The Undescended Testis

John M. HUTSON

Testicular descent has been a confusing subject for many years because it is not a simple mechanism. Numerous hormonal and mechanical factors were alleged to be important, but often after conflicting experimental evidence. The proposal that normal descent occurs in two separate mechanical stages under independent hormonal control has helped resolve some of the controversy.

Normal descent

For a short while after sexual differentiation at 7-8 weeks of gestation, the location of the developing testis and ovary is identical. After 10 weeks, the testis moves relatively closer to the inguinal region than the ovary. This process has been termed "transabdominal descent", although in fact the testis is held near the groin while the ovary moves further away with embryonic growth, staying near the kidney, as in rodents, or the pelvic brim, as in humans [33,40].

The mechanical cause for transabdominal descent of the testis is likely to be the gubernaculum, or genito-inguinal ligament [15], although the cranial suspensory ligament of the gonad is also sexually dimorphic [41,42]. In the male, the gubernaculum enlarges at its caudal end by accumulation of extracellular matrix and water; simultaneously the cranial suspensory ligament regresses. By contrast, the female gubernaculum remains thin and elongates in proportion to fetal growth; the cranial suspensory ligament persists.

The hormonal control of the first phase is non-androgenic. In patients with a mutation in the gene for Müllerian inhibiting substance (MIS), the gubernaculum does not enlarge normally and the testes fail to undergo normal transabdominal descent, which suggests that MIS may mediate this step [16,20]. Direct experimental evidence, however, is lacking, with some studies failing to show a role for MIS [5,38].

The second, or inguinoscrotal phase, occurs at 28-35 weeks of gestation in humans, or the first postnatal week in rodents [4,13]. The gubernaculum bulges through the future external inguinal ring and then migrates across the pubis and into the scrotum. Meanwhile the processus vaginalis develops as a peritoneal diverticulum within the gubernaculum so that the intra-peritoneal testis can descend to the scrotum. The distance across which the 1 cm diameter gubernaculum must traverse is 3-5 cm. Control of this migration until recently has been obscure.

Androgens are responsible for initiating inguinoscrotal migration [21], but there has been scant evidence for a direct action on the gubernaculum [12,30]. Most studies have suggested that androgens may act indirectly since androgen receptors have not been identified in the gubernaculum [30] or have been found at a different time [7].

Some years ago we proposed that androgens control inguinoscrotal migration via the central nervous system and the genitofemoral nerve, which supplies the gubernaculum [18]. A large body of evidence now has been collected to support this apparently counter intuitive view (Table 1). The GFN motor nucleus in the lumbar spinal cord develops sexual dimorphism in response to prenatal exposure to testosterone [25]. Furthermore, the nucleus was found to contain sexually dimorphic amounts of Calcitonin Gene-related Peptide (CGRP) [25]. Surgical in-

Table 1. Role for GFN in inguinoscrotal descent

Neonatal GFN transection causes UDT in rats (2)
Neonatal GFN transection blocks gubernacular migration (4)
36% UDT in boys with L1-3 spina bifida (17)
Neonatal thoraco-lumbar cord injury in rats causes UDT (17)
GFN supplies scrotum before gubernaculum migrates
GFN motor nucleus sexually dimorphic (25)

terruption of either the GFN peripheral fibres or the spinal cord in neonatal rats predisposes to cryptorchidism [2,17] while myelomeningocele affecting the GFN nucleus leads to cryptorchidism [17].

Following identification of CGRP in the GFN, we have investigated its involvement in testicular descent, using whole animal studies and an organ culture system for the gubernaculum (Table 2). The cremaster muscle within the gubernaculum contains receptors for CGRP [46] which are upregulated after prior denervation at birth [45]. In organ culture, the gubernaculum responds to exogenous CGRP with rapid, rhythmic contractions of its tip, similar to fetal heart contractions [26,27,32]. Contractility in organ culture and receptor binding are maximal in the first postnatal week of mice, which coincides with migration *in vivo* [36,45]. Synthetic analogues of CGRP can block both contractility in organ culture [26] and migration *in vivo* [31]. All these studies, taken together, are consistent with the hypothesis that androgens control gubernacular migration indirectly via release of CGRP from the nerve.

Table 2. Role for CGRP in inguinoscrotal descent

Neonatal male GFN contains CGRP (25)
CGRP receptors in gubernacular cremaster muscle (46)
CGRP receptors up-regulated after neonatal GFN transection (45)
CGRP receptors maximal in gubernaculum during migration (45)
CGRP causes rhythmic contractility of rodent gubernaculum in vitro and in vivo (26,27)
CGRP (8-37) inhibits contractility of rodent gubernaculum in vitro (26)
CGRP (8-37) delays descent in neonatal mice in vivo (31)
CGRP induced contractility maximal in vitro at time of migration in vivo (36)

Cause of undescended testes

Most undescended testes are caused by abnormal or deficient migration of the gubernaculum during the inguinoscrotal phase, as they are palpable in the groin. Derangement of the transabdominal phase with intra-abdominal testes is uncommon, being less than 10 % in most series [19]. At surgery for the common inguinally-located undescended testis, traction on the gubernaculum shows that it is attached just above or lateral to the neck of the scrotum. This is consistent with deficient unilateral migration and may indicate ipsilateral anomaly of the GFN.

A few undescended testes are caused by recognizable anomalies in hormone function, such as androgen deficiency syndrome or persistent Müllerian duct syndrome. Many genetic disorders of connective tissue metabolism have cryptorchidism which may be secondary to disruption of migration through the tissues.

In a number of laboratory animals cryptorchidism is caused by abnormality of the GFN and/or CGRP (Table 3). Both the androgen-resistant mutant mouse (testicular feminizing mouse, TFM) and rats exposed prenatally to the anti-androgen, flutamide, have an androgenic defect. In both models gubernacular migration is deficient and the GFN spinal nucleus is smaller and contains less CGRP than normal [8,9,25]. Gubernacula removed from these animals show decreased or absent endogenous con-

Table 3. Summary of studies of 3 models of cryptorchidism

Model	TFM mouse	Flutamide rat	'TS' rat
Cause	absent androgen receptor	prenatal anti-androgen	unknown
Gonadal position	bladder neck	external ring	external ring
Gubernacular migration	absent	deficient	deficient
Gubernacular contractions	absent	deficient	deficient
CGRP receptors	-	increased	decreased
Receptors after GFN cut	-	-	increased
Contractions with CGRP	hypersensitivite	hypersensitive	insensitive
Contractions with CGRP after GFN cut	-	-	sensitive
Gubernacular growth with CGRP in vivo	increased	-	-
Size of GFN nucleus	decreased	decreased	increased
CGRP content of nucleus	decreased	decreased	increased
References	(25)	(9,10,35)	(8,10,35,37)

tractions in organ culture, however, on exposure to exogenous CGRP they have greatly enhanced contractility [10].

In another mutant rat with cryptorchidism (TS) gubernacular migration is deficient but the GFN spinal nucleus is larger and contains more CGRP than normal [8]. The gubernaculum is inert in organ culture, even with exogenous CGRP [10], which is correlated with down-regulation of CGRP receptors [35]. These results suggested that the GFN released excess CGRP which "swamped" the gubernaculum, so recently we have examined the effect of denervation in TS rats. After GFN transection at birth both the CGRP receptors and the contractility recovered to normal [37].

The cryptorchid animal models provide convincing evidence that different aberrations of the androgen-GFN-CGRP axis can lead to the same end point of deficient gubernacular migration and undescended testes. This idea has important implications for treatment of humans, as it implies that exogenous CGRP may be useful as a treatment for cryptorchidism.

Acquired undescended testes

Nearly 5 % of male term infants have an undescended testis at birth, although over half of these subsequently descend in the first 12 weeks [22]. Longitudinal studies have shown, however, that many testes that descend postnatally become secondarily undescended later in childhood [1,23,43], and have come to be called "ascending testes". In addition, it has been observed that many boys present at 5-10 years of age with "undescended" or retractile testes but no past history of an anomaly. Surgeons assumed that the diagnosis made has been missed previously. An alternative, and potentially iconoclastic view is developing that these older children have acquired malposition.

In a review of cryptorchid boys with cerebral palsy, the distance from the external ring to the testis was measured in infants and compared with older boys. The spermatic cord in normal controls increased in length from 6.1 cm in infants to 7.3 cm at 8 years, while in cerebral palsy patients the cord was 5.2 cm in infants and 5.6 cm in 7.6 years [34]. This suggested that elongation of the spermatic cord is necessary for the testis to remain within the scrotum as the boy grows. By contrast, factors which prevent cord elongation (eg: spasm of cremaster muscle), lead to delayed malposition.

Classification of undescended testes into congenital and acquired categories enables a more rational approach to both aetiology and management. Failure of gubernacular enlargement or migration may lead to congenital cryptorchidism, while failure of the spermatic cord to grow postnatally leads to acquired anomalies such as ascending and retractile testes. The underlying cause for the latter may be either abnormality of the cremaster muscle (eg: cerebral palsy) or failure of the processus vaginalis to obliterate completely. Orchidopexy for older children often requires division of a fibrous remnant of or even a patent processus vaginalis, suggesting that it may be tethering the spermatic cord.

Treatment

Undescended testes need treatment to correct the cosmetic deformity, allow normal fertility and prevent the development of tumours later in life. The cosmetic problem is easily corrected, but it is less certain whether intervention alters the risk of infertility or malignancy. In patients with ambiguous genitalia and dysplastic testes in association with cryptorchidism, there is a clear primary anomaly. By contrast, most patients with undescended testes have nothing else wrong; biopsies of these testes in infancy show normal histology, with dysplasia seen later (after 1-2 years) and worsening with age.

Recent studies of hormonal function [44] show no abnormality at birth but derangement within the first year; germ cell becomes abnormal after 6-12 months [14]. The postnatal surge in testosterone at 2-4 months is blunted in patients with undescended testes [6], as is the peak of secretion of MIS between 6-12 months [44]. The function of these hormones in the first year is unknown, but there is recent evidence that MIS may be involved in early development of the germ cells, which has important implications for subsequent fertility [48].

Organ culture of the neonatal mouse testis shows that early maturation of germ cells is dependent on the presence of MIS; deficiency or blockade of MIS with antibodies arrests germ cells at the gonocyte stage. Importantly, this is the same stage that is arrested in humans with undescended testes [14]:

Failure of transformation of gonocytes. Depletion of the prepubertal germ cell population is the cause for oligo- or azoospermia in adults. The promising effect of MIS in experimental animals suggests that a clinical trial is required to see if MIS treatment could correct the defect in germ cell maturation. Orchidopexy should be timed to prevent significant hormonal and morphological derangements in the testis, although whether this goal can be achieved by early operation is not yet proven in humans.

Animal studies, however, suggest that orchidopexy prior to the development of secondary anomalies allows normal adult function [28,29]. At present we can only extrapolate from these studies to the human, and recommend operation in infancy (6-24 months), with the proviso that elective surgery in small infants requires a surgeon to be adequately trained in pediatric surgical technique. Neonates with combined inguinal hernia and undescended testis should have immediate operation to avoid strangulation of the hernia. Boys with undescended testes presenting later in childhood should have orchidopexy once the testis is no longer resident within the scrotum; doubtful cases of ascending or retractile testes should be reviewed annually, as the situation may worsen with growth. My own view is that the testis should be able to remain in the scrotum without traction on the cord, although this is not standard teaching. Once it was thought that being able to pull the testis into the scrotum was sufficient, however, this is more a demonstration of clinical skill than an estimate of testicular function.

Secondary degeneration of the undescended testis is caused by the abnormally-high temperature of the groin; inhibiting most cell functions [49]. The scrotum is a specialized, low-temperature environment (38° C) for the testis, and testes that are not resident within it will develop slowly progressive dysfunction.

The standard orchidopexy for an undescended testis is well described and needs no elaboration; of more importance is the new ways to approach special situations, such as the impalpable testis. Unilateral impalpable testes may be intra-abdominal or atretic, perhaps secondary to perinatal torsion during testicular descent. Identifying the exact location or fate of the testis is now accomplished readily by laparoscopy: atretic gonads can be identified by blindending testicular vessels, dysplastic testes can be removed, and well-formed gonads can be brought to the scrotum in one or two stages. A staged Fowler-Stephens procedure with clipping or ligation of the vascular pedicle laparoscopically is becoming popular.

Bilateral impalpable testes need an hCG-stimulation test to determine whether any gonadal tissue is present. It is prudent to remember that this test determines the presence of Leydig cells by their androgen production, but intra-abdominal testes may contain only Sertoli cells, and be "silent". Newer tests, such as serum MIS levels, may be useful to identify the presence of Sertoli cell-only gonads.

Acquired maldescent is easily corrected by a scrotal approach, as described by Bianchi [13] although hormone therapy may induce descent [11,24]. Indeed, hCG treatment has been suggested as a test to discriminate between congenitally undescended testes (which are unresponsive) and retractile testes (which do respond) [24]. Hormone therapy is effective because it induces precocious pubertal development with growth and relaxation of the cremaster muscle; it also causes precocious germ cell development [47]. At present there are some concerns that precocious germ cell antigens may be exposed to the immune system prior to the normal development of the blood-testis barrier [39].

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John M. Hutson, MB MD FRACS
Department of General Surgery
Royal Children's Hospital
Victoria