Male Genital Tract

69

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Abstract

Until the 12th week of gestation it is difficult to ascertain the sex of a human embryo based on the appearance of the external genitalia and yet the process is complete by 16–17 weeks. Our understanding of the complexity of the genetic and endocrinological interactions controlling this process continues to develop. There is emerging evidence that penile development has much in common with the development of limb buds. The developmental direction the indeterminate external genitalia take is driven by gonadal development which in turn is controlled by genetic sex determination. Though presented as sequential events, much of this happens in parallel. Between the 4th and 6th weeks the cloaca becomes divided into a posterior anorectal canal and an anterior urogenital sinus by the formation of the urorectal septum, the tip of which will eventually form the perineum. Simultaneously the mesoderm antero-lateral to the developing urogenital sinus expands to create the genital tubercle. When the cloacal membrane ruptures it exposes the floor of the urogenital sinus that will form the urethral plate. The mesoderm on either side of the urethral plate expands to form urogenital folds that extend into the genital tubercle. These are flanked by a pair of labioscrotal swellings. During the 6th week the urethral plate develops into a urethral groove which becomes the penile urethra as a result of fusion of the urogenital folds from proximal to distal, and is usually complete by 14 weeks. The formation of the glanular urethra is still under investigation and it is still unclear if it occurs by tubularization of the endoderm as in the penile urethra or through

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canalization of ectoderm distally. The prepuce itself develops as a result of ectodermal folding and cellular ingrowth resulting in the glans penis and inner prepuce sharing a common mucosal lining which gradually separates over years.

Keywords
Male genital tract • Newborns • Phimosis • Buried penis • Hypospadias
Undescended testes • Varicocoele • Acute scrotum

69.1 Penis

69.1.1 Phimosis

Until the 12th week of gestation it is difficult to ascertain the sex of a human embryo based on the appearance of the external genitalia and yet the process is complete by 16–17 weeks. Our understanding of the complexity of the genetic and endocrinological interactions controlling this process continues to develop. There is emerging evidence that penile development has much in common with the development of limb buds [1]. The developmental direction the indeterminate external genitalia take is driven by gonadal development which in turn is controlled by genetic sex determination. Though presented as sequential events, much of this happens in parallel. Between the 4th and 6th weeks the cloaca becomes divided into a posterior anorectal canal and an anterior urogenital sinus by the formation of the urorectal septum, the tip of which will eventually form the perineum. Simultaneously the mesoderm anterolateral to the developing urogenital sinus expands to create the genital tubercle. When the cloacal membrane ruptures it exposes the floor of the urogenital sinus that will form the urethral plate. The mesoderm on either side of the urethral plate expands to form urogenital folds that extend into the genital tubercle. These are flanked by a pair of labioscrotal swellings. During the 6th week the urethral plate develops into a urethral groove which becomes the penile urethra as a result of fusion of the urogenital folds from proximal to distal, and is usually complete by 14 weeks. The formation of the glanular urethra is still under investigation and it is still unclear if it occurs by tubularization of the endoderm as in the penile urethra or through canalization of ectoderm distally [2]. The prepuce itself develops as a result of ectodermal folding and cellular ingrowth resulting in the glans penis and inner prepuce sharing a common mucosal lining which gradually separates over years.

The penile condition for which most medical opinion/intervention is sought is phimosis, which derives from the Greek phimoo (=muzzle) or phimos (=gag) and the suffix -osis (= process or state). Over the millenia since its original description by the Greeks it's meaning has been extended to include normal physiological states such as a non-retractile prepuce, residual glanulo-preputial adhesions and even 'excessive' or 'redundant' preputial length [3]. This unfortunate confounding with a genuine pathological process such as Balanitis Xerotica Obiterans has resulted in innumerable unnecessary circumcisions and even more unnecessary medical consultations. Rickwood's efforts to restrict the use of the term to BXO are doomed to fail and the more pragmatic approach is to adopt a classification into physiological or pathological phimosis.

Physiological phimosis describes normal anatomical findings that tend to disappear/resolve with growth. At birth a small minority of boys (4%) will have a foreskin that is fully retractable over the head of the penis, a further 54% will have a partially retractable foreskin but in the remaining 42% the glans is not at all visible [4]. The rate of separation of the glans and prepuce is exponential such that 20% of boys had a fully retractable foreskin by 6 months of age, 50% by 1 year, 80% by 2 years and 90% by 3 years. Oster took Gairdner's work and extended to older boys

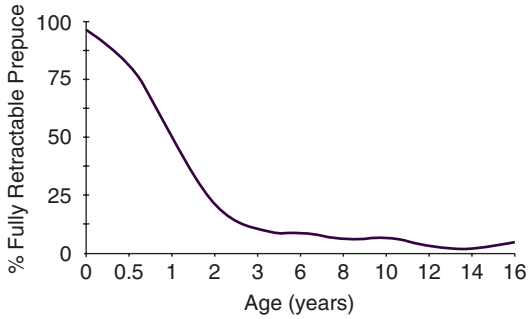

Fig. 69.1 Percentage of boys with a fully retractable foreskin [4, 5]

(see Fig. 69.1) and a significantly larger study population (>9500) of which a subset, 173 boys were reviewed annually for 7 years confirming that they had a similar trend to the graph for the overall population [5]. I would agree with Gairdner that the term 'preputial adhesions' is misleading as it implies that the glans and prepuce were previously separated and have adhered together. This misunderstanding perpetuates the false impression that forcible retraction of the prepuce from an early age is necessary for penile hygiene to clean a space that does not yet exist.

That said physiological phimosis is associated with some pathological and non-pathological processes. Smegma pearls are collections of shed epithelial cells, keratin and natural oils that accumulate in the developing space between the glans and prepuce and present as a mobile, non-tender, non-fluctuant swelling on the penis. Their formation contributes to the natural separation of the prepuce occasionally presenting as a non-offensive 'discharge'. Ballooning on micturition, especially if fusiform along the shaft of the penis, rather than spherical at the base as discussed below, is often a presenting complaint. Hutton and Babu found no evidence of obstructed urine flow when comparing uroflowmetry of uncircumcised boys when comparing those with and without ballooning [6]. After non-retractability the most common reason for referral for circumcision is recurring balanitis often misdiagnosed as recurrent UTIs when in fact it is posthitis! Posthitis is an inflammation of the prepuce, balanitis inflammation of the glans and balanoposthitis inflammation of both. The 'redundancy' of the foreskin encourages retention of urine subpreputially which then develops an ammoniacal dermatitis or inflammation which if left untreated may develop a secondary cellulitis. The initial posthitis, because of its association with dysuria is often diagnosed as a UTI, is best treated with topical barrier agents, simple hygiene advice and patient, parent and GP education.

Paraphimosis is an acquired condition thought to result from failure to reduce a tight foreskin that has been withdrawn over the glans and causes glanular oedema secondary to constriction which then makes spontaneous reduction unlikely. It tends to occur at the extremes of life in children whose foreskin has been retracted 'to clean', post sexual intercourse and in the elderly post urethral catheterization. It is a surgical emergency as failure to reduce has been associated with necrosis, gangrene and necrotising fasciitis. There are a number of treatment options including manual reduction with or without the aid of an ice glove, multiple needle punctures (The Dundee technique) to facilitate evacuation of oedema [7], injection of hyaluronidase or the topical application of granulated sugar [8]. All methods have been shown to work with no comparative studies to demonstrate superior efficacy of any individual technique [9]. That said topical osmotic agents (sugar etc.) take a long time to work and are probably best used where there is a delay in manual reduction [10]. Occasionally surgical intervention in the form of a dorsal slit is required especially where there is a delay in seeking medical attention. Once reduced there are mixed opinions on the merits or necessity of circumcision as recurrence of paraphimosis is notably uncommon.

The majority of cases of pathological phimosis can be attributed to Balanitis Xerotica Obliterans or BXO. More correctly known as penile lichen sclerosis it is a progressive sclerosing condition that affects the prepuce, glans and if left untreated, the urethra. It has a reported incidence of 0.07% [11]. Clinically it is distinguishable from physiological phimosis by virtue of the indurated pallor of the prepuce that prevents retraction of the foreskin in patients presenting in acute urinary retention or with a penile discharge.

However it is rare for referring doctors to make the diagnosis [12]. Its exact aetiology is unknown but it largely occurs in uncircumcised males thought possibly to be due to chronic irritation/inflammation from sub-preputial epithelial debris or an as yet unidentified infectious agent. In the paediatric population at least circumcision is curative in half [12] but may need supplementation with topical steroids especially if the glans/meatus is affected. Glanular lesions usually disappear within 6 months in >99% of patients [13]. Treatment with topical or intra-lesional steroid therapy may be sufficient in milder cases [14]. Topical steroid therapy alone was associated with resolution of symptoms and signs in 17% of boys with mild BXO after 3 months of therapy and this increased to 30% after 17 months [15].

The topical application of steroid ointment to treat both physiological and pathological phimosis has its origins here in Melbourne when proposed by Kikiros, Beasley and Woodward. Since that time there have been multiple publications of control trials of topical steroid versus placebo demonstrating statistically greater efficacy [16–18]. Despite this the optimal steroid treatment regimen has not been determined. Twice daily application appears to be as effective as three-times (without the need for application during the school day) with success rates approaching 85% [19]. Success is enhanced when application is coupled with routine preputial retraction. Topical steroid ointment has been shown to significantly more cost-effective than circumcision with potential annual savings in France in 2001 of 150 million Francs. One of the problems with topical steroid therapy is accurate dose application/administration sometimes resulting in non-compliance from steroid phobia, as has been demonstrated in up to a third of patients [20]. Of greater concern to physicians is over administration resulting in exogenous Cushing's syndrome or suppression of the hypothalamic-pituitary-adrenal axis. This has been demonstrated in infants treated with potent steroids for nappy rash i.e. a large area. Similarly absorption of preputially administered oestrogen cream has been shown to have systemic effects in a boy with phimosis [21]. However no evidence of H-P-A axis suppression was found in a study of topical Clobetasol [22]. Clobetasol proprionate is a Class I super potent topical steroid so the more commonly used Betamethasone valerate, a Class II or potent agent, should have even fewer side effects provided administered correctly.

69.1.2 Circumcision

For an operation to remove a few cm [2] of skin, practised for over 5000 years and carried out on over 1/3rd of the world's male population, circumcision still manages to generate a great deal of debate and controversy. No one knows exactly when circumcision was first practised. Sir Grafton Elliot Smith a British Egyptologist suggests it started over 15,000 years ago. Egyptian mummies as far back as 2300 BC were found to have been circumcised [23]. It has been demonstrated on 6000-year-old reliefs on the wall of the tomb of Ankh-Mahor at Saqqara near Cairo, Egypt [24]. There are many theories as to the origins of circumcision from a necessity in arid/desert regions to address the accumulation of sand under the prepuce through a humiliating 'branding' of slaves in ancient Egypt to a 'rite of passage' into adulthood [23]. Whatever the origins or indications circumcision continues to be performed amongst Jewish and Muslim cultures for religious reasons and for cultural reasons amongst some western societies.

In Judaism circumcision (*Brit Milah*) is a commandment (a *mitzvah*) from God representing a covenant between God and Abraham and all of Abraham's descendants—Genesis 17:10–14:

> 10. This is my covenant, which ye shall keep, between me and you and thy seed after thee; Every man child among you shall be circumcised.
>
> 11. And ye shall circumcise the flesh of your foreskin; and it shall be a token of the covenant betwixt me and you.
>
> 12. And he that is eight days old shall be circumcised among you, every man child in your generations, he that is born in the house, or bought with money of any stranger, which is not of thy seed.

> 13. He that is born in thy house, and he that is bought with thy money, must needs be circumcised: and my covenant shall be in your flesh for an everlasting covenant.
>
> 14. And the uncircumcised man child whose flesh of his foreskin is not circumcised, that soul shall be cut off from his people; he hath broken my covenant.

It is the father's obligation to perform the circumcision himself or as is more usual to appoint a *mohel* to carry it out. The rules and requirements are set out in the *Talmud* including the requirement that the entire glans be uncovered when the penis is flaccid [25]. In the UK *mohelim* are trained and regulated by the Initiation Society, under the guidance of the Chief Rabbi of Great Britain. Training takes 6 months, they have to see 40–50 before being permitted to perform one and have to pass a two-part practical and theoretical exam before being licensed. As has happened in those cultures that practice social circumcision there are people in the Jewish community who question its validity and relevance in modern society [26].

Among the six schools of Islam only one, the Shafiite school considers circumcision obligatory (*wajib*). The remaining five consider it to be recommended as a tradition (*Sunnah*) attributed to the Prophet Abraham [27]. Unlike Judaism a specific age, technique or person is not designated. This in part explains why, with the exception of bleeding, more complications are seen in circumcisions performed on Muslim boys than in Jewish boys.

It was in the nineteenth century that circumcision as a 'treatment' for widespread ills became increasingly common. Circumcision was advocated as a treatment for impotence, sterility, priapism, masturbation, 'wet dreams', syphilis, epilepsy, spinal paralysis, bedwetting, club foot, crossed eyes and even to prevent black men from raping white women (Dunsmuir:1999wd, http://www.icgi.org/medicalization). The sequelae from this can still be seen in the estimated 1.25million boys circumcised annually in the USA or one child every 26 s! [28]. That said there has been a reduction, in recent years, in the number of circumcisions performed annually in the western societies such as USA, UK and Australia. Circumcision rates in the USA have fallen from 65% in 1980 to 57% in 2009, continuing a downward trend from ever higher rates in the 1960s [29]. There is still marked regional variation with more circumcisions carried out in the mid-west that on the coast, with the exception of Maryland where the rate approached 83% [29, 30]. A similar downward trend though starting from a very low initial level has demonstrated in the UK. Korea where non-medically indicated 'social' circumcision is believed to be an after-effect of American occupation, is the one developed culture that is bucking this downward trend [31]. The reasons for this trend are varied. Given that the main reasons for circumcising one's child, outside of religious indications, are because his father is circumcised or because of a belief that it is cleaner or more hygienic [32]. As fewer fathers are circumcised, naturally the rate will fall and similarly position statements such as that released by the American Academy of Pediatrics suggesting that circumcision was unnecessary will have both a direct effect and an indirect one by influencing Medicaid to no longer reimburse the cost in some American states. In Australia a similar government initiative to not reimburse hospitals for carrying out non-medically indicated circumcision has had a similar effect. That said circumcision rates for phimosis in Western Australia are more than seven times the expected incidence of phimosis [33].

There is an ever growing anti-circumcision lobby driven, to be fair, by men who have been circumcised. Groups such as NOHARMM (National Organization to Halt Abuse & Routine Mutilation of Males), NORM (The National Organization of Restoring Men) and NoCirc (National Organization of Circumcision Information Resource Centers). Their objections are based on reports (from selected series of men) of dissatisfaction with penile appearance following circumcision in 1/3–1/2 men, due to scarring, or insufficient penile skin restricting erections and erectile curvature [28]. A number of women also object to routine circumcision primarily because of the pain it causes their child and some because of concerns regarding its impact on

sexual function later in life for both their child and his potential female partner [34].

There is an equally strong pro-circumcision lobby promoting the public health benefits of circumcision. Ever since the first report in 1989 describing an association between circumcision status and susceptibility to HIV infection [35] there have been a number of randomized control trials in sub-Saharan Africa demonstrating a 50–60% reduction in HIV susceptibility [36–38]. Furthermore research has shown that circumcision in areas with a high prevalence of HIV is cost effective [39]. Given the high rates of circumcision required to have a significant impact, circumcision in the neonatal period has been shown to be even more effective given the potential higher take-up rates, lower procedural costs and lower complication rates [40]. Male circumcision has been shown to associated with a reduced risk of sexually transmitted diseases, penile cancer and urinary tract infections [41–43]. Despite some predictions there is no evidence that circumcision as an adult to mitigate HIV risk is associated with increased sexual risk taking behaviour. What is not clear is the protective effect on male-to-female HIV transmission of male circumcision. In the only trial to-date looking at this, what was found was an increased susceptibility of female partners of HIV-positive males who underwent circumcision and resumed sexual intercourse before complete wound healing [44]. Other advantages for female partners are a reduced susceptibility to Human Papilloma Virus infection and cervical carcinoma [45].

Extrapolating data from sub-Saharan African trials with a very high prevalence of HIV among heterosexuals to more developed westernized cultures with a higher rate of male-to-male infection is prone to error. Many of the trials had difficulty distinguishing the relative impacts of circumcision status and genital ulcer disease and hence the ongoing need to wear a condom cannot be underestimated. The high complication rates of 17–35% in adults undergoing circumcision, compared with 0.2% of neonates [46], give cause for consideration when proposing population-wide intervention [47]. Though the neonatal period is the best time to circumcise [48], the ethics and legality of performing circumcision on infants without their consent as a public health measure to minimize the risk of contracting a disease for which there are readily available and credible prevention strategies is still under discussion [49–53]. The psychological impact of circumcision both on the neonatal patient and subsequently as an adult is still being calculated [54].

Whatever the indication or justification there are a limited number of circumcision techniques. A detailed discussion of operative technique is beyond the scope of this text. Most open operative techniques are modifications of the 'sleeve resection' originally described by Treves in 1903 [23], normally carried out under general anaesthesia [55, 56]. The techniques carried out under local or regional anaesthesia generally make use of some form of clamp such as the Gomco, Winkleman or Mogen removed once the foreskin has been excised or the Plastibell designed to fall off within a week.

Whatever the technique employed circumcision, as with any procedure, is associated with some complications though the risks are largely overstated. Wiswell looking retrospectively at over 100,000 neonatal circumcisions performed at army hospitals over a 5-year period found a complication rate of 0.19% [42]. The majority of these were bleeding (43%), of which half required surgical haemostasis and only 3 (0.003% of total) required blood transfusion. Infection was a close second in 42% and only 25 boys (0.025% of overall) suffered any surgical trauma. The complication rate for circumcisions performed outside the hospital system is hard to quantify given the unknown denominator. What little is published suggests that Plastibell circumcision is associated with a higher complication rate, especially in obese children [57]. Other less frequent complications include recurrent phimosis leading to a buried penis, inclusion cysts, skin bridges and fistula. More significant but less frequent are glanular injuries. Meatal stenosis, thought to be due to contact with urine in the diaper and, historically reported to occur in 8–31% of boys is rarely seen nowadays possibly due to advances in diaper technology [24]. This is supported by the

still relatively high incidence (20%) of meatal stenosis in Iran, possibly related to use of more traditional diapers [58].

Preputioplasty is an option for those boys with recurring preputial inflammation or restriction, despite topical steroids and who wish to keep an uncircumcised appearance. Not an operation to be considered in the presence of BXO, preputioplasty offers the possibility of increasing preputial girth at the expense of preputial length. There are a number of different publications advocating one, three or multiple longitudinal incisions which are closed transversely (alá Heineke-Mikulicz) [59]. A Y-V preputioplasty has been shown to be associated with higher success rates [60] and to be finding acceptibility with adult surgeons [61]. Preputioplasty as a credible alternative to circumcision is finding an expanding role in the management algorithm of phimosis [62]. It must be remembered that as with topical steroids much of the success relates to regular post intervention preputial retraction and hence patient age at selection is a crucial determinant.

Despite the absolute wealth of information, albeit largely conflicting, it would appear that providing information to parents has little impact on their decision to circumcise their newborn son or not as their decision had been made before the third trimester [32, 63].

69.1.3 Paraphimosis

Paraphimosis is an acquired condition resulting from retraction of the prepuce proximal to the coronal sulcus with consequent oedema and engorgement and entrapment of the glans. It is associated with failure to return the foreskin after male urethral catheterisation, post-coitally and post-masturbation but the majority in adolescents have no clear aetiology. The presumed association with phimosis is not born out by the fact that post reduction and resolution of swelling only 29% of patients have evidence of phimosis [10].

There are a number of differing techniques described to enable reduction, none of which have any proven superiority [9]. The most common method, initially trialled with topical anaesthesia but proceeding to penile block or general anaesthesia as necessary involves sustained manual compression of the prepuce and glans to reduce swelling (can take 15 min or more!) [64]. Then with a firm grip on the preputial ring the glans is invaginated. Others have suggested augmenting this approach with use of an ‘ice’ glove to help reduce the swelling. The use of topical osmotic agents such as glycerine magnesium sulphate, granulated sugar [8] or 50% dextrose. Others report the use of multiple needle punctures (the Dundee technique) to facilitate reduction of the oedema [7], enhanced by others by injection of hyalurinidase.

A failure of these methods especially under general anaesthetic may precipitate the need for a dorsal slit and either immediate or delayed circumcision. For those that did reduce without surgery it is no longer considered imperative to circumcise to prevent recurrence which is very rare [10].

69.1.4 Hypospadias

A condition that appears to be increasing in incidence, typically presenting at birth to obstetricians but occasionally detected antenatally, especially when severe [65, 66]. The term hypospadias is derived from the Greek for rent or defect “spadon” and ‘hypo’ meaning below. It is usually composed of three elements—a ventral opening of the urethra, ventral curvature (chordee) of the penis and an incomplete or hooded foreskin.

The development of the external male genitalia begins in the 7th week of gestation and is completed by 16–17 weeks [2]. The process begins earlier in the 4th–7th weeks with differentiation of the primitive sex streaks into testes under the influence of the SRY gene on the Y chromosome. The initial development of Sertoli cells triggers the development of germ cells and Leydig cells which in turn produce testosterone that is converted to dihydrotestosterone to exert its effect on the genital tubercle. Over the past decade a number of similarities between limb bud development and that of the genital tubercle

have been discovered. The penis develops from ecto-, meso- and endodermal layers. The endodermal layer gives rise to the urethral folds on either side of the urethral groove, which fuse to form the urethra from the veru-montanum to the glans. The glanular urethra is formed by canalization and joins the tubularizing urethral plate. There is some evidence that this endodermal layer is crucial to penile development—endodermal differentiation—thus explaining the association of incomplete urethral development with incomplete preputial development [67]. These have been shown at a molecular level to interact through a number of signalling mechanisms including *Sonic hedgehog, BMP, WnT, Fgf* etc. [1]. How systemically circulating testosterone interacts with these signal transduction genes is still being elucidated.

For a long time hypospadias has been classified according to the position on the phallus of the meatal opening into Anterior (glanular and subcoronal)—50%, Middle (Distal penile, midshaft and proximal penile)—30% and Posterior (Peno-scrotal, scrotal and perineal)–20%. It is well recognized that this classification underestimates the severity of hypospadias as the meatal opening tends to adopt a more proximal position once the chordee has been released. Furthermore the quality of the urethral tissue immediately proximal to the meatal opening is highly variable and tends to be hypoplastic or atretic proximally to the level of the bifurcation of the Corpus Spongiosum [68]. They describe a method of estimating the bifurcation of the spongiosum by drawing intersecting lines between the preputial skin and inner preputial mucosa. This understanding has prompted a new classification based on division of Corpus Spongiosum and pubic symphysis [69]. This changes the proportions to Middle 21% and Posterior 30%, of relevance when deciding whether the defect is best managed with a single or staged repair. This classification has the potential to enable more accurate comparisons between differing series of patients. It must be remembered though that this remains only one descriptive parameter of a complex anomaly that should also include an assessment of peno-scrotal transposition, penile size, glans size, nature of glanular groove, penile torsion and degree of chordee. Even by their own admission Orkiszewski have identified that in hypospadias with the most proximal meatal openings the division of the corpus spongiosum may be more distal on the penis than the meatal opening. Ultimately the classification of hypospadias is finalized intra-operatively. It is important that surgeons undertaking hypospadias repair be able to operate on all severities of hypospadias as pre-operative assessment will occasionally be an under-estimate.

There is marked variability in the incidence of hypospadias worldwide with 32 cases per 10,000, in 1992, reported from Southampton [70] and only 10 per 10,000 from South America [71]. In line with other male genital anomalies there are numerous reports of increasing incidence of hypospadias in recent years and this has been linked to increased environmental exposure to endocrine disrupting pollutants. Some of this variability will be due to under-reporting in less developed countries of minor degrees of hypospadias, however there is evidence of a genuine increase in the incidence of hypospadias in the developed world with a doubling of the incidence in America from 20 per 10,000 in 1970 to 39.7 per 10,000 in 1993. The majority of the increased incidence appears to be in less severe degrees of hypospadias which is consistent with some theories that the increase is not due to a real increase but rather due to increased reporting, previous under-reporting or a lowering of the threshold for reporting [72, 73]. Because of the confusion surrounding changing trends in the incidence of hypospadias there have been calls for more accurate registration of patients especially if endeavoring to link to potential emerging epidemiological data [74].

There is increasing evidence suggestive of an association between the incidence of hypospadias and environmental pollution by compounds with endocrine disrupting activity [75]. There are a large number of compounds with oestrogen-like activity (xeno-oestrogens—found in insecticides such as DDT, and industrial chemicals, phyto-oestrogens—plant derived chemicals with oestrogenic activity found in grains, nuts, Soya

etc.) or with anti-androgenic activity [76]. For example the odds ratio of developing hypospadias is 2.4–3.4 if the patient's mother worked in agriculture in the month prior to conception [77, 78] and is 1.96 if the patient lives within 3 km of a landfill site [79]. A maternal professional exposure to hair spray products including phthalate is associated with a 2.4-fold increase risk of having a son with hypospadias [80]. An exclusive vegetarian diet has been demonstrated to have an almost fivefold increased risk of hypospadias [81]. The latter is felt to be due to an increased consumption of phyto-oestrogens especially found in Soy-based foods [76], hence their recommended intake in peri- and post-menopausal women. There are however a few reports that question the increased incidence and association with vegetarianism etc. [80, 82, 83]. Interestingly epidemiological data have unveiled a protective effect of folate supplementation during the first trimester [80].

There are a number of associated anomalies such as cryptorchidism (9%), persistent utriculus masculinus (10–57%), bifid scrotum and scrotal transposition all of which again suggest a common aetiology due to ineffective androgenisation. Severe forms of hypospadias can present as ambiguous genitalia. In some series up to 50% of patients with hypospadias and cryptorchidism had an underlying genetic, gonadal or phenotypic abnormality. All patients with hypospadias and cryptorchidism should be investigated to exclude congenital adrenal hyperplasia, a potentially lethal condition if undetected but eminently treatable. Apart from *in-utero* exposure [84], other risk factors for the development of hypospadias include placental insufficiency evidenced by an association with prematurity, very low birth weight, small for gestational age and multiple births [77].

A familial or genetic predisposition to hypospadias has been well described with a presumed multifactorial model of inheritance dependent on genetic-environmental interactions. The risk of a sibling developing hypospadias has been estimated to be between 6–10% [85]. It has been reported that as many as one in four boys with hypospadias will have a family member with hypospadias, and 1 in 14 will have two [86]. The more extensive the hypospadias the more likely for a family member to be affected with 3.5% of mild, 9% of moderate and 17% of severe cases having an affected relative. As our knowledge of the genetic mechanisms that underly development of the external genitalia increases so too does the ever expanding list of candidate genes associated with the development of hypospadias. These genes are not exclusively restricted to androgen development, conversion and effect such as 5 alpha-reductase type 2 gene (SRD5A2), 17 Beta-Hydroxysteroid dehydrogenase type 3 (HSD17B3) or Mastermind-like domain containing1 (MAMLD1) also known as Chromosome X open reading frame 6 mutation (CXorf6) to name but a few. They also include sonic hedgehog, fibroblast growth factors, bone morphogenic proteins (BMP), homeobox genes (HOX) and WnT/Beta catenin. For a detailed review the reader is directed to Kojima et al. and Kalfa et al. [87, 88]. There is some emerging evidence from in-vivo modelling of up-regulation of some of the candidate genes in response to exposure to oestrogen providing initial evidence to support the genetic-environmental interaction theory [89].

Hypospadias is a diagnosis that is almost always made at birth and generally investigations are not required. Exceptions include boys with associated undescended testes and those with proximal hypospadias who are known to have an increased incidence of utricular and renal abnormalities. Cryptorchidism is found in 8–10% of boys who have hypospadias [90]. The incidence of cryptorchidism increases with more severe forms of hypospadias such that almost a third of boys with a proximal hypospadias have an undescended testis. This latter group have a much greater incidence of chromosomal abnormalities (22%) than those with simple hypospadias (5–7%) or those with isolated hypospadias (3–6%). More severe degrees of hypospadias are also associated with an increased risk of disorders of sexual development, and persistent or enlarged utricular remnants. Boys with associated cryptorchidism or proximal hypospadias should at least undergo karyotyping. Endoscopic examination at the time of hypospadias repair

may reveal an enlarged prostatic utricle in more than half of those with severe hypospadias. Whilst not mandating surgical immediate surgical intervention it may portend urinary tract infection, epididymo-orchitis, stone formation or urinary incontinence.

Despite the immortal words of Durham Smith "There is nothing new in surgery not previously described" [91], there have been over 250 described operations for hypospadias. All aim to produce a penis that is straight when erect, voids from the tip with a terminal meatus and looks cosmetically acceptable, whether that be with a circumcised or uncircumcised appearance. Broadly speaking the operative techniques can be subdivided in single or staged procedures, tubularised or grafted repairs and pedicled or free grafts. The majority of surgeons will only undertake half a dozen or so different types of hypospadias operation and a detailed operative description is best obtained elsewhere. For distal hypospadias the author's approach is dictated by the nature of the urethral plate, the depth of the glanular groove, the extent of any associated chordee and the parental desire for preputial reconstruction or not. The author prefers not to perform a preputial reconstruction in association with a Snodgrass repair [92, 93] and in that setting or where the urethral plate is deemed too narrow (<6 mm) prefers to use a meatal-based flap repair or Mathieu. Foreskin reconstruction as an option is being increasingly requested by parents who wish a cosmetic result more aligned with the general population.

For more proximal or severe hypospadias we perform a two-stage free graft or Bracka repair. For the Bracka repair we prefer to use inner preputial skin from the hooded prepuce as this is non-hair-bearing epithelium that is used to being in contact with urine. Other options for graft material include buccal mucosa—our next choice, bladder mucosa, as a last resort and never taken to the tip as constant exposure to a dry environment has lead in the past to unsightly mucosal overgrowth through the meatus, and finally posterior auricular skin graft. A necessary consequence of the Bracka repair is that the patients will ultimately end up looking circumcised. Again there are a wide range of alternative operations including but not limited to the single stage Koyanagi or modified Koyanagi [94], the Macedo 'three-in-one' [95] or the Duckett Onlay [96] or the two-stage Durham-Smith [97].

The ideal timing of hypospadias surgery continues to be debated with a trend towards surgery at a younger age. It is the author's preference to undertake hypospadias repair between 10 and 14 months of age for a number of reasons. Firstly there is a period after birth lasting approximately 6 months, often referred to as 'mini-puberty' where under the influence of circulating testosterone there is penile growth in excess of the remainder of the baby. Secondly, there are some emerging concerns regarding the impact of volatile anaesthetic agents on the developing brain. Thirdly, the surgery still takes place before the patient becomes 'genitally aware'. Finally, it is occasionally necessary in some patients to increase penile size prior to surgery and this can be achieved through the topical application of testosterone gel or intra-muscular depot testosterone. This can take as long as 3 months. When surgery is undertaken at around 1 year of age, the fact that the baby is still in diapers and yet to start toilet-training makes post-operative care simpler.

In part the wide variety of hypospadias operations is a response to a desire to improve functional and cosmetic outcomes but also a response to a need to reduce the complication rate associated with this surgery. The most common complication is urethrocutaneous fistula. There is marked variability in the reported incidence rate for fistula ranging from 2–30%. Fistulae account for 75% of complications [98] and have a 25–50% recurrence rate following repair [99, 100]. Other rarer complications include stricture, meatal stenosis, both of which should be excluded prior to fistula repair to minimize recurrence, meatal retraction, glans dehiscence, urethral diverticulum, residual chordee and unsatisfactory cosmesis with Bracka reporting up to 50% requesting further surgery. Most paediatric urologists believe that the repairs being currently performed have a much better cosmetic outcome than repairs performed 15–20 years ago and that Bracka's report

is not applicable to current repairs. It is widely recognized however that there is poor agreement between patient and surgeon in relation to cosmetic outcome. It has also been reported that up to 33% of hypospadiacs are inhibited in seeking sexual contact compared to 12% of controls. For these reasons Bracka believes it is not appropriate to discharge these patients until they are fully grown and sexually active to allow time for both physical and psycho-sexual complications to manifest.

69.1.5 Inconspicuous or Concealed Penis

In 1986 Maizels developed a classification to describe a group of conditions resulting from or giving the appearance of a small penis. They consist of (1) poor penile suspension; (2) buried penis; (3) webbed penis; (4) trapped penis; (5) concealed penis; (6) dimunitive penis and (7) micropenis.

While the majority present in infancy there is a second peak in later childhood/early adolescence (pre-pubertally) [101]. The latter group tend to be primarily buried in excess pre-pubic fat [102]. For this group time to allow penile growth, diet and exercise to encourage weight loss and only in a selected group is surgical intervention appropriate or required. When surgery is indicated it usually involves some form of lipectomy or liposuction and fixing of the penile shaft skin at the base of the penis [103]. Increasingly frequently a penis buried in excess pre-pubic fat is seen in infants, presenting prior to learning to walk, for whom surgical intervention is inappropriate and parents should be reassured that with weight loss the appearance will approve [104].

A buried penis, sometimes referred to as a Congenital Megaprepuce, tends to present between 6 and 12 months of age with a history of significant, spherical ballooning on micturition (not to be confused with the fusiform ballooning seen in physiological phimosis). Parents will usually report the need to manually express urine from within the prepuce. The exact aetiology of congenital megaprepuce is unknown. Most theories focus on abnormal attachments of fascial layers, others on penile skin deficits or crural abnormalities [105]. The overwhelming majority do not present at birth rather they become apparent over 6–12 months and hence whilst there is a congenital predisposition the act of micturition must play a contributing role in the progression of the condition. The natural history is unknown as most undergo some form of surgical intervention with generally speaking good outcomes [101]. There are a number of different surgical approaches all of which emphasize the importance of not removing external shaft skin, which tends to be deficient, and focusing instead on the inner preputial and Dartos layers [105–108].

Webbed penis is a form of peno-scrotal fusion anomaly for which surgical intervention may be necessary in severe cases. El-Gohary and El-Koutby recently proposed a classification of webbed penis into primary or secondary to circumcision and into simple or compound [109]. Simple merely describes a web that extends for variable lengths along the shaft of the penis. Compound is either a broad based web or one associated with scrotal transposition or chordee. The nature of the repair is based on the severity of the problem ranging from simple excision to the use of skin flaps [102, 110].

Trapped Penis is a post-operative complication following circumcision that if detected early may respond to topical steroid application [111]. It has been reported to occur in as many as 2.9% of boys circumcised as neonates [112]. More often surgical release is required which may be a simple scar revision or rarely a complex staged repair with skin grafting [113].

A concealed penis is one of the more poorly defined entities and could conceivably be any of those listed above. It would also include those that are masked by large herniae or hydroceles in neonates and infants.

Micropenis differs from other forms of concealed penis in that the underlying problem is the size of the penis which by definition is a stretched penile length of more than 2.5 standard deviations less than the mean for age [114]. For neonates this means less than 1.9 cm and for an adult 9.3 cm. This reference range does not take

account of some ethnic differences and for that reason <7 cm is advocated for diagnosis of micropenis in adults [115]. It is essentially an endocrinological rather than a surgical problem resulting from a failure to produce gonadotrophins (hypogonadotropic hypogonadism), a failure of the testis to respond (hypergonadotropic hypogonadism) or idiopathic. For a more detailed review readers are directed to Wiygul and Palmer [114]. Treatment is essentially medical and aimed at improving appearances not restoring normality. When medical therapy fails surgical intervention may be appropriate with increases in length varying from 1 to 4 cm [115].

Peno-scrotal transposition describes the appearance when the penis is partially or completely enveloped by the scrotum. It can be an isolated presentation but more often appears in association with hypospadias and chordee. Primarily a cosmetic condition, more severe cases may have functional implications especially when associated with chordee. Most repairs involve flap rotation of the scrotum to drop it back but others move the penis [116].

69.2 Undescended Testis/ Cryptorchidism

69.2.1 Introduction

Cryptorchidism is the most common congenital abnormality. The incidence is increasing and currently stands between 2.4 and 6.9%, averaging around 5% of all boys born at full term [117, 118] and being more common in pre-term and low birth weight infants. Descent of the testes has been the subject of extensive research. Despite this there are still large gaps in our knowledge of the aetiology of this condition.

69.2.2 Embryology

Currently the unifying theory describes testicular descent as occurring in two stages, the abdominal and the inguino-scrotal phase. Development of the gonads begins during the 4th intrauterine week. During the 6th week Testis Determining Factor, encoded by the SRY (sex-determining) region of the Y chromosome the developing gonad differentiates into a testis. Testicular descent begins during the 7th week. This phase, the abdominal phase, said to be under the control of Mullerian Inhibiting Substance (MIS) released from Sertoli cells, is attributed to regression of Mullerian structures and enlargement of the gubernaculum under the influence of Leydig cell produced insulin-like hormone 3 [119]. In addition testosterone causes regression of the Cranial Suspensory Ligament permitting the testis to remain near the internal inguinal ring during somatic growth and hence apparent trans-abdominal movement, complete by 15 weeks gestation.

The second or inguino-scrotal phase is largely under the control of testosterone and takes place during the 28th–35th intra-uterine weeks. During this phase testosterone is believed to act on the nucleus of the genitofemoral nerve in the spinal cord to cause the ipsilateral release of Calcitonin-gene related peptide (CGRP) from the end of the Genitofemoral nerve [120]. It is postulated that CGRP induces swelling and cavitation of the Gubernaculum into which the Processus Vaginalis protrudes. The growth and expansion of the gubernaculum has been shown to have a number of similarities with developing limb buds [121, 122]. This provides a space through which the testis can pass into the scrotum possibly driven by intra-abdominal pressure.

69.2.3 Classification

A fully descended testis is one that normally resides in the scrotum. An undescended testis is best described as one that cannot be manipulated to the bottom of the scrotum without undue tension on the cord. Undescended testes can be classified on the basis of whether they have become arrested in the line of normal descent and are described as intra-abdominal, canalicular or emergent. Testes that are not in the line of normal descent are called ectopic and can be Femoral, Perineal, Pre-penile, Transverse Testicular Ectopia. Histological examination of testicular

biopsies suggests that ectopic and undescended testes have similar pathological origins [123].

The cremasteric reflex serves to elevate the testis in the scrotum either to help with the maintenance of testicular temperature in cold weather or to protect it from trauma. This reflex, weak at birth, becomes stronger in infancy and diminishes again after age 10. Retractile testes are those with a marked cremasteric reflex. They can be seen in the scrotum when the child is warm and fully relaxed, but retract into the superficial inguinal pouch with the slightest provocation. They can usually be diagnosed clinically in the out-patient department as the testes can be brought to the bottom of the scrotum, without tension on the cord. Occasionally this cannot be demonstrated in the OPD and may require examination under anaesthesia. Retractile testes per se do not require surgical intervention as the weakening of the reflex with age and the increase in testicular size make retraction in latter life unlikely. These patients should be followed up annually, until after puberty, as some will go on to develop acquired cryptorchidism, often referred to as Ascending Testes. Of boys diagnosed at 5 yo with retractile testes 1/3 will descend, 1/3 will remain retractile and 1/3 will ascend or become an acquired undescended testis [124]. With growth the distance from the bottom of the scrotum to the external inguinal ring increases and the excessive cremasteric reflex may prevent the spermatic cord from lengthening with age. It is more common in boys whose retractile testes are diagnosed before 7 yo rather than after 7 yo. Acquired cryptorchidism has been reported as occurring in almost 50% of post-pubertal boys with spastic diplegia. The other form of acquired cryptorchidism is that which occurs after inguinal surgery and can be referred to as iatrogenic testicular ascent. This has been reported to occur in 1.2% of boys following inguinal herniotomy.

What is relevant from a clinical point of view is whether the undescended testicle is palpable or impalpable. A palpable undescended testicle can usually be dealt with at open surgery. Unilateral or bilateral impalpable testes may require further investigation and laparoscopic techniques (described below).

69.2.4 Incidence

A large population-based study by the John Radcliffe Hospital Cryptorchidism Study Group reported that in the 1980s the incidence at birth was 5.4%, which fell to 1.85% by 3 months [125]. Those testes that had not descended by 3 months of age were unlikely to do so spontaneously. This represents a doubling of the incidence of undescended testes in 3-month-old boys since Scorer's report in 1964 [126]. The frequency of undescended testes is higher in premature infants. Approximately 45% of infants weighing less that 2000gms at birth will have undescended testes, many will descend spontaneously such that at 3 months of age 7.7% have persistent cryptorchidism.

There is worldwide concordance in the prevalence of cryptorchidism with no geographical sparing. There is a peculiar peak incidence in the UK amongst children born in March/April and a trough in boys born between June and October [127]. Similar Spring peaks and summer troughs have been reported in Austria, Sweden and Hungary. Additional associations include other congenital anomalies, low birth weight, twins, pre-eclampsia and previous stillbirth. These associations may be due to placental insufficiency, intrauterine infection, maternal pituitary hypogonadism and *in-utero* oestrogen or anti-androgen exposure.

69.2.5 Diagnosis

69.2.5.1 History

The history is usually straightforward when the absence of testes is noted at delivery or at the routine 6-week check-up. Children with a unilateral undescended testis can usually be seen at a routine OPD appointment at or after 3 months of age, by which stage the majority of those testes that will descend spontaneously will have done so. One must beware the newborn male with bilateral impalpable undescended testes and these must be seen more urgently. A diagnosis of bilateral cryptorchidism in association with Hypospadias must

never be made on clinical grounds alone, as there is a very real possibility that these children may actually be over-androgenised females with Congenital Adrenal Hyperplasia (CAH), one form of which can be life-threatening if not treated.

69.2.5.2 Examination

When examining the scrotum a lot can be learned from inspection alone. With a relaxed patient in a warm environment both testes may be seen in the scrotum and observed to retract under the threat of palpation. Obvious scrotal asymmetry would suggest a unilateral undescended testis. The penis itself can be considered a "bio-assay" for testosterone and if a normal phallus is seen it is very suggestive that the developing penis was exposed to normal amounts of testosterone *in-utero*. Assessment of testicular size is helpful, especially in unilateral cryptorchidism, as there may be compensatory hypertrophy of a solitary testis; however this is not sufficient evidence that one would not actively look for the other testis. Testicular size can be measured by comparison to a Prader Orchidometer. In pre-pubertal boys the testes should be approximately equivalent to the size of the glans penis. When palpating for the 'impalpable' testis it is important to have a non-threatening approach and warm hands. Starting lateral to the superficial inguinal ring and 'milking' the contents of the inguinal canal towards the scrotum using the other hand to prevent retraction. Once located the testis is grasped between thumb and forefinger and under gentle traction an assessment is made of the distance into the scrotum that the testis can be drawn. If not palpable, remember to examine all potential sites (perineum, femoral, penile, other hemiscrotum) for an ectopic testis.

69.2.5.3 Investigation

Imaging investigations and biochemical tests are usually of little benefit in the pursuit of the impalpable testis particularly in the presence of a normally descended contralateral testis. The investigation of choice for an impalpable undescended testis is laparoscopy.

69.2.5.4 Pathological Changes in UDTs

Testes that remain out of the scrotum undergo tubular dysplasia, evident on Electron Microscopy at 6–12 months of age, light microscopic changes at 3–4 years, macroscopic testicular atrophy in school-aged children and irreversible azoospermia if still not in the scrotum at puberty. There is some evidence to suggest that cryptorchid testes that are higher in the line of descent have more significant reductions in fertility index (spermatagonia per seminiferous tubule) than testes that have progressed further or fully descended testes [128]. Furthermore there is evidence that the longer a testis spends in an undescended position the more significantly the fertility index is negatively affected [129]. As well as a greater reduction in germ cells the longer a testis is undescended Cortes et al. found that reduction in germ cells starts from 28th week of gestation suggesting that there is more at play here than merely testicular location [130].

69.2.6 Management

69.2.6.1 Medical

Hormonal manipulation of undescended testes enjoyed a brief flurry of interest with the use of two differing regimens. Patients received either Human Chorionic Gonadotropin (HCG) by intramuscular injection twice weekly for 6–8 weeks or intra-nasal Leutenising Hormone Releasing Hormone (LHRH) up to 6 times a day for 3–4 weeks. Randomised trials showed no difference in incidence of testicular descent compared to untreated boys. Where hormonal studies are particularly useful are in boys with bilateral cryptorchidism [131]. In this group of patients if there are no palpable testes, a HCG stimulation test may be undertaken to detect functioning testicular tissue. A positive test suggests the presence of testicular tissue, however a negative test does not obviate the need for laparoscopy to look for the gonads, as they may be present but abnormal/dysplastic. One fifth of those testes that descend with hormonal therapy reascend at a later date [132]. There is also some evidence of

testicular damage following HCG treatment and therefore hormonal treatment.

69.2.6.2 Surgical

Aims of Surgery

The purpose of orchidopexy is to locate the testis and place it in its normal environment. Testes are located in the scrotum so that they are 2–3° cooler than body temperature. This is possible because of the scrotal rugosity, which gives a large surface area relative to scrotal volume from which to lose heat, the absence of subcutaneous fat and a counter-current heat exchange mechanism—warm testicular arterial blood looses heat to the returning cooler blood of the pampiniform plexus of veins which surrounds it, with greater than 90% efficiency [133].

As well as achieving a cosmetically normal scrotum, placing the testis in the scrotum enables earlier detection of malignant transformation should it occur and may have some beneficial effect on fertility.

69.2.6.3 Palpable UDTs

The first successful orchidopexy was carried out by Thomas Annandale in Edinburgh in 1877 [134]. The surgical management of palpable undescended testes is reasonably straightforward with patients usually undergoing a single-stage, day-case open orchidopexy under general anaesthesia. Traditionally the testis is exposed via a groin crease incision but particularly for ascending testes some surgeons prefer a lateral scrotal margin incision or a trans-scrotal (Bianchi) approach with similar outcome results [135]. Whatever the approach the testis is identified, mobilized by dividing the gubernaculum, maximum length is obtained by separating and suture transfixing the associated patent processus vaginalis. The testis is delivered from within the tunica vaginalis and a Hydatid of Morgagni, if present, excised. The testis is then placed in the scrotum and secured. The most common method of securing is to place in an extra-Dartos or Sub-Dartos pouch where it is secured by co-apting the Dartos layer around the spermatic cord [136]. Whilst still commonly used I do not place sutures through the testicle to secure in the scrotum as I believe this to be unnecessary and have potential complications.

69.2.7 Impalpable Testis

Laparoscopy is the diagnostic test of choice for the impalpable testis. Open insertion of the umbilical port, CO_2 insufflation and a second port to manipulate the intestines are necessary [137]. Once visualized the vas must be followed throughout its full extent, as must the testicular vessels. There are a number of possible findings: (1) blind ending vas and vessels with no evident testis—so called 'vanishing testis'; (2) Normal or attenuated vas and vessels entering the inguinal canal through the internal ring—these patients require open surgical exploration of the inguinal canal with orchidopexy of a normal testis or more likely excision of a testicular remnant. The nubbin is excised as it provides no useful reproductive or endocrine function but retains its enhanced malignant potential. A single-stage orchidopexy, utilizing a pre-peritoneal or Jones approach is suitable for a normal sized-testis; (3) Good-sized testis within the peritoneal cavity that cannot be brought to the scrotum in a single stage—the surgical options for these patients are either a single stage microvascular transfer with the gonadal vessels being divided high near the renal vessels and anastamosed onto the inferior epigastric vessels or a two stage Fowler Stevens Orchidopexy. We favour the latter approach the basis for which is division of the gonadal vessels as a first stage; encouraging collateralisation of the remaining gonadal blood supply i.e. the cremasteric and vasal vessels. Followed 6 months later by the second stage, where the testis is mobilized on a pedicle of peritoneum that includes the vas and its now enhanced blood supply. This is brought through the abdominal wall medial to the inferior epigastric vessels (the Prentiss maneuver [138]) to reduce tension and placed in an extra-dartos scrotal pouch. Both of these stages can be performed as open operations, as originally described. However, we favor a laparoscopic approach for both. The first stage is an extension

of the diagnostic laparoscopy with the addition of simple dissection of the gonadal vessels prior to their ligation. The second stage requires laparoscopic mobilization of the testis and then the introduction of a 10 mm port through the scrotal wound through which the testis is drawn into the scrotum and secured in the usual manner. A large meta-analysis by Elyas et al. has demonstrated that a 2-stage Fowler-Stephens approach is marginally better than recent attempts to undertake a single-stage orchidopexy with division of testicular vessels [139], with no difference between the open and laparoscopic approaches.

69.2.8 Complications of Surgery

Fortunately post-operative complications are rare and include the usual culprits of wound infection and bleeding. Testicular ascent occurs but the rate varies in relation to the extent of mobilization needed such that it is <1% for testes that are in the superficial inguinal pouch pre-operatively but close to 30% for those testes managed with a 2-stage Fowler-Stevens approach. Injury to the vas and vessels is very uncommon but vasal injury may be underestimated. Animal studies have demonstrated vasal injury from simple handling. Intimal vasal injury may never be detected therefore extreme care must be taken when mobilizing the vas off the sac to protect and preserve its patency.

69.2.9 Outcome Following Surgery

69.2.9.1 Testicular Size and Position

Testes that have undergone orchidopexy are usually smaller than normal testes and in general the higher the position of the testis initially, the smaller the final volume. Approximately 85% of all testes remain in the scrotum long term, 3% undergo testicular atrophy and 12% retract to a higher position requiring further surgery.

69.2.9.2 Fertility

Undescended testes have an obvious implication for fertility and it is difficult to get an accurate measure of this as the most commonly used indicator is paternity which is clearly prone to error in the absence of genetic testing. Remember that 15–20% of married couples have difficulty conceiving and of these 1/4–1/3 are identifiable as being due to an abnormality in the prospective father. When looking at couples who have attempted to conceive a child in the preceding 12 months Lee et al. [140] found that compared with controls (93.2% successful) men with a history of unilateral undescended testis were 89.7% successful and those with a history of corrected bilateral cryptorchidism were 65.3% successful [141]

69.2.9.3 Semen Analysis

Semen analysis would be a more objective way of assessing the effect of cryptorchidism on fertility. Only 25% of men with a history of bilateral UDTs have normal sperm counts and more than 50% have azoospermia. Amongst men with a history of unilateral orchidopexy, 20—70% have subnormal and about 50% have normal sperm counts. These figures are based on men who underwent surgery more than 25 years ago at which time surgery was often delayed until later in childhood. Recent studies are more optimistic of a benefit for testicular function with earlier orchidopexy such that 100% of those men whose orchidopexy was carried out at less than 4 years of age had normal semen analysis. The implications for fertility are equally optimistic with a report by McAleer who developed a fertility index based on the number of spermatagonia per cross-section of tubule in 50 tubules on histological examination of testicular biopsies [129]. When compared with normal controls patients whose orchidopexies were carried out at less than 1 year of age had a normal fertility index while those >5 years old had a decreased fertility index.

69.2.10 Malignancy

The absolute risk of developing malignancy in an undescended testis is hard to quantify. The majority does so in the third and fourth decades of life and 60% of the tumours are seminomas. The

frequency for testicular malignancy in the population in general is 0.07%. The relative risk of developing cancer in an undescended testis has been calculated at between 5 and 10 times higher. There is no evidence of an association between likelihood of developing malignancy and initial location of testis. More importantly, there is no evidence of a reduction in malignant transformation with earlier surgery. Given the long lag-time of 30- to 40 years it may be some time yet before we are in a position to ascertain the impact of orchidopexy on those less than 2 years old on the subsequent development of malignancy.

69.3 Acute Scrotal Pathology

69.3.1 Introduction

A child who presents with an acute scrotum is the most urgent of urological emergencies. A torted testis may show signs of atrophy after 6 h and viability is compromised with a longer history. Surgery can be avoided if a confident diagnosis of torsion of an appendix testis, idiopathic scrotal oedema or epididymo-orchitis can be made but if in doubt—explore.

69.3.2 Torsion of Appendix Testis

Torsion of a testicular appendage almost always affects the appendix testis or Hydatid Cyst of Morgagni, a remnant of the cranial end of the Müllerian duct, present in 90% of boys. Other appendages include the appendix epididymis, the vas aberrans of Haller and the Paradidymis or Organ of Giraldes, all remnants of the Wolffian duct [142]. The peak incidence is between 10 and 12 years of age. The appendix testis is pedunculated and peri-pubertally may increase in size in response to hormonal stimulation. The pain is typically more gradual in onset, of longer duration and less severe than that of testicular torsion. If seen early in their clinical course it may be possible to distinguish between these two conditions. Torsion of the appendix testis has discrete localized tenderness, a palpable nodule and visible 'blue dot' of the infarcted appendix testis. With a history of longer duration it can be impossible to distinguish from testicular torsion and surgical exploration is imperative.

The diagnosis is clinical, substantiated with Doppler Ultrasonography if appropriate. Where doubt exists it is prudent and more rapid to explore the scrotum. Where a diagnosis of a torted appendix testis has been made the treatment options can be discussed. The choices are symptomatic management using oral analgesia and anti-inflammatory drugs. The alternative is surgical exploration under general anaesthesia with excision of the torted nodule, that is sent for histological examination. Contra-lateral scrotal exploration is not indicated [143]. Surgery is generally associated with a more rapid resolution of the patient's symptoms.

69.3.3 Testicular Torsion

The peak incidence occurs between the ages of 14 and 16 years and accounts for 90% of acutely presenting scrotal symptoms in post-pubertal boys. The annual incidence has been estimated at approximately 1 in 4000 males below 25 years of age [144]. The left side is more commonly affected than the right. Exercise, trauma, cold weather and cryptorchidism are possible predisposing factors. Testicular torsion takes two main forms, intravaginal and extravaginal.

69.3.4 Intravaginal Torsion

Intravaginal torsion is the more common, occurring at any age. It occurs because of a high attachment of the tunica vaginalis to the cord resulting in what is often referred to as a 'bell-clapper' testis. This allows the testis to rotate around the axis of the spermatic cord inside the tunica vaginalis. The testis may rotate internally or externally through one or more complete revolutions i.e. 360° or 720°. Manual detorsion is not recommended.

Numerous studies support prompt surgical exploration and detorsion. There is evidence that

if torted for 6–8 h a testis will show signs of atrophy and after >8–10 h ischaemic necrosis is almost inevitable. However all acute scrotums should be explored given the often inaccurate nature of the duration of symptoms and the occasional occurrence of intermittent torsion where testes are said to have twisted and untwisted spontaneously.

Less than 50% of boys with testicular torsion present with a classic history of sudden onset of severe scrotal/testicular pain and swelling associated with a high riding, tender testis on physical examination. Because of the pathways of testicular innervation the initial pain is often referred to the groin or lower abdomen. The association of lower abdominal pain and vomiting can be misleading causing a misdiagnosis of acute appendicitis if the scrotum is not examined.

69.3.5 Extravaginal Torsion

Extravaginal torsion, also referred to as intrauterine or neonatal torsion is thought to occur pre-natally or during birth. The anatomical arrangement is normal but a lack of fixation between the tunica vaginalis and the scrotal/dartos tissues permits the testicle and tunica to rotate about the spermatic cord. Typically these patients present in the early neonatal period with an indurated and discoloured scrotum that is not tender. Published reports would suggest that testicular salvage is not possible is this setting. The anatomical arrangements are such that contra-lateral torsion is extremely unlikely. Rare cases of synchronous or metachronous extravaginal torsion have been reported. Our current policy is to not explore these testes immediately but to proceed to an elective exploration as soon as it can be arranged. This provides an opportunity to fix the contra-lateral side, remove the dead testis and exclude the rare possibility of a congenital testicular tumour.

The management of testicular torsion is based on immediate surgical exploration. The scrotum may be entered via a transverse scrotal crease incision over the affected side or through a midline sagittal incision in the raphe. Once exposed the testis and spermatic cord is untwisted and assessed for viability based on the prompt return of perfusion as evidenced by a change in colour or bleeding of oxygenated blood when the tunica albuginea is incised. In prepubertal boys there is no contraindication to detorting an apparently non-viable testis. However, in post-pubertal boys there is evidence of impaired fertility following testicular torsion. It may be that detorting and preserving a testis of dubious viability predisposes to the production of anti-sperm antibodies (there are no sperm present pre-pubertally) and may explain the reduced sperm quality, up to 50%, in later life. It is our policy to detort all testes and give the benefit of the doubt to the testis where possible. Once detorted and deemed viable the testis should be fixed, the contralateral side explored and prophylactically fixed to reduce the likelihood of torsion. There is much debate as to the method of fixation with some authors advocating placement in an extradartos pouch without suture fixation and others who support intra vaginal 3-point fixation with a non-absorbable suture. We employ the latter approach. All patients must be warned that testicular fixation makes recurrent testicular torsion very unlikely but not impossible and they should take the recurrence of sudden and severe testicular/scrotal pain seriously, seeking urgent medical attention.

69.3.6 Idiopathic Scrotal Oedema

Sometimes this idiopathic and enigmatic condition represents a cutaneous infection spreading forward from the anus, others that it is an allergic phenomenon and still others that it perhaps results from an insect bite. It usually presents with an asymptomatic patient whose parents have noticed a marked oedema and erythema of the scrotum. Typically the erythema involves one hemi-scrotum, but may be bilateral, extends beyond the confines of the scrotum up onto the anterior abdominal wall or back towards the anal verge. The usual age range is 5–6 years but it has been seen in up to 10 year olds. It is often confused with testicular torsion or cellulitis. The

absence of testicular tenderness, pyrexia and malaise mitigate against these diagnoses. Treatment usually consists of reassurance but antibiotics and anti-histamines, of no proven benefit, have been advocated in the past. It resolves in 1–2 days and recurrence is unusual.

69.3.7 Epididymitis

Epididymitis or epididymo-orchitis, is the consequence of the retrograde passage of urine along the patent vas deferens. Because patency of the vas is critical to its aetiology it tends to occur either in early infancy (<6 months) or in adolescence as the vas is generally occluded in the intervening years becoming patent again with the onset of puberty. Though usually associated with reflux of infected urine it may occur with vasal reflux of sterile urine usually in patients with a predisposing anatomical abnormality such as ectopic ureter or persistent Müllerian remnant. All patients with epididymo-orchitis should at least undergo ultrasound examination of the urinary tract; additionally infants should have a micturating cystourethrogram.

As testicular torsion is significantly more common, a clinical diagnosis of epididymo-orchitis must be reached very carefully and ideally supported by evidence of a urinary tract infection; up to 50% of patients will have fever and pyuria, urinary tract abnormality or sonographic evidence that the testis has not torted. Management is based on administration of analgesia and antibiotics, usually intravenous Gentamicin or Ciproflaxacin, until the results of urine culture have been. If epididymo-orchitis is found at surgical exploration it is customary to take a swab or fine-needle aspirate from the epididymis for culture and sensitivity.

69.3.8 Orchitis

True orchitis is very rare but may occur in association with Mumps or septicaemia. Mumps orchitis, unilateral in 80% of patients, is extremely rare prior to puberty. In orchitis the testis tends to be larger and harder than in epididymitis. Approximately one third of patients will develop testicular atrophy and have an increased risk of infertility and malignancy.

69.3.9 Other

69.3.9.1 Hernia/Hydrocoele

Incarcerated inguino-scrotal herniae or a hydrocoeles may present as an acute scrotum but an experienced clinician can usually easily distinguish these conditions.

69.3.9.2 Malignancy

Testicular malignancy is rare but it may be primary as in adenocarcinoma, seminoma or secondary as in the malignant infiltration seen in leukemia.

69.3.9.3 Henoch-Schönlein Purpura

This vasculitic condition typically presents with a purpuric rash that extends from the buttocks and lower limbs to the remainder of the body. In addition to scrotal discolouration it occasionally affects the testis itself causing tenderness. A history of rash preceding the testicular symptoms may help with the diagnosis. Treatment is generally supportive though some paediatricians advocate steroid therapy.

69.3.10 Summary

As a general rule unless the diagnosis of testicular torsion can be confidently and completely excluded urgent surgical exploration should be undertaken in all cases. Investigations such as Doppler Ultrasonography and Isotope Scintiggraphy should not delay prompt exploration and rather are usually used to provide reassurance where testicular torsion has been clinically excluded.

69.4 Varicocele

A varicocele is an abnormal dilatation of the testicular vein and pampiniform plexus within the spermatic cord and scrotum leading to the classic

description of "a bag of worms". It is rarely seen before 10 years of age but approximates 15% by late adolescence, similar to the rate seen in adults. They are typically asymptomatic, presenting as an incidental finding, although occasionally associated with vague symptoms of 'heavy scrotum' or 'dragging pain'. They are more commonly found (40%) in men with primary infertility [145] and it is the implications for fertility that cause the greatest confusion regarding treatment.

Varicoeles are graded clinically into one of three grades:

- Grade 1—small and only palpable with Valsalva
- Grade 2—easily paplable when patient examined upright
- Grade 3—visible when patient upright

Patients must be examined when both erect and supine. Varicoceles that do not resolve when the patient is recumbent and/or right-sided varicoceles are more likely to be secondary to intra-abdominal pathology and should prompt an abdominal examination and further imaging. More than 90% of varicoceles are on the left side. There are a number of possible reasons for this—the longer course of the left gonadal vein, valvular incompetence of the gonadal vein, the left vein drains into the smaller left renal vein than the right which joins the IVC, the 'nutcracker effect' where the left gonadal vein is compressed between the superior mesenteric artery and the aorta [146].

During physical examination testicular volume, using an orchidometer or an ultrasound, and testicular consistency must be assessed. The role of ultrasound is controversial. It is highly accurate, repeatable and non-invasive and more accurate than orchidometer at detecting volume differentials [146, 147]. However the cost implications of implementing Diamond et al.'s suggestion for annual surveillance ultrasonography would be somewhere between $364 and $795 million per annum [148]. For adolescent boys with equal sized testes at time of diagnosis of varicocele 25% will have demonstrable testicular growth arrest, regardless of the grade of their varicocele [149]. For those patients with right sided or non-reducing varicoceles a combined abdominal and scrotal ultrasound may yield additional benefit however for others regular self-examination and annual review with clinical examination and orchidometry makes the most sense.

Biochemical tests reported in the literature but rarely used include Gonadtrophin releasing Hormone stimulation assay, serum Inhibin levels and FSH stimulation test [146]. Semen analysis on the other hand is of immense practical use in adults and late adolescence and possible in early adolescence, however there no established norms for early adolescence [150].

The clinical significance of varicocele lies in its relation to male infertility after all 40% of men with primary infertility have a varicocele yet only 20% of men with a varicocele are infertile [150]. There are a number of theoretical pathophysiological mechanisms by which varicoceles amy impact fertility—poor venous drainage with resultant interference with counter-current heat exchange and relative hyperthermia causing oxidative stress impairing spermatogenesis [150], endocrine disruption with reduction in intratesticular testosterone and reduced Sertoli cell response to FSH [146].

Deciding on whom to surgically intervene continues to remain controversial. The American Urological Association [151] recommends treatment for:

- Male partners in a couple attempting conception where the varicocele is palpable, they have documented infertility, the female has normal fertility or potentially correctable infertility and there are demonstrated abnormalities on semen analysis.
- Adult males with a palpable varicocele and abnormal semen analysis but are not currently attempting to conceive.
- Young men who have a varicocele and normal semen analyses should be followed with annual semen analysis.
- Adolescents who have a varicocele and objective evidence of reduced ipsilateral testicular size

should be offered repair. Those without testicular size discrepancy should be followed annually with assessment of size and semen quality.

In adults with fertility issues and poor semen analysis the decision to intervene is relatively simple however in adolescents there is still significant uncertainty of the indications for and outcome of surgery. It is the most common correctable cause of male infertility with improvement in semen qualities, especially motility, in 66% and 40% of female partners conceiving [146]. That said a Cochrane review by Evers et al. found no significant impact on fertility where the treated varicocele was the only abnormality found in either partner [152].

In adolescents a testicular discrepancy of 20% between sides is considered an indication for surgery and there are numerous studies demonstrating catch-up growth in 85% of those undergoing surgery compared with 30% when observed [150]. Given that surgery alters venous and lymphatic drainage it has been postulated that the reduction in size discrepancy may reflect testicular oedema rather than true growth [150].

Once a decision to intervene has been made next is a decision about the best approach: whether it is to be embolization by an interventional radiologist [153] or surgery. There are a number of surgical approaches—subinguinal (Marmar), inguinal (Ivanissevich) and retroperitoneal (Palomo) that may be augmented by the use of microsurgical instruments [154] in the inguinal and distal approach or laparoscopic for the retroperitoneal (Table 69.1 (A detailed discussion of the various surgical approaches is beyond the scope of this text).

Table 69.1 Comparison of surgical approaches [158]

Approach	Failure rate	Hydrocele rate
Embolization	4.3% (1.9–9.3%)	
Inguinal	15.6% (3.5–17.5%)	7.5% (4.3–17.5%)
Microscopic	2% (1.4–14.8%)	0.3% (0–0.7%)
Retroperitoneal	12.5% (7.3–15.5%)	7.6% (4.6–9%)
Laparoscopic	11% (4–26.5%)	7.5% (1.7–12.7%)

Once a decision to operate has been made and a choice of approach made all that remains is the timing and for those in whom infertility is the indication operating in those with <1 year history of infertility does not result in an increased pregnancy rate above untreated males and given the rate of spontaneous resolution of infertility in couples with a history of less than 2 years then it has been suggested to reserve surgical intervention for those with more than 2 years of fertility struggles [155].

69.5 Epididymal Cyst/ Spermatocele

Epididymal cysts are benign cystic lesions of the epididymis that contain serous fluid in pre-pubertal boys and spermatoceles which are seen post-pubertally contain sperm. These are benign lesions that for the most part (80%) are asymptomatic and incidental pick-ups [156]. The remaining 20% were either discovered on self examination or rarely presented clinically with acute torsion. The incidence of epididymal cysts increases over time from 3.3% in boys <5 yo, 4.2% in 5–10 yo, 20.1% in 10–15 yo and 35% in boys >15 yo. Surgical intervention is generally reserved for large cysts.

For a more detailed review of other intrascrotal lesions the reader is referred to Rubenstein et al.*'s* review article [157].

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