Chapter 3

The Tall Child

The classification of causes of tall stature is more straightforward than that of short stature. Idiopathic or genetic tall stature is by far the commonest cause. There are a relatively small number of primary syndromes of large size and secondary causes of increased adult height are rare. Some secondary conditions produce largeness for a period of the child's growth span, then a normal or even reduced adult height due to early fusion of the epiphyses. There are also primary disorders of blood supply or intrinsic to the growth plate that can produce areas of localized overgrowth.

NORMAL-VARIANT TALL STATURE

Normal-variant tall stature is defined by the absence of abnormalities in the history and physical examination. It can be subdivided similarly to short stature, described in Chapter 2.

Familial tall stature

This is characterized by:

- tall stature during the growth period and an increased adult height.
- a normal height velocity (varying around the 75th centile. As the height centile lines diverge with increasing age, a tall child on the 97th height centile will show a velocity that varies around the 75th velocity centile.)
- a height within the range defined by parental size, although doubtful paternity may sometimes cause confusion.
- bone age consistent with chronological age (±2 SD).
- a normal age of onset of puberty.
- often relatively long legs compared with sitting height.

Constitutional tall stature with advance in growth and adolescence

This type is characterized by:

- normal to tall stature during childhood.
- adult stature within the range defined by parental size.
- a moderately advanced bone age (not more than +2 SD above chronological age).
- an increased height velocity (>75%) in the later childhood years.
- early onset and cessation of puberty, often following the same pattern as one or both of the parents.

Combination

A combination of familial and constitutional conditions is often seen.

GROWTH HORMONE EXCESS

Pituitary gigantism (**Figs 3.1 & 3.2**) is extremely rare. It is usually produced by growth hormone (GH)

Fig. 3.1 Pituitary gigantism, age 9 years, in comparison to father.

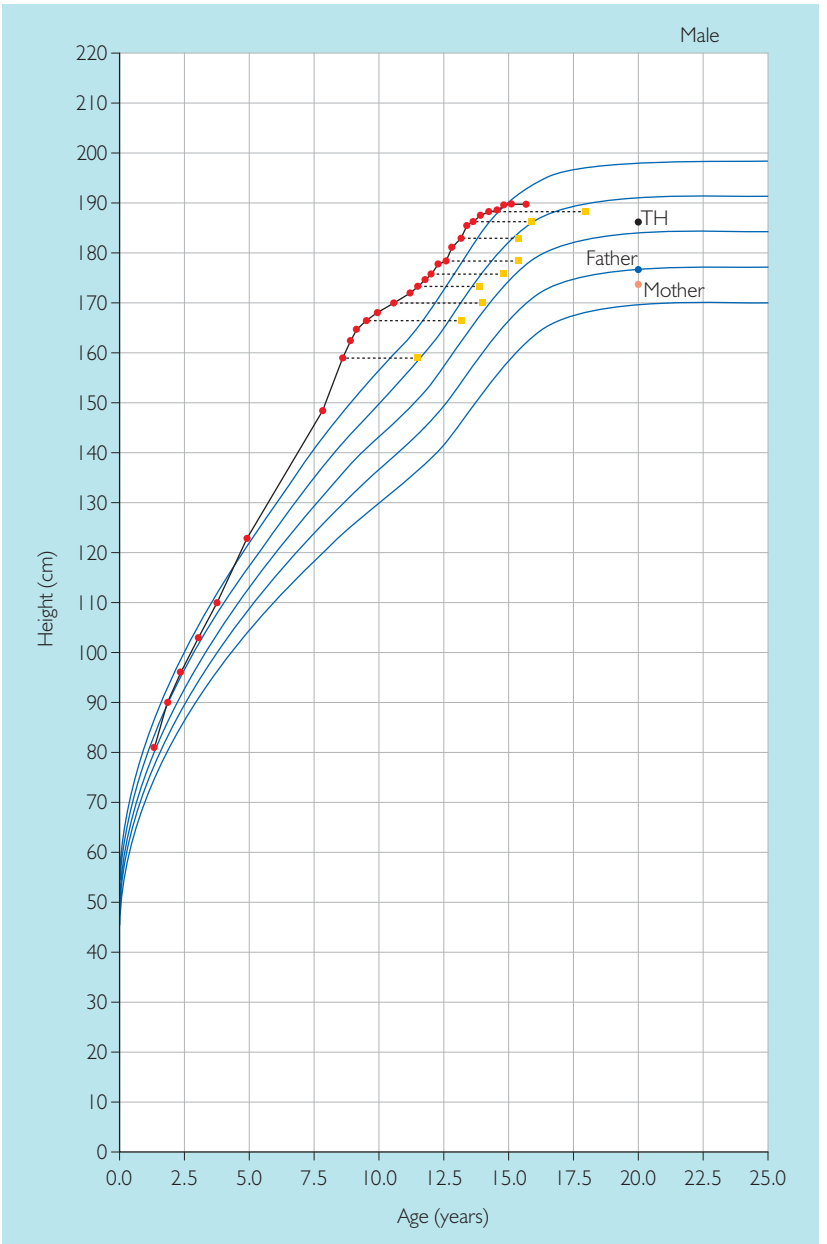


Fig. 3.2 Pituitary gigantism presenting as tall stature (+4.1 SDS) at 9 years of age with evidence of previous accelerating height velocity. Adenoma resected at 9.2 years with fall in SDS to an adult height of +1.6 SDS.

excess caused by a GH-producing adenoma in the pituitary. This may be seen as part of the McCune–Albright syndrome. Even more rarely, growth hormone releasing hormone (GHRH) excess, from tumorous sources, produces excessive growth. Proportionate, worsening tall stature with an increased height velocity is seen and, if no treatment is given, can produce heights in excess of 200 cm up to 247 cm in the female and 274 cm in the male. The same disease process produces acromegaly in adulthood after the fusion of the epiphyses, and a number of patients with a late childhood onset share many features of both conditions. There may be prognathism, and signs and symptoms of optic chiasm compression. There may be increased sweating and a yellowish discoloration of the palms (see **Fig. 1.44**).

DYSMORPHIC SYNDROMES

Sex chromosome abnormalities (including aneuploidy)

Many abnormalities involving duplication of the X or Y chromosomes can occur, but only two are commonly associated with disproportionate tall stature, the

Fig. 3.3 XXY, final height (with treatment) 208 cm.

Klinefelter (XXY, XXYY, XXXY and mosaic forms) and the XYY syndromes. In both the legs are relatively long compared with the back (**Fig. 3.3**).

Klinefelter syndrome is most commonly associated with the XXY karyotype, but variants with XXYY and mosaic forms can occur. (An XXXY form is more likely to be associated with slow growth.) There tends to be minor intellectual deficit, often exacerbated by behavioral problems and hypergonadotrophic hypogonadism. In later life there is a high incidence of diabetes mellitus. Infertility is usual but there are descriptions of successful intracytoplasmic sperm injection.

XYY males have a mild intellectual deficit and specific motor coordination problems. In the past it was said that there was an increase in antisocial behavior, but this is not now thought to be commonly the case. Cryptorchidism occurs but is not as universal as in the Klinefelter syndrome.

Both conditions are relatively common, occurring more than twice as frequently as the Ullrich–Turner syndrome in birth karyotype surveys; however, the relatively mild learning difficulties and the social acceptability of tall stature mean that they often present in late childhood or early adult life.

XXX females have few external phenotypic features, but tend to be slender and tall with a proportion showing late puberty, amenorrhea or infertility. The mean IQ is 85.

Dysmorphic syndromes due to metabolic or connective tissue abnormality

The Marfan syndrome is a relatively common dominantly inherited disorder of one of the copies of a fibrillin gene on chromosome 17q. It is characterized externally by disproportionate tall stature (**Figs 3.4 & 3.5**) with relatively long legs (**Fig. 3.6**), arachnodactyly (**Fig. 3.7**), joint laxity (see **Figs 1.18–1.21**), hernias, scoliosis and chest deformities (see **Fig. 1.87**), myopia, dislocation or poor fixation of the lens (see **Fig. 1.119**) and a high arched palate (see **Fig. 1.70**). Internally there may be weakness of the collagenous structures, especially on the left side of the heart, producing mitral and aortic valve incompetence, aortic dilatation and dissection. Spontaneous pneumothorax may occur. Lumbosacral dural ectasia may be seen on magnetic resonance imaging (MRI) (see **Fig. 3.35**).

Beals contractural arachnodactyly (**Fig. 3.8**) is a rare, dominantly inherited, disorder of another copy of a fibrillin gene on chromosome 15q, and has some similarities with the Marfan syndrome. There are contractures at the knees, elbows and hands, and micrognathia. The ears may be 'crumpled' and there may be kyphoscoliosis.

Homocystinuria is an aminoaciduria that is associated with marfanoid tall stature (**Fig. 3.9**) but that presents more frequently because of the ocular complications such as ectopia lentis and severe myopia. Intellect is usually impaired and complications associated with thromboembolism occur.

Total lipodystrophy (see Ch. 4) produces extreme leanness and relative tall stature.

Dysmorphic syndromes with symmetrical overgrowth

Most of these syndromes are associated with intellectual impairment:

- Sotos syndrome (**Figs 3.10–3.14**).
- Weaver syndrome (**Figs 3.15 & 3.16**).
- Marshall–Smith syndrome.
- Beckwith–Wiedemann syndrome (**Figs 3.17–3.19**), which includes macrosomia (often more marked on one side of the body), with other dysmorphic features and hypoglycemia. There may be associated intellectual deficit as a result of the

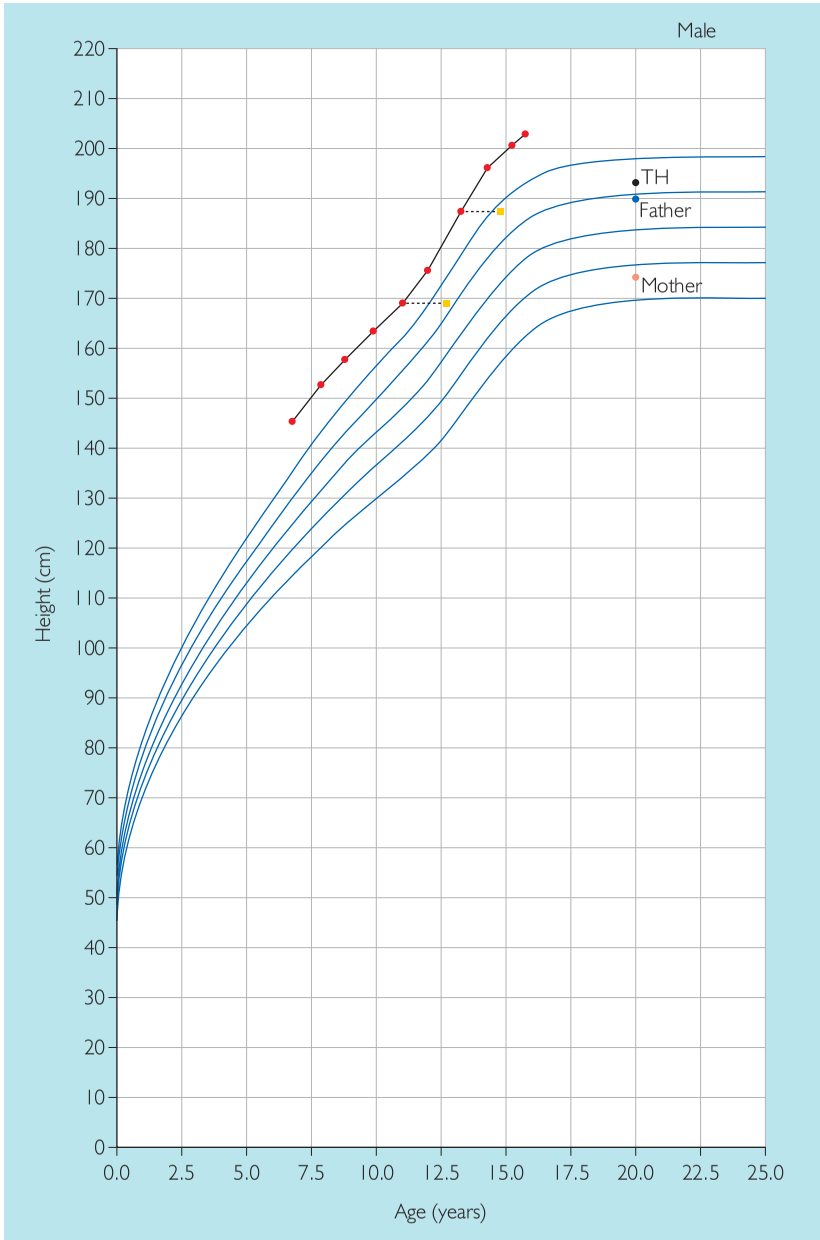


Fig. 3.4 Marfan syndrome occurring as a new mutation (note the normal parental heights). Moderate tall stature, +3.8 SDS; the disproportion is evident from comparison of the standing to the sitting height chart (Fig. 3.5).

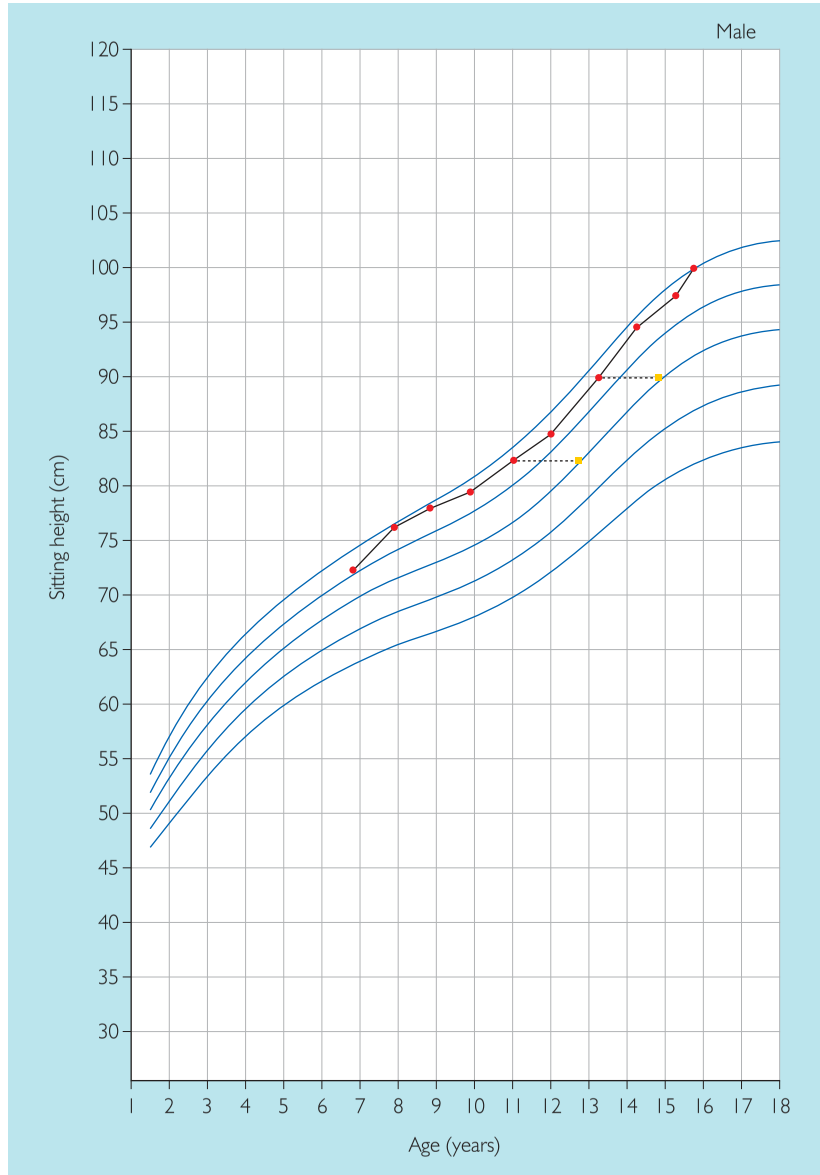


Fig. 3.5 Sitting height chart (+2 SDS) of the patient in Fig. 3.4.

Fig. 3.6 Marfan syndrome.

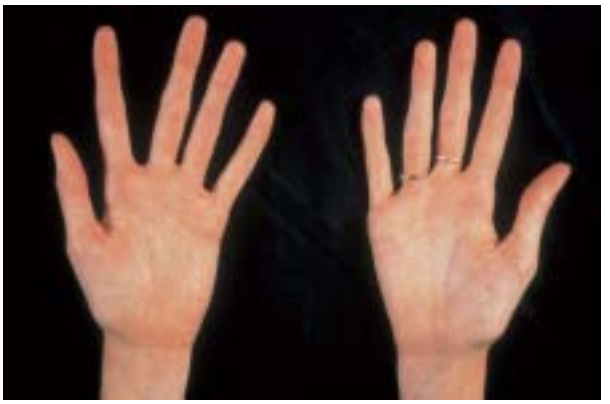


Fig. 3.7 Arachnodactyly in the Marfan syndrome.

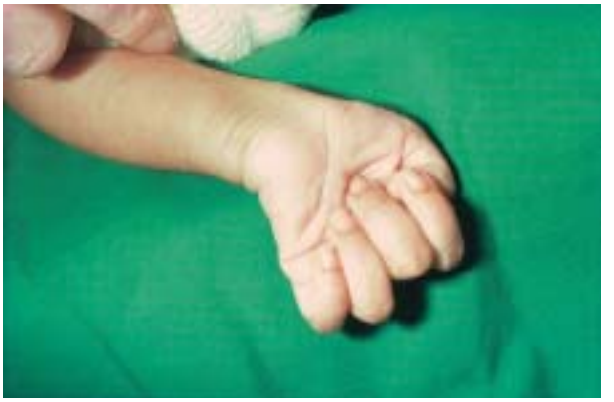


Fig. 3.8 Beals contractural arachnodactyly.

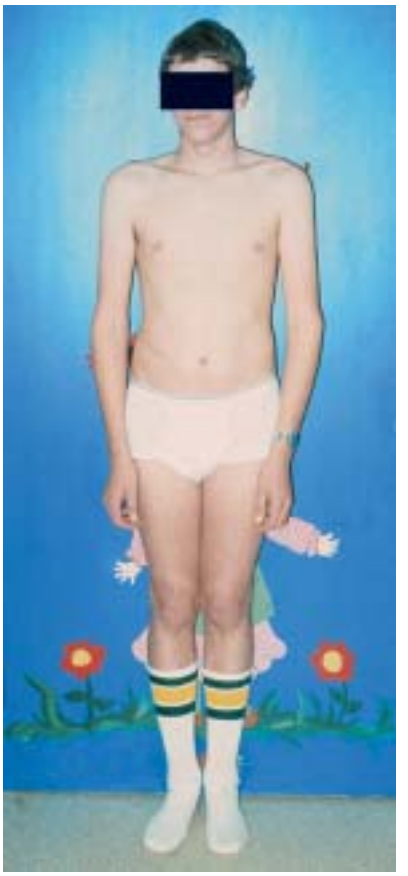


Fig. 3.9 Homocystinuria, 190.5 cm at 13.5 years.

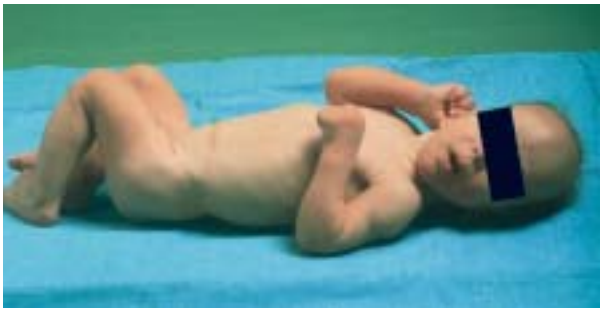


Fig. 3.10 Sotos syndrome as baby.

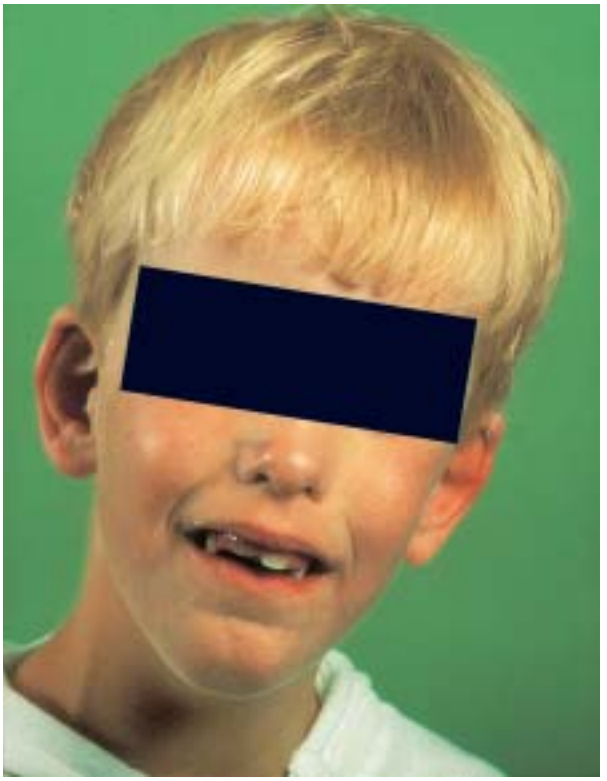


Fig. 3.11 Sotos syndrome as child.

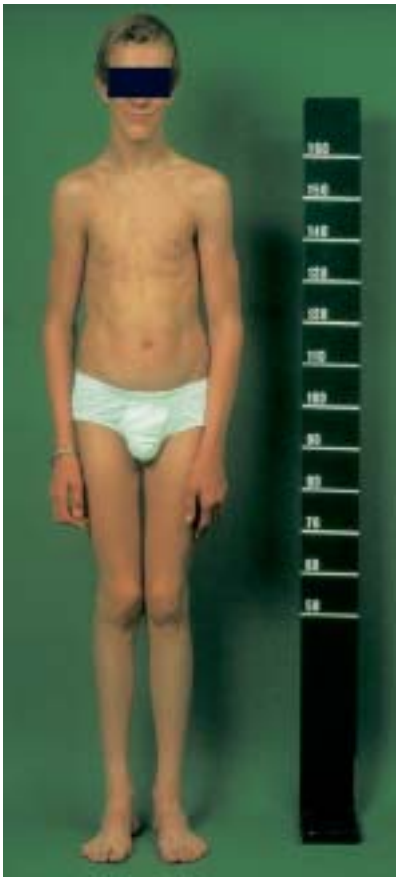


Fig. 3.12 Sotos syndrome as young adult (185 cm).

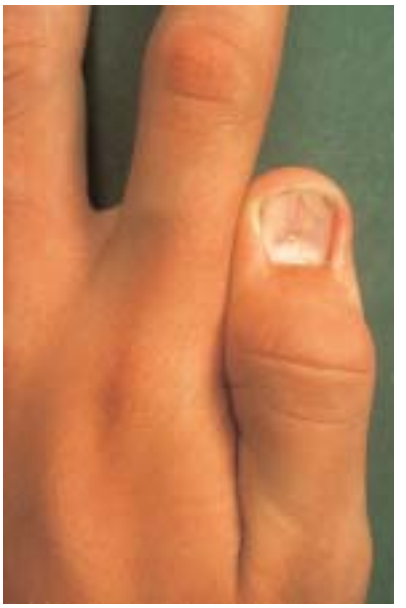


Fig. 3.13 Deep-set concave nails in Sotos syndrome.

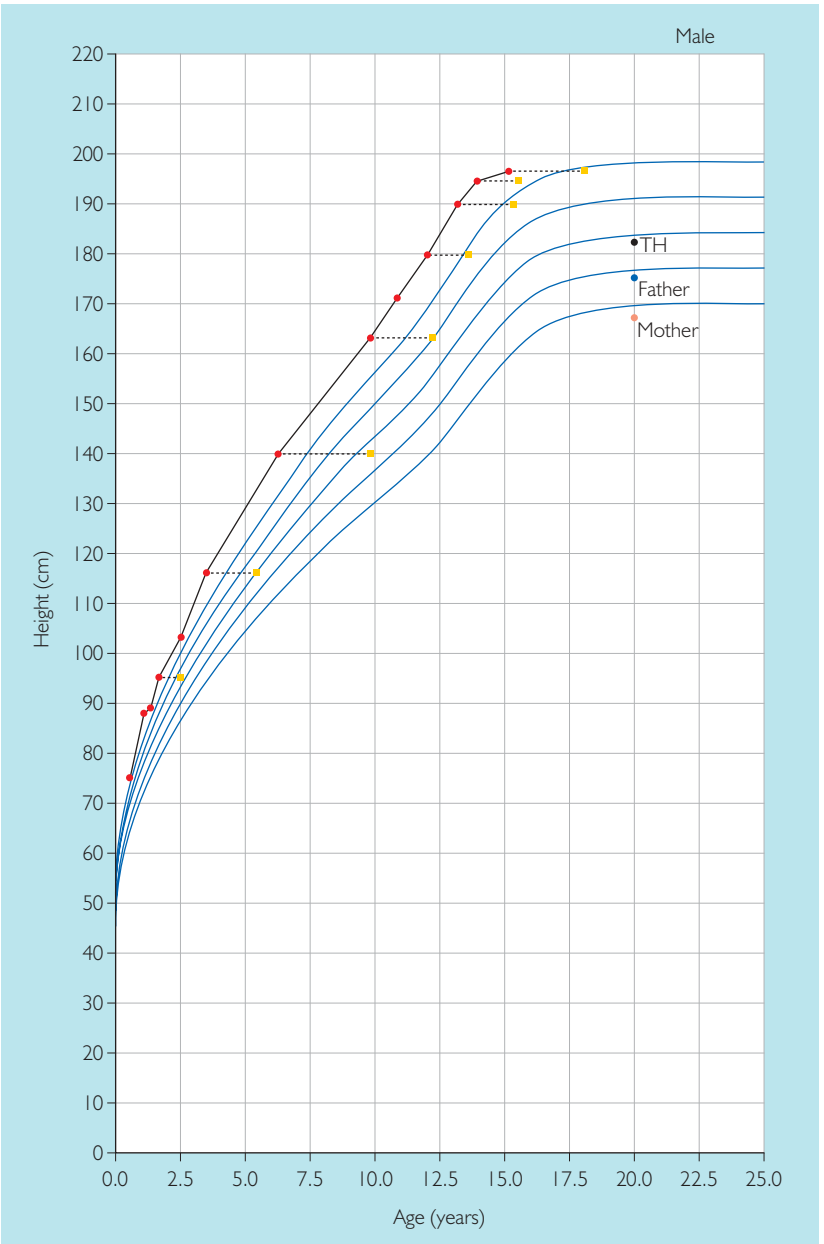
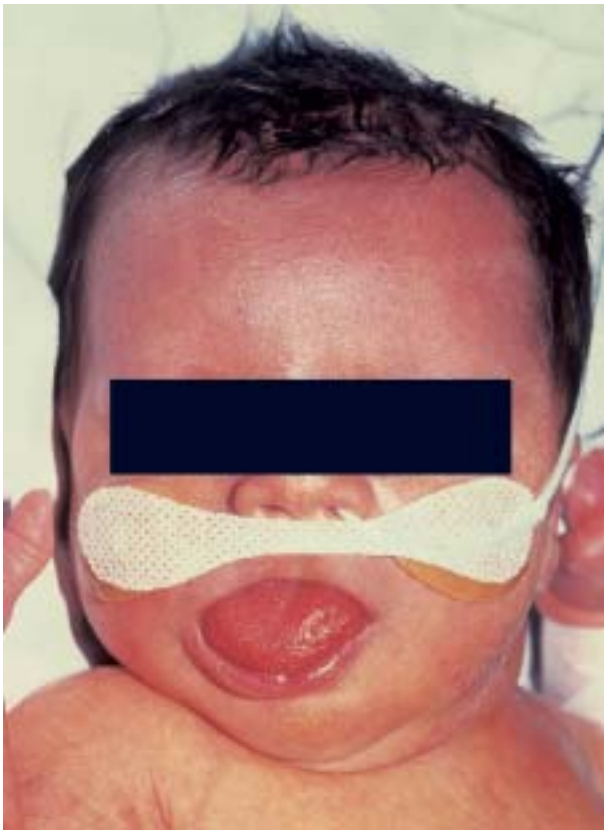


Fig. 3.14 Sotos syndrome, height at 1 year +2.4 SDS with a final height of +2.68 SDS, but +3.6 SDS in mid-childhood. Target height was –0.2 SDS.

Fig. 3.15 Weaver syndrome, height >97%.



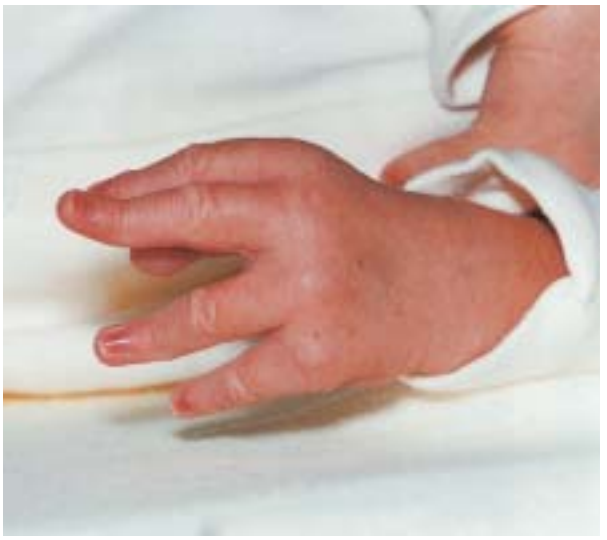
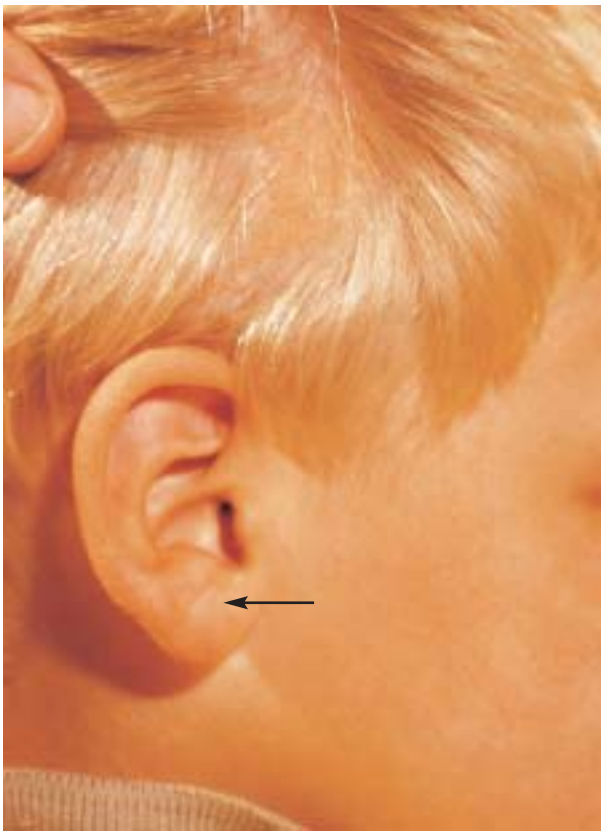


Fig. 3.16 Weaver syndrome, camptodactyly, broad middle phalanges and narrow nails.



Figs 3.17 (Top right), **3.18** (Bottom right) Beckwith–Wiedemann syndrome, face and demonstration of ear crease.

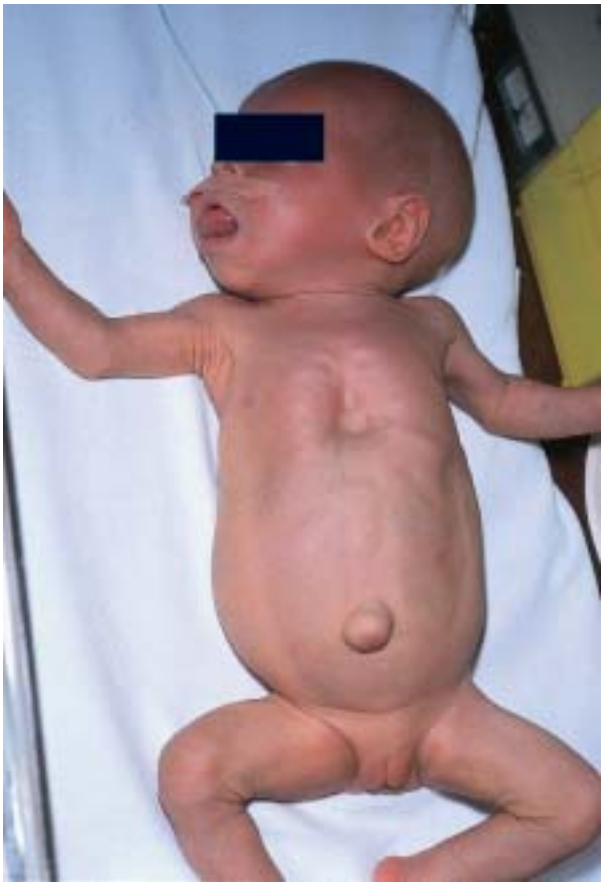


Fig. 3.19 Beckwith–Wiedemann syndrome, showing umbilical hernia and abdominal distension from organomegaly.

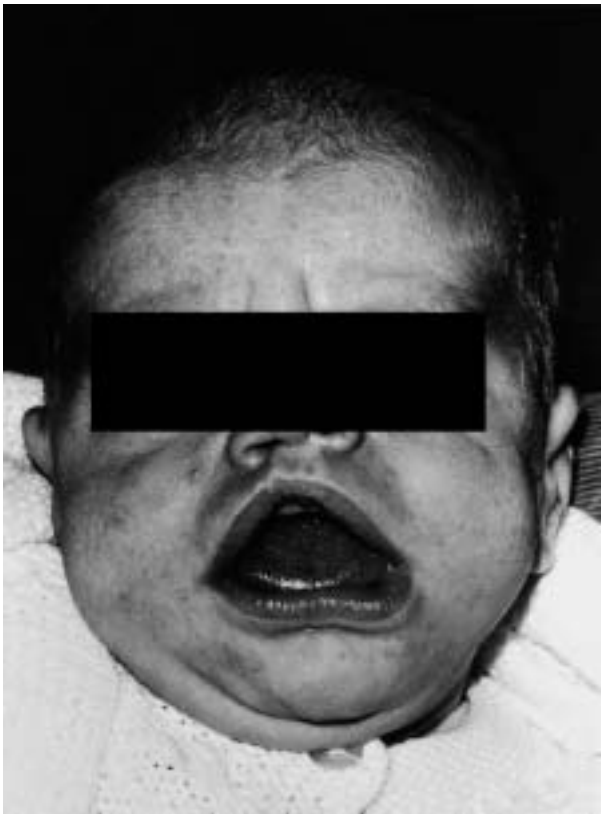
hypoglycemia. There is evidence of relative overexpression *in utero* of the growth factor, insulin-like growth factor (IGF-2) and a tendency to Wilms tumor as a result of this. Simpson–Golabi–Behmel syndrome ('bulldog' syndrome; **Figs 3.20 & 3.21**) has overlapping features and is due to a deleting mutation of glypican 3, a membrane-bound proteoglycan that usually sequesters IGF-2 to make it unavailable to its receptor.

The main distinguishing features of these conditions are given in **Table 3.1**.

Fragile X syndrome, Bannayan–Riley–Ruvacalba, Elejade and Nevo syndromes may be associated with overgrowth.

Dysmorphic syndromes with partial or asymmetric overgrowth

The overgrowth in Beckwith–Wiedemann syndrome may be asymmetric, producing hemihypertrophy. Klippel–Trenaunay–Weber syndrome is tissue overgrowth in association with cutaneous vascular nevi (**Fig. 3.22**). Proteus syndrome (**Figs 3.23–3.25**) is due to a chimeric tissue abnormality resulting in progressive overgrowth, lipomas and deformity.



Figs 3.20 (Top), **3.21** (Bottom) Simpson–Golabi–Behmel syndrome with macrostomia and cleft palate with neonatal dental eruption.

SECONDARY CAUSES OF LARGE SIZE

Hyperinsulinism

Intrauterine hyperinsulinemia secondary to maternal diabetes (**Figs 3.26 & 3.27**) or persistent hyper-

	Beckwith–Wiedemann	Sotos	Weaver	Marshall–Smith
Head and face	Big at birth. Large muscle mass till teens Prominent occiput Facial hemangiomas Ear lobe crease Small mid-face Macroglossia	Big at birth. Growth rate slows after 4 years Prominent forehead Macrocephaly Hypertelorism, squint Prognathism Early teeth, narrow palate	Variable Flat occiput Macrocephaly Large ears Micrognathia Thin head hair, hypertrichosis	Ht > Wt. Bone age very advanced Prominent forehead Long head Big nose Shallow orbits Hypertrichosis
IQ, CNS	Hypoglycemia – may cause secondary IQ reduction	Abnormal glucose tolerance test. Mild/moderate primary IQ reduction	Primary IQ reduction	Primary IQ reduction. Myopathy
Other	Organomegaly Hemihypertrophy Cardiac defects	Deep-set nails – Cardiac defects	Hoarse voice. Nail hypoplasia. Hernias Stiff joints, camptodactyly Cardiac defects	Blue sclerae Immunity reduced Cardiac defects
Tumors	Wilms tumor. Hepato-, neuro-, gonado-blastomas	Wilms tumor. Vaginal, hepatic, parotid, neuro-ectodermal carcinomas	Neuroblastoma	?

Table 3.1 Features of the major syndromes associated with large size

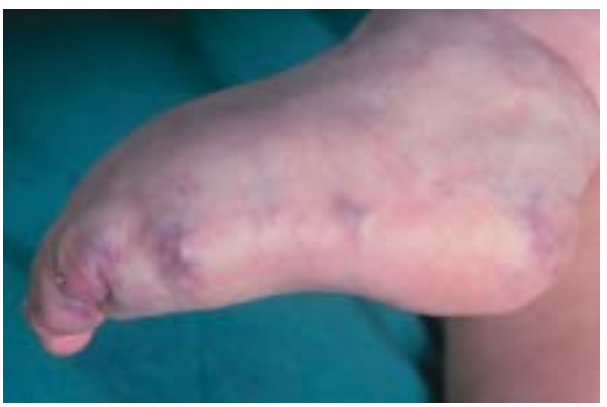


Fig. 3.22 Klippel–Trenaunay–Weber syndrome causing overgrowth of foot.

insulinemic hypoglycemia of infancy (PHHI) (previously called pancreatic endocrine dysregulation syndrome or nesidioblastosis) (**Fig. 3.28**) (see Ch. 11) both cause early macrosomia because insulin is a potent fetal growth factor. This increase in size is usually transient and followed by 'catch-down' growth once the abnormal insulin-secreting environment has been removed.

Hyperinsulinism may occur secondary to obesity (see Ch. 5). In childhood excess calorie intake is available for growth and may provoke hyperinsulinism, so producing a relatively tall stature characterized by: tall stature (at upper end of predicted target range), with weight ≥ height centile (**Fig. 3.29**), relatively early puberty, striae and high cheek color mimicking mild Cushing syndrome (**Fig. 3.30**), but with the contrasting rapid growth compared with the universal growth failure of steroid excess. There is frequently a similar habitus in one or both parents and siblings. If the hyperinsulinism is severe there may be coexisting acanthosis, and in the HAIR-AN (hyperandrogenization, acrochordons, insulin resistance and acanthosis nigricans) syndrome (see Ch. 10, **Fig. 10.18**) the facial features are described as 'acromegaloid'. Hypothalamic tumors and dysfunction

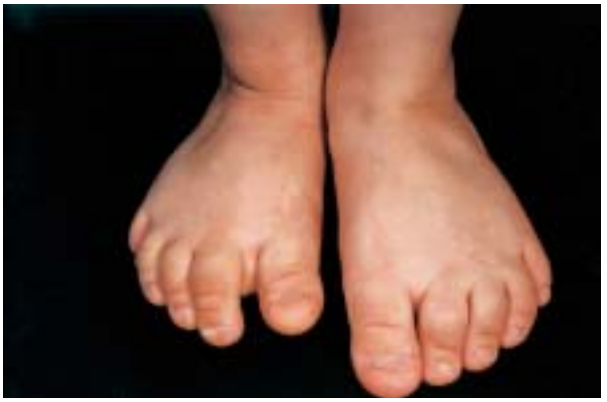


Fig. 3.23 Proteus syndrome, isolated areas of overgrowth.

Fig. 3.24 Proteus syndrome with linear nevi.

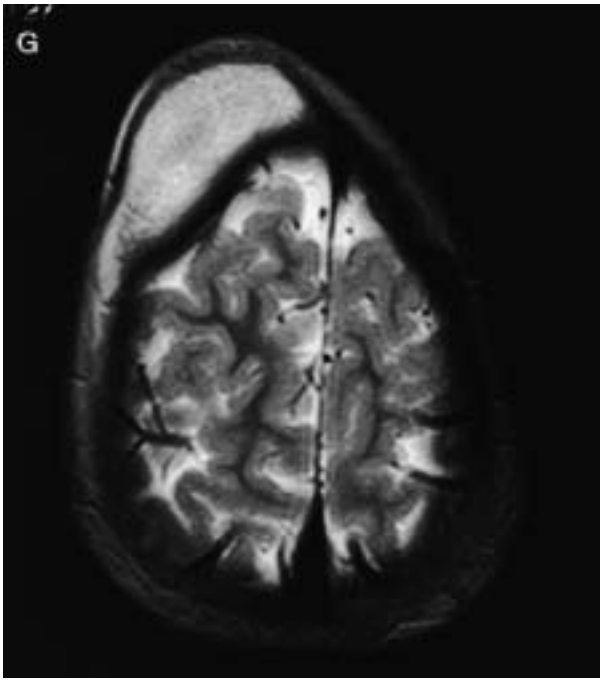


Fig. 3.25 Proteus syndrome with lipomata.

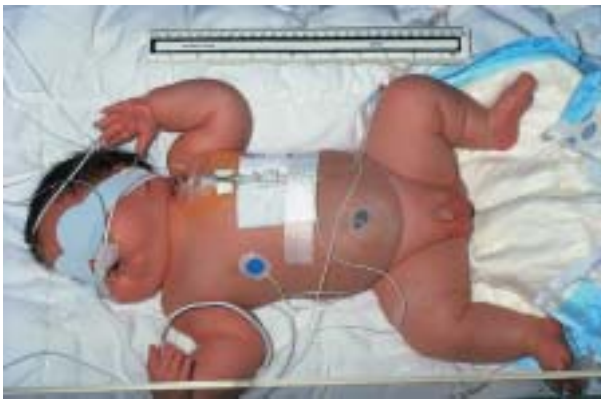


Fig. 3.26 Infant of a diabetic mother – macrosomia, plethora and jaundice requiring exchange transfusion.

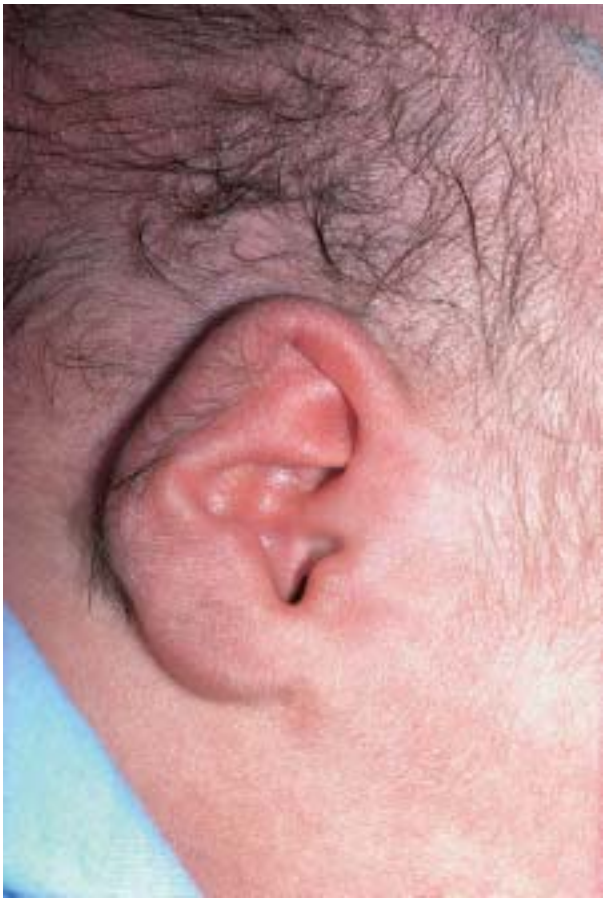


Fig. 3.27 Hairy ears in the infant of a diabetic mother, an unexplained but common finding.

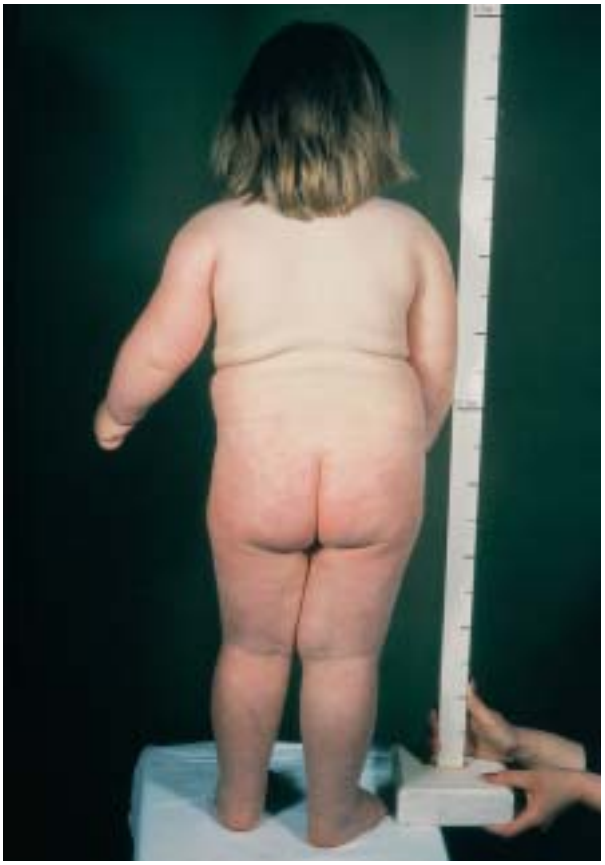


Fig. 3.29 Nutritional obesity, height >97%, target height 75%; 15 kg (33 lb) overweight for height at age 3 years.

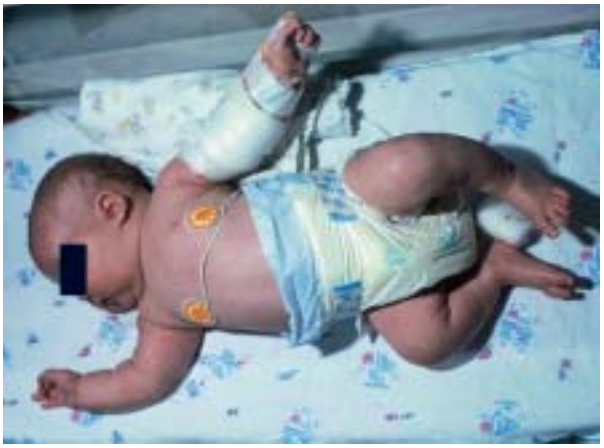


Fig. 3.28 Neonatal hyperinsulinism secondary to persistent hyperinsulinemic hypoglycemia of infancy (PHHI).

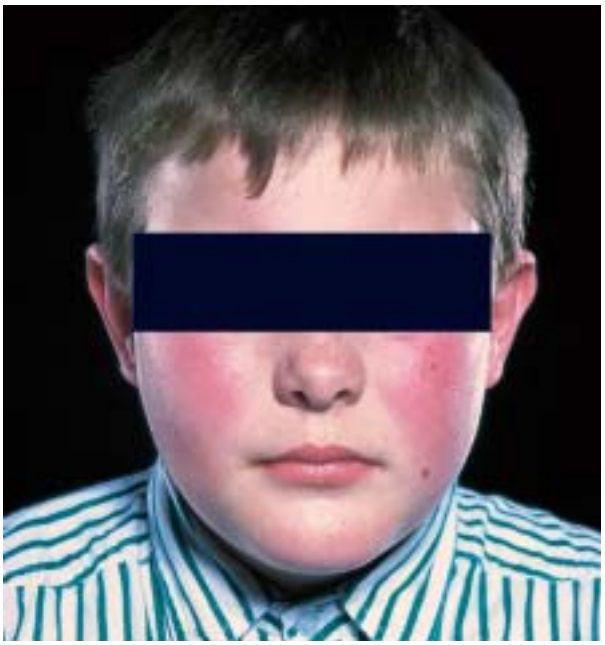


Fig. 3.30 High cheek color mimicking Cushing syndrome in nutritional obesity.

may produce overeating, obesity and overgrowth as a secondary phenomena (see **Figs 5.14 & 5.15**).

Thyrotoxicosis

If mild and hence unrecognized and untreated, thyrotoxicosis produces an acceleration of growth rate and relative tall stature in mid-childhood, although there is advanced osseous maturation and the eventual height is likely to be in the genetic range (**Figs 3.31 & 3.32**) (see also Ch. 9).

Precocious puberty

Precocious puberty is discussed in detail in Chapter 6; it leads to tall stature in childhood but not a tall adult height. Untreated, the increasingly advanced bone age leading to early epiphyseal fusion means that adult height is usually short.

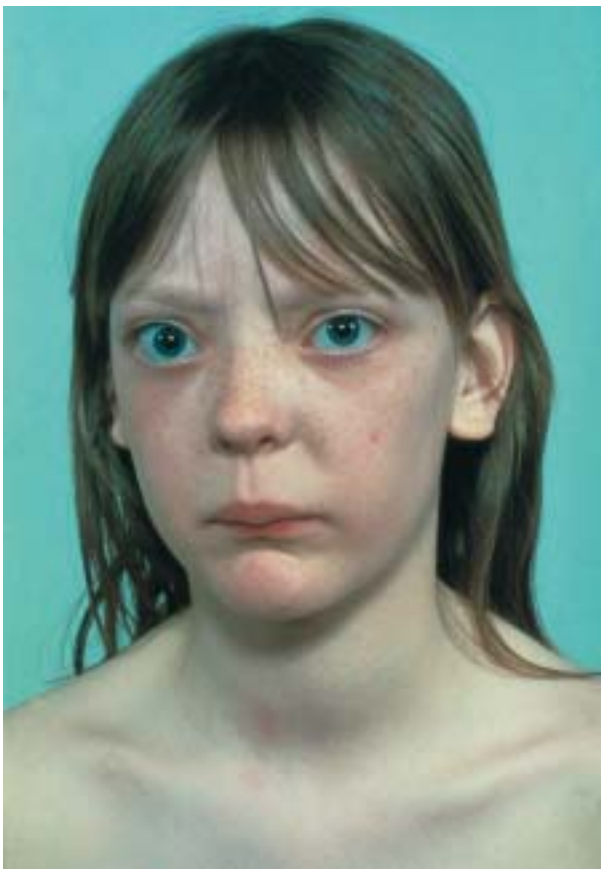


Fig. 3.31 Thyrotoxicosis.

OTHER CONDITIONS ASSOCIATED WITH DISPROPORTION AND RELATIVE TALL STATURE

Multiple endocrine adenomatosis or neoplasia (MEA or MEN) type IIb is a familial condition in which the occurrence of medullary carcinoma of the thyroid and pheochromocytoma is associated with mildly tall stature and a marfanoid habitus along with neuromas of the mucous membranes (see **Fig. 1.72**), bowel and conjunctiva (**Fig. 3.33**).

Hypogonadism can cause a modestly increased adult height with long legs (the so-called 'eunuchoid body habitus'), on the basis of late closure of the epiphyses and prolonged childhood growth of the legs coupled with failure of the sex hormone-mediated growth of the spine. The causes and work-up of hypogonadism are discussed in Chapter 7.

Similarly, but more severely, aromatase deficiency prevents the conversion of testosterone to estrogen in the male (as do estrogen receptor defects), and hence there is no stimulus for epiphyseal fusion. These rare individuals continue growing into adulthood; they have osteoporosis and infertility in association with massively raised follicle stimulating hormone (FSH) levels.

Familial glucocorticoid resistance may be associated with tall stature.

DIAGNOSTIC WORK-UP OF TALL STATURE

MEDICAL HISTORY AND PHYSICAL EXAMINATION

The following are the most relevant points to explore when taking a history of a child presenting with large size:

- Birth size, mother's health and gestational history, mode of delivery. Was mother virilized during pregnancy? (= aromatase deficiency in the offspring).
- Parental size and timing of puberty.
- Any family history of early heart disease or eye problems. Family history of endocrine malignancy, adrenal abnormalities (MEN-IIb, familial glucocorticoid resistance).
- Any symptoms suggestive of early sexual development.
- Any symptoms of sweating, tremor, frequent stool habit, anxiety or heat intolerance.
- Dietary intake.
- Neurologic symptoms including headache and visual disturbance. Is the sense of smell normal?

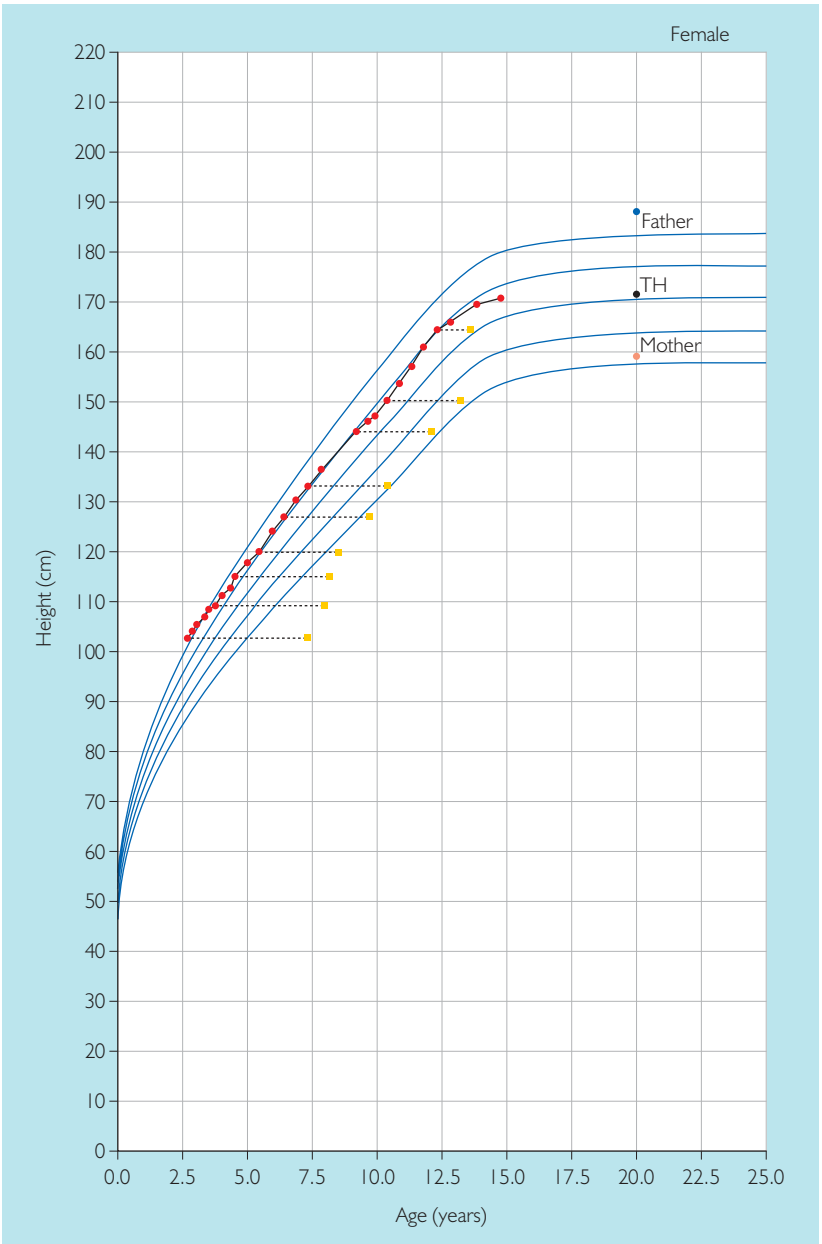


Fig. 3.32 Thyrotoxicosis presenting at 2.8 years with a bone age of 7.4 years and height of +2.4 SDS. Subsequent growth on antithyroid therapy for 4 years, followed by eventual remission, was normal (adult height + 0.6 SDS).

Fig. 3.33 Multiple endocrine adenomatosis type IIb, neuroma on right lower conjunctiva (arrow).

(Anosmia is associated with hypogonadism in the Kallmann syndrome; see Ch. 7.)
- Developmental or educational level. Any specific motor or behavioral defects?

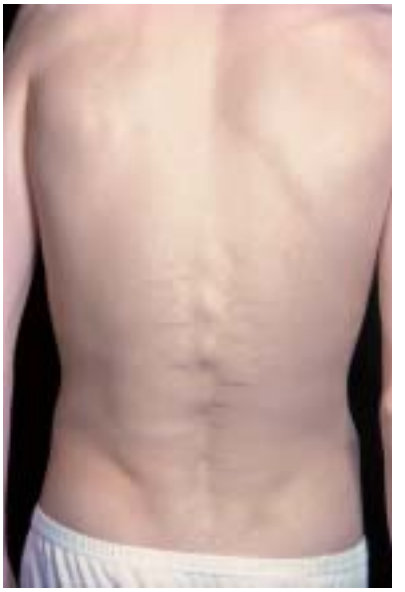
On examination, look especially for:

- The pattern of growth of height, sitting height, weight and head circumference. The presence or absence of disproportion is an important feature. Head circumference is large in Sotos syndrome and, because the height standard deviation score (SDS) stabilizes after 2 years of age, these individuals become less noticeably tall.
- Horizontal skin striae on the back are often seen in rapidly growing tall individuals, for whatever cause (**Fig. 3.34**).
- Dysmorphic features as outlined in **Table 3.1**.
- Neuromas, enlarged thyroid or hypertension (paroxysmal initially), in MEN-IIb.
- Any evidence of hypogonadism or cryptorchidism; macro-orchidism (seen in fragile X syndrome, aromatase deficiency).
- Plethora and hairy ears are seen in infants of diabetic mothers.
- Discoloration of the palms, (ingigantism).
- Visual field deficit, optic disk appearance and the position of the lens.
- Goiter, tremor, exophthalmos or other signs of thyrotoxicosis.

INTERPRETATION OF THE CLUES

The absence of any physical abnormalities or disproportion with no evidence of sexual precocity indicates:

Fig. 3.34 Horizontal striae in idiopathic tall stature.



- If weight ≤ height centile = familial tall stature.
- If weight > height centile (or abnormal (>97%) weight-for-height plot) = nutritional.

Large size with specific dysmorphic features and intellectual defect:

- = one of the overgrowth syndromes.

Disproportion with normal intellect:

- With arachnodactyly = Marfan or Beals syndromes. There may be no family history if a new mutation has occurred.
- With only moderate tallness, neuromas on lips, tongue or eyelids and a positive family history (although new mutations occur frequently) = MEN type IIb.
- With moderate tall stature, hypogonadism and anosmia = Kallmann syndrome.
- With moderate tall stature and hypogonadism = isolated or iatrogenic (i.e. following irradiation), hypogonadism; aromatase deficiency.

Disproportion with intellectual defect:

- If hypogonadism or cryptorchidism = X chromosome duplication.
- If ocular and neurologic problems predominate = homocystinuria; fragile X syndrome.

Enlargement of one side of body or one limb:

- If associated with dysmorphic features as shown in **Table 3.1** = Beckwith–Wiedemann syndrome.

- If associated with hemangioma = Klippel–Trenaunay–Weber syndrome.
- If associated with linear nevi and lipomas = Proteus syndrome.

Large size with no disproportion:

- If present at birth = neonatal hyperinsulinism.
- If accelerating height velocity, neurologic signs of optic chiasm compression, sweatiness, prognathism or skin signs = pituitary gigantism.
- If goiter, exophthalmos, tremor, tachycardia = thyrotoxicosis.
- If early sexual development (less than 8 years in a girl, less than 9 years in a boy) = precocious puberty.

RADIOLOGICAL AND LABORATORY INVESTIGATIONS

These are less commonly required than in the investigation of short stature.

A hand and wrist radiograph for bone age will serve the dual purpose of providing an estimation of physiologic maturity and allow quantification of arachnodactyly. Lumbosacral dural ectasia in Marfan syndrome requires MRI, although this investigation is rarely indicated in the absence of lower-limb neurologic abnormalities (**Fig. 3.35**).

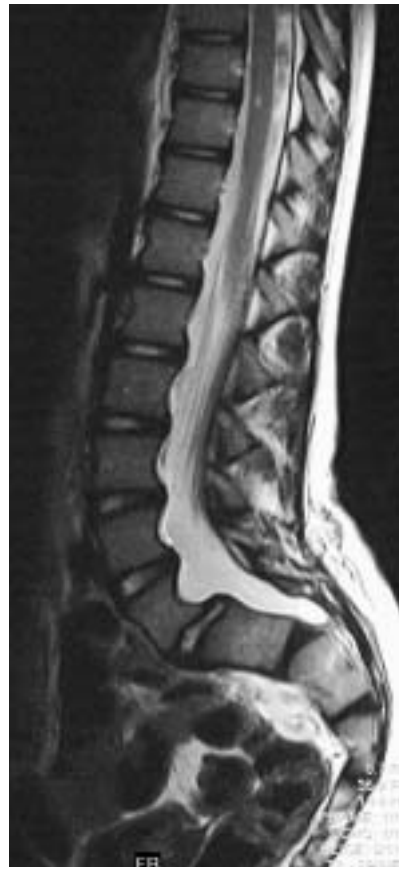


Fig. 3.35 Lumbosacral dural ectasia in Marfan syndrome.

The bone age is mildly advanced in familial tall stature/early puberty, and more so in precocious puberty and thyrotoxicosis. The bone age is very advanced in the Marshall–Smith syndrome and less so in the other dysmorphic overgrowth syndromes. In the Weaver syndrome only the maturation of the carpal bones is in advance of the small bones of the hand.

A metacarpal index compares the average length: width ratios of the 2nd and 5th metacarpal bones in an attempt to define arachnodactyly as a value of more than 8.5. In practice, it adds little to an external clinical assessment.

In the presence of genital abnormalities the karyotype should be checked.

If there is any possibility of MEN-IIb, either because of a positive family history or the presence of mucosal neuromas in a child with a marfanoid habitus, it is essential rapidly to check the calcitonin level and urinary vanillylmandelic acid (VMA) level, and confirm the diagnosis by analysis of the *ret* proto-oncogene on chromosome 10q, because the implications for missing an early diagnosis of medullary cell carcinoma of the thyroid are so severe.

Neonatal hyperinsulinism in infants born to non-diabetic mothers can be confirmed by the demonstration of inappropriately high insulin levels at the time of hypoglycemia.

If suspicion exists then thyroid function tests, to demonstrate a suppressed thyroid stimulating hormone (TSH) level, or urine estimation of homocystine levels are indicated.

The assessment of sexual precocity is described in Chapter 6 and hypogonadism in Chapter 7.

If pituitary gigantism is a possibility, a raised IGF-1 level may be a useful screening test, followed by either a physiologic GH profile (**Fig. 3.36**) or the demonstration of a failure of suppression of GH levels to a glucose load (see Appendix).

Uniparental isodisomy (producing failure of IGF-2 imprinting on 11p) may be demonstrated in 80% of those with Beckwith–Wiedemann syndrome.

THERAPY

The treatment of children to limit their adult height is a highly specialized area that should be confined to experienced centers.

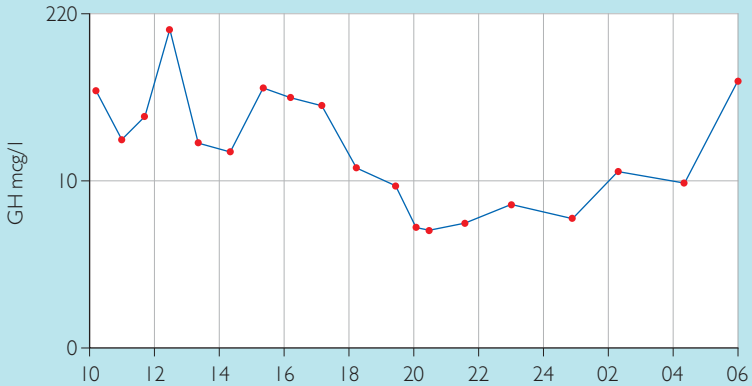


Fig. 3.36 GH profile in pituitary gigantism.

In idiopathic tall stature, a likely adult height of more than 185 cm (6 ft 1 inch) in a girl or 200 cm (6 ft 6½ inches) in a boy may be arbitrarily defined as 'excessive', although much depends on the psychologic adjustment of the child and support from parents and peers. It is a mistake to treat children because of abnormal perceptions of tallness or past adverse experiences of one or both parents.

Artificial induction of an accelerated puberty will serve to limit adult height to a degree. This is usually performed by administering high daily doses of oral ethinylestradiol (100–200 μg) to girls and depot injections of testosterone (up to 500 mg every 2 weeks) to boys. Associated with this therapy are the psychologic problems of a sudden entry into sexual maturity and the physical ones of tender breasts and genitalia, a sudden onset of acne, etc. Priapism in boys on depot testosterone and thromboembolism in girls on estrogen treatment have been described. The future risks of long-term side effects, especially in girls of families with a strong history of breast cancer, are unknown but of concern.

Trials of recombinant long-acting somatostatin analog treatment are in progress and offer a more physiologic approach to therapy, but the late results of this treatment are still unknown.

There is probably no justification for treating the majority of those affected by the primary overgrowth syndromes as adult height is seldom a problem cosmetically.

It is often stated that sex hormone treatment of the Marfan syndrome should be approached with caution, as there may be theoretical risks of increasing the likelihood of early cardiovascular disease, although published data to support this contention are lacking.

If a diagnosis of MEN-IIb is made, there should be urgent referral for prophylactic thyroidectomy, followed by thyroxine, vitamin D and calcium replacement therapy, and life-long surveillance for the development of pheochromocytoma.

Most boys with X duplication will need testosterone replacement therapy in order to undergo secondary sexual development and minimize disproportion. Conventionally this is performed with depot testosterone injections (50–100–250 mg sequentially; for details see Ch. 7), although patches and oral preparations may be used in some centers. All these treatments may worsen behavioral problems.

Surgical resection of long bone segments has been attempted to reduce height in various tall stature syndromes, but with limited success and a high morbidity due to resulting asymmetry. Drilling out the epiphyses at the upper tibia and lower femur may produce better results in experienced centers.

The treatments of sexual precocity, hypogonadism and thyrotoxicosis are discussed in Chapters 6, 7 and 9 respectively.

Basal brain tumors causing obesity should be referred to a specialist pediatric neurosurgeon for assessment and treatment. Likewise the trans-sphenoidal resection of a pituitary adenoma requires great expertise.