Early Sexual Development

HORMONAL CHANGES IN PUBERTY

The earliest biochemical event of puberty is the appearance of intermittent serum peaks of luteinizing hormone (LH) and follicle stimulating hormone (FSH) at night, caused by a pulsatile secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus. The pituitary GnRH receptors are responsive only to pulsatile GnRH: continuous administration blocks the secretion of gonadotropins. The intermittent production of LH and FSH stimulates the gonads, leading to sex hormone secretion and the development of the germinal epithelium. Initially the sex hormone levels are raised for only part of the day.

In the male the enlargement of the testes from a prepubertal 3-mL volume to 4 mL heralds the onset of puberty as the Sertoli cell volume increases. It is possible to have functioning Leydig cells and testosterone secretion in damaged testes, for instance in the Klinefelter syndrome after irradiation, without a volume increase. Testicular testosterone (via target cell conversion to dihydrotestosterone; see Ch. 8) produces pubic hair and penile growth, and is slightly augmented by androgen secretion from the adrenal gland. Acne, mood swings, the breaking of the voice, attainment of an adult body odor and sweat pattern are all androgen-mediated events.

In the female the first external sign of puberty is an enlargement of the breast bud as estrogen is produced from the ovary. Some of the androgen-mediated effects seen in a girl, including pubic and axillary hair growth, are secondary to increased androgen secretion from a maturational change in the adrenal gland – adrenarche. Adrenarche is a separate event from puberty, with different regulation, and occurs in both sexes. Its androgenic features are usually subsumed in the male by testicular androgen production. In the female, along with some ovarian-derived androgens, adrenarche forms an important component of normal sexual development.

Leptin produced by white fat also acts as a peripheral signal to start hypothalamic activation of gonadotroph secretion once a certain fat mass has been attained (see Ch. 5). Cyclic LH and FSH production leads to ovarian enlargement, follicle production and ultimately to maturation of the uterus and endometrium, followed by menarche. These changes can be monitored by ultrasonography (**Figs 6.1–6.7**).

Peripheral aromatase conversion of testosterone to estrogen, especially by fatty tissue, is possible, and is
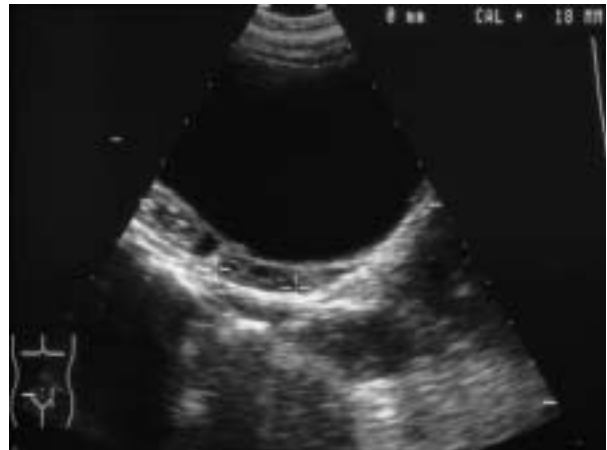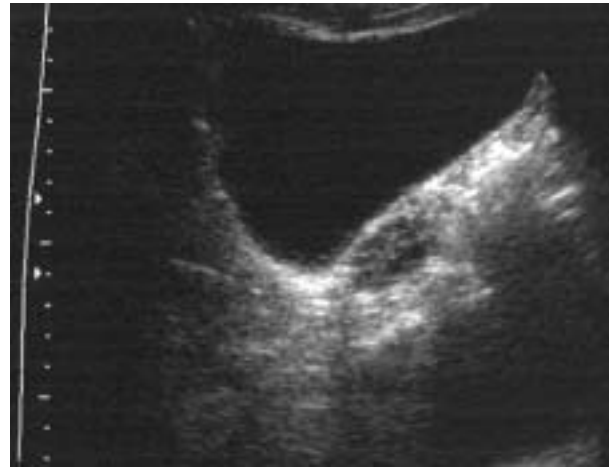

Fig. 6.1 After the neonatal period the ovaries are small (long axis 18 mm +   + in this section) and contain only one tiny follicle. Ovarian volume < 2 mL prepubertally.
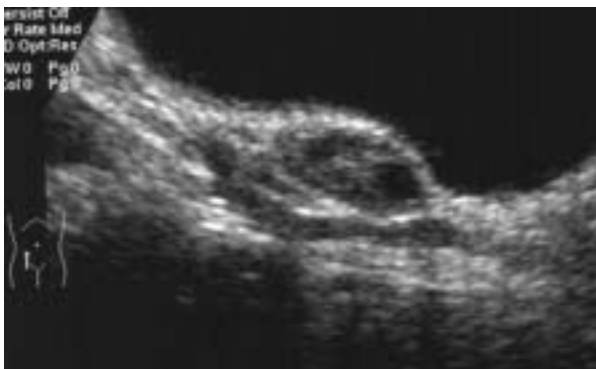

Fig. 6.2 Prepubertal uterus is small (16-mm long +   +) and tubular, and is not steeply angled in relation to the cervix (13-mm long ×   ×). Uterine volume <2 mL prepubertally.

Fig. 6.3 In early puberty the uterus starts to enlarge (36 mm × ×, 6 mL) and become pear shaped.

Fig. 6.4 In early puberty the ovaries become larger (here 2 mL) and contain one or two small cysts.

Fig. 6.5 In mid to late puberty a clear endometrial echo is seen and can be measured (× × 30 mm).

Fig. 6.6 In late puberty the ovaries enlarge (here 4-mL volume) and contain larger, peripheral follicles. During the menstrual cycle one such follicle will become dominant, enlarge until ovulation, then regress to form a corpus luteum.

Fig. 6.7 The late pubertal uterus is clearly pear shaped (61-mm long + +) and contains a midline endometrial echo. It is steeply angled in relation to the cervix (22-mm long × ×) and the vagina can be clearly seen extending upwards to the right.

responsible for estrogen-mediated breast enlargement, gynecomastia, in some males. Estrogen in both sexes causes epiphyseal fusion and the eventual cessation of growth.

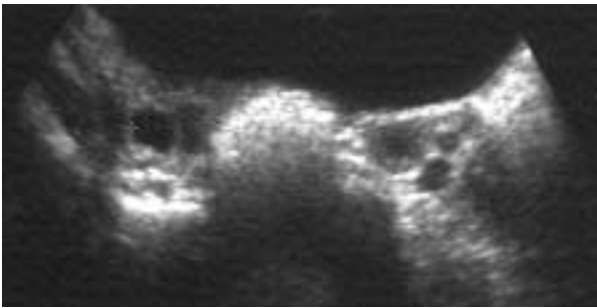Neonates are exposed to the maternal hormone environment and may manifest changes secondary to natural or iatrogenic hormone exposure. Withdrawal bleeding in females (**Fig. 6.8**) and neonatal breast enlargement (see **Fig. 1.98**) in both sexes are a physiologic result of this process. Additionally there is a physiologic activation of the hypothalamic–pituitary–gonadal axis in the first months of life, especially in boys, which then subsides until puberty (**Figs 6.9–6.11**).
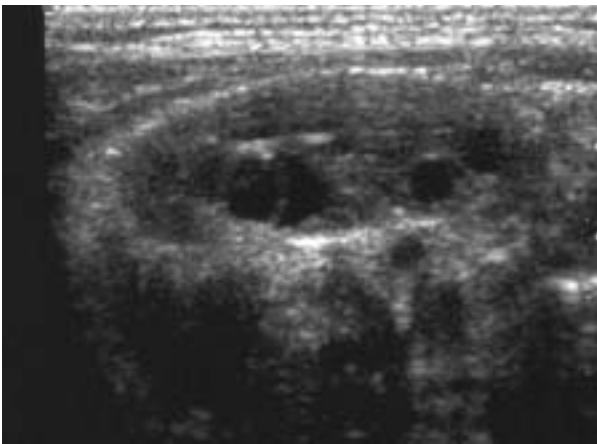
Fig. 6.8 Physiologic withdrawal bleeding in a neonate.

Fig. 6.9 Transverse section of neonatal pelvis. Uterus is the solid midline structure behind the bladder. Both ovaries contain large follicles secondary to physiologic neonatal activation of the hypothalamic—pituitary—ovarian axis.

Fig. 6.10 Another view of a neonatal ovary with physiologic follicle formation and 2-mL volume.

CLASSIFICATION OF EARLY PUBERTY

Early or precocious puberty (also called sexual precocity) is traditionally defined by the onset of puberty

Fig. 6.11 The neonatal uterus can be quite bulky, with an endometrial echo, before settling down to the appearance shown in Fig. 6.1.

before the age of 8 years. In Europe this still seems a valid cut-off, but in the USA it has been proposed to use 7 years for white girls and 6.5 years for the African American population. The difference between Europe and the USA may be related to ethnic causes, a different prevalence of obesity or methodologic issues. This is earlier than in previous generations, although there is little evidence that menarche is occurring at a younger age, suggesting that the tempo of puberty in the early developers may be slower than previously. In boys 9 years remains the suggested cut-off for the start of normal sexual development. It can be subdivided into 'true' (or 'central') precocious puberty and 'pseudo' sexual precocity. True precocious puberty is all of the events of normal puberty occurring early, whereas in pseudo-precocious puberty only some aspects of sexual development occur, depending on whether androgens or estrogens are produced. Excess or early estrogen production in the female or testosterone in the male leads to iso-sexual development. Alternatively, excess or early estrogen production in the male or testosterone in the female leads to hetero-sexual development.

There are also two forms of partial development, which are usually considered as variations of normal: premature adrenarche or pubarche (early pubic hair) and premature thelarche (breast development). (Note that, as the first sign of true precocious puberty in a girl is breast development, the differentiation between early puberty and premature thelarche cannot be made only on the basis of a single physical examination: both growth pattern and bone age, which are normal in premature thelarche and accelerated in precocious puberty, must be considered.)

1 TRUE SEXUAL PRECOCITY (OR CENTRAL PRECOCIOUS PUBERTY)

This is characterized by:

- Concordant development of all structures usually involved in puberty: in a girl breast then pubic hair growth (**Fig. 6.12**), and uterine and ovarian maturation followed by menarche; in a boy testicular enlargement, and penile and pubic hair growth (**Fig. 6.13**).
- The simultaneous development of secondary effects such as mood swings, acne (**Fig. 6.14**), body odor.
- A pubertal height spurt (**Fig. 6.15**).
- Advanced bone age that continues to progress rapidly and leads to premature epiphyseal closure and hence reduced final height.

True sexual precocity may be idiopathic (in girls by far the most frequent form) or caused by abnormalities in the CNS (most commonly in boys). These can be congenital anomalies, hypothalamic hamartomas (**Figs 6.16–6.18**), raised intracranial pressure or tumors

Fig. 6.13 Male genitalia in central precocious puberty showing concordant pubertal development.
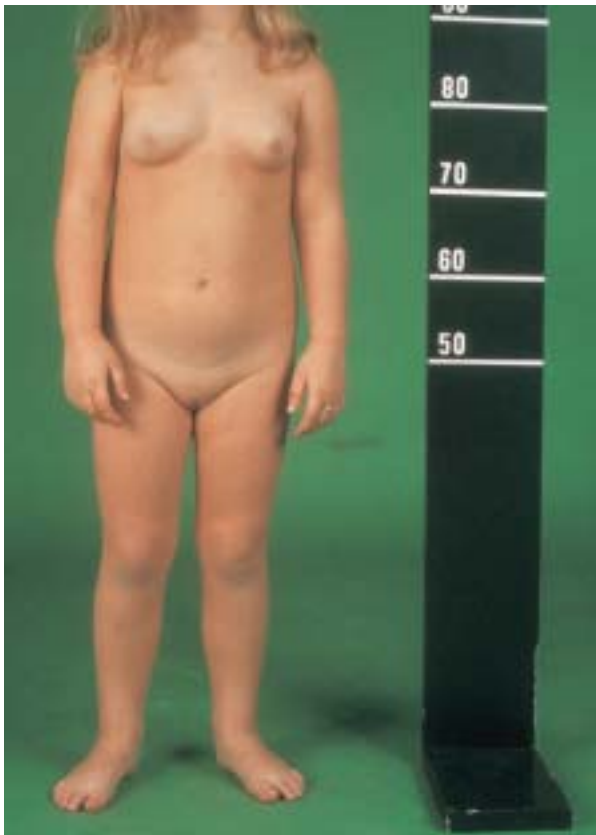
Fig. 6.12 Central precocious puberty in female, breasts stage 3, pubic hair stage 2, height 114 cm (3 ft 9 in or +1.3 SDS) at age 5.5 years.
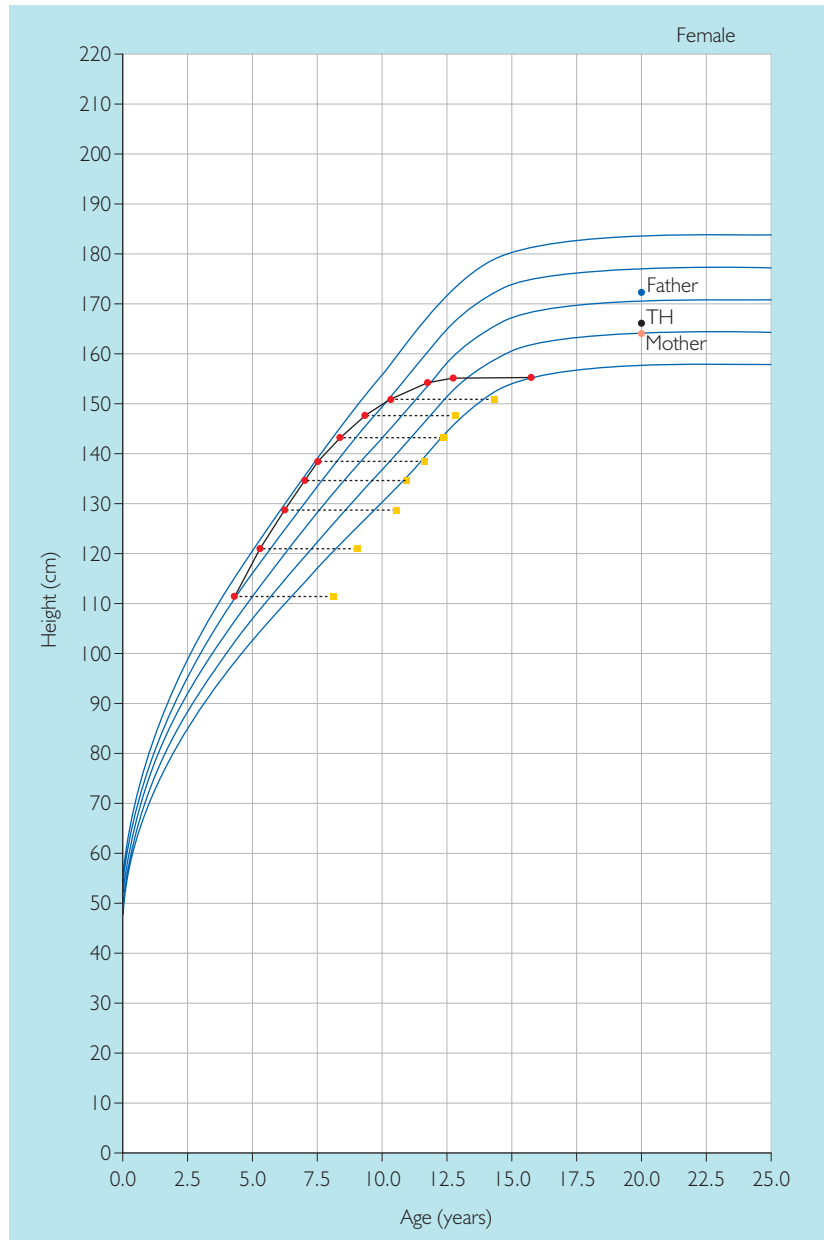

Fig. 6.14 Early acne in male precocious puberty.

Fig. 6.15 Precocious puberty presenting at 4.3 years with a bone age of 8.2 years. Treatment with intranasal gonadotropin analog therapy delayed menarche to 11.5 years and subsequent bony fusion to around 12 years, but with evidence of a reduced adult height of —2 SDS.

(**Fig. 6.19**), and may follow cranial irradiation, especially in girls (see Ch. 11). The intracranial lesions may arise *de novo* or be part of a predisposing condition such as neurofibromatosis (**Figs 6.20–6.22**). Sexual precocity can also rarely be seen with primary long-standing hypothyroidism due to a sequence homology between thyroid stimulating hormone (TSH) and human chorionic gonadotropin (hCG).

Girls adopted from developing countries to the developed world may demonstrate puberty that starts a little early but with rapid progression to menarche at 11+ (versus 12+) years and loss of adult stature.

Subacute torsion of the ovaries produces massive edema and maturation of stromal cells; there is often virilization from ovarian testosterone production followed by estrogenization and breast development. This can be very difficult to differentiate clinically from true central precocity other than the suppression of the LH–FSH axis and the typical ultrasonographic appearance (see below).
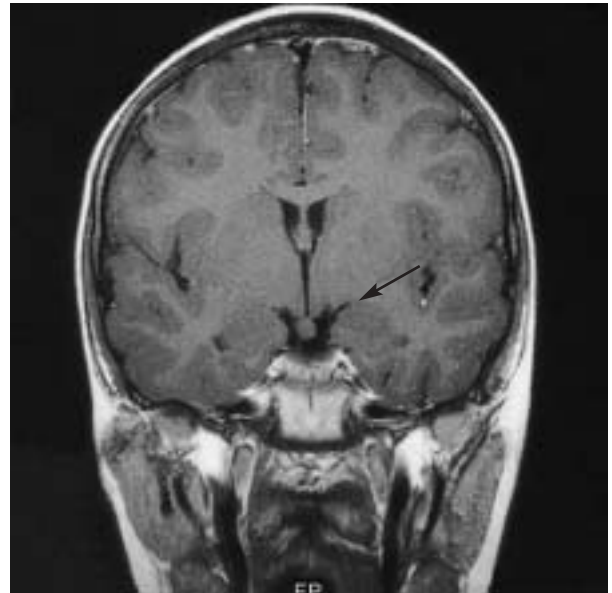
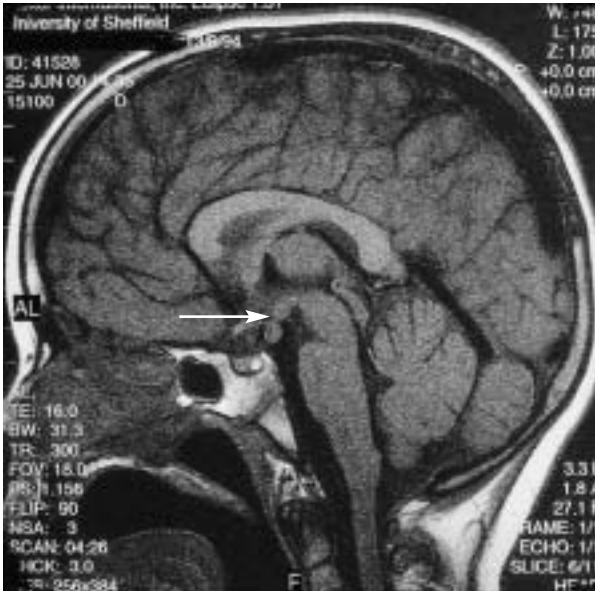## 2 PSEUDO-SEXUAL PRECOCITY

This is characterized by:

- Hypertrophy of the target tissue of the hormone being secreted in excess.

Fig. 6.16 Male precocious puberty due to hamartoma, with unaffected twin brother.

Fig. 6.18 Hamartoma of the tuber cinerum producing precocious puberty, transverse MRI.

Fig. 6.17 Hamartoma of the tuber cinerum producing precocious puberty, lateral MRI.

- Regression or inhibition of the structures that usually secrete the hormone at puberty.
- Advanced bone maturation.
- Accelerated growth rate.

**Fig. 6.19** Male central precocious puberty with sixth nerve palsy secondary to intracranial astrocytoma.

Figs 6.20 (left) and **6.21** (right) Precocious puberty in neuro bromatosis secondary to optic glioma. Note site of gonadotropin analog injection (with plaster), as well as enlargement of testes and penis with consonant pubic hair growth.

Fig. 6.22 Optic glioma in neuro bromatosis producing precocious puberty.
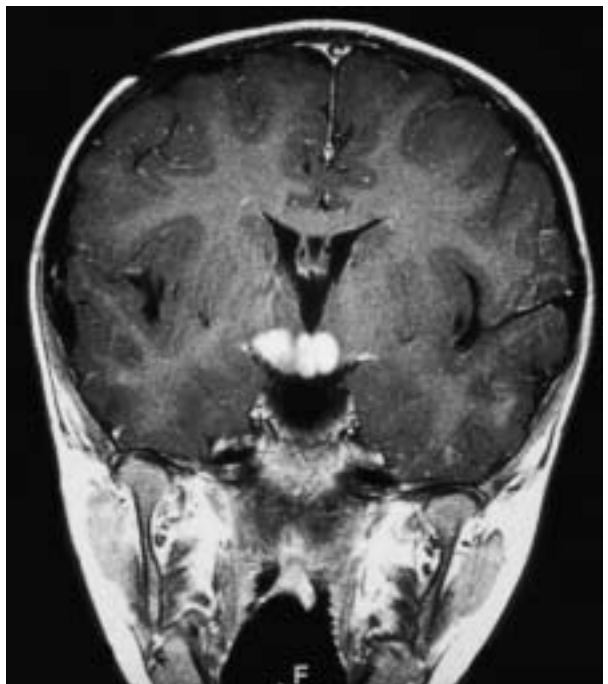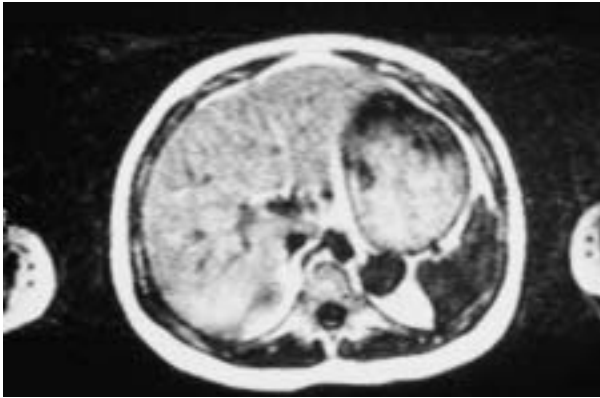
Fig. 6.23 Adrenal carcinoma producing virilization.

The development may be iso-sexual or less commonly hetero-sexual, and causes include adrenal tumors (**Fig. 6.23**) producing either testosterone or estrogen, non-salt-losing congenital virilizing adrenal hyperplasia (**Fig. 6.24**; see also Chs 8 & 11), exogenous gonadotropin or sex steroid administration, gonadal tumors producing estrogen or testosterone, gonadotropin- or hCG-producing tumors and estrogen-secreting ovarian cysts (**Figs 6.25 & 6.26**). Hetero-sexual pseudo-precocity in a female will often result in considerable clitoral hypertrophy (see Ch. 8), and this helps in the differentiation from premature adrenarche (see below).

Additionally the McCune–Albright syndrome produces discordant sexual development. The syndrome consists of irregular pigmented café-au-lait patches, usually unilateral and on the upper body (see **Fig. 1.135**). There are areas of bony dysplasia and cysts in the long bones (**Fig. 6.27**) and skull (**Fig. 6.28**). Pubertal signs are usually discordant with early bleeding in females and no evidence of gonadotropin cyclicity. It is much commoner in girls than boys and can also rarely cause thyrotoxicosis, gigantism and Cushing syndrome. It results from a generalized mutation of part of the G protein (a secondary messenger signaling receptor activation) in endocrine tissues, leading to overactivity.

Separate from the pathologic secretion from tumors described above, excess production of estrogen from peripheral aromatase conversion of testosterone in an often overweight male can cause pubertal gynecomastia (**Fig. 6.29**). Male breast development and lactorrhea from a prolactinoma is extremely uncommon (see below).

Testotoxicosis is a rare condition of familial male pseudo-precocious puberty leading to generally consonant changes of male puberty but with testes that are often small for the degree of virilization

Fig. 6.24 Non-salt-losing 21-hydroxylase de ciency presenting late in a male with penile enlargement, pubic hair growth but small testes (indicating a non-testicular source of androgen).

present (**Figs 6.30 & 6.31**). There is an absence of cyclic gonadotropin activation, but a mutation causing a 'locking on' of the testicular LH receptor is present, leading to early production of testosterone in the absence of circulating LH.

## 3(a) PREMATURE ADRENARCHE OR PUBARCHE

This is characterized by:

- Pubic and axillary hair growth (**Figs 1.108 & 6.32**).
- Acne, body odor and other androgen-mediated effects.
- A mildly advanced bone age.
- Usually no acceleration of height velocity.

The event termed 'adrenarche' is a normal age-related physiologic maturation of the adrenal cortex, probably under the influence of adrenocorticotropic
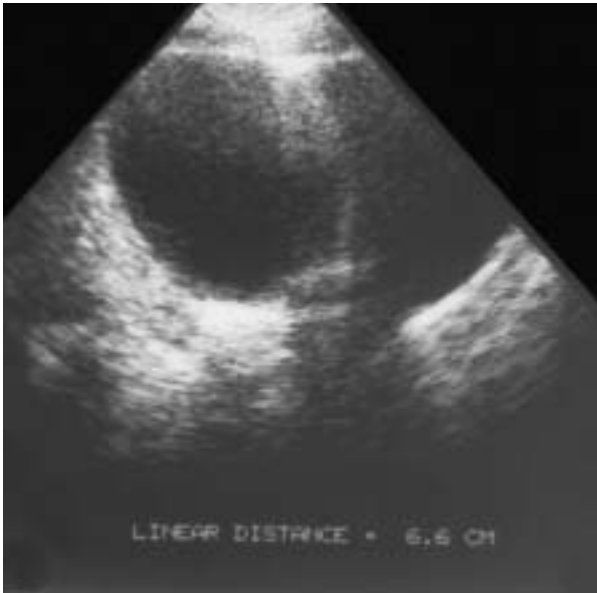
Fig. 6.25 Large estrogen-secreting ovarian cyst (on left), pushing bladder and uterus to the right.

Fig. 6.26 Premature breast development secondary to an ovarian cyst.

hormone (ACTH) (or another postulated 'central adrenarche stimulating hormone' (CASH)), producing increased secretion of dehydroepiandrosterone (DHEA) and other androgenic precursors of testosterone. Its effects are usually incorporated into puberty. If early maturation occurs, the mild virilizing effects become cosmetically noticeable. Idiopathic dislocation of adrenarche from puberty is commoner in girls than in boys. There is some evidence that a genetically determined overactivity of one of the 17, 20-desmolase pathways for adrenal steroid production may result in familial adrenarche and in some cases of familial polycystic ovarian syndrome (PCOS). A large proportion of girls with premature adrenarche seem to go on to develop a
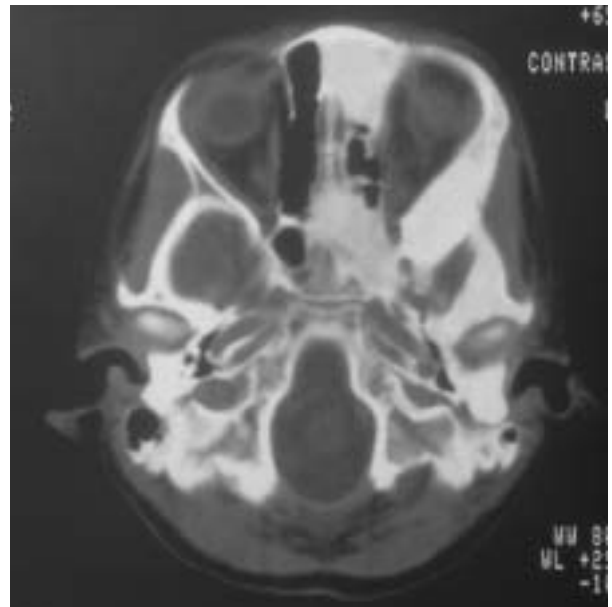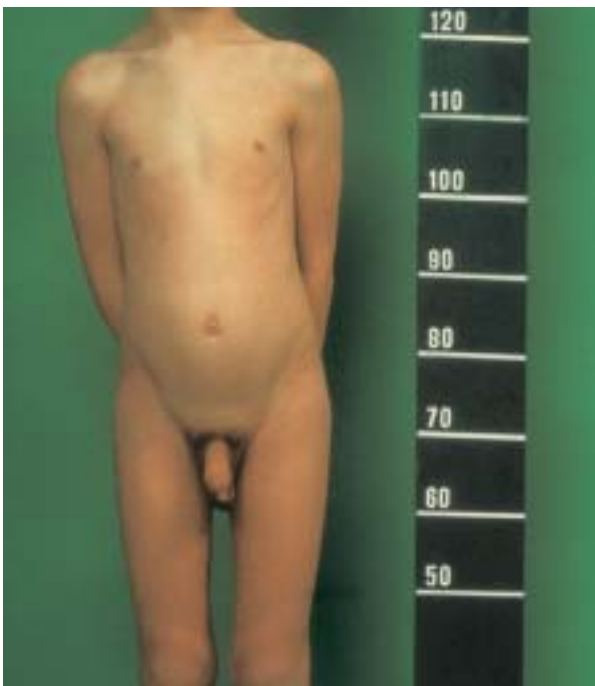

Figs 6.27 (top) **6.28** (bottom) Fibrous dysplasia of upper femur and brous dysplasia of base of skull and left orbit.

Fig. 6.29 Gynecomastia — required surgical resection.

Fig. 6.30 Testotoxicosis — stage 4 penis and pubic hair growth but only 6-mL testes.

Fig. 6.31 Genitalia in another case of testotoxicosis. More concordant development but a family history of the condition.

are hydrocephalus and following meningitis (especially tubercular meningitis). Because it may occasionally be severe and a familial event, differentiation from late presenting atypical or non-classic congenital hyperplasia (CAH; see below) may be required.

3(b) HIRSUTISM

Other than adrenarche, excess hair production in the female (with or without later male-pattern baldness) may be due to other causes of excess adrenal activity or androgen production:

- Classic simple CAH.
- Late-onset CAH is common but often undiagnosed. The non-classic subtype is associated with human leukocyte antigen (HLA) types B14 and B35 (see Ch. 8).
- Cushing syndrome.
- Secondary to abnormal levels of testosterone produced by polycystic ovaries, which can

PCOS-like phenotype, including the 'metabolic syndrome X' (**Fig. 6.33**). Premature adrenarche may also be secondary to non-progressive intracranial lesions, presumably mediated by abnormal production of ACTH or CASH. The commonest intracranial causes

Fig. 6.32 Premature adrenarche/ pubarche. No breast development and stage 3 pubic hair growth. There was an adult body odor and mild acne but no cliteromegaly. Sibling illustrated in Fig. 1.108.

Fig. 6.34 Hirsutism secondary to insulin resistance, mild acanthosis seen in neck skin creases.

Fig. 6.35 Massive cystic ovarian changes in patient in Fig. 6.34.

Fig. 6.33 Large ovarian cyst in CAH.

themselves be due to adrenal overactivity and hyperinsulinemia or occur as a primary event after puberty (**Figs 6.34 & 6.35**).

■ Idiopathic hirsutism is possibly due to overactivity of skin 5α-reductase levels. This can be treated with enzyme blockers such as finasteride.

■ Some girls or their parents perceive cosmetic problems that are due only to normal growth of dark hair.

It is said that hirsutism confined to the lower body is indicative of an adrenal source of androgens.

As well as treating any identified underlying cause it is also appropriate to advise cosmetic treatments such as bleaching, depilation and electrolysis.

4 PREMATURE THELARCHE

This benign condition is characterized by:

■ Early breast enlargement (**Fig. 6.36**), usually in infancy, but which may occur throughout childhood and is often cyclic over periods of months.

■ The absence of the subsequent appearance of any other pubertal changes.

■ Normal growth and skeletal maturation.

In premature thelarche, waves of follicular development (above 3–4 mm) occur with FSH induction of aromatase. Low levels of estrogen can be detected by means of ultra-sensitive assays.

A variant condition with features intermediate between true central precocious puberty and thelarche

Fig. 6.36 Premature thelarche.

Fig. 6.37 Genitalia of patient shown in Fig. 6.23, showing early maturation of vulval mucosa.

has been described, in which FSH levels predominate (unlike true puberty, where LH > FSH levels).

5 ISOLATED PREMATURE MENARCHE

This is an ill-understood condition affecting prepubertal girls, often in the summer months. There may be cyclic bleeding every 4–6 weeks, for 3–4 days, for several months in a row. At no point are levels of gonadotropins raised, but there is a small endometrial echo visible on ultrasonography during the bleeding phase. The differential lies between sexual abuse, vaginal malignancy and cervical erosions, so examination under anesthesia may be required if the history and investigations are not typical.

DIAGNOSTIC WORK-UP

MEDICAL HISTORY AND EXAMINATION

The following items are of importance in the history:

- The exact timing of the onset of pubertal signs, including in a girl whether breast development occurred earlier or later than pubic hair growth.
- Vaginal discharge, which may be creamy or blood-stained.
- Growth pattern (any rapid growth recently? – this may be manifested by change relative to peers or changes in clothes and shoe size).
- Any symptoms suggestive of hypothyroidism.
- Any neurologic or visual symptoms.

- Any family history of precocity or suggestive of neurofibromatosis.
- Previous diseases leading to neurologic damage.
- Any exposure to drugs (estrogens, androgens, cimetidine). This can be iatrogenic, accidental (i.e. ingestion of the contraceptive pill) or factitious. There are also reports of traditional Chinese herbal remedies leading to both male and female precocity. Organochlorine pesticides related to DDT may cause sex steroid-like effects.
- Dietary exposure to contaminated poultry or beef where excessive veterinary administration may be a possibility.

The physical examination should concentrate on:

- A precise description of pubertal stage. (For longitudinal follow-up it is useful to measure breast diameter.)
- Height, sitting height and weight, and their evaluation versus age references and previous measurements. (As growth of the back is mediated partly by sex hormone secretion, early puberty will tend to produce a somewhat longer sitting height in relation to leg length.)
- Inspection of the color of the vulval mucosa; a pale color indicates estrogen activity (**Fig. 6.37**).
- Signs of hyperandrogenization (hirsutism, clitoral or penile enlargement, acne). Hirsutism may be

Score	1	2	3	4
Lip	Few outer hairs	Outer margin	>50%	Full
Chin	Few hairs	Scattered	Light cover	Heavy
Lower abdomen	Few, midline	Midline streak	Band	Inverted 'Y'
Thigh	Sparse, <25%	>25%	Complete, light	Heavy

Score each feature and add up the total. A score greater than 5 is indicative of significant hirsutism. The score can be used to document progression or regression of the signs.

Table 6.1 Simple grading of hirsutism

graded according to a simple scale (**Table 6.1**). Hirsutism exclusively on the lower body is most commonly due to an adrenal cause.

- Blood pressure (increased in the 11β-hydroxylase form of adrenal hyperplasia or with raised intracranial pressure).
- A search for pigmented birthmarks.
- Thyroid size and signs of hypothyroidism (see Ch. 9). (In the hypothyroid male the testicular volume may be increased to a greater extent than might be expected from the other pubertal signs. In the hypothyroid female periods may occur earlier than would be expected for the stage of breast development.)
- Hepatomegaly or abdominal mass.
- Pelvic mass (e.g. ovarian cyst or tumor) on abdominal or rectal examination.
- Neurologic examination (including fundoscopy).

INTERPRETATION OF THE CLUES

True precocity

- In a girl with no other signs or symptoms = likely to be idiopathic, but check with computed tomography (CT) or magnetic resonance imaging (MRI).
- With neurologic signs or symptoms = CNS lesion.
- With more than five café-au-lait spots and axillary freckles, with or without a positive family history = neurofibromatosis and optic glioma or other CNS tumor.
- Thyroid enlargement and/or typical symptoms and signs = hypothyroidism.

In tall boys and girls with a history of early pubic hair growth, sweatiness followed by other signs of puberty could be non-salt-losing CAH that has caused
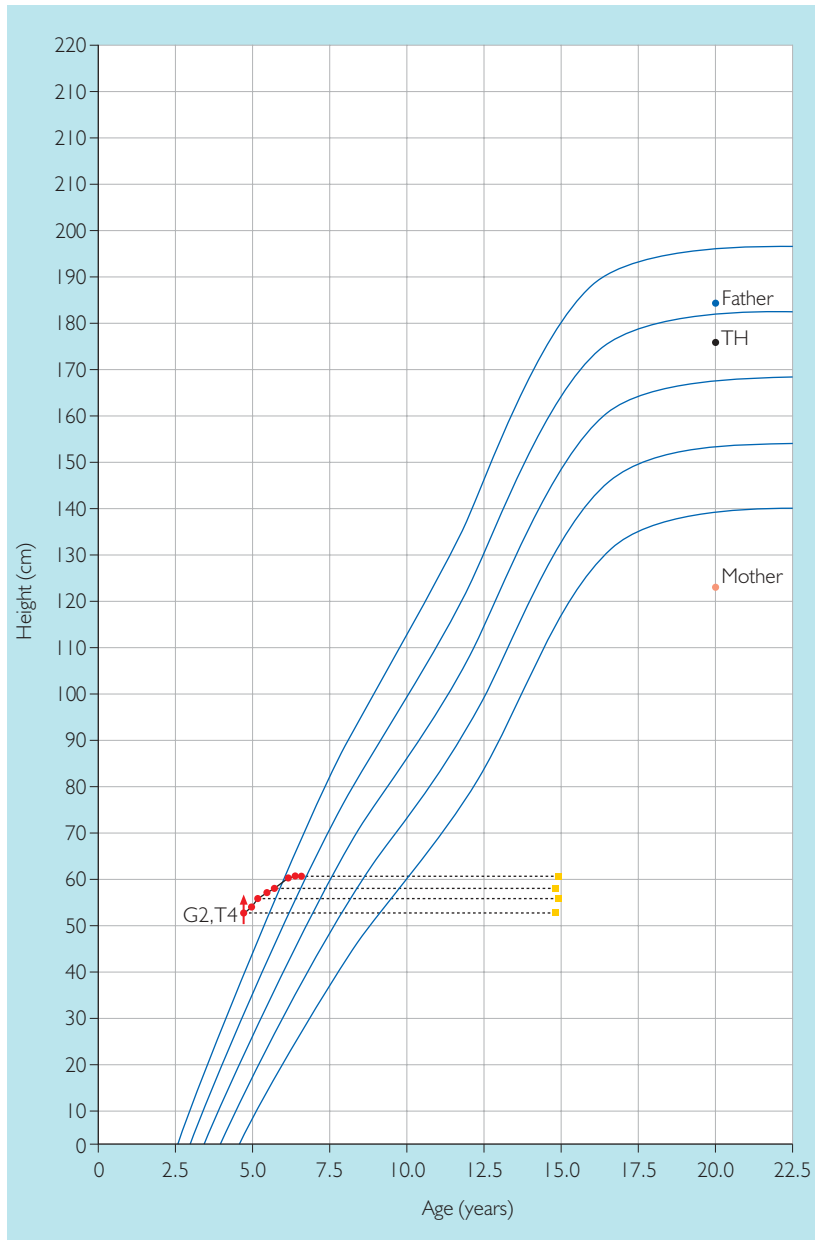
massive advance of bone age and true puberty supervening on pseudo-precocity (**Fig. 6.38**).

Pseudo-precocity

- A positive family history = adrenarche or atypical 21-hydroxylase deficiency.
- Hypertension in a girl with virilization or a boy with pseudo-precocious puberty = 11β-hydroxylase deficiency.
- Cliteromegaly plus advanced bone age and accelerated growth = androgenization *not* secondary to adrenarche.
- Irregular café-au-lait spots and/or lytic bone lesions on radiography = McCune–Albright syndrome.
- Pelvic mass or mass felt per rectum = ovarian tumor.
- Hepatomegaly = hepatic tumor (producing hCG).
- Abdominal mass = adrenal tumor.
- Gynecomastia with unilateral testicular enlargement = germ cell tumor.
- Gynecomastia with no testicular enlargement = intra-abdominal tumor (often impalpable) or extraglandular aromatase conversion at puberty (commonest in, but not exclusive to, obese subjects).
- Previous diseases leading to neurologic damage = premature adrenarche.
- Early onset with cyclic breast enlargement = premature thelarche.
- Positive family history in a boy = familial testotoxicosis.

FURTHER INVESTIGATIONS

Evaluation of the growth pattern in the light of the pubertal stage is crucial for determining the number

Fig. 6.38 Non-salt-losing CAH presenting as true central precocious puberty supervening on the massive advance in bone age due to adrenal testosterone. At presentation at 4.7 years of age, height +3.5 SDS with bone age of 14.8 years. Commenced treatment with hydrocortisone to suppress ACTH and LHRH agonists to suppress true puberty with no further progression of bone maturation.

of further investigations. The sex of the child is also relevant.

Girls

If there is only a minor degree of breast enlargement in a young girl, with no other signs of estrogen activity and a normal growth pattern, further investigations can be limited to a hand and wrist radiograph for bone age. If bone age is not accelerated, the child could be reviewed after some months to see whether the signs have subsided or progressed with pubic hair growth; height velocity 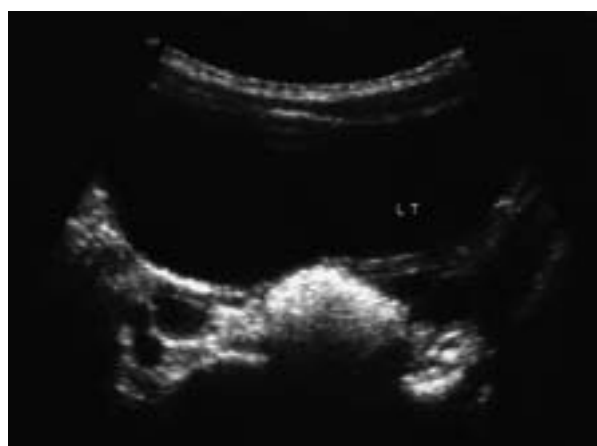could also be measured. If there is no progression of pubertal signs and a normal growth rate, the diagnosis is most likely to be premature thelarche or a temporary exposure to exogenous estrogens. Further review should be arranged and the care-giver instructed to return urgently if any more pubertal changes occur. Pelvic ultrasonography that showed one or two follicles in a low-volume ovary with no sign of uterine enlargement would give further reassurance (**Figs 6.39 & 6.40**).

If there are definite signs of estrogen activity (active breast development, pale mucosa of introitus, psychologic changes, growth acceleration and bone age acceleration), the following investigations are indicated:

Fig. 6.39 The ovaries in premature thelarche show a few large cysts/follicles in small-volume glands. The uterus (not shown) is of prepubertal size (<2 mL) and shape.

Fig. 6.40 Transverse section of both ovaries in thelarche.

Fig. 6.41 Low-volume ovaries (26 × 13 mm) with large cysts in thelarche.

- Basal estradiol (E_2), LH, FSH.
- Thyroid function tests: (free) thyroxine (FT_4) and TSH.
- Abdominal ultrasonography (ovarian and uterine size) (F**igs 6.41–6.44**).
- Levels of inhibin B (a granulosa-derived glycoprotein that feeds back to the pituitary to inhibit FSH secretion) are raised in thelarche (but not inhibin A which comes from the corpus luteum) as opposed to true puberty where levels of both inhibin A and B levels are rasised.
- In case of doubt about the estrogen results, vaginal cytology can be considered (percentage of squamous cells).
- Luteinizing hormone releasing hormone (LHRH) test (see Appendix) in a specialized center. Before puberty, the increase in LH and FSH levels is low, with usually a greater rise of FSH than of LH concentration. During puberty, the increase in the levels of both gonadotropins is higher, with LH rising higher than FSH concentration in mid to late puberty. Therefore, the ratio of LH to FSH (>1) can be used as a marker of 'established' puberty.

If there is positive evidence for true precocious puberty (E_2 concentration greater than 50 pmol/L, LH/FSH ratio > 1, LH peak raised) and no hypo-thyroidism, further investigations to find the precise cause are needed with MRI or CT of the brain.

If there is positive evidence for pseudo-precocious puberty (raised E_2 concentration, depressed LH and FSH levels even after administration of LHRH), further investigations should be aimed at elucidating the precise cause. Sonography of the ovary, liver and adrenals should show the majority of tumors, although they may occasionally be intrathoracic. Occasionally CT
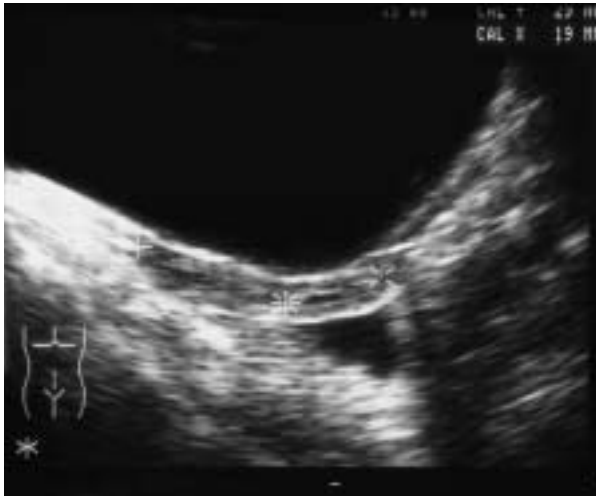
Fig. 6.42 Central precocious puberty demonstrated in girl presenting at 5 years with breast stage 2. There is enlargement of the uterus such that the body (+ + 29 mm) is greater than the cervix (× × 19 mm).
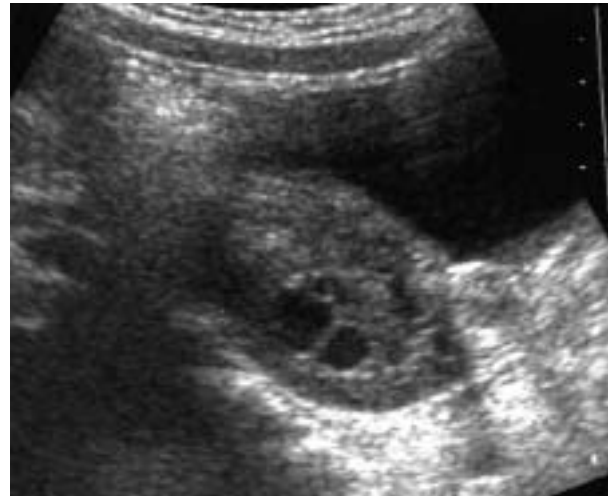
Fig. 6.44 Massively enlarged ovaries with peripheral follicles and central solid component. At laparoscopy to exclude tumor, bilateral twisting of the pedicles was observed and the diagnosis of massive ovarian edema secondary to chronic torsion con rmed on biopsy.

Fig. 6.43 Ovarian enlargement with the beginnings of peripheral follicle formation in the patient in Fig. 6.42. This can occur only as part of cyclical gonadotropin secretion.

Fig. 6.45 Abdominal CT showing normal small tricorn adrenal.

of the adrenal may be required to look for small lesions (**Fig. 6.45**).

If there are mild signs of androgen excess and if growth and bone age are normal, the diagnosis is almost certainly benign precocious adrenarche and no further investigations are needed. (For documentation, plasma levels of DHEA sulfate (DHEAS), which is usually slightly elevated, can be measured, and a urinary steroid profile will show a mild increase in adrenal cortical metabolites.) In non-classical 21-hydroxylase deficiency, which may mimic precocious adrenarche, a short ACTH

(Synacthen) test (see Appendix) to provide an estimate of the basal levels and rise of 17α-hydroxyprogesterone may be required to confirm the diagnosis.

If there is more severe virilization with cliteromegaly, accelerated height velocity and bone maturation, a urinary steroid profile and measurement of plasma or salivary 17α-hydroxyprogesterone, DHA, DHEAS and androstenedione will allow the diagnosis of most forms of CAH and androgen-producing tumors. Tumors can be localized by means of ultrasonography or CT.

If there is abnormal pigmentation, radiography of the skeleton will help to confirm McCune–Albright

syndrome, in which case thyroid and adrenal function should also be checked.

Boys

If there are definite signs of puberty with enlarging testes, basal serum testosterone, LH and FSH levels should be measured and an LHRH test performed in a specialist center. If the level of testosterone is increased (>1.0 nmol/L) and the LHRH test shows a pubertal pattern (see above), true precocious puberty is diagnosed. As the frequency of cerebral abnormalities in boys with true precocious puberty is relatively high, CT or MRI is mandatory (**Figs 6.46 & 6.47**).

If the testosterone level is increased, with small soft testes, pseudo-precocious puberty is likely and LH and FSH levels will remain suppressed during the LHRH test. Further determinations of other steroids in the urine and plasma (androstenedione, DHEAS, DHEA and 17α-hydroxyprogesterone) are indicated to determine the source of the androgens. It is possible to use the relative values to distinguish between premature adrenarche (relatively rare in the male), exogenous anabolic steroid administration, the various non-salt-losing forms of CAH and adrenal tumors.

If isolated gynecomastia is present then testosterone, prolactin, E_2, hCG and LH levels should be measured. hCG and/or E_2 concenetrations are raised in some estrogen-secreting tumors, which may be testicular (detected by ultrasonography) or extragonadal (detected by further ultrasonography or CT). Primary testicular damage with increased menopausal LH levels – and hypothalamic or pituitary hypogonadism with undetectable LH levels – also may present with gynecomastia (obviously in the absence of other signs of sexual maturation; see Chs 7 & 8). Prolactinomas in childhood (**Fig. 6.48**) are extremely rare and usually present with CNS signs, although this is the only cause, if seen, of lactorrhea (**Fig. 6.49**). If the estrogen level is only slightly raised or all the tests are normal, then extraglandular aromatase conversion of testosterone to estrogen is likely.

THERAPY

True precocious puberty will result in a reduced final height, and early pubertal development can lead to psychologic problems. For these reasons treatment is usually offered in specialist units. Current therapy uses depot slow-release LHRH analogs i.m. or s.c. (depending on the preparation) every 4–12 weeks.

To prevent initial hyperstimulation and worsening of the precocity it is usual to treat concurrently for the
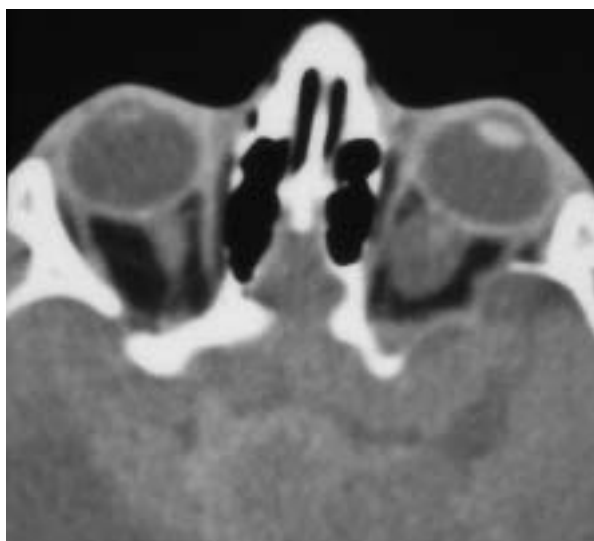

Fig. 6.46 Optic glioma producing sexual precocity in a male with neuro bromatosis. Thickened left optic nerve.
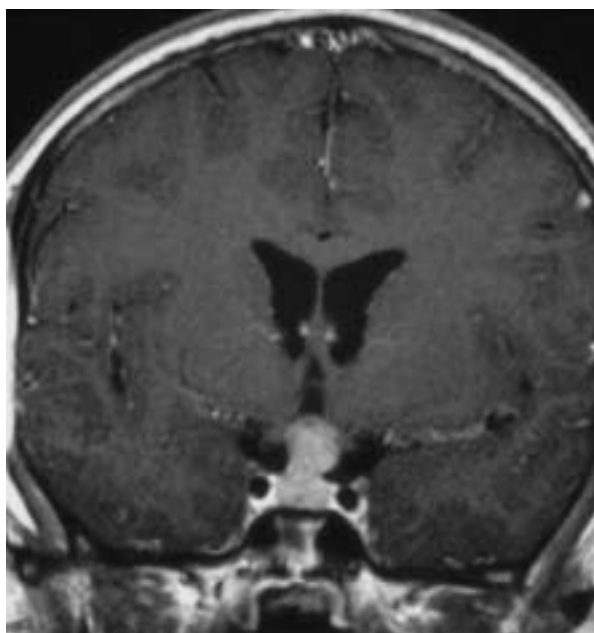
Fig. 6.47 Chiasmatic tumor in boy with precocious puberty.

first 6 weeks with the oral sex-steroid synthesis blocker, cyproterone acetate (100 mg/m² body surface per 24 h, divided into two or three doses). (Cyproterone acetate alone can be used as prolonged therapy for sexual precocity but, whilst effective in stopping the progress of pubertal development, it does not influence final height. It may have associated side effects such as fatigue, and biochemically it leads to hypocortisolism so that a stress regimen of glucocorticoids is necessary.)
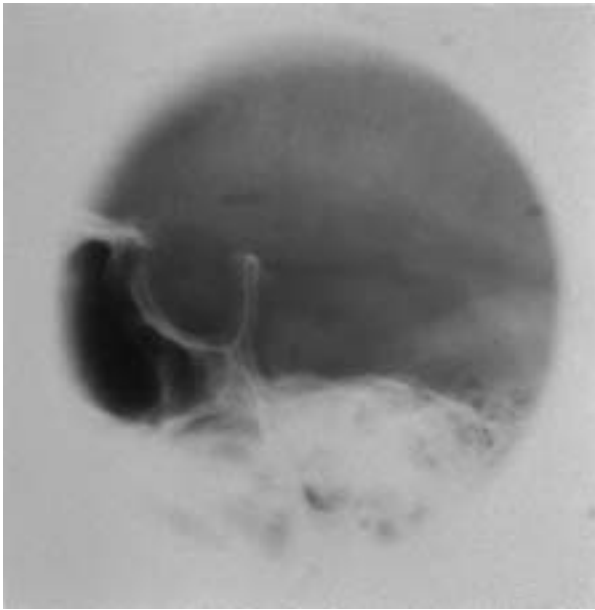
Fig. 6.48 Massive enlargement of pituitary fossa secondary to prolactinoma.

Fig. 6.49 Lactorrhea in a male with a prolactinoma.

GnRH analog treatment is continued until the final height prediction has become acceptable and the child's peer group is showing pubertal changes. Puberty will then continue from the point of initiation of therapy and there are currently no long-term recognized side effects.

Testotoxicosis and the McCune–Albright syndrome, both being gonadotropin independent, will not respond to LHRH analog treatment and hence cyproterone acetate or ketoconazole (which blocks several steps in adrenal steroid synthesis, including testosterone) represents the most reasonable choice of therapy. If the bone age has been pushed much past 12 years by these conditions, central puberty will supervene and additional GnRH treatment may be necessary.

Pseudo-precocity secondary to tumorous sources of sex steroids requires expert oncologic and surgical intervention. Any of the forms of CAH presenting with virilization with or without hypertension are treated with steroid replacement, as should late presenting non-classic 21-hydroxylase deficiency (see Chs 8 & 11). If true central precocity has supervened, LHRH analogs are additionally required.

Adrenarche is benign, although of cosmetic importance, as is isolated hirsutism. Later polycystic ovaries may require treatment to regularize periods. In the older patient anti-androgens combined with a contraceptive preparation could be considered under careful supervision. Excess hair can be treated with depilatory creams and electrolysis. Skin cleansers and topical antibiotic preparations may ameliorate acne.

Thelarche usually requires no intervention, although a progressive FSH dominant form ('thelarche variant') is sometimes treated with LHRH analogs, with limited success.

Idiopathic gynecomastia is best treated by an experienced plastic surgeon, because the results of medical therapy are disappointing.