short stature, obesity, ‘moon face’ and shortening of the metacarpals (most often the IVth (Fig. 2.51) with cone-shaped epiphyses). The hypocalcemia is resistant to treatment with parathyroid hormone (PTH)
Pseudo-Cushing syndrome secondary to nutritional obesity. Note the high cheek color and central obesity. There was also hypertension and easy bruising. Height was, however, at top-end of familial range and there was supranormal growth rate with slightly early puberty.

Fig. 2.48

Type 1 glycogen storage disease with hyperlipidemia.

Fig. 2.50

Type 1 glycogen storage disease.

Fig. 2.49

Pseudohypoparathyroidism with short third to fifth metacarpals and cone epiphyses.

Fig. 2.51
and may result in learning difficulties, cataracts and ectopic calcification. Primary hypoparathyroidism and central hypogonadism may coexist. (Differentiation between pseudohypoparathyroidism (with hypocalcemia) and pseudo-pseudohypoparathyroidism (without hypocalcemia) has been abandoned because the hypocalcemia is variable and both types have been described in the same family.)

**Hypophosphatemic rickets**
This condition (Fig. 2.52) is described in Chapter 11.

**Osteogenesis imperfecta**
Osteogenesis imperfecta (Fig. 2.53) and other disorders affecting collagen and fibrin production, such as the various Ehlers–Danlos syndromes, may also be included in this category.

**5. Iatrogenic short stature**
This may be either a result of treatment of childhood malignancy or caused by glucocorticoid treatment. The dose of steroids that may produce growth failure is far less than that needed to produce the other features of Cushing syndrome, and all children taking steroids – topical, inhaled or oral – should have their growth monitored regularly (Fig. 2.54).

**6. Psychosocial short stature**
An extremely poor emotional environment causes psychosocial short stature – also called emotional or psychosocial dwarfism. Although there is usually relative thinness, this is not always the case and there can be considerable diagnostic confusion between deprivation dwarfism and GHD. Hyperphagia may occur as a component of the syndrome. The GH response to stimulation testing can be severely, but reversibly, blunted and there is diminished spontaneous overnight GH secretion. There is a lack of response to GH therapy and a rapid catch-up is seen with a change of caregiver (Figs 2.55 & 2.56). There is commonly a preservation of more infantile body proportions than may be expected from the age of the child (see Fig. 1.145).

More minor degrees of short stature are a consequence of more minor deprivation, which may contribute to the well-known social class gradient in height.

**DIAGNOSTIC WORK-UP OF SHORT STATURE**

**MEDICAL HISTORY AND PHYSICAL EXAMINATION**

The following are the most relevant points to include when taking the history of a child presenting with short stature (see also Ch. 1):
Growth failure secondary to treatment with inhaled beclometasone dipropionate, 200 µg twice daily from 6 to 12 years of age, nadir —3.5 SDS. There is also constitutional short stature that led to the clinical presentation of this case. Adult height is within the target range (—2.5 SDS).

Failure to grow secondary to neglect and non-accidental injury, showing complete catch-up in height.
Fig. 2.56 Patient in Fig. 2.55, showing weight after child was fostered (then subsequently adopted) at 0.7 years of age. Change in height —2 to +0.6 SDS; change in weight —3.0 to —0.5 SDS.
Pattern of growth in height and weight. Include birth weight and length (in relation to duration of pregnancy).

Presentation at birth (breech delivery is associated with GHD and many syndromic disorders).

Parental heights: calculate the target height and compare its centile position with the patient’s height centile. (Beware the dominantly inherited, relatively mild disorders of growth that may be undiagnosed in one parent, such as hypochondroplasia.)

Family history: ask about the onset of puberty of the mother (age at menarche) and father (late onset? – the father may remember that he continued to grow in late teenage life or shaved later than his friends did).

Milestones of puberty in the patient (onset of breast development, menarche; onset of penile enlargement, pubic hair).

Nutritional assessment.

Previous diseases and operations.

Drug administration including inhaled and topical preparations, over-the-counter medication and herbal remedies.

Neurologic symptoms; especially headache and disturbance of vision).

Gastrointestinal, pulmonary, cardiac, urogenital symptoms.

Psychosocial situation.

A full physical examination has to be performed, with special emphasis on the following:

- Accurate measurements of height, weight, sitting height, head circumference. Other special measurements may be required.
- Calculate the ratio between sitting height and leg length, and compare this with reference values.
- Nutritional state, fat distribution – skinfold thickness if possible.
- Pubertal stage.
- Dysmorphic stigmata in the hands, feet, head and neck, etc.
- Heart, lungs and abdomen to exclude other organic diagnoses.
- Neurologic examination (including fundoscopy and visual fields; see Figs 1.112 & 1.113).

Relaxation of the Achilles tendon reflex is slow in hypothyroidism. Hypotonia and developmental delay are a feature of some dysmorphic syndromes.

- Skin signs.
- Palpation of the thyroid gland (see Ch. 9).

INTERPRETATION OF THE CLUES

If height is below the third centile and no physical abnormalities are found, there are several possibilities:

- Height is concordant with the target height centile = familial short stature unless a parent has a demonstrable pathology.
- Height is discordant with parental height = non-familial idiopathic short stature, including constitutional delay of growth and adolescence or mistaken paternity.
- Isolated growth hormone deficiency and late-presenting celiac disease may be very silent in their manifestations.

Clues that point to one of the primary growth disorders include:

- Specific dysmorphic features and/or intellectual impairment = one of the syndromic causes of short stature.
- Low birth weight and length for gestational age = intrauterine growth retardation with failure to catch up.
- Body disproportion: (1) legs < back = skeletal dysplasias; (2) back < legs = disorders of bone metabolism, spondyloepiphyseal dysplasia and storage disorders (but also to a more minor degree can be seen in delayed puberty of whatever cause).

Pointers to chronic disease are:

- Specific signs in any system.
- Low growth rate or short stature accompanied by thinness.
- Anemia.

Pointers to an endocrinopathy include:

- A history of breech position and prolonged jaundice. The finding of a low height velocity, frontal bossing, increased abdominal fat, delayed puberty and a high-pitched voice = GHD (± signs of an additional pituitary deficiency).
- Low height velocity, obesity, sparse hair, discordant pubertal development, delayed bone age, irregular or heavy periods, constipation, goiter, pretibial myxedema, slow relaxation of the Achilles tendon reflex = hypothyroidism.
- Low height velocity, sudden rapid weight gain with a centripetal distribution, hirsutism, hypertension, weakness, glycosuria, striae, bruising and ‘moon face’ = Cushing syndrome.
Table 2.4 Radiographs to be taken as part of a limited skeletal survey

- Lateral skull
- Chest
- Lateral lumbar spine
- Hips and pelvis including lower lumbar spine
- Left hand and wrist (also for bone age)
- One long bone — tibia and bula are the best
- Forearm bones if any limitation of movement or external abnormality

Fig. 2.57 Achondroplasia, short tubular bones, metaphyseal flare, square beaked pelvis.

Fig. 2.58 Hypochondroplasia — less marked shortening of bones than in achondroplasia, bula relatively long.

Fig. 2.59 Hypochondroplasia — lack of widening of the lumbar interpeduncular distance.
Fig. 2.60 Hypophosphatemic rickets.

Fig. 2.61 Severe type 3, autosomal recessive, osteogenesis imperfecta.

Fig. 2.62 The common (80% of all cases) type I, dominantly inherited, osteogenesis imperfecta.

Fig. 2.63 Dysostosis multiplex in mucolipidosis 3.
Fig. 2.64 Dysostosis multiplex with abnormal beaked vertebra in mucolipidosis 3.

Fig. 2.65 Platyspondyly in spondylometaphyseal dysplasia.

Figs 2.66, 2.67 Limb bone and skull radiograph in craniometaphyseal dysplasia. Note thickened base of skull.

Fig. 2.68 Wrist bones in spondylometaphyseal dysplasia.
If the clinical assessment and analysis of the growth curve indicate a pathological growth pattern, further investigations are warranted. In such cases a radiograph of the left hand and wrist for bone age should always be performed. Other investigations should be aimed at confirming or ruling out the most likely diagnoses.

**Disproportion present**

- In cases with body disproportion or obvious skeletal abnormalities, a limited skeletal survey should be performed (Table 2.4, Figs 2.57–2.71).
- If a storage disorder is likely, several urine specimens should be collected for analysis of mucopolysaccharides, and consideration should be given to an assay of white cell enzyme levels; a simpler screening test may be to ask for...
examination of a blood film, looking for vacuolation of lymphocytes.

- Serum calcium, phosphate and alkaline phosphatase levels are measured to evaluate bone diseases. Assays of collagen metabolites or genetic studies may be available in specialist centers.

**Proportionate short stature**

If no body disproportion is present, a short screening program can be carried out (Table 2.5), consisting of:

- Full blood count, mean corpuscular volume (MCV) and erythrocyte sedimentation rate (ESR). Anemia may be present, especially in inflammatory bowel disease, celiac disease and renal failure, although it may be associated with almost any prolonged illness. Microcytosis is an indication of nutritional deficiency and blood loss, and macrocytosis may indicate malabsorption.
- Acid–base status, urea and electrolytes, creatinine, liver function, calcium, phosphate and alkaline phosphatase levels. These will exclude occult renal failure and hepatic disease, the Bartter syndrome and metabolic bone disease.
- Urine analysis (simple biochemistry and microscopy).
- Stool analysis (giardiasis can produce profound growth retardation and may be picked up only if the stool is inspected microscopically for cysts). Test for reducing substances to exclude lactose intolerance. The presence of red blood cells and fat globules may point towards celiac disease and the need for a jejunal biopsy.
- Thyroid stimulating hormone (TSH) ± free thyroxine (FT₄; F₄ levels are preferable to total T₄ levels as they are not prone to interference with drugs, renal or hepatic disease; see Chs 9 & 11).
- IGF-1 and IGFBP-3 (see below).
- Antigliadin antibody screen.
- Chromosome analysis.

**Table 2.5** Suggested brief screening program for investigation of proportionate short stature

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count and MCV</td>
</tr>
<tr>
<td>Renal and liver function tests, calcium/phosphate, alkaline phosphatase and acid—base status</td>
</tr>
<tr>
<td>Urinalysis</td>
</tr>
<tr>
<td>Stool analysis for fat globules, <em>Giardia</em> cysts, red blood cells, etc.</td>
</tr>
<tr>
<td>Thyroid stimulating hormone ± FT₄</td>
</tr>
<tr>
<td>IGF-1 and IGFBP-3</td>
</tr>
<tr>
<td>Antigliadin antibodies (or antiendomysial antibodies and IgA levels)</td>
</tr>
<tr>
<td>Chromosome analysis</td>
</tr>
</tbody>
</table>

**Proportionate short stature with relative overweight**

The consensus opinion of the Growth Hormone Research Society is that the GH axis should be tested if height is more than 3 SD below the mean or more than 1.5 SD below target height centile. Additionally investigations should be performed if height is more than 2 SD below the mean and height velocity over 1 year is more than 1 SD below the mean for 2 years (or more than 2 SD over 1 year), or if there are signs of other pituitary hormone deficiency or intracranial pathology.

If GHD is suspected, further testing of the GH–IGF-1/IGFBP-3 axis should be performed. Normal levels of IGF-1 or IGFBP-3 largely (but not completely) exclude GHD. Normal levels of IGFBP-3 are often seen in post-irradiation GHD. Low levels of IGF-1 may be due to several causes, including nutritional inadequacy, and do not prove GHD; hence one or two GH provocation tests should be performed at an experienced center (see Appendix).

Plain skull radiographs may show abnormalities suggestive of raised intracranial pressure or craniopharyngioma (Fig. 2.72), but may also be normal and...
are thus unreliable as a primary investigation. Magnetic resonance imaging (MRI) or computed tomography (CT) is thus advisable in all cases of proven deficiency to exclude craniopharyngioma (Figs 2.73–2.75) or other tumors (Fig. 2.76) and to document anatomic abnormalities such as empty sella, ectopic pituitary tissue or stalk disruption (Figs 2.77–2.79). Cysts of Rathke’s cleft (Fig. 2.80) can occasionally expand and produce hypopituitarism, and midline defects of the brain are associated with the septo-optic dysplasia sequence (Fig. 2.81). Hydrocephalus or hydranencephaly (Fig. 2.82) can also be associated with hypopituitarism (sometimes with sexual precocity).

In the Laron syndrome there is a failure to generate IGF-1 in response to normal or high levels of GH, which may be confirmed by an IGF-1 generation test (see Appendix).

The commonest forms of hypothyroidism may be detected by raised TSH levels in the preliminary screen. If found, this should prompt assay of antithyroid antibody levels. Isolated central hypothyroidism is rare but will be detected by the low–normal TSH level at the same time as a low free T₄ level. Further details of thyroid function testing are given in Chapters 9 & 11, and in the Appendix.

If Cushing syndrome is suspected, an estimation of 24-h urinary free cortisol (UFC) should be obtained.
Fig. 2.76 MRI scan of bifocal germinoma presenting with panhypopituitarism.

Fig. 2.77 Ectopic posterior pituitary bright spot (arrow) and absent pituitary stalk following head injury.

Figs 2.78 (top) and 2.79 (bottom) Ectopic bright spot and normal MRI scan for comparison showing pituitary stalk, posterior pituitary bright spot.
followed by a serum cortisol rhythm (early morning (0700–0900 hours) and late evening (2200–2400 hours)) and a simultaneous measurement of adrenocorticotropic hormone (ACTH) concentration. Suppression of ACTH implies an adrenal cause. Raised cortisol levels, UFC and loss of diurnal variation should prompt referral to a specialist center for further evaluation with dexamethasone testing (see Appendix) and localization of the source by MRI of the pituitary or CT of the abdomen and chest (Figs 1.94 & 2.83). Sampling for ACTH from the inferior petrosal sinus can help lateralize pituitary adenomas in 60–70% of cases where scanning is equivocal, in experienced units.

**THERAPY OF SHORT STATURE**

**Idiopathic and primary short stature**

Treatment of idiopathic short stature remains both experimental and controversial, and should remain in the realm of specialist centers. There may be early acceleration of growth rate but a shortened duration of growth, and there is currently little evidence to suggest that adult height is markedly increased. Growth hormone treatment should probably still be offered only as part of a formal clinical trial.

In the Ullrich–Turner syndrome there is currently convincing evidence for benefit on adult height
Fig. 2.84 Ullrich—Turner syndrome. Growth hormone therapy initiated at 11.8 years. There is an improvement in height from —3 to —2 SDS for normal Dutch girls, or from +1.5 to +2 SDS on the Turner chart shown.
The GH dose is 0.05 mg/kg daily, given as a daily subcutaneous injection. Anabolic steroids such as oxandrolone (dose 0.06 mg/kg daily) may have an added benefit.

Therapy with GH (up to 0.06 mg/kg daily) for 2–3 years has been used in patients with IUGR who have not shown catch-up after the age of 5 years, to promote growth to the normal centile range, although data on adult height are not available. Occasionally longer treatment regimens may be used in trial settings, with anecdotal benefit (Fig. 2.85).

GH therapy in Prader–Willi syndrome has been shown to improve body composition as well as growth rate at a dose of 0.035 mg/kg daily.

In the skeletal dysplasias, surgical leg-lengthening techniques in specialist units (Figs 2.27, 2.86–2.88) offer the possibility of height gain in the order of 10–25 cm (4–10 inches). The use of medical growth-promoting therapies is being explored, but is likely to be of lesser importance than surgery.

In the storage disorders there may be a role for bone marrow transplantation to reduce the metabolic and skeletal consequences of the underlying defect. There is some evidence that the skeletal, if not many...
Secondary growth failure

If the growth failure is due to a systemic illness, successful treatment of the specific systemic disorder may produce catch-up growth. This is particularly true of disorders that are active in late childhood and early teenage life, where even a relatively brief period of amelioration of a disease process may allow for a more normal pubertal growth and an increased height prognosis.

GHD is treated with daily subcutaneous administration of synthetic growth hormone at a dose of 0.025–0.05 mg/kg daily (Figs 2.89 & 2.90). Laron syndrome may be treated with recombinant IGF-1 in specialized centers.

Hypothyroidism is easily treated with L-thyroxine tablets at a dose tailored to suppress the TSH level, usually between 50 and 150 µg/day. The catch-up growth that might be expected from the degree of skeletal immaturity present at diagnosis may not occur, especially if the growth failure is long-standing or occurs during puberty (Fig. 2.91).

Treatment of Cushing syndrome is always highly specialized. If due to an adrenal adenoma, it is treated by unilateral adrenalectomy. Adrenal carcinomas are highly aggressive, and combined medical and surgical treatment is required for any hope of success. Pituitary adenomas causing Cushing disease may be treated with trans-sphenoidal adenomectomy followed by temporary adrenal replacement therapy until adrenal function recovers. If resection of the pituitary adenoma is not possible, and in cases of the syndrome

of the other, symptoms of these conditions can at least be stabilized by this procedure.

Fig. 2.86 Leg lengthening in achondroplasia with bilateral tibial xators.

Fig. 2.87 Results of leg lengthening in achondroplasia after 2-year program of tibial and femoral lengthening. Before surgery unable to reach light switch.

Fig. 2.88 Same patient as in Fig. 2.87 after surgery, with a height gain of 28 cm.
Fig. 2.89 Growth hormone deficiency presenting at 6 years of age (height —4.7 SDS). Human GH treatment until 8.5 years (height —3.3 SDS) when withdrawn for 6 months because of possible contamination of pituitary-derived hGH with the Creutzfeldt–Jakob disease (CJD) prion, during which time growth almost ceased. Recomenced recombinant GH at 9.2 years. Central hypothyroidism diagnosed at 12.4 years and hypoadrenalism at 17.4 years. Spontaneous normal puberty at 14 years with adult height —0.9 SDS, at target height.
Fig. 2.90 Panhypopituitarism presenting late because the discrepancy between the subject's actual height (−2 to −4 SDS in mid-childhood) had not been interpreted in the context of the tall parents (target height +1.7 SDS). Thyroxine and hydrocortisone started at 13.2 years, recombinant GH at 14 years and ethinylestradiol at 16 years. Adult height —0.6 SDS, below target height but within normal range.
caused by bilateral nodular adrenal hyperplasia, then bilateral adrenalectomy may be required (but at the risk of causing the Nelson syndrome (see Fig. 1.138), followed by life-long replacement therapy with glucocorticoids and mineralocorticoids.

The growth failure and obesity due to systemic glucocorticoid administration are usually reversible in the early stages if remission is achieved. If vertebral collapse occurs, and if treatment is continued through pubertal years, then stunting is permanent. GH trials are ongoing, indicating that growth can be partially restored.

Psychosocial deprivation dwarfism may show impressive catch-up if it is possible to change the circumstances of care. Recovery of height and weight gain whilst separated from the usual carers can be used as retrospective evidence of the nature of the problem.