## CONTENTS

13  **INTRODUCTION & OUTLINE OF THE THESIS**

19  **CHAPTER 1: DESCENT OF THE TESTIS**

21  1.1 Testicular descent: a review

41  **CHAPTER 2: DIFFERENT ASPECTS OF ACQUIRED UNDESCENDED TESTIS**

43  2.1 Prevalence of acquired undescended testis in 6-year, 9-year, and 13-year old Dutch schoolboys
    W.W.M. Hack, K. Sijstermans, J.M. van Dijk, L.M. van der Voort-Doedens, M.E. de Kok, M.J. Hobbelt-Stoker
    Arch Dis Child 2007;92(1):17-20

53  2.2 Puberty stage and spontaneous descent of acquired undescended testis: implications for therapy?
    Int J Androl 2006;29(6):597-602

63  2.3 Reduction in the number of orchidopexies for cryptorchidism after recognition of acquired undescended testis and implementation of expectative policy
    Acta Paediatr 2007;96(6):915-918

73  2.4 The high scrotal (“gliding”) testis revised
    W.W.M. Hack, K. Sijstermans, L.M. van der Voort-Doedens, R.W. Meijer, K. Haasnoot
    Eur J Pediatr 2007;166(1):57-61

83  **CHAPTER 3: DIFFERENT ASPECTS OF CONGENITAL UNDESCENDED TESTIS**

85  3.1 Congenital undescended testis: findings at orchidopexy
    Submitted for publication

95  3.2 Long term testicular growth and position after orchidopexy for congenital undescended testis
    K. Sijstermans, W.W.M. Hack, L.M. van der Voort-Doedens, R.W. Meijer
    Submitted for publication
CHAPTER 4: DIFFERENT ASPECTS OF UNDESCENDED TESTIS

4.1 The frequency of undescended testis from birth to adulthood: a review
K. Sijstermans, W.W.M. Hack, R.W. Meijer, L.M. van der Voort-Doedens

4.2 Undescended testis: current views and advice for treatment
Ned Tijdsch Geneeskd 2008;152(5):246-252 (Original in Dutch)

CHAPTER 5: GENERAL DISCUSSION & FUTURE PERSPECTIVES

5.1 General discussion
5.2 Future perspectives
5.3 Guidelines on the treatment of undescended testis
5.4 The National Testis Centre (N.T.C.)

CHAPTER 6: ELECTRONIC LETTERS & CORRESPONDENCE

6.1 Rapid Responses to: Common paediatric problems
A.R. Prem
BMJ 2006;333:486-489

6.2 Response to: This is the first study
Jamie D.C. Martin
Arch Dis Child online 17 January 2007

6.3 Correction of cryptorchidism and testicular cancer
W.W.M. Hack, K. Sijstermans, L.M. van der Voort-Doedens

CHAPTER 7: SUMMARY

7.1 Summary
7.2 Samenvatting
7.3 Samenvatting voor de niet-medische lezer

CURRICULUM VITAE

DANKWOORD
INTRODUCTION

Cryptorchidism or undescended testis (UDT) is the most common birth defect of male genitalia in which either one or both testes fail to descend fully into the scrotum. UDT is associated with reduced fertility and an increased risk of developing testicular cancer. To reduce these risks, UDT are usually brought into the scrotum in infancy by a surgical procedure called orchidopexy (ORP).

Although, at present, many articles have been published on UDT, there still remain unanswered questions. For example, the process of testicular descent is still not fully understood. In addition, many elderly boys presented with UDT undergo surgery, although at present, the age of election for operation of UDT is between 6-12 months after birth, instead of 2 to 3 years as recommended in the 1980s.

In recent years it became apparent that UDT has to be categorised into congenital and acquired forms. In 1986 a “Development Conference on Non Scrotal Testis” was held in the Netherlands. It was agreed upon that each UDT should be treated (surgically) before the age of 2 to 3 years old and not to treat a non-scrotal testis until at least puberty in case of fully descent of the testis at birth. Therefore, a national testis registration at birth was introduced. Consequently, this conference focussed attention on the importance of meticulous registration of testis position in each boy at birth and in earlier years. The registration of the testis at subsequent examinations eventually led to recognition of acquired UDT and is nowadays of great meaning to differ between congenital and acquired forms.

A congenital UDT is a testis which has never been descended in contrast to an acquired UDT, which has been previously fully descended into the scrotum. The cause of congenital UDT is usually considered multifactorial, including endocrine and mechanical factors. The pathogenesis of acquired UDT is still unknown. It is assumed that a remnant of the processus vaginalis prevents normal elongation of the cord structures, which causes testicular ascent. Also, cremaster muscle spasticity may play a role. There is growing evidence that acquired UDT is a frequent but underdiagnosed phenomenon and that this form probably accounts for the high rate of orchidopexies found later in childhood. The concept of recognition of congenital and acquired UDT as distinct and separate entities has been evolving over the last two decades. This concept, which is not yet still generally accepted, arises major challenges such as: What is the optimal treatment for acquired UDT? Does acquired UDT indeed explain the disparity between the apparent incidence of UDT at birth and the (high) number of ORP performed? How frequent is the phenomenon of acquired UDT? What is the long-term prognosis, like the fertility potential and malignancy status, of both congenital and acquired UDT? Some of these answers will be found wanting in the future, but they will serve as a guide to future advances.

The concept of congenital and acquired UDT results in a need for further data such as on the prevalence and the natural course of acquired UDT as well as on testicular descent. One might speculate that congenital and acquired UDT are probable quite different entities with apparently also a quite different prognosis.
In this thesis we assess the following major unanswered questions regarding UDT:
1. What are the current opinions of the concept of testicular descent?
2. How frequent is the phenomenon of acquired undescended testis?
3. What is the tendency and the approximate timing of spontaneous descent of the acquired form?
4. Does acquired undescended testis explain the disparity between the apparent incidence of undescended testis at birth and the (high) number of orchidopexies performed?
5. Is the phenomenon of the high scrotal testis a separate entity or part of the spectrum of either congenital or acquired undescended testis?
6. What are the surgical aspects of congenital undescended testis found at orchidopexy?
7. What are the consequences on long-term testicular growth and position after orchidopexy for congenital undescended testis?
8. What is the frequency of undescended testis from birth to adulthood given from the literature?

OUTLINE OF THE THESIS
The aim of the work presented in this thesis is to elucidate different aspects of congenital and acquired UDT.

Chapter 1 reviews the descent of the testis. The current opinions of the fetal and neonatal development of the testis, the concept of testicular descent, and the abnormalities of these processes in cryptorchidism are addressed.

Chapter 2 describes the different aspects of acquired UDT. The prevalence of acquired UDT among Dutch schoolboys is determined and spontaneous descent of this acquired form in the pubertal period is investigated. In addition, the influence of acquired UDT on the high rate of ORP is analysed. Finally, in this chapter, the high scrotal testis is evaluated.

Chapter 3 describes the different aspects of congenital UDT. The surgical aspects of congenital UDT, as found at ORP, are presented and the consequences of ORP on the long-term testicular growth and position is investigated.

In Chapter 4, the different aspects of both congenital and acquired UDT are described by reviewing the literature on the frequency of UDT from birth to adulthood and by presenting an overview of the current views. Also, practical guidelines for the treatment of boys with UDT are given.
SYNOPSIS: In this chapter the mechanisms of testicular descent and maldescent are reviewed.
1.1 TESTICULAR DESCENT: A REVIEW

K. Sijstermans
1.1 TESTICULAR DESCENT: A REVIEW

1.0 Introduction

2.0 Historical review

3.0 The development of the testis
3.1 Sexual differentiation

4.0 Normal testicular descent
4.1 Embryology
4.2 Phases of testicular descent
   4.2.1 Transabdominal phase
   4.2.2 Inguinoscrotal phase

5.0 Aetiology of cryptorchidism
5.1 Congenital
   5.1.1 Hormonal and genetic factors
   5.1.2 Mechanical factors
   5.1.3 Neurological factors
   5.1.4 Environmental factors
5.2 Acquired
   5.2.1 Acquired factors

6.0 Spontaneous descent

7.0 Conclusion
‘With such a long distance to travel, we should be wondering why scrotal descent occurs at all, rather than why undescended testis is common’

In this review the following abbreviations are used:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMH</td>
<td>Anti-Müllerian Hormone</td>
</tr>
<tr>
<td>CGRP</td>
<td>Calcitonin Gene-Related Peptide</td>
</tr>
<tr>
<td>EGF</td>
<td>Epidermal Growth Factor</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle Stimulating Hormone</td>
</tr>
<tr>
<td>GFN</td>
<td>Genitofemoral Nerve</td>
</tr>
<tr>
<td>HCG</td>
<td>Human Chorionic Gonadotrophin</td>
</tr>
<tr>
<td>HPG-axis</td>
<td>Hypothalamic Pituitary Gonadal axis</td>
</tr>
<tr>
<td>INSL3</td>
<td>Insulin-like Hormone 3</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinising Hormone</td>
</tr>
<tr>
<td>MIS</td>
<td>Müllerian Inhibiting Substance</td>
</tr>
<tr>
<td>PMDS</td>
<td>Persistent Müllerian Duct Syndrome</td>
</tr>
<tr>
<td>PV</td>
<td>Processus Vaginalis</td>
</tr>
<tr>
<td>SRY</td>
<td>Sex-determining Region Y gene</td>
</tr>
<tr>
<td>UDT</td>
<td>Undescended Testis</td>
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</table>
1.0 INTRODUCTION
Cryptorchidism, the failure of the testis to descend into the scrotal sac, was first described by Galen in the 2nd century and Galen’s writings enjoyed a revival at the hands of Vesalius in the 16th century. The word cryptorchidism is derived from the Greek words kryptos, which means “hidden”, and orchis, which means “testis”. The terminology “undescended testis” (UDT) is also frequently used.

The mechanism of testicular descent and maldescent is still largely an enigma. The study of testicular descent begins with the observations of the Scottish surgeon-scientist, John Hunter (1), more than 200 years ago. During these last 200 years numerous theories have been proposed to explain the mechanism of descent.

Much of the unresolved controversy is due to difficulties and limitations of research on fetal processes in humans, since experimental work is mainly performed on laboratory animals (2-8).

In recent years, a number of new concepts on testicular descent have been developed. However, only a few of the current ideas are novel and most of the relevant observations on descent were extraordinary enough reported more than a century ago (9-12).

In this chapter the current thoughts on testicular descent are summarised, focusing on the following items:
- the history of testicular descent,
- the development of the testis,
- the normal testicular descent,
- the aetiology of cryptorchidism and
- the spontaneous descent.

2.0 HISTORICAL REVIEW
The importance of the testes has been recognised since the 13th century before Christ. For example, Moses mentioned castration of animals in the book of Leviticus (22:24) (13). Human castration was practised on a large scale on slaves, and defeated enemies, by the priesthood of various cults, and by the male attendants in harems in imperial Rome (14). Impotence has always been regarded as disastrous. For example, France and Spain at one time forbade the marriage of men with undescended testis because of sexual impotency (15,16). Its importance was also appreciated by the church in the middle ages when a female pope (Pope Joan) was elected in the 850s, leading to a scandal when she gave birth to a baby during a papal procession through Rome. Following this episode, the porphyry chair was produced as a way of determining definitely whether any future pope was a man and hence could become the Holy Father. The chair has a cut out in the seat such that the elected cardinal can sit on the chair, suitably robed, and a junior cardinal can reach from behind and palpate the scrotum. If the scrotum contains 2 testes, he would chant “duo testes bene pendulum” (he has 2 testes and they hang well), confirming masculinity and eligibility for the papacy (17). To this day, a fused scrotum containing two testes is still the best test for manhood and is still better than any genetic or hormonal test for a “man” (18).

It is usual to consider John Hunter as the first person to describe the testis and the epididymis
in the abdomen of the foetus and the pattern of testicular descent (19). He introduced the term “gubernaculum testis”, the rudder that guides the testis out of the abdomen and into the scrotum. However, there is some dispute as to who first described this unique structure attached to the fetal testis. According to Weil (20), von Haller discovered this structure and named it “vagina cylindrical” because he regarded it as a hollow cylinder through which the testis descends. Backhouse (21) finally refuted the view that Haller, rather than Hunter, first described the gubernaculum testis, and pointed out that Haller himself attributed the first description to Hunter. Albrecht von Haller, however, showed, in 1755, that the fetal testis is intra-abdominal and that the Processus Vaginalis (PV) is open (22). Hunter’s descriptions of both the structure and function of the gubernaculum were cautious. He stated, “It is hard to say what the structure or composition of this ligament may be”. He thought that the gubernaculum was vascular and fibrous and covered by fibres of the cremaster muscle. Hunter was uncertain of the function of the cremaster muscle in the fetus. Since Hunter’s first description, the gubernaculum has been described by many. Numerous early authors (e.g., Paletta 1777, Wrisberg 1779, Vicq d’Azyr 1780, Martin 1780, and Brugnoni 1785) are quoted by Backhouse (21) as describing a structure covered by peritoneum extending from testis to the scrotum, containing fibrous and/or muscular tissues, yet being essentially soft and jelly-like. In 1817 Seiler (23) misquoted Hunter by stating that a cremaster muscle running up in the fibromuscular gubernaculum pulled the testis down. Seiler’s views received support from Curling (24). Cloquet (25) and Carus (26) believed the cremaster was formed mechanically and Robin (27) thought that the testis finished its descent into the scrotum either due to abdominal pressure or to its own weight. Weber (28) ascribed only secondary importance to the cremaster fibres and regarded as the main force the PV as a closed sac independent of the peritoneum, which he was the first to describe. Another theory, favoured by Lockwood (29), attempted to show that distal muscular attachments of a fibro-muscular gubernaculum testis were responsible for the position of ectopic testes. He postulated that a fan-shaped leash of muscle fibres might sequentially pull the testis down and that the ectopic testes may be caused by abnormal traction of one of the projections of gubernacular muscle, which were later described as the “tails of Lockwood”. Furthermore, Cooper (30), Turner (31), Mc Gregor (32), Browne (33) and Keith (34) have added points to our knowledge of the anatomy of the descending testis.

The twentieth century has seen the advent of hormonal theories and there was a “rush” to explain testicular descent in endocrinological terms, undermining the credibility of mechanical theories of their anatomical basis.

3.0 THE DEVELOPMENT OF THE TESTIS
3.1 SEXUAL DIFFERENTATION
In the embryo the testes arises from the medial portion of the urogenital ridges. The urogenital ridge in humans is identical morphologically in males and females up to 7-8 weeks of gestation (35), when the Sex-determining Region Y gene (SRY) on the Y chromosome initiates development of the testis (36). SRY activates male development by germinal cord cells differentiating into Sertoli cells. The Sertoli cells secrete Müllerian inhibiting substance (MIS) (also known as the anti-Müllerian hormone, AMH), which causes regression of the
Müllerian ducts at 8-10 weeks which otherwise would form the fallopian tubes, uterus and upper vagina (37). By the end of week 9 the interstitial cells arise, and differentiate into steroid secreting Leydig cells (38). Around 10-11 weeks’ gestation, the developing steroid secreting Leydig cells secrete testosterone, which stimulates the Wolffian ducts to persist and continue their development into the epididymis, vas deferens and seminal vesicles (39). Masculinisation of the external genitalia occurs between 10-15 weeks’ gestation and is dependant on the conversion of testosterone into di-hydrotestosterone by the enzyme 5-alpha-reductase, which is present in the tissues of the developing external genitalia (40).

Furthermore, between the 15th and 25th week the central and peripheral nerve system, especially the nucleus of the genitofemoral nerve, possibly has to be masculinised by androgens (41). In addition to testosterone, the Leydig cells secrete Insulin-like Hormone 3 (INSL3), which induces male-like development of the gubernaculum, at least in mice (42).

Generally, differentiation of fetal gonocytes into spermatogonia begins around gestational weeks 13-15 with down regulation of stem cellmarkers and appearance of additional germ cell specific proteins in an increasing proportion of germ cells. Differentiation of gonocytes (the fetal stem cell pool) is morphologically recognised in semithin sections as the appearance of adult dark spermatogonia (the adult stem cell pool) during the first months of life (43,44). The last remaining gonocytes disappear in infancy (45).

4.0 NORMAL TESTICULAR DESCENT

4.1 EMBRYOLOGY

The testis in the developing urogenital ridge is anchored by two embryonic ligaments to the body wall, the cranial suspensory ligament and the caudal genito-inguinal ligament or gubernaculum (1). At the cranial end, the suspensory ligament regresses in the male fetuses (with androgen) but not in female fetuses, which allows the testis to move relative to the ovary (46). Both genders have the gubernaculum, which becomes surrounded by peritoneum, except where it is attached to the abdominal wall. The testis glides over the genital ducts, becomes embedded caudally in the gubernaculum, together with the epididymis, and enters the internal inguinal ring. Before the testis and epididymis descend through the inguinal canal the mass of the gubernaculum increases. In males at 10-15 weeks of gestation the caudal end of the gubernaculum enlarges (known as the “swelling reaction”) (47-49) to form a short, broad column preventing the gubernaculum from elongating as the embryo enlarges. The swelling reaction of the gubernaculum holds the testis close to the future internal inguinal ring. The testis continues to descend to near the deep ring of the future inguinal canal between the 10th and 15th week of gestation, where it will remain as the abdomen lengthens.

The gonad deviates further after 25 weeks of gestation, when the gubernaculum bulges beyond the future external ring and descends into the scrotum, while simultaneously it is hollowed out by a peritoneal diverticulum called the PV (47,48). The PV allows the previously intraabdominal testis to exit from the abdominal cavity (50). The intra-abdominal pressure and the shrinkage of the gubernaculum may force the testis through the inguinal canal. After the testis has reached the bottom of the scrotum the distal part of the PV is called the tunica vaginalis and the connection to the peritoneum involutes. The gubernaculum shrinks, becomes more fibrous and persists as the scrotal ligament (48,51).
Chapter 1

The cremaster muscle developed in the outer rim of the gubernaculum, outside of the PV (52).

4.2 PHASES OF TESTICULAR DESCENT

Currently, testicular descent is considered to occur in two stages with separate anatomical mechanisms and hormonal control is assumed (41,51,53). Testicular descent begins after sexual differentiation at 8-10 weeks in the human embryo and is categorised in an initial transabdominal phase and a second inguinoscrotal phase.

4.2.1 Transabdominal phase

The first or transabdominal phase starts after 10 weeks of gestation and is completed by the 15th week of gestation. This phase is one in which the testis is anchored to the inguinal region, while the rest of the abdominal organs move away during the growth of the embryo (differential growth). The process is triggered by hormonally controlled enlargement of the distal gubernaculum (41). Simultaneously, the cranial suspensory ligament regresses under the control of testosterone (46), allowing the testis to be held near the developing inguinal canal as the abdominal cavity enlarges. This androgen effect is necessary but not sufficient alone for normal testicular descent. It seems that the first phase of testicular descent is successful even without androgens (54). MIS was first believed to promote gubernacular development thereby anchoring the testis in the inguinal region, and to promote regression of the Müllerian ducts. Estrogens given to male mice inhibit MIS and result in retention of the Müllerian ducts and UDT (55,56). In addition, male children with MIS deficiency, a genetic disorder, have completely undescended testes and retained Müllerian ducts (57). This association of retained Müllerian ducts and UDT is evidence for a common etiology with MIS control of both processes. Several experimental models have suggested that MIS is not the major factor (58-60). It seems that MIS is responsible in male fetuses for regression of the Müllerian ducts but changes in the gubernaculum might be regulated by other factors. In the late 1990s, a new testicular hormone was discovered, known as the INSL3, which is related to insulin and relaxin and is also known as relaxin-like factor. The INSL3 is produced, as stated earlier, by the Leydig cells in the fetal testis, and a gene knockout of INSL3 produced a mouse with intraabdominal testes and a feminised gubernaculum with no swelling reaction (61,62). This suggested that INSL3 was the missing factor causing the swelling reaction. Previously, Adham & Agoulnik (42) and Bogatcheva & Agoulnik (63) established that a deficiency of INSL3 signalling in mice hampers transabdominal descent. It also seems that the fetal expression of INSL3 does not require gonadotropins, since mice lacking an active pituitary-gonadal axis express INSL3. Accordingly, these mice and LH receptor knockout mice show a normal transabdominal phase of testicular descent although the inguinoscrotal phase is impaired (64).

The role of INSL3 and its receptor, INSL3-LGR8/GREAT, (65) (which is expressed by cells within the gubernaculum) encouraged the search for naturally occurring mutations in these genes. Published studies indicate that mutations in these two genes might account for (a small portion of all cases of) UDT in humans (63). The only clinical consequence of alteration of these genes seems to be failure of the testis to normally descend to the scrotum, without affecting the spermatogenic and endocrine components of the testis (66). Alterations of the INSL3-LGR8/GREAT system could be responsible, at least in part, for failure of the testicular descent.
29

Descent of the testis

The HOXA-10 gene is another candidate gene which deserves attention in the context of UDT. Targeted disruption of the HOXA-10 gene caused uni- or bilateral UDT and abnormal development of the gubernaculum, PV, inguinal canal and scrotal sac in male mice (64). Moreover, in mice, maternal exposure to estrogens caused down regulation of INSL3 expression in fetal Leydig cells, intra-abdominally located testes and a female-like development of the gubernaculum, providing a possible mechanism of UDT (67,68). It also seems that excess of estrogens in mice probably can cause a feedback inhibition of the hypothalamic-pituitary-gonadal (HPG) axis, leading to hypoandrogenaemia (69). In addition, Hadziselimovic et al. (70) reported increased expression of placental estradiol in cryptorchid boys. At present, however, there is not enough data to confirm that an excess of maternal estrogen might be a cause of UDT.

Therefore, the transabdominal phase of testicular descent is regulated anatomically by the cranial suspensory ligament and the gubernaculum, acting in concert to hold the testis near the inguinal region (71). Hormonally it is regulated by androgens which causes cranial suspensory ligament regression (46) and INSL3, possibly aided by MIS, which stimulates gubernacular cell proliferation (“the swelling reaction”) (67,72,73).

4.2.2 Inguinoscrotal phase

In the second phase, or inguinoscrotal phase of testicular descent, between 26-40 weeks of gestation (74), the gubernaculum grows out from the inguinal abdominal wall and physically migrates across the pubic region into the scrotum (48). Inside the gubernaculum, the PV enlarges to create an extension of the abdominal cavity into the scrotum (75). It appears to be controlled by androgens, specifically testosterone and dihydrotestosterone. Evidence for their action is provided by the observation that descent of the testis stops at the inguinal region in completely androgen resistant males (testicular feminising syndrome) (76). In addition, androgen antagonists prevent inguinoscrotal descent in rats (77). Androgens are believed to stimulate androgen receptors in the gubernaculum causing it to grow and migrate into the scrotum, thereby drawing the testis into the scrotal pouch. To date, these androgen receptors have only been detected early in the development of the gubernaculum and not at the stage of inguinoscrotal migration of the testis (78). Hutson & Beasley (56) have suggested that these androgens act on the gubernaculum indirectly through the sensory branch of the genitofemoral nerve (GFN) which releases calcitonin gene-related peptide (CGRP) into the gubernaculum. This neurotransmitter controls the growth of the tip of the gubernaculum and the direction of migration of the gubernaculum to the scrotum (79). Cain et al. (80) reported that epidermal growth factor (EGF) can reverse antiandrogen-induced cryptorchidism in rats. EGF stimulates gonadotropin secretion by the placenta and enhances androgens from the testis (81,82). However, data regarding the role of EGF in testicular descent in humans are sparse.

Experimental data suggest that abdominal pressure can push the testis to reach the scrotum by way of an open PV (83-85). A rapid growth in the epididymis has also been ascribed to a motile force, resulting in testicular movement (86). It is not clear whether or not these pressures/forces are androgen-dependent or independent.
**5.0 AETIOLOGY OF CRYPTORCHIDISM**

**5.1 CONGENITAL**

Testicular descent is believed to be the result of a complex interaction of hormonal and mechanical or anatomical factors as described above. Therefore, the aetiology of cryptorchidism, i.e. undescended testis (UDT) is usually considered multifactorial. Any disruption of this process has the potential to cause UDT in the human male. Although the common causes of UDT are still unknown, transabdominal descent, rarely goes wrong, as in most instances testes have descended to or beyond the inguinal canal (87). Intra-abdominal testes comprise a small group of about 5-10% of all cases of UDT. By contrast, inguinoscrotal descent is much more prone to mishap (88).

UDT can occur as an isolated disorder in healthy boys, but can also be part of endocrine or genetic disorders, syndromes and morphological abnormalities. A variety of factors have been postulated as potential etiologies of UDT (however, many of these factors are mutually interrelated):

- **5.1.1 Hormonal and genetic factors**
- **5.1.2 Mechanical factors**
- **5.1.3 Neurological factors**
- **5.1.4 Environmental factors**

**5.1.1 Hormonal and genetic factors**

Attention has been focused on defects in the hypothalamic-pituitary-gonadal (HPG) axis as a cause of UDT. UDT is more common in boys with anencephaly, pituitary aplasia or hypoplasia, and in syndromes associated with diminished gonadotropin production such as Kallmann and Prader-Willi. There are also a number of other causes, which affect the HPG-axis by disrupting gonadotropin synthesis (Klinefelter syndrome), androgen production (testicular atrophy), or androgen function (androgen insensitivity syndrome) (89). These account for most cases of bilateral UDT. In addition, UDT occurs in caudal developmental field defects (90,91) and familial occurrence in some cases suggests a possible genetic background of UDT (92,93).

Androgens are believed to play an important role in testicular descent through the inguinal canal to the scrotum. This leads researchers to believe that defects of (prenatal) androgen secretion may be a primary cause of UDT, secondary to either deficient pituitary gonadotropin stimulation, or low production of human chorionic gonadotrophin (HCG) by the placenta (86,94). The human fetal testis binds HCG and physiological levels of HCG already stimulate testosterone production during early pregnancy (95). Because hypogonadotropic hypogonadism often results in UDT, regardless of normal placental HCG production, endogenous fetal pituitary luteinising hormone (LH) seems to be a more important regulator of fetal testosterone synthesis in late pregnancy (96). UDT has also been proposed to be associated with an increased GGN repeat length of the androgen receptor gene, which may cause decreased function of the androgen receptor (97). Humans with complete or incomplete androgen insensitivity syndrome show normal transabdominal descent, but hampered inguinoscrotal descent (98). Furthermore, it has been suggested that bilateral UDT may
be associated with an increased length of the CAG repeat in the androgen receptor gene (99), although previous studies regarding UDT found no such association (97,100). However, mutations for instance in androgen receptor gene or in the gene of 5-alpha-reductase seems to be rare in isolated UDT (101,102). Finally, mutations in the HOXA 10 gene seems to be rare among cryptorchid patients (103).

**INSL3 and LGR8 genes** have a key role in the descent of the testis in mice, and mutations of these genes have been identified in some cryptorchid cases. However, only heterozygous mutations of these genes have been described in humans with UDT (42,104) and these mutations remain rare (105,106). Furthermore, in a recent study UDT was associated with an increased incidence of a polymorphic allele of SF-1, that has a reduced transcription activity (107). In humans, SF-1 may affect the in vitro expression of both INSL3 and LGR8 (42). It has been suggested that UDT is associated with increased minipubertal gonadotropin levels and reduced levels of INSL3 and inhibin B (96,108).

Intra-abdominal testes might also be due to the persistent Müllerian duct syndrome (PMDS), which is caused by lack of synthesis or action of the AMH (109,110). Patients have normal male external genitalia, but the internal genitalia include fallopian tubes and an uterus as well as totally UDT. In PMDS the testes are usually located in a pseudo-ovarian position, but the testis may also be located in an inguinal hernia together with a fallopian tube, the uterus and even the contralateral testis (111).

**5.1.2 Mechanical factors**

Other causes of maldescent include mechanical or structural anomalies. A common example of a mechanical cause of UDT is the presence of an inguinal hernia, due to an open PV, which is frequently associated with UDT (112-115). In fact, any abnormality that can cause the inguinal canal to be closed prior to testicular descent, or fail to close after descent, has the potential to cause UDT.

Ectopic testes lying beyond the normal line of descent are rare and may occur secondary to specific anatomical defects. Rodent studies, for example, show that transection of the gubernaculum can lead to accidental descent down the contralateral canal (transverse testicular ectopia) (5). According to Wensing & Colenbrander (116) aberrant gubernacula are frequently encountered in pigs, resulting in an ectopic position of the testis.

Intra-abdominal pressure has been implicated in the mechanism of testicular descent. Boys with congenital abdominal wall defects, such as gastrochisis, omphalocele and umbilical hernia, reportedly have an increased incidence of UDT. The supposedly low intra-abdominal pressure in these boys has been thought to inhibit testicular descent (117,118). However, it has been shown that an experimentally created abdominal wall defect alone does not wholly prevent testicular descent in rats (119).

It has been speculated that an epididymal abnormality may interfere with the normal descent of the testis (120-122). This is based on evidence including the dependence of epididymal development on androgens, the attachment of the (caudal) epididymis to the gubernaculum and the fact that the gubernaculum guides the testis into the scrotum. Of additional importance is the finding that epididymal abnormalities have been reported to range up to
50% in humans with UDT (123,124). However, the exact mechanisms by which epididymal abnormalities and/or epididymis-testis interaction could lead to UDT remain unclear.

Certain rare causes of UDT have been identified. For example, in both Prune Belly syndrome and posterior urethral valves, the enlarged fetal bladder may block the entrance to the internal inguinal ring, preventing testicular descent (56). The alternative, less plausible, explanation for UDT in Prune Belly syndrome is that the syndrome is associated with low abdominal wall pressure preventing descent. However, most infants with UDT have no obvious genital anomaly or abnormality of hormone levels at birth. In addition, the fact that UDT are more commonly unilateral than bilateral also suggests that they are caused by mechanical rather than hormonal factors.

5.1.3 Neurological factors
The GFN, which releases CGRP to stimulate gubernacular elongation and migration to the scrotum has been associated with UDT in rodents. However, mutation screening in patients with idiopathic UDT showed no pathogenic sequence changes in the CGRP pathway (125). On the other hand, CGRP caused fusion of the PV in human inguinal hernia sacs in vitro. Thus, the GFN and CGRP may control the obliteration of the PV after testicular descent (41). Furthermore, the frequency of UDT is generally increased to about 20% in boys with spina bifida, and to about 35% in cases of high lumbar lesions, suggesting that the GFN may also be important in humans (126). At present, androgen deficiency may be manifested by abnormal physiology of the GFN, which may disrupt migration of the gubernaculum. Unilateral UDT are likely to occur because androgens act independently on each side, via the ipsilateral GFN. Therefore, defects in neuronal development or CGRP action could lead to unilateral UDT.

5.1.4 Environmental factors
UDT has also been proposed to be part of a testicular dysgenesis syndrome, which also includes hypospadias, reduced semen quality, and testicular cancer. These conditions are thought to have a common origin in prenatal testicular maldevelopment, which affects both Leydig and Sertoli cells and germ cell differentiation (127). There is emerging evidence that such testicular dysgenesis may be caused by environmental factors (128). Besides, several studies indicate an increase in the prevalence of UDT within a few generations, supporting the hypothesis that lifestyle changes and environmental factors may be involved. Prenatal phthalate exposure in male offspring, for example, was associated with a short anogenital distance and these boys had less complete testicular descent (129). Furthermore, many pesticides have estrogenic and/or antiandrogenic effects, which might increase the risk of UDT (130). Regular alcohol intake and/or maternal smoking during pregnancy also appear to increase the risk of congenital UDT in boys (131,132).

5.2 ACQUIRED
5.2.1 Acquired factors
In recent years, the concept of acquired UDT has been recognised and progressively accepted (133-135). Ascent of the testis is thought to result from absorption of the peritoneal aspect of the PV, with subsequent traction on the spermatic cord (136,137). An additional
cause might be failure of the PV to completely obliterate. Following inguinal hernia closure, the peritoneal membrane and adjacent fibrous tissue must completely disappear, so that the spermatic cord can elongate with age. Should the inguinal hernia tissue not completely disappear, a fibrous remnant in the spermatic cord remains, which prevents elongation (98). Correlation with persistent muscle spasm has also been argued (138,139).

6.0 SPONTANEOUS DESCENT

It was generally believed that spontaneous descent of the testis during extrauterine life is a phenomenon that occurs mainly in the first year of life (140-142). Earlier studies, however, have shown spontaneous descent on a large scale in the peripubertal period (143). Therefore, two periods of (postnatal) spontaneous descent should be recognised:

First year of life: Complete descent of the testis normally occurs before birth. If, in a newborn full-term infant, descent has not occurred, it may do so in the first weeks of life. In a premature infant the equivalent time may be up to 3 months. Spontaneous descent is generally believed only to occur in the first 3 to 6 months after birth (144). Scorer (145) found that descent finally ceases altogether some time between 3 and 4 months of age and concluded that any significant descent of the testis never occurs in a full-term infant after 3-4 months. In contrast, Mau & van Schnakenburg (146) found some evidence for spontaneous descent in a proportion of cases during the first 3 years of life.

Peripubertal period: Several authors report spontaneous descent in the peripubertal period. Baumrucker (147) suggested that three quarters of pre-adolescent UDT descend to the scrotum, and Ward (148) suggested that at the age of puberty most testes descend without treatment. In contrast, others (149,150) considered spontaneous descent between one year of age and young adults very rare. Recently, it has been shown that three quarters of acquired UDT descend spontaneously at puberty (151). This might be explained by surges of LH and testosterone as is also seen during the first 3 months after birth (152). In addition, it has been hypothesised that the fibrous remnant of the PV is sensitive to testosterone (153). Acquired UDT probably explains the spontaneous descent in the peripubertal period. However, the factors immediately responsible for spontaneous testicular descent, in both congenital and acquired cryptorchidism, are difficult to ascertain definitively.

7.0 CONCLUSION

The control of normal testicular descent and the causes of cryptorchidism have been discussed. A combination of both hormonal controlling mechanisms and mechanical events lead to testicular descent.

One conclusion about the aetiology of cryptorchidism, which should no longer be controversial, is that there are multiple causes of cryptorchidism, and in the majority of the cases, it is impossible to establish the aetiology with certainty.

There are two periods of (postnatal) testicular descent: the first year, specifically the first three months after birth, and the peripubertal period. These different periods of spontaneous descent can probably be explained by the recognition of the acquired form of UDT.
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