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Undescended testis: The underlying mechanisms and the effects on germ cells that cause infertility and cancer

John M. Hutson*

Urology Department, Royal Children's Hospital, Melbourne, Australia

Douglas Stephens Surgical Research Group, Murdoch Childrens Research Institute, Melbourne, Australia

Department of Paediatrics, University of Melbourne, Melbourne, Australia

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Abstract Testicular descent is a complex morphological process that occurs in at least 2 stages, with different hormonal control. *Ins13* controls the first step of gubernacular enlargement, although the abnormality long gubernacular cord in persistent Müllerian duct syndrome remains unexplained. Androgens control inguinoscrotal migration, which may be triggered by local signalling from the mammary line, and which requires the genitofemoral nerve. However, there is still much to learn about this phase, which when abnormal frequently leads to cryptorchidism. Orchidopexy is being recommended in the first year of age, because increasing research suggests that the stem cells for spermatogenesis form between 3 and 9 months, with surgery aiming to permit this normally, although this is not yet proven. Acquired cryptorchidism is now becoming accepted and is likely to be caused by inadequate elongation of the postnatal spermatic cord. It is not yet known whether orchidopexy is always needed, as this remains controversial.

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Testicular descent is a complex embryological process that has evolved over the last 200 million years in mammals, delivering the fetal intra-abdominal testis initially to a subcutaneous inguinal position and then into a fully developed scrotum [1]. It was first proposed that descent occurred in two distinct steps over 25 years ago [2], based on the inguinal position of the testes in both mice and children with complete androgen insensitivity.

Many recent reviews of testicular descent by researchers with a background in endocrinology or molecular biology focus on the hormones and the genes involved [3–5]. By

contrast, this brief review will describe the anatomical details of testicular descent in both rodent models and children, with emphasis on recent findings from our own laboratory. First will be a section on evolution of testicular descent, and the recent observation that the mammary line may have a key role in the process. Then there will be a section on the how the gubernaculum migrates to the scrotum with many of the properties of a limb bud, followed by a brief summary of all the evidence we have collected showing a role for the genitofemoral nerve (GFN) and its contained sensory neurotransmitter calcitonin gene-related peptide (CGRP). We conclude this brief tour of this normal process with the evidence that the GFN and CGRP may be important in humans, and not just in rodent models. We also summarise the literature on the causes of cryptorchidism.

* Royal Children's Hospital, Parkville, Victoria 3052, Australia. Tel.: +61 03 9345 5805.

E-mail address: john.hutson@rch.org.au.

In the second half of this review I discuss the timing of orchidopexy and how this is now based on normal germ cell development. Finally, I address the newly appreciated variant of ascending or acquired undescended testis, and how this is altering not only our understanding of cryptorchidism, but also the timing of surgery and prognosis.

1. The stages of testicular descent

At the onset of sexual development at about 7–8 weeks in a human, the ambisexual gonad is on the front of the urogenital ridge. As the mesonephros regresses posterior to the gonad, this leaves it on a mesentery, the so-called mesorchium or mesovarium. The onset of testicular development with production of hormones triggers regression of the Müllerian duct by Müllerian inhibiting substance or anti-Müllerian hormone (MIS/AMH), while the testosterone diffuses down the Wolffian duct and triggers its further differentiation into epididymis, vas deferens and a caudal bud which forms the seminal vesicle [6].

Initially the intra-abdominal fetal testis is held in the peritoneal cavity by the cranial suspensory ligament and the caudal genito-inguinial ligament, or gubernaculum (Latin: helm or rudder). John Hunter named it in 1762 because he thought it steered the testis to the scrotum. The cranial suspensory ligament regresses quite early in response to testosterone, while the gubernaculum responds to a newly-described Leydig cell hormone, insulin-like hormone 3 (INSL3), first found in 1999 in knockout mice [7,8].

INSL3 causes the gubernaculum to swell, and as its distal end is embedded in the anterior abdominal wall at the site of the future inguinal canal; this “swelling reaction” not only dilates the future inguinal canal but also holds the testis near the groin as the fetal abdomen enlarges between 8 and 15 weeks of development. By contrast, in the female the gubernaculum has no swelling reaction, and merely elongates in proportion to fetal growth to form the ligament of the ovary and the round ligament.

INSL3, which evolved from a common ancestor of relaxin [9] is now recognised as the primary hormone regulating the first phase of descent [10], as it is produced at the right time and has receptors in the gubernaculum (the relaxin-family peptide receptor 2 [RXFP2], also known as the GREAT or LGR8 receptor). It acts via cyclic AMP with downstream effects via Wnt, β -catenin and BMP pathways [11–13]. In the rodent it stimulates the proximal attachment of the gubernaculum to the testis and epididymis, the gubernacular cord, to remain short, and also triggers the processus vaginalis to develop inside the gubernaculum [14,15].

When the 2-stage model of testicular descent was first proposed, it was suggested that MIS/AMH might control the swelling reaction, however the role of INSL3 is well established now in rodent models. However, there is one

situation which hints at a role for MIS/AMH in gubernacular development, and that is the rare anomaly of persistent Müllerian duct syndrome (PMDS). In this rare genetic anomaly of the MIS/AMH gene or its receptor the Müllerian ducts persist in a boy who usually has cryptorchidism [16], and the gubernacular cord is excessively elongated to often more than 10 cm! It is suggested that UDT in this anomaly is secondary to mechanical effects of the retained uterus [17], although it is still quite possible that MIS/AMH has an effect on shortening the gubernacular cord, at least in humans.

Hormonal regulation of the second phase of descent is clearly by androgen, but how it works remains contentious. The first phase of descent ends at about 15 weeks in a human fetus and the second phase starts at about 25 weeks, with the reason for this gap unknown. However, given the mechanical complexity of the inguinoscrotal phase compared to the transabdominal phase, there is likely to be a lot happening behind the scenes.

In the human the gubernaculum bulges out of the inguinal muscles and elongates across the pubis and into the scrotum, which is a perilous journey of 3–5 cm. After it reaches the scrotum at around 35 weeks of gestation two further processes occur: the extracellular matrix is resorbed in a major remodelling, and the initially loose gubernaculum develops a fibrous attachment to the inside of the scrotum [18].

In rodents around birth the extracellular matrix in the swollen gubernaculum is resorbed and the gubernaculum remodels and everts through the future inguinal canal, creating the processus vaginalis (PV). It then migrates to the scrotum in a similar fashion to the human, and then becomes adherent inside the scrotum. Delayed adherence to the inside of the scrotum is the likely cause of perinatal torsion, leading to the vanishing testis.

2. Evolution of testicular descent and the role of the mammary line

What triggers the genito-inguinial ligament to suddenly become motile and elongate out of the abdominal wall? Further, what controls the elongation process and what regulates the direction of migration? A search for the answers to these questions has taken us on an astounding journey, which begins in early vertebrate evolution [19].

Two hundred million years ago marsupials and early mammals diverged from other vertebrates, but kept two anatomical features in common: breasts and testes descended to various levels. Modern marsupials provided a clue to how this happens when we realised that the scrotum in kangaroos develops directly over the inguinal canal, and not in the perineum as in the human. The second phase of descent is much simpler than in the human, as the bulging gubernaculum is already inside the scrotum right from the start. More importantly, the marsupial scrotum in males develops at the

same time and site as the breasts in females. The most surprising feature, however, was that in female marsupials the gubernaculum becomes attached to the inguinal breasts, so that the homologue of the human cremaster muscle, the ilio-marsupialis, is not only supplied by the genitofemoral nerve (GFN) but becomes the suspensory muscle of the nipples [20,21].

The connection between the marsupial gubernaculum and the breast seemed so striking it made us wonder whether we were missing a similar link in mammals. When we looked at fetal rodents we immediately found that one of the inguinal mammary buds was right next to the end of the gubernaculum, and was also supplied by the GFN [22,23]. The mammary buds regress before birth in rodents, but after androgen blockade the gubernacular connection to the persisting mammary ducts remains [24]. These studies suggested a possible role for the mammary line in the second phase of descent.

Human foetuses have a “mammary line”, but what is it? It is the line along which normal (and abnormal) breasts can develop, from the axilla to the femoral region in humans. In early mammalian embryos the mammary line forms along the lateral edge of the embryo, between the apical ectodermal ridges (AER) that trigger development of the outgrowths from the trunk that form the limb buds. Importantly, it has the same inductive properties as the AER to stimulate the underlying mesenchyme to grow, producing a bulge in the trunk, such as a breast or a marsupial scrotum, which has many similarities with limb buds.

Does the rodent gubernaculum display properties like an embryonic limb bud? We found both *Hoxa10* and *Fgf10* in the gubernaculum and overlying mammary bud in fetal mice [25]. In addition, the rodent gubernaculum contains a cluster of undifferentiated mesenchymal cells that behaves very like the “progress zone” in a limb bud [26] and it can be excised and grafted to make an ectopic gubernaculum similar to a limb bud in a chick embryo [27]. The inductive properties of the overlying mesenchyme in the mammary line may trigger the gubernaculum to acquire limb bud properties, and may also be how the GFN becomes masculinised [22,24,28], as described in the next section.

3. The role of the GFN and CGRP

Lewis (1948) [29] first showed that the GFN was important for inguinoscrotal migration in rodents, as cutting the nerve at birth stopped migration. We have spent a lot of effort studying the GFN and the neurotransmitter we eventually localised in its sensory fibres, calcitonin gene-related peptide (CGRP), as described in previous reviews [19,30]. Here I will just highlight some key features. The rat gubernaculum contains CGRP receptors and contracts rhythmically like cardiac muscle in response to CGRP.

The tip of the gubernaculum, where we found a “progress zone”, responds to CGRP with mitosis and suppression of

apoptosis [31], and the tip also responds to exogenous CGRP *in vitro* in a way suggesting chemotaxis [32].

Presence of CGRP in the GFN is sexually dimorphic, as it is absent in TFM mice with androgen insensitivity and also in the rat after androgen blockade with flutamide [33]. So where are the androgen receptors (AR)? Many authors assumed AR would be in the gubernaculum, but this is only after the well-described window of sensitivity to flutamide in a fetal rat, around E16-E19 [24,34,35]. We expected AR to be in the cell bodies of the dorsal root ganglia, but this was also negative [24]. We now suspect that the GFN is masculinised by the mammary mesenchyme releasing a neurotrophin in response to androgen stimulation, although this remains speculative [36].

Although more research is needed to unravel this mechanism, we propose that the mammary line triggers the gubernaculum to begin remodelling so it can grow into a “limb bud” and migrate, and that trophic effects on the GFN produce CGRP which guides the elongating gubernaculum to the scrotum by chemotaxis.

Many colleagues who have heard about our work on limb buds, GFN and CGRP in rodents are sceptical that these are important for the clinical situation in humans. My response is that first we should not ignore the evolution of testicular descent, as we have descended from early mammals by modification, as elegantly described by Darwin. Secondly, we wondered whether the PV growth inside the gubernaculum and its closure after testicular descent might be controlled by the same regulatory factors as testicular descent (ie: GFN and CGRP), as the PV develops inside the gubernaculum. When we collected human inguinal hernia sacs and put them in organ culture, the peritoneal lumen obliterated in 48 h in response to exogenous CGRP (!) [37]. This suggests that not only might human inguinal hernia be potentially treated medically, but also that the GFN and its transmitter, CGRP, are likely to be extremely important in children as well as rodents.

4. Cryptorchidism

The aetiology of cryptorchidism has been discussed in many recent reviews, so I won't reiterate all the evidence and controversy [10]. Most reviews focus on hormonal deficiency, but I think it is still quite likely that somewhere in the complex remodelling of the gubernaculum and its migration to the scrotum are many more possible causes of cryptorchidism.

A more topical issue is determining the time to operate on undescended testes. In the 1950's surgery was done in 10–15 year olds as pediatric surgeons of the era were general surgeons who liked children, yet surgery in babies was seen as dangerous. Furthermore, the germ cells were thought to be quiescent between birth and the onset of spermatogenesis at puberty.

In 1971, Scorer and Farrington suggested that orchidopexy was unable to prevent malignancy and wondered whether the operation was even justified [38]. At that time, adults with previous cryptorchidism had had surgery in their teens. By the mid 1970's it was appreciated that testicular atrophy occurred at 4–6 years, and by the 1980's it was known that germ cells were depleted by 2 years, and hence this was the recommended age for surgery [39].

In the 1950's orchidopexy in adolescents depended on 2 assumptions: that earlier surgery was dangerous because the tissues were delicate, and that the testis was in "suspended animation" till puberty when spermatogenesis started. With the progressive realisation that important germ cell development is occurring very early postnatally, it is important to note that the current recommendation for surgery in the 1st year (somewhere between 3–9 months (?)) is now based on 4 assumptions: germ cell loss begins at 3–6 months in UDT; this loss is preventable by placing the testis at the correct temperature in the scrotum; no spontaneous descent occurs after 3 months; and early surgery is safe with adequate training plus magnification.

5. Normal germ cell development and the time for orchidopexy

The neonatal gonocyte moves from the centre of the cord to reach the basement membrane and transforms into an adult dark spermatogonium around 6/12 (and this step is inhibited in UDT) [40]. Some adult dark spermatogonia (AD-S) remain as the putative stem cells for later spermatogenesis, and some continue developing into type B spermatogonia (B-S) and then into primary spermatocytes (PS), which appear in the tubule about 3–4 years of age. Not all gonocytes transform into AD-S, suggesting a possible screening process to select the optimal cells for spermatogenic stem cells. The remainder normally undergo apoptosis, which is also inhibited in UDT.

Gonocyte transformation and subsequent maturation require both normal testicular hormones (T, MIS/AMH, inhibin B, and Ins13(?)) as well as a normal temperature of 33 °C [41,42]. Our current hypothesis is that both transformation and apoptosis of gonocytes are inhibited in UDT because of the abnormally high temperature of the malpositioned testis [19]. Lack of AD-S causes infertility, and impaired apoptosis allows a few gonocytes to persist and possibly become carcinoma-in-situ (CIS) with progressive mutation and/or cellular derangement, and finally malignancy in adulthood.

Is the testis abnormal in UDT? Clearly if there is a DSD it is abnormal, but otherwise the physiological derangement is likely to be secondary to its malposition. The scrotum evolved as a specialised, low-temperature environment for the testis 200 million years ago, so that human testes are adapted to it, and the cellular processes presu-

mably alter to work at 33°C immediately after birth. When maldescent occurs, the testis remains at 35–37 °C. Orchidopexy is based on the assumption that this temperature effect is reversible once the testis is placed in the scrotum. Around 6/12 of age is currently safe in paediatric centres, which allows for postnatal descent up to 3/12, and anaesthetic considerations.

The justification of this age for surgery will only come after long-term follow-up, although studies by [43] Kollin et al. (2010) already show improved testicular growth (measured by ultrasonography) with orchidopexy at 9/12 versus 3 years of age.

6. Acquired cryptorchidism

This variant has been gradually accepted over the last 20 years, following the realisation that postnatally the spermatogenic cord must double its length between birth and puberty. Acquired UDT occurs when this elongation fails, so that the initially descended testis gets left behind as the scrotum moves further from the groin as the boy enlarges. We have previously suggested that this is secondary to a fibrous remnant of the processus vaginalis [44], which links acquired UDT to hydrocele and hernia. It may be that they all have a common aetiology, which is likely to be slightly deficient prenatal or postnatal androgens and inadequate CGRP from the GFN. Acquired UDT is also common in boys with cerebral palsy who have adductor spasm, as this also affects the cremaster muscle by a shared segmental nerve supply [45]. In Melbourne, presumed acquired UDT accounts for about half of all our orchidopexies [46].

The prognosis for acquired UDT is predicted to be better than congenital UDT as gonocyte development and/or apoptosis in the first year should be normal while the testis is still in the scrotum. Fertility however, will be impaired somewhat if the acquired UDT remains in the groin (at a higher temperature) between 5 to 15 years, even if it descends spontaneously at puberty (which occurs about ½ the time). Acquired UDT may therefore respond to hormonal treatment, although orchidopexy via a scrotal approach is very satisfactory. Currently, whether acquired UDT needs surgery (or hormonal treatment) remains controversial, although my own current practice is to operate once the testis no longer can reside spontaneously in the scrotum (and hence at the right temperature). Where the testis is high in the scrotum, I recommend annual review so see if it will become an acquired UDT out of the scrotum.

7. Conclusions

Testicular descent is a very complex process, and we are still a long way from a full understanding of the normal process, let alone the causes of cryptorchidism, despite

recent progress. However, it is becoming clearer that the prognosis and timing of surgery depend on understanding germ cell development, which will be an area of active research in the next few years.

On the knowledge we currently have, we can say that congenital UDT probably needs surgery in the first year (perhaps 3–9 months), aiming to prevent abnormal gonocyte maturation. For acquired UDT presenting later in childhood, we expect that early development should have been normal, so that if we are correct in assuming that persisting gonocytes will lead to cancer, then this will not occur in this group. Orchidopexy remains controversial for acquired UDT, but many surgeons (including the author) recommend a scrotal operation once the testis no longer sits spontaneously in the scrotum.

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