

# CRYPTORCHIDISM

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Cryptorchidism (from the Greek *kryptos*, meaning “hidden,” and *orchis*, meaning “testis”) refers to absence of a testis from the scrotum. During embryonic life, the testes form beside the mesonephric kidneys and descend via the inguinal canal to the scrotum. If this process is faulty, a cryptorchid testis may halt along the normal path of descent (undescended or retractile testis), may travel off the normal path of descent (ectopic testis), or may die or never develop (absent testis). Therefore, the terms “cryptorchid” and “undescended” are not synonymous.

Isolated cryptorchidism is the most common congenital anomaly of the male genitalia, affecting almost 1% of full-term infants at the age of 1 year.<sup>1</sup> Despite intense study both experimentally and clinically for the last century, the cause of this condition remains poorly understood. Although there have been surgical advances in the techniques of orchiopexy, areas of clinical controversy remain.

## OVERVIEW OF MALE SEXUAL DEVELOPMENT

In mammals, sexual determination, wherein the undifferentiated gonad converts to either a testis or an ovary, is genetically determined. The molecular basis of testicular determination is better understood than that of ovarian determination. Sexual differentiation, wherein the internal and external genitalia differentiate as appropriate to the gonadal sex, is dependent on hormonal function of the differentiated gonad. Therefore, the normal male and female phenotypes are the result of cascades of gene activations and hormone-receptor interactions that are tightly regulated temporally and spatially in the developing embryo.

In the 5th week of human gestation, the coelomic epithelium and underlying mesenchyme proliferate medial to the mesonephros, producing the bipotential gonad with a cortex and medulla. This process is dependent on such genes as the Wilms’ tumor gene (*WT1*) and steroidogenic factor 1 (*SF1*).<sup>2</sup> In week 6, under the activation of the *SRY* (sex-determining region Y-linked) gene on the short arm of the Y chromosome and other downstream testis-determining genes including *SOX9*, *FGF9*, and *DAX1*,<sup>2</sup> the cortex regresses and medullary testicular cords develop. In week 6, primordial germ cells in the yolk sac wall migrate along the hindgut dorsal mesentery and populate the gonad. Sertoli cells, producing anti-müllerian hormone (AMH), appear by week 6 and Leydig cells, producing testosterone and insulin-like factor 3 (INSL3), appear by week 8.

To achieve the normal male phenotype (including male internal and external reproductive organs and male secondary sex characteristics), these hormones require normal hormone and receptor function, quantity, location, and timing. In the absence of these critical testicular hormone interactions, female sex differentiation (or abnormal male sex differentiation) ensues. Each hormone has a strong ipsilateral paracrine effect. Internally, AMH causes involution of the müllerian duct, INSL3 causes masculinizing outgrowth of the male gubernaculum, and testosterone masculinizes the wolffian

duct and causes male gubernacular regression. In weeks 10 to 15, male external genital development requires the conversion of testosterone to dihydrotestosterone by the enzyme 5 $\alpha$ -reductase type 2 in these tissues. Proper scrotal development enables the testis to reside in an extracorporeal position.

## TESTICULAR DESCENT

Testicular descent is necessary for normal spermatogenesis, which requires the 2° C to 3° C cooler scrotal environment. Embryonic testicular descent can be divided into three phases:

1. Transabdominal migration of the testis to the internal inguinal ring
2. Development of the processus vaginalis and the inguinal canal
3. Transinguinal descent of the testis to the scrotum

### Transabdominal Migration

During the 6th gestational week, the testis is located ventromedial to the mesonephros, relatively close to the inguinal region. As the fetus and abdominal cavity enlarge, the testis remains relatively stationary, whereas the ovary ascends. To achieve this differential movement, the key structure in humans is the gubernaculum (or caudal genital ligament). Before gonadal differentiation, the male and female gubernaculum is a short, thin ligament extending from the lower pole of the undifferentiated gonad and its duct to the genital swellings, the precursors of the male scrotum and female labia majora. After testis formation, the male gubernaculum masculinizes via outgrowth, with mesenchymal proliferation and increased hyaluronic acid content, anchoring the testis. In females, the gubernaculum remains thin and lengthens in proportion to fetal growth, allowing ascent. This sexually dimorphic outgrowth of the mesenchymal gubernacular cone in males, the hallmark event during the male transabdominal phase, is not dependent on androgens<sup>3</sup> but is stimulated by the testis hormone, INSL3 (also known as Leydig insulin-like hormone or relaxin-like hormone) (see later discussion).

Because rodent models are frequently used to study testicular descent, it is noteworthy that, in these animals, the testis and ovary are suspended to the abdominal wall by a second ligament, the cranial gonadal suspensory ligament. In male rodents, testosterone stimulates cranial gonadal suspensory ligament regression, thereby permitting caudal testicular mobility. In females, this ligament persists due to the absence of testosterone, and caudal ovarian mobility is thus prevented.<sup>4</sup> The cranial gonadal suspensory ligament is present but becomes vestigial in humans.

In summary, INSL3 causes the early masculinizing gubernacular swelling reaction in males, and androgen causes regression of the cranial suspensory ligament (in mice). The coordinated result of masculinization of the gubernaculum during transabdominal migration in humans is positioning

of the testicle at the internal inguinal ring by the 12th week of gestation.

### Processus Vaginalis

In gestational month 3, an elongated pocket of peritoneum, called the processus vaginalis, grows along and partially encircles the gubernaculum, creating a potential space in the inguinal canal and scrotum. Although the testis is stationary between the 3rd and 7th months of fetal life, the gubernaculum and the processus vaginalis together distend the inguinal canal and scrotum,<sup>5</sup> creating a “path” for testicular descent.

### Transinguinal Descent

This final phase of testicular descent occurs very rapidly, usually between weeks 24 and 35 of gestation.<sup>6</sup> During this time, testosterone shrinks the enlarged, masculinized gubernaculum by decreasing its turgidity and viscoelastic properties, yielding the gubernacular ligament.<sup>3</sup> Normally, the processus vaginalis obliterates completely before birth, but if the testis does not descend, the processus vaginalis usually remains patent, resulting in an open internal ring to the inguinal canal.

About two thirds of cryptorchid neonates have spontaneous postnatal testicular descent, typically within 6 months.<sup>7</sup> If the testis is undescended at birth, descent is presumably caused by the burst of testosterone (mini-puberty) that occurs during the first 3 months postnatally,<sup>8</sup> secondary to activation of the hypothalamic-pituitary axis by loss of negative feedback from the maternal endocrine environment. Some data suggest that the postnatal rise in serum testosterone is lower in boys with cryptorchidism than in those with normal testicular descent, possibly because of a primary deficiency in pituitary secretion of luteinizing hormone (LH).<sup>9</sup> However, Barthold and colleagues recently reported conflicting data showing no significant hormonal differences between these groups.<sup>10</sup>

## FACTORS IN TESTICULAR DESCENT

The observation by John Hunter<sup>11</sup> that the testis might fail to descend because it is intrinsically abnormal—rather than being abnormal because it fails to descend—remains a focus of investigation and debate. Several different animal models have been used to study testicular descent, but they add to the controversy because of the differing anatomic structures in different species, including the cranial gonadal ligament, gubernaculum, and cremasteric muscles. Although animal models may not exactly represent testicular descent in man, much useful information has been gained from studies of hormonal and mechanical factors.

### Hormonal Factors

Key hormonal factors implicated in testicular descent include the androgens, INSL3, estrogens, and AMH.

#### Androgens and the Androgen Receptor

In 1931, Engle suggested that an intact hypothalamic-pituitary-testis axis is essential for normal testicular descent<sup>12</sup>; this is supported by clinical evidence. Boys born with hypogonadism or androgen insensitivity are likely to be affected with cryptorchidism. Complete androgen insensitivity syndrome (CAIS), caused by an androgen receptor mutation, is associated with bilateral cryptorchidism in most cases and with intra-abdominal location in 52%.<sup>13</sup> However, androgen insensitivity

is associated with a complete female phenotype or male pseudohermaphroditism, which is not observed in most cases of human cryptorchidism. Similarly, anti-androgens prevent testicular descent (by blocking gubernacular regression) in 50% of prenatally exposed rodent and porcine models.<sup>14,15</sup> Lastly, prenatal exposure of rodents to estrogenic compounds induces cryptorchidism, and this effect can be overcome by simultaneous treatment with dihydrotestosterone or human chorionic gonadotropin (hCG). These observations support the role of androgens in descent. However, the variability in testicular position among children with abnormal androgen actions and the partial success of anti-androgen-induced cryptorchidism in animal models shed a negative light. In addition, this clinical situation and this animal model are both associated with genital ambiguity. Prenatal estrogenic exposure can induce partial persistence of the müllerian structures. However, most children with cryptorchidism have unilateral disease, no genital ambiguity, and no persistence of the müllerian structures. In summary, these clinical and experimental observations suggest a partial role of androgens in testicular descent.

#### Insulin-like Factor 3 and Its Receptor

For more than 30 years, it has been recognized that (1) exogenous androgens are unable to stimulate outgrowth of the gubernaculum in female fetuses, (2) anti-androgens fail to block outgrowth of the gubernaculum in male fetuses, and (3) gubernacular outgrowth is normal in humans or animals with testicular feminization.<sup>16</sup> In contrast, androgenic stimulation clearly induces the regression phase of the gubernaculum after the initial outgrowth phase. These observations and animal experiments in which fetal orchiectomy induced failure of gubernacular growth led to the theory of “descendin,”<sup>17</sup> a testicular hormone with specific local effect on gubernacular cell growth. In 1993, this hormone, now called INSL3, was first discovered. Its function was identified in 1999, when INSL3-knockout mice<sup>18,19</sup> were found to have bilateral intra-abdominal undescended testes due to absent gubernacular outgrowth phase yet had normal androgenization of the other male internal and external genitalia.

INSL3 is produced by the fetal testis and not by the fetal ovary. The gubernaculum, which expresses the INSL3 receptor, LGR8, is stimulated to outgrow in males by INSL3; females do not make INSL3 during fetal life. Therefore, INSL3 and its receptor, LGR8 (a member of the G protein-coupled receptor family, sometimes called GREAT), are the critical regulators of the transabdominal phase of masculinizing gubernacular outgrowth. Approximately 2% of patients with isolated cryptorchidism have functionally deleterious mutations in the INSL3 or LGR8 gene, but further study is needed to identify other regulators of the INSL3 signaling pathway in humans.

### Estrogens

Several studies have suggested that human maternal estrogens may modulate testicular descent. Gill and associates noted an increased incidence of cryptorchidism in the male offspring of women treated during pregnancy with diethylstilbestrol (DES), a nonsteroidal estrogenic compound.<sup>20</sup> In addition, Bernstein and colleagues<sup>21</sup> observed that male infants born to mothers with high levels of free estradiol had a higher frequency of cryptorchidism. Evidence indicates that there may be an increased expression of estradiol in the placenta of boys born with undescended testes.<sup>22</sup> In support, one method to generate rodent male offspring with cryptorchidism is through prenatal estrogen exposure<sup>23,24</sup>; and more recent mouse work has shown that estrogens ablate INSL3 messenger RNA

expression, accounting for the cryptorchidism.<sup>25</sup> Of note, this experimental model also induces retention of müllerian structures to some degree.

### Anti-müllerian-Inhibiting Substance

The observation that patients deficient in AMH (also called müllerian inhibiting substance, or MIS) typically have intra-abdominal testicles led to the suggestion that AMH may play a role in testicular descent.<sup>26</sup> However, AMH deficiency in humans probably prevents testicular descent indirectly, through the obstruction produced by the persistent müllerian structures, rather than by a direct lack of hormone.<sup>27,28</sup> In addition, most males with intra-abdominal cryptorchid testes have no persistent müllerian structures. Other pieces of experimental evidence refute the role of AMH in testicular descent, including prenatal exposure to anti-AMH antibodies<sup>29</sup> and the phenotypes of AMH or AMH receptor knockout mice.<sup>30</sup>

### Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide (CGRP) is a neuropeptide released from the genitofemoral nerve, which originates from the cremaster nucleus in the spinal cord. Evidence that the cremaster nucleus is sexually dimorphic and androgen dependent, and that its efferent neuron secretes a neuropeptide that can cause contraction of the rat gubernaculum, has implicated CGRP and the genitofemoral nerve as important factors in testicular descent. However, contrary evidence that masculinization of the cremasteric nucleus may not be androgen dependent<sup>31</sup> and that the gubernaculum of primates contains almost no muscle<sup>6</sup> suggests that CGRP may play only a minor role in this process in humans. *Hoxa10* mutant mice demonstrate cryptorchidism; the cause may be anterior homeotic transformation of L1 and L2 nerves with incorrect specification of genitofemoral nerve motoneurons or abnormal target tissue innervation or both.<sup>32</sup> Allelic variants in *HOXA10*<sup>33</sup> and *HOXD13*<sup>34</sup> have been reported in a few cryptorchid boys.

### Epidermal Growth Factor

Epidermal growth factor (EGF) can cause persistence of the wolffian ducts in the absence of androgens,<sup>35</sup> and it has also been shown to act on the placenta and, secondarily, to increase testosterone production. In mice, maternal EGF appears to precede testosterone secretion by the fetal testis and may therefore play some role in testicular descent<sup>36</sup>; however, this has not been investigated in humans.

### Mechanical Factors

First described and named by John Hunter in 1762,<sup>37</sup> the term *gubernaculum* means “helm” or “rudder,” and this structure was thought to guide the testis into the scrotum. Perhaps the most important mechanical factor, the gubernaculum begins as a mesenchymal band that originates on the lower pole of the testis/mesonephric duct and inserts in the scrotum. Separate extrascrotal bands or “tails” were described by Lockwood,<sup>38</sup> which may explain the occurrence of testicular ectopia. Its morphogenesis includes an “outgrowth” phase mediated by INSL3 and a regression phase mediated by androgens, as detailed earlier. The exact mechanism through which the gubernaculum mediates testicular descent is debated and may involve traction, muscular contraction, or differential growth around a fixed point. Most likely, the gubernaculum, in conjunction with the processus vaginalis, serves to dilate the inguinal canal and thereby facilitate descent of the testis into the scrotum.<sup>16</sup>



**Figure 43-1** Significant epididymal dissociation in a left undescended testis at inguinal exploration.

In 1969, Gier and Marion proposed that intra-abdominal pressure may be responsible for testicular descent.<sup>39</sup> Clinically, males with prune-belly syndrome or other abdominal wall defects such as gastroschisis, omphalocele, or umbilical hernia<sup>40</sup> frequently have cryptorchidism. However, against this is evidence that intact abdominal wall musculature is not necessary for testicular descent.<sup>41</sup> The intra-abdominal pressure theory is also insufficient to explain unilateral cryptorchidism.

The role of the epididymis in testicular descent is based on the fact that it is androgen dependent, adjacent to the gubernaculum, and often abnormal in boys with cryptorchidism.<sup>42</sup> The epididymis precedes the testis into the scrotum but does not significantly enlarge until after scrotal positioning. Removal of the epididymis does not prevent testicular descent,<sup>43</sup> and congenital absence of the wolffian ducts does not impair testicular descent.<sup>44</sup> Therefore, it is unlikely that the epididymis plays a significant role in descent. Epididymal anomalies are seen adjacent to undescended testes in 33% of cases (Fig. 43-1), but they are five times more common in patients with an inguinal hernia than in patients with cryptorchidism,<sup>45</sup> suggesting that other factors may be involved.

## DEFINITIONS AND CLASSIFICATION

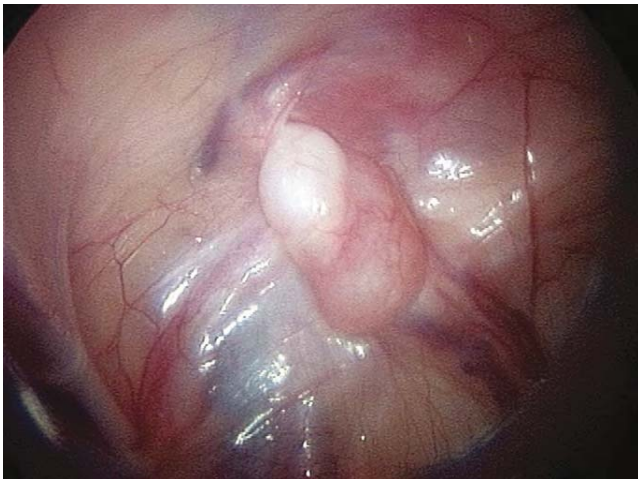
Based on physical findings, cryptorchidism is classified as palpable testes in 80% of the cases, and as nonpalpable testes in 20%. Knowing the location and existence of the testis directly influences clinical management. *Palpable testes* include true undescended testes and ectopic testes; because retractile testes are often misdiagnosed as palpable undescended testes, they are also discussed in this category. *Nonpalpable testes* include intra-abdominal, inguinal, and absent testes.

### Palpable Testes

#### Undescended Testis

A true *undescended testis* is a testis halted along its normal path of descent. Depending on its location, it may or may not be palpable. Inguinal testes are an excellent example because they have halted along the normal path of descent in the inguinal canal, but they may or may not be palpable. When viewed laparoscopically, “peeping” testes move in and out of the internal inguinal ring (Fig. 43-2). An “emergent” or “gliding”





**Figure 43-2** Intra-abdominal view of a “peeping” right nonpalpable testis. (From Baker LA, Lorenzo A, Jordan GH, Docimo SG. Laparoscopy and cryptorchidism. In: Docimo SG, ed. *Minimally Invasive Approaches to Pediatric Urology*. London: Taylor & Francis Publishers; 2005:161-176. Used by permission from Taylor & Francis.)

undescended testis moves in and out of the external inguinal ring, but because these terms have been confused with testes at the internal ring, they are best avoided. Higher testes are associated with foreshortened, fixed spermatic vessels; more wolffian duct anomalies; and a greater incidence of inguinal hernia.

### Ectopic Testis

An *ectopic testis* is one that is located in an aberrant position off the path of normal descent (Fig. 43-3). The most common site of palpable ectopia is the superficial inguinal pouch of Denis-Browne, located between Scarpa’s fascia and the external oblique fascia above the external inguinal ring. Less common ectopic sites include the femoral, pubic, penopubic, penile, and perineal positions. In crossed or transverse ectopia, a testis crosses the scrotal septum or descends into the opposite inguinal canal. Nonpalpable ectopic sites include anterior abdominal wall, retrovesical, and other intra-abdominal positions. Ectopic descent is thought to result from overdevelopment of one segment of the gubernaculum (i.e., a tail of Lockwood) or from scrotal inlet obstruction. An ectopic testis is fixed in position by fibrous attachments and therefore cannot spontaneously descend; only surgery will correct this position.

### Retractile Testis

A *retractile testis* is one that has completed the process of descent but may be found in the groin because of an overactive cremasteric reflex. The cremasteric reflex is a function of the genitofemoral nerve (L1) and is present in all boys older than 2 years of age.<sup>46</sup> When the reflex is elicited by tactile stimulation of the thigh, the cremaster muscle contracts and draws the testis out of the scrotum toward the inguinal canal. Teleologically, the cremaster reflex protects the testis by drawing it out of harm’s way, but it may cause a normal testis to mimic an undescended testis.

A retractile testis should be suspected in the 2- to 12-year-old child with a possible undescended testis. A retractile testis can be manipulated into the scrotum, where it will remain (at least temporarily) after its release. In contrast, the undescended testes retracts into the groin immediately. Retractile testes are typically normal in size and consistency, whereas undescended testes may be smaller and softer than normal.



**Figure 43-3** Empty left hemiscrotum with scrotal right testis. The left testis is located in a laterally ectopic position.

However, retractile testes may not be normal and should be annually monitored during childhood, because 30% descend, 38% remain retractile, and 32% ascend (become “undescended”).<sup>47</sup> At orchiopexy for an “undescended testis,” examination under anesthesia may reveal a scrotal testis, indicating that it is really retractile and obviating the need for surgery. However, orchiopexy via either an inguinal or a scrotal approach may still have merit under these circumstances, to prevent potential testicular ascent in the future.

### Nonpalpable Testes

Approximately 20% of all cryptorchid testes are nonpalpable. Between 50% and 60% of these are intra-abdominal, canalicular (within the inguinal canal), or “peeping” (just inside the internal inguinal ring). Approximately 20% of nonpalpable testes (4% of all cryptorchid testes) are absent, and another 30% (6% of the total) are atrophic or rudimentary.

### Intra-abdominal Testes

Intra-abdominal testes are located in a variety of intra-abdominal positions, the majority less than 2 cm from the internal ring. However, a testis can be adjacent to the kidney, on the anterior abdominal wall, retrovesical, and in other intra-abdominal positions. In rare cases, the wolffian ducts do not connect with the gonad (epididymal disjunction), leading to a large space between the cranial testis and the caudal epididymis/vas.

Intra-abdominal testes may be associated with a closed or an open internal ring. In the closed ring variant, the processus vaginalis does not develop, the gubernaculum is absent, and the internal inguinal ring is closed. This is the typical configuration seen with the prune-belly syndrome. In the open ring variant, a patent processus vaginalis exits the internal inguinal ring, and the gubernaculum is present. With the open ring variant, the testis may be “peeping” into the inguinal canal, depending on the length of the processus vaginalis and the testicular vessels.

### Absent Testes

Although unilateral absence (monorchidism) occurs in 4% of patients with cryptorchidism, bilateral absence (anorchidism) occurs in fewer than 1%. Testicular agenesis and atrophy after intrauterine torsion are two mechanisms for testicular absence.

Table 43-1 Evaluation of Bilateral Nonpalpable Cryptorchidism

	Cryptorchidism	Anorchidism	Female Pseudohermaphroditism
<b>Karyotype</b>	46,XY	46,XY	46,XX
<b>Serum testosterone</b>			
Baseline	Normal	Low	Variable
hCG stimulation test	Positive	Negative	Negative
Gonadotropins	Normal	Increased	Normal
AMH/MIS	Positive	Negative	Negative
Adrenal steroid precursors	Normal	Normal	Increased
<b>Ultrasonography</b>			
Gonads	Testes or negative	Negative	Ovaries or negative
Internal ducts	Negative	Negative	Uterus/müllerian system
Genitogram	Male urethra	Male urethra	Urogenital sinus and/or müllerian structures
<b>Laparoscopy</b>			
Gonads	Testes	Blind-ending vessels	Ovaries
Internal ducts	Wolffian	Wolffian	Müllerian

AMH/MIS, anti-müllerian hormone/müllerian inhibiting substance; hCG, human chorionic gonadotropin.

#### VANISHING TESTIS

The term *vanishing testis* indicates that the testicular vessels and a vas deferens are found on surgical exploration, but a testis is absent. In utero infarction of a normal testis by gonadal vessel torsion after gestational weeks 12 to 14 is hypothesized, because ipsilateral wolffian duct differentiation and müllerian duct regression, both of which require ipsilateral testicular hormones, occur normally. Supporting evidence for testicular infarction includes the common finding of hemosiderin and calcium deposits in testicular remnants (“nubbins”) found on exploration.<sup>48</sup> Contralateral compensatory testicular hypertrophy, defined as a testis length of 1.8 cm or greater, has been found to be 90% accurate in predicting monorchia<sup>49</sup> but does not eliminate the need for surgical exploration.

In the evaluation and surgical treatment of nonpalpable testes, the presence of palpable ipsilateral scrotal appendages (i.e., tunica vaginalis, gubernaculum, or vas deferens) and a contralateral descended testis with no hypertrophy is associated with a 93% likelihood of discovering a testis that can be successfully relocated to the scrotum. Conversely, if the ipsilateral scrotal appendages cannot be palpated and the contralateral descended testis is hypertrophied, there is a 96% probability that the impalpable testis is vanished.<sup>50</sup>

#### TESTICULAR AGENESIS

Testicular agenesis may result from failure of the testicular blood supply to develop or from abnormal gonadal ridge differentiation. An example of the latter is 46,XY complete gonadal dysgenesis. However, these individuals are characterized by streak gonads, either female or ambiguous genitalia, and persistence of müllerian structures. The variable phenotypic appearance, including the presence and form of the external genitalia, relates to the time during gestation when the testis differentiation becomes abnormal. True congenital absence of a testis is extremely rare, and absence of both testes results in a female phenotype.

#### BILATERAL UNDESCENDED TESTES

At birth, approximately 1 of every 600 babies has bilateral undescended testes, representing 10% to 25% of patients with cryptorchidism. Because testicular descent is an event of the third trimester, this may be a common physical finding in premature male neonates. It is estimated that at least 6% of patients with bilateral undescended testes have an endocrine disorder as the cause.<sup>51,52</sup>

Bilateral undescended testes, if each testis is palpable, are managed in the same fashion as a unilateral palpable undescended testis. However, the finding of bilateral nonpalpable testes represents a special situation that can have life-threatening implications in the neonatal period, especially in association with hypospadias. The differential diagnosis of bilateral nonpalpable cryptorchidism includes anorchidism, undescended testes (bilateral or unilateral with contralateral absence), and ambiguous genitalia due to female pseudohermaphroditism or another intersex condition. It is this last possibility that necessitates an urgent and thorough evaluation to rule out life-threatening congenital adrenal hyperplasia (CAH). A karyotype, endocrine testing, radiographic studies, and, if indicated, laparoscopy usually provide the necessary information to make an intersex diagnosis (Table 43-1). A normal-appearing masculinized phallus with bilateral nonpalpable testes does not eliminate this possibility (Fig. 43-4). Routine neonatal screening for CAH has aided detection of this entity, but often these state-mandated test results are not available until 7 to 14 days after birth.

In the case in which an intersex disorder has been excluded, endocrine studies (hCG stimulation test, serum AMH level, or serum inhibin B level) may be useful to differentiate bilateral nonpalpable cryptorchidism from anorchia.<sup>53</sup> Administration of hCG can be used to stimulate testosterone production by testicular tissue, to detect its presence biochemically, and may also cause the gonads to become palpable by physical examination. However, false-negative hCG stimulation test



**Figure 43-4** A and B, Newborn infant with bilaterally nonpalpable testis, normally formed scrotum, 3-cm phallus with mild chordee, and urethral meatus at the tip of the glans with complete foreskin. This child is a Prader 5 severely virilized 46,XX female with congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency.

results can occur if there is an unresponsive population of Leydig cells. Therefore, hCG stimulation testing is combined with the measurement of gonadotropins to diagnose anorchia. Markedly elevated gonadotropins before puberty are indicative of anorchidism,<sup>53</sup> but all boys with normal serum gonadotropin levels must undergo exploration regardless of the outcome of the hCG stimulation test.

Measurement of serum AMH can be used to provide additional evidence that testicular tissue is present, and recently this test has become widely available. In prepubertal cryptorchid children, the serum inhibin B level has been shown to negatively correlate with serum (basal or hCG-stimulated) levels of follicle-stimulating hormone (FSH)<sup>54</sup> and to positively correlate with the lack of testosterone response to hCG stimulation.<sup>55</sup> However, serum inhibin B levels can also be somewhat low in children with gonadal dysgenesis or a history of testicular trauma. If the clinical experience with serum AMH and serum inhibin B continues to show reliability, these tests may supplant the need for the hCG stimulation test. The determination of testosterone, its precursors, and dihydrotestosterone, after hCG stimulation, should be reserved for situations in which Leydig cell function needs to be specifically assessed.<sup>56</sup>

Therefore, in an infant with a male genotype, the diagnosis of anorchia can be made based on a low serum testosterone level, a negative hCG stimulation test, increased serum gonadotropins, a negative serum AMH result, a low basal serum inhibin B level, normal levels of adrenal steroid precursors, and radiographic studies demonstrating the absence of

müllerian structures. In equivocal cases, diagnostic laparoscopy and/or open surgical exploration with gonadal biopsy may be required to confirm the diagnosis of anorchia (see Table 43-1).

### TESTICULAR ASCENT

An *ascended testis* refers to a cryptorchid testis, usually one that is palpable, that was previously identified as descended in the scrotum. In the past, this was considered a misdiagnosis caused by an error in physical examination,<sup>57</sup> but the cumulative experience of qualified examiners suggests that it is a real phenomenon.<sup>58</sup> The risk of ascent may be as high as 32% to 50% in cases in which one testis is significantly retractile.<sup>59,60</sup> Ascended testes are typically unilateral (77%), identified in mid-childhood, and located distal to the inguinal canal (77%).<sup>59</sup> Ascended and significantly retractile testes may be prone to the same germ cell maldevelopment seen in congenital cryptorchidism.<sup>59</sup> Ascent is thought to be caused by relative shortening, or lack of elongation, of spermatic cord structures as the affected child grows.<sup>61</sup> The finding of a fibrous remnant within the spermatic cord, possibly an obliterated processus vaginalis, may limit cord growth.<sup>62</sup> Patients younger than 7 years of age who have tight, inelastic spermatic cords appear to be at highest risk for acquired cryptorchidism and should be examined annually until puberty.<sup>60</sup> Ascent may also be iatrogenic after an inguinal hernia repair.<sup>63</sup>



## INCIDENCE AND NATURAL HISTORY

The incidence of cryptorchidism is age dependent, because testicular descent is completed during the third trimester of gestation. Approximately 33% of premature male infants are cryptorchid. The incidence in full-term males at birth is 2% to 4%, and at age 1 year it is 1%.<sup>59</sup> Most undescended testes that descend spontaneously do so during the first 3 months after term, and very few descend after that.<sup>1,7</sup> Unilateral cryptorchidism is more than twice as common as bilateral cryptorchidism (68% versus 32%, respectively), and the right side is affected more often than the left (70% versus 30%).

## RISK FACTORS

### Maternal, Paternal, and Gestational Factors

Maternal obesity, cesarean section, low birth weight, and prematurity have been associated with cryptorchidism, each independently doubling the relative risk over that of the general population.<sup>64</sup> In addition, shorter menses and later menarche were noted in mothers of cryptorchid boys versus controls.<sup>65</sup> Davies and colleagues noted an increased tendency toward threatened abortions, prior miscarriage, and decreased fertility.<sup>66</sup> These observations suggest that the maternal-placental-fetal hormonal state may be abnormal in affected individuals. Cryptorchidism was associated with paternal exposure to pesticides, which may indicate an effect on the paternal germline.<sup>67</sup> Race does not appear to be a significant risk factor.

### Genetic Factors

Cryptorchidism frequently has strong familial clustering, and 14% of cryptorchid boys come from families in which other males are cryptorchid. Cryptorchidism is transmitted in a multifactorial pattern; fathers are affected with an incidence of approximately 4%, and siblings with an incidence of 6% to 10%. The increased incidence of cryptorchidism in first- and second-degree relatives warrants counseling and monitoring of families with cryptorchidism for its appearance in subsequent male children, including nephews and cousins. The frequency of sporadic and familial cryptorchidism suggests that genetic factors are involved.

With the recent increase in mutant mouse models of cryptorchidism, several investigators have performed candidate gene mutation screenings in cryptorchid patients. Mutations have been identified in the following genes: *INSL3*,<sup>68-70</sup> *LGR8*,<sup>70,71</sup> androgen receptor polymorphisms,<sup>72</sup> *HOXA10*,<sup>33</sup> and *HOXD13*.<sup>34</sup> Some of these mutations have been proved to be causal in cryptorchidism.

### Environmental Factors

Some literature suggest that the incidence of cryptorchidism is increasing. One possible explanation is prenatal environmental exposure to a growing group of compounds termed *endocrine disruptors*. Such compounds include DES (synthetic estrogen), DDT (pesticide), nonylphenol (industrial surfactant), bisphenol-A and certain phthalates (plastics additives), and natural phytoestrogens (common in soy products).<sup>73</sup> These chemicals act as estrogen or androgen agonists or antagonists. Ample data from animal and human exposures demonstrate a causal relationship between such chemical exposures and cryptorchidism.<sup>74</sup> The necessary level of exposure (range of parts per billion) is probably very low, so exposure is commonplace. The future challenges lie in defining whether certain individuals are more susceptible,

in delineating whether certain combinations of chemical exposures are more potent, and, ultimately, in effecting prevention of exposure.

## ASSOCIATED ANOMALIES

Multiple factors are involved in normal testicular descent. As a result, many clinical syndromes that affect genetic integrity or the endocrine, musculoskeletal, and nervous systems can be associated with this condition. For example, abnormalities in chromosome number, such as autosomal trisomy, triploidy, and Klinefelter's syndrome (XXY), are commonly associated with cryptorchidism. Deficiencies in pituitary function, testosterone production, 5 $\alpha$ -reductase activity, and androgen receptor sensitivity effectively interrupt androgen activity and can result in cryptorchidism. Infants with abdominal wall defects such as omphalocele, gastroschisis, or umbilical hernia, as well as prune-belly syndrome or bladder or cloacal exstrophy, often have undescended testes. Cryptorchidism is commonly present with an anomalous central nervous system, as in cerebral palsy, mental retardation, and spinal cord abnormalities. Overall, 15% of males with myelomeningocele are cryptorchid, with a 50% incidence among those affected above L4.

When hypospadias is accompanied by bilateral or unilateral cryptorchidism, a thorough investigation to exclude underlying genetic or endocrine abnormalities causing an intersex condition must be undertaken,<sup>75,76</sup> because disorders of sex development (DSD) are present in approximately 30% of these children. If the undescended testis is palpable, there is a 15% risk of intersex; if the undescended testis is nonpalpable, the risk is increased to 50%.<sup>76</sup>

Wolffian duct abnormalities have been reported in approximately 50% of those with undescended testes, including vasal and epididymal agenesis, segmental atresia, and elongation. Frank discontinuity may occur between the testis and epididymis. An elongated, or "long-looping," vas deferens is usually associated with an intra-abdominal testis but may also be seen with an inguinal testis. Patients with bilateral or nonpalpable undescended testes have a higher incidence of such anomalies, and the more proximal the location of the testis, the more severe the epididymal malformation.<sup>77</sup> Epididymal abnormalities are clinically important for three reasons. First, an abnormal vas deferens and epididymis may preclude the option of orchiopexy based on vasal and epididymal collateral blood supply. Second, in cases of disjunction between the testis and epididymis, epididymal tissue in the scrotum may be mistaken for an atrophic testis if surgical exploration is not performed. Third, epididymal anomalies may cause future infertility despite a technically successful orchiopexy.

## DIAGNOSIS

### History

Maternal and paternal prenatal risk factors, including hormone exposures, should be ascertained when evaluating a cryptorchid newborn. A family history of cryptorchidism or genetic or hormonal disorders might suggest further evaluation. In an older child, a history of previously descended testes suggests testicular ascent<sup>57,58,78</sup> and should not prompt criticism of previous examinations. A history of prior inguinal surgery suggests secondary cryptorchidism, though occasionally an inguinal hernia has been repaired without orchiopexy in an infant with an undescended testis, with the erroneous thought that the testis will descend spontaneously.

In adults with undescended testis, a fertility history may be pertinent.

### Physical Examination

A general physical examination is carried out, and any abnormalities are noted. If a testis is not in the scrotum, the cryptorchid testis is sought by gently advancing the examining fingers along the inguinal canal toward the pubic tubercle. This examination is best facilitated by applying lubricant to the groin. The inguinal testis will be felt to “pop” under the fingers. The child may be examined in sitting or squatting position, which occasionally results in identification of a palpable testis that was not palpable in the supine position. If the testis is not found in the inguinal canal, all ectopic sites should be thoroughly examined. Some testes that seem retractile at a young age actually are ectopically attached testes that will ascend with linear growth.<sup>57</sup> Differentiating the true undescended testis from a retractile testis can be challenging, and a second examination in the office is often quite helpful. With experience, these can be delineated, prompting close observation or surgical repair, depending on the certainty of the diagnosis. Nevertheless, in some cases of retractile testes, the diagnosis is confirmed only after examination with the child under anesthesia.

If bilateral nonpalpable cryptorchidism exists, any evidence of intersexuality, including genital ambiguity and scrotal hyperpigmentation, should prompt further evaluation. In cases of unilateral or bilateral cryptorchidism, hypospadias may be a sign of an intersex condition.<sup>75,76</sup> In cases of unilateral nonpalpable cryptorchidism, the contralateral descended testis is examined. Any enlargement may suggest testicular absence or atrophy, although this sign is not specific enough to preclude surgical exploration.

### Localization Studies

If a testis is not palpable, radiographic studies are often employed to localize and assess the presence or absence of a testis. Frequently, cryptorchid patients are referred to the pediatric urologist after an ultrasound study has been obtained. Elder found that 66% of ultrasound studies performed were unnecessary, because he was able to palpate the testis in question during the office visit.<sup>79</sup> Radiographic localizing studies cannot determine with certainty that a testis does not exist, and they cannot rule out the presence of an intra-abdominal testis.<sup>80</sup> Therefore, laparoscopy is the diagnostic procedure of choice for the nonpalpable testis because of its superior accuracy compared to other modalities.<sup>81-83</sup> However, radiographic imaging studies may be useful in certain clinical circumstances, such as the overweight boy with a nonpalpable inguinal testis and in follow-up of cryptorchid boys who, because of comorbid conditions, are not surgical candidates.

## TREATMENT OF CRYPTORCHIDISM

### Age

Therapy for cryptorchidism is usually carried out between 6 months and 1 year of age. Histologic deterioration of the cryptorchid testis has been noted as early as 12 to 18 months. Because testes rarely descend after 6 months,<sup>7</sup> there may be surgical advantages to orchiopexy within the first 6 months, especially in patients with high undescended testis. Decisions regarding orchiopexy after 1 year of age are based on the benefit of the testis to the individual. Although an undescended testis may function poorly for fertility, the usefulness in terms of androgen production must be considered, especially in cases of a solitary testis.

In some cases, a testis is found to be cryptorchid in an adult. Care of the postpubertal unilateral cryptorchid testis depends on the testicular size, ease of placement into the scrotum and health comorbidities. In 2002, a reassessment of the surgical and anesthetic risks and benefits in management of a postpubertal cryptorchid testis was published. For American Society of Anesthesiologists (ASA) class I or II cases, the anesthetic and surgical mortality risk of orchiectomy was greater than the risk of mortality from testicular germ cell malignancy after 50 years of age, and therefore the recommendation was for orchiectomy up until age 50 years.<sup>84</sup> For some patients with comorbid conditions, the risks of surgery may be significant even before this age is reached.

### Indications

The four commonly cited indications to treat cryptorchidism are reduced fertility, testicular cancer, inguinal hernia, and testicular torsion.

### Fertility

At birth and into the first year of life, undescended testes have normal histology, including a normal population of germ cells. Beyond 18 months of age, both light and electron microscopy demonstrate histologic changes suggesting deterioration of the germ cell population of the testis.<sup>85,86</sup> Such histologic changes can also be seen in a contralateral, descended testis after 2 years, suggesting that both the undescended and the scrotal testes can be intrinsically abnormal.<sup>86</sup> Grossly, this deterioration may result in testes that are smaller and softer than normal. Retractable testes are believed to be intrinsically normal, although there has been some debate on this point, possibly because of varying definitions of the term “retractile” and the selection of patients with infertility for adult testicular biopsy, which introduces bias.<sup>87</sup>

Clinically, decreased fertility is a well-recognized consequence of cryptorchidism. Data derived from orchiopexies performed in the 1950s to 1970s indicate that paternity is impaired in approximately 10% to 13% of boys born with one undescended testis and in 33% to 35% of those born with two undescended testes.<sup>88,89</sup> These rates are not significantly different from the control infertility rate of 7% in unilateral cryptorchids but are significantly lower than control in bilateral cryptorchids.<sup>89</sup> Although histologic deterioration was thought to be worse with higher-positioned testes, paternity (which does not necessarily correlate with histology of the undescended testis in cases of unilateral maldescent) may be similar in both abdominal and extra-abdominal unilateral undescended testes.<sup>90</sup> The serum level of inhibin B, an indicator of Sertoli cell function and seminiferous tubule integrity, is lower in boys with a history of cryptorchidism. This may predict impaired spermatogenesis later in life, although there is much overlap of hormone levels between fertile and infertile men.<sup>89</sup> Therefore, it is still not clear whether early orchiopexy ultimately improves fertility, but serum inhibin B levels are suggestive of this trend.<sup>91</sup> Without treatment, bilateral cryptorchidism ultimately results in infertility. Antisperm antibodies, abnormalities of the epididymis and vas deferens, and surgical injury to the vas deferens during orchiopexy may also contribute to infertility in patients with a history of cryptorchidism.

### Malignancy

Given that in all men the lifetime risk of testicular cancer is 0.3% to 0.7%,<sup>92</sup> there is a 3.7- to 7.5-fold increased risk in individuals born with an undescended testis.<sup>93</sup> Approximately



10% of all testis tumors develop in men with a history of an undescended testis. Whereas previous data suggested a four-fold greater incidence of malignant degeneration in an abdominal compared with an inguinal testis, more recent studies failed to confirm this increased risk. The observation that 10% to 20% of testicular tumors in cryptorchid patients occur in the normally descended testis<sup>94,95</sup> suggests that an intrinsic abnormality is present in both testes even if only one is undescended. It was hoped that earlier orchiopexy (age <2 years) would prevent testis cancer, but the data on the timing of orchiopexy are conflicting in this regard.<sup>96,97</sup>

Despite the increased risk compared with the general population, the likelihood of developing testicular cancer in a man with a history of cryptorchidism is no more than 1 in 2000. For this reason, removal of undescended testes is not warranted in the general case. Orchiopexy allows easy examination of the scrotal testis for earlier detection in cases of testicular cancer. The most common testicular tumor in untreated undescended testes is seminoma, whereas the most common type in successfully treated testes is embryonal carcinoma.<sup>94</sup>

Testicular biopsy at the time of orchiopexy may reveal carcinoma in situ (CIS) in both the undescended and the contralateral descended testis.<sup>98</sup> CIS is more common in abdominal testes than in more caudal cryptorchid testes,<sup>99</sup> but such premalignant changes may not be seen in cryptorchid testes treated before adulthood.<sup>100</sup> Although some cases of CIS progress to testicular tumors, the fact that most do not makes the clinical significance and management of this finding controversial. Therefore, the routine use of testicular biopsy at the time of orchiopexy is not generally recommended. However, biopsy is recommended for patients with prune-belly syndrome, abnormal karyotype, ambiguous genitalia, or age greater than 12 years.<sup>97</sup>

### **Inguinal Hernia**

About 90% of undescended testes are associated with an occult inguinal hernia, especially those with minimal descent and those coupled with epididymal abnormalities. Ectopic testes are associated with an inguinal hernia in about 50% of cases. Conversely, up to 6% of inguinal hernias are associated with an undescended testis.<sup>101</sup> Repair of the hernia, if present, is an integral part of orchiopexy.

### **Risk of Torsion**

Testicular torsion occurs more frequently than normal in undescended abdominal testes and is associated with poor surgical salvage rates (~10%).<sup>102</sup> Torsion of the testis in the inguinal canal is unusual. If an undescended testis undergoes postnatal torsion, it can indicate the presence of testicular tumor.<sup>103</sup> Torsion in an undescended testis should be suspected in any male with groin or abdominal pain, an empty hemiscrotum, and a negative surgical history.

### **Risk of Trauma**

An inguinal testis is subject to blunt traumatic injury by compression against the pubic bone. This risk is prevented by orchiopexy or orchiectomy.

### **Psychological Factors**

Preoccupation with a solitary scrotal testis, uncertainty regarding the presence and location of a cryptorchid testis, embarrassment with peers and sexual partners, a tarnished body image, fear of sterility, and other adverse concerns and personality

changes may result as a consequence of cryptorchidism.<sup>104</sup> Theoretically, orchiopexy or placement of a testicular prosthesis could prevent such psychological fears, although this has not been formally studied.

## **NONSURGICAL THERAPY**

Medical treatment for cryptorchidism is based on the hormonal dependence of testicular descent.<sup>105</sup> Both hCG and gonadotropin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LHRH) have been used to induce testicular descent. Systemic testosterone has not been used, because the key factor in testicular descent is a high *local* level of androgens (a paracrine effect).

### **Agents**

#### ***Human Chorionic Gonadotropin***

hCG is structurally similar to LH and stimulates endogenous testosterone production by the testis. An example of a therapeutic dose is 1500 units given intramuscularly per square meter of body surface area twice a week for 4 weeks. The total dose should not exceed 15,000 units. In the United States, hCG is the only approved medication for use in cases of undescended testis. A testicular descent rate of 25% is achieved with hCG, and 18% with GnRH.

#### ***Luteinizing Hormone–Releasing Hormone***

Therapy with LHRH is not approved for use in the United States. A typical course of therapy consists of 1.2 mg/day, in divided doses, for 4 weeks. Trials comparing intranasal LHRH with placebo yielded complete testicular descent rates of approximately 20% versus 5%, respectively.<sup>106</sup> Neoadjuvant GnRH treatment before orchidopexy was found to improve the fertility index in prepubertal cryptorchidism.<sup>107</sup>

#### ***Buserelin***

Buserelin, a synthetic LHRH superanalogue, is administered in very small doses, such as 10 µg every other day for 6 months. It induces testicular descent in 17% of cryptorchid boys,<sup>108</sup> which is similar to the results achieved with either LHRH or hCG. Buserelin may also improve germ cell histology and spermograms obtained after spontaneous descent or orchiopexy.<sup>109</sup> It is available in Europe but it is not approved for use in the United States. Another GnRH analogue, nafarelin, has demonstrated preliminary results similar to those of buserelin.<sup>110</sup>

Success of medical therapy is better for lower testes,<sup>111</sup> although inclusion of retractile testes in some studies may overestimate the success of medical therapy. After successful therapy, the patient should be reexamined periodically, because approximately 15% of successfully treated testes reascend. If a course of medical therapy is unsuccessful, an additional course with the same or another agent is not likely to be beneficial.

Hormone administration is contraindicated in newborns, in patients who are unlikely to respond (e.g., those with postoperative undescended testes or ectopic testes), in patients who cannot anatomically respond (e.g., boys with prune-belly syndrome), and in patients beyond puberty who are endocrinologically normal.

Penile enlargement, frequent erections, scrotal rognation and pigmentation, increased appetite and weight gain, and aggressive behavior are all seen to some degree with hormonal

administration. A potential serious complication of excessive hormonal therapy is premature closure of the epiphyseal plate, limiting long bone growth. Possible imprinting due to high androgen levels in the central nervous system has not been proven to occur but remains a remote possibility.

The overall efficacy of medical treatment in cryptorchid boys is less than 20% and significantly depends on the pretreatment testicular location. Surgery remains the gold standard.

## SURGICAL THERAPY

### Surgical Anatomy

The testis is supplied by the spermatic cord, which contains the ilioinguinal (L1) and genital branches of the genitofemoral nerve (L1-L2), the cremaster muscle, the testicular vessels, the vas deferens, sympathetic and parasympathetic nerves, and the remnants of the processus vaginalis. The fascial layers of the spermatic cord and scrotum include the external spermatic fascia (an extension of the external oblique fascia), the cremasteric or middle spermatic fascia (an extension of the internal oblique fascia), and the internal spermatic fascia (an extension of the transversalis fascia).

The testicular artery, also termed the gonadal or internal spermatic artery, is a branch of the abdominal aorta. The testis also receives blood supply via the cremasteric (external spermatic) artery and the artery of the vas deferens, which are branches of the inferior epigastric and inferior vesical arteries, respectively. Venous drainage of the testis is via the pampiniform plexus of veins, which drains through the gonadal vein into the renal vein on the left and the inferior vena cava on the right. The gonadal vessels course in the retroperitoneum ventral to the ureter before entering the internal inguinal ring just lateral to the inferior epigastric vessels. In 1960, Prentiss and colleagues described the indirect course of the testicular vessels in the retroperitoneum and methods to achieve length by releasing the lateral attachments, thus creating a straight course to the inguinal canal.<sup>112</sup> Lymphatic drainage of the testis is to the retroperitoneal lymph nodes adjacent to the aorta and vena cava but may be altered after orchiopexy to include the superficial inguinal lymph nodes.

### Surgery for the Palpable Testis

The historical outcomes of surgical therapy for cryptorchidism are contrasted in Table 43-2.

### Inguinal Orchiopexy

Examination under anesthesia is performed before any orchiopexy to confirm the choice of incision site. For an inguinal orchiopexy, an inguinal incision is made in the lower abdominal skin crease. After Scarpa's fascia is opened, dissection should be done carefully in case the testis is in the superficial inguinal pouch between the external oblique and Scarpa's fascia. The inguinal ligament and external ring are exposed, and the external oblique is opened in the direction of its fibers. The ilioinguinal nerve is carefully preserved. Cremasteric muscle fibers are separated sharply to expose the spermatic cord. As the testis is drawn out of the wound, the gubernaculum is carefully thinned and divided, with care taken to prevent injuring a looping vas deferens that may precede the testis into the canal. The anterior wall of the tunica vaginalis is opened to expose the testis. Typically, any testicular or epididymal appendages are excised. The spermatic cord is freed proximally to the internal inguinal ring, and all tethering cremaster muscle fibers are teased off the cord or divided. The hernia sac is separated from

**Table 43-2 Historical Results of Surgical Therapy for Cryptorchidism**

Type of Surgery	Success Rate (%)
Surgery based on testicular position	
Abdominal	74
Peeping (internal inguinal ring)	82
Inguinal	87
Prepubic	92
Surgery based on surgical procedure	
Inguinal orchiopexy	89
Transabdominal orchiopexy	81
One-stage Fowler-Stephens orchiopexy	67
Two-stage Fowler-Stephens orchiopexy	77
Microvascular autotransplantation orchiopexy	84

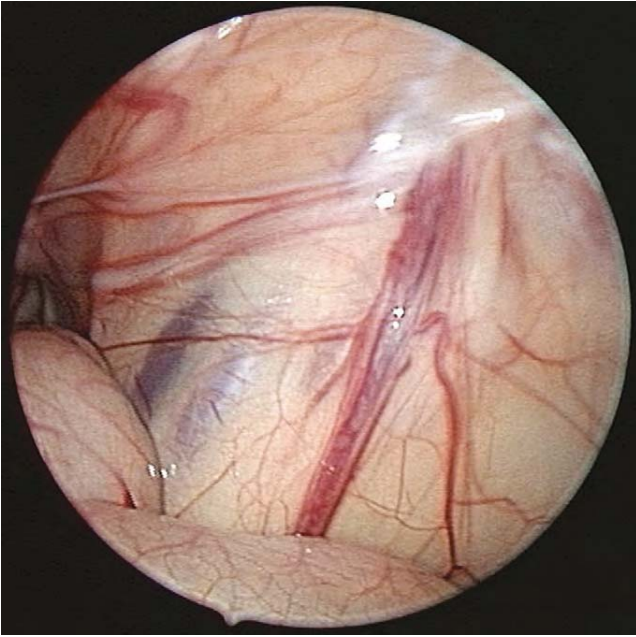
Data from Docimo SG. The results of surgical therapy for cryptorchidism: a literature review and analysis. *J Urol.* 1995;154:1148-1152.

the anteromedial aspect of the spermatic cord at the level of the internal inguinal ring. The hernia sac is ligated at the internal inguinal ring with absorbable suture, and the ligature is held to help expose the retroperitoneal space if additional dissection is necessary to gain cord length. If the cord is still short, preventing a tension-free orchiopexy, the internal inguinal ring is opened laterally, and the peritoneum is bluntly elevated off of the testicular vessels. The lateral spermatic fascia is sharply divided, allowing the vessels a straighter course to the scrotum.<sup>112</sup> The Prentiss maneuver, which consists of dividing the inferior epigastric vessels and transposing the testicular vessels medially to provide a straight vascular course to the scrotum, may be performed, although the length achieved by this maneuver is probably insignificant.

Although there has been some theoretical concern, testicular fixation or intrinsic developmental alterations of the cryptorchid testis do not elicit an autoimmune response against sperm surface antigens at puberty.<sup>113</sup> Fixation in the scrotum has been achieved in various ways. Commonly, a subdartos pouch is created in the anterior wall of the scrotum. The testis may be secured by tightening the dartos behind it or by passing a stay suture through the inferior wall of the scrotum. The placement of this suture is beneath the lower pole of the testis, in gubernacular tissue, in order to avoid the risk of testicular atrophy.<sup>114</sup> The vascular pedicle is inspected to confirm the absence of tension and torsion. The procedure is generally performed on an outpatient basis unless comorbidity requires overnight observation.

If a scrotal stay suture is used, it is usually removed 1 week after surgery. Patients are seen 6 months postoperatively to determine testicular position and size. Recommendations are made for evaluation at puberty to confirm testicular growth and to teach self-examination. For those with congenital or surgical monorchia, warnings are given regarding the benefits of scrotal protection during contact sports activities.

At the time of orchiopexy, ectopic tissue may rarely be identified adjacent to the testis. Examples include spleen and liver tissue (from splenogonadal or hepatogonadal fusion) and adrenal tissue in the form of an adrenal rest. Preoperative awareness and intraoperative recognition of these variations in anatomy should allow proper management and prevent complications.



**Figure 43-5** Laparoscopic view of normal right internal ring anatomy, including vas and testicular vessels exiting a closed internal ring.



**Figure 43-6** Laparoscopic view of abnormal right internal ring anatomy, including vas and blind-ending testicular vessels adjacent to a closed internal ring. (From Baker LA, Jordan GH. Laparoscopic management of the nonpalpable testis. In: Graham SD Jr, ed. *Glenn's Urologic Surgery*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2004:1015-1026. Used by permission from Lippincott Williams & Wilkins.)

### Transscrotal Orchiopexy

Testes that are low in the canal and are believed to be ectopic are good candidates for a transscrotal approach.<sup>115,116</sup> In this approach, the inevitable scrotal incision is made at the beginning of the procedure. The testis is manipulated through the incision, and a stay suture is placed. The ectopic gubernacular attachments are divided, looking for the course of the vas deferens. Any testicular or epididymal appendages are excised. The processus vaginalis is probed to check for patency. In 20% of cases, an inguinal incision will be needed to correct the hernia.<sup>116</sup> The testis and cord are mobilized through the scrotal incision until enough laxity is obtained to achieve orchiopexy without tension. Fixation is achieved as described previously. The technique has been especially useful for reoperative orchiopexy after prior inguinal hernia repair when the testis is close to the scrotum.

### Surgery for the Nonpalpable Testis

Surgery for the nonpalpable testis must determine whether a testicle is present and, if one is found, either place it in the scrotum or remove it. The easiest and most accurate way to locate an intra-abdominal testis is by diagnostic laparoscopy,<sup>117</sup> which can be followed by laparoscopic orchiopexy methods to simultaneously achieve therapeutic goals if a testis is found.<sup>118</sup> Contraindications to laparoscopy include prior abdominal surgery with potential peritoneal adhesions or a body habitus that will not allow for proper placement of abdominal wall ports and laparoscopic instruments.

#### Laparoscopic Surgery

##### DIAGNOSTIC LAPAROSCOPY

As in adults, pediatric diagnostic laparoscopy requires placement of a nasogastric tube and a Foley catheter. Peritoneal access for carbon dioxide insufflation is achieved with the use of techniques specific to the infant and young child.<sup>119</sup>

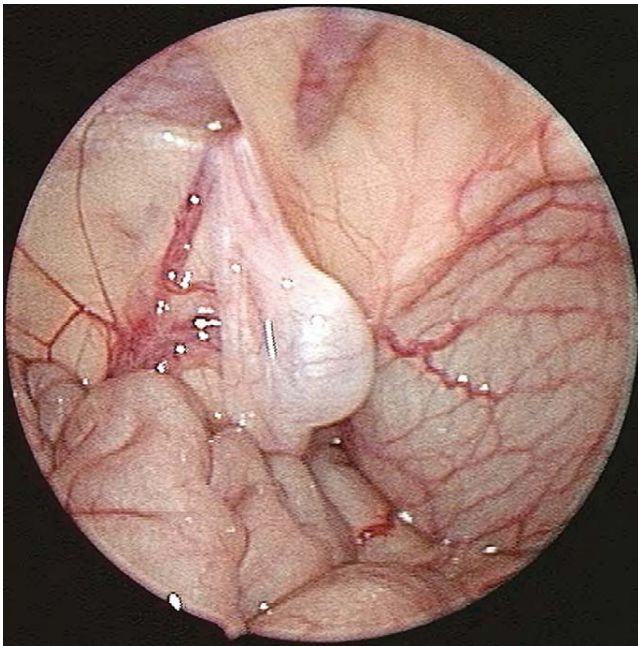
With the patient in Trendelenburg position, each internal ring of the inguinal canal, located just lateral to the inferior epigastric vessels, is inspected. At each internal ring, the spermatic vessels approach in a cranial to caudal direction while the vas deferens courses medial to lateral. Possible anatomic findings on the side of the nonpalpable testis include the following<sup>82</sup>:

1. The spermatic vessels enter the inguinal canal (40%) (Fig. 43-5).
2. A canalicular or peeping testis is found (11.2%) (see Fig. 43-2).
3. The spermatic vessels end blindly (9.8%) (Fig. 43-6).
4. A viable intra-abdominal testis is identified (37%) (Fig. 43-7).

If the vas and spermatic vessels exit the internal inguinal ring, groin pressure can be applied to express a canalicular testis back into the abdomen. If not, inguinal and scrotal exploration for a testicle or testicular remnant should be performed even if the internal inguinal ring is closed, although this is a controversial point.<sup>120</sup> If vessels proceed through the internal ring and there is a closed internal ring, the likelihood of functioning testicular tissue is between 3% and 25%, whereas if a patent internal ring is present, the groin should be explored, because the testis could be present in 75% to 97% of cases.<sup>121</sup>

The observation of blind-ending spermatic vessels is the sine qua non of a vanishing testis, which is considered to be caused by prenatal testicular torsion. In such cases, no further exploration is warranted. If a vas deferens and epididymis are seen but blind-ending spermatic vessels are not identified, testicular-epididymal disjunction may be present, and further exploration<sup>122</sup> near the pericolic gutter or the lower pole of the kidney<sup>123</sup> is required. Placement of secondary cannulas may assist in this examination by allowing retraction and reflection of the colon. If no testis or testicular vessels are found, the imperative to continue exploration and examine the renal hilum remains controversial. As with preoperative





**Figure 43-7** Laparoscopic view of abnormal left internal ring anatomy, including an intra-abdominal testis obscuring the view of its vas and testicular vessels adjacent to the open left internal ring. (From Baker LA, Jordan GH. Laparoscopic management of the nonpalpable testicle. In: Graham SD Jr, ed. *Glenn's Urologic Surgery*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2004:1015-1026.)

localization, radiographic imaging to look for a testis postoperatively has limited value.

When an intra-abdominal testis is found, the appearance of the testis and its position in relation to the internal inguinal ring are noted. Testes lying more than 1 to 2 cm above the ring may not reach the scrotum without division of the testicular vessels.<sup>82</sup> Abnormal testes and those that are clearly dissociated from the vas deferens and epididymis may be removed as the primary form of therapy, depending on the clinical situation and the wishes of the family.

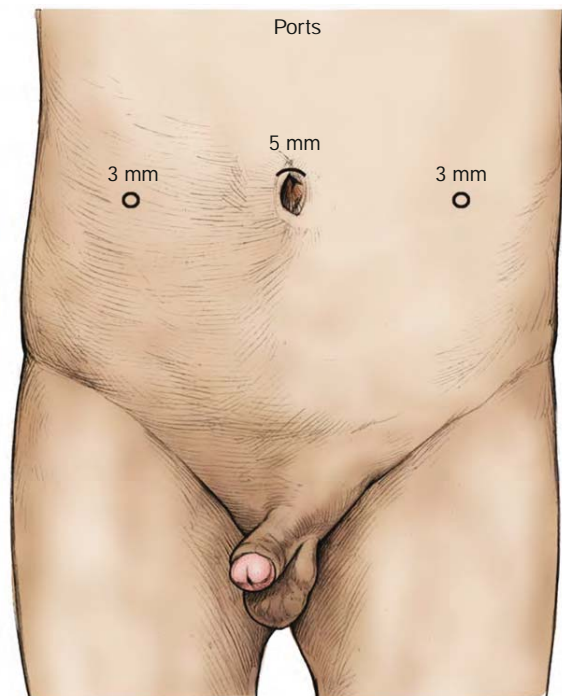
Preoperative administration of hCG has been used by some to try to stimulate descent of the testis to a palpable position and thereby obviate the need for laparoscopy.<sup>124,125</sup> However, approximately 50% of these patients can receive no potential benefit from hormonal therapy because they have an absent or atrophic testis. Virtually all patients with nonpalpable testes will require surgical intervention, even if there is a response to hCG, so the value of hormonal therapy in this situation is debatable.

#### THERAPEUTIC LAPAROSCOPY

There are three laparoscopic procedures that are commonly performed to treat the intra-abdominal testis:

1. Primary one-stage orchiopexy with preservation of the spermatic vessels
2. Orchiectomy
3. Division of the spermatic vessels as the first stage of a two-stage Fowler-Stephens orchiopexy<sup>126</sup>

The second stage of a two-stage Fowler-Stephens orchiopexy can also be performed laparoscopically. In addition to these procedures, laparoscopic-assisted microvascular autotransplantation has been described.<sup>127</sup>

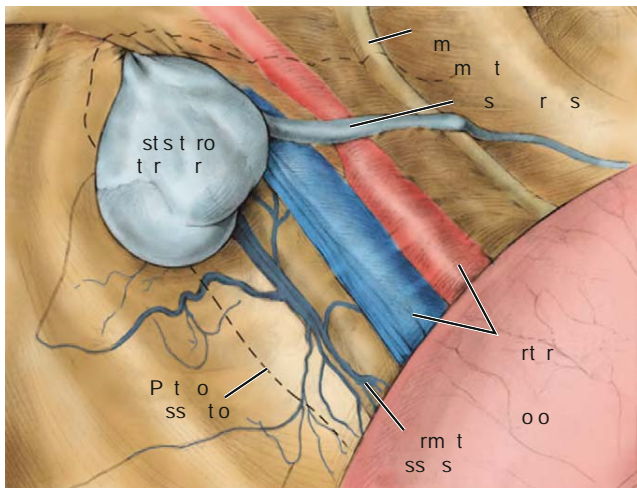


**Figure 43-8** Laparoscopic port placement for standard orchiopexy. A radially dilating trocar is used for open access in the umbilicus, and 2-, 3-, or 5-mm instruments are used laterally as shown. (From Mathews R, Docimo S. Laparoscopy for the management of the undescended testis. *Atlas of the Urologic Clinics of North America*. 2000;8:91-102. With permission from Elsevier.)

Laparoscopic orchiopexy has developed as a standard technique for treatment of the intra-abdominal testis because of its distinct advantages, which include

1. The ability to achieve an extensive vascular dissection to the origin of the gonadal vessels
2. Dissection of the proximal vessels without disturbance to the peritoneum between the vas deferens and the distal spermatic cord, thus preserving the option of a Fowler-Stephens approach
3. High-magnification (15 $\times$ ) and improved visualization during mobilization of the proximal spermatic vessels and gubernaculum
4. The ability to create a new internal ring medial to the inferior epigastric vessels, to achieve a straight vascular course to the scrotum
5. Minimal morbidity in older children and adolescents

To perform laparoscopic orchiopexy after diagnostic laparoscopy,<sup>128</sup> two 2- to 5-mm trocars are placed under direct vision from the umbilical camera (Fig. 43-8). These trocars are placed in the anterior axillary line, just below the level of the umbilicus, on each side. The peritoneum is incised distal to the vas and processus vaginalis and lateral to the spermatic vessels (Fig. 43-9). The peritoneal triangle overlying the distal spermatic cord is left intact to enhance collateral circulation to the testis and to allow a Fowler-Stephens approach, if necessary.<sup>129</sup> A plane of dissection is developed behind the cord (or gubernaculum), and retraction allows identification of the distal extent of the vas deferens. The gubernaculum is divided distal to the vas by electrocautery, and the testis is retracted medially to allow extensive dissection of the vessels for length. If additional length is needed, the proximal peritoneum can be



**Figure 43-9** The laparoscopic anatomy of the undescended left testis. The dotted line indicates the initial peritoneal incision. (From Mathews R, Docimo S. *Laparoscopy for the management of the undescended testis. Atlas of the Urologic Clinics of North America.* 2000;8:91-102. With permission from Elsevier.)

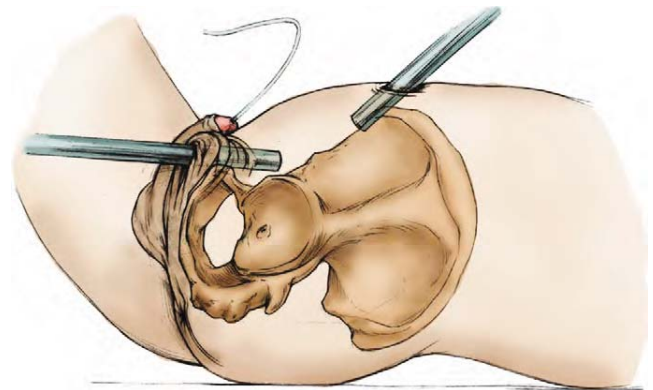
carefully stripped off the anterior surface of the spermatic vessels, leaving the distal peritoneum intact. The testis is drawn toward the opposite inguinal canal as a rough indicator of adequate vascular length. Most testes can be brought down with the spermatic vessels intact. A 2-mm grasper is passed from the ipsilateral trocar, over the pubis, and through an anterior scrotal incision. A radially dilating trocar sleeve is introduced over this grasper into the abdominal cavity and is dilated to 10 mm (Fig. 43-10).<sup>128</sup> A laparoscopic Allis clamp is used to draw the testis out through the scrotal incision as the scrotal trocar is removed. The testis is fixed in a subdartos pouch as for an inguinal orchiopexy. The intra-abdominal gas is expressed, and the trocar sites are closed. The patient is allowed to go home on the day of surgery. Postoperative care is identical to that for an open orchiopexy.

If indicated, laparoscopic orchiectomy is similar to laparoscopic orchiopexy except that, after mobilization of the testis, the vascular pedicle and vas deferens are ligated with endoscopic hemoclips and divided. One 5-mm trocar site is necessary for the clip applicator. The testis is then passed out an abdominal port with graspers, and the procedure is completed as described previously.

Primary division of the testicular vessels as part of a two-stage Fowler-Stephens orchiopexy is a reasonable option if primary orchiopexy is judged to be unwise because of short testicular vessels.<sup>126</sup> The procedure is easily performed laparoscopically, with identification and hemoclip ligation of the testicular vessels. At a second-stage procedure, usually at least 6 months later, the orchiopexy is completed laparoscopically, with special attention to preservation of the collateral blood supply to the testis.<sup>128</sup>

A small testicular remnant, sometimes referred to as a "nubbin," may be identified during exploration for the nonpalpable testis and represents the remains of a vanishing testis. Approximately 10% contain tubular structures with germ cell elements that could potentially undergo malignant degeneration.<sup>48</sup> Some practitioners remove these nubbins based on the presence of germ cells, not the incidence of testicular cancer, which remains undefined for this entity.

Surgical outcomes for the intra-abdominal testis using open versus laparoscopic methods are contrasted in Table 43-3.



**Figure 43-10** Schematic drawing demonstrates the course of the scrotal trocar over the pubic bone and into the peritoneal cavity. (From Mathews R, Docimo S. *Laparoscopy for the management of the undescended testis. Atlas of the Urologic Clinics of North America.* 2000;8:91-102. With permission from Elsevier.)

Despite common belief, on a population basis, initial laparoscopic evaluation of the clinically nonpalpable testicle has been shown to have a cost-saving advantage over initial inguinal-scrotal exploration when reusable laparoscopic equipment is primarily used, disposable equipment costs are kept low, and operating room time for diagnostic laparoscopy meets national standards.<sup>130</sup>

### Open Surgery

Diagnostic laparoscopy for the intra-abdominal testis can be followed by open surgical orchiopexy. An option is the Jones approach, an extraperitoneal approach that utilizes a higher incision than the standard inguinal orchiopexy, extending from the anterior superior iliac spine medially.<sup>131,132</sup> The retroperitoneum is explored through a muscle-splitting incision, and orchiopexy is performed in the usual fashion if a testis is found.

Fowler-Stephens orchiopexy<sup>129</sup> is useful for the short testicular vessels. The testicular vessels are divided, and the testicular blood supply relies on collateral circulation of the artery of the vas deferens and the cremasteric artery. This method can be performed as an open procedure or laparoscopically in one or two stages. However, an open one-stage Fowler-Stephens procedure must be planned in advance before the cord is skeletonized. Temporary occlusion of the gonadal vessels, incision of the tunica albuginea, and inspection of the testis for color and arterial bleeding can be used to confirm adequate collateral blood supply (the Fowler-Stephens test), although this does not necessarily correlate with lack of testicular atrophy.<sup>133</sup> Traditionally, division of the testicular artery has been performed near its origin, but an alternative recently proposed by Koff and Sethi is to divide the testicular artery close to the testis, to preserve collateral blood flow to the vasal artery from the proximal spermatic vessel.<sup>134</sup> The Fowler-Stephens approach requires a vas deferens with adequate length to extend the testis into the scrotum. Contraindications include segmental vas atresia or a detached epididymis, which may interrupt the collateral blood supply to the testis. The Fowler-Stephens technique must be performed meticulously. Testicular atrophy may occur in 20% to 50% of the cases.<sup>134</sup> Although the use of hCG before Fowler-Stephens orchiopexy has been suggested to improve collateral blood flow,<sup>125</sup> there is no experimental or clinical evidence to support this approach.<sup>135</sup>

Table 43-3 Success Rates\* of Open versus Laparoscopic Orchiopexy from Two Large Published Series

	Primary Orchiopexy		One-Stage F-S		Two-Stage F-S	
	n	%	n	%	n	%
Open <sup>133</sup>	80	81.3	321	66.7	56	76.8
Laparoscopic <sup>141</sup>	178	97.2	27	74.1	58	87.9

\*Success was defined as scrotal position and lack of atrophy.

F-S, Fowler-Stephens orchiopexy; n, number of testes.

From Baker LA, Lorenzo A, Jordan GH, Docimo SG. *Laparoscopy and Cryptorchidism. Minimally Invasive Approaches to Pediatric Urology*. London: Taylor & Francis; 2005:161-176. Used by permission from Taylor & Francis.

If the spermatic cord has been dissected and cord length is insufficient for scrotal placement, the options are orchiectomy or staged orchiopexy. The staged orchiopexy is usually performed unplanned.<sup>136</sup> In the first stage, the testis is fixed without tension to the lowest possible site, usually the periosteum over the pubis. The testis and spermatic cord can be wrapped with a Silastic membrane, to facilitate dissection during the second-stage procedure, although there may be little benefit to this maneuver. The second-stage procedure is performed 6 to 12 months later to complete the orchiopexy.

If there is only one testis with extremely short vessels, a microvascular autotransplantation can be considered. Autotransplantation is a technically challenging procedure, and atrophy rates may approach 20%,<sup>137</sup> although higher success rates have been reported.<sup>138</sup> Therefore, this approach may be considered excessive if there is a contralateral normal scrotal testis. Laparoscopy may help identify those testes that would require such an approach.<sup>127</sup> Microvascular autotransplantation requires plastic surgical anastomosis of the testicular vessels to the ipsilateral inferior epigastric artery and vein. The scrotal pouch is developed. After the inferior epigastric pedicle is prepared, the testis is dissected as for a Fowler-Stephens approach, but the vessels are divided as high as possible. A microvascular anastomosis is then performed by someone familiar with the technique. Postoperatively, bed rest is maintained for 48 hours; the use of anticoagulants has not been routinely described.

Surgery after prior failed orchiopexy or for testicular ascent after hernia repair can be especially challenging.<sup>139</sup> Parents must be aware that the procedure might result in orchiectomy if sufficient vascular length cannot be achieved. The approach depends on the position of the testis but usually proceeds through a standard inguinal incision. Sometimes, an en bloc dissection of the cord with surrounding structures is necessary to preserve the vessels, but in other circumstances, the vascular pedicle and vas can be dissected free of surrounding structures in a fairly straightforward manner. The method of dissection depends on the anatomy at hand, but the principles of orchiopexy are similar to those in the primary situation.<sup>140</sup> It is important to realize that the testis often has flipped up over a fixed cord, so the orientation of the testicle is unpredictable.

## COMPLICATIONS OF ORCHIOPEXY

Complications of orchiopexy are relatively uncommon. The most important surgical complication of orchiopexy is *testicular atrophy*, which may result from four causes:

1. Injury to the spermatic vessels during standard orchiopexy
2. Tension on the spermatic vessels with subsequent ischemia
3. Inadvertent torsion of the spermatic vessels when passing the testis into the scrotum
4. Intentional ligation of the vessels as part of a Fowler-Stephens orchiopexy

Any of the complications of inguinal hernia repair can also occur during orchiopexy. Testicular retraction may result from short testicular vessels, inadequate mobilization of the testicular vascular pedicle, incomplete division of the cremasteric muscle fibers to the testis, or improper scrotal fixation of the testis.

## CONCLUSION

The etiology of testicular maldescent remains unknown, although recent advances in molecular understanding of testicular descent are shedding some light. Whatever the underlying cause, the undescended testis deserves treatment early in life to prevent loss of spermatogenic potential and to allow early detection of testicular malignancy, should it occur. Treatment can be through hormonal manipulation or surgery, and the choice depends on age and testicular location. Surgery for the palpable testis remains most commonly an inguinal approach with retroperitoneal dissection as necessary. The nonpalpable testis is most commonly approached laparoscopically, and the success rate of laparoscopic orchiopexy may exceed that of more traditional open approaches. In the future, a more complete understanding of the biology of testicular descent may allow more specific non-surgical therapy or decrease the need for orchiopexy.

## REFERENCES

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