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Anatomical and Functional Aspects of Testicular Descent and Cryptorchidism*

JOHN M. HUTSON, SUZANNE HASTHORPE, AND CHRIS F. HEYNS

F. Douglas Stephens Surgical Laboratory, Royal Children's Hospital Research Foundation, and Department of Paediatrics, University of Melbourne Urology Department, Parkville, Victoria, Australia (J.M.H., S.H.); and Tygerberg Hospital and Faculty of Medicine, University of Stellenbosch, South Africa (C.F.H.)

I. Normal Development

A. Anatomical aspects

TESTICULAR descent to the scrotum is a profound example of sexual dimorphism that cannot be fully explained as yet. It is not a simple process, but appears to be multistaged, with various anatomical factors and hormonal influences. During mammalian evolution the male gonad has assumed a progressively lower position relative to that of the ovary, eventually taking up an extraabdominal location within a scrotum in most modern mammals (1, 2). The exact site and structure of the scrotum varies among species with, for example, some modern marsupials having a prepenile scrotum (3). The essential physiological feature, however, is that the scrotum is a specialized, low-temperature environment that allows the extraabdominal testis to be maintained at a temperature below that of the rest of the body (4).

1. Sexual development. The urogenital ridge in humans is identical morphologically in males and females up to 7–8 weeks of gestation (5). Sexual differentiation begins with the testis-determining gene (SRY) on the Y chromosome triggering testicular differentiation by unknown mechanisms (6). Recent studies suggest a role for steroidogenic factor 1 (the Ad4-binding protein) in gonadal development (7, 8) and regulation of the Müllerian inhibiting substance (MIS) or anti-Müllerian hormone gene (9). MIS itself also has been proposed to have a role in gonadal differentiation (10). Once a testis is formed, both MIS and testosterone are involved in altering the anatomy of the male embryo (11, 12). MIS causes regression of the Müllerian ducts whereas testosterone secretion directly into the Wolffian duct permits its continuing development into epididymis, vas deferens, and seminal vesicles (13, 14).

In human embryos between 10 to 15 weeks of gestation, the testis remains close to the future inguinal region during enlargement of the abdominal cavity while the ovary moves relatively more cranially (5). Similar relative movement is observed in fetal mice between 14 and 18 days of gestation on scanning electron microscopy (EM) (15) (Fig. 1) and in fetal rats (16). There have been numerous suggestions that no actual movement of the testis occurs (17, 18), although quantitative assessment of fetal mice confirms relative movement (15) (Fig. 2).

The testis is anchored near the future inguinal canal by enlargement of the caudal ligament of the testis, known as the gubernaculum, and regression of the cranial suspensory ligament. The gubernaculum was described first in 1762 as the genitoinguinal ligament or 'gubernaculum,' because it appeared to direct the course of the testis to the scrotum (19). In this century, enlargement of the gubernaculum in males was observed to tether the testis near the groin while the kidney migrated cranially (20, 21). Simultaneously, regression of the cranial ligament holding the urogential tract near the developing diaphragm allows gonadal descent (22) (see Fig. 1).

The gonadal positions deviate further after 25 weeks of gestation, when the gubernaculum bulges beyond the external inguinal ring and descends to the scrotum, while simultaneously it is hollowed out by a peritoneal diverticulum called the processus vaginalis (23, 24) (Fig. 3). The processus vaginalis allows the previously intraabdominal testis to exit from the abdominal cavity (18). The bulky caudal end of the gubernaculum, which is known as the bulb, is resorbed after completion of migration in humans (24) and pigs and before

Address reprint requests to: J. M. Hutson, M.D., General Surgery, Royal Children's Hospital, Parkville Victoria 3052, Australia.
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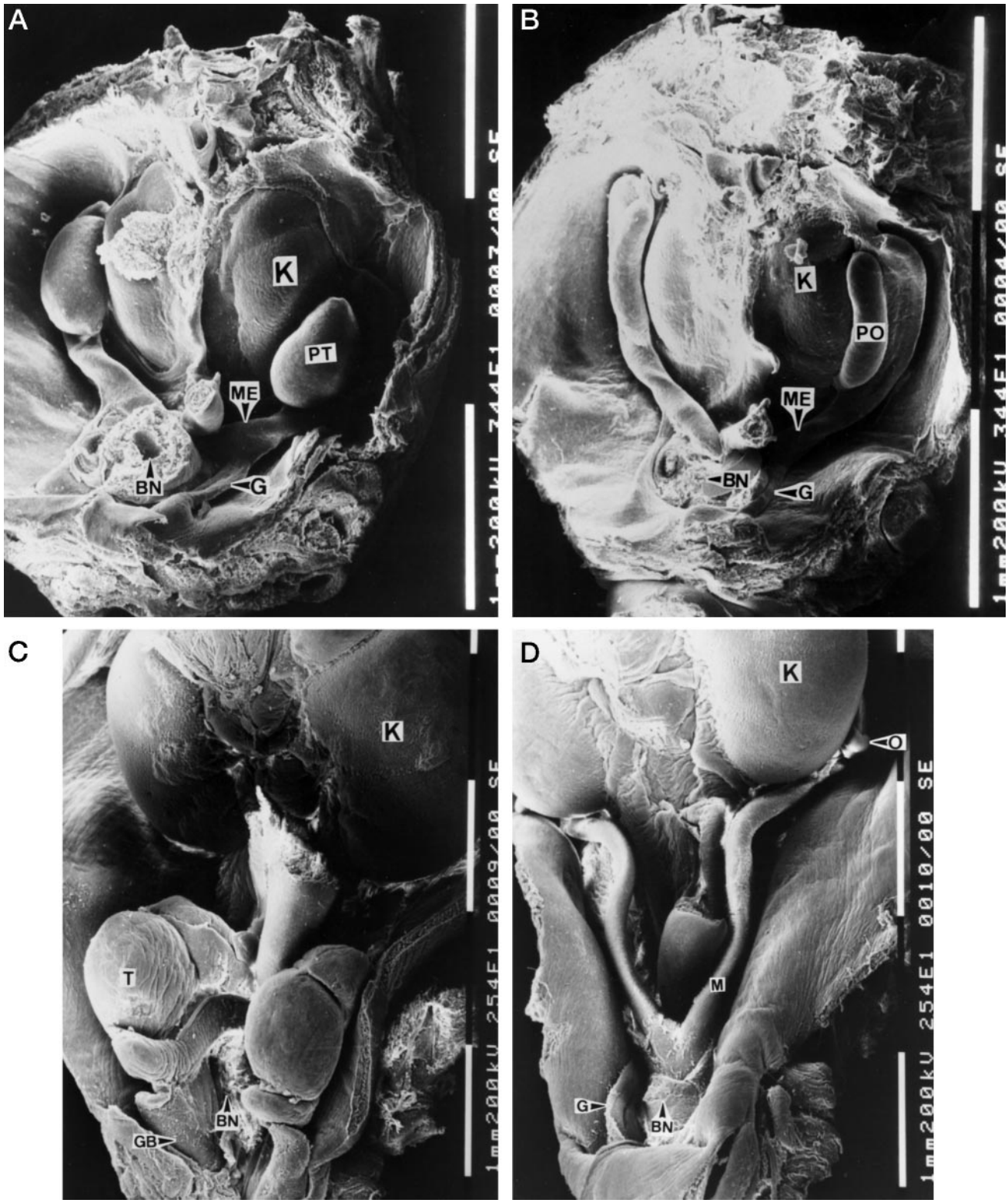

FIG. 1. Scanning EM of male and female fetal mice. A, Day 14 male. Primitive testis (PT) and kidney (K) are situated near bladder neck (BN). Mesonephros (ME) is connected to inguinal region by gubernaculum (G). B, Day 14 female. Primitive ovary (PO) and kidney (K) are located near bladder neck (BN) as in male. Gubernaculum (G) is also similar to the male. C, Day 18 male. The testis (T) is near bladder neck (BN) while the kidney (K) is now higher. The gubernacular bulb (GB) is enlarged. D, Day 18 female. The ovary (O) and kidney (K) are both high in the abdomen. The Müllerian ducts (M) are developing into the uterus while the gubernaculum (G) remains long and thin. [Reproduced with permission from T. Shono *et al.*: *J Urol* 152:781–784, 1994 (15). © Williams and Wilkins.]

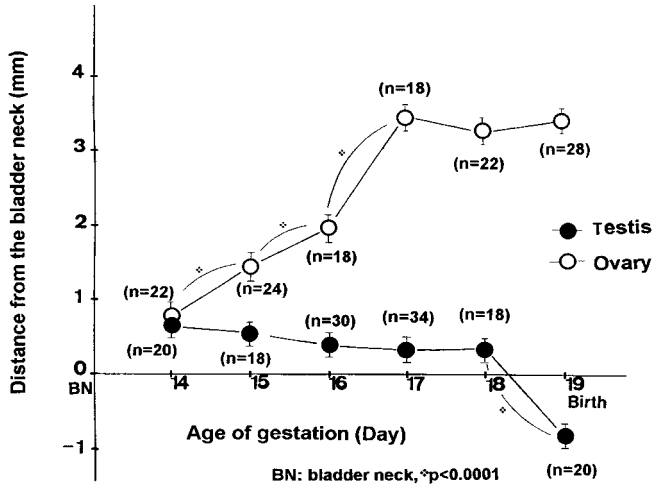

FIG. 2. Distance from lower pole of gonad to bladder neck (mm) *vs.* age of gestation (days). *Positive numbers* reflect gonads cranial to bladder neck (n = number of gonads measured). [Reproduced with permission from T. Shono *et al.*: *J Urol* 152:781–784, 1994 (15) © Williams and Wilkins.]

migration in rodents (25). The differences in timing of matrix resorption among species are unexplained but do not change the fundamental anatomical processes.

Multistaged testicular descent was proposed first by Gier and Marion (26) as initial downward displacement of the gonads by the developing metanephros, transabdominal movement to the groin, and finally descent through the inguinal canal and down to the scrotum. By 7 weeks of gestation the first step is complete, thereby precluding it having a major role in sexual dimorphism. Separate phases of testicular descent have been proposed by other authors (27, 28, 30); however, a two-stage model with separate morphological steps and hormonal control has been suggested more recently (31, 32) (Fig. 4).

2. The gubernaculum. Caudal enlargement of the gubernaculum during relative transabdominal movement of the testis is known as the "swelling reaction" or "gubernacular outgrowth" and is caused by cell division and an increase in glycosaminoglycans and hyaluronic acid (33). The hydrophilic nature of hyaluronic acid makes the end of the gubernaculum bulky and gelatinous. Subsequently, the gubernaculum involutes, presumably by removal of the extracellular matrix, leaving a fibrous remnant that attaches the testis and caudal epididymis to the scrotum after descent.

The proximal gubernacular cord appears to shorten during testicular descent, as it becomes incorporated into the enlarging bulb (34–36). Shortening of the cord may be an important part of the mechanism of positioning the testis over the inguinal ring to permit abdominal pressure to push the testis out of the abdomen (18, 37–39).

Transection of the cord frequently leads to either accidental gonadal descent into the contralateral inguinal canal or to aberrant intraabdominal sites (38, 40–42). For example, abnormally long gubernacular cords associated with intraabdominal testes have been found recently in transgenic mice with a mutant *Hoxa-10* gene (43, 44). Both the cord and the bulb are sites of strong *Hoxa-10* expression, both during sexual differentiation and postnatally in the male.

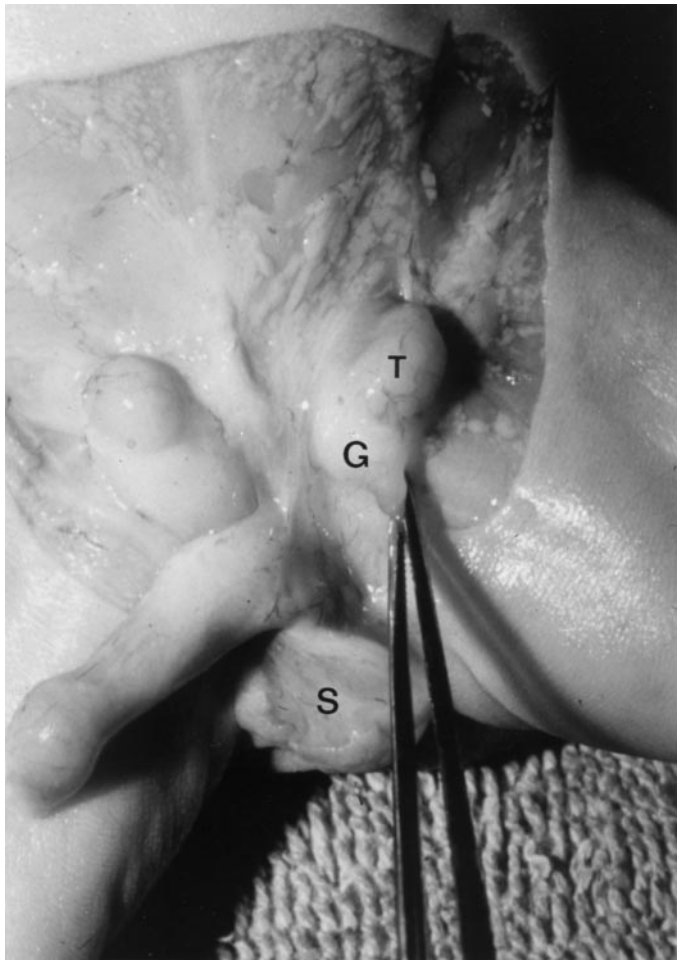

FIG. 3. Dissection of 32-week human fetus showing the testis (T) and gubernaculum (G) migrating across the pubic region toward the scrotum (S). A pair of forceps holds the caudal end of the gubernaculum.

The inguinoscrotal phase of descent requires significant movement of the gubernaculum. Regression of the bulky gubernacular bulb, which is particularly prominent in the pig, was thought to be sufficient to allow the testis to reach the scrotum (34–36). A significant migratory phase of the gubernaculum in humans (23) and rodents (25) has been demonstrated recently, although this is disputed by some authors in favor of inversion/eversion of the gubernacular cone, as seen in rodents (45–47). The caudal end of the gubernaculum extends progressively from the inguinal ring across the pubic bone and into the scrotum. This migration cannot be explained by eversion of the gubernacular cone, as its length is significantly less than the distance to the scrotum (S. Lam, T. Clarnette, and J. M. Hutson, unpublished results).

3. Cranial suspensory ligament. The cranial suspensory ligament regresses in male embryos to allow normal gonadal descent (22). Whether or not it is the key factor in descent, however, is disputed. Most authors agree that the cranial

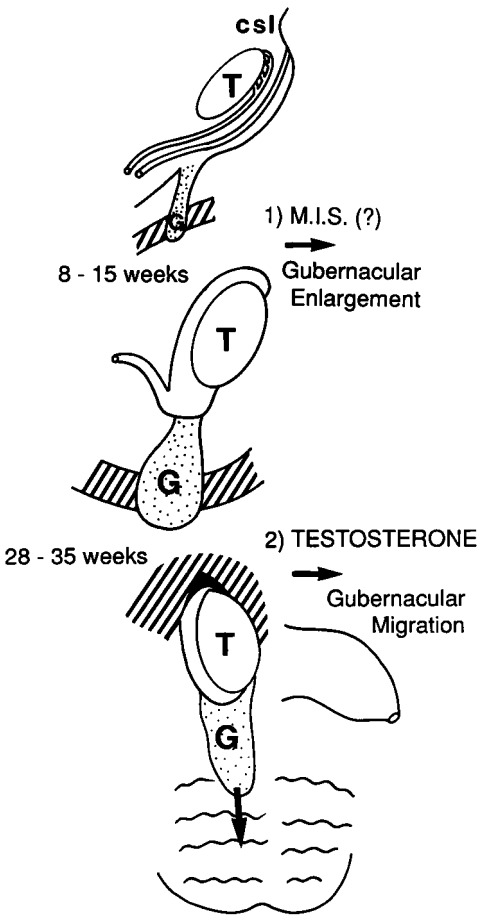

FIG. 4. Schema proposing two main steps of testicular (T) descent in the human. Between 8 and 15 weeks the gubernaculum (G) enlarges in the male, holding the testis near the groin. The cranial suspensory ligament (CSL) regresses. At 28–35 weeks, the gubernaculum migrates across the pubic region to the scrotum. [Reproduced with permission from J. M. Hutson and S. W. Beasley: *Descent of the Testis*, 1992 (149).]

ligament, and probably also the gubernacular cord, has a limited role in at least some species (37, 48, 49).

4. Abdominal pressure. Abdominal pressure has an ancillary role in facilitating gonadal exit from the abdomen (18, 39, 41). While intraabdominal pressure is not a factor during transabdominal descent, it assumes much greater importance in transit through the inguinal canal and subsequent migration to the scrotum (26, 40, 41, 45, 46). Pressure to push the gonad down the processus vaginalis is likely to be important in males but nevertheless does not occur in females because of their different gubernacular and cranial suspensory ligament anatomy (37). The force of intraabdominal pressure not only may be applied directly to the testis, but also may act indirectly by creating the tip of the processus vaginalis and thereby stabilizing it so that the gubernaculum can exert some traction on the testis (49).

In summary, although controversial, current knowledge suggests that transabdominal testicular descent is associated with regression of the cranial suspensory ligament and enlargement of the gubernacular bulb with traction applied by the bulb through the gubernacular cord to the urogenital ridge. The net effect of these processes appears to be to anchor the developing testis near the inguinal region during growth of the fetal abdomen (Fig. 5). Passage through the inguinal canal needs development of the processus vaginalis, prior dilation of the canal by the gubernacular bulb, and some intraabdominal pressure to force the testis through the canal. Inguinoscrotal descent requires migration of the gubernaculum over a considerable distance compared with its size, along with an increase in length of the processus vaginalis. The force for movement may come from the intraabdominal pressure, transmitted directly and indirectly to the testis via the lumen of the processus vaginalis and the gubernacular cord, respectively. The factor(s) controlling the direction of migration remain unknown.

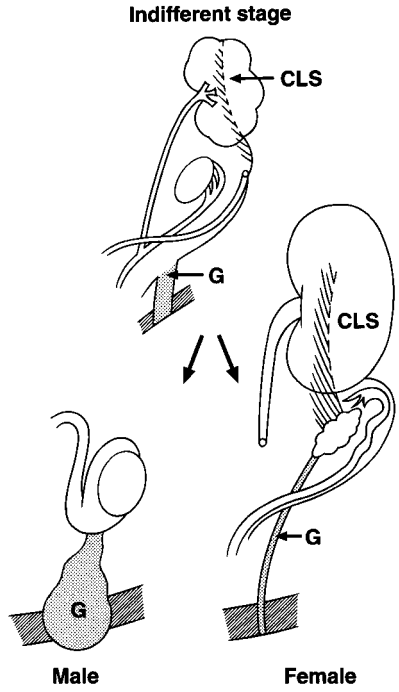

FIG. 5. Schema showing cranial suspensory ligament (CSL) and gubernaculum (G) in sexual differentiation of rodents. Both ligaments are present in the indifferent stage. In males, the CSL regresses while the gubernaculum enlarges. By contrast, in females the CSL persists and the gubernaculum also remains, but as thin and elongated.

B. Hormonal control and functional aspects of testicular descent

Regulation of transabdominal descent centers around the control of gubernacular enlargement and regression of the cranial suspensory ligament. A detailed historical review of the endocrine factors that may be involved is available (18); therefore the emphasis here is on recent developments. In 1985 it was suggested that the swelling reaction in the gubernaculum was not under androgenic control because it occurred normally in both mice and humans with complete androgen resistance (31) and also in rats exposed prenatally to flutamide (50). Because estrogen-treated fetal male mice and rats had retained Müllerian ducts, atrophy of the gubernaculum, and high intraabdominal testes (50, 51), a causal

link between MIS and the gubernacular swelling reaction was suggested (32, 52, 53) (Fig. 6).

1. Müllerian inhibiting substance. MIS (or anti-Müllerian hormone) is a 140-kDa glycoprotein produced by Sertoli cells and is responsible for regression of the embryonic Müllerian ducts (10–12). The gene for MIS has been cloned for the human (54) cow (54), rat (55), and mouse (56). It contains five exons and is localized to chromosome 19p13.3 (57). Cleavage of the glycosylated dimer by a protease produces a carboxy terminus dimer that is still biologically active (58). Although once thought to be a paracrine factor in the male fetus (59), it is now known to be produced postnatally by both testis and ovary (60). A number of functions have been suggested for MIS in addition to regression of embryonic Müllerian ducts,

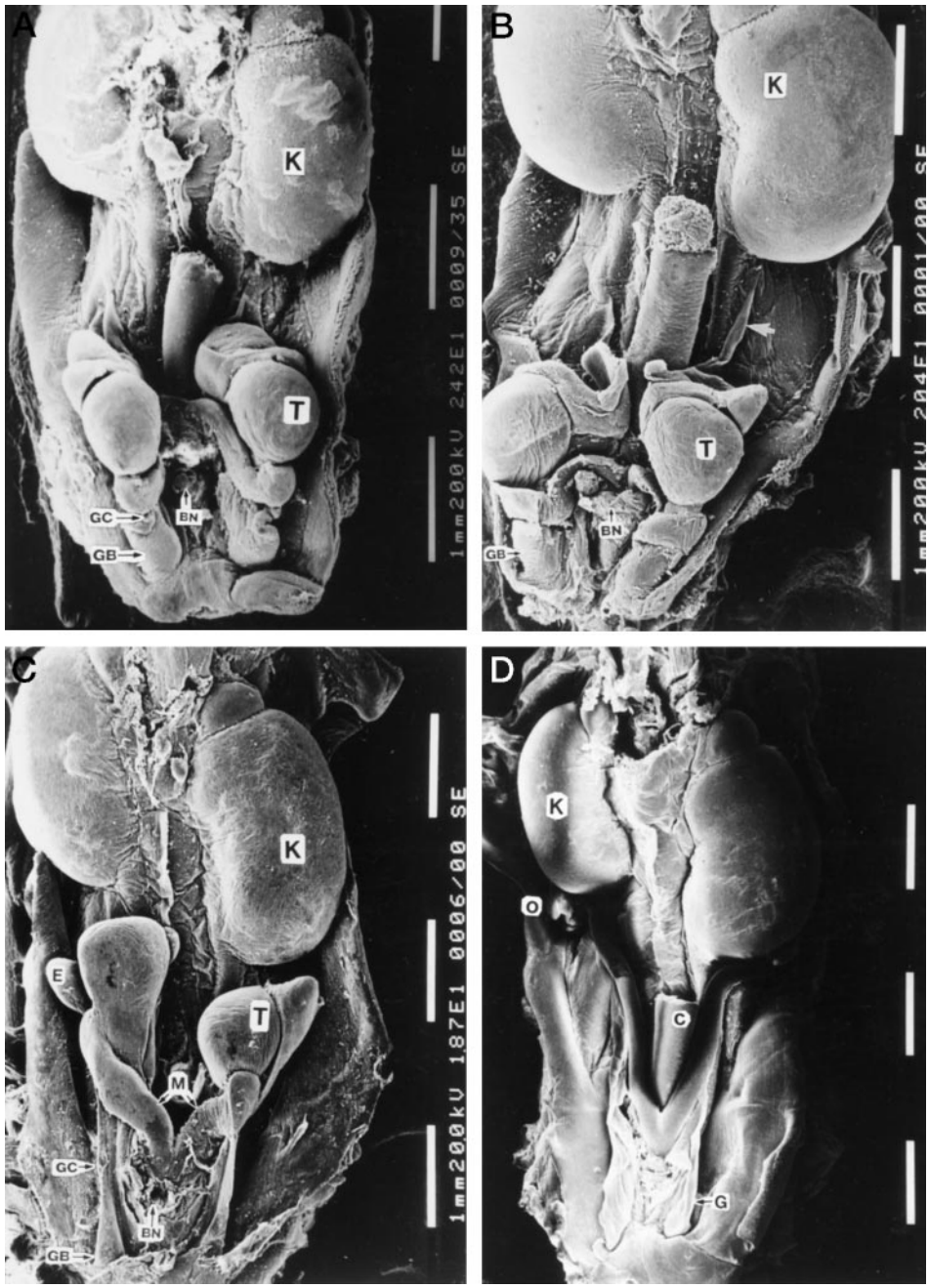

FIG. 6. Scanning EM of day 20 rat fetuses exposed to flutamide (100 mg/kg per day 16–19) or estradiol benzoate (15 mg/day 16). A, Control male. Testes (T) have descended from kidney (K) to lower abdomen near bladder neck (BN). The gubernacular bulb (GB) and cord (GC) are visible. B, Flutamide-treated male, with testes in a similar position to that in control, despite persistence of cranial suspensory ligament (*white arrow*). Note well-developed gubernacular bulb (GB). C, Estrogen-treated male with high testes near kidney. The retained Müllerian ducts (M) are adjacent to the epididymis (E). The gubernacular bulb (GB) and cord (GC) are longer and thinner than in controls. D, Control female with ovary (O) just under lower pole of kidney (K). Colon (C) is seen between Müllerian ducts and elongated gubernacula (G). [Reproduced with permission from T. Shono *et al.*: *Int J Androl* 19:263–270, 1996. © Blackwell Science Ltd.]

including early differentiation of the testis (11, 61), prenatal lung maturation (62), and postnatal germ cell maturation (63–65).

A number of observations support a role for MIS in the first phase of testicular descent (Table 1A). First, animal models with intraabdominal cryptorchidism also have retained Müllerian ducts (52, 53, 66) (Fig. 6C). Second, gonadal maldescent is proportional to Müllerian duct retention in humans with intersex (67, 68) as well as in estrogen-treated fetal mice (53). Third, in humans with genetic defects in the MIS gene or its receptor with so-called persisting Müllerian duct syndrome (PMDS) (69), the testes are undescended and the gubernaculum is thin and enlongated (70) (Fig. 7). The latter defect suggests that the gubernacular swelling reaction fails to occur in PMDS, leading to cryptorchidism (70, 71). Transgenic mice with MIS deficiency have retained Müllerian ducts and variable gonadal position depending on their androgenic status: those with normal androgen receptors have almost normally descended testes while those with combined androgen resistance have completely undescended testes (UDT) (72).

Arguments against a role for MIS in the gubernacular swelling reaction include the failure of fetal rabbits immunized against bovine MIS to have UDT, despite persistence or partial persistence of the Müllerian ducts (73) (Table 1B). In addition, semipurified bovine MIS failed to cause cell division of cultured fibroblasts from the fetal pig gubernaculum, suggesting that MIS does not stimulate the swelling reaction (74). A further argument against a role for MIS is the view that the intraabdominal testes in patients with PMDS are caused, not by absence of the gubernacular swelling reaction, but by anatomic connection of the testis with the persistent Müllerian ducts (12, 75). Cryptorchidism was believed to be caused by anatomic blockade by the retained Müllerian ducts, a view supported by Husmann and Levy (37), who also cite a final argument against MIS, which is the finding that nearly all patients with intraabdominal cryptorchidism do not have persistent Müllerian ducts (76).

Studies of the gubernaculum in intersex and normal pigs have indicated that growth of the gubernaculum may be stimulated by a nonandrogenic hormone from the testis (27, 77–81). Proliferation of pig fetal gubernaculum in culture appears to be stimulated by a low molecular weight testicular factor that is distinct from known polypeptide growth factors and MIS (74, 82). Fentener van Vlissingen *et al.* (74) proposed the name "descendin" for this hormonal activity, whereas Visser and Heyns (82) suggested that, in line with the names of other trophic hormones (*e.g.* gonadotropin, thyrotropin), "gubernaculotropin" would be a more appropriate name for the putative hormone responsible for the proliferation of gubernaculum cells.

Several factors may account for the above contradictory opinions, not the least of which is that most studies focus on gonadal position while few examine the swelling reaction in the gubernaculum, which is the likely target organ for hormonal action. Also, despite strong evidence that it is an important accessory factor, the role of the cranial suspensory ligament has been ignored (22). The cranial ligament is responsive to androgens, which induce its regression (83, 84). Because gonadal position appears to be the net result of the opposing actions of the cranial suspensory ligament and the gubernaculum, it cannot be assessed without considering these opposing actions (Fig. 8).

In the normal male, the gubernacular outgrowth and regression of the cranial ligament act in concert to permit the

TABLE 1. Evidence for and against a role for MIS in the first phase of descent

A. For:
First phase independent of androgens [Wensing, 1973 (27)]. Low MIS activity in undescended testes [Donahoe *et al*, 1977 (28)].
Maldescent proportional to Müllerian duct retention in intersex patients (Scott, 1987) (67).
Maldescent proportional to Müllerian duct retention in estrogen-treated mice (Hutson *et al*, 1990) (53).
Maldescent and abnormal gubernacular development in persistent Müllerian duct syndrome (Hutson *et al.*, 1994) (70).
Severe maldescent and persisting Müllerian ducts in transgenic mice with combined MIS deficiency and androgen resistance (Behringer *et al*, 1994) (72).
B. Against:
Fetal rabbits immunized against bovine MIS still have testicular descent (Tran *et al*, 1986) (73).
MIS does not cause cell division of cultured fibroblasts from fetal pig gubernaculum (Fentener van Vlissingen *et al*, 1988) (74).
Ovaries not descended in female transgenic mice overexpressing human MIS (Behringer *et al*, 1994) (72).
Testes "descended" in transgenic mice with MIS deficiency but normal androgen levels (Behringer *et al*, 1994) (72).

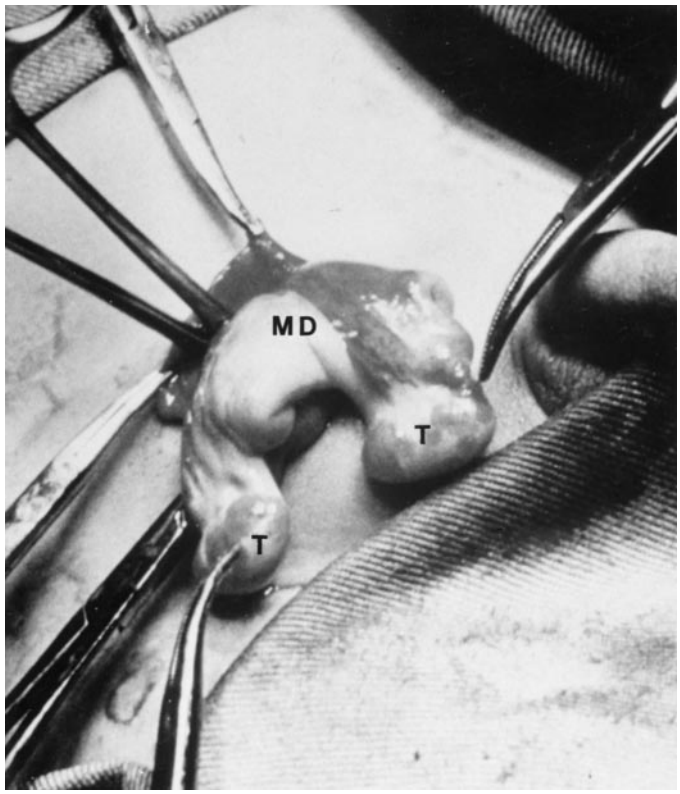

FIG. 7. Surgical photograph of a patient with PMDS presenting with bilateral UDT and an inguinal hernia containing both testes (T) and Müllerian ducts (MD). Note the fact that the gonads and uterus are free inside the hernial sac, and the absence of a normal gubernacular bulb or any attachment of either testis to the scrotum. [Reproduced with permission from J. M. Hutson *et al.*: *Pediatr Surg Int* 2:191–194,1987 (71).]

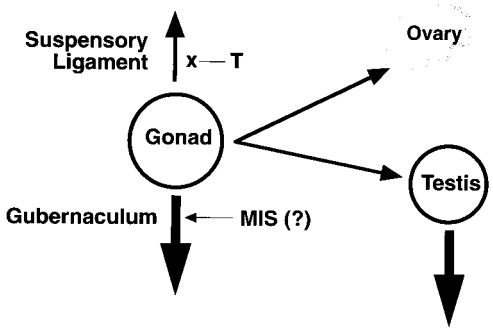

FIG. 8. Schema showing the gonadal position as a vector summation of the opposing forces of the cranial suspensory ligament and gubernaculum. Evidence would suggest that testosterone causes regression of the cranial ligament and MIS is proposed as the possible cause of gubernacular enlargement. Without gubernacular swelling, the ovary is held high in the abdomen by the cranial ligament. In the male, the enlarged gubernaculum holds the testis low near the groin.

gubernaculum to hold the testis near the inguinal region. By contrast, in the female, the cranial ligament holds the ovary higher in the abdomen, and the gubernaculum remains long and thin as the round ligament and ligament of the ovary. Complete androgen resistance in the mouse (or human) does not prevent gubernacular swelling but does prevent regression of the suspensory ligament; as the testes descend to the bladder neck, it can be inferred that the suspensory ligament cannot overcome the traction of the gubernaculum (31, 85).

In the estrogen-treated, androgen-resistant mouse the testes are high in the abdomen at birth, similar in position to ovaries (52) (Fig. 9). The gubernacular swelling reaction is absent, and the unopposed cranial suspensory ligament is now able to keep the testis and ducts high in the abdomen. This gonadal position is similar in the combined MIS/TFM mutant, in which the testis, with retained Müllerian duct, is near the kidney (72). The cranial suspensory ligament alone apparently anchors the gonad in this model, although the status of the gubernacular swelling reaction was not described.

In the MIS-deficient mouse, the testes appear to be normally descended (72). However, here the cranial suspensory ligament is absent (as androgen function is normal), and whether the swelling reaction occurs in the gubernaculum is not yet known, but hypermobility of the gonads could allow accidental descent, which is observed in the equivalent human mutant with PMDS.

Recent studies of the anatomy of an MIS receptor-deficient transgenic mouse show normal transabdominal testicular descent but lack the swelling reaction with minimal deposition of extracellular matrix in the mutant gubernaculum. (R. R. Behringer and J. M. Hutson, unpublished). In addition, the MIS receptor deficiency fails to prevent cell division within the gubernaculum, consistent with the view that this is not dependent on MIS (74, 82). Further detailed analysis of the MIS-deficient and receptor-deficient transgenic mouse models is needed, but these preliminary observations suggest that MIS may indeed control deposition of matrix in the gubernacular swelling reaction.

Mutations of both the MIS gene and its receptor lead to PMDS in the human (75, 86). The gonadal position in this syndrome is variable, but all have retention of the Müllerian ducts and normal masculinization of androgens (71, 87). A review of the literature reveals that most testes are intraabdominal, while in some patients one or both testes may be found in an inguinal hernia (70, 71). A recent surgical patient was observed to have a very long, thin gubernacular cord similar to the round ligament in females (70). This led to the suggestion that the transverse testicular ectopia commonly seen in this syndrome is caused by prolapse of one or both testes into the patent processus vaginalis (88) (Fig. 10). Hypermobility of intraabdominal testes in PMDS is supported by the high frequency of bilateral torsion and involution of the testes (89). Rather than the retained Müllerian duct blocking descent (12, 75), the hypoplastic uterus and tubes appear to play no role; meanwhile, the absence of tight anchoring by either cranial or caudal gonadal ligaments allows accidental descent, transverse ectopia, or gonadal torsion. Nearly all surgical photographs of PMDS show extremely mobile gonads and elongated ducts (90), suggesting that blockade of the MIS gene increases, rather than restricts, gonadal mobility. A telling factor in the argument in favor of MIS causing the gubernacular swelling reaction is its apparent absence in PMDS.

The failure of most patients with intraabdominal testes to have Müllerian duct remnants does not preclude a role for MIS, as suggested by Husmann and Levy (37). There are numerous potential anatomical anomalies, such as the atrophic gubernaculum found in the recent transgenic Hoxa-10 mutant mouse, that could be present in the gubernaculum or developing inguinal canal that could prevent the gonad leaving the abdominal cavity (43, 44).

2. Androgen. It is generally agreed that the inguinoscrotal phase of testicular descent requires androgen (18, 37, 76, 91). Migration of the gubernaculum beyond the inguinal region is absent in gonadotropin-deficient animals (92) and those with complete androgen resistance (85). About 50% of animals treated prenatally with the antiandrogen flutamide also have deranged gubernacular migration and delayed regression (50, 93–97) (Fig. 11). Regression of gubernacular bulk also appears androgen-dependent since in the human with complete androgen resistance the gubernaculum remains enlarged, with failure of extracellular matrix resorption (32, 47). Recent studies suggest that regression of the gubernacular cord may also be androgen dependent, as the prenatal flutamide treatment prevented its regression (98).

The site of androgenic action on the gubernaculum remains controversial. High local concentrations are thought to be required (17, 46). The gubernaculum of the newborn rat, however, contains only 20% of the level of androgen binding ([^{3}H]dihydrotestosterone) seen in the urogenital sinus, which is a known target organ (99). Fibroblast cultures from fetal pig gubernacula also are reported to contain binding for androgen analogs (^{3}H-R1881) (100), although other studies have found that the total androgen receptor concentration in the fetal pig gubernaculum was much less than in a recognized androgen target organ such as the prostate (101). In a more detailed study of androgen binding in the gubernaculum of fetal pigs, Heyns and Pape (102) found [^{3}H]methyltrienolone (^{3}H-R1881) binding in the gubernaculum was of

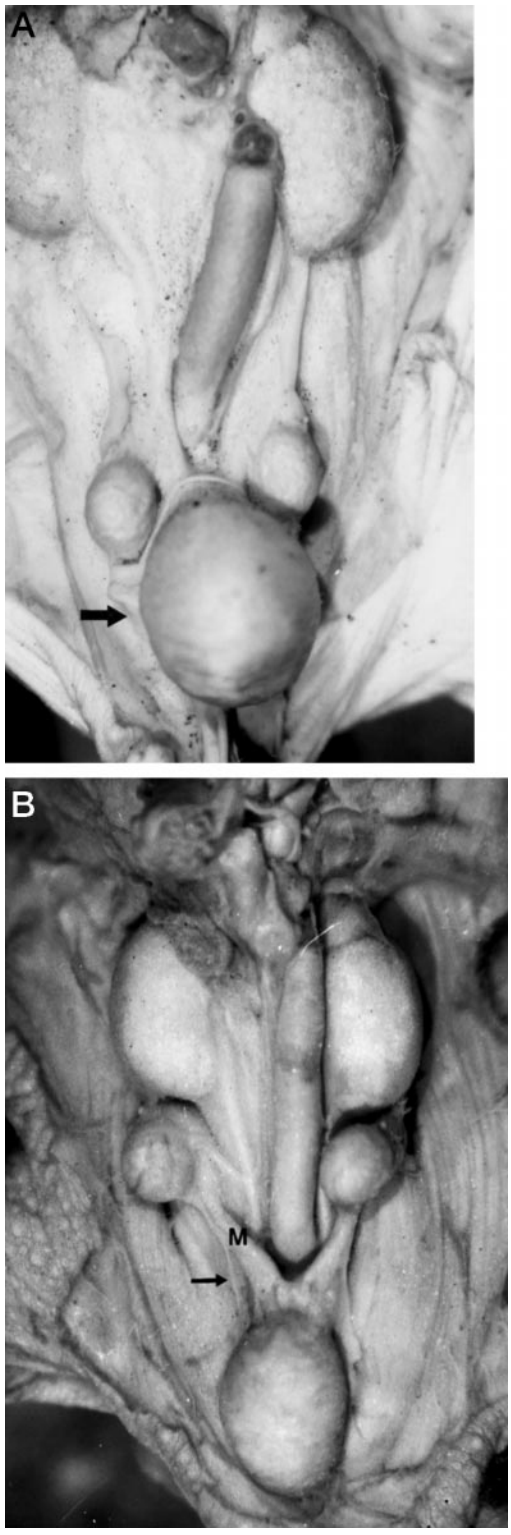

FIG. 9. A, Untreated neonatal male mouse with complete androgen resistance (TFM). The testes are in the normal position near the bladder neck despite absence of Wolffian duct structures. The gubernacular swelling has occurred (*big arrow*). B, Neonatal male TFM mouse treated with estradiol benzoate *in utero*. Testes are located high in the abdomen near the kidneys. The Müllerian ducts (M) are retained and the gubernaculum is long and thin (*arrow*) as in normal females. [Reproduced with permission from J. M. Hutson: *Pediatr Surg Int* 2:242–246, 1987 (52).]

lower affinity and capacity than in prostate, and on a par with that in striated muscle (male or female). They concluded that direct androgen stimulation may not account for growth of the gubernaculum during descent. In addition, 5α-reductase activity in the gubernaculum remained constant throughout gestation in the pig, at levels well below that seen in the prostate and urethra (103).

The possibility that androgens may act by indirect means on the gubernaculum was considered after a literature review identified a 1948 study by Lewis (21), who transected the genitofemoral nerve (GFN) while testing the traction theory. At that time the cremaster was being considered as a source of muscular traction to pull the testis into the scrotum. Neonatal nerve transection would theoretically prevent traction by denervation of the muscle: cryptorchidism was produced, but the study was not followed up until many years later (104). It was intriguing that denervation should block a process that is under apparent androgenic control, leading to the speculation that androgens may act via the nerve (105). This hypothesis was consistent with the results of distal transection of the gubernaculum in neonatal rats, which prevents postnatal migration of the gubernaculum and testicular descent (42, 106). The GFN supplies the gubernaculum from its posterior and caudal surface, so that distal transection of it would also cause denervation (107, 108). Proximal transection of the neonatal gubernaculum, which preserves its inguinal attachment and nerve supply, failed to block inguinoscrotal descent (42, 106).

This "GFN hypothesis" stimulated a number of new studies to test its predictions. Androgens should lead to modification of the GFN prenatally, as even in species with postnatal gubernacular migration, the nervous system would require earlier modification. Studies with antiandrogens confirm that inguinoscrotal migration, although occurring postnatally in rodents, can only be blocked by prenatal treatment (50, 94–98). This coincides with the time of development of other sexually dimorphic nuclei (109).

3. The genitofemoral nerve (GFN). The spinal nucleus of the GFN is located at L1–2 in the spinal cord and is sexually dimorphic in rodents (97, 110). Prenatal blockade of androgens with flutamide does inhibit the sexual dimorphism (97) (Table 2). Rather than induce feminization of the nucleus in the male, flutamide appears to partially masculinize the nucleus in the female (97). Other authors have claimed that androgens had no effect on the GFN nucleus, as the nucleus in TFM rats was found to be of similar size as in normal male rats (48). This is similar to our own results in the TFM mouse (110) (Table 2).

The location of androgen receptors that might mediate androgenic modification of the genitofemoral nerve remains controversial (37), since androgen binding was not reported in the rat spinal cord until 1 week after birth.

A specific search for androgen receptors in the fetal rat spinal cord has recently shown androgenic binding as early as 15 days of gestation, which would be consistent with androgens stimulating differentiation of the GFN and its nucleus (111). Alternatively, the androgen receptors affecting the gubernaculum may be in the cremaster muscle itself, similar to the situation in the bulbocavernosus muscle (37,

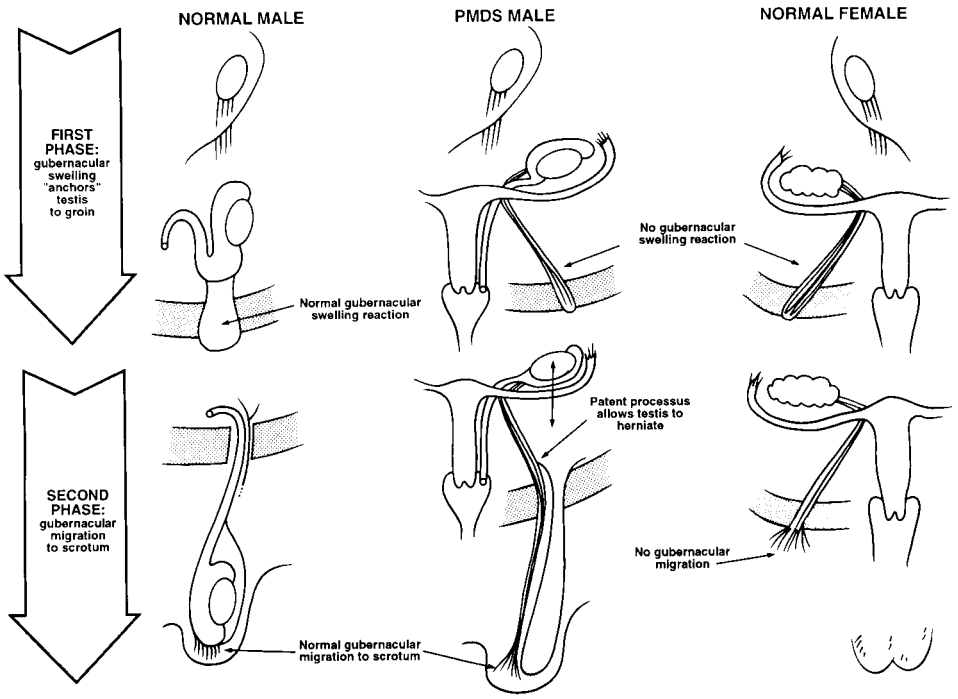

FIG. 10. Schema of gonadal descent showing two phases in normal males compared with those with PMDS and normal females. Normal development of the processus vaginalis, which is part of the second phase of descent, along with hypermobility of the testis because the gubernaculum is long allows the testis (± ducts) to prolapse into the groin. [Reproduced with permission from J. M. Hutson and M. L. Baker: *Pediatr Surg Int* 9:542–543, 1994 (88).]

112), although this has not been supported by studies in the pig fetus (103). The fetal rat gubernaculum, however, does show staining with antiserum raised against the androgen receptor at 18 and 20 days post coitum and 1 day after birth but declines rapidly thereafter (96). During the migration phase of the rat gubernaculum, between 3–10 days postnatally (25), the developing cremaster muscle shows minimal staining for androgen receptors (96).

The GFN hypothesis predicts that neuronal anomalies affecting the GFN nucleus should be associated with cryptorchidism. In 345 boys with spina bifida, in whom the position of the testes and the neurological defect were recorded, 23% had UDT. Cryptorchidism was present in 19% of 186 boys with lesions below L4 compared with 36% of 59 boys with high lumbar defects (113). In rats undergoing transection of the spinal cord at birth, 39% had cryptorchidism (7/18) with midlumbar transections (113, 114).

4. Calcitonin gene-related peptide (CGRP). Anatomical studies of the GFN in neonatal rodents identified CGRP in the nerve (97, 110). CGRP is a neuropeptide with close homology with calcitonin and is produced by alternative splicing of the calcitonin RNA transcript (115). Numerous studies in recent years have demonstrated multiple sites and functions for this peptide in the nervous system (116). In motor nerves it is involved in regulation of acetylcholine receptor synthesis in skeletal muscle (117). It has an important role in pain perception in sensory nerves (118) while in the autonomic system it has different effects on smooth muscle, including peripheral vasodilation (119–121).

Sexually dimorphic nuclei, such as the bulbocavernosus spinal nucleus which contains CGRP, may be regulated by retrograde transport of a soluble factor(s) from the bulbocavernosus muscle (112). Castration of adult male rats stimulates the expression of CGRP mRNA and increases the amount of CGRP in the cell bodies of the bulbocavernosus spinal nucleus (112). The mature GFN or cremaster spinal nucleus in adult rats contains only a few CGRP-positive cell bodies (122), and neonatal castration leads to a decrease in the size of the GFN nucleus in adult rats (123), which is in contrast to the bulbocavernosus nucleus. The adult GFN nucleus contains neuropeptide Y immunoreactivity (124) and progressive postnatal connections with nerve endings containing substance P and 5-hydroxytryptamine (125). The mature male rat has a GFN nucleus with 3-fold more cell bodies than the female (122), but the androgen-resistant (TFM) rat (King-Holzman) has similar nuclear size and connections as a normal male. By contrast, the bulbocavernosus nucleus is significantly feminized (126).

CGRP has been localized in the soma of GFN neurons in the first and second lumbar segments (97, 110, 127), using both immunofluorescence and immunohistochemistry (Fig. 12). The total number of neurons in the nucleus was determined by retrograde labeling of the GFN with fluorescent dyes (diamidinophenyl indole and Fast Blue): neonatal rats/mice underwent laparotomy, exposure of the GFN in the retroperitoneum where it runs caudally on the anteromedial border of the psoas muscle, transection of the nerve, and application of a few dye crystals to the cut ends. The spinal cord was removed after a further 48 h (Table 2). Vasoactive intestinal peptide, TRH, neuropeptide Y, met-enkephalin, 5-hydroxytryptamine, substance P, and somatostatin-8 were not present above background levels. The reason for these

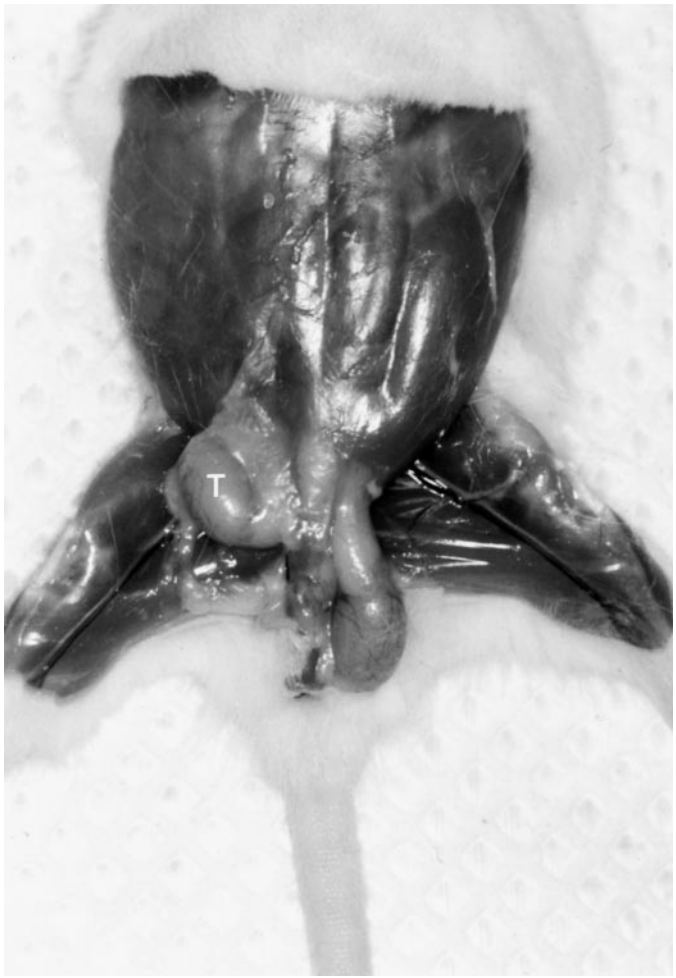

FIG. 11. A 30-day-old flutamide-treated rat after 100 mg/kg/day on days 16–19 of fetal development. The right testis (T) is undescended in the suprainguinal position. (Unilateral cryptorchidism is common in this model and is unexplained.)

differences compared with Newton's work on the cremaster nucleus is not known. Several possible explanations include alteration of the GFN nucleus at sexual maturity, differences in different strains of rats, or the fact that the GFN nucleus in the neonatal animal, as identified by retrograde labeling, is different from the cremaster nucleus localized by its synapses in adult rats. The presence of CGRP, but not neuropeptide Y, in the neonatal nucleus and a difference in the sex ratio of nerves suggests that either the neurons undergo major changes at puberty or are not identical in location.

One argument against the GFN nucleus and CGRP having a role in descent is the notion that the cremaster muscle, at least after sexual maturity, controls neural morphology rather than the nerve regulating the target organ (37, 123, 128). Regardless of whether the cremaster controls or is controlled by the GFN, the neonatal gubernaculum responds as if the GFN is the primary regulator (see below). Other views include the fact that CGRP is known to be a neuromuscular transmitter (129) and that CGRP receptors are localized to the developing rat cremaster (130), whereas the primate gubernaculum is mostly mesenchyme and extracellular matrix rather than muscle (23). In addition, in some dimorphic nuclei CGRP is released by withdrawal of androgens rather than stimulation (112, 131). These views are reasonable conclusions by analogy with the bulbocavernosus nucleus, but are contrary to what has been found in the GFN and rodent gubernaculum. How they can be applied to the human remains speculative.

Rodent models with cryptorchidism have abnormalities in their GFN nucleus that may support its putative role in testicular descent. As mentioned previously, the TFM rat GFN is not feminized (48), which is similar to what our own studies had shown for the TFM mouse (110) (Table 2). However, the gubernaculum of TFM mice, which is hypersensitive to CGRP in organ culture (see below), is consistent with failure of CGRP to be released in the TFM. In the flutamide-treated rat the male GFN had a small decrease in neuron number and CGRP-positive cells, but the female rat had a similar number as the male (97) (Fig. 13A). Although the nucleus in male flutamide-treated rats was not the same as normal females, the gubernaculum responded as if the nerve was not releasing CGRP, as it became hypersensitive to the exogenous CGRP added to the culture (see below). In a new rat model of cryptorchidism, androgen function appears normal (132), but the scrotum was initially thought to be ectopic, hence the name TS or "trans-scrotal" rat. Dissections of this rat during development have shown, however, that the scrotum is not ectopic but normally located, hypoplastic, and empty (133). The GFN nucleus in TS rats has similar numbers of neurons in males and females and increased numbers of CGRP-immunoreactive neurons compared with normal controls (127) (Fig. 13B). The target organ, which is the TS gubernaculum, behaves as if it is desensitized and is not responsive to exogenous CGRP in culture (see below).

The effect of CGRP on the rodent gubernaculum has been investigated extensively *in vitro* and *in vivo*. In male neonatal rats under anesthetic, the gubernaculum, which has not yet reached the scrotum, shows spontaneous rhythmic contractility, which is enhanced by increased intraabdominal pressure and direct application of human CGRP (134). In organ culture, neonatal rat gubernacula contract rhythmically in a dose-responsive manner on exposure to CGRP (Fig. 14A), but not to other neuropeptides such as vasoactive intestinal peptide, serotonin, somatostatin 8, met-enkephalin, TRH, or neuropeptide Y (134). Control tissues such as female rat gubernacula, skeletal muscle from the abdominal wall, and umbilical cord showed no rhythmic contractions. Rhythmic contractility also was pronounced in the neonatal mouse gubernaculum, with some endogenous contractions and dose response to CGRP (135). By contrast, exposure to the inhibitory analog of CGRP, CGRP(8–37), caused suppression of contractions (Fig. 14B). *In vivo* CGRP(8–37) also caused inhibition of gubernacular migration, with weekly injections of 25 μl 10^{-4} molar CGRP(8–37) causing delayed descent. By 2 weeks of age 43% of the saline-treated controls already had descended testes whereas all experimental animals had UDT. At 3 weeks, 17% of testes in experimental animals were still undescended (136).

The contractility of the mouse gubernaculum observed *in vitro* is maximal in the first postnatal week, which coincides with gubernacular migration from the inguinal canal to the scrotum (137). CGRP causes an increase in both frequency

TABLE 2. Number of GFN motor neurons and their CGRP-immunoreactivity in different animal models

Author	Model	Age	Total neuron no. (mean ± SD)	CGRP positive no. (mean ± SD)
Larkins *et al.*, 1991 (110)	Male mouse	10 day (D)	251 ± 104	114 ± 53
	Female mouse	10 D	107 ± 22	32 ± 14
	TFM male mouse	10 D	184 ± 33	70 ± 40
	Male rat	6 D	298	148
	Female rat	6 D	163	35
Barthold *et al.*, 1994 (48)	Male rat		256 ± 44	
	Female rat		70 ± 14	
	TFM male rat		231 ± 42	
Goh *et al.*, 1994 (127)	Flutamide male rat	9 D	220 ± 70	120 ± 41
	Flutamide female rat	9 D	210 ± 76	120 ± 41
	Male control	9 D	250 ± 69	150 ± 24
	Female control	9 D	120 ± 26	70 ± 24
Goh *et al.*, 1994 (97)	TS male rat	5 D	556 ± 129	563 ± 50
	TS female rat	5 D	560 ± 100	500 ± 120

and amplitude of contractions, with most gubernacula also responding with increased isotonic tension. In response to acetylcholine, the gubernacula showed a single twitch contraction, but no rhythmic contractions (138). The contractility of the gubernaculum requires influx of calcium ions via dihydropyridine receptors in a manner similar to that seen in immature cardiac or smooth muscle; acetylcholine receptors are not involved, as nifedipine was unable to block contractions (139).

The gubernacular contractility *in vitro* can be altered by a change in the status of the GFN before removal from the animal. Prior transection of the GFN at birth sensitizes the normal rat gubernaculum to exogenous CGRP (138).

The TFM gubernaculum has no endogenous contractility *in vitro* but is hypersensitive to exogenous CGRP, consistent with diminished release of CGRP from the GFN (135) (Fig. 15A). In addition, exogenous CGRP can induce elongation of the gubernaculum in intact TFM mice postnatally (Fig. 15B) (140). Similarly, in the flutamide-treated rat the neonatal gubernaculum has reduced endogenous contractility but is hypersensitive to exogenous CGRP (141) (Fig. 16A). By contrast, the neonatal TS rat gubernaculum remains inert in organ culture, even on exposure to exogenous CGRP (141) (Fig. 16B). *In vivo* the TS gubernaculum fails to respond to exogenous CGRP (W. H. Park and J. M. Hutson, unpublished). The inert TS gubernaculum has a decreased number of CGRP receptors, but these can be restored to normal number and the gubernaculum can be restored to normal contractility by prior transection of the GFN (142). This is consistent with the hypothesis that cryptorchidism in this mutant may be secondary to excess CGRP release from the nerve that disrupts inguinoscrotal migration by down-regulation of CGRP receptors.

Specific binding sites for CGRP have been found on the developing cremaster muscle fibers within the gubernaculum (143). Sections of gubernacula from neonatal male rats were incubated with ^{125}I-labeled CGRP (human) and various cold neuropeptides, with quantification of the autoradiographs by computer densitometry. The binding was concentrated over the cremaster muscle whereas the mesenchymal component was not labeled. A single class of high-affinity receptors was found, which was maximal during the first week after birth, coincident with gubernacular migration (130). CGRP and CGRP [8–37] showed high-affinity specific binding and calcitonin and CGRP [28–37] bound with low affinity (Fig. 17A). Serotonin, substance P, vasoactive intestinal peptide, and somatostatin showed no specific binding. When binding was compared between normal rats and the flutamide-treated and TS rats, the flutamide-treated rat had higher CGRP binding in the gubernaculum, while the TS rat had lower binding (Fig. 17B). Prior transection of the GFN increased the binding capacity of the gubernaculum (130). Furthermore, GFN transection in the TS rat was able to restore CGRP binding, which initially was significantly lower than in normal rats, to the normal levels (142).

A number of issues remain unresolved when considering a possible role for CGRP. For instance, CGRP is described as a neuromuscular transmitter, which would not be expected to be important in migration of the human gubernaculum, where there is very little cremasteric muscle (37). The data from the above mentioned studies, however, show that CGRP acts independently of acetylcholine receptors. In addition, CGRP has so many effects in different systems, including chemotaxis of cells (144–146), that alternative mechanisms other than contractility may be applicable in the human. In some sexually dimorphic nuclei, CGRP release is increased by androgen blockade (122), but the cryptorchid rodent models show a clear association between androgen resistance or blockade and increased gubernacular sensitivity to CGRP, which is consistent with decreased release from the GFN. It remains unknown why flutamide-treated rats have about 50% of testes descended, despite almost complete blockade of prostatic development (96).

Houle and Gagne (147) attempted recently to induce premature testicular descent in postnatal mice by exogenous CGRP. The neurotransmitter inhibited descent in this model, which was similar to our own findings (148). Normal production of CGRP by the GFN, as well as failure to replicate regular release of the neuropeptide by the GFN, may account for failure to induce descent prematurely.

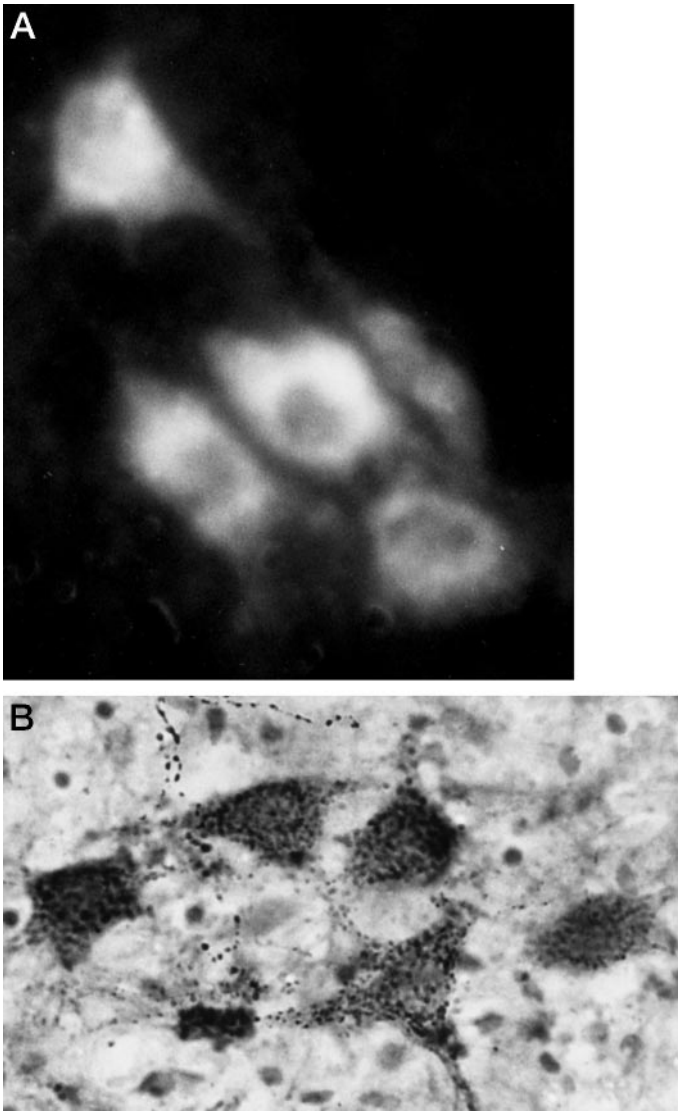

FIG. 12. A, Retrograde Fast Blue fluorescent labeling of motor neurons in the genitofemoral nerve (GFN) spinal nucleus of a neonatal rat (×400). B, CGRP-like immunoreactivity of cell bodies in GFN nucleus (different section from panel A) (×400) [Reproduced with permission from D. W. Goh *et al.*: *J Reprod Fertil* 102:195–199, 1994 (127).]

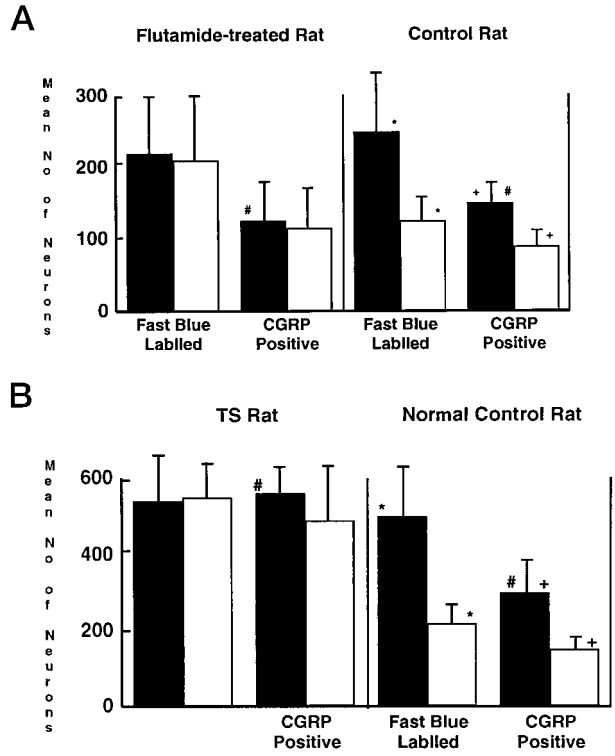

FIG. 13. A, Fast Blue-labeled and CGRP-immunoreactive neurons in GFN spinal nuclei of flutamide-treated neonatal rats (n = 16 each sex) *vs.* control rats (n = 18 each sex). *Bars*, mean ± SD Males, *filled columns*; females: *open columns*; comparisons between bars (#; +; * all significant ($P < 0.001$) [Reproduced with permission from D. W. Goh *et al.*: *J Pediatr Surg* 29:836–838, 1994 (97).] B, Fast blue-labeled and CGRP-immunoreactive neurons in GFN spinal nucleus of TS rats (n = 14 each sex) *vs.* control rats (n = 10 each sex) [Reproduced with permission from D. W. Goh *et al.*: *J Reprod Fertil* 102:195–199, 1994 (127).]

When a flutamide rat was used, the direction of gubernacular migration could be diverted by ectopic CGRP administration (148).

II. Cryptorchidism

A. Etiology

Cryptorchidism will be caused by any anomaly that disrupts normal testicular descent (149). The normal mechanism of descent is such a complex interaction of hormonal and mechanical or anatomical factors that it is not surprising that the cause of UDT is multifactorial (Table 3). Although the common causes of UDT are not known, the transabdominal phase is rarely affected, as in most instances testes have descended to or beyond the inguinal canal (150). Intraabdominal testes comprise a small group of about 5–10% of cases perhaps because the transabdominal phase merely requires holding the testis near the groin during growth of the embryo. By contrast, the active migration of the gubernaculum during the inguinoscrotal phase is much more prone to mishap. The UDT is commonly located near the neck of the scrotum or just outside the external inguinal ring; the latter position, when just lateral to the pubic tubercle, is described as the superficial inguinal pouch. Here the testis, within its tunica vaginalis, is constrained anteriorly by the superficial abdominal wall fascia (Scarpa) and posteriorly by the external oblique muscle.

The commonest cause of UDT is believed to be a defect in prenatal androgen secretion secondary to either deficient pituitary gonadotropin stimulation or low production of gonadotropin by the placenta (37, 76, 91). Work from our own laboratory has suggested that androgen deficiency may be manifested by abnormal physiology of the GFN (49), which may disrupt migration of the gubernaculum. Androgen deficiency during the second and third trimester would necessarily be mild or transient, as no genital anomaly, save inadequate growth of the epididymis, is present at birth (151–154). Furthermore, endocrine assessment at birth in babies with UDT has not revealed a consistent anomaly (64, 155, 156). Only later in infancy is a deficiency of androgen pro-

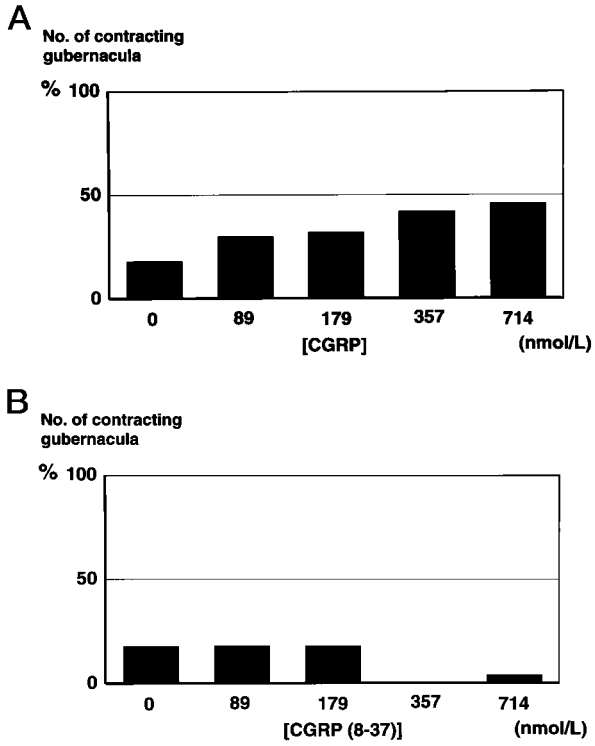

FIG. 14. A, Number of contractile gubernacula from normal neonatal mice (n = 50 at each dose level) *vs.* CGRP concentration. Rhythmic contractions were recorded by video camera connected to a dissecting microscope. A positive correlation between CGRP dose and contractility was present ($r = 0.95$; $P < 0.05$). B, Number of contractile gubernacula from normal neonatal mice (n = 50 at each dose) *vs.* CGRP (*-37) concentration. A negative correlation was present ($r = 0.98$; P 0.05) [Derived from Ref. 135.]

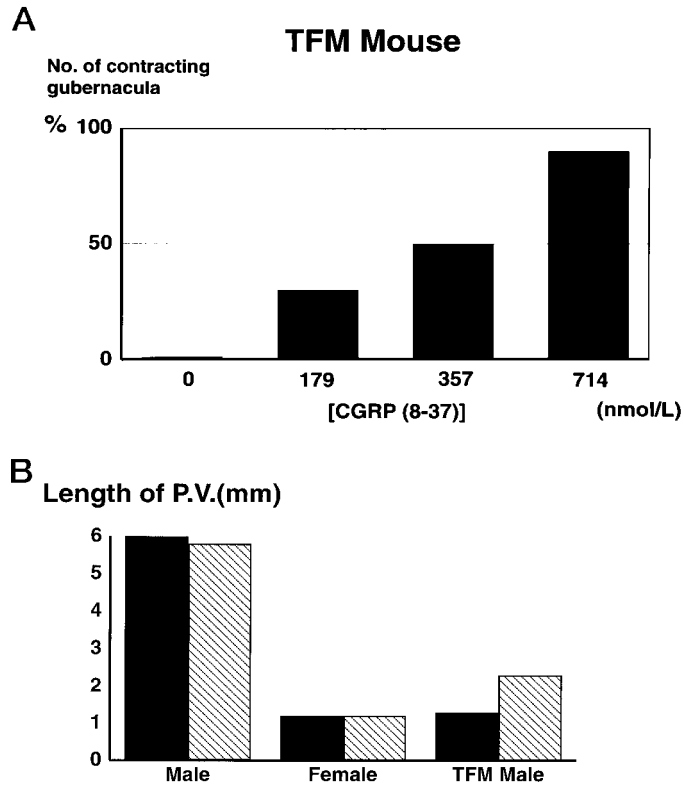

FIG. 15. A, Contractile reponse to CGRP on neonatal gubernacula from androgen-resistant (TFM) mice (n = 10 per dose) [Derived from Ref. 141.] B, Length of the procesus vaginalis in 15-day-old normal male, female, and androgen-resistant male (TFM) mice (n = 10) after injections of CGRP into the groin postnatally (*hatched bar*) or control (*black bar*) [Derived from Ref. 140.]

duction (2–4 months) or MIS production (4–12 months) noted (11, 12, 63, 157). Whether postnatal endocrinopathy in UDT is evidence of a primary defect in the testis or is secondary to temperature-dependent degeneration is controversial, although many authors believe that it is secondary (147).

Recognizable endocrine disorders, such as defects in testosterone synthesis or receptor function, do cause UDT but are rare (17, 85). Defects in MIS production or the MIS receptor also cause UDT, in the context of the PMDS (71, 75, 86, 88). As discussed previously, controversy centers around whether in PMDS the Müllerian ducts and/or broad ligaments mechanically prevent descent (69) or whether UDT is caused by failure of gubernacular development (88). The hypermobility of the gonads and genital tract in PMDS is evidence against a simple mechanical block.

Ectopic testes lying beyond the normal line of descent are rare and may occur secondary to particular anatomical defects. Rodent studies show that transection of the gubernaculum can lead to accidental descent down the contralateral canal (transverse ectopia) (40, 42). In the perineal testis the migration process itself has occurred to a normal extent but is misdirected (Fig. 18); we have proposed that this may be caused by the GFN being in the wrong site, thereby controlling migration to a different place (49).

UDT is common in inherited syndromes with multiple anomalies. Microcephaly is a common feature, which is consistent with hypothalamic or pituitary dysfunction (158). Peripheral mechanical anomalies are also common and may lead to external compression of the inguinoscrotal region (159–161). Specific urological disorders, such as prune belly syndrome and posterior urethral valves, have a high frequency of UDT (162–167). The possible mechanisms proposed include massive but transient prenatal urinary tract obstruction or a mesodermal defect. Abdominal wall defects predispose to UDT (15% in gastroschisis; >30% in exomphalos) (168). Three proposed mechanisms include lower abdominal pressure (38), traumatic disruption of the gubernaculum, or a defect in the hypothalamus (158). Neural tube defects have a very high frequency of UDT as discussed previously (113, 169).

B. Frequency

UDT occurs in up to 4–5% of males at birth (170), but less than half of these still have an abnormality by 6–12 months. In the last 30–40 yr the frequency of UDT at 1 yr of age appears to have increased in the United Kingdom from 0.96% to 1.58% (170–173). Elsewhere in the world an increasing frequency has been noted also, but there are few reliable studies with sufficient population number and standardized methods of assessment (174). The very high frequency of UDT reported for premature infants is related to birth before

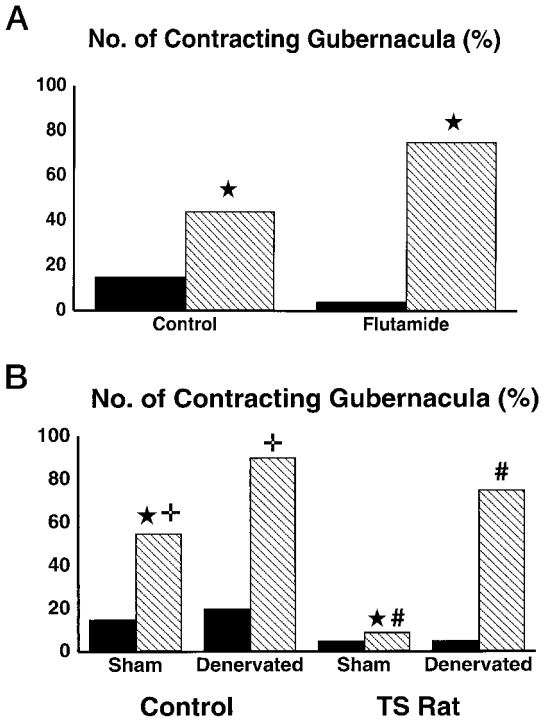

FIG. 16. A, Neonatal rat gubernacular contractile response to CGRP 715 nmol/liter (*hatched bars*) *vs.* no added CGRP (*black bars*) in normal control rats and rats exposed to flutamide *in utero*. Flutamide induced a significant increase in contractility to CGRP compared with untreated rats ($P < 0.05$) [Derived from Ref. 141.] B, Neonatal rat gubernacular contractile reponse to CGRP 715 nmol/liter (*hatched bars*) *vs.* no added CGRP (*black bars*) in sham-operated and GFN-transected normal and TS rats. Contractile response with CGRP is enhanced in control rats after denervation (+, $P < 0.01$). Sham-operated TS rats have suppressed response to CGRP (*, $P < 0.01$), but this recovers significantly after denervation (#, $P < 0.01$). [Derived from Ref. 142.]

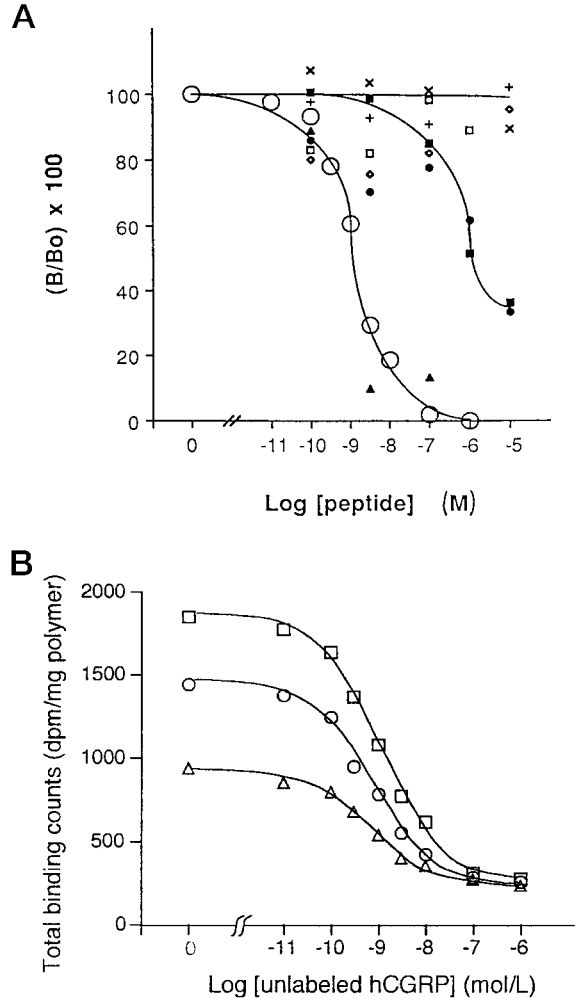

FIG. 17. A, Specificity of binding displacement of ^{125}I-labeled human CGRP (hCGRP) to neonatal rat gubernaculum by unlabeled hCGRP (*open circles*) rat CGRP ([8–37]) (*filled triangles*), rat CGRP [28–37] (*filled squares*), salmon calcitonin (*filled circles*), vasoactive intestinal peptide (*open squares*), somatostatin (*open triangles*), substance P (+), serotonin (x). Binding (B) is expressed relative to binding in the absence of unlabeled hCGRP (Bo). [Reproduced with permission from J. Yamanaka *et al.*: *Endocrinology* 132:1–5, 1993 (130). © The Endocrine Society] B, Total ^{125}I-labeled hCGRP (50 pmol/liter) binding with various concentrations of unlabeled hCGRP. (*squares*, flutamide rat; *circles*, normal rat; *triangles*, trans-scrotal (TS) rat. Each *point* represents 10–12 sections. [Reproduced with permission from M. Terada *et al. J Urol* 152:759–762, 1994. © Williams and Wilkins.]

completion of inguinoscrotal migration (175, 176). Longitudinal study of the Oxford region cohort demonstrated that postnatal descent is common, but only during the first 12 weeks after term (171, 172).

Orchidopexy rates, when used as a measure of the prevalence of UDT, suggest that cryptorchidism is present in up to 5% of males by the time they reach puberty (171, 172). The apparent discrepancy between the number of infants with UDT by 1 yr of age and the higher number undergoing surgery subsequently has provoked some observers to blame unnecessary surgical intervention (171, 172, 177). High rates of operative treatment, however, are documented in many countries, even those with public health systems and no obvious financial gain to the surgeon (171, 172). Recent studies suggest that surgery is common for "retractile" or "ascending" testes, which may in part account for an increased incidence.

C. Are some UDT acquired?

The cremaster muscle controls testicular temperature and protects the gonad from trauma (178). Low temperature stimulates the cremasteric reflex, in which the testis is pulled up out of the scrotum into the inguinal region, thereby insulating the testis by the subcutaneous fat. The GFN mediates the reflex by temperature receptors in its cutaneous branch, which supplies the inner surface of the thigh. At birth the cremasteric reflex is weak, while later in childhood it is quite pronounced until 10–11 yr of age when it begins to wane. The high frequency of a prominent reflex in 3- to 10-yr-old boys is associated with low androgen levels during this time, prompting Farrington (179) to suggest that the reflex is modified by androgens.

The clinical dilemma with retractile testes is determining whether they are normal or abnormal. There is little consensus (180), although some appear to become more abnormal in position with increasing age (181). One explanation proposed recently is that at least some "retractile testes" are

TABLE 3. Possible causes of cryptorchidism

A. Androgen deficiency/blockade
Pituitary/placental gonadotropin deficiency
Gonadal dysgenesis
Androgen synthesis defects (rare)
Androgen receptor defects (rare)
B. Mechanical anomalies
Prune belly syndrome (bladder blocks inguinal canal)
Posterior urethral valves (bladder blocks inguinal canal)
Abdominal wall defects (low abdominal pressure/gubernacular rupture)
Chromosomal/malformation syndromes (? connective tissue defects block migration)
C. Neurological anomalies
Myelomeningocele (GFN dysplasia)
GFN/CGRP anomalies
D. Acquired (?) anomalies
Cerebral palsy (cremaster spasticity)
Ascending/retractile testes (? fibrous remnant of processus vaginalis)

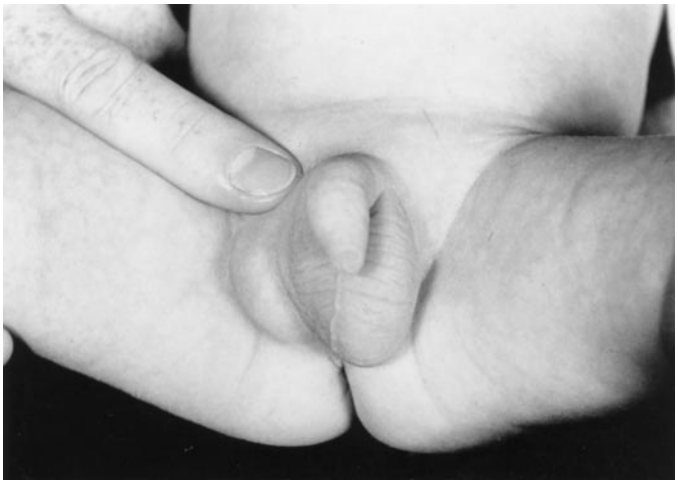

FIG. 18. Perineal ectopic testis, caused by misdirected rather than deficient gubernacular migration. [Reproduced with permission from S. W. Beasley, J. M. Hutson, and N. A. Myers: *Pediatric Diagnosis: An Illustrated Guide to Disorders of Surgical Significance.* Chapman and Hall Publishers, New York.]

testes with acquired maldescent, secondary to failure of normal elongation of the spermatic cord (182).

The "ascending testis" is defined as a testis that resides in the scrotum in early infancy but is too high later in childhood (183). Delayed descent in the first 12 weeks after birth, with subsequent ascent out of the scrotum, is a common feature (171, 172). Ascending testes have been described by many authors (181, 183–185), but whether or not they are the same as "retractile" testes is not known.

Despite early orchiopexy in infancy, large numbers of older boys are still presenting with cryptorchidism at ages well beyond that recommended for correction of congenital UDT (174). Persisting patency of the processus vaginalis, which prevents normal elongation of the spermatic cord, was proposed by Atwell (184) as the cause. Pathological spasticity of the cremaster muscle occurs in children with cerebral palsy and spastic diplegia, leading to a high incidence of secondary maldescent (186).

To explain why UDT occurs in older boys as well as at birth, gonadal position is proposed to depend not only on normal prenatal gubernacular migration, but also postnatal elongation of the spermatic cord (187). Acquired, as compared with congenital, UDT could then be caused by failure of cord elongation (Fig. 19) because the distance from the inguinal canal to the scrotum increases with age (178). Clarnette and Hutson (187) have suggested that failure of complete disappearance of the processus vaginalis may be a common cause of acquired UDT; this would link inguinal hernia (widely patent processus vaginalis), hydrocele (narrow processus vaginalis), and ascending/retractile testes (partially obliterated lumen but persistence of processus vaginalis) on a common spectrum.

D. Risks of infertility/malignancy

Secondary degeneration of the cryptorchid testes is presumed to be related to a higher temperature (35–37°C) compared with the normal location in the scrotum (33°C) (4, 188, 189). Steroidogenesis becomes deranged within a few months of birth (155, 190), although it is uncertain, at least in humans, whether this is a primary or secondary defect. It is also unknown whether it is temporary or persistent. Animal studies, however, show clearly that UDT causes secondary degeneration particularly of germ cells (191–193). Serum levels of MIS are normal in neonates with UDT but are lower than normal at 4–12 months of age (11, 63, 64, 157) (Fig. 20). Decreased secretion of androgens and/or MIS are proposed as the cause for postnatal failure of normal germ cell maturation.

Recent studies show that germ cell development becomes abnormal in early infancy (194–196) in biopsies of the UDT, confirming previously held suspicions that the

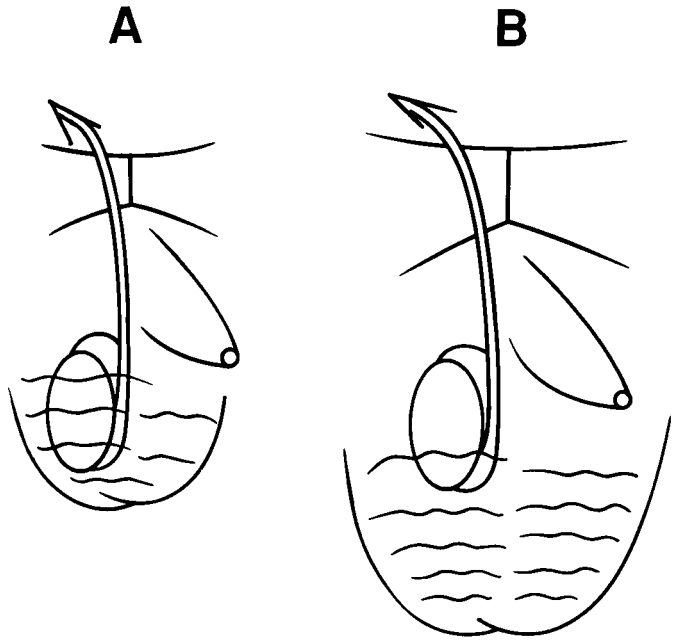

FIG. 19. Failure of the spermatic cord to elongate in proportion to body growth may be a cause of "ascending" or "retractile" testes. The testis that is fully descended in infancy (A) assumes a relatively higher position later in childhood (B). [Reproduced with permission from J. M. Hutson and S. W. Beasley: *Descent of the Testis*, 1992 (149)].

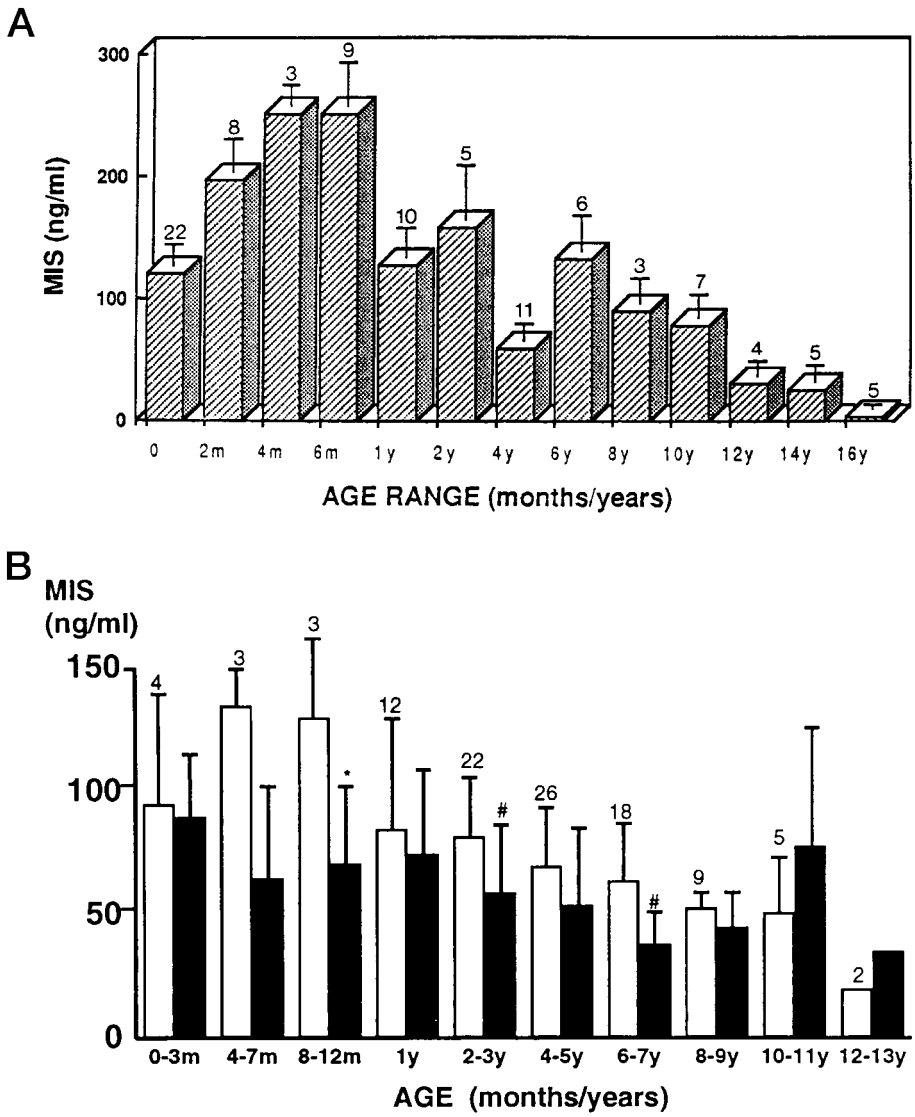

FIG. 20. A, Mean (±SE) levels of serum MIS at different ages [Reproduced with permission from M. L. Baker *et al.*: J Clin Endocrinol Metab 70:11–15, 1990 (63). © The Endocrine Society.] B, Levels of serum MIS (± SD) in cryptorchid boys (*filled bars*) *vs.* paired, age-matched controls (*open bars*) [Reproduced with permission from J. Yamanaka *et al.*: *J Pediatr Surg* 26:621–623, 1991.]

gonocytes fail to transform to type A spermatogonia. Deficiency of spermatogenesis was considered congenital at one time (178), but in recent years evidence has accumulated to support a secondary degeneration of germ cells (197–199). Huff *et al.* (194–196) have shown that the maturation of gonocytes to type A spermatogonia, which is the first step in postnatal spermatogenic development, is deficient in cryptorchid infants. Where the gonocytes fail to mature into spermatogonia, they persist for a while in the testis and then degenerate, leading to deficiency in total germ cell numbers (200). Although controversial, persisting gonocytes could be the source of carcinoma *in situ* (CIS) cells later in adolescence (201).

The higher risk of infertility in men with a past history of cryptorchidism is believed to be secondary to temperature-induced degeneration (4). Rats rendered cryptorchid surgically at birth have reduced fertility (202, 203), at least as measured by sperm analysis. Assessment by paternity rates, however, fails to reflect the same degree of anomaly. The cause of the UDT, whether surgical or hormonally induced by postnatal estrogen treatment, did not alter the prognosis for fertility (204). Testes that are intracanalicular or intraabdominal are associated with a poorer prognosis for fertility than inguinal testes (205). Significantly, retractile testes are reported to lead to reduced sperm counts in adulthood (206, 207), although this is not found in paternity studies (208, 209).

UDT is associated with a risk of malignant tumor of the testis in adulthood. At one time the risk was thought to be 35- to 50-fold greater than normal (210), but more recent calculations of relative frequency suggest the risk is closer to 5- to 10-fold (211, 212). The relative frequency of a history of UDT in men with testicular tumors is 15-fold for unilateral UDT and 33-fold for bilateral UDT (213–215). The increased risk of malignancy is considered to be caused by germ cell degeneration and dysplasia within the UDT (196, 216, 217). An alternative proposal, however, is that there is an intrinsic defect in the testis (218), as CIS germ cells may be found in neonates with dysgenetic testes and ambiguous genitalia. CIS germ cells are believed to be premalignant (201), but their origin is uncertain.

E. Role of hormone therapy

Medical treatment of UDT with various hormone preparations has been attempted since the 1940s (219). The underlying basis for hormonal therapy is the view that a deficiency of the hypothalamic-pituitary-gonadal axis is the common cause of UDT (76). Whether or not UDT is secondary to androgen deficiency, treatment of cryptorchid boys with human CG (hCG) or LHRH has been of mixed success, from 10%–20% (220–223).

Despite overall poor results (147), hormone treatment is effective in certain special groups. When the testis lies near the neck of the scrotum or when the anomaly is bilateral, the results of treatments are better. Older children and those with retractile testes also respond better to hormone therapy (223). As retractile testes are known to descend spontaneously at puberty (224, 225), it has been suggested that their favorable response to hormone stimulation is secondary to induction of precocious puberty (226).

The effectiveness of hormonal therapy is difficult to determine because congenital UDT has not been separated from its apparently acquired variants, ascending and retractile testes. Nearly all studies include boys between 5 and 12 yr, in whom an acquired anomaly could be present, while few studies examine the effectiveness of hormone treatment solely in infants, where congenital UDT is likely. Certainly, infants with unilateral UDT in the superficial inguinal pouch have the lowest success rate, which is consistent with the widely held view that congenital UDT is relatively resistant to hormone treatment. Although hormone treatment is in common use in many European and American centers, elsewhere it is uncommon. A further factor in its waning popularity may be the need for multiple intramuscular injections of hCG (227, 228). Nasal application of LHRH several times a day for 1 month also has been tried (220, 223, 229, 230) but this method is not available in some countries, including Australia.

Hormonal therapy may be advantageous in distinguishing retractable testes from congenital UDT (223). In addition, hormone stimulation may restore normal testicular function after surgery, as measured by increased numbers of germ cells and Leydig cells (231).

F. Timing of surgery

The optimal time for surgical correction of UDT remains unknown, although numerous studies suggest that early intervention is beneficial. Early correction of UDT does prevent degeneration, as is relatively easily shown in animal studies (204, 232–236). In humans, degeneration of germ cells is first seen at 6–12 months (194–196). Morphological changes are detected at the EM level at 1–2 yr (198), light microscopic signs of degeneration appear by 3–4 yr (237), and clinical atrophy of the testis is detected by 5–7 yr. Based on EM evidence of degeneration (197), orchiopexy in humans has been recommended at 1–2 yr of age. The recent recognition of germ cell maldevelopment by 6 months of age, however, suggests that even earlier surgery may be needed to prevent germ cell death or dysplasia: a number of centers are now offering orchidopexy at 6–18 months of age.

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