NORMAL DEVELOPMENT OF THE GENITALIA

For the purpose of this book, only a few aspects of genital development will be highlighted to facilitate understanding of the various disorders.

A crucial point is that the external genitalia develop 'automatically' in the female direction unless there is testosterone activity in a critical period between 4 and 12 weeks of gestation. Furthermore, the Müllerian ducts develop into the uterus and fallopian tubes unless Müllerian inhibiting factor (MIF) is produced and is effective. Both hormones are produced only by the testis. Therefore the testis and the two hormones it produces are essential for the development of the genitalia, while the ovary and estrogens do not appear essential in that period.

The primitive gonads condense from the genital ridges and are populated by germ cells that have migrated in from the yolk sac. Factors transcribed from autosomal chromosomes (chromosome 11, WT1; chromosome 9, SF1; chromosome 17, SOX9; chromosome 2, LHR) help control the early process of gonadal development. A gene on the X (short arm) chromosome, DAX1, acts as an anti-testis factor if present in a 'double dose'. Thereafter the presence of one gene, called testis determining gene (TDG or SRY), which usually resides on the Y chromosome, leads to the development of the undifferentiated gonad into a testis (Fig. 8.1). SRY is a 240 amino acid transcription factor active for only 36 hours of embryogenesis. A further gene, encoding spermatogenesis factor (SGF), is required for normal Sertoli cell function.

Therefore, several disorders at the chromosomal level can prevent the testis from differentiating. These disorders include duplication of DAX1, campomelic dwarfism (SOX9 mutation (Fig. 8.2), Leydig cell agenesis (LHR mutation), Drash syndrome (WT1 mutation) and mosaicism of the sex chromosomes (e.g. 46XY/45X in mixed gonadal dysgenesis, and many others). Translocation of the TDG to another chromosome, for instance an X chromosome (XX males; Fig. 8.3), and deletion of the TDG (XY female). At a more subtle scale, abnormalities of TDG (deletions, mutations) also lead to insufficient differentiation of the testis (XY females with gonadal dysgenesis). These disorders (which may be generalized, chimeric or localized to the gonads) can lead to either an undifferentiated gonad or a dysgenetic testis. A combination of testicular and ovarian tissue, as seen in true hermaphroditism, may have many complex causes including tissue mosaicism and chimerism, causing XX- and Y-containing tissue to be expressed simultaneously in the gonads.

After differentiation the normal testis produces testosterone, inhibin and MIF. Inhibin B is a glycoprotein that feeds back to the pituitary to inhibit the secretion of follicle stimulating hormone (FSH). Its presence can serve as a useful marker of the presence of gonadal tissue. The presence of MIF leads to regression of the Müllerian ducts. If MIF production does not occur in the presence of a normal testosterone secretion, for example due to agenesis of Sertoli cells or a mutation in the MIF gene, the Müllerian duct develops into a uterus while the external genitalia are those of a normal male (Fig. 8.4). As would be expected, MIF receptor abnormalities lead to a similar persistent Müllerian duct syndrome as is seen in MIF gene mutations or deletions.

The presence of testosterone normally leads to male differentiation of the external genitalia and development of the wolffian ducts. If testosterone production does not occur, the external genitalia do not develop in the male direction and the Wolffian duct does not develop into the internal male duct (vas deferens). Lack of testosterone production may be due to agenesis of the Leydig cells, luteinizing hormone (LH) receptor mutations, an inability of Leydig cells to produce testosterone (SF1 mutations and enzyme deficiencies of testosterone biosynthesis, which are common to the testis and adrenal gland) or a lack of stimulation of testosterone secretion as a result of insufficient production or action of placental human chorionic gonadotropin (hCG) and pituitary gonadotropins.

Although directly active on embryonic Wolffian structures and muscle, testosterone can exert its effect on the external genitalia only if it is converted to dihydrotestosterone (DHT) within the target cells by 5α-reductase. DHT is subsequently bound to an
androgen receptor and acts on the nucleus to exert its effects on the synthesis of virilizing proteins. Therefore, even if testosterone is produced normally, there can be disorders at the enzymatic, receptor and post-receptor level causing complete or partial insensitivity to the hormone.

For instance, if the converting enzyme (5α-reductase) is absent or mutated there will be incomplete virilization, but because 5α-reductase is present in at least two isoforms, which are differentially expressed with age, an initially externally phenotypic female may undergo masculinization at puberty.

If the androgen receptor is absent or mutated, or if there are post-receptor disorders, the external genitalia will be either completely female or masculinized to an extent determined by the completeness of the defect – complete or partial androgen insensitivity syndrome (formerly called testicular feminization).

The commonest cause of excessive testosterone production leading to virilization in the female is congenital adrenal hyperplasia (CAH). Cortisol secretion is regulated in a classic feedback loop with adrenocorticotrophic hormone (ACTH), and hence if cortisol secretion is blocked by any enzymatic deficiency in the adrenal there is no negative feedback, and increased ACTH secretion leads to an enlargement of the adrenal and over-secretion of steroid precursors and steroids not on the affected pathway (Figs 8.5 & 8.6).

Of all the possible adrenal enzyme deficiencies, 21-hydroxylase deficiency is by far the most frequent, with an incidence of between 1 in 5000 and 1 in 20 000 births, depending on the population. There are two clinical variants of the ‘classic’ condition: the simple virilizing form and the salt-wasting form. (There is also a late-onset ‘non-classic’ subtype with less prominent clinical features.) Copies of the gene CYP21 and its inactive pseudogene CYP21P are carried on chromosome 6p and are closely linked to the human leukocyte antigen (HLA) type of the individual. The gene may
be deleted, inactivated by a point mutation or converted to a pseudogene during cross-over. The defect is expressed in only the zona fasciculata in the simple virilizing form, and in both the fasciculata and glomerulosa in the salt-wasting form. The salt-wasting form is strongly associated with HLA types BW47 and DR7. Similar variation in the expression of salt loss or the balance of over- or under-virilization seen, for instance, in 3β-hydroxysteroid dehydrogenase deficiency is presumably explained in a similar fashion.

The mechanism of synthesis of testosterone is the same in the adrenal and the testes. Enzyme deficiencies on this pathway leading to cortisol deficiency will thus lead to male pseudo-hermaphroditism with adrenal hyperplasia. Defects ‘lower down’ the pathway (after 17, 20-desmolase) will have no effect on cortisol production and present with simple under-virilization.

Dehydroepiandrosterone is relatively overproduced in adrenarche (see chapter 7) and in tumors. It is also metabolized by the placenta to estriol, which appears in the maternal urine and can serve as a surrogate marker for fetal adrenal function.

GENDER IDENTITY

Every individual, whatever the disturbance in the process of genital differentiation, develops a gender identity, i.e. feels himself or herself to be a male or female. This gender identity is based partly on the physical appearance of the external genitalia but also on the poorly understood effects of antenatal hormone exposure on the brain, and other unknown factors.
The genital appearance largely determines the initial behavior of the parents and, to an extent, that of young children themselves. Gender-specific behavior may be observed during early childhood, for instance in the masculinized play behavior of girls with CAH. There may be subsequent readjustment of perceived gender identity and sexual behavior by the child at puberty, or later. A schematic picture of the development of gender identity is shown in Fig. 8.7.

In cases in which the physical appearance of the external genitalia is ambiguous, a decision about the sex of rearing has to be made by the parents and pediatrician in the best interests of the child. The diagnosis and the long-term need for surgery (which may be on several occasions) and medication should be discussed. The likelihood of testosterone responsiveness and the size of the phallus are important, although there are reports of good male sexual function with extremely small phallus size. A normal female phallus is very difficult to create surgically. It may be possible to predict later fertility, but current advances in fertility preservation and in vitro methods may make this advice less certain. The least predictable aspect relates to the likely gender identity of the child and future sexually functioning adult. There is a strong argument for doing as little irreversible as possible in the early years that is compatible with good health and social functioning, and to allow the competent older child to decide the issue. However, this may present practical difficulties at school, and some early surgical or medical intervention may still be required.

Clitoral reduction and later vaginoplasty can produce acceptable appearance and function in the severely masculinized XX individual (e.g. with CAH), who will be fertile. There are, however, increased problems with sexual identity, and some women request gender reassignment as adults.
There are four groups of intersex disorders based on the appearance of the gonads.

1. **Undifferentiated or absent gonads**

Abnormal gonadogenesis may occur with or without chromosomal abnormalities. There is some confusion about the classification if gonadal dysgenesis is associated with an XY chromosomal pattern: some authors classify these forms in the group of male pseudo-hermaphroditism and others in the group of undifferentiated gonads; in the present classification only the gross abnormalities of the gonads (XY pure gonadal dysgenesis, congenital anorchia (vanishing testes)) are included in this group. If all or part of the short arm of the X chromosome is duplicated, it is possible to have an XY karyotype but two doses of the DAX1 gene. This acts to suppress testicular formation and leads to under-virilization and variable persistence of Müllerian structures (Fig. 8.8).

2. **True hermaphroditism**

This involves the presence of both ovarian and testicular tissue (Figs 8.9–8.11); any pattern of sex chromosomes can be found in these cases.

3. **Male pseudo-hermaphroditism**

This condition – insufficient masculinization in the presence of a testis – can be due to absent testes,
absent biosynthesis, target organ resistance, or other effects.

**Absent testes**
- Insufficient stimulation by gonadotropins: hypopituitarism or isolated gonadotropin deficiency (Fig. 8.12), which may be part of a syndrome (Fig. 8.13). The association of isolated gonadotropin deficiency with anosmia is called the Kallmann syndrome. These defects present more commonly with isolated micropenis, but testicular development can sometimes be so poor that incomplete virilization occurs.
- Leydig cell agenesis and LH receptor mutations.
- Drash syndrome with nephritis and later Wilms tumor due to WT1 hemizygosity.

**Absent biosynthesis**
- Disturbed androgen synthesis, because of enzymatic disorders: StAR (steroid acute

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**Fig. 8.8** DAX1 duplication leading to severe undervirilization.

**Fig. 8.9** True hermaphrodite. Right-sided descended testis, internal left ovo-testis, hypospadias.

**Fig. 8.10** Histology of gonad in true hermaphroditism showing ovo-testis. Ovarian tissue is shown as dense stroma with oocytes; testicular tissue shows tubule formation. Peripheral blood karyotype 46XX. Skin and gonad showed chimeric 46XX–69XXY karyotype.

**Fig. 8.11** External genitalia of same case.

**Fig. 8.12** Micropenis and cryptorchidism in panhypopituitarism. Infant had cleft palate and developed hypoglycemia.
regulatory protein; Figs 8.14 & 8.15) deficiency also called congenital lipoid hyperplasia, 17α-hydroxylase, β-hydroxysteroid dehydrogenase (Fig. 8.16), 17, 20-desmolase, 17-ketosteroid reductase (Figs 8.17–8.21) (also called 17β-hydroxysteroid dehydrogenase deficiency).

Smith–Lemli–Opitz syndrome with genital ambiguity in the male, cleft palate and digital abnormalities (see Figs 1.30 & 1.69).

Reduced 5α-reductase activity (Fig. 8.22).
Target organ resistance

- Androgen insensitivity syndrome (complete or partial): androgen receptor or post-receptor defect (Figs 8.23–8.25).

Other

- Timing defect (late hormonal secretion *in utero*).
- Isolated MIF deficiency.
- Maternal ingestion of anti-androgens.
- Idiopathic.

4. Female pseudo-hermaphroditism

Excessive masculinization in the presence of ovaries is by far the commonest cause of abnormal genitalia. It may be subclassified as:

- CAH; 21-hydroxylase (accounting for 90% of all intersex conditions), 11β-hydroxylase (approx. 5%) or 3β-hydroxysteroid dehydrogenase deficiency (approx. 1%).
- Excess of maternal androgens either as ingestion of androgens (or 19-nortestosterone-derived...
progestagens) or virilizing tumors, luteomas and maternal CAH.

- Non-specific, associated with other congenital anomalies.
- Idiopathic.

Additionally isolated micropenis and cryptorchidism are considered in this chapter.

**DIAGNOSTIC WORK-UP OF INTERSEX CONDITIONS**

**HISTORY AND CLINICAL EXAMINATION**

As with most congenital defects, the history should concentrate on maternal health, pregnancy details and family history:

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**Fig. 8.22** 5α-Reductase deficiency.

**Fig. 8.23** Partial androgen insensitivity with descended testes in bifid labio-scrotal folds.

**Fig. 8.24** Less severe partial androgen insensitivity with severe hypospadias and maldescent of testes.

**Fig. 8.25** Partial androgen insensitivity syndrome at adolescence, male sex of rearing – note gynecomastia from peripheral aromatase conversion of testosterone to estrogen. Abundant pubic hair implies only partial resistance.
Figs 8.26–8.33 Stages of masculinization in 21-hydroxylase deficiency from relatively minor to complete.
Symptoms of virilization in the mother.
■ Drugs during pregnancy.
■ Unexplained infant deaths.
■ Genital ambiguity, short stature or pronounced hirsutism in the family.
■ Parental consanguinity.

The physical examination should include a thorough inspection and palpation of the external genitalia, blood pressure (raised in 11β-hydroxylase deficiency) and a search for other congenital anomalies. Ambiguous genitalia include the whole spectrum from the normal male to normal female genitalia. Five intermediate stages have been distinguished by Prader (Figs 8.26–8.33). Any abnormality of the external genitalia should lead to further investigations, including apparently normal female genitalia with palpable gonads in the labia or inguinal area, females with bilateral inguinal hernias or apparently normal males with impalpable gonads. Male infants with CAH may show signs of excess testosterone production by an increase in scrotal pigmentation and a slight increase in penis size (Figs 8.34 & 8.35); these signs are often missed, however, and then the presentation is as collapse with hyponatremia and acidosis or, in non-salt losers, as the ‘infantile Hercules syndrome’ (see Ch. 11).

In cases of female pseudo-hermaphroditism the mother should be examined for signs of virilization and hypertension that would indicate a maternal source of testosterone.

**Interpretation of the clues**
If gonads are palpable externally, there is at least a TDG (testis determining gene) present, usually on a Y chromosome. (A proportion of patients with complete androgen insensitivity syndrome will present with apparently normal female external genitalia but bilateral hernias that contain testes.) Otherwise, in the absence of obvious maternal pathology or family history, it is not wise to try to base a diagnosis on external appearance alone. Further elucidation will come from investigation in specialist centers.

**INVESTIGATIONS**

**Karyotype**
Many laboratories can provide a result at least on the presence or absence of a Y chromosome within a few days. The final result of the karyotype may take several weeks. (Buccal smears can be taken and investigated for the presence of Barr bodies. If seen, at least two X chromosomes are present. This investigation should be abandoned if rapid chromosome testing is available.)

Further investigations are determined by the karyotype.

**XX karyotype**
- Biochemical assessment should include several estimations of serum sodium and potassium concentrations; some forms of CAH can lead to salt loss, which is not always present in the first weeks.
- Kidney function should be checked to detect any associated renal disorders and, if suspected, in addition to ultrasonography, a renogram or intravenous pyelogram (IVP) should be obtained.
- The anatomy of the internal genitalia is investigated by ultrasonography (to check for gonads, uterus and vagina) and a contrast examination of the urogenital sinus – a cervical imprint seen with a contrast examination proves

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**Fig. 8.34** Male genitalia in 21-hydroxylase deficiency.

**Fig. 8.35** Male genitalia in 21-hydroxylase deficiency.
the presence of a uterus (Figs 8.36 & 8.37) that may not be apparent on ultrasonography.

- Cystoscopy may be performed to evaluate the urethra and bladder.
- Laparoscopy may allow for the further differentiation of internal anatomy and direct visualization of the gonads, along with possible gonadal biopsy.

- Plasma 17α-hydroxyprogesterone concentration is raised in the commonest form of CAH, 21-hydroxylase deficiency (see Fig. 8.6). Additionally levels of testosterone, androstenedione and dehydroepiandrosterone (DHEA) will be increased and are responsible for the virilization that occurs. Cortisol production will be diminished and in 80% of cases there will be salt losing secondary to aldosterone deficiency.

- In 11β-hydroxylase deficiency, plasma deoxycorticosterone (DOC) concentration will be raised in addition to the above androgens (and there will be hypertension due to the salt-retaining properties of DOC). Cortisol production will be diminished.

- In 3β-hydroxysteroid dehydrogenase deficiency there will be salt losing and cortisol deficiency with an increased DHEA concentration. The level of pregnenolone will be raised and a urinary steroid profile will show a characteristic increase in pregnenediol and pregnenetriol concentrations. This deficiency can cause both male and female pseudo-hermaphroditism, presumably depending on the activity of accessory pathways of testosterone synthesis from DHEA.

- Occasionally a urinary steroid profile, plasma steroid levels, ultrasonography and radiography will have to be performed on the mother to determine the source of androgens in an infant virilized secondary to a maternal cause.

**XY karyotype**

- Measurements of serum levels of testosterone, DHT and its steroid precursors androstenedione and DHEA should be performed, both before and after one hCG injection of 1500 units i.m (see Appendix). A normal testosterone rise excludes Leydig cell agenesis and enzymatic disorders of testosterone biosynthesis, and is more compatible with a partial androgen insensitivity syndrome (as an individual with the complete syndrome will have phenotypically normal female genitalia: Fig. 8.38). The ratio between testosterone and its precursors indicates the precise level of enzyme defect in disorders of testosterone biosynthesis (see Fig. 8.5): a high ratio (>1.25) between androstenedione and testosterone indicates 17β-hydroxysteroid dehydrogenase deficiency; a high DHEAS concentration indicates a 3β-hydroxysteroid dehydrogenase defect; very low levels of 17α-hydroxyprogesterone, androstenedione and testosterone in the
presence of high progesterone levels indicate 17α-hydroxylase deficiency; high progesterone and 17α-hydroxyprogesterone levels with low androstenedione and testosterone levels indicate a 17, 20-desmolase deficiency. Very low levels of all steroids are seen in Leydig cell aplasia and when the first set of proteins that transports cholesterol from the mitochondrion outer leaflet to the inner one to allow the desmolase enzyme system to cleave the side chain (StAR) is deficient. If the level of testosterone increases and there is little or no rise in DHT (T: DHT ratio >25) then the defect has in the conversion of testosterone to DHT by 5α-reductase.

- The sex hormone binding globulin (SHBG) response to the anabolic steroid stanozolol can be used to estimate the degree of androgen insensitivity (unfortunately the test is reliable only after 4 months of age). In normal individuals there is a 50% reduction in SHBG concentration from the baseline 4 days after a 3-day course of treatment (0.5 mg/kg). In complete androgen insensitivity syndrome there is no response or even a slight rise in the level. Those with a fall of less than 20% will probably not respond sufficiently to later treatment to be raised successfully as males.
- It is possible to search for duplication of \(DAX1\), and mutations of \(WT1\), \(SFI\), \(SOX9\) and the LH receptor \(LHR\) genes in cases where there has been an early failure of testicular development.
- Genital skin fibroblasts can be obtained for assay of androgen receptor levels and elucidation of post-receptor defects in specialist units. Fibroblast karyotyping should also be performed (preferably from the skin as well) to exclude tissue mosaicism.
- Hematuria and proteinuria are seen as early as the first day of life in Drash syndrome.
- 7-Dehydrocholesterol levels are raised in Smith–Lemli–Opitz syndrome.
- Anti-Müllerian hormone (MIF) can be assayed in cases of persistent müllerian duct syndrome and also gives a clue as to the presence of functioning testicular tissue.

**True hermaphrodites**

In true hermaphroditism, and in the presence of a Y chromosome with internal genitalia and female sex of rearing, laparoscopy is indicated to inspect the internal genitalia (gonads and uterus) and to biopsy or remove gonadal tissue incompatible with the assigned sex. Tissue karyotyping should again be performed.

**THERAPY**

From the outset the physician should explain to the parents that there is some doubt concerning the sex of the infant and that further investigations are needed. The parents must be told to delay registration of the child until there is a degree of certainty about the sex of rearing. Psychologic support and counseling are essential and much attention should be directed towards this neglected aspect of care. Preferably a psychologist or social worker should be involved.

**FEMALE SEX OF REARING**

Therapy is dependent on the precise diagnosis. If a female sex is assigned and the clitoris is enlarged, then cliteroplasty should be considered, preserving the venous and nervous supply to the glans (Figs 8.39 & 8.40). Alternatively, if a less permanent approach has been recommended, the clitoris may be ‘buried’. If there is complete or partial fusion of the labial folds, either a one-stage or two-stage operation schedule can be designed. Highly specialized surgeons tend to perform vaginoplasty early in life, and to ensure connection to the uterus, if present (e.g. in CAH). A drawback is that regular dilatation may be needed in childhood. Others may perform initial cliteroplasty together with a separation of the fused labia, and at puberty perform vaginoplasty and connection to the uterus, if required. The vagina can be widened by regular use of dilators in collaboration with a gynecologist.

In all cases of CAH, treatment with hydrocortisone is indicated to suppress ACTH levels and to maintain normal growth rate and skeletal maturation. This
treatment and its monitoring are highly specialized and should be confined to experienced centers. Some authorities recommend the use of regular multiple daily profiles of blood or salivary $\alpha$-hydroxyprogesterone and androstenedione along with plasma renin activity to monitor control (by confirming day-long suppression). Othersonly use regular (at least 6-monthly) measurement of bone age coupled with accurate estimations of height velocity to monitor control: a raised height velocity (>50%) and rapidly advancing bone age (>chronological advance) demonstrate under-treatment; a low height velocity usually indicates over-treatment or other pathology (Figs 8.41 & 8.42).

In neonates with 21-hydroxylase deficiency the hydrocortisone dosage is often close to 30 mg/m$^2$ daily. Later it can gradually be decreased to 15–25 mg/m$^2$ daily, and 12–15 mg/m$^2$ daily from 2 years onwards. Hydrocortisone should be divided as a three times a day dose, usually with 50% given on waking to mimic the normal diurnal secretion of cortisol.

In forms of CAH in which salt loss is present, either clinically or subclinically (i.e. detected only by raised plasma renin activity (PRA) levels; see Ch. 11), then 9α-fluorocortisone (fludrocortisone acetate) should be added at a dose of between 0.03 and 0.12 µg per day. The dose should be adjusted by measurement of blood pressure and PRA (raised PRA levels mean that the dosage should be increased; a low PRA concentration indicates over-treatment). At the time of diagnosis, in hot weather and in some severely affected individuals, sodium chloride, 1 g per 10 kg body weight, may also be needed. Adequate salt and mineralocorticoid replacement is necessary to achieve satisfactory overall control.

If there is presence of even a portion of a normal ovary then secondary sex characteristics should develop at puberty (although fertility will be less certain). In cases of prolonged exposure to high androgen levels, for instance in late-presenting CAH, a polycystic change may occur in the ovaries leading to dysmenorrhea and later hirsutism even in the presence of adequate replacement therapy (see Fig. 6.33). If no ovarian tissue is present, estrogen treatment is necessary from around 10 years of age (see Ch. 7).

In the more complete forms of androgen insensitivity syndrome, the testes are removed either in early life or after puberty, as there is an increased risk of later malignancy. The presence of testes at puberty allows for some normal female sexual development without medication as testosterone is converted by aromatase to estrogen. However, the risk of malignancy before puberty, although very low, may still be considered too high to accept, and gonadectomy is increasingly performed in early life. Estrogen treatment is then necessary for the development of female secondary characteristics (see Ch. 7).

MALE SEX OF REARING

To normalize the external genitalia initially, a hypospadias repair may need to be performed in one or several stages, depending on the severity of the defect (Fig. 8.43). Vaginal remnants and any internal female structures can also be removed. Three-month courses of gonadotropin releasing hormone (GnRH) analogs or hCG can be used to attempt to induce

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**Fig. 8.39** Late presenting simple virilizing 21-hydroxylation deficiency (height + 1.8 SDS, chronologic age 7.5 years, bone age 14.7 years) – before clitoroplasty.

**Fig. 8.40** Same patient as in Fig. 8.39 after clitoroplasty. In this case the vaginal orifice was adequate and no later surgery was required. (The stage 5 pubic hair has been shaved off.)
testicular decent; however, at least 80% will still require surgery. Orchidopexy, again in one or several stages, should bring the testes to the scrotum, if possible. If the testes are internal and there is no possibility of successful orchidopexy to bring them to a position where they can be examined externally, then careful consideration should be given to gonadectomy to remove the potential risk of later undetected malignant change.

Testosterone injections (25 mg testosterone esters i.m. every 3 weeks on three occasions) can be given to increase the infant’s penile size. Topical testosterone cream, 2.5% for 3 months, may also prove effective (but if applied by female care-givers, they must wear gloves).

At puberty, in the absence of functioning testes, testosterone replacement treatment is required. A mixture of testosterone esters given as a depot intramuscular injection is commonly used, which gives acceptable testosterone levels for about 3–4 weeks. This treatment is started at approximately 12–13 years of age, and the dosage is slowly increased from 50 to 250 mg every 3–4 weeks. Testosterone buccal lozenges, transdermal patches and gel are becoming available as alternative modalities of application. Even a relatively small, damaged testicular remnant may be able to

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**Fig. 8.41 Simple congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency in a male.**

Bone age 5.6 years at 4.7 years of age with height –2 SDS, within target range but with evidence of early virilization. With hydrocortisone replacement therapy there is an improvement in height to –0.9 SDS, within the target range and a gradual normalization of the bone age.
produce sufficient testosterone to allow spontaneous (see Fig. 7.3) virilization, although fertility will be unlikely. Intracytoplasmic sperm injection (ICSI) is being used in some centers to allow fertilization from small damaged testes.

In cases due to forms of CAH, replacement therapy as outlined above should be commenced at diagnosis.

**MICROPENIS**

Micropenis is defined as a stretched penile length of more than 2 SD below the average for age. This equates to less than 2 cm at birth and less than 4 cm before normal puberty. The stretched penile length is measured by taking a wooden spatula and pressing it alongside the penis on to the pubic bone. A mark is then made at the level of the top of the penile glans, and the length measured (Fig. 8.44). This procedure is to ensure that the part of the penis that is buried in the subcutaneous fat is being measured. A ‘hidden’ penis may be misdiagnosed as micropenis unless this technique is used.

**Fig. 8.42** Congenital adrenal hyperplasia in a female subject presenting with ambiguous genitalia. There is evidence of undertreatment between 5.5 and 7.4 years with an advancing bone age and increased height velocity indicating non-suppression of testosterone levels. There is subsequent regaining of control with gradual improvement of height prediction but a mildly reduced adult height (–0.5 SDS) in relation to the target range (+0.2 SDS).
ETIOLOGY
Micropenis can be caused by hypogonadotropic hypogonadism, either isolated or in combination with other pituitary deficiencies, especially growth hormone (GH) deficiency. It is also seen in cases of primary hypogonadism and in incomplete forms of the androgen insensitivity syndrome.

DIAGNOSTIC WORK-UP
Initially exclude pituitary dysfunction. This can be done by measuring serum free thyroxine (T₄) and thyroid stimulating hormone (TSH), as well as the serum cortisol level at 0900 hours (before 3 months of age there is no circadian rhythm, and three or four random levels or a Synacthen test can be used as a substitute). Low basal values are suggestive of other pituitary problems. If hypoglycemia occurs (see Ch. 11), take blood for cortisol and GH estimation. If the cortisol value is abnormally low, the diagnosis is likely to be hypopituitarism without the need for further stimulation tests. A rise in GH concentration in response to hypoglycemia may not always occur in the neonatal period and the GH axis should thus be re-evaluated if there is evidence of later faltering of growth.

If the infant is seen between birth and 4 months of age, a basal serum testosterone measurement is useful, as in this period there is a physiologic rise with a peak at 8 weeks. A normal testosterone level rules out a serious disorder of testicular androgen secretion. Also during the first 4 months (and in the pubertal age range), measurements of basal serum LH and FSH may be useful. Grossly increased values indicate primary gonadal failure, and undetectable levels indicate the need for further testing.

At any other age, or if the baseline testosterone level is low or inconclusive, a short hCG test is performed, measuring testosterone and DHT levels 3 days after the injection (see Appendix). A rise in testosterone and DHT indicates normal testicular function and 5α-reductase activity.

Outside the first 4 months basal levels of LH and FSH are also not very helpful and, although an LHRH test can be performed (see Appendix), the results often do not provide certainty about the differentiation between hypogonadotropic hypogonadism and normal function (see Ch. 7).

THERAPY
Micropenis should be treated by a series of three or four depot intramuscular injections of testosterone esters or topical testosterone, as described above. In infants and small children the injectable dosage is 25 mg (and larger doses can be given at puberty). If the micropenis is associated with cryptorchidism, it may be more appropriate to use hCG or gonadotropins for 2–3 months to try to achieve testicular descent and penile growth from endogenous secretion of testosterone (see below). If there is poor response in terms of growth of the penis, a form of androgen insensitivity is likely, and in extreme cases a lack of response in infancy may give rise to reconsideration of the decision about sex of rearing, although sexual function is often adequate. Late presenting cases who respond poorly have the unsatisfactory options of augmentative surgery or gender reassignment.

CRYPTORCHIDISM

ETIOLOGY
If the testes are impalpable in a phenotypic male, the possibility of an XX individual with severe female pseudo-hermaphroditism should always be considered
first. Congenital anorchia may occur after the production of MIF has occurred, presumably as a result of late in utero torsion (Fig. 8.45) or infarction.

Simple cryptorchidism is, however, common. In premature babies, the testes can still descend during the first year of life. Cryptorchidism may be caused by either mechanical factors or a failure of the normal hormonal environment. Rarely it may be due to mutations of a gene, RLF (relaxin-like factor), which controls gubernacular contraction.

Cryptorchidism is seen with increased frequency in:

- gonadotropin deficiency.
- testicular dysgenesis, including chromosomal abnormalities.
- association with other congenital malformations and syndromes.

**DIAGNOSTIC WORK-UP**

**Medical history and physical examination**

The history should concentrate on maternal health and treatment during pregnancy, mode and time of delivery, and family history of genital abnormalities. In later presenting cases enquiry should be made regarding the sense of smell and mental development (see Ch. 7).

The physical examination should exclude other dysmorphic features or malformations and be performed in both the supine and squatting positions. The maximal descent of the testes is noted, and the ease of retraction after manipulation. Highly retractile testes can mimic maldescent.

**Interpretation of the clues**

Impalpable testes:

- With no other abnormalities = simple cryptorchidism, anorchia, female pseudohermaphroditism.
- With micropenis, with or without hypospadias = partial androgen synthesis or insensitivity syndromes.
- With anosmia and micropenis = the Kallmann syndrome.
- With intellectual impairment or dysmorphic features = syndromic abnormality.
- With micropenis and/or midline defects = gonadotropin deficiency.
- Above features plus neonatal hypoglycemia = multiple pituitary hormone deficiency.
- With tall stature (testes may be high in the inguinal canal and small and firm) = Klinefelter syndrome.

**THERAPY**

Orchidopexy is performed if there is cryptorchidism with no possibility of descent when assessed by an experienced surgeon. The optimal time for operating is debated, but surgery is usually performed at around 2–3 years of age. If there is any doubt about the possibility of descent, and in cases of presumed central gonadotropin deficiency, a course of hCG can be given (500 units twice a week i.m. for 5 weeks at 1–6 years of age, and 1000 units twice a week in later childhood). If there is no satisfactory result, surgery is necessary.

**MISCELLANEOUS GENITAL ABNORMALITIES**

Many variations on normal anatomy exist in both sexes. They are usually spontaneous malformations, although they may be associated with other syndromic abnormalities.

Hernias are common in males but, occasionally, may unexpectedly contain müllerian structures (Fig. 8.46). The male may have a shawl scrotum of varying severity (Figs 8.47 & 8.48), with or without a bifid appearance (Fig. 8.49). The shaft of the penis may be completely within the scrotal skin and require operative release. These abnormalities may be isolated or exist as part of a chromosomal abnormality or eponymous syndrome.

Hypospadias and epispadias are usually isolated, but severe hypospadias (Fig. 8.50) may represent the incomplete form of androgen insensitivity syndrome. Other bizarre abnormalities, including reversed genitalia (Fig. 8.51) and trifid scrotum (Fig. 8.52) may also occur.

In the female there may be complete absence of the uterus and vagina (Fig. 8.53). The hymen may be
Fig. 8.46 Large inguinal hernia containing testis and Müllerian duct structures.

Fig. 8.47 Shawl scrotum (moderate).

Fig. 8.48 Shawl scrotum (severe).

Fig. 8.49 Bifid scrotum.

Fig. 8.50 Severe hypospadias and micropenis, 46XY.

Fig. 8.51 Reversed male genitalia.
imperforate (Fig. 8.54) or there may be a transverse vaginal septum, both of which may present early with distension or late with hydrocolpos (Figs 8.55 & 8.56) or primary amenorrhea (Figs 8.57–8.59). If vaginal abnormalities are associated with renal and/or skeletal abnormalities, this forms the Rokitansky syndrome (Fig. 8.60).

Labial adhesions are a common finding and of no pathologic significance (Fig. 8.61). They resolve spontaneously and surgical intervention should be discouraged. Topical treatment with estrogen cream will result in resolution but with local pigmentation as a side effect. Attempts at parting the adhesions are often painful and result in readhesion.

**GONADAL TUMORS**

**OVARIAN**

Large cysts may present with torsion as an abdominal emergency or as a palpable mass (see Figs 6.34, 6.35 & 10.9). They may be seen as incidental findings (Figs 8.62–8.64). Because hemorrhage into an incompletely ruptured follicle can mimic tumor, it is important to re-scan at a different stage in the cycle (Fig. 8.65) before causing concern in the menstruating female.

Only about 1% of childhood malignancies are ovarian in origin, although other tissues in the pelvis can give rise to lesions (neuroblastoma, sarcoma, adenocarcinoma). Patients with ovarian lesions may present with sexual precocity (see Ch. 6), which can be iso- or hetero-sexual. Germ-cell tumors (dysgerminoma, endodermal sinus tumors, embryonal carcinoma, immature teratomas, choriocarcinoma and mixed forms) and juvenile granulosa cell tumors may be unilateral or bilateral, and present with hormonal effects, abdominal pain and masses, and vaginal bleeding. Dysgerminomas may occur in abnormal ovarian tissue, such as that found in Turner syndrome with an unsuspected Y-cell line.

Ultrasonography, computed tomography and magnetic resonance imaging are required along with laparoscopic biopsy. Multidisciplinary management is required depending on the histologic findings and stage of the
Fig. 8.55 Hydrocolpos secondary to transverse vaginal septum.

Fig. 8.56 CT scan of same case showing massive hydrocolpos.

Fig. 8.57 Imperforate hymen presenting as primary amenorrhea with abdominal distension.

Fig. 8.58 Same patient as in Fig. 8.57 at operation, showing blueish discoloration of imperforate hymen.

Fig. 8.59 Resulting discharge of old blood following surgical incision of patient in Fig. 8.57.

Fig. 8.60 Rokitansky syndrome.
Tumor markers such as α-fetoprotein, hCG, lactate dehydrogenase (LDH) and carcinoembryonic antigen may be helpful in diagnosis and at follow-up.

TESTICULAR

Testicular tumors are rare in childhood. The majority of testicular tumors arise from germ cells. Undescended testes (especially bilateral) are a risk factor. Any dysgenetic internal testis in the undervirilized male may lead to gonadoblastoma. Dysgerminomas and seminomas also occur in childhood, more in primarily abnormal testes than in normal testes. Adrenal rests may hypertrophy in poorly controlled CAH, leading to palpable scrotal masses.
Prenatal Management of 21-Hydroxylase Deficiency

As 21-hydroxylase deficiency is an autosomal recessive disease, the risk for subsequent siblings of an affected proband is 25%. The most serious consequence of the disorder is the genital ambiguity in females. Therefore it is most important to prevent masculinization of the external genitalia in affected female fetuses. The following strategy has been developed in specialist centers.

Identifying the HLA genotype of the index case and parents along with the restriction fragment length polymorphisms (RFLPs) of the 21-hydroxylase gene or detection of the exact mutation will allow for later identification of affected fetuses in informative kindreds. The mother is instructed to start dexamethasone therapy at a dose of 20 µg per kg body weight per day when she is sure she is pregnant. A chorionic biopsy is performed at 9–10 weeks’ gestation, or amniocentesis at 15–18 weeks, which allows the fetus to be sexed and the HLA type and genotype to be assessed. If the fetus is female and affected, dexamethasone is continued throughout pregnancy; otherwise treatment is discontinued. After birth the infant is carefully reassessed and treatment with hydrocortisone and 9α-fluorocortisone is commenced if the diagnosis is confirmed.