THE TREATMENT OF CRYPTORCHIDISM WHY HOW WHEN

CLINICAL STUDIES IN PREPUBERAL BOYS

De behandeling van cryptorchidisme Waarom Hoe Wanneer

Klinische studies bij prepuberale jongens

On the cover: **Orchis serapias secundus maior**
its tubers hidden (underground)
in semblance of the hidden namesake
κρυπτος ὀρχις - hidden testicle

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PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD
VAN DOCTOR IN DE GENEESKUNDE
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. A. H. G. RINNOOY KAN
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
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Alblasserdam

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aan Johannes
en mijn ouders

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LIST OF ABBREVIATIONS

ABP	=	androgen-binding protein
AMH	=	anti-Müllerian hormone
APL	=	anterior-pituitary-like
cmc	=	cross-median curve
CNS	=	central nervous system
CR	=	crown-rump (length)
$\Delta 4$	=	androstenedione
DHEA(S)	=	dehydroepiandrosterone (sulfate)
DHT	=	dihydrotestosterone
E_2	=	oestradiol
FSH	=	follicle-stimulating hormone
GRF	=	gonadotropin-releasing factor
GnRH	=	gonadotropin-releasing hormone
HCG	=	human chorionic gonadotropin
HMG	=	human menopausal gonadotropin
HVH	=	hypophysen-vorderlappen hormone
i.m.	=	intramuscular
i.n.	=	intranasal
IU	=	international units
i.v.	=	intravenous
LH	=	luteinizing hormone
LHRH	=	luteinizing-hormone-releasing hormone
MIS	=	Müllerian inhibiting substance
MRC	=	Medical Research Council
17 OHP	=	17 α-hydroxyprogesterone
17 OHPreg	=	17 α-hydroxypregnenolone
P	=	progesterone
RIA	=	radio-immunoassay
SHBG	=	sex-hormone-binding globulin
T	=	testosterone
TFI	=	tubular fertility index

SUMMARY

Chapter 1 - The genesis of the testis and the male genital tract is dealt with including the evolution of testicular descent, followed by a description of the anatomical structures of the male genital system to the extent that this may contribute to a better understanding of the whole process of testicular descent. In recent years, various causative factors have been proposed for the failure of testicular descent whereby hormonal dysfunction has assumed increasing prominence.

According to the literature, there are various reasons WHY undescended testes should be treated, such as an increased risk of infertility, malignant degeneration, and disturbance of normal psychosexual development. The decision as to HOW undescended testes should be treated, hormonal or surgical, has to be carefully weighed. It is subject to a great deal of controversy as is the question of WHEN undescended testes should be treated. Recently, early treatment has been recommended in view of histological changes that might occur in the nonscrotal testis. It has also been suggested that early treatment would improve the potential for fertility. A divergence of patient series and other criteria complicates assessment of reported results, fanning the flame of controversy.

These aspects constituted the motivation for combined hormonal and surgical, clinical studies of the entity of undescended testes. An abbreviated definition and classification of undescended testes is given to avoid confusion of e.g. retractile and truly undescended testes. The aims of the various studies are supplied in detail.

Chapter 2 - The framework of the clinical studies is introduced stipulating the guidelines and various methods applied. The classification of cryptorchidism is further elucidated with a complete description of all aspects of incomplete testicular descent.

Determination of the incidence of cryptorchidism is complicated by a lack of longitudinal studies of long duration and frequent inclusion of retractile testes.

A great deal of attention is paid to the process of reaching the proper diagnosis, outlining the procedure for physical examination and registration of the spontaneous and most caudal testicular position. This is illustrated with photographs and sample registration forms. The methods of hormonal evaluation and statistical analyses are also described.

Chapter 3 - The literature is reviewed concerning the hormonal influences on the development and descent of the testis, as well as the feasibility of a hormonal cause of the failure of testicular descent. There are indications that hormones play a part in testicular descent, but the nature or phase of such a hormonal action remains uncertain. Consequently, there is still no certainty concerning the extent to which cryptorchidism may be due to hormonal failure.

In boys with normal testicular descent, elevated serum testosterone levels have been noted during the first months of life, followed by a decrease to normal prepuberal levels within the first year. Diverse basal and stimulated LH and FSH serum values have been reported for the first year of life. The hormonal findings of Job and coworkers concerning boys with undescended testes during the first year of life are discussed in great detail because these studies have been cited frequently by others. Job's group felt that the reduced LH and testosterone secretion, which they observed in boys with undescended testes during the first months of life, might furnish the explanation for the failure of testicular descent. The same group found in boys with delayed, spontaneous descent during the first months of life, LH and testosterone values similar to control values and higher than those for persistent cryptorchids.

In the prepuberal period after the first year of life basal serum testosterone and gonadotropin values are low for boys with normal testicular descent, but a clear response to stimulation tests has been observed. For boys with undescended testes, markedly divergent results of LHRH and HCG tests have been reported. At a certain age level, even agonadal patients cannot be distinguished from boys with gonads by means of an LHRH test. Bilateral anorchia can only be demonstrated by means of an HCG test.

The clinical and hormonal study of boys born with undescended testis during their first year of life revealed:

- delayed, spontaneous descent within the first year in 40-50% of all patients, at times even occurring after the sixth month of life;
- similar serum testosterone values and stimulated gonadotropin values for persistent cryptorchids, boys with spontaneous descent in the first year of life, and boys born with descended testes.

These findings donot support the hypothesis of a (transient) insufficiency of the hypothalamo-pituitary-gonadal axis in boys with incomplete testicular descent. The hormonal evaluation was of no prognostic value for spontaneous testicular descent in the first year of life. No disorders in the biosynthesis of testosterone nor signs of enzyme inhibition were found in boys with undescended testes.

Chapter 4 - The results of hormonal treatment of undescended testes by means of gonadotropins, as reported in the literature, show extreme divergence in the percentage of success, 25-100%! There is disagreement concerning a number of factors that may influence the rates of success, but there is a consensus regarding the prominent role of testicular position; the lower the pretreatment testicular

position, the bigger the chance that hormonal treatment will induce descent. No author gives a clear explanation for the mode of action of treatment with gonadotropins.

When LHRH was first used to treat undescended testes, it was administered by means of intramuscular injection. Once the extent of absorption in the blood stream of intranasally administered LHRH had been established (1-2%), LHRH nasal spray came into use. Diverse dosage schedules are reported with diverse rates of success; 13-78% in open studies and 17-38% in placebo-controlled studies.

Personal experience with LHRH nasal spray therapy for boys with undescended testes is described in detail. The results of the pilot study were encouraging; 17 of 29 testes (65%) descended completely. The results of the subsequent double-blind, placebo-controlled study involving 252 boys with 301 undescended testes were far less promising. During the double-blind period (eight weeks) a similar percentage of descent was achieved with LHRH therapy (9%) and placebo (8%). After the subsequent open study period, after a maximum of two courses of LHRH therapy, total testicular descent induced with LHRH reached 18%. However, in the open study a placebo effect cannot be excluded.

Logistic regression analysis confirmed the clinical observation that the most caudal testicular position was the major factor influencing the results of LHRH treatment. The lower the pretreatment position of the testis, the bigger the chance of induced descent. In this respect, LHRH therapy is comparable to HCG treatment. The dependence of the therapeutic success on pretreatment testicular position may explain the diversity of percentages of success for the various studies, including our own. In other words, the rate of success for a series of patients depends on the ratio of lower-positioned testes in a given series. Retrospective evaluation of our study population revealed a previous intrascrotal position or retractility of testes in approximately 50% of the boys successfully treated with LHRH.

Hormonal evaluation before and after LHRH treatment, gave no indication of a deficient hypothalamo-pituitary-gonadal axis or a reduced Leydig cell function in boys with undescended testes. In a number of bilateral cryptorchids higher stimulated FSH levels were observed. Permanent stimulation of the hypothalamo-pituitary-gonadal axis could not be demonstrated. A limited auxiliary study served to demonstrate absorption of LHRH i.n. in the blood stream, causing a rise in LH levels in a number of cases. In addition, comparison of results of an HCG test before and after LHRH therapy, revealed elevated peak serum testosterone values, possibly indicating Leydig cell stimulation. Our findings did not explain the mode of action of LHRH treatment, although we did find some indications that LHRH treatment may reduce the contractility of the cremaster muscle.

CHAPTERS 3 AND 4 CONSTITUTE PART A OF THE CLINICAL STUDIES, DEALING

WITH THE ENDOCRINOLOGICAL ASPECT OF CRYPTORCHIDISM, CONCLUDED WITH A GENERAL DISCUSSION OF THAT ASPECT BY THE AUTHOR OF THIS PART, S.M.P.F. de Muinck Keizer-Schrama.

Chapter 5 - According to the literature, failure of testicular descent may be due to hormonal or mechanical disturbance, while undescended testes are histologically divergent from normally descended testes. The major anomaly found in a nonscrotal testis is a reduced number of spermatogonia per tubule. It is not clear whether this is a primary histological abnormality (dysgenesis) or the result of a higher temperature in the nonscrotal environment. There is a clear connection between the severity of the histological abnormality and the postion of the nonscrotal testis; the "higher" the arrest of testicular descent, the more severe the histological abnormality. In 25-60% of the boys with unilateral undescended testes, the contralateral, descended testes also appear to be histologically abnormal. Investigation of the previously undescended testis after orchiopexy, revealed no increase of the number of spermatogonia, but at best further maturation of the existing spermatogonia.

The clinical implications of a disturbance of testicular descent as reported in the literature are discussed. There is a definite link between failure of testicular descent and infertility, while this relationship becomes even more marked if cryptorchidism is bilateral. The results of numerous fertility studies are markedly divergent because the factors that may influence fertility, such as type or timing of treatment, testicular position, criteria for fertility assessment, etc. are not consistently taken into account.

Testicular tumour is a rare occurrence, but seems to be more prevalent in (previously) undescended testes. The premise that (early) treatment would prevent subsequent manifestation of a testicular tumour has not been substantiated. Scrotal placement of the testis does make the testis more accessible to examination and treatment if malignant degeneration does occur.

A disturbance of the psychosexual development requiring treatment will only occur in boys with undescended testes if there are other psychological problems, apart from the aspect of an abnormal appearance of the genitalia, involving the boys's mental stability and parent-child relationship. Regarding the psychosexual development, early treatment is obviously preferable, because this means that the child has recovered before discovering that he is "different". Surgical treatment does call for special measures to reduce separation between parents and child to a minimum (rooming-in, day-surgery, etc.).

The anatomical aspects of cryptorchidism are dealt with in detail, describing various abnormal anatomical structures related to testicular nondescent. Other congenital anomalies that may be associated with cryptorchidism are mentioned briefly.

Following a description of the evolution of orchiopexy, the various techniques are discussed. Apart from the standard orchiopexy, generally involving fixation of

the testis in a subcutaneous scrotal pouch (Schoemaker technique), there are a number of special surgical procedures that may be required for impalpable testes (intra-abdominal or high-lying, inguinal testes). These special procedures included staged orchiopexy, orchiopexy with testicular vessel transection (Fowler-Stephens), orchiopexy using microvascular techniques, and finally, transabdominal orchiopexy with abdominal wall reconstruction in a neonate with prune belly syndrome.

Chapter 6 - Personal experience and results of surgical treatment of cryptorchidism are discussed, beginning with the management of retractile testes. Boys with (markedly) retractile testes have to be examined at regular intervals (e.g. once a year) until puberty, even though retractile testes normally do not require treatment. Ascent of a previously retractile testis may occur, resulting in a permanent nonscrotal position of this testis.

In contrast, the impalpable testis always requires treatment. The impalpable testis, usually located in the abdomen or high in the inguinal canal, always requires surgery, because hormonal treatment is pointless. A good scrotal position of the testis can usually be achieved with a standard orchiopexy. Surgery of the impalpable testis almost always amounts to a combined diagnostic and therapeutic intervention, rendering separate diagnostic evaluation by means of frequently invasive techniques, such as CT-scan, angiography, or laparoscopy, superfluous.

There are various special surgical procedures (as described in chapter 5) for the impalpable testis that cannot be brought to the scrotum by conventional orchiopexy. Personal experience with these special techniques and results are discussed in relation to literature data, supplying indications for the uses of each technique. Orchiopexy involving transsection of the testicular vessels (Fowler-Stephens procedure) is the method of choice for an impalpable testis with a "long loop" vas and epididymis, provided the decision is taken before pre-emptive retroperitoneal dissection has taken place. A second-stage orchiopexy is pointless unless there is uncertainty regarding the extent of funicular mobilization at the initial operation. In case the first operation did include optimal retroperitoneal dissection, a second-stage procedure may still be required, provided this involves autotransplantation of the testis. If the testicular vessels hamper scrotal placement of the testis, these vessels may be divided to be anastomosed to the epigastric vessels. Based on our own results, the lower age limit for this microvascular orchiopexy is set at approximately seven years. The limited need for orchidectomy is discussed, whereby the importance is stressed of preserving hormonal function. Bilateral orchidectomy should be avoided at all cost. Insertion of a prosthesis (after orchidectomy) depends on personal circumstances and may safely be postponed until the puberal period.

A schematic presentation of the treatment protocol for impalpable testes is included in the general discussion following this chapter.

The remainder of the chapter deals with the findings and results of orchiopexy of 170 boys with 196 testes that failed to descend with LHRH nasal spray (see chapter 4). In 80% of these testicular operations anatomical anomalies were found explaining the failure of hormonal treatment. The most frequent finding was an open processus vaginalis with insufficient outgrowth into the scrotum and an abnormal, subcutaneous course of the fascia of Scarpa. Wound-related postoperative complications were never severe occurring in only 5% of the operations. Practically all operations resulted in a scrotal position of the testis. At follow-up, 4-10 months postoperatively, 2% of the operated testes appeared to have become atrophic. Age at operation appeared to have had no effect on the result (position of testis in scrotum), postoperative complications or the frequency of testicular atrophy.

CHAPTERS 5 AND 6 CONSTITUTE PART B OF THE CLINICAL STUDIES, DEALING WITH THE SURGICAL ASPECT OF CRYPTORCHIDISM, CONCLUDED WITH A GENERAL DISCUSSION OF THAT ASPECT BY THE AUTHOR OF THIS PART, F.W.J. Hazebroek.

Chapter 7 - Based on the findings of the clinical studies in relation to literature data, an attempt is made to answer the question of WHY, HOW, and WHEN cryptorchidism should be treated.

The risk of infertility, the rather rare occurrence of testicular tumour, and a disturbance of the psychosexual development, are reasons WHY the undescended testis should be treated. Before treatment is initiated, the proper diagnosis has to be made.

HOW the undescended testis should be treated, hormonal or surgical, depends entirely on the position of the testis. Although the results of our double-blind study period (eight weeks) were no better for LHRH than for placebo, the results of the entire study (maximally two LHRH courses) showed that LHRH nasal spray may induce descent in testes that have emerged from the inguinal canal and can be manipulated to at least the scrotal entrance. LHRH nasal spray is our hormonal treatment of choice, rather than intramuscular injections of HCG, because the side effects and invasiveness are least for LHRH, while the treatment results are similar for either modality. Surgical treatment is indicated for all undescended testes that have not emerged from the inguinal canal as well as all ectopic testes, and for those testes that failed to descend with hormonal therapy.

Before any treatment can be initiated, the proper diagnosis has to be reached. Any documentation of previous testicular position should be traced. These data together with the age of the cryptorchid boy will decide WHEN treatment should take place.

The treatment protocol for all types of nonscrotal testes is discussed and schematically presented in a comprehensive figure.

The chapter ends with a number of questions that can only be answered in the future, such as:

- should all undescended testes be treated, or is a "wait-and-see" approach feasible for testes that have been documented as intrascrotal or at least retractile at some point in the past?

Only a longitudinal study of long duration would supply an answer to such questions.

SAMENVATTING

In *Hoofdstuk 1* wordt de ontwikkeling van de testis en de mannelijke geslachtsorganen besproken, gevolgd door een overzicht van de testiculaire indaling en van die anatomische structuren van het mannelijk genitale stelsel, die bijdragen tot een beter begrip van het indalingsproces van de testis. De afgelopen jaren worden verschillende factoren verantwoordelijk gesteld voor het niet indalen van de testis, waarbij het accent steeds meer is komen te liggen op een hormonale dysfunctie. Hierdoor heeft tevens de hormonale behandeling van niet ingedaalde testes opgang gemaakt.

De redenen die aangevoerd worden WAAROM niet ingedaalde testes behandeld moeten worden, zijn de verhoogde kans op onvruchtbaarheid, maligne ontaarding en verstoring van de normale psychosexuele ontwikkeling. HOE niet ingedaalde testes behandeld moeten worden, hormonaal of chirurgisch, dient zorgvuldig afgewogen te worden en ook omtrent de vraag WANNEER een behandeling moet worden ingesteld bestaat verschil van mening. De laatste jaren zijn stemmen opgegaan voor vroege behandeling, dat wil zeggen rond het tweede levensjaar, om histologische afwijkingen van de niet ingedaalde testis te voorkomen en de fertiliteit te verbeteren. Bewijs hiervoor is echter nog niet geleverd.

Alvorens echter tot behandeling over te gaan zal de juiste diagnose, werkelijk niet ingedaalde testis, gesteld moeten worden. Hierop wordt in het volgende hoofdstuk uitgebreid ingegaan, maar om spraakverwarring te voorkomen worden nu al definities gegeven van cryptorchidisme, de retractiele testis en niet ingedaalde testes. Laatstgenoemden zijn te verdelen in onvolledig ingedaalde testes en ectopische testes. Vervolgens worden de doelstellingen van de klinische studies uiteengezet.

Hoofdstuk 2 presenteert in eerste instantie de richtlijnen voor de klinische studies. Classificatie en definities van de indalingsstoornissen en testisposities worden gegeven. Benadrukt wordt dat naast de spontane testispositie de meest caudale positie van groot belang is. Het vaststellen van de incidentie van de niet ingedaalde testis wordt gecompliceerd door het nagenoeg ontbreken van langdurig longitudinaal onderzoek en het niet herkennen van retractiele testes. Om tot de diagnose te komen moet het lichamelijk onderzoek lege artis worden uitgevoerd en moet niet alleen de spontane, maar ook de meest caudale testispo-

sitie worden geregistreerd. Bovenstaande wordt in woord en beeld weergegeven.

De methoden van de hormonale bepalingen en van de statistische analyses gebruikt bij de klinische studies worden beschreven.

In *Hoofdstuk 3* worden vanuit de literatuur de hormonale invloeden op de testisontwikkeling en -indaling besproken alsmede de mogelijkheid van een hormonale oorzaak van het niet indalen van de testis. Hoewel er aanwijzingen zijn dat hormonen een rol spelen bij de testiculaire indaling is nog niet met zekerheid vastgesteld welke hormonen in welke fase een rol spelen. Dientengevolge blijft ook de vraag of cryptorchidisme een hormonale oorzaak heeft onvolledig beantwoord.

In het eerste levensjaar worden bij jongens met normale testiculaire indaling hoge serum testosteronwaarden gevonden gedurende de eerste levensmaanden met een daarop volgende daling. De bevindingen omtrent basale en gestimuleerde LH en FSH serumwaarden in het eerste levensjaar lopen uiteen. De hormonale bevindingen van Job en medewerkers betreffende jongens met niet ingedaalde testes in het eerste levensjaar worden uitgebreid besproken, omdat deze studies frequent door anderen worden aangehaald. Deze groep meende dat de verminderde LH en testosteronsecretie, die zij in de eerste levensmaanden bij jongens met niet ingedaalde testes vaststelden, een verklaring kan vormen voor het niet indalen van de testes. Bij jongens met spontane indaling gedurende de eerste levensmaanden werden LH en testosteronwaarden gevonden vergelijkbaar met controle waarden en hoger dan van jongens die cryptorch bleven.

In de prepuberale periode na het eerste levensjaar zijn de serum testosteron- en gonadotrofinenwaarden onder basale omstandigheden laag bij jongens met ingedaalde testes, maar zij vertonen een duidelijke response op stimulatietesten. Bij jongens met niet ingedaalde testes worden zeer wisselende resultaten voor LHRH en HCG testen opgegeven. In een bepaalde leeftijdsfase kunnen zelfs agonadale patiënten niet door middel van de LHRH test van jongens met gonaden onderscheiden worden. Alleen de HCG test kan bij bilaterale anorchie uitsluitsel geven.

Onze klinische en hormonale evaluatie gedurende het eerste levensjaar van jongens geboren met niet ingedaalde testes toonde aan dat:

- spontane indaling voorkomt in 40-50% van de gevallen, zelfs na de zesde levensmaand;
- de serum testosteronwaarden en basale en gestimuleerde gonadotrofinenwaarden van jongens die cryptorch bleven vergelijkbaar zijn met die van jongens met spontane indaling in het eerste levensjaar en van jongens geboren met ingedaalde testes.

Deze bevindingen geven geen steun aan de hypothese van een (tijdelijke) insufficiëntie van de hypothalamus-hypofyse-gonade as bij jongens met niet ingedaalde testes. De hormonale evaluatie bleek geen voorspellende waarde te

hebben voor spontane indaling in het eerste levensjaar. Wij vonden geen afwijkingen in de testosteron biosynthese noch tekenen van enzym inhibitie bij jongens geboren met niet ingedaalde testes.

In *Hoofdstuk 4* wordt vanuit de literatuur de hormonale behandeling van niet ingedaalde testes door middel van gonadotrofinen besproken. Hierbij vallen de sterk uiteenlopende indalingspercentages op: 25-100%! Omtrent een aantal factoren, die mogelijk van invloed zijn op het indalingspercentage, bestaat verschil van mening, maar de onderzoekers zijn unaniem van oordeel dat de positie van de testis voor behandeling een belangrijke rol speelt: hoe lager de testispositie voor behandeling, hoe hoger de kans op indaling! Voor het werkingsmechanisme van de behandeling met gonadotrofinen wordt door geen enkele auteur een duidelijke verklaring gegeven.

Na het isoleren en synthetiseren van het gonadoreline (LHRH) werd het releasing hormone aanvankelijk door middel van intramusculaire injectie toegepast bij de behandeling van niet ingedaalde testes. Vervolgens werd, na het vaststellen van de absorptie in de bloedbaan na intranasale toediening (1-2%), het LHRH per neusspray in verschillende doseringen toegepast met wisselende indalingspercentages: 13-78% in open studies, 17-38% in placebo-gecontroleerde studies.

Vervolgens worden de eigen ervaringen met het intranasaal toegediende LHRH voor de behandeling van jongens met niet ingedaalde testes beschreven. De resultaten van de pilot-studie waren zeer bemoedigend: 17 van de 29 testes (65%) daalden volledig in. De resultaten van de daaropvolgende dubbel-blind, placebo-gecontroleerde studie, waarin 252 jongens met 301 niet ingedaalde testes werden behandeld, waren heel wat minder rooskleurig. In de dubbelblinde periode (na acht weken) bleek het indalingspercentage na LHRH behandeling (9%) niet hoger dan na placebo (8%). Na de daarop volgende open studieperiode, na maximaal twee LHRH kuren, bleek 18% van de testes in te dalen. In de open studie is echter het placebo-effect niet uit te sluiten. Met een logistische regressie analyse bevestigden wij de klinische observatie dat met name de positie van de testis voor behandeling van invloed is op het welslagen ervan. Hoe lager de testispositie vóór behandeling des te groter de kans op indalen. In dit opzicht is de LHRH behandeling vergelijkbaar met de HCG behandeling. De afhankelijkheid van het therapeutisch succes van de testispositie vóór behandeling kan een verklaring geven voor de uiteenlopende succespercentages van de verschillende studies, ook die van onze eigen studies. De evaluatie van testisposities in het verleden leerde dat bij ongeveer 50% van de jongens, die met succes op de LHRH behandeling reageerden, de testes vroeger ooit eens als intrascrotaal of retractiel beschreven waren.

De hormonale evaluatie rond de LHRH behandeling gaf geen aanwijzingen voor een deficiente hypothalamus-hypofyse-gonade as of een verminderde Leydig cel functie bij jongens met niet ingedaalde testes. Bij een aantal jongens met

bilateraal niet ingedaalde testes werden hogere gestimuleerde FSH waarden gevonden. Blijvende stimulatie van de hypothalamus-hypofyse-gonade as kon niet worden aangetoond. Een beperkte studie toonde echter wel aan dat het intranasaal toegediende LHRH in de bloedbaan wordt opgenomen en in een aantal gevallen LH stijging veroorzaakt. Tevens leerde de HCG test voor en na LHRH behandeling dat na behandeling de gestimuleerde testosteronwaarden significant hoger waren dan voor behandeling, mogelijk een aanwijzing voor Leydig cel stimulatie. Bovenstaande bevindingen kunnen het werkingsmechanisme van de LHRH behandeling niet verklaren. Wij vonden echter aanwijzingen dat door de LHRH behandeling de retractiliteit van de cremasterspier afneemt.

DE HOOFDSTUKKEN 3 EN 4 VORMEN DEEL A VAN DE KLINISCHE STUDIES, DIE HET ENDOCRINOLOGISCHE ASPECT BELICHTEN, HETGEEN WORDT AFGESLOTEN DOOR EEN UITGEBREIDE DISCUSSIE DOOR DE AUTEUR VAN DIT DEEL, S.M.P.F. de Muinck Keizer-Schrama.

Hoofdstuk 5 - Allereerst wordt in dit hoofdstuk ingegaan op het feit waarom een testis soms niet indaalt. Zowel hormonale als mechanische stoornissen kunnen hiervoor een oorzaak zijn. Niet ingedaalde testes zijn histologisch gezien afwijkend in vergelijking met ingedaalde testes. De belangrijkste afwijking in de niet ingedaalde testis is het verminderd aantal spermatogoniën per tubulus. Het is nog een onduidelijke zaak of de niet ingedaalde testis primair histologisch afwijkend is (dysgenesie) of dat ten gevolge van temperatuursinvloeden de aanvankelijk histologisch normale testis beschadigd wordt. Er is een duidelijk verband tussen de ernst van de histologische afwijkingen en de ligging van de niet ingedaalde testis, hoe "hoger" de testis is blijven liggen hoe ernstiger de histologische afwijkingen zijn. In 25-60% blijkt bij de unilaterale niet ingedaalde testis ook de ingedaalde testis afwijkend te zijn. Na orchidopexie wordt in de vroeger niet ingedaalde testis geen toename gezien van het aantal spermatogoniën, maar hooguit een verdere rijping van de reeds aanwezige spermatogoniën.

Vervolgens worden de klinische consequenties van de testiculaire indalingsstoornissen besproken. Er is een onmiskenbaar verband tussen testiculaire indalingsstoornissen en onvruchtbaarheid, waarbij dit verband des te uitgesprokener is indien er sprake is van bilateraal niet ingedaalde testes. Dat de resultaten van de vele gepubliceerde fertiliteitsstudies zo sterk wisselen, wordt veroorzaakt doordat in wisselende mate rekening wordt gehouden met factoren die de fertiliteit beïnvloeden, zoals soort van behandeling, tijdstip van behandeling, testispositie, fertiliteitsonderzoek enz.

Een op zichzelf zeldzame testistumor komt vaker voor in een (tevoren) niet ingedaalde testis. Het is nog geen vaststaand feit dat (vroege) behandeling het zich later manifesteren van een testistumor kan voorkomen. Wel is de testis door plaatsing in het scrotum beter toegankelijk voor onderzoek en behandeling van eventueel toch voorkomende maligniteit.

Ten aanzien van de psychosexuele aspecten van kinderen met niet ingedaalde testes kan gezegd worden dat psychische stoornissen, die behandeling noodzakelijk maken, slechts voorkomen indien er naast het probleem van de niet ingedaalde testis zelf nog andere psychische stoornissen voorkomen die verband houden met de persoonlijkheid van het betreffende kind of de relatie tussen ouder en kind. Ten aanzien van de psychosexuele ontwikkeling heeft vroege behandeling een duidelijke voorkeur, omdat dan het kind hersteld is voordat hij zijn "anders" zijn zou ontdekken. Rond de behandeling (orchidopexie) dienen wel maatregelen genomen te worden (rooming-in, dagbehandeling) die scheiding tussen ouders en kind zoveel mogelijk beperken.

Nadat hierna een uitgebreid overzicht is gegeven van de anatomische afwijkingen die voorkomen bij de diverse vormen van niet ingedaalde testes wordt een korte samenvatting gegeven van andere aangeboren afwijkingen die soms samengaan met cryptorchidisme.

Het hoofdstuk wordt besloten met een beschrijving van de ontwikkeling van de diverse vormen van orchidopexie. Naast de standaard orchidopexie, meestal uitgevoerd met fixatie van de testis in een subcutane scrotale ruimte (Schoemaker techniek) zijn er diverse speciale chirurgische technieken die hun toepassing hebben voor de hoge (intra-abdominale of hoog in het lieskanaal liggende) testis: orchidopexie in twee tempi, orchidopexie met doornemen van de testiculaire vaten (Fowler-Stephens), orchidopexie gebruikmakend van microvasculaire technieken en ten slotte de in de neonatale periode uitgevoerde transabdominale orchidopexie met buikwandreconstructie (Prune Belly syndrome).

Hoofdstuk 6 - In dit hoofdstuk worden de ervaringen en resultaten van de eigen chirurgische studies besproken. Allereerst wordt ingegaan op het te voeren beleid ten aanzien van de retractiele testis. In het algemeen behoeft de retractiele testis geen behandeling. Aangezien er echter een ascendens van een tevoren retractiele testis kan voorkomen, met als gevolg een blijvende niet scrotale positie van deze testis, is het raadzaam om jongens met (sterk) retractiele testes met grote tussenpozen (bijv. eenmaal per jaar) te controleren.

Vervolgens wordt het diagnostische en therapeutische beleid van de niet palpabele testes besproken. Hormonale behandeling van de niet palpabele testis is, zoals in hoofdstuk 4 is besproken, zinloos. De niet palpabele testis, die meestal intra-abdominaal of hoog in het lieskanaal ligt, dient dan ook chirurgisch behandeld te worden. Meestal is door middel van een conventionele orchidopexie een goede scrotale positie van de testis te verkrijgen. Deze operaties zijn bijna altijd diagnostische en therapeutische ingrepen die aparte diagnostische, vaak invasieve ingrepen zoals CT-scan, angiografie of laparoscopie, overbodig maken.

Indien met een conventionele orchidopexie de niet palpabele testis niet in het scrotum gebracht kan worden, zijn er enige speciale operatietechnieken die ieder hun eigen indicatiegebied hebben. Eigen ervaring met deze speciale technieken worden, getoetst aan de literatuurgegevens, verder besproken. De orchi-

dopexie met transsectie van de testiculaire vaten (Fowler-Stephens procedure) is een juiste chirurgische techniek indien er sprake is van een "long loop" vas en epididymis, mits hiertoe wordt besloten voordat retroperitoneale dissectie deze ingreep bij voorbaat onmogelijk maakt. Een orchidopexie in twee tempi heeft alleen zin, indien het onduidelijk is hoe uitgebreid bij de eerste liesexploratie de retroperitoneale dissectie van de funiculus heeft plaatsgevonden. Bij een tweede ingreep kan het noodzakelijk zijn om autotransplantatie van de testis uit te voeren, wanneer de dissectie bij de eerste ingreep wèl optimaal is uitgevoerd. Indien de testiculaire vaten een belemmerende factor zijn waardoor de testis niet in het scrotum geplaatst kan worden, kunnen deze vaten worden doorgenomen om vervolgens weer te worden geanastomoseerd met de epigastrische vaten. Op grond van de eigen resultaten wordt de leeftijdsgrens van deze microvasculaire orchidopexie gesteld op ongeveer zeven jaar.

De beperkte indicatie voor orchidectomie wordt besproken, waarbij de nadruk wordt gelegd op het behoud van hormonale functie. Bilaterale orchidectomie is uit den boze. Het plaatsen van een prothese (na orchidectomie) hangt af van persoonlijke omstandigheden en kan gevoeglijk uitgesteld worden tot de puberale periode.

In de uitgebreide discussie die op dit hoofdstuk volgt, bevindt zich een schematisch behandelingsplan van prepuberale jongens met niet palpabele testes.

Het laatste deel van dit hoofdstuk betreft de bevindingen en resultaten van orchidopexie bij 170 jongens met 196 niet ingedaalde testes die zonder succes met de LHRH neusspray zijn behandeld. Bij ongeveer 80% van de verrichte operaties was het mogelijk om vanuit de gevonden anatomische afwijkingen een verklaring te geven, waarom de aan de operatie voorafgegane hormonale behandeling niet succesvol is geweest. De afwijkingen die het meest voorkomen zijn een onvolledige, niet tot in het scrotum uitgegroeide processus vaginalis en een abnormaal verlopende subcutane fascie van Scarpa. Bij 5% van de uitgevoerde operaties was er sprake van een meestal niet ernstige gestoorde wondgenezing. Bijna alle niet ingedaalde testes konden in een scrotale positie worden geplaatst. Bij na-onderzoek, 4-10 maanden na operatie, bleek dat 2% van de geopereerde testes atrofisch was geworden. De leeftijd waarop orchidopexie is uitgevoerd blijkt niet van invloed te zijn op het operatieresultaat (testispositie in scrotum), de postoperatieve complicaties of het voorkomen van testisatrofie.

DE HOOFDSTUKKEN 5 EN 6 VORMEN DEEL B VAN DE KLINISCHE STUDIES DIE HET CHIRURGISCHE ASPECT BELICHTEN, HETGEEN WORDT AFGESLOTEN DOOR EEN UITGEBREIDE DISCUSSIE DOOR DE AUTEUR VAN DIT DEEL, F.W.J. Hazebroek.

In *Hoofdstuk 7* proberen wij door de bevindingen van het eigen onderzoek en de literatuur te integreren de vragen te beantwoorden WAAROM, HOE en

WANNEER jongens met niet ingedaalde testes behandeld moeten worden.

De dreiging van infertiliteit, het voorkomen van een overigens zeldzame testistumor en stoornissen in de psychosexuele ontwikkeling zijn redenen WAAROM de niet ingedaalde testis behandeling behoeft. HOE behandeld moet worden, hormonaal dan wel chirurgisch, wordt uitsluitend bepaald door de positie van de testis. Alhoewel onze studie niet bewezen heeft dat na één behandelingsperiode (acht weken) LHRH beter is dan placebo, suggereren de resultaten van het gehele onderzoek (maximaal twee LHRH kuren) dat de behandeling met LHRH per neusspray indaling kan geven van testes die het lieskanaal gepasseerd zijn en tenminste in de scrotumingang gebracht kunnen worden. Een placebo-effect kan echter in deze open studie niet uitgesloten worden. Bij de keuze van de hormonale therapie gaat onze voorkeur uit naar de LHRH neusspray boven de intramusculair toegediende HCG injecties, omdat de bijwerkingen en de belasting voor het kind minder zijn, terwijl de indalingspercentages vergelijkbaar zijn. Chirurgische behandeling is geïndiceerd voor alle vormen van niet ingedaalde testes die het lieskanaal nog niet gepasseerd zijn, voor alle ectopische testes en wanneer de hormonale behandeling geen indaling heeft gegeven.

Alvorens tot behandeling over te gaan moet de juiste diagnose gesteld worden en is het van groot belang te informeren naar de testispositie in het verleden. Deze gegevens bepalen samen met de leeftijd van de jongen WANNEER de behandeling dient plaats te vinden. Vervolgens wordt een schematisch behandelingsplan voorgesteld.

Het hoofdstuk wordt afgesloten met een aantal vragen die pas in de toekomst beantwoord kunnen worden, zoals:

- moeten alle niet ingedaalde testes behandeld worden of kan, wanneer de testis in het verleden als intrascrotaal of retractiel werd beschreven, een afwachtende houding aangenomen worden?

Longitudinaal prospectief onderzoek tot na de puberteit is de enige mogelijkheid om deze vragen te beantwoorden.

CHAPTER 1

GENERAL INTRODUCTION

Few subjects have been so belaboured in the medical literature as the entity of CRYPTORCHIDISM, or undescended testis. In 1762 John Hunter first made a connection between undescended testes and infertility. Since then the undescended testis has never ceased to be a subject for investigation. One of the main reasons why so many publications, frequently contradicting one another, continue to appear is that the complicated process of testicular descent is still poorly understood, let alone a disturbance of this process and the consequences of such a disturbance.

To gain more insight into this matter we have carried out extensive clinical studies supported by a comprehensive review of the literature. Before going into the aims of our studies, it is important to define the (physical) area of research.

1.1. THE DEVELOPMENT OF THE TESTIS

The human testis is composed of the following elements:

- the seminiferous tubules, containing the germ cells necessary for reproduction, and the Sertoli cells, which provide support, protection and nutrition for the germ cells;
- the interstitial cells of Leydig, for the production of testosterone;
- the peritubular cell system, supporting the germinal epithelium.

Male gonadal development can be divided into an indifferent stage and a stage of testicular differentiation.

1.1.1. Indifferent stage

The genital glands are formed from two types of cells, the primordial germ cells and the coelomic epitheloid cells. Human primordial germ cells are discernable about three weeks after conception in the umbilical vesicle wall near the allantois. The coelomic epitheloid cells line the anterior, internal side of the Wolffian body (= mesonephros). This epitheloid lining thickens, forming the gonadal or genital ridge (figure 1.1.). Early in the fourth week the primordial germ cells can be observed among these epitheloid cells of the genital ridge. The fusion of this part of the coelomic wall with the primordial germ cells eventually forms the

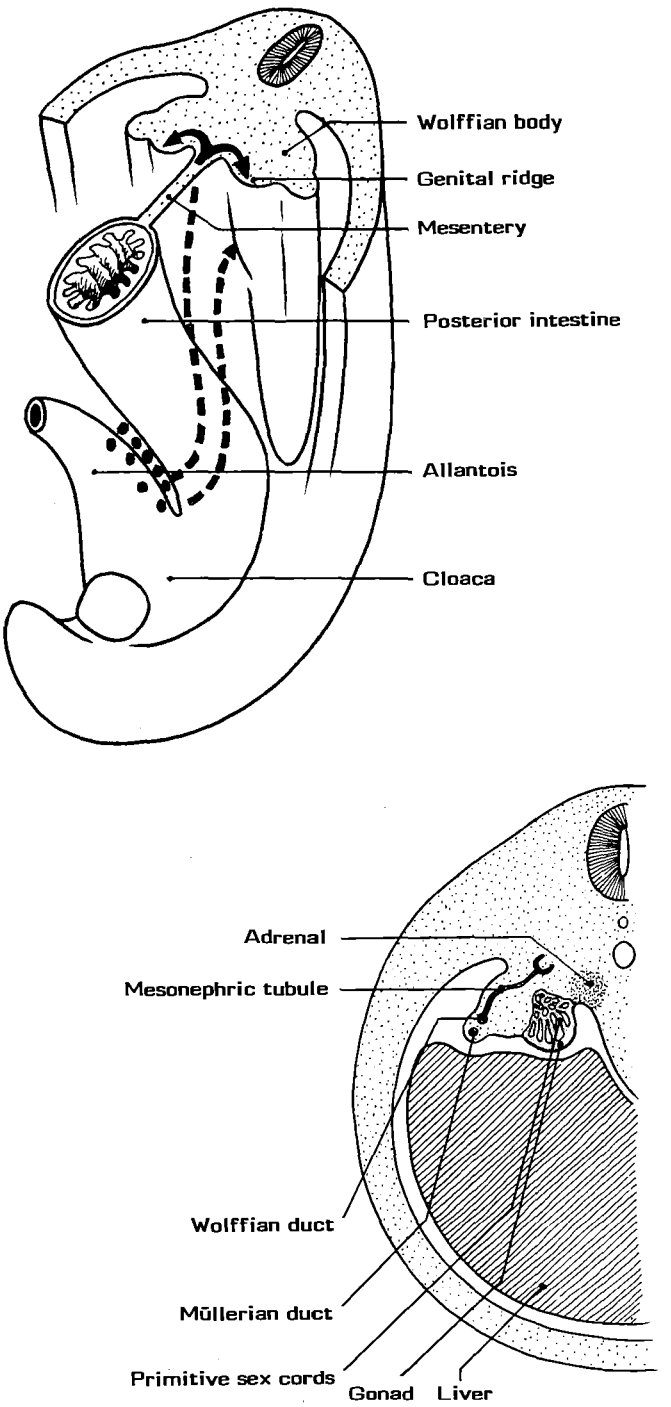


Figure 1.1. Gonadal development: indifferent stage (Tuchmann-Duplessis and Haegel, 1974; with permission).

gonadal blastema. In the fifth week after conception, changes occur in the genital ridge, whereby the coelomic wall gradually loses its epitheloid character and at this stage a proliferation of so-called primitive sexual cords can be observed. By the sixth week, the primordial germ cells have become embedded between the primitive sexual cords. Modern embryologists assume that all testicular cells other than the germ cells are derived from the epitheloid cells of the coelomic wall.

1.1.2. Testicular differentiation

Up till the end of the sixth week of embryonic life, the gonads of both sexes are identical in appearance. Subsequently, differentiation into testis or ovary takes place. According to Jost (1970, 1972) sex determination may be viewed as comprising sequential processes:

- establishment of genetic sex (XX or XY) at fertilization;
- translation of genetic sex into gonadal sex (ovary or testis);
- translation of gonadal sex into body sex (female or male).

The gonadal sex differentiation is controlled by the H-Y antigen, a cell surface antigen that is found in tissues of mammalian males but not in those of normal females. It is not yet completely clear where the genes involved in the formation of the H-Y antigen are located. On the Y-chromosome? Or on the X-chromosome requiring the Y-chromosome for activation? The theory of Wolf (1979) is that the structural testis-determining H-Y gen is located on an autosome suppressed by the X-chromosome and activated by the Y-chromosome.

The testis can first be identified as such in embryos of about 17 mm crown-rump (CR) length when the male gonadal blastema becomes subdivided into testicular cords. The cords, containing germ cells surrounded by the nutrient supporting cells (later Sertoli cells), are first noticeable in the central portion of the gonadal ridge near the mesonephric tubules. This is the start of formation of the *seminiferous tubules*. At a CR length of about 25 mm the *tunica albuginea* develops, a dense fibrous layer which separates the testicular tubules completely from the mesothelial lining of the gonad. The testicular cords extend into the region of the gonadal mesentery where they form a network, the *rete testis*. The cords then become canalized to form the *seminiferous tubules*. At a CR length of 50-90 mm the rete testis is also canalized and in part becomes continuous with some of the mesonephric tubules forming the *vasa efferentia*.

1.1.3. Testicular cords

During early development, the diameter of the growing testicular cord depends on the intratubular situation. Rapid proliferation of germ cells or supporting cells coincides with a rapid increase of the diameter of the cords. During late prenatal and subsequent postnatal development the process of growth

becomes slow and steady (Wartenberg, 1981). Throughout the entire prepuberal period, a continuous and linear increase in the tubular diameter was observed (Städtler and Hartmann, 1972). The mean diameter of a given number of testicular cords or seminiferous tubules at a certain age can be used as a parameter for normal testicular growth. Another test of testicular maturation, correlating with the diameter of the cords, is a count of germ cells in 50 or 100 circular cross-sections of the tubules.

1.1.4. Germ cells

As mentioned earlier, the male gonadal blastema becomes subdivided into testicular cords in the presence of the H-Y antigen at about day 42 (CR length 17-20 mm) and the development of the germ cells commences. Various descriptions of germ cell development have been reported. Hilscher (1974) followed by Wartenberg (1981) proposed the following sequence: primordial germ cells or gonocytes give rise to M-prospermatogonia which transform into T_2 prospermatogonia or fetal spermatogonia via a transitional phase: the T_1 prospermatogonia. The T_2 prospermatogonia transform into the adult A spermatogonial stage. Hadziselimovic (1983[a]) stated that a major problem of this classification of germ cell development is that it does not include all types of cells observed in the human testis throughout embryonal life and childhood. He proposed a sequence of germ cell development, whereby primordial germ cells differentiate into gonocytes by entering the testicular cords. The gonocytes attached to the basement membrane give rise to the fetal spermatogonia, while the gonocytes resting in the centre of the seminiferous tubules degenerate. Fetal spermatogonia thus transform via the transitional type of spermatogonia into A-type spermatogonia (AP and AD spermatogonia) and B-type spermatogonia. This transformation would take place after birth. From age four he also observed primary spermatocytes. Spermatogenesis then ceases, to recommence at puberty (Hadziselimovic and Herzog, 1977). Städtler and Hartmann (1972) observed a linear increase of spermatogonia count in the whole prepuberal period.

1.1.5. Sertoli cells

The first signs of differentiation of the primitive gonad into a testis is the formation of cords of primitive Sertoli cells that encompass germ cells (Jost et al., 1974). There is substantial evidence that after cord formation the Sertoli cell takes an active part in germ cell differentiation (Wartenberg, 1978) and somatic sex differentiation (anti-Müllerian hormone; see 3.1.4.). Hadziselimovic (1983[a]) described the Sertoli cell in the first year of life as the most common cell in the seminiferous tubule. From the first to the fourth year, a transformation takes place from fetal Sertoli cells into Sa- and Sb-type cells. The Sa-type cell is the most common of the Sertoli cells in children. In the fourth year, Sb-type Sertoli cells appear in increas-

ing numbers simultaneous with the appearance of the B-spermatogonia and primary spermatocytes. During puberty, increased gonadotropin and testosterone stimulation causes the Sertoli cells to mature and increase in size, resulting in a transition to the Sc-type cells. In connection with the Sertoli cell maturation, Ritzén and coworkers (1981) described the formation of special inter-Sertoli-cell, tight junctions which constitute a major component of the functional blood-testis barrier. The adult Sertoli cells have a number of other important functions including the production of unique proteins that are secreted in the seminiferous tubular lumen (Bardin and Paulsen, 1981). The first secretory protein to be characterized as deriving from the Sertoli cell was the testicular *androgen-binding protein* (ABP). ABP has been detected in various concentrations in several species, but so far conclusive evidence for human ABP is lacking. Increased understanding of the hormonal control of Sertoli cells was derived from animal studies of this protein. The Sertoli cell is also the most likely site of origin for a water soluble testicular product: *inhibin*. The effect of inhibin is usually felt to be specific for inhibition of FSH release but it is difficult to exclude an effect of inhibin on LH secretion (Bardin and Paulsen, 1981). A few other specific hormones have been identified as secretory products of the Sertoli cell in the postnatal testis. Several animal studies have revealed that the Sertoli cell is a major target for FSH and androgens in the testis. There were indications that these two hormones, known to be of decisive importance for spermatogenesis, exert at least part of their influence through the Sertoli cells (Ritzén et al., 1981).

1.1.6. Leydig cells

Early development of Leydig cells and their activity in fetal human testes is well-documented. Among others, Holstein et al., (1971) investigated Leydig cell development in embryos and fetuses from the 7th to the 22nd week of gestation and found that the Leydig cells start to differentiate from mesenchymal cells at the beginning of the eighth week of gestation. These mesenchymal cells are derived from the coelomic epitheloid cells, which may proliferate and loose their epitheloid character. In the human fetal testis, the period characterized by a highly developed interstitial cell system lasts from the 8th to the 18th week. At about the 14th week, it has reached maximum expansion and constitutes more than 50% of the testicular volume (Holstein et al., 1971). In this period, the same author found a highly developed endoplasmic reticulum in fetal Leydig cells, characteristic for steroid-producing cells. After the 15th week, there is a gradual regression of Leydig cells and at birth or a few months later, the intertubular space in the human testis is devoid of Leydig cells (Wartenberg, 1981). However, Hadziselimovic observed fetal Leydig cells in human testes up till the second year of life. He reported that the interstitium contains mainly precursors of Leydig cells up till puberty but occasionally, particulary between the age of four and eight years, he found juvenile Leydig cells grouped around the vessels (Hadziselimovic,

1983a). Hayashi and Harrison (1971) also found Leydig cells in prepuberal human testes up till one year of age. He observed that they disappear completely by the fifth year of age to reappear in quantity around the eighth year. According to Hadziselimovic (1983a) a renewed differentiation of Leydig cells takes place at the onset of puberty. The puberal Leydig cells are well developed with a remarkable increase in the amount of smooth endoplasmic reticulum. The initial differentiation of Leydig cells is an autonomous fetal occurrence, but the subsequent maintenance, proliferation, and regression of these cells is under gonadotropic control (see 3.1.).

1.1.7. Peritubular cell system

The peritubular cells are assumed to arise from the intertubular mesenchymal cells, which are derived from the coelomic epitheloid cells. Wartenberg (1978) described a peritubular sheet of epitheloid cells coinciding with the appearance of transitional prospermatogonia in the tubuli. The peritubular cells form a multi-layered envelope which is different from the characteristic composition in the lamina propria of the adult testis. According to Burgos and coworkers (1970) the peritubular tissue or lamina propria of the seminiferous tubules in the adult testis comprises a basement membrane plus a framework of fibres and cells which support the germinal epithelium.

1.2. DEVELOPMENT OF THE MALE GENITAL TRACT

1.2.1. Upper portion of the male genital tract

The mesonephros (or Wolffian body) is derived from the intermediate mesoderm located on the posterior abdominal wall. Figure 1.2. is a schematic presentation of the anatomic relationship of the undifferentiated urogenital excretory system. Differentiation of the mesonephros, containing the Wolffian tubules, begins in the first week. In the cross-section, the mesonephros appears to be a mass projecting into the peritoneal cavity. The urogenital cord, containing the Wolffian or mesonephric duct, is attached to the anterolateral edge of the mesonephros by the urogenital mesentery. At a later stage (about 10 mm CR length) it also contains the Müllerian or paramesonephric duct. The gonadal primordium is attached to its antero-internal side by the gonadal mesentery. Posteriorly it is attached to the dorsal body wall by the Wolffian body mesentery. The inguinal ligament is formed by a band of mesenchyme from the caudal end of the mesonephros to the genital swellings. The urogenital mesentery and the Wolffian mesentery extend upward above the mesonephros to form the diaphragmatic or suspensory ligament.

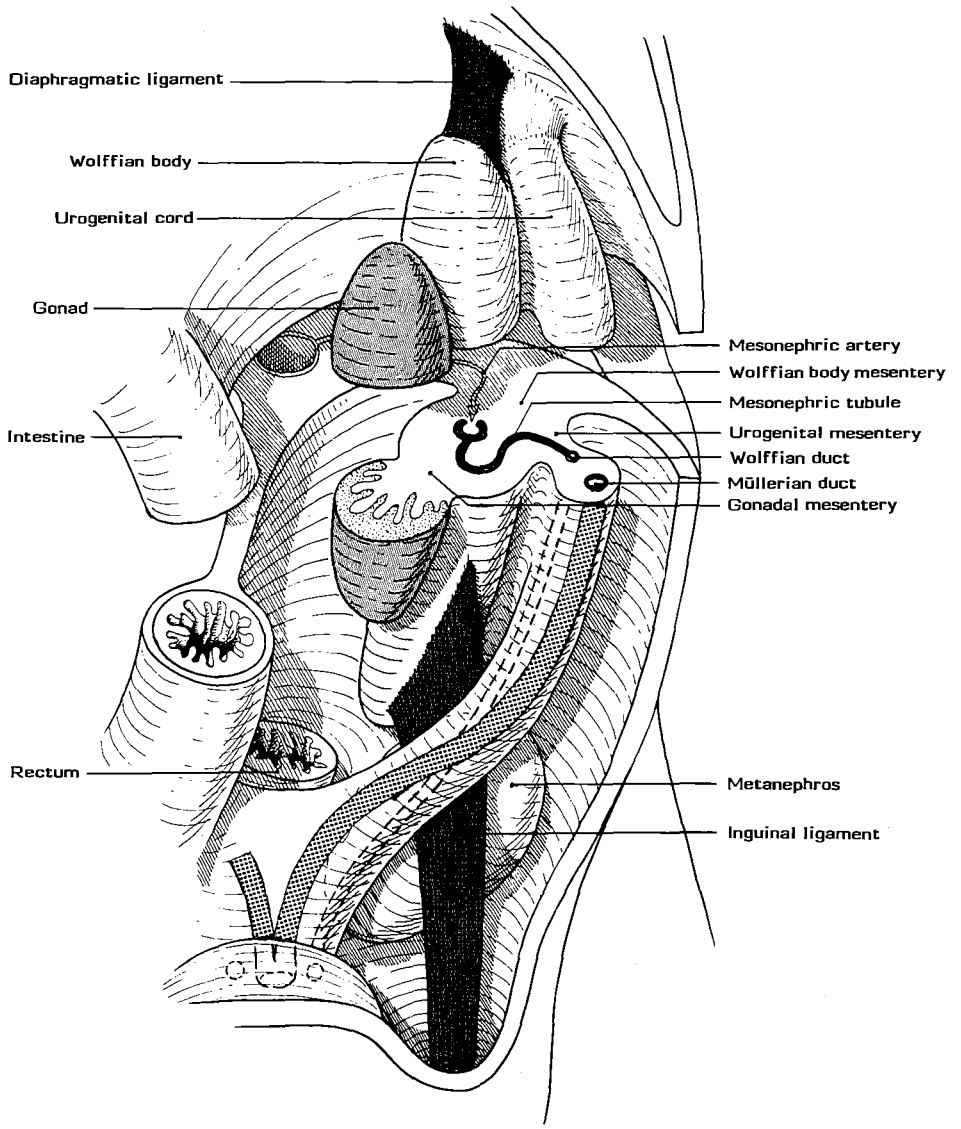


Figure 1.2. Anatomic relationship of undifferentiated urogenital excretory system (modified from Tuchmann-Duplessis and Haegel, 1974).

Figure 1.3. shows the differentiated male urogenital excretory system. Regression of the Wollfian body starts at eight weeks, to be completed by the end of the fourth month. The inguinal ligament now becomes part of a whole mesenchymal column with the testis at the apex extending to the genital swellings, the *gubernaculum testis*. Regression of the Müllerian duct occurs at 11 weeks. The remaining vestiges of the Müllerian duct are the *appendix testis* at the cranial end

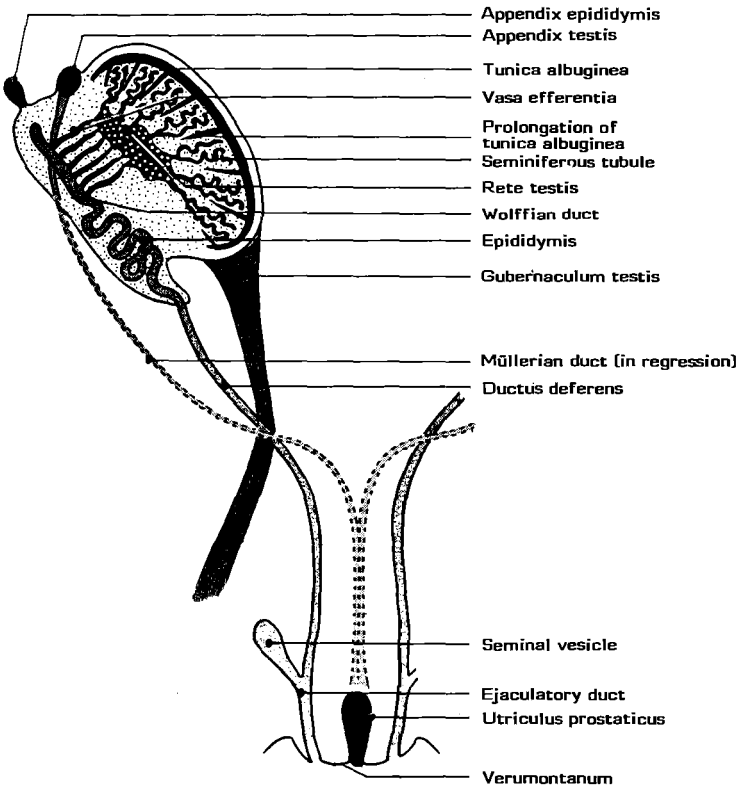


Figure 1.3. Differentiated male urogenital excretory system (Tuchmann-Duplessis and Haegel, 1974; with permission).

and the *prostatic utricle* at the opposite end. At 14 weeks (CR length 90 mm), the cranial part of each mesonephric duct becomes connected to the seminiferous tubules through the vasa efferentia and the rete testis. The portion of the mesonephric duct opposite the testis becomes greatly elongated and convoluted to form the *epididymis*. The *appendix epididymis* is formed at the most cranial end of the epididymis. Below the epididymis, certain isolated mesonephric tubules form the *paradidymis* (not shown in figure). At a later stage, the remainder of the Wolffian duct adopts a thick muscular coat to become the *ductus deferens*. The *seminal vesicles* are formed at the distal end of the ductus deferens. Caudally the ductus deferens becomes the *ejaculatory duct*. The *utriculus prostaticus* arises between the two ejaculatory ducts.

1.2.2. Lower portion of the male genital tract

The development of the lower portion of the male genital tract is schematically presented in figure 1.4. During early development, the cloacal membrane is

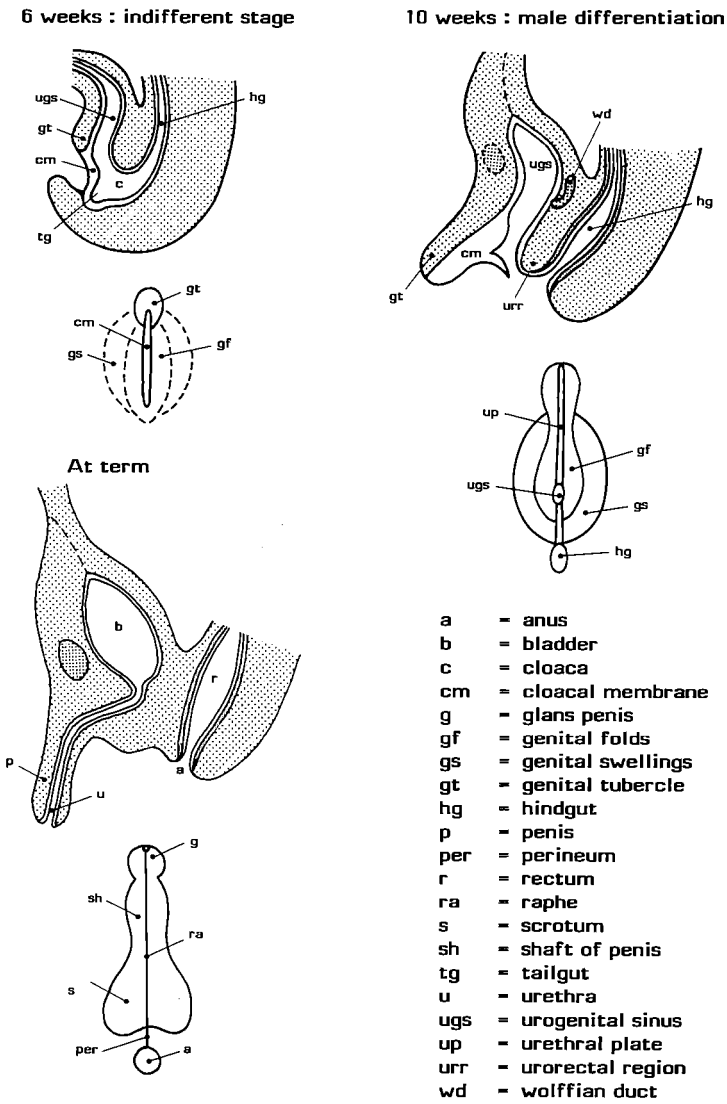


Figure 1.4. Development of the lower portion of the male genital tract.

formed at the caudal end of the embryonic disc where the ectoderm and the entoderm remain in contact. The cloaca can be defined as the space into which the hindgut, the urogenital sinus and the tailgut end. The two Wolffian ducts terminate in the urogenital sinus on the dorsal side. The urogenital sinus and hindgut are separated by a mesenchymal column, the urorectal region, which erroneously has been described as a septum (Van der Putte, 1986). The genital tubercle develops above the cloacal membrane. The straightening of the embryo, the outgrowth of the genital tubercle and the disappearance of the tailgut may create the impression that the urorectal region "descends". The

genital folds and genital swellings develop on both sides of the cloacal membrane. At approximately eight weeks, the posterior portion of the cloacal membrane becomes thinner to rupture at approximately ten weeks. The urogenital sinus and hindgut are now open to the amniotic cavity. The *perineum* is formed from the entodermal epithelium lining the urorectal region. At ten weeks, the genital tubercle elongates, forming the *glans penis*. The urethral plate develops from the distal part of the ventral wall of the urogenital sinus and grows out at the ventral side of the genital tubercle subsequently forming the *urethra*. The genital folds form the *shaft of the penis* and the genital swellings develop into the *scrotum*. The orifice of the urethra shifts from the ventral side to the top of the genital tubercle. The *raphe* is then formed from the basal part of the urorectal region. The *prostate* develops from the entodermal epithelium of the dorsal wall of the urogenital sinus.

1.3. TESTICULAR DESCENT

The descent of the testis may be divided into two phases:
- the first phase of descent or intra-abdominal descent;
- the second phase of descent, or "true descent", during which the testis emerges from the inguinal canal and into the scrotum.

1.3.1. First phase of descent

Many authors, including Habenicht and Neumann (1983), cite the theories of Gier and Marion (1970) who divided this phase of descent into two stages:
- *nephric displacement;* this stage is closely related to the degeneration of the mesonephros. The metanephros grows rapidly in size and migrates in an anterior direction, dorsal to the mesonephros. In the process, the metanephros forces the mesonephric remnants and the gonads to move further caudally. In man, this stage is completed by the eighth gestational week;
- *transabdominal movement;* the decisive factor for this stage of descent is the increase in coelomic fluid pressure and its transmission to the testis via the gubernaculum.

In his *differential growth theory,* Hart (1909) surmised that testicular descent occurs as a rapid growth of the body wall in relation to the diminished growth of the relatively immobile gubernaculum. As a result, the testis assumes an inguinal position and in the second phase of descent it is drawn into the scrotum. In contrast, Lemeh (1960) found that the gubernaculum increases in size faster than the body as a whole. Backhouse (1982[a]) described the formation of the inguinal gap in the first stage of testicular descent. This gap is the place where the plica gubernaculi meets the abdominal wall and no muscle cells are formed. This eventually becomes the inguinal canal. He was very explicit about the develop-

ment of the cremaster muscle which, in his opinion, originates later and apart from the abdominal wall muscles. He disagreed with the theory that the cremaster muscle grows up towards the testis and by contracting pulls the testis into the scrotum (Backhouse, 1965). He further described the developing processus vaginalis as an extension of the peritoneal cavity; a diverticulum from the coelom, which forms a shallow gutter around the gubernacular column at its attachment to the anterior abdominal wall. Neither the cremaster muscle nor the processus continues to grow much at this stage of descent. According to Backhouse (1982[a]) the first stage of descent *"is more a question of the gonad retaining its link through the mesonephric duct (vas deferens) and the gubernaculum with the bladder and the anterior wall whilst the rest of the fetus grows in length leaving the gonad behind."*

1.3.2. Second phase (true descent)

In the seventh month the testis passes through the inguinal canal. Normally it reaches the scrotal sac by the end of the eighth month (Hamilton and Mossman, 1978). Most investigators agree that the *gubernaculum* plays an important part. There is, however, no consensus of opinion regarding the morphological character of the gubernaculum and the precise role in the mechanism of descent. John Hunter (1762) was the first person to describe the pattern of testicular descent with emphasis on the gubernaculum. To him we owe the name of the gubernaculum (= the Latin name for shipshelm). He is very cautious in his description of the structure and function of what he called a ligament, which connects the testis with the scrotum and directs its course in its descent. He described the nature of the gubernaculum as vascular and fibrous, with the fibres running in the direction of the ligament itself, which is covered by the fibres of the cremaster or musculus testis. Backhouse (1965) described the gubernaculum as a mesenchymatous column, which during the time of descent increases in bulk and in the scrotum comes to resemble Wharton's jelly. Other authors described the gubernaculum as a fibromuscular or muscular cord (Sonneland, 1925; Lemeh, 1960). In animal studies, likewise, the gubernaculum is frequently described as having muscular or fibromuscular components (Elger et al., 1977; Radhakrishnan and Donahoe, 1981; Elder et al., 1982; Somerville et al., 1983), thus claiming that at least in some animals the gubernaculum is a contractile organ. On the other hand, Wensing and Colenbrander (1977) found that the gubernaculum in pigs and other mammals had a mesenchymal structure only. It may be that some authors saw the cremaster muscle as part of the gubernaculum, situated peripherally, describing these structures as one and the same organ. Lemeh (1960), for example, observed that the internal abdominal oblique muscle layer gives off skeletal fibre bundles which surround and blend with the inguinal ligament of the mesonephros (= gubernaculum testis). Elder et al. (1982) stated that the muscular investment of the gubernaculum becomes the cremaster layer of the scrotum. Apart from the

confusion caused by divergent descriptions of the gubernaculum, there is controversy concerning the precise role of the gubernaculum in the mechanism of descent.

Backhouse (1982[b]) is frequently quoted in his description of testicular descent. In his opinion (figure 1.5.), the gubernacular mesenchyme increases in bulk particularly within the scrotum. There is a rapid growth and extension distally of the cremaster muscle close to the outer surface. The processus vaginalis also extends rapidly, distally in the gubernacular mesenchyme, separating this into a central core and a thin tube outside the processus containing the cremaster muscle. The gubernacular mesenchyme shortens and the apical testis can slip through the canal possibly assisted by intra-abdominal pressure. The vas deferens and the testicular vessels grow rapidly in length. Once descent has been completed, the gubernaculum ceases to have a function and differentiates into fasciae found in relation to the testis and epididymis, the internal and external spermatic fasciae.

Other theories were offered for the final phase of descent. Some of them were also suggested for the first phase of descent:

- the *traction-theory* of the gubernaculum (Sonneland, 1925; Radhakrishnan and Donahoe, 1981; Somerville et al., 1983). This theory was already questioned in 1943 by Wyndham, who stated that the flimsy attachment of the gubernaculum to the scrotum is an obstacle exerting much traction on the testis;
- the *differential growth theory* (Hart, 1909, see first phase of descent);

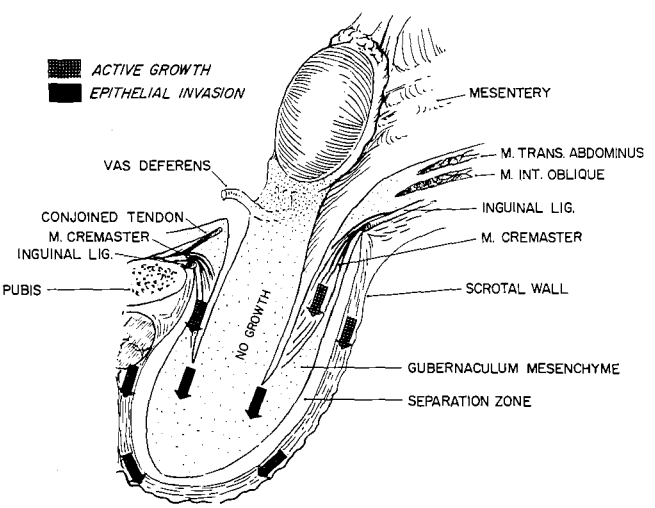


Figure 1.5. A schematic representation of the patterns of growth related to testicular descent. The dots on the gubernaculum are an indication of cell population of the region, i.e., much more intercellular swelling in the scrotum than close to the testis (Backhouse, 1982b; with permission).

- the *intra-abdominal pressure theory* (Gier and Marion, 1970). This also applied to the first phase of descent;
- the *balloon theory* of the gubernaculum, which was described by Wensing and Colenbrander (1977). In animal studies, including the pig, the extra-abdominal or distal part of the gubernaculum increases enormously both in length and volume, as the intra-abdominal part decreases, which then becomes incorporated in the extra-abdominal part. Next, the testis is pulled into the inguinal canal. The subsequent gubernacular regression enables the testis to descend further and this can therefore be considered as the causal factor for the second phase of the process of descent. The degeneration and disappearance of the gubernaculum was also described by others (Rajfer and Walsh, 1978) as cause of testicular descent.

Some authors stress the importance of the *epididymis* in testicular descent without describing its precise role in the mechanism of descent. The need for migration of the cauda epididymis (the sperm-storage region) to this cooler location was suggested (Bedford, 1978). Another indication was the finding of a huge percentage of epididymal anomalies found at operation in patients with undescended testes, which might indicate a significant role for the epididymis in testicular descent (Mininberg and Schlossberg, 1983). On the other hand, it might be that failure of descent results in epididymal malformation or, alternatively, that the same agent causes failure of descent as well as epididymal malformation.

1.4. POSTNATAL ANATOMICAL STRUCTURES

1.4.1. Inguinal region and scrotum

a. Subcutaneous fasciae of the inguinal region

The subcutaneous fasciae of the inguinal region originate as a membranous portion of the superficial fasciae of the abdominal wall consisting of Camper's fascia - the superficial layer - and Scarpa's fascia - the deeper part (Anson and McVay, 1971). For a description of Camper's fascia we refer to the textbooks of anatomy. As for Scarpa's fascia, this deeper layer gradually merges into the subcutaneous fat in the upper abdomen where it can no longer be identified as a distinct membranous structure. In the lower inguinal region, Scarpa's fascia is attached to the inguinal ligament and to the fascia lata of the upper thigh just below this ligament. Passing over the superficial inguinal ring, it continues downward along the penis and the scrotum into the perineum. In the region of the perineum it is continuous with Colles' fascia. In the scrotum it becomes reinforced with smooth muscle fibres and because of its flayed appearance it then becomes known as tunica dartos (McGregor, 1929; Netter, 1961) (figure 1.6.). In infancy, Scarpa's fascia is very thick and consequently falsely identified at times as

the aponeurosis of the musculus obliquus externus abdominis. Contraction of the cremasteric muscle causes the scrotal testis to retract to a recess between Scarpa's fascia and the external oblique muscle, lateral to the superficial inguinal ring. This recess is called the "superficial inguinal pouch" (Browne, 1938; Scorer, 1962; Flach, 1977).

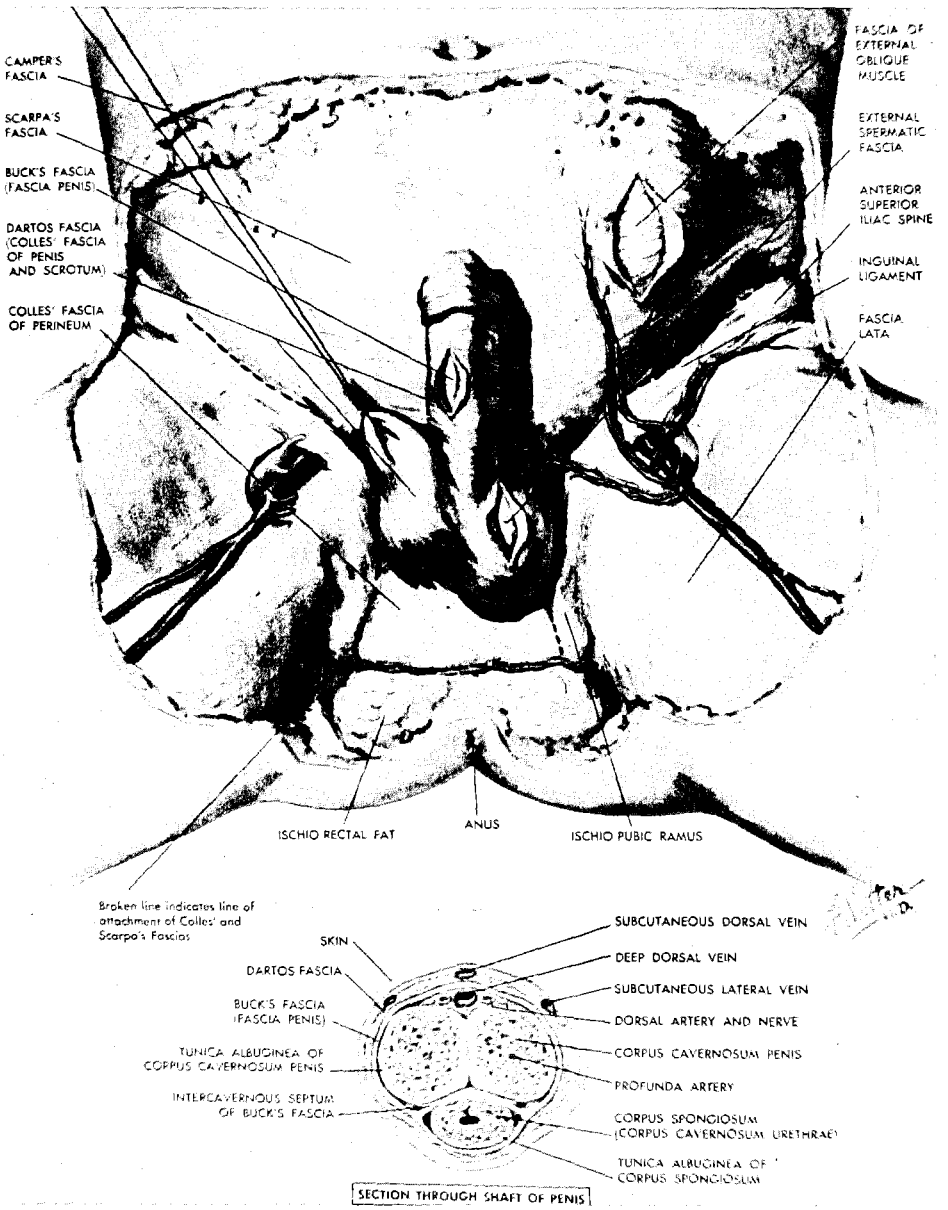


Figure 1.6. Fascial support of the inguinal region (Netter, 1961; with permission)

b. Abdominal wall and inguinal canal

The external oblique muscle becomes tendinous as it envelops the inguino-abdominal region. Its caudal fibres form the inguinal ligament, which is a thin curved structure ending in a free edge. The inguinal portion of the internal oblique muscle originates in the iliopsoas muscle beneath the lateral third of the inguinal ligament. The upper fibres have a common insertion into the linea alba. The caudal fibres continue down to insert into the body of the pubic bone. The origin of the transversus abdominis muscle is identical to that of the overlying internal oblique muscle, arising from the iliopsoas muscle. The transversus muscle fibres combine with those of the overlying internal oblique muscle to form the anterior rectus sheath, while some fibres pass along the pubic crest to insert into the pubic bone.

The transversalis fascia is the fascial layer of the transversus abdominis muscle and its aponeurosis. The term transversalis fascia applies only to the fascial lamina that invests the deep or inner surface of the transverse abdominal muscle and its aponeurosis (Anson and McVay, 1971). The inguinal canal is an oblique cleft in the abdominal wall above the medial half of the inguinal ligament. The inlet of the canal, consisting of the annulus internus or deep (internal) inguinal ring, is located in this transversalis fascia a little above the centre of the inguinal ligament. The outlet, consisting of the annulus externus or superficial (external) inguinal ring, is a gap in the aponeurosis of the external oblique muscle. The superior or deep end of the canal is lateral to the inferior or superficial end.

c. Scrotum

The scrotum is a cutaneous pouch containing the testes and parts of the spermatic cords. On the surface it is divided into two lateral portions by a raphe, which continues ventrally to the undersurface of the penis and dorsally along the midline of the perineum to the anus. The scrotal wall consists of two layers, the skin and the tunica dartos. The skin is thin and falls into folds or rugae. In the tunica dartos a thin layer of nonstriped muscular fibres continues around the base of the scrotum together with the two layers of the superficial fascia of the inguinal region and the perineum (Scarpa's and Colles' fasciae). Internally, a septum divides the scrotal pouch into two cavities, one for each testis. The tunica dartos is closely united with the skin though separated from the subjacent parts by a fascial cleft upon which it glides with the greatest of ease (Spalteholtz, 1959; Gray, 1985). At the scrotal entrance the soft, thin and corrugated skin changes abruptly to become the thick elastic skin of the lower abdomen at the upper level of the scrotal neck. The scrotal entrance is also called the "third inguinal ring" (McGregor, 1929).

1.4.2. Spermatic cord, testis and related structures (figure 1.7.)

a. *Spermatic cord*

The spermatic cord lies in the inguinal canal. It is composed of arteries, veins,

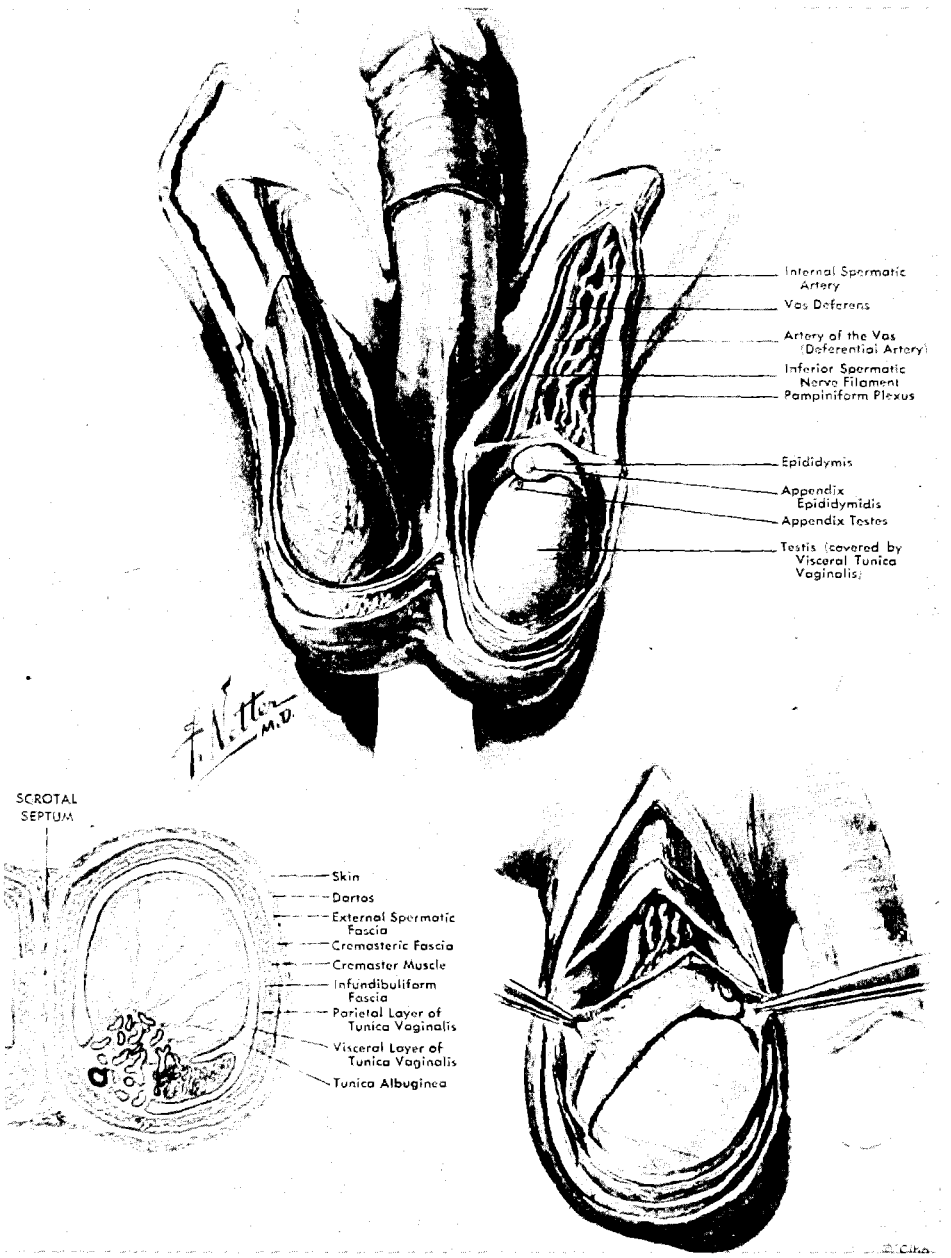


Figure 1.7. Spermatic cord, testis and related structures (Netter, 1961; with permission)

nerves, lymphatic vessels and the vas deferens. These structures have a common covering consisting of several layers:

- the external spermatic fascia - This outer covering is a thin membrane which extends distally over the cord and the testis. At the superficial inguinal ring it is continuous with the aponeurosis of the external oblique muscle, separated from the tunica dartos by a fascial cleft.
- the cremasteric layer - The middle spermatic layer is called the cremasteric layer (Gray, 1985). It consists of scattered bundles of cremaster muscle held together in a continuous membrane by the cremasteric fascia. The cremasteric muscle itself consists of loosely arranged muscle fasciculi. The whole muscle may be described as forming continuous loops from the middle of the inguinal ligament as far as the tunica vaginalis and then returning to insert into the pubic tubercle. Although striated, the fibres of the cremasteric muscle are generally not subject to voluntary control.
- the internal spermatic fascia - This fascia is a thin membrane which is continuous with the transversalis fascia at the deep inguinal ring.

b. Testis

Ellipsoidal in shape, the testis holds an oblique position in the scrotum, the upper extremity tilting antero-laterally and the lower extremity postero-medially. The epididymis lies along the lateral part of the posterior border. The fibrous covering of the testis is called the tunica albuginea. It is a membrane composed of fibrous tissue. At the upper extremity of the testis there is an oval, sessile body, which is the appendix of the testis. It is a remnant of the upper end of the paramesonephric duct.

c. Epididymis

The epididymis consists of a central portion or body with an enlarged upper extremity, which is called the head or caput, and a pointed lower extremity, which is called the tail or cauda. At the lower extremity of the testis it turns upward and gradually merges into the ductus deferens. The head of the epididymis is attached to the upper end of the testis (rete testis) by means of the efferent tubules of the gland. The tail is attached to the lower end of the testis by areolar connective tissue (Kroovand and Perlmutter, 1981). Between the body of the epididymis and the testis there is a pouch, called the digital fossa. In infants, the epididymis is relatively longer and larger than in adults, whereby the length of the epididymis far surpasses that of the testis, although it is never more than twice the length of the testis (Scorer, 1962). Likewise, the digital fossa, which is the space between testis and epididymis, is relatively larger in the infant than in the adult (0.3-0.45 cm), while the epididymis is relatively more mobile (Cooper, 1929). The head of the epididymis has a small stalked appendage.

d. Vas deferens

The vas deferens is the continuation of the canal of the epididymis. Commencing at the tail end of the epididymis, it is first tortuous but becomes gradually less twisted as it ascends along the posterior border of the testis and traverses the inguinal canal to reach the deep inguinal ring. Here it separates from the other structures of the cord and curves around the lateral side of the inferior epigastric vessels on its way to the seminal vesicle.

e. Processus vaginalis peritonei

The processus vaginalis peritonei is the serous covering of the testis and spermatic cord. It is a pouch of serous membrane derived from the peritoneum. As the testis and the epididymis descend from their retroperitoneal points of origin, they invaginate the cord and gradually merge into the posterior aspect of the processus vaginalis, thus becoming enveloped by two layers of this structure (Tuchmann-Duplessis and Haegel, 1974; Backhouse, 1981). After its descent, the portion of the processus vaginalis that extends from the deep inguinal ring almost to the upper part of the testis, becomes obliterated. The lower portion remains as a closed sac that invests the testis and may be described as the tunica vaginalis, consisting of a visceral and a parietal layer. The visceral layer covers the greater part of the testis and epididymis. The parietal layer is more extensive than the visceral layer. It may occasionally happen that the processus vaginalis does not become obliterated and as such communicates with the tunica vaginalis. This is called the hydrocele communicans.

f. Gubernaculum

In the fully descended testis, the remnants of the gubernaculum are continuous with the posterior aspect of the testis and the epididymis down to the base of the scrotum. The descended testis with its coverings can be lifted out of the scrotum without dividing more than a few strands of delicate connective tissue (Scorer, 1962).

g. Vascular anatomy of the testis

The spermatic artery, which is the main source of blood for the testis, is not an end artery. It receives collateral twigs from the artery to the vas deferens and the cremasteric artery, and also from the scrotal arteries. The latter are branches of the internal and external pudendal arteries at the lower pole of the testis (Brendler and Wulfsohn, 1967). Harrison (1949) demonstrated anastomoses between the vasal artery and the spermatic artery and also showed that no anastomotic channels reached the testis independently, always going by way of the spermatic artery or its main branches. These findings were confirmed by others (Lee et al., 1984) (figure 1.8.).

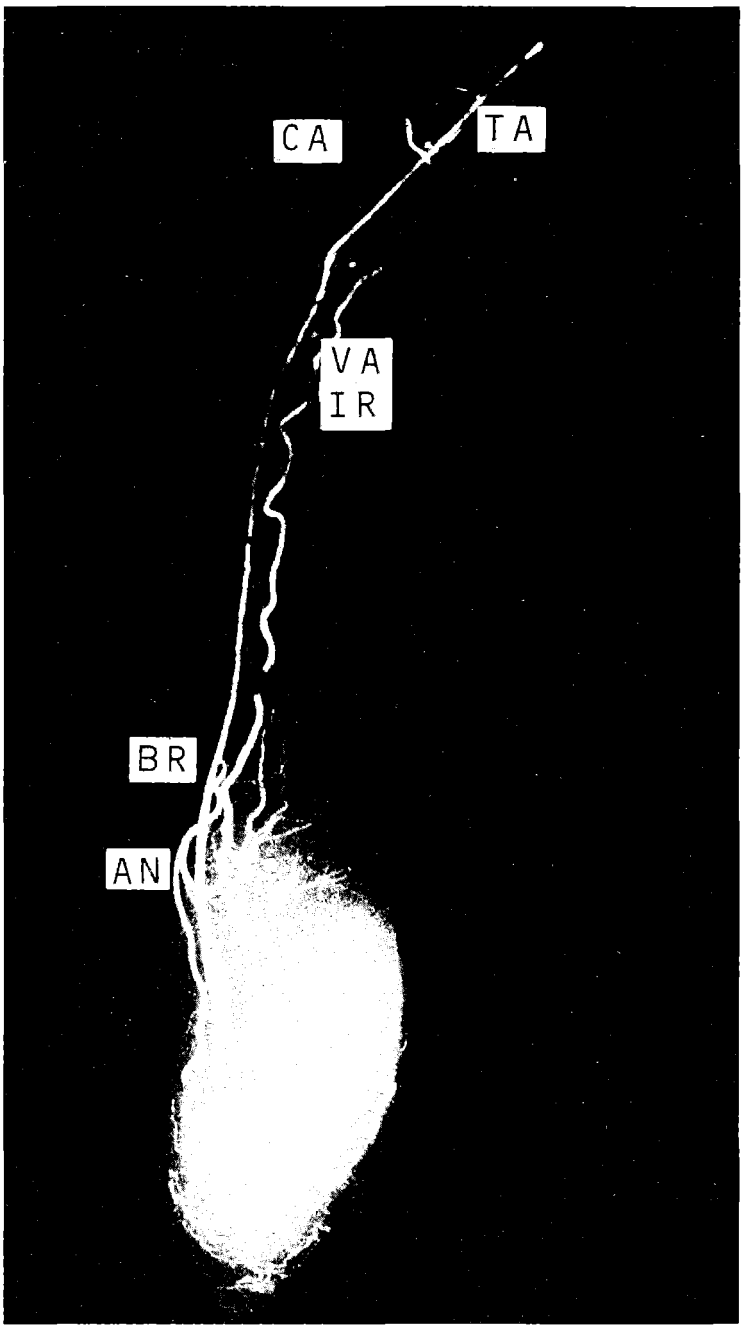


Figure 1.8. Testicular artery injection of the right testis of a paediatric cadaver, 37 weeks gestation. Retrograde filling of small cremasteric artery and large vasal artery. CA: cremasteric artery; BR: origin of anastomotic branch of testicular artery; VA: vasal artery; AN: anastomosis; TA: testicular artery; IR: position of internal ring (Lee et al., 1984; with permission).

The testicular veins emerge from the back of the testis and unite to form a convoluted plexus, the plexus pampiniformis, which constitutes the chief mass of the spermatic cord. The vessels composing this plexus are numerous and ascend along the cord. On their way through the inguinal canal, they form two or three venous trunks at the level of the deep inguinal ring. In the iliolumbar region, these venous trunks are reduced to two veins to become one vein in the lumbar region entering the inferior caval vein (Bensussan and Huguet, 1984; Gray, 1985).

The spermatic vessels course obliquely downward lateral from the renal area to exit through the internal inguinal ring. Proximal to the inguinal ring, as viewed from the sagittal plane, these vessels angulate exteriorly to reach the deep inguinal ring whereupon they course postero-medially through the inguinal canal. Throughout their course, the spermatic vessels are enveloped in the transversalis fascia. This fascia is continuous with Gerota's fascia and as such also envelops the ureter (Prentiss et al., 1960). In the inguinal canal it becomes the internal spermatic fascia.

1.5. MOTIVATION FOR STUDYING CRYPTORCHIDISM

1.5.1. Introduction

In the last few decades it has been assumed that a disturbance of testicular descent has a multicausal genesis with a growing emphasis on the hormonal process that influences testicular descent. Intra-uterine hormonal dysfunction is considered to be a major cause of failure of testicular descent. Treatment for undescended testes has since long consisted of surgical intervention, but hormonal treatment has been gaining ground, particularly in the last ten years.

It is by no means easy to make the correct diagnosis in case of an apparently undescended testis. Physical examination of prepuberal boys is particularly difficult where the testis is concerned due to the contractions of the cremaster muscle. This is one of the reasons why the incidence of undescended testes, generally based on transversal studies, is unclear. Longterm, longitudinal studies have seldom been carried out. Apart from that, there is a great deal of confusion concerning diagnosis and nomenclature of the undescended testis.

Before deciding on the treatment of choice, one has to decide WHY undescended testes have to be treated. Failure to treat undescended testes carries an increased risk of infertility, malignant degeneration, and a disturbance of the psychosexual development. Once the diagnosis of undescended testes has been reached, one has to decide HOW this should be treated. We now have a choice of either hormonal or surgical treatment. The pros and cons of both therapeutic modalities have to be weighed carefully before making a decision. And finally, one has to decide WHEN treatment should take place. There is still no consensus of opinion concerning that point. In recent years the importance of early treat-

ment, preferably around the second year of life, has been emphasized by several authors. The main argument for early treatment concerns irreversible histological changes that might occur in the germinal epithelium of the undescended testis. Apart from that, early treatment is supposed to have a favourable effect on the potential fertility of the undescended testis. This premise has not been substantiated.

1.5.2. Definitions

In order to avoid confusion concerning the nomenclature of cryptorchidism in this treatise, we have drawn up definitions for the various types of undescended testes. Both nomenclature and diagnosis will be dealt with in detail in chapter 2, but our definitions are summarized as follows:

Cryptorchidism - This term is used as a general designation describing any nonscrotal testis that cannot be manipulated into a stable scrotal position. The word "cryptorchidism" is interchangeable with "undescended testis".

Retractile testis - This is a completely descended and normally developed testis that can be lifted out of a stable scrotal position by the cremasteric reflex, whereby it moves over the pubic bone and into a stable subcutaneous position in the inguinal region.

Cryptorchid testes (undescended testes) - These testes can be subdivided into:

- incompletely descended testes. These testes always have a stable position somewhere in the path of normal descent. They may be capable of manipulation into the scrotum, but if so they will never remain there of their own accord.
- ectopic testes. These are testes that have assumed a position outside the normal path of descent, but this position is always subcutaneous.

1.5.3. Aims of the studies

Our interest was aroused by reports of the new hormonal treatment of boys with undescended testes by means of luteinizing-hormone-releasing hormone (LHRH) nasal spray. In the beginning of 1982, we decided to carry out a pilot study to investigate the efficacy of LHRH nasal spray. The pilot study created great expectations for this therapeutic modality, but also posed a number of questions indicating the need for further investigation. Consequently, the pilot study formed the basis for a number of clinical studies that we initiated in prepuberal boys with either unilateral or bilateral undescended testes, to find answers to the following questions:

1. What is the normal development and anatomy of the testis and male genital region in general and how does normal testicular descent proceed? This question was answered in the preceding paragraphs.
2. A multiple question, concerning the diagnosis of cryptorchidism:

- How should the various forms of cryptorchidism be defined?
- How should the physical examination of a cryptorchid boy be carried out?
- How should the findings of the physical examination be recorded to be of use at subsequent examinations?

These aspects will be dealt with in chapter 2.

3. Recent clinical and experimental studies reported in the literature, indicate that a (transient) functional insufficiency of the hypothalamo-pituitary-gonadal axis is an important factor in the pathogenesis of cryptorchidism. This insufficiency, found in cryptorchid boys in the first year of life, seems to argue for hormonal treatment of cryptorchidism. In this connection we were faced with the following questions:
   - Is hormonal failure a causative factor in testicular non-descent?
   - What hormonal abnormalities may be associated with cryptorchidism?
   - Is there a difference in the hormonal values from birth till puberty between boys with undescended testes and boys with normal testicular descent?
   - Does spontaneous, albeit delayed, testicular descent occur during the (entire) first year of life?
   - Is there a demonstrable (transient) functional insufficiency of the hypothalamo-pituitary-gonadal axis in boys with unilateral or bilateral cryptorchidism during their first year of life?
   - Do cryptorchid boys suffer from either a disturbance of the biosynthesis of testosterone or an enzymatic inhibition?

   Chapter 3 attempts to answer these questions.
4. What kind of hormonal treatment is available for boys with undescended testes and which seems to be the most successful according to the literature? Literature data and the results of our pilot study indicated a certain measure of success for LHRH nasal spray. With a double-blind, placebo-controlled study we attempted to find an answer to the following questions:
   - How effective is LHRH nasal spray treatment and is there a relation between success of treatment and age at treatment?
   - Can the mode of action of LHRH nasal spray be determined by means of hormonal evaluation?
   - Are the results of such hormonal evaluation of any prognostic value where LHRH treatment is concerned?

   Other questions arose in the course of this study:
   - Provided information can be obtained concerning previous testicular position (from birth), can a relationship be found between that information and the results of hormonal treatment?
   - Would a difference in absorption of the LHRH nasal spray account for the reaction of this spray being less pronounced in younger than in older boys?
   - Is there a demonstrable mode of action of LHRH nasal spray?

All these aspects are dealt with in chapter 4.

5. Does failure of testicular descent have a mechanical cause rather than a hormonal one? If so, how does the microscopical and macroscopical anatomy of the undescended testis (and surrounding structures) differ from that of a normally descended testis? Other questions in this connection are:
   - Is there an increased risk of malignant degeneration of the (previously) undescended testis?
   - Is there a relation between infertility and cryptorchidism?
   - What are the psychosexual implications of cryptorchidism?
   - What anatomical anomalies may be associated with cryptorchidism?
   - What kind of surgical procedures can be employed in the treatment of undescended testes and what are the results of these procedures as reported in the literature?

   Chapter 5 attempts to answer these questions.
6. Retractile testes are often incorrectly diagnosed as incompletely descended and unnecessarily subjected to surgery.
   - How should retractile testes be treated?

   Management of the impalpable testis merits a special place in the surgical treatment of undescended testes.
   - What diagnostic procedures should be employed in case of impalpable testes?
   - Is hormonal treatment ever indicated for impalpable testes?
   - What is the correct surgical procedure for impalpable testes?

   The boys whose testes failed to descend as a result of LHRH nasal spray in the abovementioned double-blind, placebo-controlled study, all underwent surgery.
   - Were there any anatomical anomalies in these boys that would explain the failure of hormonal treatment?
   - What is the procedure of choice in relation to testicular position found at surgery?
   - What are the specific indications for or against a certain surgical procedure?
   - What complications may occur as a result of surgical treatment?
   - Is there a relation between age at surgery and the occurrence of complications?
   - Is there a relation between success of surgical treatment and age at treatment?

   The above is dealt with in chapter 6.
7. Would the clinical studies furnish answers to the three questions posed in the paragraph on motivation (1.5.1.)?:
   - WHY, HOW, WHEN?

   If so, what protocol should be adopted for the treatment of undescended testes in the Sophia Children's Hospital?

Chapters 1 and 2 were written by the two authors in conjunction and both of them are responsible for these chapters. In contrast, chapters 3 through 6 were not written in conjunction, even though the clinical studies described in these chapters may have involved a certain measure of concerted effort. Category A of the clinical studies, involving chapters 3 and 4, represents the work carried out by S.M.P.F. de Muinck Keizer-Schrama. The general discussion that concludes this section is entirely her concern. Category B, involving chapters 5 and 6, represents the work carried out by F.W.J. Hazebroek. The general discussion at the end of this section is entirely his concern. Chapter 7 and the answers it attempts to provide once again represent a concerted effort.

CHAPTER 2

INTRODUCTION TO OUR CLINICAL STUDIES

2.1. GUIDELINES FOR THE CLINICAL STUDIES

The clinical studies were initiated in 1982 on the understanding that they would be concluded in three years. The studies would be mainly prospective with a few exceptions, e.g. when retrospective evaluation was required. For the double-blind, placebo-controlled study the population would be limited to 252 patients. While a time limit (mid 1985) was set for the evaluation of the first year of life as well as the surgical studies, the follow-up would be extended to include up-to-date information in this dissertation.

No clinical study would be started before obtaining the approval of the medical-ethical commission of the University Hospital Rotterdam, Erasmus University School of Medicine.

Before any procedure was initiated, every effort would be made to explain this procedure to the boy and his parents in as great a detail as possible, so that informed consent could be obtained from the parents.

The children would always be examined by each one of us separately (to enable an unprejudiced opinion) following a standard diagnostic procedure (see 2.3.). The boys would always be confronted by these same two doctors only in order to create mutual trust, which would be beneficial to the proceedings.

Patient data would be recorded on specially designed standardized case report forms, in particular for the double-blind, placebo-controlled study. The first two pages were devoted to the medical history of the patient and his family, to be filled out at the boy's first visit to our outpatient clinic. The following pages served to record the findings at the first and subsequent physical examinations. The page designed for registration of the spontaneous and most caudal position of the testis was used for all patients in all the studies. For the surgical interventions, case notes would be recorded on separate, surgical report forms. Samples of all case report forms are included as an appendix to this chapter.

Grants from the Sophia Foundation for Medical Research (project no 40) and Hoechst Holland would ensure financial support for the studies. The hormonal preparation Cryptocur® would be supplied free of charge by the medical department of Hoechst Holland.

2.2. CLASSIFICATION OF CRYPTORCHIDISM

Identical methods of treatment for undescended testes, for example with LHRH nasal spray, appear to have strongly divergent results (Karpe et al., 1983; Hadziselimovic et al., 1984). This divergence in the results of treatment is mainly due to the fact that many studies fail to give a clear definition of normally descended or undescended testes. As a result, boys with retractile testes may sometimes be included in the treatment protocol (Karpe et al., 1983; Wit et al., 1985; Rajfer et al., 1986). Uniformity in classification and diagnosis of cryptorchidism is essential, but this can only be achieved if the various forms of cryptorchidism have been clearly defined. Reporting the results of his study, Schoorl (1982) stressed the importance of uniformity in classification and diagnosis for the following pertinent reasons:"*to facilitate a discussion of the identical topographical anatomy of the testis and because the treatment and prognosis will differ for each type of undescended testis. For the adult male, this prognosis will concern the ultimate location of the testis and the fertility*". It is a wellknown fact that the higher the position of the testis, the greater the extent of histological abnormality in this testis (Dougall et al., 1974; Nistal et al., 1985).

We drew up a system of classification and a procedure for physical examination of boys with undescended testes based on the following:

1. Clinical data resulting from our pilot study of the efficacy of LHRH nasal spray.
2. Data reported in the literature concerning studies carried out by others (Browne, 1938; Scorer and Farrington, 1971; Lipshultz, 1976; Wyllie, 1978, Schoorl, 1982; Wyllie, 1984).

2.2.1. Definition of cryptorchidism

The term "cryptorchid" comes from two Greek words, "cryptos" meaning hidden, and "orchis" meaning testis. In other words, cryptorchid means literally hidden, unperceivable testis. However, in the literature, and consequently also in this dissertation, the term is used in a general sense describing any nonscrotal testis that cannot be manipulated into a stable scrotal position. The word "cryptorchidism" can be used interchangeably with "undescended testis". In the light of normal testicular descent, the concept of testicular positions can be subdivided into:

a. scrotal testes;
b. retractile testes;
c. cryptorchid (undescended) testes, consisting of:
   - incompletely descended testes;
   - ectopic testes.

2.2.2. Definition and movability of the retractile testis

Retractile testes are testes that have a range of movement from the scrotum to the inguinal region. The testes are capable of normal descent, but due to an overactive cremasteric reflex they are more mobile than normally descended testes. The cremasteric reflex enables retraction from the scrotum over the bar of the pubic bone and into the superficial inguinal pouch, where the testis may reside for lengthy periods. In newborns, the cremasteric reflex is absent and at that stage the retractile testis can only be moved out of the scrotum by manipulation (Scorer, 1962; Farrington, 1968). After puberty, when the cremasteric reflex no longer exists, the testis only has a range of movement from the bottom to the entrance of the scrotum according to the contractility of the cremasteric muscle and more particularly from the dartos muscle (Browne, 1938).

2.2.3. Definition and movability of the incompletely descended testis

The incompletely descended testis has assumed a permanent position somewhere within the normal path of testicular descent and is either incapable of manipulation into the scrotum, or capable of being brought down into the scrotum with gentle pressure but incapable of remaining there of its own accord. Movability of the incompletely descended testis ranges from its position at rest to its most caudal position. The position at rest is the position assumed by the testis of its own accord when it is not being manipulated during clinical examination. The most caudal position is the closest the testis can be brought to the scrotum with gentle, never painful, pressure in a caudal direction. The movability of the incompletely descended testis is always limited, depending on the one hand on the extent to which gubernaculum and processus vaginalis reach the scrotum and on the other hand on the position of the testis at rest (Browne, 1938; Scorer, 1962).

2.2.4. Definition and movability of the ectopic testis

The ectopic testis is a testis that has assumed a position outside the normal path of testicular descent after having passed the inguinal canal. The differential diagnosis includes the extremely rare perineal, femoral, peno-scrotal or crossed-ectopic testicular position as well as the frequently found superficial inguinal, ectopic testicular position, which is also referred to as the "obstructed" testis as this testis seems to be affixed to the inguinal region (Scorer and Farrington, 1971). The movability of all ectopic testes is always limited in the direction of the scrotum, while their palpability is always good due to their subcutaneous position.

2.3. DIAGNOSIS OF CRYPTORCHIDISM

2.3.1. Incidence of cryptorchidism

According to several authors (Buemann et al., 1961; Villumsen and Zachau, 1966; Hirasing et al., 1982) the incidence of failure of testicular descent in the full-term neonate amounts to 2-3%, while the incidence in the pre-term infant approaches 30% (Scorer and Farrington, 1971). The smaller the size of the premature infant, the higher the incidence of cryptorchidism (Scorer, 1964). Those testes that will spontaneously descend postnatally will do so during the first year of life and by one year of age the incidence of cryptorchidism approximates 0.8% (Buemann et al., 1961; Scorer, 1964). The diagnosis of cryptorchidism can be difficult between the first year of life and puberty because the cremasteric reflex, which is almost absent in early infancy, may become very strong and a descended testis may retract completely out of the scrotum. Ward and Hunter (1960) found that approximately 6% of boys aged 5-11 years appeared to have undescended testes at scrupulous examination. At puberty, this figure dropped to less than 1% with the decrease in strength of the cremasteric reflex (Baumrucker, 1946; Cour-Palais, 1966; Villumsen and Zachau, 1966). None of these figures should be taken at face value as all studies were transversal, involving a diversity of study populations and divers examiners. Longitudinal investigation, such as the recent study of Van Gelderen and Vermeer (1986), may provide a better insight into the true prevalence of cryptorchidism.

2.3.2. Physical examination of the cryptorchid boy

It is essential to create a certain measure of trust between examiner and child before the examination actually takes place. Consequently, it would be wrong to have the child undress before the two have become acquainted. First of all, the boy has to be reassured. By explaining the purpose and procedure of the examination in a few well-chosen words to both parents and child, much of the anxiety that they undoubtedly feel can be removed. The room in which the examination takes place should be well heated, while the examination table should be placed full-length against the wall. Even though the examination mainly concerns the genital region, the general physical and mental condition of the child should be considered in order not to miss other associated anomalies that may prove significant in reaching the diagnosis of cryptorchidism.

The examination of the genital region should always begin with the boy in a supine position with at least the entire lower half of the body undressed. Both inguinal regions and the external genitals are subjected to a close inspection in an attempt to locate the spontaneous testicular position (figure 2.1.). Subsequently, the examiner places index finger and thumb of the right hand on the two sides of the inguinal canal so that it becomes impossible for testes lying distally from the

Figure 2.1. Spontaneous position of testes. Five year old boy with his left testis in a subcutaneous position outside the inguinal canal.

inguinal canal to withdraw to the inguinal region during careful palpation of the scrotum. With the examiner standing to the right of the patient, the inguinal region is then carefully palpated with the examiner's left hand. This palpation should be carried out with the fingertips and the hand should be warm. If a testis is not located in the scrotum, an attempt should be made to locate it in the inguinal region. If a palpable testis is located in the inguinal region, the movability of this testis is assessed, again with the tips of the finger only. As if they are playing a piano, the fingertips gently push the testis in the direction of the scrotum as far as it will go (figure 2.2.). Once the testis has reached its most caudal position, it is held there for a while using gentle traction in an attempt to relax the cremasteric muscle (figure 2.3.).

By supporting the testis with the fingertips of the right hand during this "piano playing", the examiner will have reached a fair estimate of the volume of the testis by the time it has reached its most caudal position. This estimated testicular volume can then be compared with the volume of the contralateral, normally descended testis. A more exact estimate of the volume of the testis can be

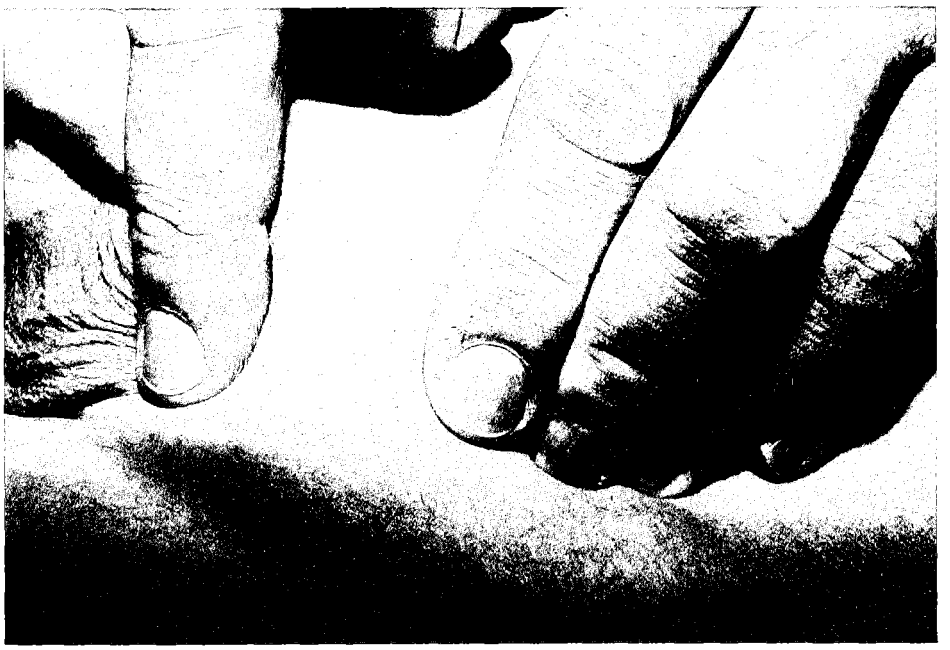


Figure 2.2. As if they are playing a piano, the fingertips gently push the testis into a direction of the scrotum as far as it will go.

Figure 2.3. Most caudal position of the testis. Same boy as in figure 2.2. Fingers hold testis outside the external annulus of the inguinal canal.

Figure 2.4. Most caudal position of the testis. Four year old boy with his left testis held in the scrotal entrance. Volume of the testis compared with an orchiometer after Prader.

reached using the so-called orchiometer after Prader (1966) (figure 2.4.). This method of measuring testicular volume was first described by Schönfeld (1943). It allows for assessment of testicular volume by comparative palpation; the testis is palpated with one hand, while models of known volume are palpated with the other hand. This technique is clinically easy to apply, while it is not invasive for the patient.

If the testis can be brought into the scrotum without immediately shooting back to the inguinal region, then this is obviously a retractile testis. The examination should never be painful (avoid funicular traction) and should be repeated several times in a row in order to exhaust the cremasteric reflex which may sometimes enable a scrotal position of the testis.

If there seems to be no palpable testis an attempt should be made to "empty" the inguinal canal by carrying out an ironing movement with the fingertips stroking in the direction of the scrotum. Sometimes this will briefly reveal a palpable testis at the level of the exit of the inguinal canal, which immediately shoots back deep into the inguinal canal. In this case estimating the volume of the testis will be sheer conjecture.

Subsequently, the entire examination should be repeated with the patient in a squatting position, or sitting cross-legged like a tailor. For stability the child

should sit with his back against the wall. Some boys will instinctively tighten the muscles of their abdomen and thighs in the supine position, which complicates and sometimes even prohibits any examination. For these boys in particular, the examination in a sitting position will proceed much more smoothly.

Retractile testes are frequently diagnosed as such at periodic physical examinations of prepuberal boys (e.g. by the school physician). However, retractile testes are not infrequently diagnosed as cryptorchid, possibly due to the examiner being unfamiliar with the proper method of examining a boy with undescended testes. The retractile testis can be distinguished from a truly undescended one in that it can be manipulated fully into a stable scrotal position at any time, while it may also descend spontaneously (figure 2.5.). The retractile testis is never found in front of the pubic bone because that is an unstable position.

If no testis can be located at all using every means described above, then the perineum, the base of the penis, and the thigh, should be closely investigated to locate or exclude an ectopic testis.

2.3.3. Registration of testicular position at physical examination

Registration of the testicular position found at physical examination is essential for making a definitive diagnosis. It will also enable comparison with the testicular position found at subsequent examination.

a. *Registration of spontaneous position of the testis*

- *testis palpable* - when the testis can be felt subcutaneously either in the inguinal region (incompletely descended testis or superficial inguinal ectopic testis) or elsewhere, e.g. in the perineum (ectopic testis), or in the scrotum;
- *testis impalpable* - when no testis can be felt. This does not necessarily mean that there is no testis, as the testis may well lie intra-abdominally or in the inguinal canal itself.

In the literature, there is a great deal of confusion concerning the palpability of testes lying in the inguinal canal. Various publications (Illig et al., 1977; Cacciari et al., 1982; Klidjian, 1985; Schwarz et al., 1985) create the impression that a testis lying in the inguinal canal is palpable. As early as 1938, Browne proved this to be a fallacy: *"A testis that is in the inguinal canal cannot be felt through the skin. It is a soft, elongated object, sunk in the soft floor of the canal, shielded from touch by the tense fascia of the external oblique muscle"*.

b. *Registration of most caudal position of the testis*

It is essential to find the most caudal position of the testis in order to determine the mobility of the cryptorchid testis, which is an important factor in the choice of

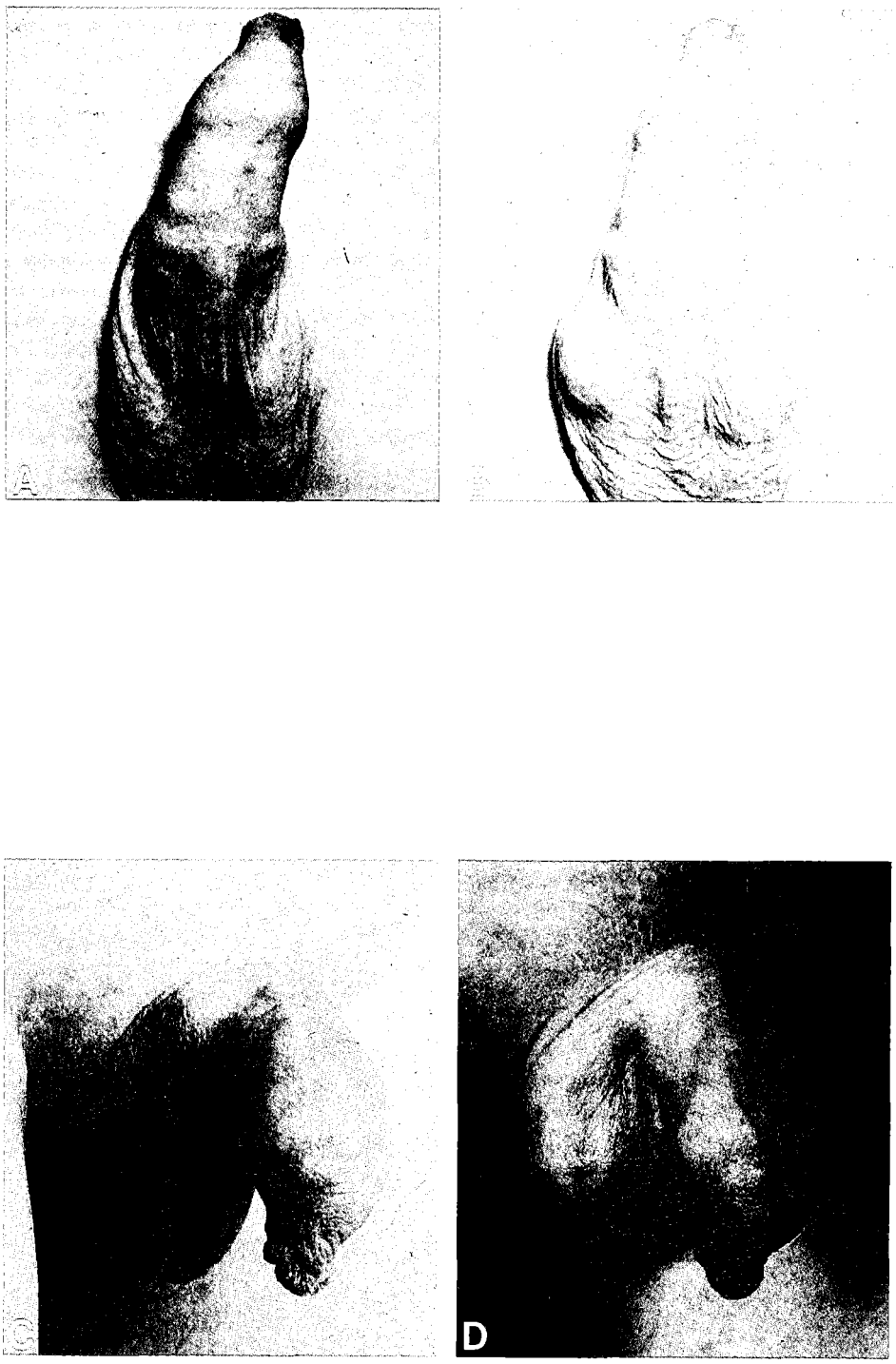


Figure 2.5. Retractile testis. a + b Boy in supine position. c + d Boy in standing position.

treatment (see chapter 4). The most caudal position of the testis should be registered as shown in figure 2.6., viz:

- *testis impalpable*. The testis may be altogether absent or may lie high in the inguinal canal or intra-abdominally;
- *testis intermittently palpable in inguinal region (emergent inguinal position)*. With gentle manipulation the testis may emerge fleetingly from the inguinal canal and become palpable for an instant, only to shoot back to its impalpable position;
- *testis palpable outside the external ring*. The testis seems to be lying on the pubic bone;
- *testis palpable in scrotal entrance*. At the scrotal entrance the thick elastic skin of the inguinal region changes abruptly to become the thin and corrugated scrotal skin. In this case the testis cannot be brought down to the scrotal entrance permanently, as this is not a stable position. When released, the testis immediately returns to the spontaneous position in the inguinal region just above the pubic bone;
- *testis palpable high or low in scrotum*. High in scrotum implies a testicular position beneath the scrotal entrance (under base of penis), while low in scrotum implies that the testis has reached the bottom of the scrotum. The difference between high or low scrotal position is not significant as far as exact location is concerned. It is much more important to determine whether the testis has reached a stable position and remains in the scrotum when released (retractile testis), or shoots back into the inguinal region immediately upon release (incompletely descended or ectopic testis).

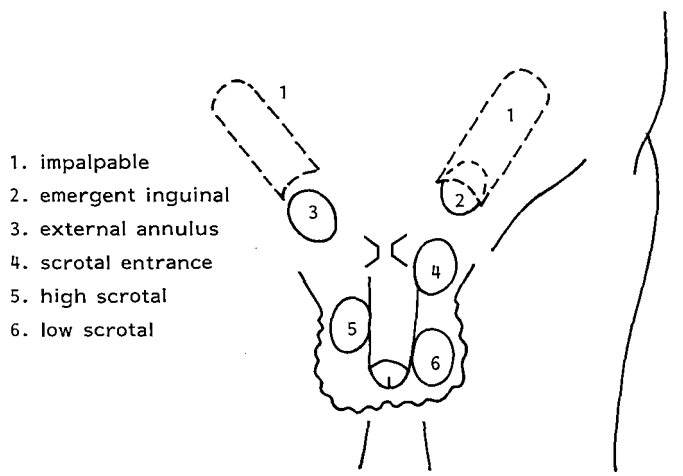


Figure 2.6. Clinical assessment of testicular position: most caudal position at clinical examination.

The relation between the spontaneous position of the testis and the most caudal (manipulated) one is shown schematically in figure 2.7. Clinically, the superficial inguinal, ectopic testis cannot always be distinguished from the testis lying outside the external inguinal ring (Ashby, 1978). Consequently, the clinical classification only mentions a testis in a subcutaneous position in the inguinal region.

Registration of the spontaneous and the most caudal position of the testis in the manner described above is obviously preferable to another method of registration, whereby the distance is measured between the upper rim of the symphysis and the centre of the testis in its most caudal, manipulated position (Hösli, 1971; Scorer and Farrington, 1971). As this measurement cannot easily be reproduced, the results of the registration are not dependable.

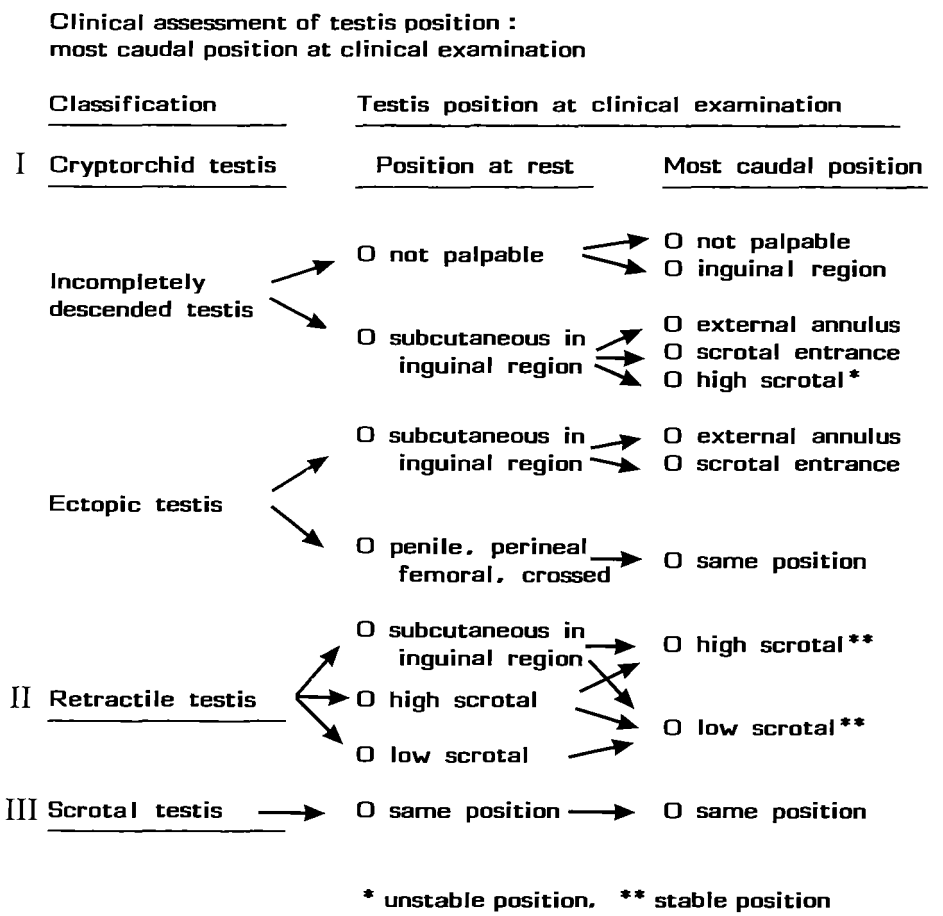


Figure 2.7. Clinical assessment of testicular position: spontaneous position in relation to most caudal position.

2.3.4. Clinical diagnosis

The final diagnosis is obviously important, not only as a basis for determining the choice of treatment, but also because it is an important factor in any subsequent evaluation of the method of treatment. The follow-up is necessarily of long duration, frequently outlasting the working life of the doctor who made the initial diagnosis. This is one of the reasons why so many fundamental questions concerning cryptorchidism remain unanswered.

A clear definition of the various forms of cryptorchidism, coupled with a properly executed physical examination and a standardized method of registration of the testicular position, will generally furnish the correct clinical diagnosis of retractile, incompletely descended or ectopic testes. If the examiner is not familiar with this kind of physical examination, or if there is uncertainty about the correct diagnosis (which may even happen to experienced examiners), the examination should be repeated at least once. All too frequently retractile testes are diagnosed as incompletely descended testes because the examination was carried out with the boy standing up, or in a superficial manner (Browne, 1938; Cour-Palais, 1966). Retractile testes generally do not require treatment, only regular checkups (see 6.2.), while for true, though rare, ectopic testes, surgical intervention is the only correct means of treatment.

2.4. METHODS OF HORMONAL EVALUATION

Androstenedione[2]) (Δ 4) was measured by radio-immunoassay (RIA) after extraction with hexane-toluene 8:2 (v/v) without chromatography. The RIA was performed as described by Van Landeghem et al. (1981). Intra- and interassay coefficients of variation were 6.7% and 11% respectively. Detection limit of the assay: 0.35 nmol/l.

Dehydroepiandrosterone sulfate[1]) (DHEAS) was measured by radio-immunoassay using kits from Radioassay Systems Laboratories (California). The antibody used in the RIA was raised in rabbits against DHEA-S-3 monohemisuccinate-HSA. Intra- and interassay coefficients of variation were 9% and 15% respectively. Detection limit of the assay: 0.02 μmol/l.

Dihydrotestosterone[2]) (DHT) was measured by radio-immunoassay after extraction with Extrelut columns (Merck). The extract was purified by means of high pressure liquid chromatography (HPLC), using a Waters HPLC apparatus with a Merck Lichrosorb column (5μ; Si 60). Hexane-isopropanol 92:8 v/v was used as an eluent (0.8 ml/min). DHT was estimated using an antiserum of Radioassay Systems Laboratories. Intra- and interassay coefficients of variation were 9% and 22% respectively. Detection limit of the assay: 0.13 nmol/l.

17 α-hydroxypregnenolone[2]) (17 OHPreg) was measured by radio-immunoassay after extraction and purification with Extrelut columns (Merck). The RIA

was performed using a commercial kit (Radioassay Systems Laboratories). The intra-assay coefficient of variation was 14%, the interassay coefficient of variation could not be calculated. Detection limit of the assay: 0.9 nmol/l.

17 α -hydroxyprogesterone[2]) (17 OHP) was measured by radio-immunoassay after extraction with Extrelut columns (Merck). The RIA was performed using a commercial kit from Institut National des Radioelements (IRE). Intra- and interassay coefficients of variation were 12% and 18% respectively. Detection limit of the assay: 1.2 nmol/l.

Luteinizing hormone[1]) (LH) and *Follicle-stimulating hormone*[1]) (FSH) were determined by radio-immunoassay, using kits from Byk-Mallinckrodt. The standards employed in these kits have been calibrated for LH versus the Medical Research Council (MRC) standard 68/40 and for FSH versus the MRC standard 69/104, both expressed in IU/l. Intra- and interassay coefficients of variation for LH were less than 4% and 9% and for FSH less than 3% and 12% respectively. Detection limit for LH and FSH: 0.6 IU/l.

Oestradiol[3]) (E2) was measured by radio-immunoassay using kits from Eidgenössisches Institut für Reaktorforschung (EIR), Wurelingen, Switzerland. Intra- and interassay coefficients of variation were 8.2% and 18.5% respectively. Detection limit of the assay: 10 pmol/l.

Progesterone[4]) (P) was measured by radio-immunoassay using a kit from Farinos Ltd. (Finland) with a slight modification. Intra- and interassay coefficients of variation were 5% and 11% respectively. Detection limit of the assay: 0.5 nmol/l.

Sex-hormone-binding globulin[3]) (SHBG) was measured as described by Hammond and Lähteenmäki (1983). Intra- and interassay coefficients of variation were 10.3% and 14.6% respectively. Detection limit of the assay: 10 nmol/l.

Testosterone[4]) (T) was determined by radio-immunoassay following extraction by n-hexane-diethylether without chromatography. The antibody used in the RIA was raised against testosterone-*7 α* -carboxyethylthioether bovine serum after Pratt et al. (1975). Intra- and interassay coefficients of variation were 11% and 22% respectively. Detection limit of the assay: 0.02 nmol/l.

HCG test: basal and peak serum testosterone values were determined before and three days after the intramuscular administration of 1.500 IU HCG.

LHRH test: basal and peak serum values of LH and FSH were determined before, 30 and 60 minutes after intravenous administration of 50 μg LHRH.

The hormonal analyses were carried out by:

[1] Department of Clinical Chemistry, University Hospital Rotterdam/Sophia Children's Hospital (Head Ir. N.C. den Boer).

[2] Paediatric Laboratory, University Hospital Rotterdam/Sophia Children's Hospital (Head Prof. Dr. H.J. Degenhart).

[3] Steroid Hormone Laboratory of Internal Medicine III, University Hospital Rotterdam/-Dijkzigt Hospital (Head Dr. F. de Jong).

[4] Laboratory for Endocrinological Chemistry, Bergweg Hospital Rotterdam (Heads Dr. W. Schopman and Dr. W.H.L. Hackeng).

2.5. METHODS OF STATISTICAL ANALYSIS

For the statistical analyses we were advised and assisted by the Institute of Biostatistics of the Erasmus University Rotterdam (Head Prof. R. van Strik). To avoid any unjustifiable assumption regarding Gaussian distribution, the following non-parametric tests were generally applied.

- *Mann-Whitney-U test* (Wilcoxon) for comparison of two independent groups (Sachs, 1984: 230).
- *Wilcoxon matched pairs signed rank test* for comparison of two dependent groups (Sachs, 1984: 244).
- *Kruskal-Wallis test* (H-test) for comparison of three or more independent groups (Sachs, 1984: 238).
- *Friedman test* for comparison of three or more dependent groups (Sachs, 1984: 422).
- *Sign test* for comparison of medians in two groups (Sachs 1984: 247).
- *Spearman's rank correlation test* for judging the correlations between two variables measured in the same individuals (Sachs, 1984: 308).
- *Chi-square test* (2 x 2 contingency table) for comparison of two proportions (Sachs, 1984: 269).
- *Logistic regression analysis* for multivariate analysis of the dependency of success rates on several study factors simultaneously (Cox, 1970).

APPENDIX

CASE REPORT FORM

PATIENT HISTORY

Patient number :

Date of birth :

Birth weight :

ANAMNESIS	yes	no	unknown
Testis seen or felt in the scrotum ? (by patient, parent or physician)	☐	☐	☐
Period of pain or redness of the scrotum ?	☐	☐	☐
Surgical intervention in the inquinal area ? (e.g.inquinal hernia, hydrocele)	☐	☐	☐
Infection of the urinary tract ? If so, specify.	☐	☐	☐
Previous hormonal treatment ? If so,specify.	☐	☐	☐
Does patient take drugs ? If so,specify.	☐	☐	☐
Has patient had mumps ?	☐	☐	☐

CASE REPORT FORM

FAMILY HISTORY

	yes	no	unknown
MOTHER — duration of pregnancy			
— did the mother use any medication during pregnancy ? If so, specify.	☐	☐	☐
— did the mother use oral contraceptives before pregnancy ? If so, for how long ?	☐	☐	☐
— did the mother use any medication to induce pregnancy ?	☐	☐	☐
FAMILY — has cryptorchidism ever occurred in the family ? If so, specify.	☐	☐	☐

CASE REPORT FORM

Patient number :
Date of birth :

INVESTIGATION AT THE START

Date :		yes	no
-General impression	normal	☐	☐
	dysmorphisms	☐	☐
explanation :			
-Scrotum	empty	☐	☐
	normal	☐	☐
	tight	☐	☐
-Penis	normal form	☐	☐
	normal size	☐	☐
	hypospadias	☐	☐
-Inquinal area, scars		☐	☐
-Testicular volume	L R		

INVESTIGATION AFTER 4 WEEKS TREATMENT

Date :			
-Scrotum	empty	☐	☐
	normal	☐	☐
	tight	☐	☐
-Penis	normal form	☐	☐
	normal size	☐	☐
-Testicular volume	L R		

CASE REPORT FORM

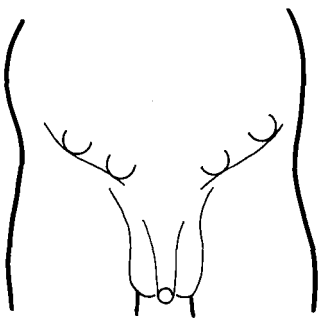
Patient number :

Date of birth :

TESTICULAR POSITION AT START OF THE TREATMENT

Date of visit :

R



L

	R	L	
Position of testis : At rest	☐	☐	Not palpable
	☐	☐	Palpable in inguinal region
	☐	☐	Intrascrotal
Movability of the testis : Most caudal testicular position	☐	☐	Not palpable
	☐	☐	Inguinal region, intermittently palpable
	☐	☐	External annulus
	☐	☐	Scrotal entrance
	☐	☐	High Scrotal
	☐	☐	Scrotal

Remarks :

Surgical findings

Name:
Date of birth:
Date of operation:
Patient number:

Testis : R L both

No testis	anorchia		O	1
"vanishing testis"	funicular remnant		O	2
testis position	intra-abdominal		O	3
	inguinal canal		O	4
	external annulus		O	5
	superficial inguinal ectopia		O	6
Processus vaginalis	processus vaginalis	wide open	O	7
		slightly open	O	8
		closed	O	9
Vas deferens and epididymis	normal vas		O	10
	blind ending vas		O	11
	no vas		O	12
	normal epididymis		O	13
	no epididymis		O	14
	partial separation		O	15
	complete separation		O	16
	"long loop" vas and epididymis		O	17
	atresia vas or epididymis		O	18
	special remarks in surgical report		O	19
Testis	volume	< 1 ml	O	20
		1 ml	O	21
		1 - 2 ml	O	22
		2 ml	O	23
		2 - 3 ml	O	24
		3 ml	O	25
Gubernacular remnant	identifiable	yes	O	26
		no	O	27
Procedure and result	orchidectomy		O	28
	excision funicular remnant		O	29
	orchiopexy	low scrotal	O	30
		high scrotal	O	31
		outside inguinal canal	O	32
	Fowler-Stephens procedure		O	33
	microvascular transplantation		O	34
	special remarks in surgical report		O	35

Remarks

CLINICAL STUDIES A

CHAPTERS 3 AND 4

S.M.P.F. de Muinck Keizer-Schrama

CHAPTER 3

HORMONAL ASPECTS OF CRYPTORCHIDISM

Recent clinical and experimental studies reported in the literature seem to indicate that a (transient) functional insufficiency of the hypothalamo-pituitary-gonadal axis is an important factor in the pathogenesis of cryptorchidism. This insufficiency, found in cryptorchid boys in the first year of life, argues for hormonal treatment of cryptorchidism. Therefore it is important to trace hormonal development from the embryonic phase through the first year of life and up till puberty.

3.1. HORMONAL INFLUENCES ON MALE GENITAL DIFFERENTIATION

The fundamental mechanism of sexual differentiation was clarified by Alfred Jost between 1947 and 1952. In his classical experiments with fetal rabbits, he established that the castrated mammalian embryo develops into a female. Although local androgen implants successfully replaced most of the masculinizing influences of the fetal testis, these could not bring about regression of the Müllerian duct (Jost, 1970; 1972). The studies of Jost demonstrated that male phenotypic sexual differentiation results from two kinds of secretions from the fetal testis, namely steroidal androgens and a non-steroidal inhibitor of Müllerian duct development.

3.1.1. Testosterone and dihydrotestosterone

As early as the sixth week of human embryonic development (CR length 14 mm) evidence for steroid metabolism was found in the genital ridge (Baillie et al., 1966). From studies of human fetuses varying in age from the phenotypically undifferentiated stage (CR length 1-3 cm) to sexually differentiated male and female embryos (CR length $>$ 21 cm) it was concluded that testosterone is the principle androgen formed by the human testis at the time of male sexual differentiation (Siiteri and Wilson, 1974). From the same studies it appeared that in the urogenital sinus and genital tubercle the capacity for dihydrotestosterone formation was maximal prior to the onset of male differentiation. In contrast, in the Wolffian ducts the ability to form dihydrotestosterone could only be demonstrated late in male differentiation. It was concluded that testosterone itself is responsible for the differentiation of epididymis, vas deferens and seminal

vesicles while dihydrotestosterone is required for differentiation of prostate, phallus and scrotum. This opinion was shared by others (Bardin and Paulsen, 1981). Another group (Reyes et al., 1973) suggested higher androgen production at the time of male genital differentiation. Peak concentrations of serum testosterone occur at 14 to 16 weeks of gestation, comparable to those of the adult male (Winter, 1982). At the gestational age of 16-20 weeks there is a drop in the testosterone concentration in the male fetus although it remains significantly higher than in the female fetus. After 24 weeks gestation, the serum testosterone levels are low and no sex-related difference is discernable. At term, however, the concentration of testosterone in cord blood appeared significantly higher in male than in female fetuses (Forest and Cathiard, 1975). Dihydrotestosterone levels in plasma are low in the human fetus throughout gestation (Kaplan and Grumbach, 1978).

What controls the androgen production in the fetal testis? Initiation of testosterone production by the fetal testis might be independent of tropic hormone stimulation. Evidence for that was supplied by in vitro studies of fetal rat testes done by Picon (1976). Likewise, Siiteri and Wilson (1974) surmised that the initiation of male sexual differentiation by the fetal testis is not controlled by tropic hormones. The subsequent rise and maintenance of testosterone production would, however, be due to gonadotropin stimulation.

3.1.2. Pituitary and placental gonadotropins

Luteinizing hormone (LH), follicle-stimulating hormone (FSH) and human chorionic gonadotropin (HCG) are glycoprotein hormones. They are composed of two subunits: α and β. The α subunit of each of the glycoproteins is similar in structure and indistinguishable immunologically, while the biological and immunological specificity of the intact hormone appears to be dependent on the β subunit. LH is virtually identical to HCG except for an additional 30 amino acids on the carboxyl terminal end of the β chain of HCG. The similarity in structure of LH and HCG undoubtedly accounts for the fact that they both stimulate testosterone synthesis and secretion by Leydig cells. LH and FSH are produced in the basophil cells of the pars distalis of the pituitary gland. The presence of gonadotropins in the fetal pituitary gland was demonstrated by bio-assay, immunocytochemical studies, radio-immunoassay and organ cultures (for review see Gluckman et al., 1980). From several studies it appeared that in the male fetus LH and FSH has been detected in the pituitary gland as early as the tenth gestational week. The LH content of the pituitary gland rises sharply between the 10th and the 27th gestational week with little subsequent change. The peak concentration of LH in the pituitary gland is achieved between 20 and 24 weeks of gestation. There is also a striking rise in FSH content in the pituitary gland between the 10th and the 25th week, remaining constant thereafter. The peak concentration of FSH in the pituitary gland occurs between 20 and 24 weeks. During the late gestational

period there is a decrease in pituitary concentration of both LH and FSH. Plasma LH was measured by radio-immunoassay and demonstrable by 12 weeks of gestation (Kaplan et al., 1976). Higher concentrations were found in midgestation with lower levels towards term. Plasma FSH has been detected by radio-immunoassay in fetal plasma by the 10th to 11th gestational week (Clements et al., 1976), with peak levels in midgestation and a fall to low concentration towards term. In cord blood LH and FSH levels are low (Reyes et al., 1974; Kaplan and Grumbach, 1978). Thus, in the male fetus the pattern of plasma concentration of LH and FSH is similar to the changing pituitary concentration of LH and FSH with advancing gestation (Gluckman et al., 1980).

Human chorionic gonadotropin (HCG) is synthesized by the syncytiotrophoblast of the placenta and is detected in maternal circulation at seven to ten days of gestation. Peak levels of HCG in fetal and maternal serum coincide in time (9-12 weeks of gestation) but the peak level is much higher in maternal than in fetal serum (Kaplan and Grumbach, 1978). The maximum rise in fetal serum HCG immediately precedes the increased synthesis and secretion of testosterone by the fetal testis at 10-12 weeks of gestation. After 12 weeks of gestation the HCG level declines. The factors that mediate the altered synthesis and secretion of HCG remain unknown, but in any case these factors are not under hypothalamic control (Kaplan et al., 1976). It appears that fetal Leydig cells acquire functional receptors for LH and HCG early in development (Josso, 1979). Figure 3.1. shows

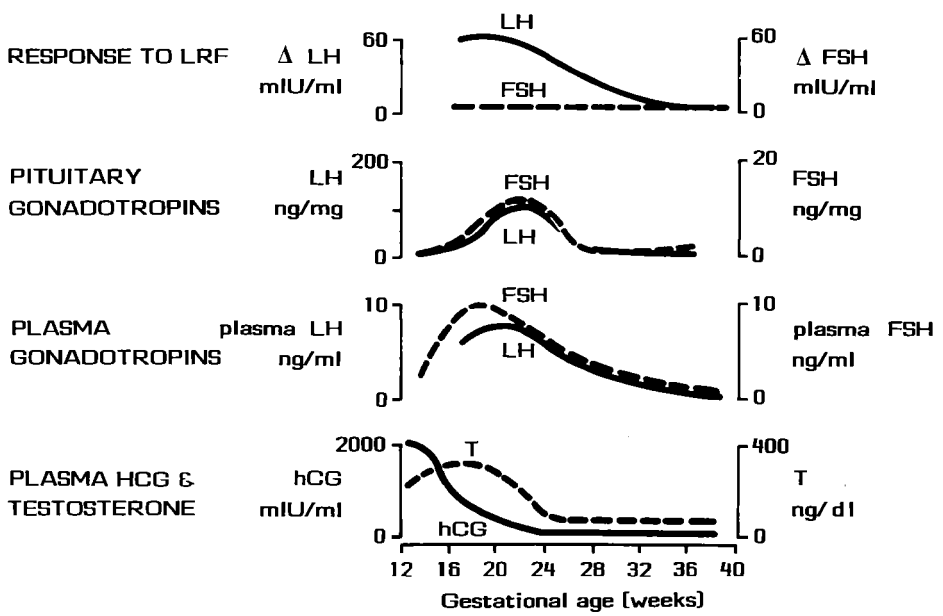


Figure 3.1. A graphic comparison of the hormonal response to luteinizing-hormone-releasing factor (Takagi et al., 1977), pituitary and plasma FSH and LH (Kaplan and Grumbach, 1976), plasma HCG (Kaplan and Grumbach, 1976) and plasma testosterone (Reyes et al., 1974) during gestation (modified from Gluckman et al., 1980).

the temporal relationships between the concentrations of fetal serum testosterone, LH and HCG, suggesting that HCG plays an important role in early testosterone secretion which then appears to be augmented and later sustained by *pituitary LH* (Kaplan et al., 1976). Thus the pituitary LH levels rise between 12-20 weeks of gestation (Clements et al, 1976) and may be instrumental in promoting androgen secretion in later stages of pregnancy during the androgen-dependent growth of the genital tubercle. This view is supported by the fact that congenital hypopituitarism is often associated with micropenis. Anencephalic and apituitary fetuses usually have hypoplastic and undescended testes. Consequently, Grumbach and Kaplan (1974) stated that it would seem that fetal serum HCG evokes sufficient testosterone secretion by the fetal testis to induce male sex differentiation. However, owing to deficient secretion of pituitary LH and FSH in these male fetuses, the growth of the testes and external genitalia is impaired.

3.1.3. The hypothalamic control of fetal LH and FSH secretion

The human fetal pituitary gland has the capacity to respond to luteinizing-hormone-releasing hormone (LHRH), also called gonadotropin-releasing hormone (GnRH) or luteinizing-hormone-releasing factor (LRF). LHRH is a decapeptide with the sequence, p Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Glu-NH_2. The hormone has both luteinizing-hormone-releasing factor and follicle-stimulating-hormone releasing factor activity. The isolation and determination of the chemical structure of LHRH was accomplished in the early seventies (Schally et al., 1971). From the classic observations of Knobil and associates in the rhesus monkey it appeared that the arcuate nucleus is the primary structure within the medial basal hypothalamus mediating the hypothalamic control of gonadotropin secretion: "the hypothalamic oscillator" (Knobil, 1980). GnRH secretion may be controlled directly or indirectly by catecholamine, endorphin-containing and dopa fibres, arising from many parts of the central nervous system (CNS) (Bardin and Paulsen, 1981). It has been suggested that there might be a separate follicle-stimulating-releasing hormone (for review see Sharp and Fraser, 1978). However, isolation of this factor has not yet been accomplished. LHRH is transported via the pituitary portal system to the hypophysis. The studies of Kaplan and Grumbach (1976) and those of Winter et al. (1974) have established the presence of immunoreactive GnRH in the human fetal hypothalamus early in gestation from 4-5 weeks after conception. This is long before the continuity of the primary and secondary plexus of the portal system is completed (by week 19 to week 21, Kaplan et al., 1976). The early influence of LHRH on gonadotropin secretion occurs either by diffusion or via the more primitive mantle plexus of the developing portal system. LHRH is found almost exclusively in the hypothalamus (Winter, 1982). An absence of significant correlation between the concentration of LHRH in the hypothalamus and sex or gestational age was reported by some workers (Kaplan et al., 1976; Aubert et al., 1977; Gilmore et al., 1978), whereas others found an increase of the

LHRH content during gestation (Siler-Khodr and Khodr, 1978; Clements et al., 1980). The following ontogenesis of the hypothalamo-pituitary-gonadal system was proposed for the fetal period (Reiter and Grumbach, 1982):

- the hypothalamo arcuate GnRH neurosecretory neurons (so-called "pulse generator") are operative by 80 days gestation;
- episodic secretion of LH and FSH by 80 days gestation;
- initially unrestrained secretion of GnRH until midgestation;
- maturation of negative sex steroid feedback mechanisms after 150 days gestation;
- low levels of GnRH secretion at term.

The primary role of sex steroids in the restraint of GnRH secretion ("negative feedback system") has been questioned. Experimental and clinical studies (Knobil, 1980; Conte et al., 1980) support the hypothesis that the central nervous system rather than the pituitary or the gonads restrains the activation of the hypothalamo-pituitary-gonadal system. This inhibition appears to be mediated through the suppression of GnRH synthesis and its pulsatile secretion.

3.1.4. Anti-Müllerian hormone

The production of anti-Müllerian hormone (AMH) or Müllerian inhibiting substance (MIS) by the fetal testis begins shortly before differentiation of the Leydig cells coinciding with the development of the seminiferous tubules, before 30 mm CR length. Josso and coworkers (1977) observed anti-Müllerian activity in a 20 mm fetus; it declined in late gestation and appeared to be very low at birth. With experimental procedures such as testicular microdissection, irradiation and cell cultures, she also demonstrated that the anti-Müllerian activity was limited to the seminiferous tubules and most probably the Sertoli cells. Although the biological significance of AMH has been recognized for a long time, biochemical analysis and purification of the hormone is still in progress. More recently, Picard and Josso (1984) described an improved method for purification of anti-Müllerian hormone. The regulation of AMH production by the testis is largely unknown (Josso, 1979). Experiments in rats gave evidence of depression of testicular anti-Müllerian activity, probably by FSH (Bercu et al., 1981).

3.2. HORMONAL INFLUENCES ON TESTICULAR DESCENT

Although the morphological process of testicular descent is a controversal issue in itself, there is even less agreement regarding the regulatory mechanisms. In animal experiments many authors have tried to answer the following questions:

- are there hormonal influences on testicular descent?
- if so, which hormones influence testicular descent?

Not having evaluated this ourselves, we can only summarize some of the extensive literature available on this subject.

3.2.1. Animal studies

The first reports of hormonal influences on testicular descent were from Engle (1932), who caused descent of the testis in immature Macacus monkeys by injecting extracts of pregnancy urine and water-soluble extracts of the anterior pituitary gland. Hamilton (1938) suggested that descent, produced by anterior pituitary-like substance, may be partially due to stimulation of the secretion of male hormone substances. He treated Macacus rhesus monkeys with injections of testosterone acetate and testosterone propionate and concluded that male hormone substance is actually responsible for growth processes of the reproductive system which result in descent of the testes. Subsequently, other animal experiments provided direct or indirect evidence of androgen dependence of testicular descent. Greene et al. (1939) achieved caudal displacement of the gonads in female fetuses by administering high doses of androgens to pregnant rats. From other experiments with rats it appeared that dihydrotestosterone was particularly responsible for testicular descent and that DHT production is influenced by gonadotropins (Rajfer and Walsh, 1977). In the rat gubernaculum, morphological alterations could be induced by DHT administration (Elder et al., 1982). Indirect evidence of androgen dependence came from experiments with the anti-androgen cyproteronacetate (Neumann and Kramer, 1964). Several experiments involved the administration of oestrogens to developing male animals in utero: inhibition of testicular descent or cessation of gubernacular development was achieved (Raynaud, 1958; Backhouse, 1965; Hadziselimovic et al., 1980[a]). However, other experimental results attenuate or even contradict this androgen dependence of testicular descent (Elger et al., 1977; Radhakrishnan et al., 1979). Remarkable in this respect are the observations of Wensing and Colenbrander (1977), who questioned the influence of androgens on testicular descent based on their investigations in pigs. In female pigs they could not initiate a gubernacular reaction by androgen administration, nor could they prevent a gubernacular reaction in male pigs by the administration of anti-androgens. They even found a pronounced and prolonged gubernacular reaction in a pig with the androgen insensitivity syndrome. They observed normal gubernacular development and testicular descent in fetal pigs decapitated seven weeks after conception (Colenbrander et al., 1978). Their conclusion was that testicular descent seems to be independent of gonadotropic stimulation, while it is not androgen-dependent but gonad-dependent (factor X ?). Moreover, administration of HCG or LHRH to naturally unilateral cryptorchid, prepuberal pigs could not induce either testicular descent or gubernacular development (Colenbrander et al., 1978).

Habenicht and Neumann (1983) carried out an extensive study in Wistar rats,

fetuses as well as adult animals, whose mothers had been treated with oestrogen or cyproteronacetate or a combination of both. They hoped to gain fresh knowledge about the regulatory mechanisms of testicular descent. They concluded that the regulatory mechanism of this process cannot be elucidated simply on the basis of androgen dependence or AMH dependence. They suggested that AMH is primarily responsible for differentiation of the gonads while androgens, either additionally or alone, are required for the final phase of descent. They added that the latter premise is supported by the fact that the further the testes have descended, the more likely the treatment of cryptorchidism with HCG or LHRH is to succeed. Hutson (1985; 1986) recently supported this theory of a biphasic hormonal control of testicular descent. He investigated the position of the testes in patients and mice with the androgen insensitivity syndrome (testicular feminization, TFM). He found the testes of the patients with androgen insensitivity syndrome located at or beyond the internal inguinal ring. The testes of the male mice with TFM had also descended to the internal ring by the time of birth. He hypothesized that the first phase of descent (the transabdominal part) is not controlled by androgens but may be regulated by Müllerian inhibiting substance, whereas the second phase (the transinguinal descent) may be androgen-dependent.

3.2.2. Observations in humans

The hormonal influences on testicular descent in man are as unclear as in animal studies. Several investigators suggested that in man the normal function of the hypothalamo-pituitary-gonadal axis is a prerogative for normal testicular descent. They hypothesized that a transient, functional impairment of this axis is at least a contributory factor to cryptorchidism (Canlorbe et al., 1974; Gendrel et al., 1977; Job et al., 1977[b]). Hamilton (1938) was the first to show that testosterone was probably the active hormone, when he successfully induced descent in cryptorchid children with synthetic male hormone substance (see 4.1.). Well-documented genetic disorders with abnormalities in gonadotropin production (Kallmann syndrome), androgen secretion (5 α-reductase deficiency) or defects in androgen action (androgen insensitivity syndrome) are frequently associated with cryptorchidism (see 3.3.). The more or less successful treatment of cryptorchid boys with gonadotropins or LHRH is used as an argument for gonadotropin and/or androgen dependence. However, the hormonal treatment of undescended testes is not based on a full understanding of the regulatory mechanisms of descent. Donahoe and associates (1977) speculated that next to Müllerian duct regression in the male embryo, MIS may influence testicular descent. They found that, up till the age of two years, MIS activity was lower in boys with undescended testes than in boys with normal testicular descent. Josso and coworkers (1983) suggested that the decrease of AMH activity in ectopic testes might be the consequence rather than the cause of their abnormal position. However, Josso

had previously questioned the role of androgens as the major factor in testicular descent, postulating that AMH might play a role in testicular descent (Josso, 1979).

Hutson supported the model of a biphasic hormonal control of testicular descent, whereby in his opinion AMH might play an important role in the first phase of descent while androgens might be the major hormones in the transinguinal phase (Hutson, 1985; 1986; Hutson and Donahoe, 1986).

In summary

There is ample evidence of hormonal influence on testicular descent. The low levels of circulating androgens in the fetus during the last weeks of gestation seem tot argue against the option of androgen dependence of the transinguinal phase of testicular descent. However, a small amount of hormone may well be sufficient.

3.3. HORMONAL FAILURE AS CAUSATIVE FACTOR IN TESTICULAR NONDESCENT

As we do not know exactly which hormones contribute to testicular descent, it is not surprising that it has not yet been established to what extent hormonal failure is the cause of testicular nondescent. Which hormones fail to play their part?

3.3.1. Defects in gonadotropin/androgen secretion or action?

Cryptorchidism is frequently found in patients with abnormalities of the hypothalamo-pituitary-gonadal axis. For example, *Kallmann's syndrome,* hypogonadotropic hypogonadism secondary to deficient LHRH secretion and combined with anosmia was first described by Kallmann (Kallmann et al., 1944). Patients with anencephaly and gross hypothalamic abnormalities also have a high rate of undescended testes.

Job and associates found a (transient) functional impairment of the hypothalamo-pituitary-gonadal axis in criptorchid boys from birth till puberty after which the condition becomes rectified (for review see Gendrel et al., 1979).

Hadziselimovic and coworkers found atrophic Leydig cells in human undescended testes in the first year of life, which in their opinion points to gonadotropin deficiency as the cause of cryptorchidism (Hadziselimovic and Herzog, 1977).

In boys with a deficiency of androgen secretion or defects in androgen action, cryptorchidism is associated with ambiguous genitalia. Table 3.1. lists six enzymatic defects that result in decreased androgen synthesis. Each of these six defects is an autosomal recessive trait and affects genitalia to a varying degree depending on the completeness of the defect. The degree of phenotypic abnormality varies from nearly normal males with hypospadias to nearly normal females. The range

of abnormalities is dealt with extensively in various textbooks and review articles (e.g. Odell and Swerdloff, 1978; Forest, 1981; Saenger, 1984).

Patients with 5 α-reductase deficiency have previously been classified under defective androgen action but since the aetiology has become known they have been included under enzymatic defects. 5 α-reductase is the enzyme responsible for intracellular conversion of testosterone to dihydrotestosterone. This conversion is an essential step in androgen action for tissues derived from the genital tubercle. At birth, patients with this deficiency present with ambiguous genitalia (see 5.4.3.d.). Sometimes they are being taken for females, although they have no female internal genitalia. The testes lie intra-abdominally or in the inguinal canal. Since testosterone itself is required to mediate Wolffian duct differentiation into epididymis, vas deferens and seminal vesicles, these tissues are normal. Similarly, testosterone appears to be able to act directly on hair follicles, muscle, larynx and bone. Farrer et al. (1985) identified a definite defect in androgen biosynthesis in the cryptorchid testis in mice, resulting in a diminution of the intratesticular testosterone contents. They surmised that cryptorchidism exerts a deleterious effect on the ability of the Leydig cell to synthesize testosterone, which might explain to a certain extent the abnormal morphology and resultant infertility seen in boys with cryptorchidism. In disorders of androgen action such as complete and incomplete androgen insensitivity syndromes, cryptorchidism is very common (Rajfer and Walsh, 1977).

Table 3.1. Six enzymatic defects resulting in decreased androgen synthesis.

20, 22-desmolase deficiency
3 β -hydroxysteroid dehydrogenase deficiency
17 α -hydroxylase deficiency
17, 20-desmolase deficiency
17-keto reductase deficiency
5 α -reductase deficiency

3.3.2. Deficiency in production or action of AMH or another, unidentified gonadal factor (factor X)?

As described above (see 3.2.) animal studies and observations in humans have revealed that MIS (or factor X) may play a role in testicular descent at least in its initial stages (Donahoe et al., 1977; Colenbrander et al., 1978; Habenicht and Neumann, 1983; Hutson, 1985; Hutson and Donahoe, 1986). In the rare persistent Müllerian duct syndrome (Josso et al., 1983; Beheshti et al., 1984; Van Lanschot et al., 1985), phenotypic males have a uterus, fallopian tubes and cryptorchidism.

The testes occupy the position of normal ovaries, which is consistent with the hypothesis that a deficiency of MIS prevents transabdominal descent (Hutson, 1985).

3.3.3. A combination of both deficiencies?

A biphasic hormonal control of testicular descent was suggested by Habenicht and Neumann (1983) and more recently by Hutson (1985; 1986; Hutson and Donahoe, 1986). It may therefore be possible that a deficiency of both hormones plays a part in the failure of testicular descent.

In summary

There are indications that incomplete testicular descent might be due to a hormonal deficiency, but it remains unclear which hormones fail to play their part. The question remains whether such a deficiency can be detected postnatally and, if so, whether a rational therapy is feasible.

3.3.4. Associated genetic and dysmorphic syndromes

Several chromosomal and non-chromosomal syndromes are associated with cryptorchidism. In most syndromes with abnormal sex chromosomes and in many syndromes with abnormal autosomes the structure of the testis is also abnormal. Primary gonadal anomalies are probably the major cause of cryptorchidism in the syndromes (for review see Odell and Swerdloff, 1978; Visser, 1982). Mininberg and Bingol (1973) found chromosomal abnormalities in cryptorchid testes in boys with normal karyotypes. They felt that these chromosomal abnormalities had caused the failure to descend in the process of inhibiting a normal hormonal and histological testicular development. Their findings were not confirmed by others (Dewald et al., 1977).

It must be emphasized that as early as 1762, Hunter wrote that the reason for its undescent lay in the testis itself. Much later, Johnston (1965) surmised that with the great majority of the undescended testes the descensive stimulus must be regarded as normal but that the testis fails to descend completely either because of an intrinsic fault that prevents its response or because of some anatomical hindrance to its movement (see 5.1.).

3.4. MALE HORMONAL DEVELOPMENT UP TILL PUBERTY

3.4.1. Introduction

The hypothalamo-pituitary-gonadal system differentiates during fetal life and early infancy, declining to a low level of activity during childhood, to be re-activated during puberty (Kaplan et al., 1976; Grumbach, 1980). According to

Reiter and Grumbach (1982) the regulatory systems that control human male and female reproduction comprise the following fundamental components:

- the arcuate nucleus of the medial basal hypothalamus and its transducer neurosecretory neurons. These translate neural signals into a periodic, oscillatory chemical signal, the gonadotropin-releasing hormone. There are indications that catecholaminergic and opioid neuronal networks as well as sex steroids modulate the release of GnRH;
- the pituitary gonadotropes, which release LH and FSH in a pulsatile manner at periodic intervals in response to the GnRH rhythmic signal;
- the gonads.

Basal plasma levels of gonadotropins are low in prepuberal boys and thus they cannot be used as an index of gonadotropic function before the onset of puberty. Since the isolation and determination of the structure and synthesis of luteinizing-hormone-releasing hormone (Schally et al., 1971), this has been administered to normal prepuberal and adult human males and females (Kastin et al., 1972; Job et al., 1972[a]). It has been shown to be efficient in stimulating release of gonadotropins (luteinizing hormone and follicle-stimulating hormone).

The concentration of testosterone in plasma of prepuberal boys is low after the first months of life, but the ability of the prepuberal testis to respond to exogenous human chorionic gonadotropin (HCG) is well documented. It enables an evaluation of Leydig cell secretory activity before puberty.

3.4.2. The first year of life

a. Boys with normal testicular descent

Very striking changes of plasma testosterone occur in the male newborn. For the first five or six days after birth there is a rapid decrease in levels (Forest et al., 1976). This decline is probably caused by the abrupt withdrawal of placental HCG (Winter et al., 1975). However, it is important to note that during this period a substantial amount of LH is already circulating (Hagen et al., 1974). Subsequently, there is an increase of plasma testosterone in the second week and the levels continue to rise to a maximum value between the 30th and 60th day. These values decrease again and between the 7th and 12th month, the concentration of plasma testosterone has reached prepuberal levels (Forest et al., 1976). Hammond and coworkers (1979) reported similar findings.

There is also an increase in the concentration of circulating gonadotropins during the first year, with levels considerably higher than those of the older prepuberal child (Winter et al., 1975; Forest et al, 1976; Sizonenko and Aubert, 1978). It is suggested that the rise of gonadotropins shortly after birth is caused by the rapid drop of circulating oestrogens, which exert a negative feedback on gonadotropin secretion (Forest and Cathiard, 1975). Hammond et al. (1979) noted

good correlations among testosterone, dihydrotestosterone and the gonadotropins in the male infant population. On the other hand, the study of Forest et al. (1974) showed a total lack of correlation between testosterone and LH or FSH levels in both male and female infants. In 1976, Forest and coworkers noted that plasma testosterone concentrations declined from the 60th day, although blood LH and FSH levels remained higher than those of prepuberal children. They offered several explanations including the immaturity of the hypothalamo-pituitary-gonadal axis, or low biological potency of the gonadotropins, but this discrepancy is still not fully understood. Previously, the same authors (Forest et al., 1974) had surmised that the increase in plasma testosterone levels in the postnatal period is likely to reflect an increase in testicular production. They found supportive evidence in the low androstenedione/testosterone (Δ 4/T) ratio at 1-3 months of age, similar to that of adult males with a progressive increase of Δ 4/T ratio after the third month of life. Their view was supported by Bidlingmaier et al. (1983) who found high plasma and testicular testosterone concentrations in boys from 1-3 months of age, which correlated significantly.

Betend et al. (1975) found a higher LH response to LHRH stimulation in infants under six months of age than in older ones. Job et al. (1977[a]) found the LH response to LHRH (100 μg LHRH i.v.) in the entire first year of life significantly higher in boys than in girls. The same group had previously studied boys only and did not find a significant difference in stimulated LH values before or after the first year of life up till puberty (Garnier et al., 1974). In contrast, Forest et al. (1974) found higher basal LH serum levels in male infants than in older prepuberal boys.

As for basal and peak FSH serum values, two studies reported very low, sometimes even undetectable, levels in male infants. These levels did not vary with age (Garnier et al., 1974; Betend et al., 1975). Forest et al. (1974) found significantly higher basal FSH serum levels in male infants than in older prepuberal boys.

In summary

Most authors agree that a postnatal testosterone surge is found in male infants in the first three months of life with a subsequent gradual decrease. There is no consensus of opinion concerning basal and stimulated LH and FSH serum values in the male infant, although higher basal and peak LH serum values have been found compared to older prepuberal boys.

b. Boys with undescended testes

Gendrel and coworkers (1979) measured plasma testosterone in 21 cryptorchid infants (13 boys with unilateral and 8 boys with bilateral cryptorchidism). In some of them the assay was repeated several times. Plasma levels of testosterone found in 14 cryptorchid boys aged 12 days to 4 months (21 samples) were compared with those found in 46 age-matched control subjects. They concluded that the regres-

sion curve (the variation of testosterone with age) in cryptorchids is at a lower level than the regression curve of the controls. However, it must be emphasized that the longitudinal and cross-sectional testosterone values were combined, while neither the degree of the polynomial regression curve nor the 95% confidence limits were supplied. In boys aged 12-90 days, they found a statistically significant difference in plasma testosterone between cryptorchids and controls. Subsequently, when the boys were between six months and one year old there was no longer a difference between cryptorchid and normal boys.

The same group collected 27 serum testosterone samples in 13 infants in whom spontaneous descent occurred during the first three months of life. They observed that the increase in testosterone in these boys was significantly higher than in the boys that stayed cryptorchid throughout the first three months of life ($p < 0.05$) and comparable to that of controls (Gendrel et al., 1978). Here again, the polynomial regression curve was based on a combination of cross-sectional and longitudinal values.

Job et al. (1977[b]) studied 12 male infants with unilateral or bilateral undescended testes between the age of one week and 11 months. Ten of them underwent an LHRH stimulation test (0.1 mg/m^2 i.v.). The mean values of basal and stimulated serum LH and FSH were compared with the mean and range values previously found in normal boys under one year of age (Garnier et al., 1974). The peak LH levels of the cryptorchid children appeared to be significantly lower than normal values ($p < 0.05$). Basal LH values and basal and peak FSH values were not significantly different from control values. No differences were found between unilateral and bilateral cryptorchids. In relation to our own study concerning the hormonal evaluation in the first year of life of boys born with undescended testes, it is important to note that in the aforementioned studies the first year was taken as a whole. Job and coworkers hypothesized that the nondescent or incomplete descent of the testis is correlated with a delay in pituitary LH secretion at least in patients without any mechanical defects of the inguinal tract or spermatic cord. In view of the role of androgens in the initiation and development of human spermatogenesis, the early defect of seminiferous tubules in cryptorchid children might result from a perinatal LH and testosterone deficiency (Gendrel et al., 1980).

In a subsequent study, the same group measured basal LH, FSH and testosterone values in boys with spontaneous descent during the first year of life and in boys that stayed cryptorchid. Serum samples were obtained during the first four months of life. FSH levels did not differ in the two groups but LH levels and the postnatal rise of testosterone were significantly lower in the persistently cryptorchid boys (Gendrel et al., 1980).

Davidson et al. (1981) determined serum concentrations of β-HCG and testosterone in 8 cryptorchid and 13 normal newborns in the first 24 hours of life. As the mean serum β-HCG concentrations and mean serum testosterone level did not differ significantly between cryptorchids and controls, the author concluded that

at that time of life β-HCG and testosterone do not play a decisive role in the mechanism of testicular descent.

Tapanainen et al. (1982) performed LHRH stimulation tests and measured basal testosterone values in 14 boys with unilaterally or bilaterally undescended, though palpable testes. He demonstrated that in cryptorchid boys as in normal boys, high postnatal levels of serum testosterone are accompanied by an elevated response of the pituitary gland to GnRH stimulation. The basal gonadotropin and testosterone levels of cryptorchid infants were similar to those measured previously in the same laboratory in apparently normal newborns. He also considered the pituitary responses to LHRH in the cryptorchid boys similar to those found by other investigators in normal boys (Garnier et al., 1974; Betend et al., 1975).

In summary

From the frequently cited studies of Job and coworkers it appeared that:

- A lower postnatal testosterone surge was found in cryptorchid infants in the first three months of life compared to controls as well as to boys with spontaneous testicular descent in the early months of life. However, the statistical analysis of the results is disputable.
- Lower stimulated LH serum values were found in cryptorchid infants compared to controls, but it must be emphasized that the first year of life was taken as a whole.
- In boys with spontaneous testicular descent in the first year of life serum testosterone values and basal LH values were similar to those of controls and higher than those of boys with persistent cryptorchidism. Here again, the statistical analysis is disputable.

Other investigators found normal testosterone and gonadotropin levels in cryptorchid boys in the first year of life.

3.4.3. From the first year of life to puberty

a. *Boys with normal testicular descent*

In both human and subhuman primates the increased LH and FSH secretion in the fetus and during infancy is followed by a long period, approximately one decade, in which the reproductive endocrine system is suppressed (Kaplan et al., 1976; Grumbach, 1980). The factors involved in this restraint of puberty are not well understood. Two mechanisms have been invoked to explain the prepuberal restraint of gonadotropin secretion:

1. *A sex steroid-dependent mechanism.* In the fetal period the hypothalamic "gonadostat" (the arcuate GnRH neurosecretory neurons) becomes increasingly sensitive to the inhibitory effects of sex steriods in the fetal circulation. This mechanism is not fully developed as birth. During the first two years of

life the hypothalamo-pituitary-gonadal axis becomes increasingly sensitive to the inhibitory feedback effect of small amounts of circulating sex steroids.

2. *A sex steroid-independent mechanism* that can be ascribed to intrinsic CNS inhibitory influences. The experimental finding that the hypothalamic oscillator regulates gonadotropin release (Knobil, 1980) coupled with the clinical observation of striking fall in gonadotropin secretion and reserve in agonadal children 4-11 years old (Conte et al., 1980) suggest the presence of CNS inhibitory influences independent of sex steroid secretion that restrain gonadotropin production and delay the onset of puberty.

It is possible that both mechanisms are involved in the restraint of secretion of GnRH and gonadotropins until puberty. Belchetz (1983) stated that GnRH secretion and steroid feedback interact, in primates principally at the pituitary level, although they are essentially independent.

Basal plasma levels of gonadotropin are low in prepuberal subjects and can therefore not be used as an index of gonadotropic function before the onset of puberty. Nevertheless it was demonstrated that LH is already secreted in prepuberal children in a pulsatile manner (Penny et al., 1977; Waldhauser et al., 1981; Jakacki et al., 1982). Boyar et al. (1972) described increased pulsatile plasma LH levels during sleep in late prepuberal and puberal children. On the other hand, Beck and Wuttke (1980) could not find nocturnal variations in plasma LH and FSH in prepuberal boys, as is found in puberty. In later puberty, pulsatile LH secretion also occurs during the day. The "gonadostat theory" (Grumbach et al., 1974) explains the onset of puberty by a change in sensitivity of the gonadostat to the negative feedback action of sex steroids. On the other hand, initiation of puberty can also be explained by the re-activation of the arcuate nucleus of the hypothalamus (Knobil, 1980; Visser, 1984). This hypothalamic oscillator controls the pulsatile release (approximately one pulse per hour) of GnRH into the portal circulation. What causes this activation after the prepuberal quiescence, however, remains to be elucidated (Knobil, 1980).

Puberty itself is beyond the scope of this book but it appears that the earliest signs of sexual maturation already begin to appear around the age of six years with the output of the weak androgens by the adrenal cortex. This phase of prepuberal development is called "adrenarche" and is not under gonadotropic control nor does it seem to be under the direct control of ACTH (Forest et al., 1976; Cutler and Loriaux, 1980). Evidence was given for the existence of a specific adrenal androgen-stimulating hormone (Parker and Odell, 1979; Sklar et al., 1980), but so far this substance has not been isolated.

From the early seventies it has been known that children have assayable gonadotropic releasable stores and their response to an intravenous injection of LHRH allows evaluation of their ability to secrete gonadotropins (Job et al., 1972[a]; Kastin et al., 1972; Winter and Faiman, 1972; Roth et al., 1972[b]). However, in prepuberal children there is a wide range of individual values of basal and stimulated gonadotropins (Job et al., 1977[a]).

From the end of the first year up till the year preceding the clinical onset of puberty, LH responses to LHRH are similar in boys and girls, but the mean FSH response is higher in girls and occasionally some normal prepuberal girls show high FSH releasable pituitary stores, while some normal prepuberal boys have no FSH response to the LHRH test (Garnier et al., 1974). In prepuberal boys no rise in plasma testosterone was observed after LHRH i.v. (Roth et al., 1972[b]).

Thirty years ago, Leach and co-workers (1955) showed that HCG has a stimulatory effect on testicular steroidogenesis. Since then it has been widely used for the evaluation of Leydig cell function in males of all ages. There has, however, been considerable variation in the dosage, duration and results of HCG stimulation tests used by different groups. In adult men the response of plasma testosterone following a single injection of HCG is biphasic with an early rise at two hours and a delayed rise reaching a maximum about 3-4 days later (Saez and Forest, 1979; Smals et al., 1979). In children (Forest et al., 1980; Tapanainen et al., 1983) there is no rapid testosterone response, only a delayed rise after 48-96 hours (mean 72 hours). There is clear evidence that in adults the maximal testosterone response to a specific dose of HCG remains the same after one to five daily injections (Smals et al., 1979; Saez and Forest, 1979; Padrón et al., 1980; Okuyama et al., 1981). Apart from the fact that it is impractical to administer as much as three to five daily injections of HCG, repeated doses of HCG to adult men cause a down-regulation of LH/HCG receptors in Leydig cells. Repeated injections cause a further increase of plasma oestradiol and 17OH-progesterone, which is compatible with the oestrogen-mediated augmentation of a 17,20-lyase block induced by the first injection (Forest et al., 1979; Smals et al., 1980).

Dunkel et al. (1985) showed that in prepuberty as well as in early puberty, the relative testosterone response to the first injection of HCG was much stronger than the response to the second and subsequent injections. He found enzyme inhibition in prepuberal boys after repeated HCG injections and he also advised a single dose of HCG for diagnostic HCG tests in prepuberal boys.

The dose of HCG varied considerably in the different protocols. From several studies it appeared that the maximally stimulating dose in adult men lies between 1,500 and 6,000 IU (Padrón et al., 1980; Okuyama et al., 1981; Smals et al., 1984). It must be recognized that both dosages are pharmacological, leading to plasma HCG levels 10-300 times higher than normal endogenous LH levels (in terms of biological potency) for at least 24 hours (Forest, 1983). For children, Forest et al. (1980) proposed a dose of 50-100 IU/kg while Tapanainen et al. (1983) suggested giving 5,000 IU/1.7 m^2, which is a some what higher dosage.

In summary

After the first year of life, basal testosterone and gonadotropin serum levels are low in the prepuberal period, although stimulation tests (LHRH tests and HCG tests) show clear responses.

b. Boys with undescended testes

The LHRH test is also used for hormonal evaluation of prepuberal boys with various sexual disorders including agonadal patients and boys with undescended testes. In agonadal boys, Job et al. (1974[a], 1976) found the same biphasic pattern in gonadotropin secretion and GnRH stimulated LH and FSH which was later observed by Conte (Conte et al., 1980) in girls with gonadal dysgenesis; high in infancy, low and comparable with normal prepuberal children in mid-childhood, and again rising to high levels in the adult castrate range at about 11 years of life. In other words, in mid-childhood the basal and stimulated concentrations of gonadotropin may not provide definitive evidence of defective or absent testes or ovaries.

Koch and Rahlf (1975) and Job et al. (1974[b]) reported normal basal serum values of LH and FSH in prepuberal cryptorchid boys. Waaler (1976) also studied urinary secretion of LH and FSH. In prepuberal bilateral cryptorchid boys, he found diminished LH excretion, while he found normal FSH excretion in unilateral and bilateral cryptorchids under eight years of age. In bilateral cryptorchid boys in the age group 8-12 years, the FSH excretion was significantly increased.

Many reports have been published concerning plasma gonadotropins in prepuberal cryptorchid boys after stimulation with LHRH i.v.. Job and associates found a reduced LH and a normal FSH response to LHRH i.v. from infancy throughout the whole prepuberal period in unilateral and bilateral cryptorchids (Job et al., 1974[b]; 1977[a]; Gendrel et al., 1977). Happ et al. (1978) also found reduced LH response to LHRH after the first year of life up till puberty. Lee et al. (1974), Cacciari et al. (1976) and Van Vliet et al. (1980) found normal basal and stimulated LH serum levels in cryptorchidism. The accompanying FSH levels were either normal (Cacciari et al., 1976) or elevated in some unilateral and bilateral cryptorchids (Lee et al., 1974). An increased FSH response with a normal LH response in bilateral cryptorchids was also reported by Sizonenko et al. (1978). He performed testicular biopsies and found low counts of spermatogonia in both testes. He found a negative correlation between the FSH response to LHRH and the number of spermatogonia and suggested an active, selectively negative feedback mechanism between inhibin and the prepuberal pituitary. Other authors did not find differences for LH and FSH after LHRH i.v. between unilateral and bilateral cryptorchids (Gendrel et al., 1977; Van Vliet et al., 1980). Some investigators found alternating elevated or decreased or normal basal and peak LH and FSH serum values (Koch and Rahlf, 1975; Illig and Werder, 1977; Skorodok et al., 1982), which according to Battin and Colle (1977) indicates the heterogenity of cryptorchidism.

The HCG-stimulation test enables detecting anorchia, provided it is bilateral, in every age group, even in infants, because there will be no increase in plasma or urinary testosterone (Knorr, 1979[a]). Diverse results of HCG tests in cryptorchid boys have been reported. Some authors found no difference in testosterone response to HCG between cryptorchid boys and controls (Cacciari et al., 1974) or

between unilateral and bilateral cryptorchids (Rivarola et al., 1970; Sizonenko et al., 1973; Canlorbe et al., 1974). Others found lower testosterone responses in cryptorchid boys than in controls and/or in bilateral cryptorchids than in unilateral cryptorchids (Zachmann, 1972; Canlorbe et al., 1974; Cacciari et al., 1974; Walsh et al., 1976; Gendrel et al., 1977; Attanasio et al., 1977; Anoussakis et al., 1978; Hafez et al., 1983). Attanasio and coworkers (1977) found a significant difference in testosterone response in bilateral cryptorchids comparing the successfully treated boys with the unsuccessfully treated ones after HCG treatment ($p < 0.001$).

Most authors found normal basal testosterone plasma levels or urinary testosterone excretion in cryptorchid boys (Rivarola et al., 1970; Zachmann, 1972; Sizonenko et al., 1973; Cacciari et al., 1974; Canlorbe et al., 1974; Koch and Rahlf, 1975; Illig and Werder, 1977; Dickerman et al., 1979). Waaler (1976) found elevated urinary testosterone excretion in unilateral and bilateral cryptorchid boys under nine years of age with a decreased urinary LH excretion.

In summary

In agonadal patients and in patients with a hypothalamo-pituitary-gonadotropic deficiency, basal and stimulated gonadotropin levels may be in the normal range in mid-childhood. Elevated, normal, and decreased LH and FSH values have been found in cryptorchidism. Only bilateral anorchia can be detected with certainty with an HCG test. No uniform responses have been elicited in cryptorchidism.

3.5. CLINICAL AND HORMONAL EVALUATION OF BOYS BORN WITH UNDESCENDED TESTES, DURING THEIR FIRST YEAR OF LIFE

3.5.1. Introduction

According to Scorer (1964) the incidence of undescended testes at birth amounts to 4.3% of male infants (2.7% for full-term and 21% for pre-term boys). During the first year of life, spontaneous descent may still occur, resulting in a reduction in the percentage of undescended testes to approximately one per cent for one year old boys. The conflicting reports described in section 3.4.2.b., prompted a clinical and hormonal study of boys born with undescended testes during their first year of life. This study ran parallel with our study of the effect of hormonal treatment of boys with undescended testes *after* the first year of life (see chapter 4). The aims of the study were:

- to follow boys with undescended testes during their first year of life and observe any spontaneous testicular descent;

- to ascertain whether there is a (transient?) functional insufficiency in the hypothalamo-pituitary-gonadal axis in infants with undescended testes;
- to investigate whether boys with undescended testes suffer from a disorder in the biosynthesis of testosterone or an enzyme inhibition.

3.5.2. Patients and methods

Between October 1982 and January 1985, a total of 48 boys with 56 undescended testes were referred to the Sophia Children's Hospital within their first year of life (see figure 3.2.). Forty-five of these boys were born after a full-term pregnancy; the remaining three were born prematurely, two with a birth weight of 2,000 g after respectively 33 and 34 weeks gestation, and one weighing 2,710 g

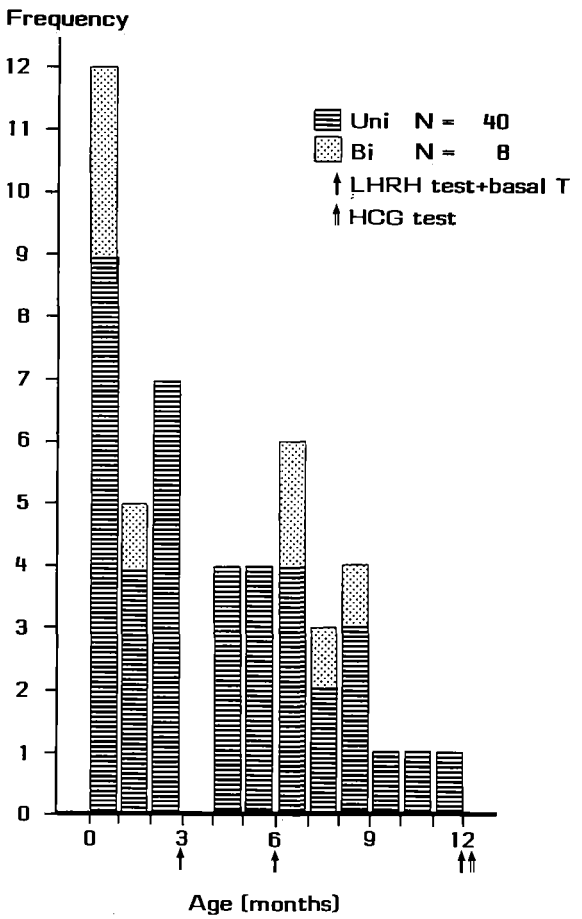


Figure 3.2. Age distribution of boys with unilateral and bilateral cryptorchidism enrolled in the study.

after 36 weeks gestation. All three were unilaterally cryptorchid. For the whole series of patients, cryptorchidism was unilateral in 40 boys (27 leftsided and 13 rightsided) and bilateral in eight. Twenty-four boys were under three months old at referral, consisting of 20 unilateral cryptorchids (11 leftsided and 9 rightsided) and 4 bilateral cryptorchids. From the moment of referral, the boys were seen regularly in our outpatient clinic, if feasible, at the age of 3, 6, 9 and 12 months. At each visit, the spontaneous and the most caudal testicular position was determined independently by each examiner (see 2.3.).

Hormonal evaluation consisted of an LHRH test and determination of basal serum testosterone at 3, 6 and 12 months of age. An HCG test was carried out at the start of the second year of life. Before and three days after an intramuscular injection of 1,500 IU HCG, we determined serum testosterone (T), dihydrotestosterone (DHT), progesterone (P), 17 α-hydroxypregnenolone (17 OHPreg), 17 α-hydroxyprogesterone (17 OHP), dehydroepiandrosterone sulfate (DHEAS), androstenedione (Δ 4) (figure 3.3.). For methods of hormonal evaluation see 2.5.

A total of 160 boys without any endocrinological anomalies served as controls with informed consent of the parents. Of this series, 153 were in their first year of life and had normally descended testes. Single blood samples were taken for serum testosterone determination from 144 of these boys coincident with routine blood tests and therefore the sampling caused no undue discomfort. Nine boys had an LHRH test. These boys had an indwelling catheter for other reasons and therefore repeat blood sampling caused no discomfort. The remaining seven boys were in their second year of life and their testes were retractile. These boys underwent an HCG test whereby testosterone, testosterone precursors and dihydrotestosterone were determined before and three days after the intramuscular administration of 1,500 IU HCG.

For the final assessment of hormonal data, the study population was divided into three groups; the boys that stayed cryptorchid became group I, those that had delayed, spontaneous descent group II, and the control subjects formed group III. In order to avoid distribution assumption, e.g. Gaussian distribution, distribution-free methods were used for significance testing (see 2.6.)

To compare the *cross-sectional* hormonal data of the three groups, the following statistical procedures were carried out:

Regarding *serum testosterone*. Every six boys of group III, equal or successive in age, were taken together. Their median values with respect to age and testosterone level were used as cross-median values (Tukey, 1977). These values were connected forming the cross-median curve (cmc). The sign test was used for comparison of the testosterone values of group I and group II with the cross-median curve of group III. In addition, the individual testosterone values of boys in group I were compared with the cross-median testosterone curve of group II. The cross-median testosterone values of group II were composed of four values determined at equal or successive ages.

Regarding *serum LH and FSH*. Because of the small number of controls, cross-

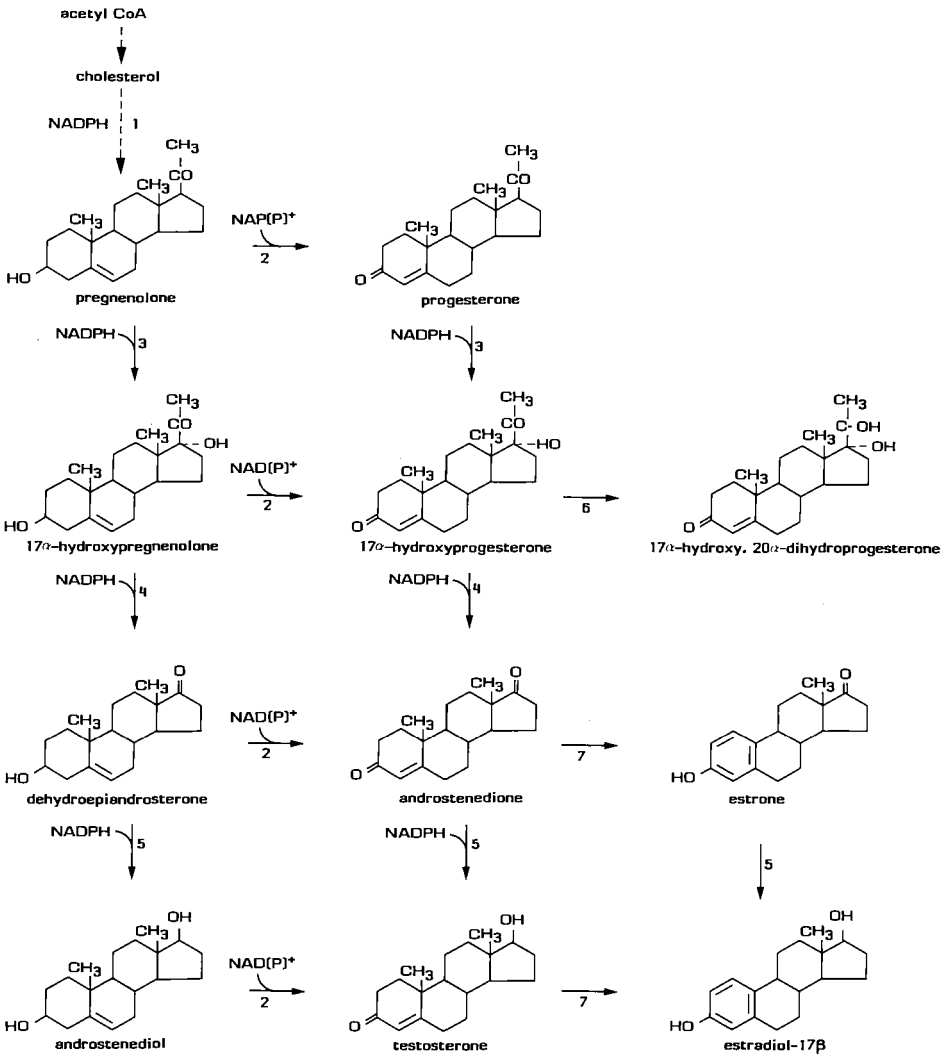


Figure 3.3. Pathways involved in the biosynthesis of testicular steroids from cholesterol: 1. cholesterol side-chain cleavage "enzyme" (20,22-desmolase?; 20 α-cholesterol hydroxylase?); 2. 3 β-hydroxysteroid dehydrogenase; 3. 17 α-hydroxylase; 4. 17,20-desmolase; 5. 17 β-hydroxysteroid dehydrogenase (= 17-keto reductase); 6. 20 α-hydroxysteroid dehydrogenase; 7. aromatizing enzyme complex (Van der Molen and Rommerts, 1981; with permission).

median values of serum LH and FSH could not be determined for group III. Consequently, the individual basal and peak LH and FSH values of boys in group I and group III were compared with the cross-median curve of group II. The same procedure was followed for comparison of the individual LH and FSH values of boys in groups II and III with the cross-median curve of group I. The groups were compared with the sign test.

For comparison of the *longitudinal* hormonal data, the following statistical procedures were carried out:
Regarding *serum testosterone*. The Kruskal-Wallis test was applied to compare the longitudinal testosterone values of groups I and II and the cross-sectional testosterone values of group III at 3, 6 and 12 months of age. If the results were significant ($p < 0.05$), the Mann-Whitney-U test was carried out as well. The changes in the longitudinal serum testosterone values within groups I and II from 3 to 6 and from 6 to 12 months of age, were compared using the test of Friedman. In case of significant results ($p < 0.05$), the Wilcoxon matched pairs signed rank test was also applied. Between the two groups these changes were compared using the Mann-Whitney-U test.
Regarding *serum LH and FSH*. The longitudinal basal and peak LH and FSH values of groups I and II at 3, 6 and 12 months of age were compared with the Mann-Whitney-U test. The changes in the longitudinal LH and FSH values within groups I and II from 3 to 6 and from 6 to 12 months of age were compared using the test of Friedman. If the results were significant ($p < 0.05$), the Wilcoxon matched pairs signed rank test was applied. Between the two groups these changes were compared using the Mann-Whitney-U test.

Correlations. We investigated the correlations of basal and peak LH values with testosterone values as well as the correlation of the ratio basal LH/T and peak LH/T with age for groups I and II. The rank correlation coefficients were calculated according to Spearman.

HCG test. The results of the HCG tests were compared between the three groups using the Kruskal-Wallis test. In case of significant result ($p < 0.05$), the Mann-Whitney-U test was applied. In addition, the basal versus peak values of the testosterone precursors, testosterone and dihydrotestosterone were compared within each group using Wilcoxon matched pairs signed rank tests.

Upon reaching the age of one year, 19 boys of group I (22 undescended testes) were enrolled in our concurrent double-blind, placebo-controlled study of the efficacy of LHRH nasal spray, where they became part of age group A (see 4.3.2.). The protocol for the double-blind study being completed at that stage, hormonal treatment for the remaining nine cryptorchid one year olds was deferred.

The foldout at the end of this book gives an explanatory survey of patient groups and age periods as well as symbols used in figures and tables.

3.5.3. Clinical results

Table 3.2. shows the frequency of spontaneous descent during the first year of life in our study population. Such delayed, spontaneous testicular descent occurred in 19 boys altogether (20 testes). Fifteen of them had unilaterally undescended testes (ten leftsided and five rightsided) while four were bilateral cryptorchids. Of these four boys only one had spontaneous descent of both testes. In the other three boys only one testis descended (two leftsided and one rightsided)

Table 3.2. Spontaneous testicular descent during the first year of life.

		spontaneous descent	
cryptorchidism	boys	boys	testes
unilateral left	27	10	10
unilateral right	13	5	5
bilateral	8	4*	5
total	48	19*	20

* three boys with bilateral cryptorchidism had unilateral spontaneous descent

Table 3.3. Spontaneous testicular descent during the first year of life in boys enrolled in the study within the first three months of life.

		spontaneous descent	
cryptorchidism	boys	boys	testes
unilateral left	11	6	6
unilateral right	9	4	4
bilateral	4	2*	2
total	24	12*	12**

* two boys with bilateral cryptorchidism had unilateral spontaneous descent

** six testes descended before the 3rd month

and they remained unilaterally cryptorchid. Subsequently, this condition will be referred to as "hemi-descent". Spontaneous, delayed descent did not occur in any of the prematurely born boys.

Table 3.3. shows the frequency of spontaneous descent in the 24 boys with 28 undescended testes, who entered the study within the first three months of life. Spontaneous descent occurred in 12 of them, consisting of 10 with unilaterally undescended testes (6 leftsided, 4 rightsided) and 2 boys with bilaterally undescended testes who had hemi-descent (one leftsided, one rightsided). In six of these boys the spontaneous descent occurred within the first three months of life, four with unilaterally undescended testes (three rightsided and one leftsided) and two boys with bilaterally undescended testes who had hemi-descent. The remaining 12 boys (including one pre-term baby) stayed cryptorchid. In 6 of altogether 19 boys that had delayed, spontaneous descent, this occurred after the sixth month. Five of them had unilaterally undescended testes (four leftsided and one rightsided) while the remaining boy, a bilateral cryptorchid, had sponta-

neous descent of both testes. At the end of the first year, 10 of the 20 testes that had descended spontaneously, had assumed a permanent scrotal position, including the six testes that had descended within the first three months of life. The other ten testes were retractile.

Table 3.4. shows the results of LHRH nasal spray treatment in 19 boys (22 undescended testes) without spontaneous descent during the first year of life, who were enrolled in the double-blind, placebo-controlled study (see 4.3.). The hormonal treatment was only successful in one boy with a righsided undescended testis and in one boy with bilaterally undescended testes in whom one testis descended only. Both these testes became retractile.

Table 3.4. Results of LHRH nasal spray treatment.

		success		failure	
cryptorchidism	boys	boys	testes	boys	testes
unilateral left	10	0	0	10	10
unilateral right	6	1	1	5*	5
bilateral	3	1**	1	2	5
total	19	2	2	17	20

* one drop-out: ectopia
** only one testis descended

3.5.4. Hormonal evaluation

There were no significant differences in hormonal values between boys with unilaterally or bilaterally undescended testes in group I or group II, possibly due to the small number of bilateral cryptorchids. Consequently, in the statistical analyses no distinction was made for unilateral or bilateral cryptorchidism in either group. Boys with bilateral cryptorchidism who had spontaneous descent of one testis only (hemi-descent) were assigned to group II.

Cross-sectional data. Cross-sectional studies should be based on one sample per patient. Therefore for the boys in groups I and II we used the first determination. For the control group we only had single samples. Figure 3.4. shows the individual serum testosterone values in the first year of life of boys in group I ($n = 29$), group II ($n = 18$) and group III ($n = 144$). For group I unilateral and bilateral cryptorchids are shown separately, while for group II differentiation also involves boys with spontaneous hemi-descent.

Figure 3.5. shows the individual testosterone values of boys in groups I and II in comparison with the cross-median testosterone curve of group III. The sign test revealed no significant differences comparing groups I and II with group III from the age of 80 to 180 days, 180 to 360 days, or at any time during that whole period.

Figure 3.6. shows the individual testosterone values of boys in group I in

comparison with the cross-median testosterone curve of group II. The sign test revealed no significant differences comparing groups I and II from the age of 80 days to 300 days.

Figures 3.7. and 3.8. show the individual basal and peak LH serum values (after LHRH i.v.) of boys in group I ($n = 29$), group II ($n = 18$) and group III ($n = 9$). For group I unilateral and bilateral cryptorchids are shown separately while for group II differentiation also involves boys with spontaneous hemi-descent.

Figure 3.9[a]. compares the individual basal LH serum values of boys in groups I and III with the cross-median curve of group II, while figure 3.9[b]. compares the individual basal LH serum values of boys in groups II and III with the cross-median curve of group I. The sign test revealed no significant difference for basal LH between groups I and II or between groups I and III ($p > 0.05$), whereas basal LH appeared to be higher in group II than in group III.

Figure 3.10[a]. compares the individual peak LH serum values of boys in groups I and III with the cross-median curve of group II, while figure 3.10[b]. compares the individual peak LH serum values of groups II and III with the cross-median curve of group I. No significant differences were found for peak LH between groups I and III, between groups I and II or between groups II and III.

Almost all (41 of 55) basal FSH serum values of boys in the three groups fell below the detection limit of the FSH assay (0.6 IU/l). Consequently, no evaluation of basal FSH was carried out.

Figure 3.11. shows the individual peak FSH values of boys in group I ($n = 28$), group II ($n = 18$) and group III ($n = 9$). For group I unilateral and bilateral cryptorchids are shown separately, while for group II differentiation also involves boys with spontaneous hemi-descent.

Figure 3.12[a]. shows the individual peak FSH values for boys in groups I and III in comparison with the cross-median peak FSH curve for group II. The sign test revealed no significant differences between group I or III and group II. The same procedure was followed for comparison of the individual peak FSH values of boys in groups II and III with the cross-median peak FSH curve of group I (figure 3.12[b].). Here again, there were no significant differences.

Longitudinal data. Figure 3.13. shows the longitudinal testosterone values of groups I and II and the cross-sectional testosterone values of group III after logarithmic transformation. These values were determined at approximately 3 months (age period X, range 80-126 days), 6 months (age period Y, range 169-236 days) and 12 months (age period Z, range 330-410 days). Table 3.5. shows the mean and SEM serum testosterone values for the three groups in the three age periods. In groups I and II the number of boys in age period Z was smaller than in either age period X or Y for technical reasons and in two cases because the parents refused another test (one in each group). The Kruskal-Wallis test revealed no significant differences between the three groups in any of the three age periods ($p > 0.05$).

Table 3.6. shows the change in serum testosterone values (mean $\pm$ SEM) in

groups I and II. The change of serum testosterone within groups I and II from age period X to Y was statistically significant ($p < 0.05$). From age period Y to Z there was no significant difference in the change within group I. While the pattern of change within group II from age period Y to Z was the same as for group I, the small number of boys did not allow for significance testing. Comparing group I with group II, there was no difference in the change in serum testosterone levels ($p > 0.05$).

Figures 3.14. and 3.15. give the longitudinal basal and peak LH serum values for groups I and II at approximately 3, 6 and 12 months of age. The mean and SEM basal and peak LH values of the two groups in age periods X, Y and Z are given in table 3.7. No significant differences were found between groups I and II for any one of the three age periods.

Table 3.8. shows the change in basal and peak LH serum values in groups I and II. In group I, the changes in basal and peak LH values from age period X to Y and from Y to Z were statistically significant ($p < 0.05$). In group II the change in basal and peak LH from age period X to Y was statistically significant but the change from age period Y to Z could not be tested for significance (small number of boys), although it did show the same pattern as in group I. A comparison of the two groups revealed no difference in the change in basal and peak serum LH ($p > 0.05$).

Figure 3.16. shows the longitudinal peak FSH values of groups I and II in the three age periods. The mean and SEM peak FSH values of the two groups are given per age period in table 3.9. A comparison of groups I and II per age period revealed no significant differences (Mann-Whitney-U test, $p > 0.05$). Peak FSH serum values did not change significantly from age period X to Y or to Z within groups I and II (test of Friedman, $p > 0.05$).

Correlations. No significant correlations were found between cross-sectional basal or peak LH and testosterone serum levels from the age of 80 days in the first year of life either in group I or in group II. The Spearman test revealed a highly significant positive correlation between the ratio basal LH/T or peak LH/T and age in the first year of life in groups I and II ($p < 0.005$). In figures 3.17[a], 3.17[b], 3.17[c] and 3.17[d], the least square regression lines are presented of the ratios in groups I and II. An increase of the ratio basal LH/T or peak LH/T with age was found in both groups.

Table 3.10. gives the basal and peak serum testosterone values (mean ± SEM) before and three days after intramuscular administration of 1,500 IU HCG at the start of the second year of life for 22 boys in group I and 7 each in groups II and III. It was not possible to carry out an HCG stimulation test in the whole study population. Many parents would not allow another blood test, particularly concerning the boys in whom spontaneous descent had occurred. No statistically significant differences were found in basal and peak serum testosterone values comparing the three groups (Kruskal-Wallis test, $p > 0.05$).

Table 3.11. shows basal and peak serum values (median and range) of testoster-

one, dihydrotestosterone and several steroid precursors of the Δ 4, and Δ 5 pathway before and after intramuscular administration of 1,500 IU HCG in the second year of life in the three groups. Group I: 11 boys; group II: 7 boys and group III: 7 boys. For technical reasons, 17 OHPreg was only determined in the boys of group I and in two boys of group II. After HCG stimulation a significant increase of serum T and DHT was found in all three groups ($p < 0.05$), whereas no significant changes could be observed for P and 17 OHP in any of the three groups and for 17 OHPreg in groups I and II. A small but statistically significant increase was found for DHEAS in groups I and III and for Δ 4 in groups I and II ($p < 0.05$). A comparison of the three groups revealed no significant differences for basal 17 OHP, Δ 4, T and DHT between the three groups or for basal 17 OHPreg between groups I and II (small number of boys). Basal P and DHEAS were slightly higher, but with statistical significance, in group II than in group I. There were no statistically significant differences between the three groups for peak values of P, 17 OHP, DHEAS, T and DHT. Peak values of Δ 4 were slightly higher, albeit with statistical significance, in group II than in group III. There was no difference in the peak values of 17 OHPreg for groups I and II.

Pages 110-136 contain figures and tables illustrating the hormonal evaluation. Foldout page 330 gives an explanatory survey of patient groups and age periods as well as symbols used in figures and tables.

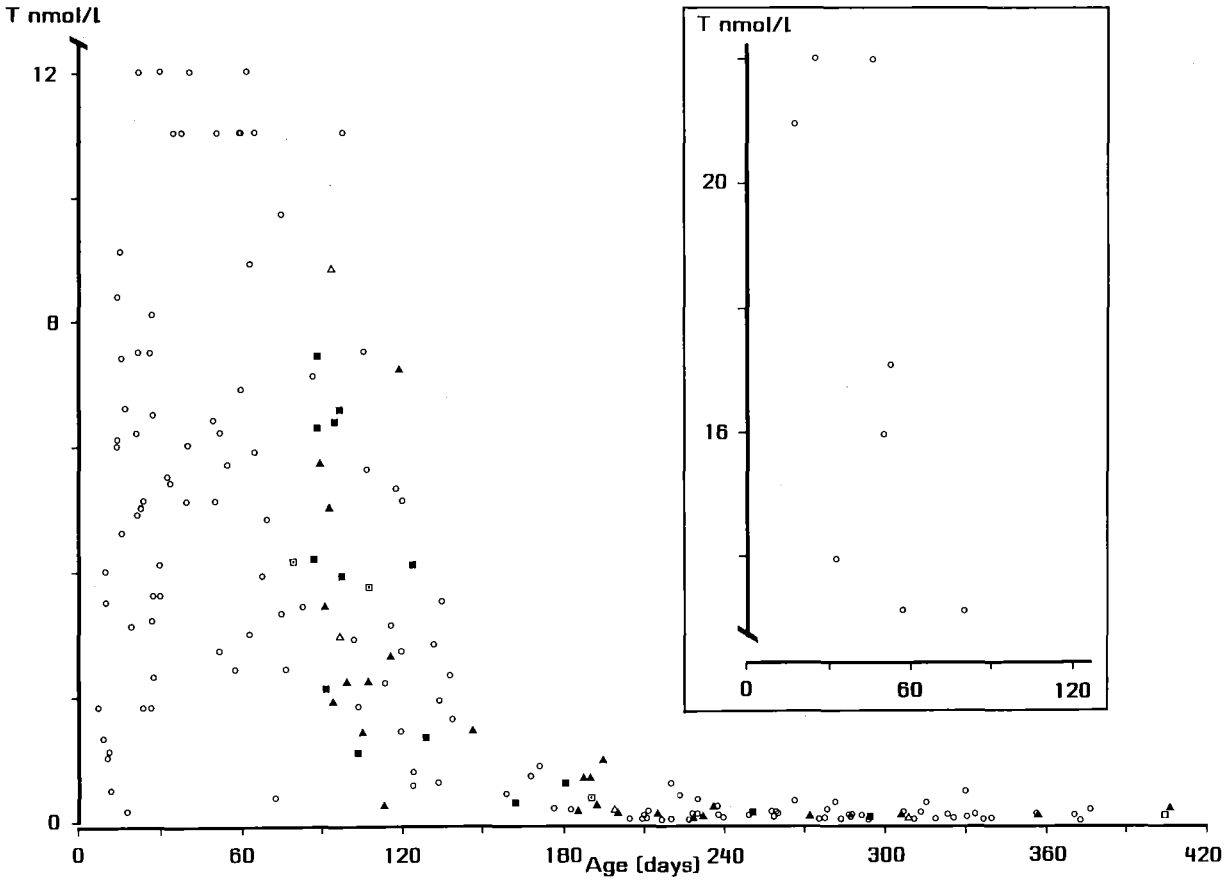
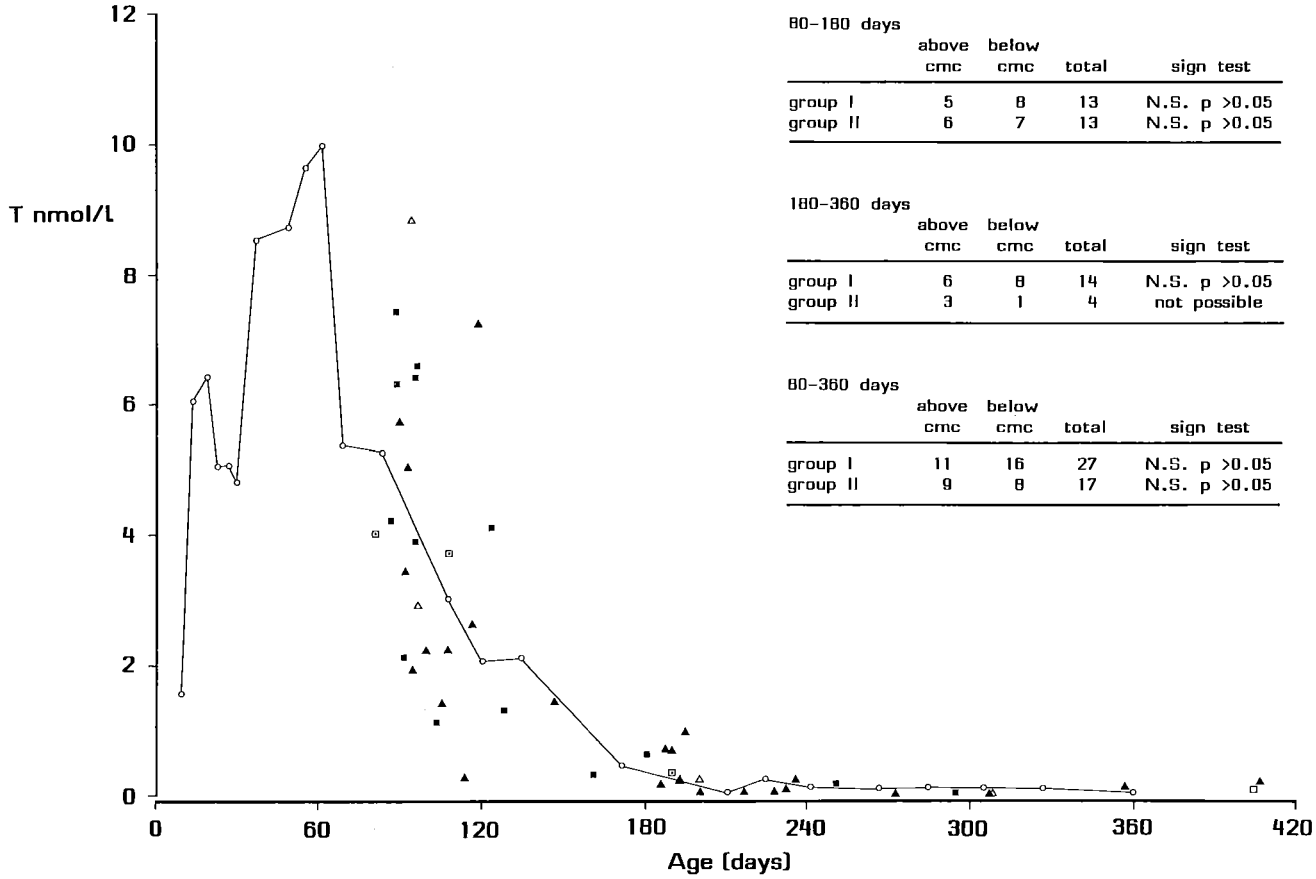


Figure 3.4. Cross-sectional testosterone serum values during the first year of life of boys of group I (n = 29), group II (n = 18) and group III (n = 144). See foldout page 330.



80–180 days

	above cmc	below cmc	total	sign test
group I	5	8	13	N.S. p >0.05
group II	6	7	13	N.S. p >0.05

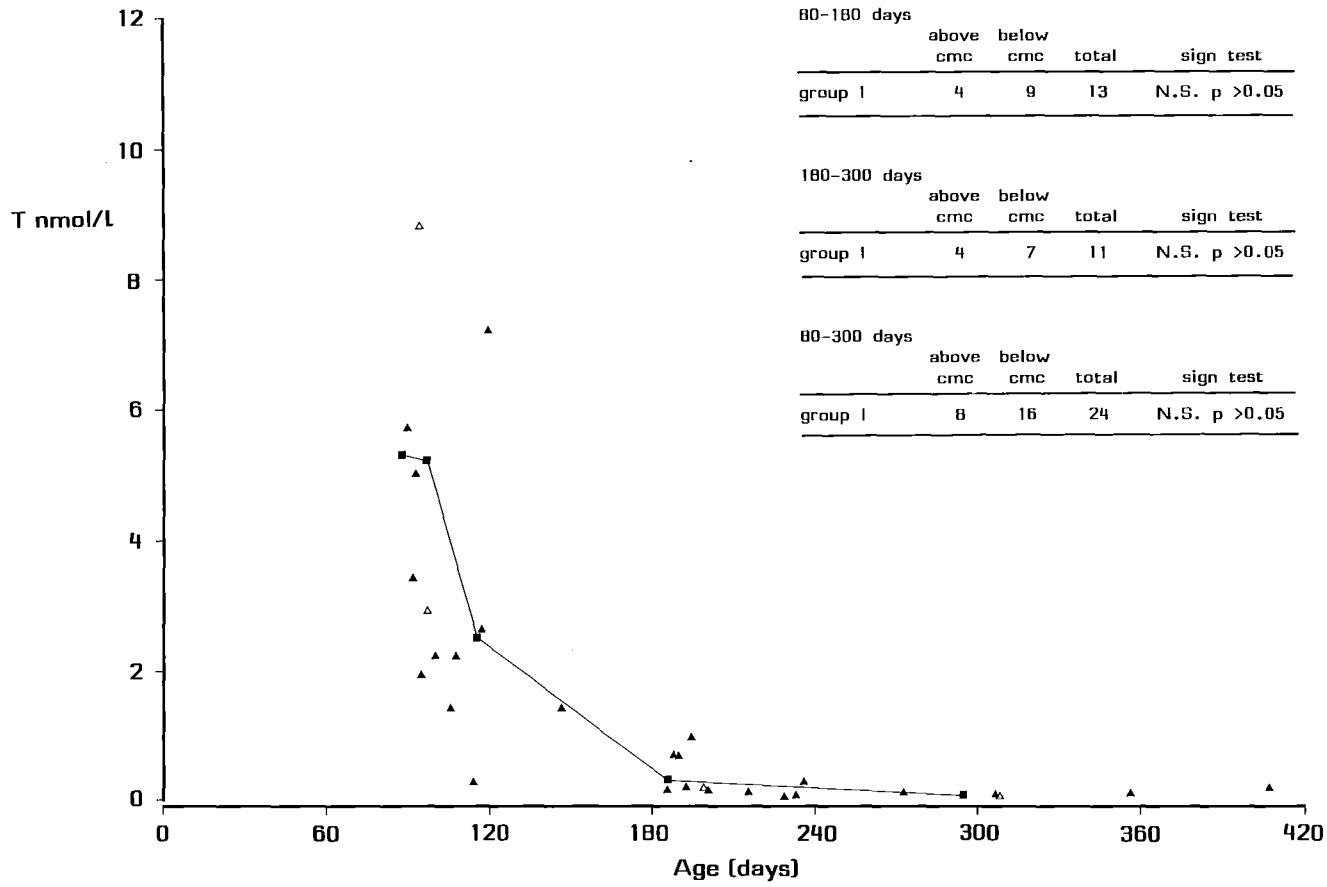
180–360 days

	above cmc	below cmc	total	sign test
group I	6	8	14	N.S. p >0.05
group II	3	1	4	not possible

80–360 days

	above cmc	below cmc	total	sign test
group I	11	16	27	N.S. p >0.05
group II	9	8	17	N.S. p >0.05

Figure 3.5. Cross-sectional testosterone serum values; comparing individual values of boys of groups I and II in relation to the cross-median curve (cmc) of boys of group III. See foldout page 330.



80–180 days

	above cmc	below cmc	total	sign test
group I	4	9	13	N.S. p >0.05

180–300 days

	above cmc	below cmc	total	sign test
group I	4	7	11	N.S. p >0.05

80–300 days

	above cmc	below cmc	total	sign test
group I	8	16	24	N.S. p >0.05

Figure 3.6. Cross-sectional testosterone serum values; comparing individual values of boys of group I in relation to the cross-median curve (cmc) of boys of group II. See foldout page 330.

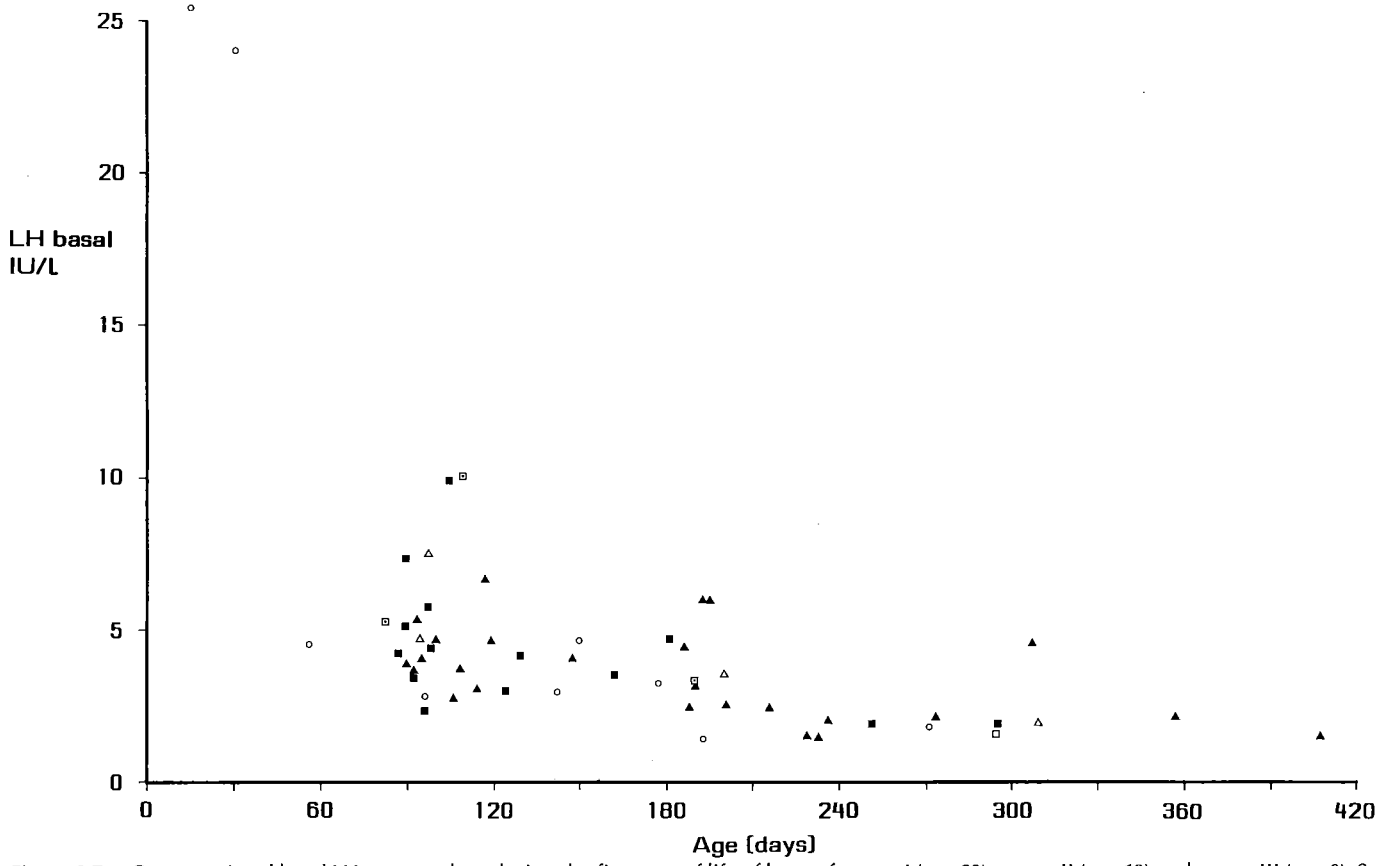


Figure 3.7. Cross-sectional basal LH serum values during the first year of life of boys of group I (n = 29), group II (n = 18) and group III (n = 9). See foldout page 330.

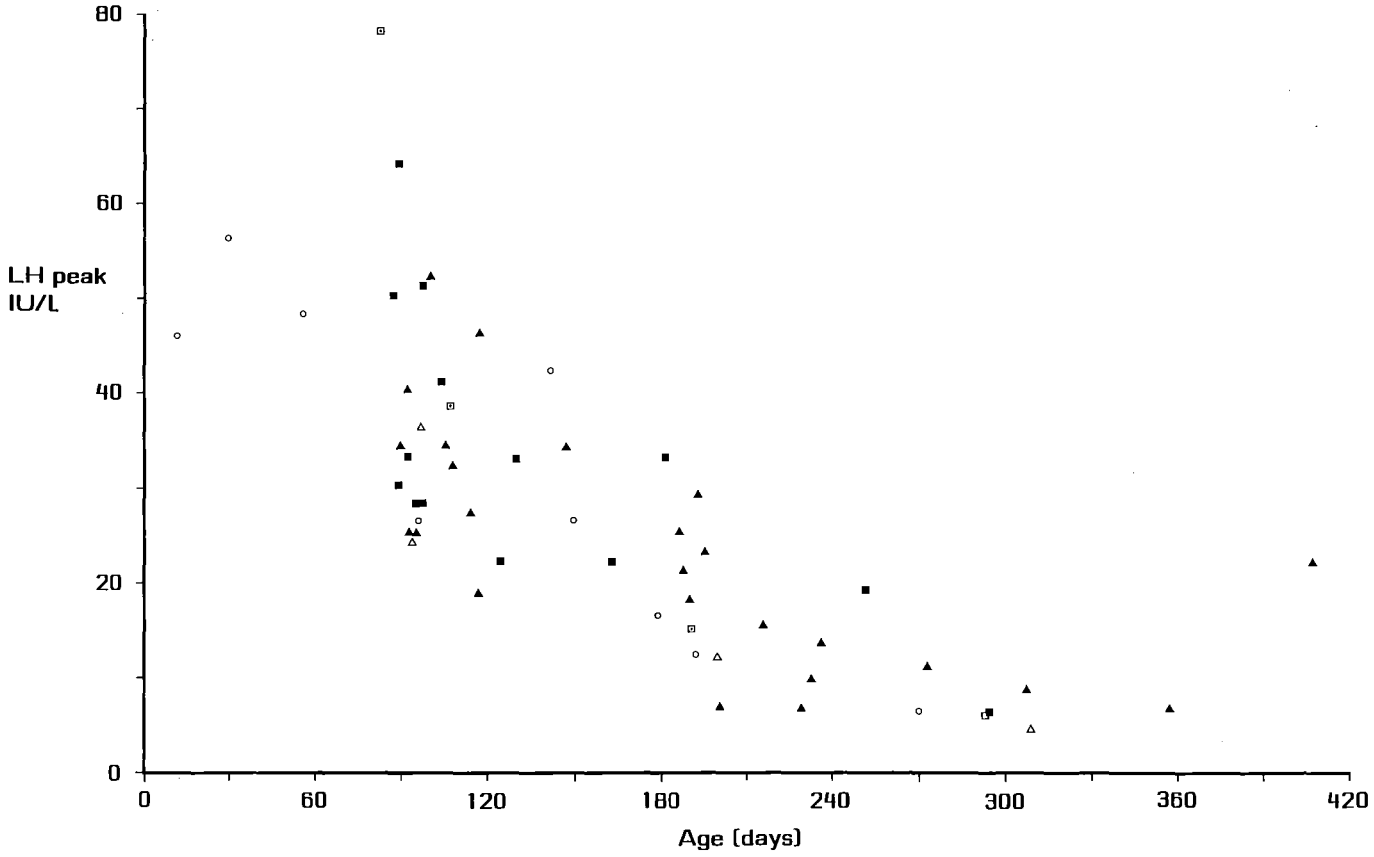


Figure 3.8. Cross-sectional peak LH serum values (after LHRH i.v.) during the first year of life of boys of group I (n = 29), group II (n = 18) and group III (n = 9).
See foldout page 330.

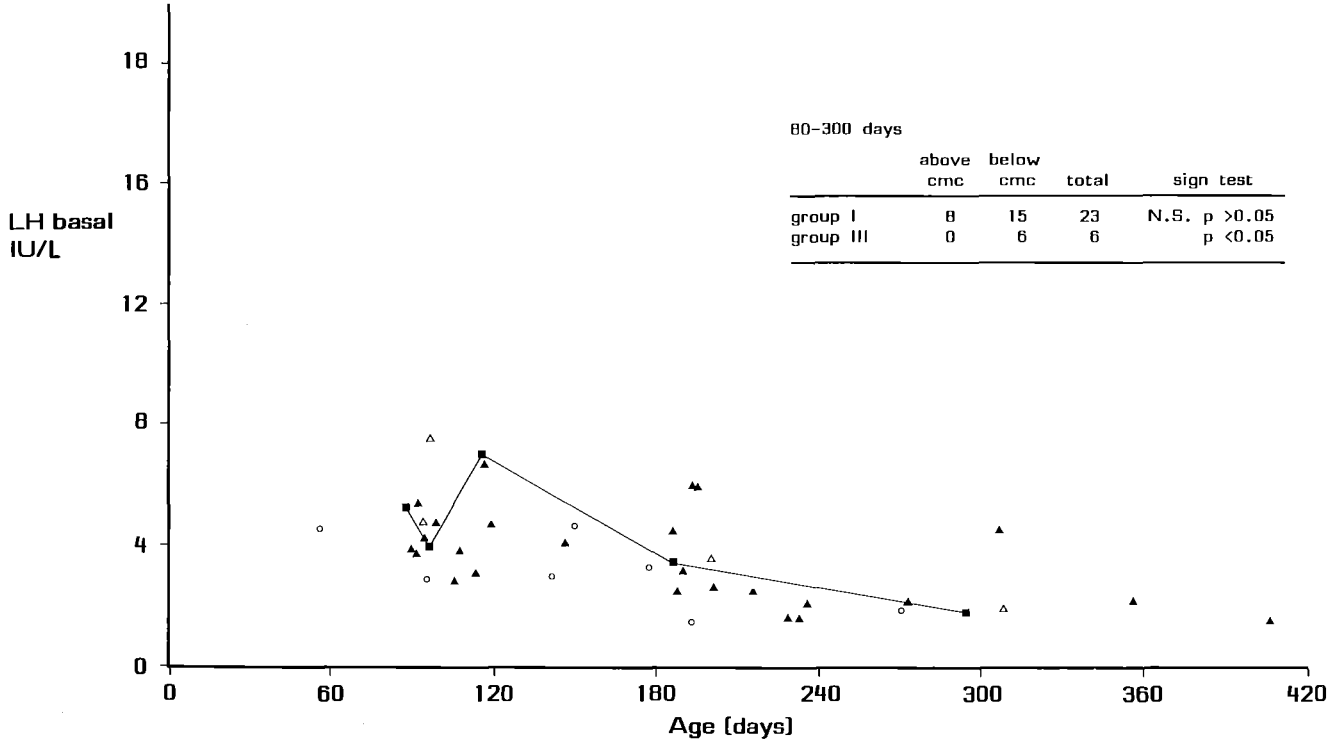


Figure 3.9[a]. Cross-sectional basal LH serum values; comparing individual values of boys of groups I and III in relation to the cross-median curve (cmc) of boys of group II. See foldout page 330.

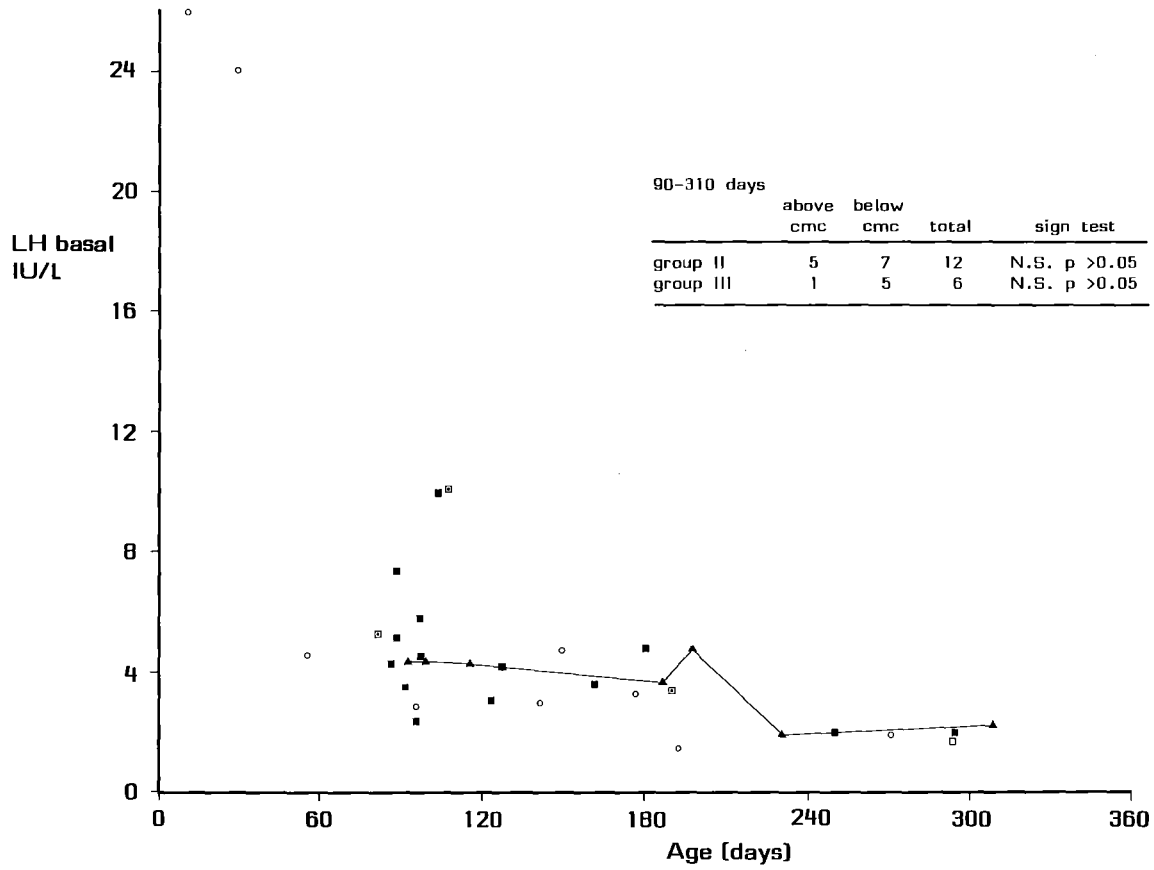


Figure 3.9[b]. Cross-sectional basal LH serum values; comparing individual values of boys of groups II and III in relation to the cross-median curve (cmc) of boys of group I. See foldout page 330.

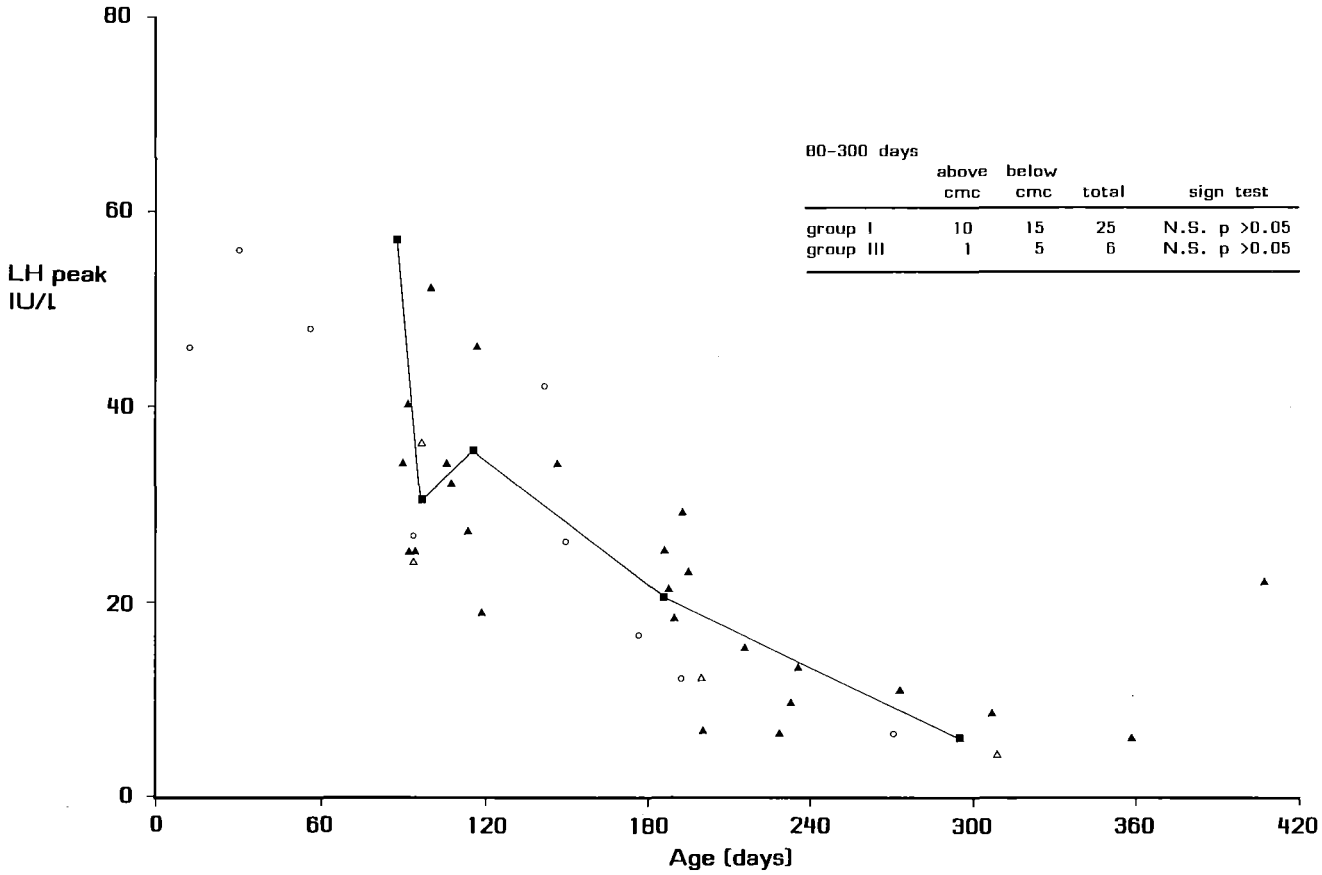


Figure 3.10[a]. Cross-sectional peak LH serum values; comparing individual values of boys of groups I and III in relation to the cross-median curve (cmc) of boys of group II. See foldout page 330.

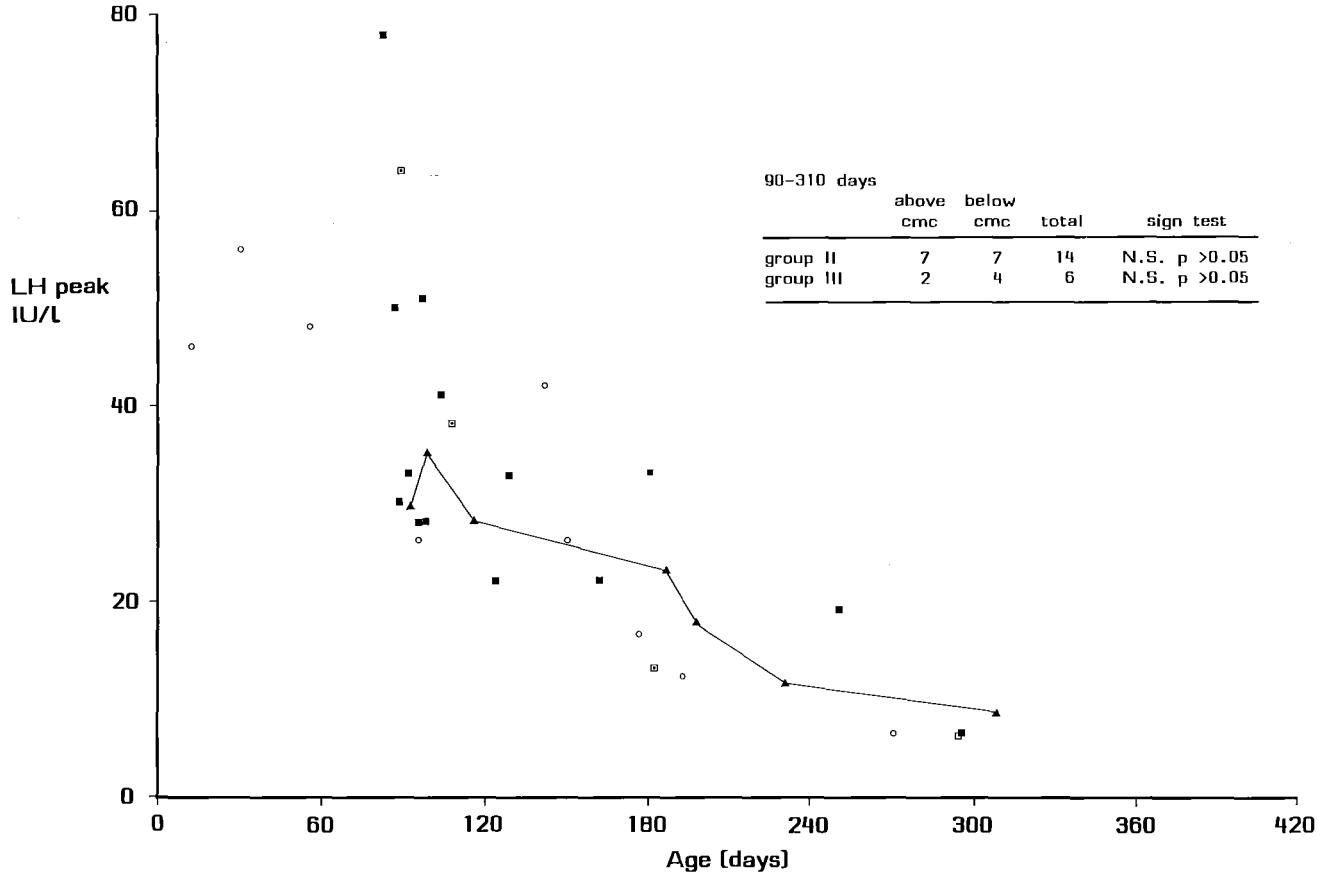


Figure 3.10[b]. Cross-sectional peak LH serum values; comparing individual values of boys of groups II and III in relation to the cross-median curve (cmc) of boys of group I. See foldout page 330.

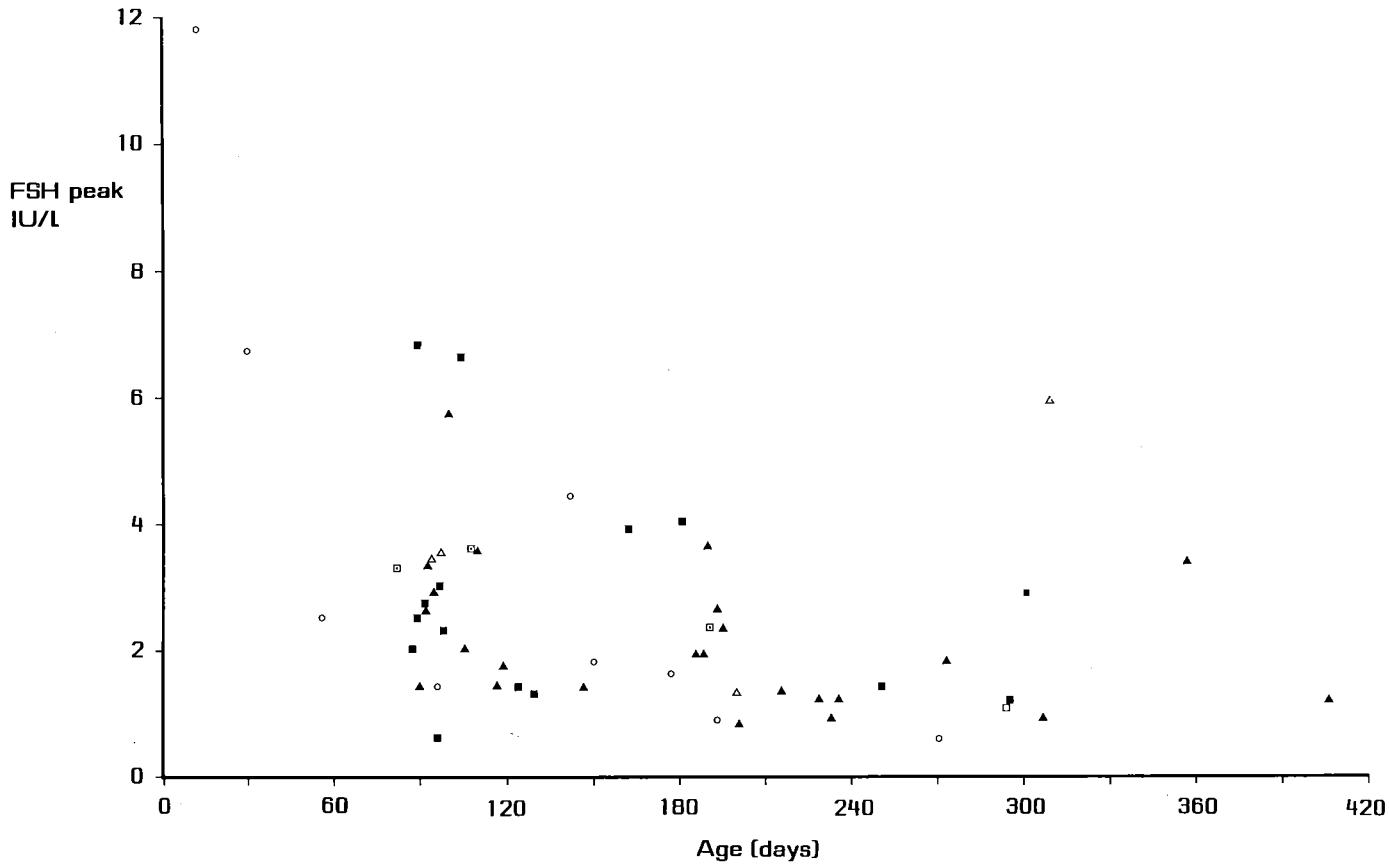


Figure 3.11. Cross-sectional peak FSH serum values (after LHRH i.v.) during the first year of life of boys of group I (n = 28), group II (n = 18) and group III (n = 9). See foldout page 330.

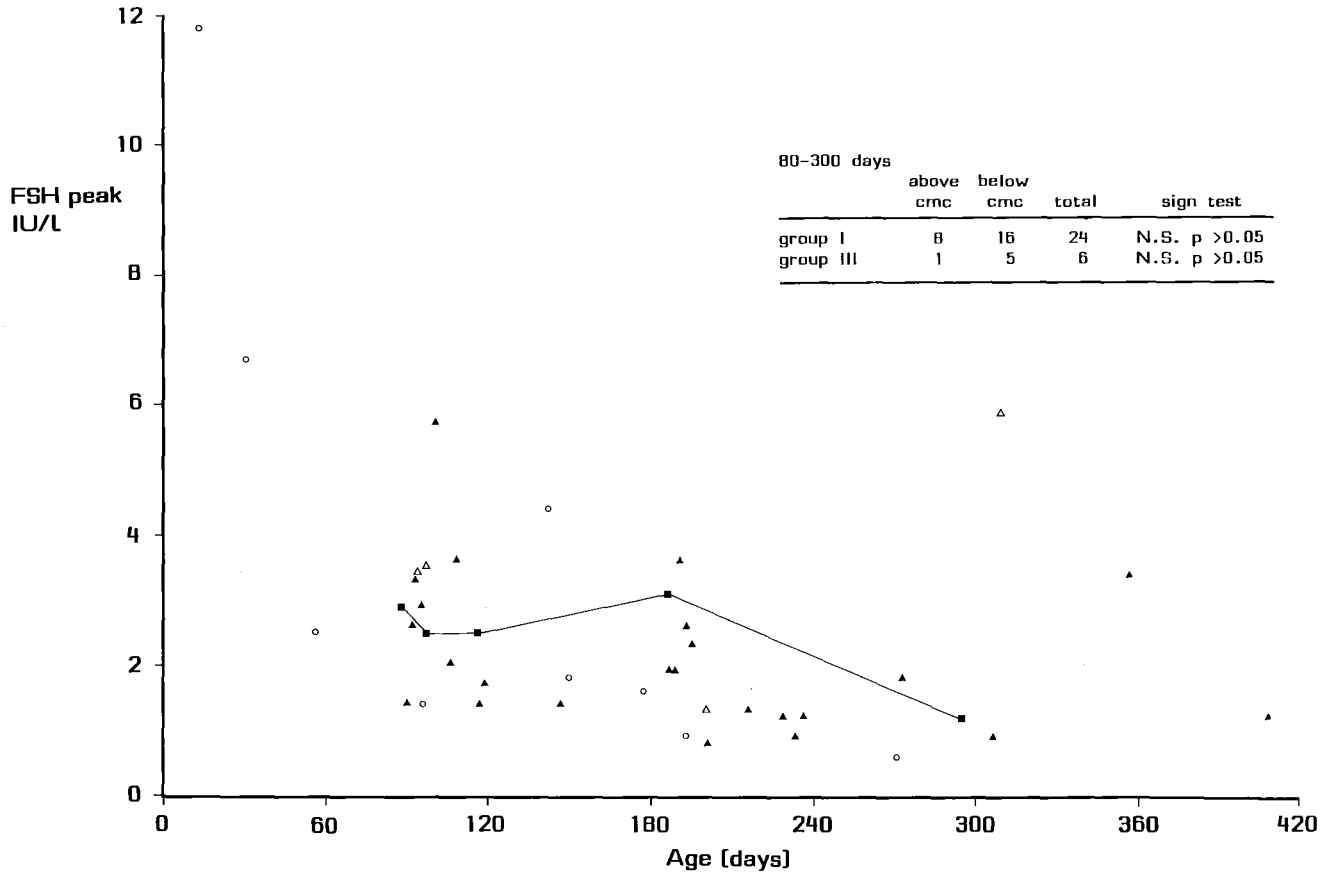


Figure 3.12[a]. Cross-sectional peak FSH serum values; comparing individual values of boys of groups I and III in relation to the cross-median curve of boys of group II. See foldout page 330.

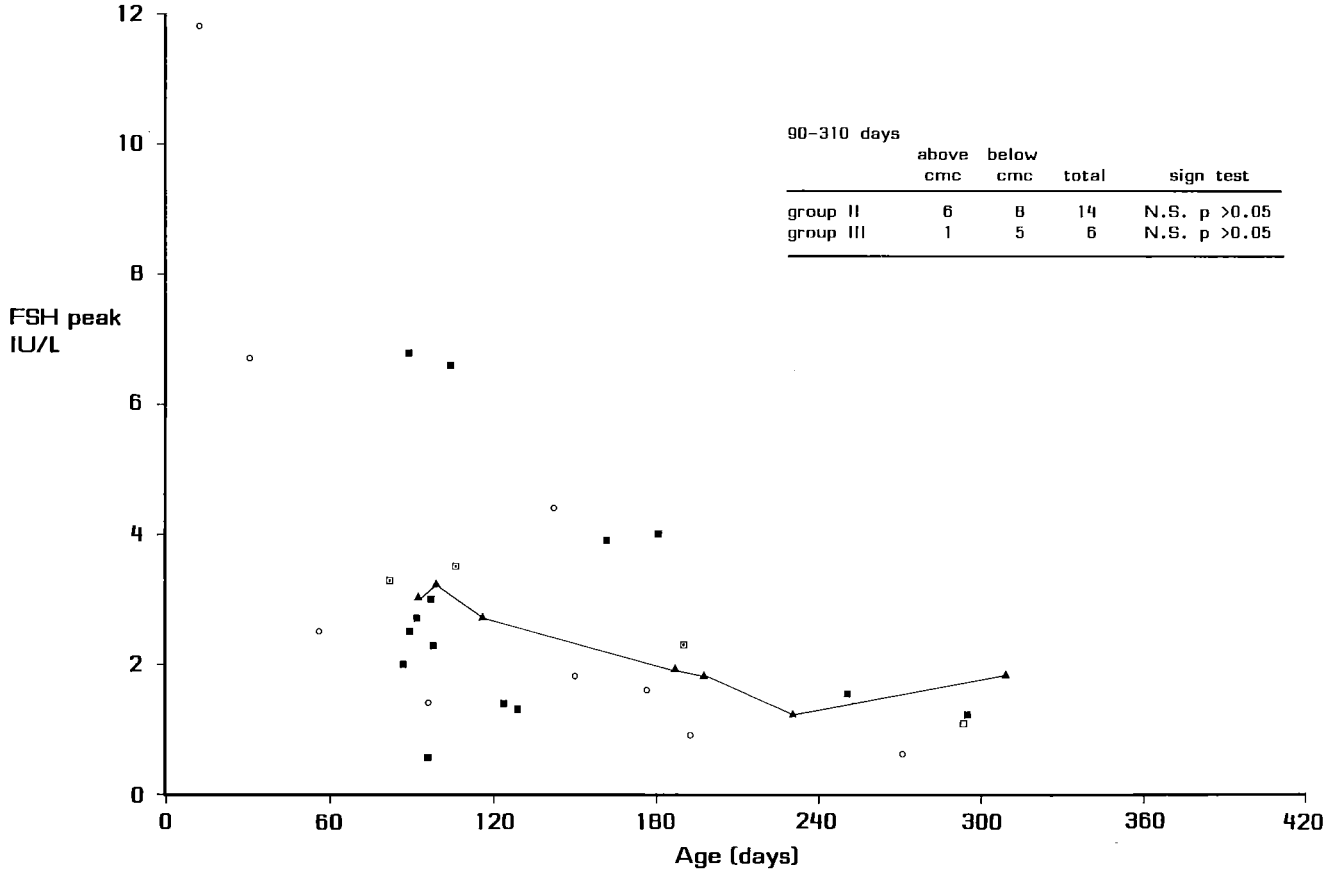


Figure 3.12[b]. Cross-sectional peak FSH serum values; comparing individual values of boys of groups II and III in relation to the cross-median curve of boys of group I. See foldout page 330.

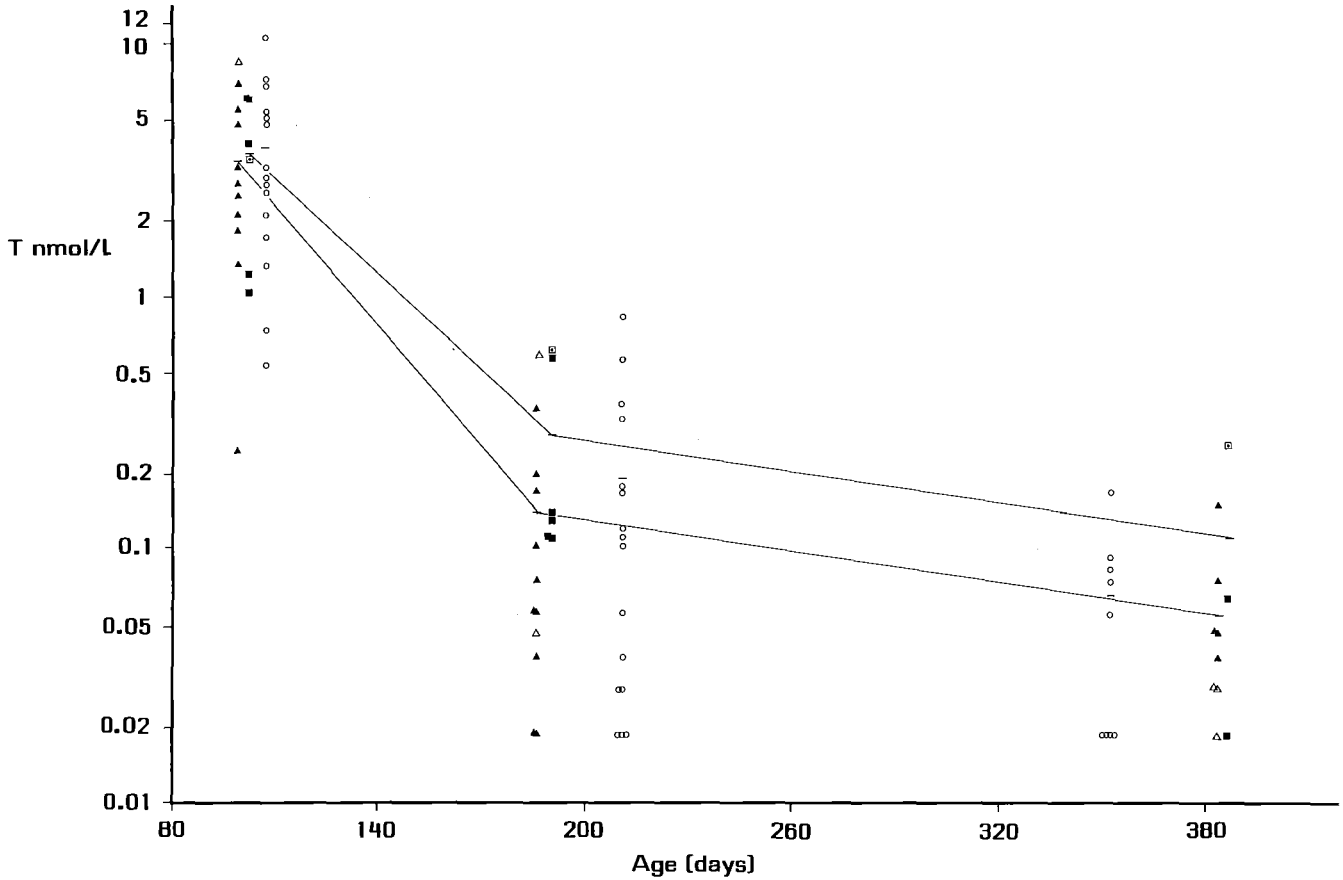


Figure 3.13. Individual longitudinal testosterone serum values (on log scale) of boys of groups I (lower line) and II (upper line) and individual cross-sectional testosterone serum values of boys of group III at approximately 3, 6 and 12 months of age (– = mean value). See foldout page 330.

Table 3.5. Longitudinal testosterone serum values (mean ± SEM) of boys of groups I and II and cross-sectional testosterone serum values (mean ± SEM) of boys of group III in age period X, Y and Z. See foldout page 330.

	age period X 80–126 days			age period Y 169–236 days			age period Z 330–410 days		
group	boys N	age (days) mean	testosterone nmol/l mean ± SEM	boys N	age (days) mean	testosterone nmol/l mean ± SEM	boys N	age (days) mean	testosterone nmol/l mean ± SEM
I persistent cryptorchidism	12	101	3.63 ± 0.73	12	188	0.15 ± 0.05	8	385	0.06 ± 0.02
II delayed spontaneous descent	6	104	3.83 ± 0.94	6	192	0.30 ± 0.11	3	388	0.12 ± 0.08
III controls	15	109	4.03 ± 0.75	17	212	0.20 ± 0.06	9	354	0.07 ± 0.02

No significant differences for serum testosterone comparing groups I, II and III per age period (Kruskal-Wallis test, $p > 0.05$)

Table 3.6. Change in serum testosterone values (mean ± SEM) of boys of groups I and II from age period X to Y and Y to Z. See foldout page 330.

group	age period X → Y: boys N	age period X → Y: change of testosterone nmol/l mean ± SEM	age period Y → Z: boys N	age period Y → Z: change of testosterone nmol/l mean ± SEM
I persistent cryptorchidism	12	-3.48 ± 0.69*	8	-0.13 ± 0.08**
II delayed spontaneous descent	6	-3.54 ± 0.91*	3	-0.19 ± 0.09

* significant change from age period X to Y (Wilcoxon matched pairs signed rank test, $p < 0.05$)
** no significant change from age period Y to Z (Wilcoxon matched pairs signed rank test, $p > 0.05$)
no significant differences in the change of serum testosterone between groups I and II (Mann-Whitney-U test)

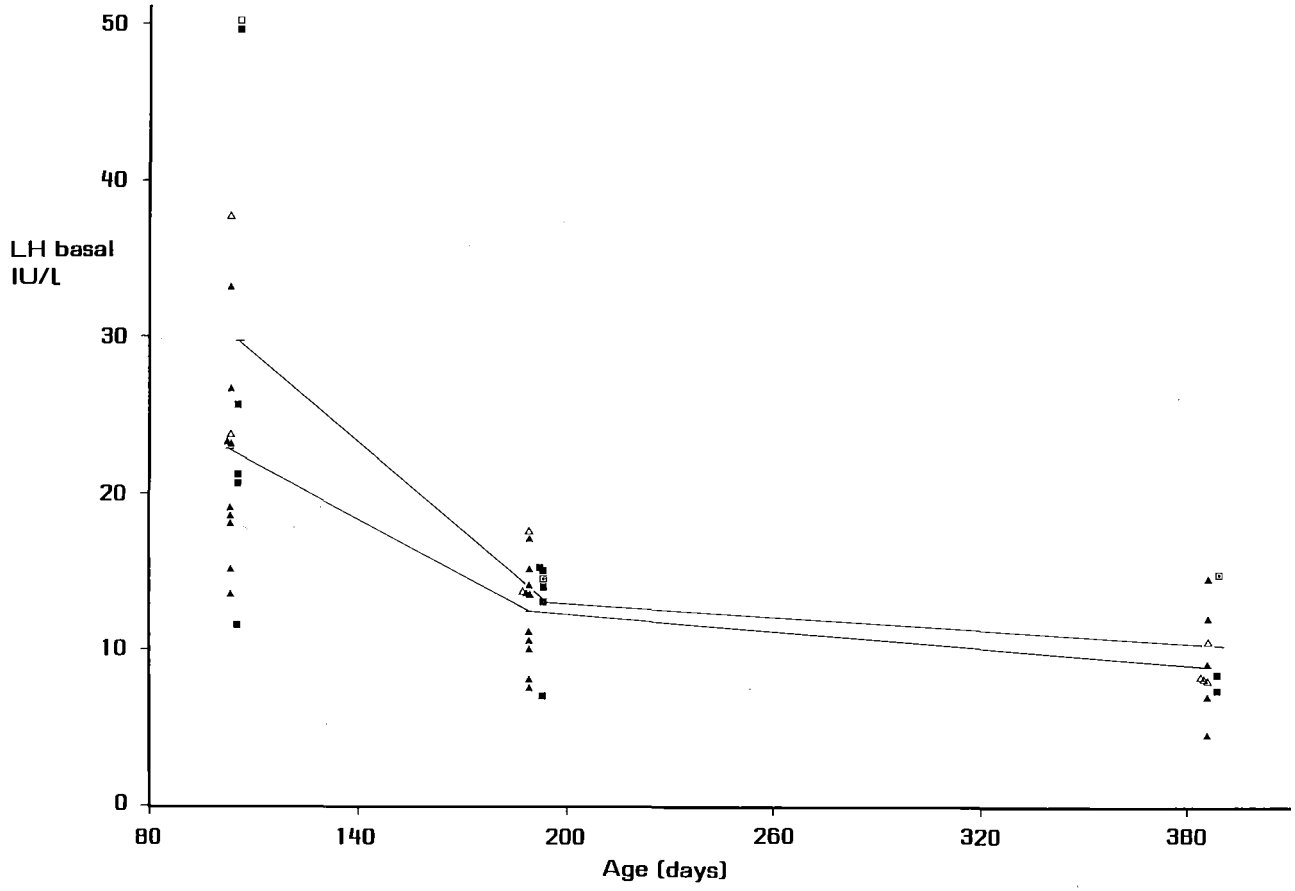


Figure 3.14. Individual longitudinal basal LH serum values of boys of groups I (lower line) and II (upper line) at approximately 3, 6 and 12 months of age (– = mean value). See foldout page 330.

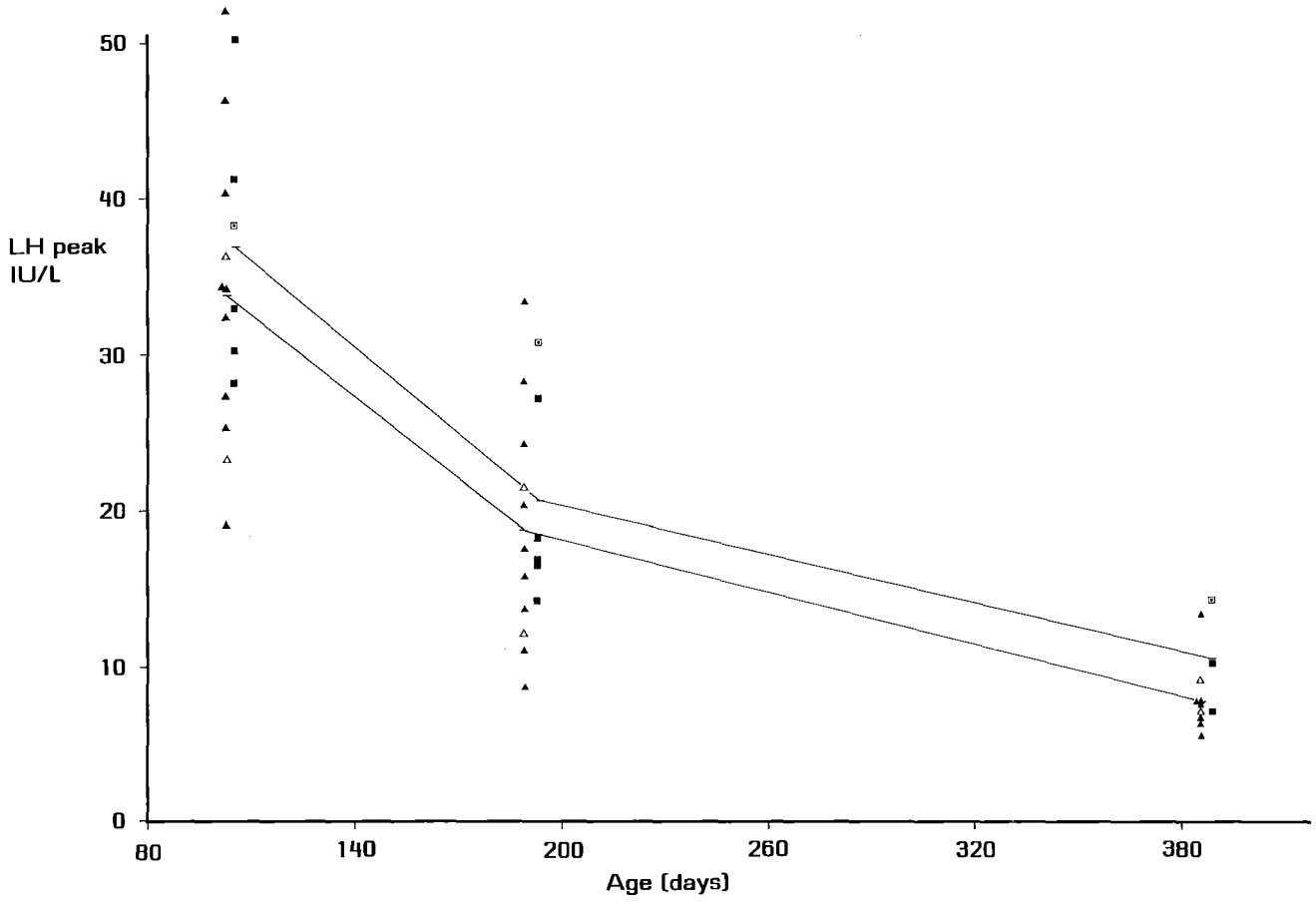


Figure 3.15. Individual longitudinal peak LH serum values of boys of groups I (lower line) and II (upper line) at approximately 3, 6 and 12 months of age (– = mean value). See foldout page 330.

Table 3.7. Longitudinal basal and peak LH serum values (mean ± SEM) of boys of groups I and II in age period X, Y and Z. See foldout page 330.

	age period X 80–126 days				age period Y 169–236 days				age period Z 330–410 days			
	boys	age (days)	LH IU/l mean ± SEM		boys	age (days)	LH IU/l mean ± SEM		boys	age (days)	LH IU/l mean ± SEM	
group	N	mean	basal	peak	N	mean	basal	peak	N	mean	basal	peak
I persistent cryptorchidism	11	102	4.55 ± 0.44	33.43 ± 3.00	11	188	2.50 ± 0.20	18.46 ± 2.30	9	385	1.81 ± 0.20	7.57 ± 0.75
II delayed spontaneous descent	6	104	5.93 ± 1.32	36.62 ± 3.33	6	192	2.62 ± 0.25	20.38 ± 2.73	3	388	2.07 ± 0.47	10.27 ± 2.08

no significant differences for basal or peak LH serum values comparing groups I and II per age period (Mann–Whitney-U test, $p > 0.05$)

Table 3.8. Change in basal and peak LH serum values (mean ± SEM) of boys of groups I and II from age period X to Y and Y to Z. See foldout page 330.

	age period X ⟶ Y			age period Y ⟶ Z		
	boys	change of LH IU/l mean ± SEM		boys	change of LH IU/l mean ± SEM	
group	N	basal	peak	N	basal	peak
I						
persistent cryptorchidism	11	- 1.96* ± 0.29	- 14.96* ± 2.64	9	- 0.68* ± 0.34	- 10.84* ± 2.81
II						
delayed spontaneous descent	6	- 3.27* ± 1.10	- 16.23* ± 4.55	3	- 0.83 ± 0.48	- 10.57 ± 3.62

* significant change from age period X to Y and Y to Z (Wilcoxon matched pairs signed rank test, $p < 0.05$)
no significant differences in the change of basal or peak serum LH between groups I and II (Mann-Whitney-U test, $p > 0.05$)

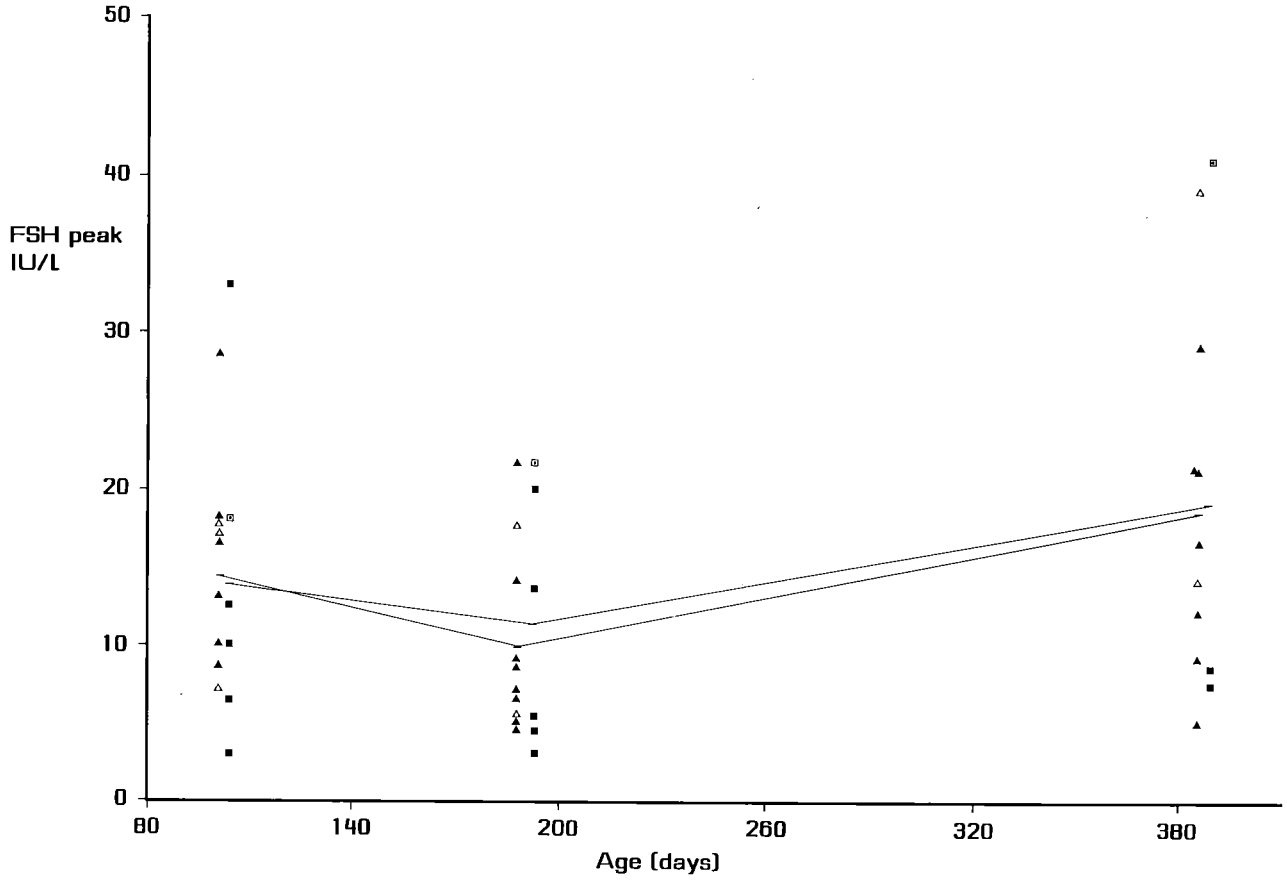


Figure 3.16. Individual longitudinal peak FSH values of boys of groups I (lower line) and II (upper line) at approximately 3, 6 and 12 months of age (– = mean value). See foldout page 330.

Table 3.9. Longitudinal peak FSH serum values (mean ± SEM) of boys of groups I and II in age period X, Y and Z. See foldout page 330.

group	age period X 80–126 days: boys N	age (days) mean	peak FSH IU/l mean ± SEM	age period Y 169–236 days: boys N	age (days) mean	peak FSH IU/l mean ± SEM	age period Z 330–410 days: boys N	age (days) mean	peak FSH IU/l mean ± SEM
I persistent cryptorchidism	10	101	2.86 ± 0.42	10	187	1.98 ± 0.37	9	385	3.70 ± 0.70
II delayed spontaneous descent	6	104	2.77 ± 0.87	6	192	2.27 ± 0.67	3	388	3.80 ± 2.20

no significant change from age period X to Y and Y to Z within groups I and II (test of Friedman, $p > 0.05$)
no significant differences for peak serum FSH comparing groups I and II per age period (Mann-Whitney-U test, $p > 0.05$)

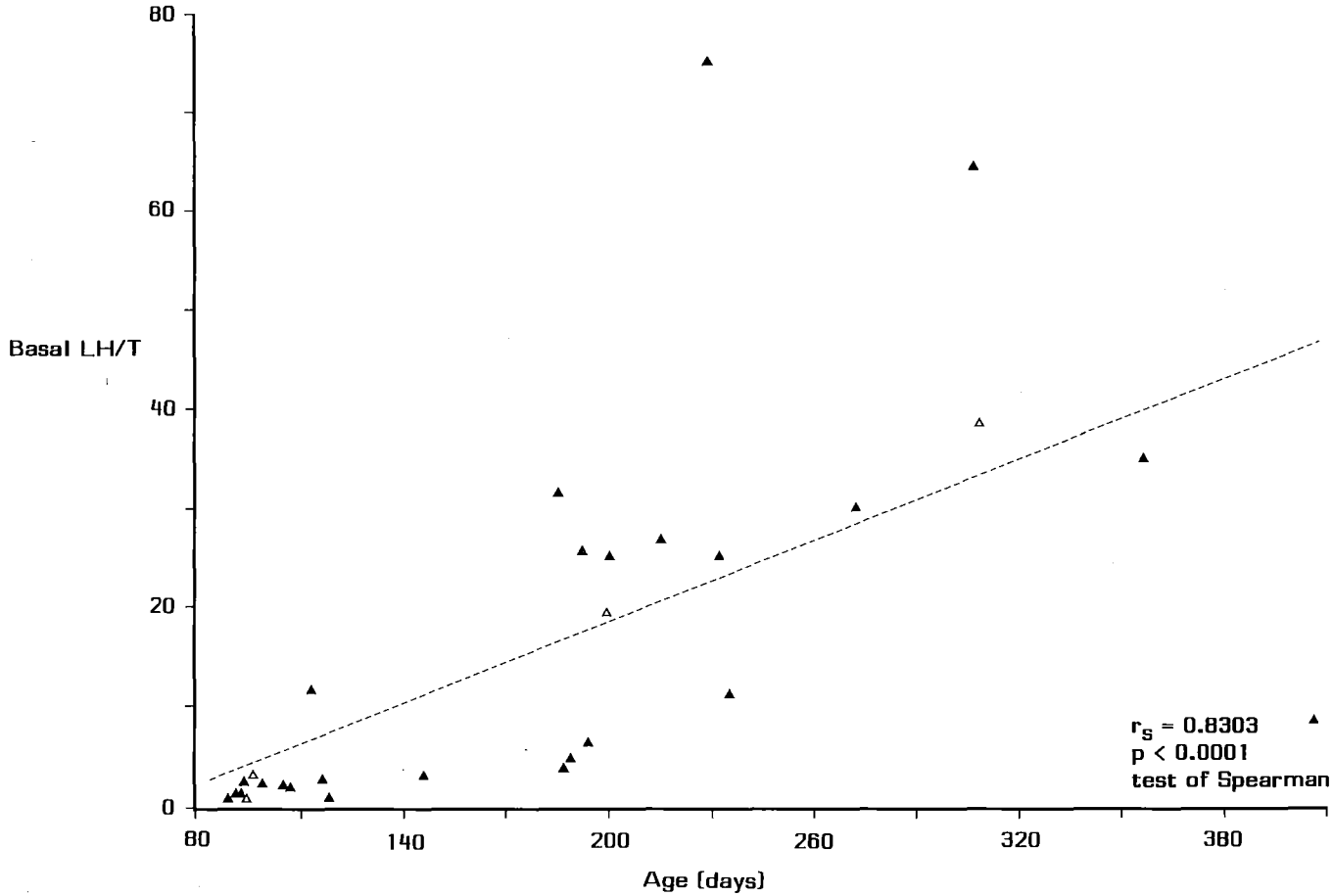


Figure 3.17[a]. Correlations between the ratio basal LH/T and age in the first year of life for boys of group I. See foldout page 330.

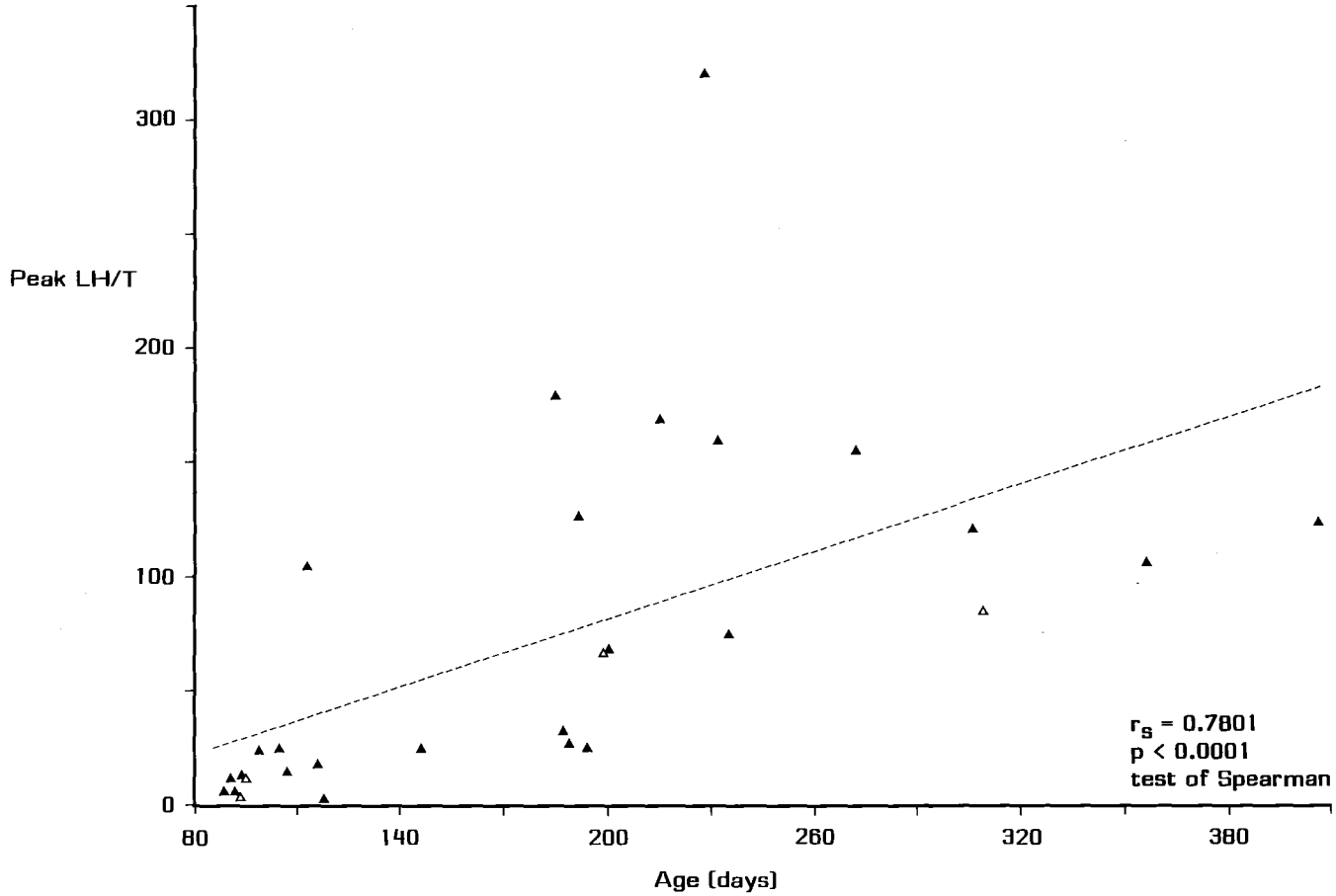


Figure 3.17[b]. Correlations between the ratio peak LH/T and age in the first year of life for boys of group I (n = 29). See foldout page 330.

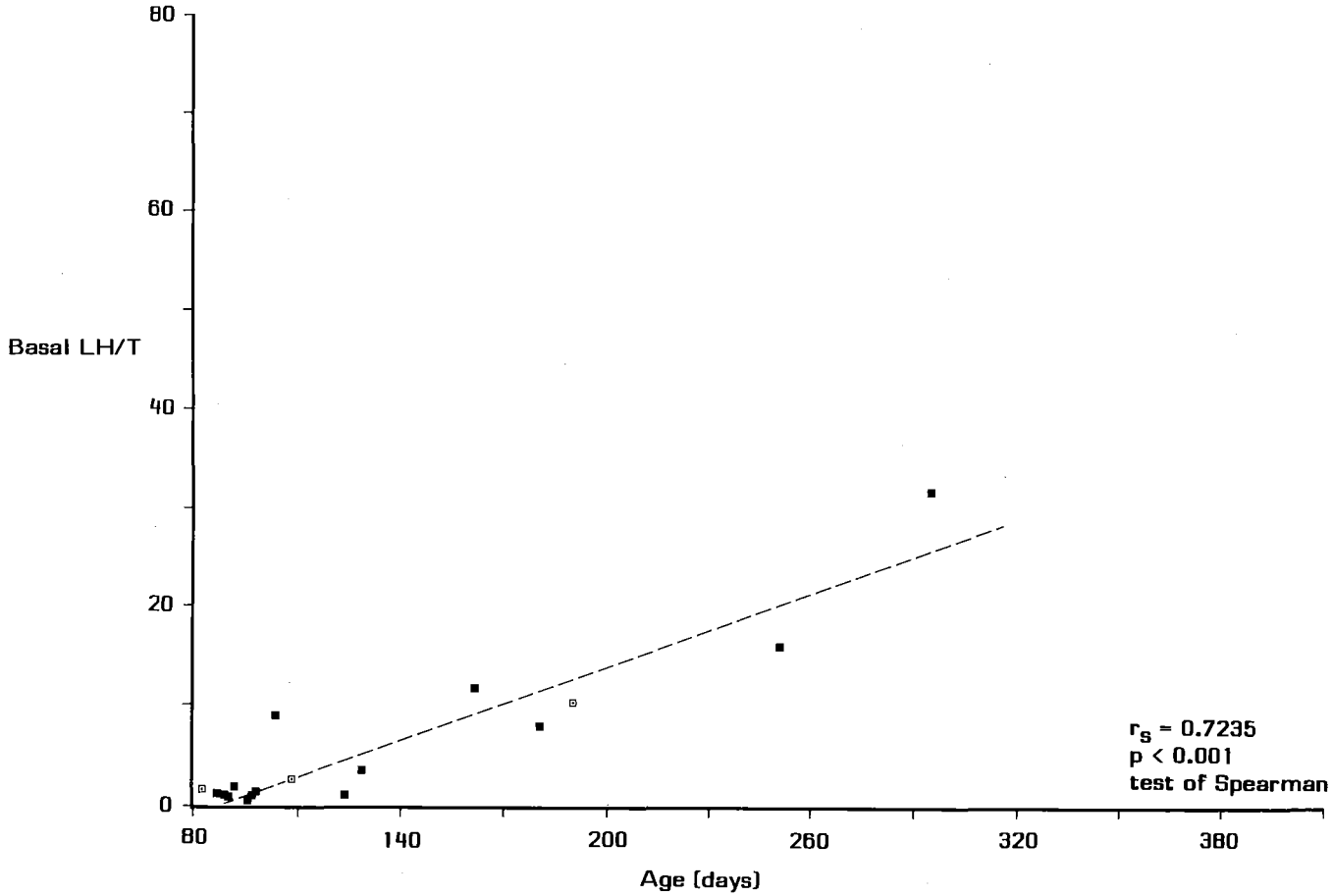


Figure 3.17c. Correlations between the ratio basal LH/T and age in the first year of life for boys of group II (n = 17). See foldout page 330.

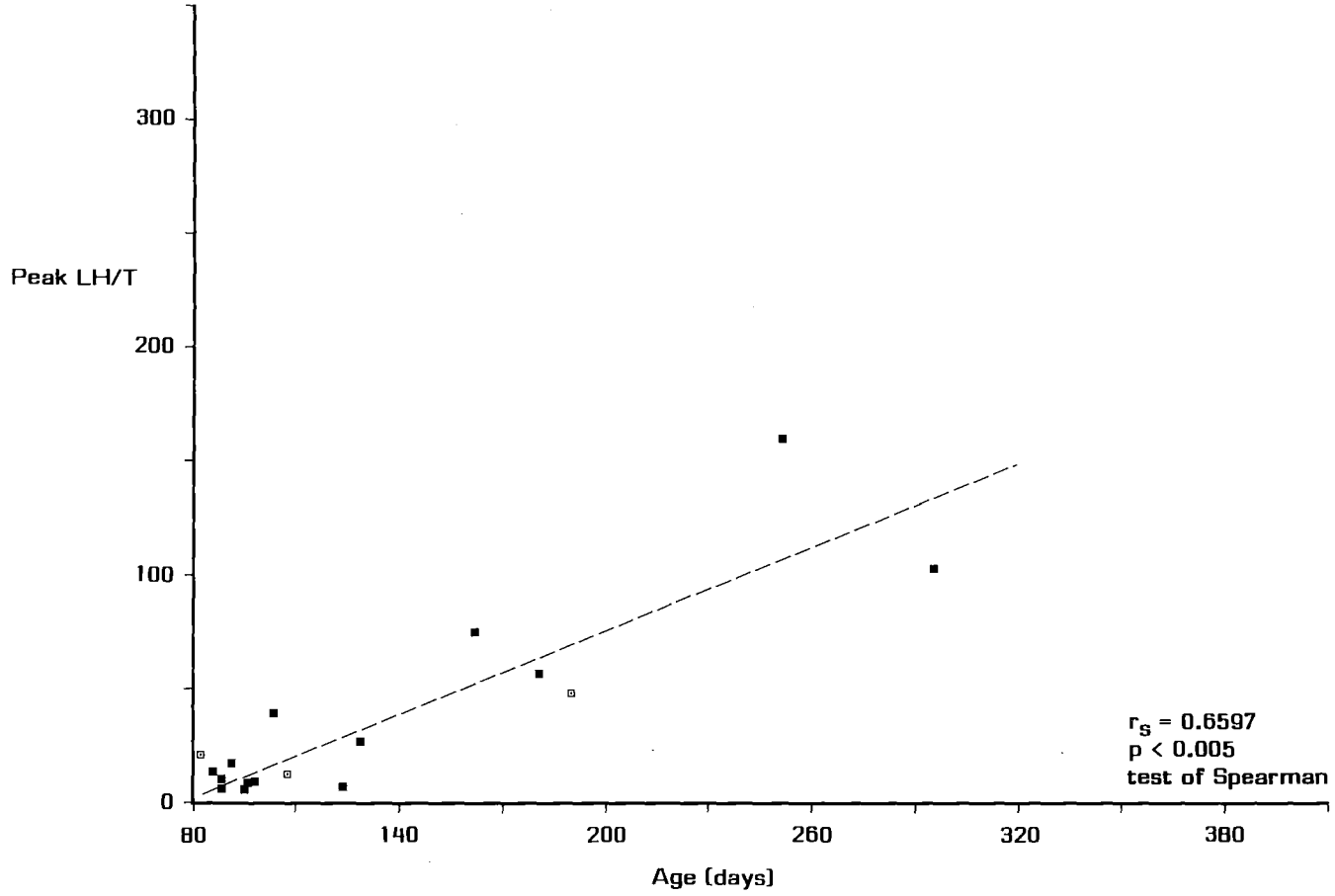


Figure 3.17[d]. Correlations between the ratio peak LH/T and age in the first year of life for boys of group II (n = 17). See foldout page 330.

Table 3.10. Results of HCG tests for serum testosterone of boys of group I (n = 22), group II (n = 7) and group III (n = 7).

group	boys N	serum testosterone nmol/l, mean ± SEM basal*	peak*
I	22	0.10 ± 0.02	13.51 ± 1.00
II	7	0.10 ± 0.03	16.00 ± 2.56
III	7	0.07 ± 0.01	10.90 ± 1.24

* comparison between group I, II and III: N.S.
(Kruskal Wallis test, $p > 0.05$)

Table 3.11. Results of HCG tests for testosterone precursors, testosterone and dihydrotestosterone for boys of group I (n = 11), group II (n = 7) and group III (n = 7).

		N	P nmol/l	N	17 OHPreg nmol/l	N	17 OHP nmol/l	N	DHEAS umol/l	N	Δ 4 nmol/l	N	T nmol/l	N	DHT nmol/l
group I															
basal	median	11	1.1	8	2.3	11	< 1.2	11	0.04	11	0.38	11	0.06	11	< 0.13
	range		< 0.5 - 2.2		1.1 - 9.0		< 1.2 - 1.9		< 0.02 - 0.58		< 0.35 - 0.84		0.02 - 0.38		< 0.13 -< 0.13
peak	median	11	1.3	8	3.5	11	1.5	11	0.12○	11	1.19○	11	15.○	11	1.83○
	range		0.7 - 3.0		1.3 - 5.8		< 1.2 - 2.2		0.07 - 1.20		0.52 - 1.54		5.6 - 20.		0.78 - 2.73
group II															
basal	median	7	2.1●	2	5.7	7	< 1.2	7	0.20□	7	0.56	7	0.07	7	< 0.13
	range		1.0 - 4.2		1.4 - 9.9		< 1.2 - 1.5		0.04 - 1.20		< 0.35 - 1.30		0.02 - 0.28		< 0.13 - 0.25
peak	median	7	2.1	2	4.4	7	2.1	7	0.30	7	1.31○■	7	14.○	7	1.66○
	range		0.7 - 2.8		0.9 - 7.8		< 1.2 - 4.4		0.11 - 1.40		0.87 - 2.20		8.8 - 30.		1.13 - 2.32
group III															
basal	median	7	1.3		N.D.	7	< 1.2	7	0.19	7	0.59	7	0.06	7	< 0.13
	range		1.1 - 3.0				< 1.2 - 1.6		0.03 - 0.59		< 0.35 - 0.80		0.03 - 0.13		< 0.13 - 0.14
peak	median	7	1.3		N.D.	7	1.5	7	0.35○	7	0.73	7	11.○	7	1.67○
	range		< 0.5 - 2.7				< 1.2 - 2.3		0.12 - 0.45		0.52 - 0.94		6.8 - 15.		1.00 - 1.96

○ significantly higher than basal values (Wilcoxon matched pairs signed rank test, $p < 0.05$)
● significantly higher than basal P of group I (Mann-Whitney-U test, $p < 0.05$)
□ significantly higher than basal DHEAS of group I (Mann-Whitney-U test, $p < 0.05$)
■ significantly higher than peak Δ 4 of group III (Mann-Whitney-U test, $p < 0.05$)
N = number of boys
N.D. = not done

3.5.5. Discussion

Delayed, spontaneous descent of the testis occurred in 50% of the boys that were enrolled in the study within the first three months of life. In 50% of these cases, the descent occurred before the third month. All boys that had delayed, spontaneous descent during the first year of life were born after a full-term pregnancy. In 6 of altogether 19 boys that had spontaneous descent during the first year of life, this occurred after the sixth month. In contrast, Scorer (1964; 1981) as well as Forest and coworkers (1984) stated that spontaneous testicular descent practically never occurs after the sixth month of life. Villumsen and Zachau (1966) were unable to time the occurrence of spontaneous descent in the first year of life, because they only saw the subjects at the fifth day of life and at one year of age.

Nineteen boys with 22 testes that had failed to descend spontaneously by the end of their first year of life, were enrolled in the double-blind, placebo-controlled study of the efficacy of LHRH nasal spray treatment (age group A, see chapter 4). Conforming with the overall low rate of success, this hormonal treatment resulted in the descent of only 2 of these 22 testes. Consequently, the other seven boys whose testes had failed to descend spontaneously by the end of the first year, were not subjected to such hormonal treatment.

In agreement with Forest and coworkers (1973; 1974), the cross-sectional testosterone serum analysis revealed elevated testosterone levels in the first six months of life in boys with descended testes. Noteworthy is the wide range, particularly in the first three months of life (see figure 3.4.).

Neither a cross-sectional nor a longitudinal evaluation of serum testosterone levels during the first year of life revealed significant differences from the age of 80 days, between boys that stayed cryptorchid and boys that had spontaneous descent or controls. These findings do not agree with those of Gendrel and co-workers (1980) who reported that up till the age of four months, plasma testosterone was significantly lower in boys who remained cryptorchid than in boys with spontaneous testicular migration.

Cross-sectional and longitudinal basal and peak LH and peak FSH serum values, likewise, showed no significant difference between boys that stayed cryptorchid and boys with delayed spontaneous descent in the first year of life. The small number of controls did not allow for a definite conclusion, although the levels of basal and peak LH and peak FSH were comparable with those of cryptorchid boys and boys with delayed, spontaneous descent. Basal LH values were even higher for boys with delayed spontaneous descent than for controls.

Consequently, there were no signs of a (transient) functional insufficiency of the hypothalamo-pituitary-gonadal axis in infants with undescended testes. This lack of a pituitary-gonadal disturbance in the boys that stayed cryptorchid through the first year of life is in conformity with our findings in the double-blind,

placebo-controlled study concerning cryptorchid boys aged 1 to 12 years (see chapter 4).

Neither serum testosterone values nor the results of the LHRH tests were of any prognostic value for spontaneous testicular descent in the first year of life.

We did not find any significant correlations between basal or peak serum LH and serum testosterone levels from 80 days through the first year of life in boys that stayed cryptorchid or in boys that had delayed, spontaneous descent. This contrasts with the positive correlations found by Gendrel et al. (1980) between testosterone and LH levels in infants that remained cryptorchid and in those that had delayed, spontaneous testicular descent. Hammond and coworkers (1979) found good correlations between serum T and gonadotropins in the male infant population, while Forest et al. (1974) found no correlations between serum T and gonadotropins. On the other hand, we did find a statistically significant correlation between the ratio basal LH/T and age as well as the ratio peak LH/T and age in the first year of life for boys who remained cryptorchid as well as for those with delayed spontaneous testicular descent. Towards the end of the first year of life, the ratio of basal LH/T and peak LH/T increased in the two groups. It emerged from the cross-sectional testosterone and LH values of our study that serum testosterone declined earlier to prepuberal levels than basal and peak LH values. Forest and coworkers (1976) described the same observations for basal LH and testosterone. The following explanations can be offered:

- High levels of maternal oestrogens drop rapidly after birth. Likewise, serum testosterone falls rapidly in the first week of life, probably due to the removal of HCG from cord blood. These two events may contribute to the rise of circulating gonadotropins, which may be responsible for the subsequent rise of serum testosterone after birth (Forest et al., 1973).
- The fall of oestrogens after birth may also provide an explanation for the subsequent rise of serum testosterone, because there is ample evidence that oestradiol directly inhibits testosterone production by enzyme inhibition (Yanaihara et al, 1972; Jones et al., 1978).
- The decrease of serum testosterone after the second month of life may be caused by a decreased response of the testes to endogenous gonadotropins. The decline of fetal Leydig cells in the infant testis after the first postnatal months may well be responsible for this decreased response.
- The decrease of basal and GnRH stimulated LH secretion in the first year of life might be due to the following mechanisms (see 3.4.):
  1. A sex steroid-dependent mechanism. In the first years of life the sensitivity of the gonadostat to circulating sex steroids increases ("low setpoint") subsequently resulting in suppression of gonadotropins by low amounts of circulating steroids.
  2. A sex steroid-independent mechanism. Intrinsic CNS inhibitory influences suppress the secretion of gonadotropins.

In our opinion, the lack of correlations between basal and stimulated serum LH

and testosterone values in the first year of life in boys with delayed spontaneous descent and boys that stayed cryptorchid favours the second theory. Our premise is in agreement with the suggestion of Winter (1982) that the reduced childhood secretion of gonadotropins might be the result of central inhibition of GnRH secretion.

Table 3.12. shows the changes in the plasma concentration of the precursors of testosterone in the five enzymatic defects affecting testicular testosterone biosynthesis as described by Forest (1981). The first three defects concern enzymes required for the formation of cortisol as well as testosterone. Consequently, each is associated with a more or less severe adrenal insufficiency and a compensatory increase in ACTH secretion resulting in a secondary increase in steroids situated above the enzymatic block. The enzymes 17,20-desmolase and 17 α-hydroxysteroid dehydrogenase (= 17-keto reductase) are only involved in the biosynthesis of testosterone. Therefore, patients with these enzymatic defects have intact glucocorticoid and mineralocorticoid secretion. In genetic males suffering from any one of these five enzymatic defects, insufficient secretion of testosterone by the fetal Leydig cells results in an absent or incomplete masculinization of the external genitalia ranging from a nearly male appearance with hypospadias to a nearly normal female appearance.

The boys of our study showed no clinical indications of a defect in the testosterone biosynthesis. All boys had a normally developed scrotum and a normal penis without hypospadias. None of them had bilaterally impalpable testes. Nor were there any clinical signs of adrenal insufficiency.

Table 3.12. Pattern of changes in the plasma concentrations of the precursors of testosterone in the five enzymatic defects affecting testicular testosterone biosynthesis (Forest, 1981; with permission).

Enzyme defect	Pregnenolone	Progesterone	17-Hydroxypregnenolone	17-Hydroxyprogesterone	DHA	Androstenedione	Testosterone
20-22 Desmolase	↘	↘	↘	↘	↘	↘	↘
17 α -Hydroxylase	↗↗	↗↗	↘	↘	↘	↘	↘
3 β -ol-Dehydrogenase	↗↗↗	↗	↗↗↗↗	↗↗	↗↗↗↗	±↗	♀±↗ ♂↘
17-20 Desmolase	↗↗	↗↗	↗↗	↗↗↗	↘	↘	↘
17-Keto-Reductase	*n*	*n*	±↗	±↗	±↗	↗↗↗↗	↘

Basal testosterone, dihydrotestosterone and steroid precursors were very similar for boys that stayed cryptorchid and boys that had spontaneous testicular descent in the first year of life, in comparison with boys that were born with normally descended testes. HCG stimulation resulted in a clear and identical rise of serum testosterone values in all three groups. In adult men, a clear rise of 17 α-hydroxyprogesterone level can be observed 24 hours after one single injection of HCG, and this level is still elevated at 72 hours, indicating inhibition of 17,20-lyase activity (Forest and Roulier, 1984). In our study, the steroid precursors

showed at best only a very small increase (Δ 4 and DHEAS) in the entire study population. Consequently, our hormonal data did not suggest enzymatic defects or enzyme inhibition in any of the boys, while their physical appearance and the normal stimulated DHT values excluded a 5 α-reductase deficiency.

3.5.6. Conclusions

Forty to fifty per cent of the testes that were undescended at birth descended spontaneously during the first year of life. Such delayed, spontaneous descent may even occur after the sixth month of life.

Our hormonal findings do not support the hypothesis of a (transient) functional insufficiency of the hypothalamo-pituitary-gonadal axis in infants with undescended testes.

Serum testosterone values and the results of the LHRH tests were of no prognostic value for spontaneous testicular descent in the first year of life.

No disorders in the biosynthesis of testosterone nor enzyme inhibition were found in our study population.

CHAPTER 4.

HORMONAL TREATMENT OF CRYPTORCHIDISM

4.1. THE HISTORY OF HORMONAL TREATMENT

4.1.1. Introduction

Hormonal treatment of undescended testes dates from the early thirties. Ascheim and Zondek (1928[a]; 1928[b]) noted the presence of a substance that stimulated the sex glands in the urine of pregnant women. Shortly afterwards, Shapiro (1930) reported genital growth and testicular descent by injections with Hypophysenvorderlappen Hormone (HVH) in a large percentage of boys and young men with hypogenitalism and cryptorchidism. Hamilton (1938; Hamilton and Hubert, 1938) induced descent in monkeys as well as in humans with testosterone propionate administered subcutaneously. They surmised that descent of previously retained testes obtained by anterior-pituitary-like (APL) substances might to some extent be due to the production of male hormone substances. The year before, Thompson et al. (1937) had published a literature review of APL treatment results. The success rate varied from 25 to 100%, but some studies involved very small numbers of patients. In his own study, descent occurred in only 4 of 21 undescended testes. None of the impalpable testes descended. Of the descended testes, two were of the migratory type, one testis could be pushed into the upper end of the scrotum before treatment and the fourth down to the lower end of the inguinal canal. He stated that in three of the four successful cases, the testes were of the type that commonly descends at puberty! He further stated that the findings at operation in several of the unsuccessful cases would suggest that anatomical factors were responsible for failure of descent. The dose and duration of the administration of APL substance varied but generally approximated 200 rat units three times a week by intramuscular injection for an average of five months. In most of the patients growth of penis, increase of testicular size and of pubic hair, higher erection frequency, more active, particularly masculine behaviour was reported.

In a study of 71 boys with 91 undescended testes, Bigler et al. (1938) evaluated the treatment of undescended testes with injections of either the gonadotropic substance of the urine of pregnant women or the gonadotropic substance of the anterior lobe of the pituitary gland. The success rate was 48% in the first group and 25% in the second group. Return to the former, undescended position occurred

in both groups. He thought that the better result in the first group was due to the greater number of rat units administered. Treatment was equally successful at any age after the first year but in view of the side effects was not recommended before the age of seven years. The APL substance of urine of pregnant women was advocated because of its higher potency (100 rat units/cm^3) so that smaller amounts could be used.

Almost 20 years later, Deming (1952) again evaluated the percentage of success of hormonal therapy for cryptorchidism with APL substance derived from pregnancy urine (chorionic hormone). He found extremes of 0% to 90% with many variations in between. He stated that if one testis descends while another one remains cryptorchid there must be some factor other than hormonal which influences the retention of the testis along the canal. The success rate in his own group was only five per cent and he advocated using chorionic hormone primarily adjuvant to surgery.

4.1.2. Human chorionic gonadotropin (HCG)

Human chorionic gonadotropin (HCG), which came into use at a later stage and is still being used today, is also derived from the urine of pregnant women. This product possesses mainly LH activity. Some investigators employed human menopausal gonadotropin (HMG) which chiefly possesses FSH activity. However, the results of treatment with HMG either alone or in combination with HCG seemed no better than those of HCG alone (Bergada and Mancini, 1973; Confalonieri et al., 1979).

Diverse schedules have been proposed for HCG treatment, varying in dosage as well as duration. In 1975, the International Health Foundation recommended an HCG dosage scheme related to age:

3-12 months	-	250 IU	per i.m. injection
1- 6 years	-	500 IU	two times a week
6 years and over	-	1,000 IU	for five weeks

Forest and coworkers (1984) found no fault with the total dose of this scheme, ranging from 2,500 IU to 10,000 IU, but they questioned both dosage and duration. They tried out various schemes, starting with seven intramuscular injections over a period of two weeks and eventually reached an optimal dosage scheme of four injections at intervals of either four or five days. It appeared that four HCG injections given at five day intervals generated similar testosterone secretion as seven injections over the same period of time, while circulating levels of HCG remained elevated in terms of LH equivalent biopotency and in the puberal range for about four days. The dose they used was 100 IU/kg or approximately 2,500 IU/m^2 per injection, twice the amount recommended by the International

Health Foundation, but their total dose was not much different, ranging from 4,000 to 15,000 IU.

Many studies have been published over the years concerning the results of HCG treatment and the various factors that may influence the success of hormonal therapy. In a study of more than 1200 patients, Bergada (1979) found that 30-40% of the testes responded satisfactorily to HCG. The group of Job (Canlorbe et al., 1979) reported complete descent in 40% of more than 300 cryptorchid boys. In a review of three large European studies, Bierich (1982) described the individual rates of success as being very similar. The overall success rate amounted to a good 50% with HCG treatment, resulting in the descent of 753 of 1400 testes. Dickerman and coworkers (1983) reported a success rate of 25% in 128 prepuberal boys. With their diverse protocols, the group of Forest et al. (1984) achieved an overall success of 36% in the treatment of 558 undescended testes.

All authors agreed that the position of the testis before treatment is of the utmost importance for successful hormonal therapy. The lower the pretreatment location of the testis, the better the treatment results. For prescrotal or gliding testes, Knorr (1970) reported a success rate of 99%. Bierich (1982) felt that of all undescended testes, the prescrotal ones would benefit most from hormonal therapy. He suggested that the lower success rate reported by Bergada compared with the three European studies was due to the fact that the Argentine author had not included prescrotal testes. The rate of success reported for impalpable testes contrasts shrilly with that for prescrotal testes, ranging from 32% (Knorr, 1970) to zero (Dickerman et al., 1983).

The age of the patients also seemed to play an important part in the outcome of hormonal therapy. Most authors stated that the success of hormonal treatment was lower in the first years of life (Knorr, 1970; Dickerman et al., 1983; Forest et al., 1984). Garagorri et al. (1982) found only nine per cent success in patients treated from 6 to 35 months of age. Bierich (1982) found lasting success in 20% of the boys treated before their sixth year against 70% for older children. He felt that the difference in response was due to the age-related increment of Leydig cells. The increase of plasma testosterone after HCG treatment in the age group of 10 to 13 years was twice as high as that found in infancy (Bierich, 1979).

Bierich (1979) found significantly higher post-treatment testosterone values in successfully treated than in unsuccessfully treated boys. In contrast, Canlorbe et al. (1979) found a lower testosterone response in successfully treated patients. Forest (1979) found no differences in end-treatment testosterone values from six months to puberty.

Bierich (1979) observed approximately the same treatment results in unilateral and in bilateral cryptorchidism. Others found a higher success rate in bilateral than in unilateral cryptorchidism (Bergada, 1979; Canlorbe et al., 1979), or just the opposite (Garagorri et al., 1982; Dickerman et al., 1983).

A second HCG course was advocated by several investigators if the first HCG treatment had partial success (Bierich, 1979; Dickerman et al., 1983; Forest et al.,

1984). Pagliano Sassi (1979) felt a second HCG course was useless.

A return of the testis to the former, undescended position was reported by several groups (Bierich, 1979; Forest et al., 1984). Therefore, these authors recommended that the therapist follows the child for a considerable length of time after cessation of HCG administration and, if necessary, repeats the treatment.

Whatever protocol was used, a clear reaction was usually observed in the genitalia, such as increased size of penis and testes, increased frequency of erection, roseate oedema of the scrotum as well as psychic alterations, (Forest et al., 1984). The symptoms generally disappeared soon after cessation of treatment.

Two large prospective studies have been reported concerning the fertility of cryptorchid boys treated with HCG in the prepuberal period. Knorr (1979[b]) examined the ejaculate of 138 boys over 17 years of age, who were treated for undescended testes at the age of 6 to 13 years. The treatment consisted of HCG alone, surgery alone or unsuccessful HCG treatment followed by surgery. He concluded that only 39% of the patients treated for whatever type of undescended testis presented with a normal spermatogram and that the prognosis for fertility is no poorer after HCG treatment than after surgery. Fertility was significantly lower in bilateral (29%) than in unilateral (46%) cryptorchidism. The age at treatment, ranging between 6 and 13 years seemed to have no significant influence on the results. Therefore, he felt that placing the undescended testis in the right position at school age in no way guaranteed a normal spermatogenesis in later life. Zamudio-Albescú (1979) examined 66 men who had all been treated with HCG at the age of 6 to 14 years followed by surgery if the hormonal treatment was unsuccessful. Fertility was evaluated by means of serial studies of sperm. The fertility rate for the whole group was 59%. The fertility rate was higher for the patients cured with HCG alone (74%) than for the patients submitted to complementary orchiopexy (51%). Furthermore, he also found that the post-treatment fertility rate was higher for unilateral cryptorchidism (81%) than for treated, bilateral cryptorchidism (38%).

Few authors described the mode of action of treatment with gonadotropins for undescended testes. Deming (1952) studied pre-adolescent macaque monkeys before and after injection of gonadotropic hormone. He found a 50% increase in testicular size, consisting mainly of an increase in the diameter of the tubules with some increase in interstitial tissue. The vas deferens had enlarged and elongated and the vascularity of the whole cord was greatly accentuated. The cremaster muscle fibres were twice the size of the control fibres. He surmised that the same changes may be produced by the hormonal therapy in the human male child causing testicular descent unless mechanical obstructive factors or structural abnormalities are present. Bierich (1979) assumed that the high local concentration of testosterone produced by the interstitial cells under the influence of HCG exerts a strong effect on the germinal epithelium and thus on growth and development of the gonad. However, he did not suggest in what way the actual

descent of the testis might be influenced. Forest and coworkers (1984) stated that the mode of action of HCG in postnatal testicular descent is still poorly understood, but that both HCG itself and testosterone, produced in response to HCG, play a role. Here again, remarks concerning the actual descent of the testis were lacking.

4.1.3. Luteinizing-hormone-releasing hormone (LHRH)

The effect of intranasally administered LHRH on gonadotropin secretion was first evaluated in 1973. London et al. (1973) showed that in adult men the response of LH and FSH to 5 mg LHRH, administered intranasally, is comparable to the gonadotropin response to 100 μg LHRH, administered intravenously. Therefore it was concluded that 2% of the intranasally administered LHRH was absorbed. Of the various doses of LHRH administered intranasally (1.25, 2.5, 5 mg) 2.5 mg was the minimal amount of LHRH required to produce the maximal LH response. The minimal amount required to produce the greatest change in FSH levels remained to be determined, since there was no significant difference between the mean response to 1.25, 2.5 or 5 mg. Evaluating gonadotropin release after intranasally administered LHRH in adult men and women, Dahlén et al. (1974) found a dose-dependent LH release after 0.5-2.0 mg LHRH. FSH release was not apparent. Furthermore, he found the LH release after 2.0 mg LHRH in the same range as seen after i.v. injection of 25 μg indicating that approximately 1% of the intranasal LHRH reaches the circulatory system.

Bourguignon et al. (1974) measured serum levels of LHRH by radioimmunoassay in four young men following the intranasal administration of 2 mg synthetic LHRH. The initial rise of serum LHRH was seen at 2.5 minutes and the peak was reached at 15 minutes. A rapid response in serum LH was observed, the peak occurring between 30 and 45 minutes, while FSH levels did not change significantly. It was calculated that 1.25% of the dose was absorbed.

Hagberg and Westphal (1982) made a dose response curve for LH and FSH release in five prepuberal boys with undescended testes, after i.n. administration of a total of 1.2 mg LHRH in three doses over a period of eight hours. Only a small increase of LH was found at the end of the period. Höcht, likewise, showed profiles of gonadotropin secretion after the administration of 400 μg LHRH i.n. in three doses without clear results (Von der Ohe, 1982). Rajfer and coworkers (1984) demonstrated that in adult male volunteers 200 μg LHRH was the minimal intranasal dose capable of achieving a significant LH response, which usually occurred within 30 minutes after insufflation. In cryptorchid boys, the same group found a significant increase of serum LH levels at 30 and 60 minutes after intranasal administration of 200 μg LHRH (Rajfer et al., 1986). No reports have appeared concerning serum levels or urinary excretion of LHRH after intranasal administration of LHRH in prepuberal boys.

The first successful attempt to treat cryptorchid boys with LHRH was reported

by Bartsch and Frick in 1974. By administering 20 μg LHRH intramuscularly once a day for 14 days, they achieved complete descent in 14 of 16 undescended testes (87.5%).

Happ and coworkers (1975) were the first to report the effect of intranasal LHRH therapy in boys with undescended testes. Subsequently, LHRH nasal spray treatment has been used in open and placebo-controlled studies with a success rate varying from 9-78% (table 4.1.). Dosage and duration of the LHRH intranasal administration differed in the various studies. Happ et al. (1978) treated their patients with 200 μg LHRH six times daily (before and after meals, one puff of 100 μg in both nostrils) for a duration of ten weeks at most. They concluded that distinctly increased gonadotropin serum levels could be attained in prepuberal cryptorchid boys with as little as 200 μg of LHRH i.n. The repeat stimulation after an interval of one hour was performed to take advantage of the priming effect of an initial dose, as previously suggested by Beck and coworkers (1976). Other workers subsequently reported the administration of 400 μg LHRH, three times a day for a period of four weeks with similar results (Hagberg and Westphal, 1982; Hadziselimovic et al., 1982; Borkenstein et al., 1983). It is suggested that more frequent LHRH stimulation may lead to down regulation (Hadziselimovic, 1983[b]).

Table 4.1. Success rates reported for LHRH nasal spray treatment.

	LHRH nasal spray			patients		testes	complete descent %	
author	dose/24 h	duration (wks)	-/+*	N	age (yrs)	n	patients	testes
Happ et al., 1978	6 x 200 ug	1-10	-	25	1-11	36		64
Pirazzoli et al., 1978	6 x 200 ug	1	-	9	5-12	9	22	22
	2 x 500 ug	1	-	13	5-12	13	39	39
Zabransky, 1981	6 x 200 ug	4	-	40	1-14	50		78
Cacciari et al., 1982	6 x 200 ug	1	-	23	3-12	23	22	22
	2 x 500 ug	1	-	24	3-12	24	38	38
Hagberg and Westphal, 1982	3 x 400 ug	4	-	49	2-10	56		61
Hadziselimovic et al., 1982	3 x 400 ug	4	-	60	10mos-14	81		62
Borkenstein et al., 1983	3 x 400 ug	4	-	53	median 5,6	68	49	57
Van der Meijden et al., 1984	6 x 200 ug	4	-	29	2-12	39		13
Schwarz et al., 1985	3 x 400 ug	4	-	119	1-12	171		37
De Muinck Keizer et al., 1986	3 x 400 ug	2x 4	-	227	1-13	271		18
Illig et al., 1977	6 x 200 ug	4	+	46	1-12	61		38
Bertelsen et al., 1981	6 x 200 ug	4	+	23	5-12	34	26	24
Hagberg and Westphal, 1982	6 x 100 ug	4	+	47	2-10	61		28
Karpe et al., 1983	6 x 200 ug	4	+	25	3- 8	25	20	20
Wit et al., 1985	3 x 400 ug	4	+	26	1-12	35		17
De Muinck Keizer et al., 1986	3 x 400 ug	4	+	121	1-13	151	9	9

* - open study. + placebo controlled study

4.1.4. Discussion

Reviewing the literature regarding treatment for undescended testes with gonadotropic hormones (APL and HCG) reveals a remarkable divergence in the rates of success reported for this modality. In the early years, involving treatment

protocols of long duration, percentages of testicular descent varying from 25% to 100% were reported. For human chorionic gonadotropin, which subsequently came into use, the rate of success varied from 25% to 50% in a number of large series. Several factors may have influenced the divergent results:

1. All authors agree that the pretreatment testicular position is a determining factor. The lower the pretreatment location of the testis, the better the results of treatment. This is illustrated by the fact that the percentage of success for impalpable testes has been reported as being zero, while a success rate of 99% has been reported for prescrotal testes.
2. Most authors agree that the age at treatment plays an important role. The success rate of hormonal therapy was lower in the first years of life.
3. Most authors agree that a repeat course of HCG enhances the final rate of success if the first treatment course had partial success, or in case the testis returns to its former, undescended position after complete descent had been achieved.
4. There is less agreement concerning the influence of laterality on the success of hormonal treatment (unilateral vs. bilateral, leftsided vs. rightsided).
5. The importance of an optimal, minimal dose of HCG is not disputed. Too small a dose may be ineffective, while large doses result in considerable side effects. However, it appears to be extremely difficult to determine the optimal dosage scheme. The percentages of success are no yardstick, as these percentages are influenced by many factors as listed above. Forest's final protocol alleviates the burden of treatment as it reduces frequency and duration compared with the schedule suggested by the International Health Foundation, while the rate of success appears to be similar. The higher dose per injection caused obvious side effects.
6. There is no consensus of opinion regarding any correlation between testosterone response to HCG treatment and the rate of success. Most authors do not mention the mode of action of hormonal treatment or merely state that the mechanism is poorly understood.

In the discussion and conclusions of our own study of LHRH treatment for cryptorchidism (see 4.3.), the clinical and hormonal data reported in the literature for this hormonal treatment will be discussed and, if feasible, compared with the results of HCG treatment.

4.2. LHRH NASAL SPRAY TREATMENT FOR CRYPTORCHIDISM; A PILOT STUDY

In view of the good results reported by some authors for LHRH treatment of cryptorchidism, we decided to carry out a clinical investigation of this modality. We first initiated a pilot study, lasting from June to October 1982, involving 22 prepuberal boys with either unilateral or bilateral undescended testes.

4.2.1. Patients and methods

Twenty-two healthy, prepuberal boys aged 3 to 13 years, with 26 undescended testes, were treated with LHRH nasal spray (Cryptocur®) after informed consent had been obtained from the parents. For a period of four weeks, one puff (= 200 μg) LHRH was sprayed into each nostril three times a day before meals. If the results were insufficient, the procedure was repeated after an interval of four weeks. Before, during, and after the therapeutic regimen, the children were examined independently by both authors as described in chapter 2. Utmost care was taken to ensure exclusion of retractile testes.

4.2.2. Results

As shown in table 4.2., LHRH nasal spray therapy resulted in the complete descent of 17 testes (65%) in 13 boys (59%). Figure 4.1. shows the most caudal position of the testis before and after LHRH treatment. It appeared that 13 (76%) of the 17 testes that descended completely could be manipulated to at least the scrotal entrance before treatment. Return of the testis to the former, undescended position occurred in one boy with unilateral cryptorchidism, three months after successful treatment. He underwent another course of LHRH therapy, which once again resulted in complete descent. No adverse effects of the hormonal treatment were observed in any of the boys. No compliance problems occurred.

Table 4.2. Results of pilot study.

patients			testes	complete descent	
	age (years)			patients	testes
N	range	mean ± SD	n	N (%)	n (%)
22	3–13	8.9 ± 2.8	26	13* (59)	17 (65)

* eight boys needed two LHRH courses and one relapse also required a second LHRH course

4.2.3. Discussion

The results of this pilot study seemed to indicate that LHRH nasal spray therapy was indeed an effective modality for treating boys with undescended testes. The patient series was too small to draw definite conclusions, but the results did warrant further investigation.

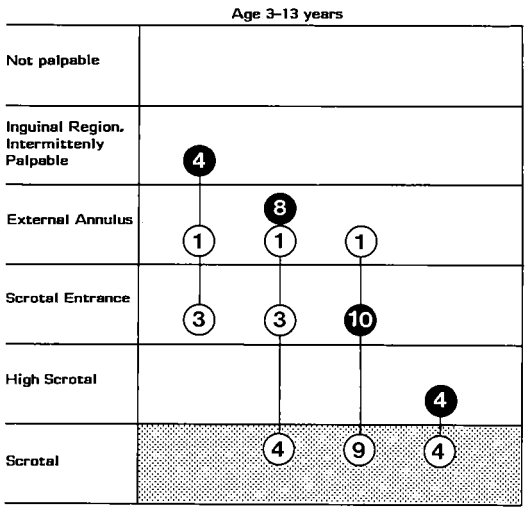


Figure 4.1. Most caudal testicular position before ● and after ○ LHRH treatment in the pilot study.

4.3. LHRH NASAL SPRAY TREATMENT FOR CRYPTORCHIDISM; DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

4.3.1. Aims of the study

The positive results achieved with LHRH nasal spray in the pilot study, prompted a double-blind, placebo-controlled clinical investigation, involving a large series of prepuberal boys of various ages, with unilateral or bilateral cryptorchidism. We also wanted to determine whether hormonal analysis might indicate the mode of action of LHRH and provide a prognostic aid.

4.3.2. Patients and methods

Between October 1982 and April 1985, a total of 252 prepuberal, cryptorchid boys were enrolled in the double-blind, placebo-controlled study and treated with LHRH nasal spray. Cryptorchidism was unilateral in 203 boys (104 rightsided, 99 leftsided) and bilateral in 49. The study population was divided into three age groups: A = 1-2 years (52 boys); B = 2-6 years (100 boys); and C = 6-12 years (100 boys). Table 4.3. gives the particulars for each age group. Our study population did not include boys who had previously undergone either hormonal or surgical treatment for cryptorchidism; boys with retractile testis; boys with truly ectopic testes (perineal, penile, etc.); boys with concomitant inguinal hernia; or boys with chromosomal or dysmorphic syndromes.

Table 4.3. Classification of study population.

age group	boys	age (years) range	age (years) mean ± SD	cryptorchidism unilateral right	cryptorchidism unilateral left	cryptorchidism bilateral
A	52	1- 2	1.5 ± 0.3	16	30	6
B	100	2- 6	4.3 ± 1.2	45	41	14
C	100	6-12	9.0 ± 1.7	43	28	29
total	252	1-12	5.6 ± 3.3	104	99	49

The children were all examined independently by both authors, following a standard procedure and using standardized case report forms as described in chapter 2.

After obtaining informed consent from the parents, we allocated the patients randomly and blindly to treatment with either synthetic LHRH (Cryptocur®) or placebo. The daily intranasal dose amounted to 1.2 mg, one puff of 200 μg in each nostril three times a day before meals. After four weeks of treatment followed by another four weeks without treatment, the code was broken and the results evaluated. If treatment proved unsuccessful, LHRH-treated subjects were given a second course of treatment, while the boys that had been on placebo received one or two courses of LHRH, as required. For a schematic presentation of the study protocol excluding follow-up period, see figure 4.2.

Treatment was considered successful if the testis was either spontaneously intrascrotal, or capable of being manipulated fully into the scrotum without retracting immediately. If so, the patient was re-examined after 3, 6 and 12 months, and subsequently once a year. In case of withdrawal of the testis to the former, undescended position, the patient was given another course of LHRH nasal spray.

Testicular volume was determined before and after the double-blind period with an orchiometer after Prader (see 2.3.2.). In view of the limited accuracy of

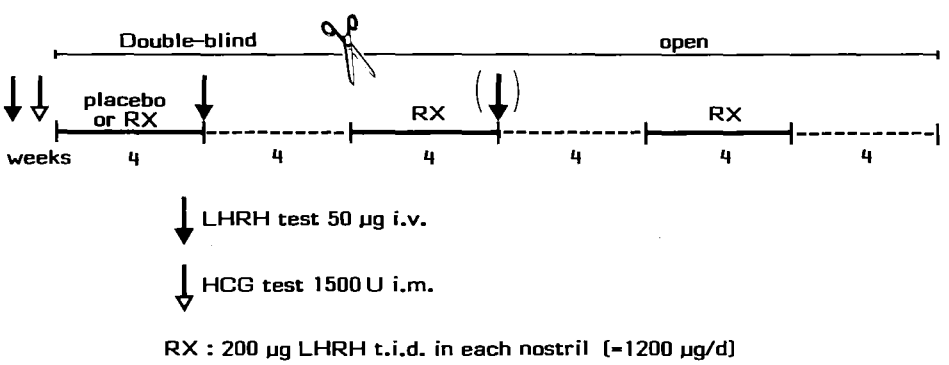


Figure 4.2. Study protocol.

this measuring technique, we only recorded an increase of testicular volume if this amounted to at least 1 ml.

Basal and stimulated LH and FSH levels were determined with two LHRH tests, one carried out before and one immediately after the first four weeks. The placebo group had a third LHRH test after their first true treatment course. An HCG test was only carried out once, before treatment. After treatment, basal testosterone values were determined in the course of the LHRH test. The procedure for hormonal evaluation is described in detail in chapter 2.

Sixty-one, age-matched, healthy prepuberal boys served as controls for the hormonal analyses, with informed consent from the parents. These boys had been referred to us for evaluation of their testicular position; the testes were found to be fully descended. Divided for age, there were 10 boys in group A (1-2 yrs), 28 in group B (2-6 yrs), and 23 in group C (6-12 yrs). The age distribution for control subjects and cryptorchid boys is given in figure 4.3. Frequency calculation is relative to total.

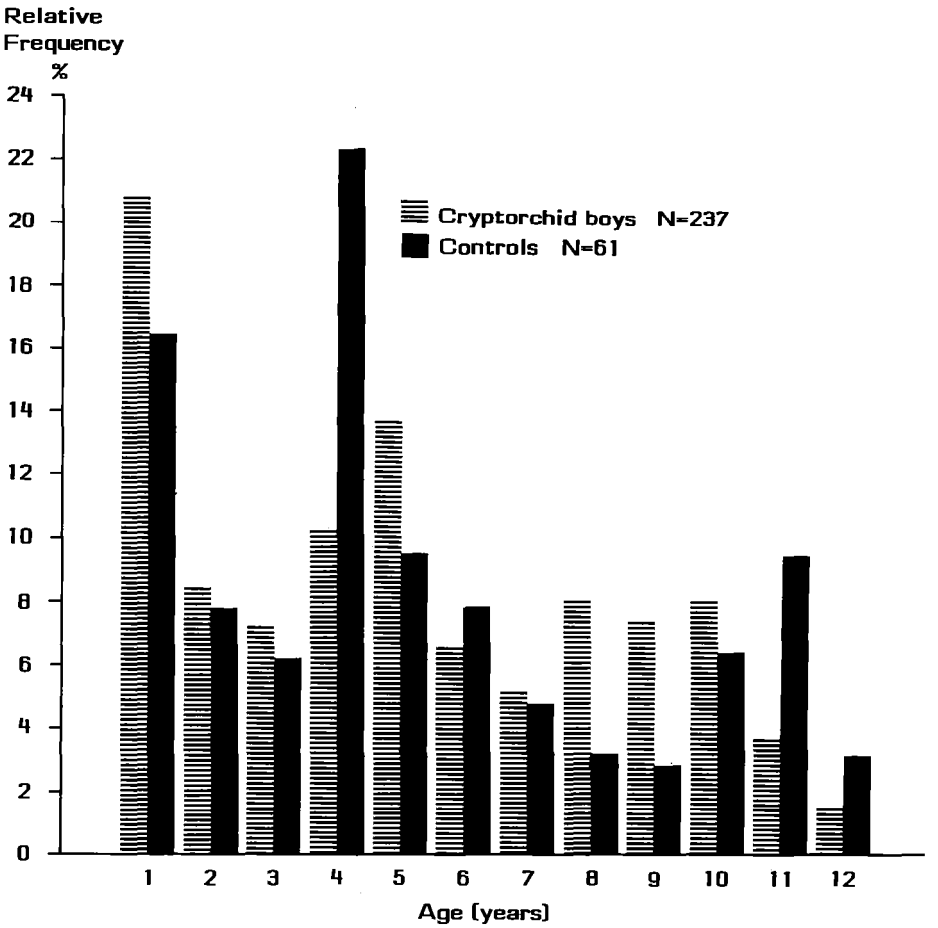


Figure 4.3. Age distribution of study population (minus dropouts) and controls.

Statistical analysis of the results was carried out using methods described in chapter 2. The success rate for the double-blind period was evaluated on the basis of both individual patients and individual testes. When the outcome proved identical, subsequent analysis was based on the testes only, as usually reported in the literature. The chi-square test was used to compare the percentages of testicular descent. The same test was used for comparison of an increae ≥ 1 ml in testicular volume after either LHRH therapy or placebo. In order to evaluate the dependency of the success rates on several study factors simultaneously, a logistic regression analysis was performed.

4.3.3. Results

For a small number of patients data were incomplete because of poor compliance (13 boys, 18 undescended testes). These patients were excluded from the analyses except for success of treatment, in which case an analysis based on intention-to-treat was performed as well. In addition, two boys (two undescended testes) were excluded because of anomalies (inguinal hernia, ectopic testicular position) found during treatment.

Standardized success rates were included in our presentation of this study in The Lancet (De Muinck Keizer-Schrama et al., 1986). However, we have since learned that a condition for the application of standardization is that the ratio of the percentages within two (or more) populations should be constant over categories of the stratification factor (i.e. the factor that might influence the rate). This condition was not met in our study, which may explain why the outcome of standardization contradicted the outcome of the logistic regression analysis. Consequently, all further mention of standardized success rates was excluded from this presentation of the results.

a. *Patient history*

According to information supplied at the start of the investigation, none of the undescended testes had ever been seen or felt in the scrotum. No episodes of pain or redness of the scrotum were reported. None of the patients had previously undergone surgery in the inguinal region, nor had anyone ever had hormonal treatment. Urinary tract infection was reported for 11 of the 237 boys (5%) included in the evaluation. Seventy-one boys had suffered from mumps, 157 never had mumps, and in nine cases it was not known. Medication was used during the study by 17 of the 237 boys: antihistamine (two boys); antibiotics (three boys); laxatives (three boys); iron and vitamin supplements (three boys); homeopathic remedies (six boys). The incidence of a gestational age under 37 weeks and a birth weight under 2,500 g was 11% and 15% respectively. In 39 cases the mother took medication during pregnancy, such as antibiotics (six cases); iron and vitamin supplements (nine cases); anti-emitics and antipruritics (six cases); drugs

to prevent miscarriage (seven cases); diuretics (two cases); drugs to prevent premature labour (two cases); insulin (one case); sedatives (two cases); antihistamine (one case); unknown drug (three cases). Fifty-nine per cent of the mothers used oral contraceptives before pregnancy. Familial incidence of cryptorchidism (1st and 2nd degree of relationship) was reported by the parents of 79 boys (33% of study population). We did not inquire further into the exact incidence and nature of this familial cryptorchidism.

b. Physical examination

At the first physical examination, the general impression of all boys was normal, with one exception. This was a ten year old, mentally retarded boy, who had been born prematurely and small for gestational age. He had suffered from hypoglycaemia in the neonatal period. His physical appearance was normal and his scrotum and penis were normally developed. Both testes (volume 2.5 ml) were palpable in the inguinal region and capable of being manipulated to the scrotal entrance. Dysmorphisms were noted in three boys: epicanthus and hypertelorism in one of them, congenital ptosis in the second boy, and clinodactyly in the remaining one. A tight and small scrotum was observed in eight boys; five of them had bilateral undescended testes. Three boys had hypospadias. In all other boys the penis was normal in size and shape. There were no scars in the inguinal region of any one of the boys.

Physical examination after four weeks of LHRH treatment or placebo (double-blind period) revealed no changes in either scrotum or penis, except for the fuller aspect of the scrotum in case of testicular descent. This will be dealt with later.

Table 4.4. gives the testicular volume of the palpable testes (descended as well as undescended) of the study population before treatment. In 30 boys (43 testes) the testicular volume was $\geq$ 2.5 ml. In two boys of group A with unilateral absence of testis, the contralateral, descended testis had a volume of 2.5 ml. In four boys of group B with unilateral cryptorchidism, the volume of the contralateral, descended testis was $\geq$ 2.5 ml. In one of them, the undescended testis also had a volume of 2.5 ml. In 24 boys of group C with unilateral or bilateral undescended

Table 4.4. Volume of palpable testes before treatment.

volume	testes [n] per age group			total
ml	A	B	C	testes [n]
1	25	45	7	77
1.5	35	64	30	129
2	16	50	101	167
2.5	2	4	27	33
3	0	1	7	8
3.5	0	0	1	1
4	0	0	1	1
total	78	164	174	416

testes, the testicular volume was ≥ 2.5 ml in 17 incompletely descended testes as well as in 19 fully descended testes. In general, a testicular volume ≥ 3 ml was only observed in contralateral, descended testes (ten testes). The volume of the contralateral, descended testis in boys with unilateral testicular absence was variable: age group A: 1-2.5 ml; age group B: 1-2 ml; and age group C: 2.5-3.5 ml.

Table 4.5. shows the increase of testicular volume ≥ 1 ml after LHRH treatment or placebo during the double-blind period. After LHRH therapy, an increase was observed in 13 boys (18 testes, 9%) and after placebo in five boys (five testes, 2%). This difference was statistically significant (chi-square test, $p < 0.002$). In eight boys (eight testes) the increase in volume was observed in the descended testis, while in six boys (seven testes) the volume of the undescended testis increased. In four boys (eight testes) the volume of both testes increased. In most of the patients, with an increase of testicular volume the treatment was without success. Complete descent was never achieved in boys of age group A that had an increase of testicular volume. In group B there was one boy with an increased testicular volume and complete descent after placebo. In group C the volume of the contralateral, descended testis increased in one successfully treated boy. In another boy of this same age group, with bilateral cryptorchidism, the volume of both testes increased while complete descent was achieved in both of them.

Table 4.5. Number (%) of testes with volume increase ≥ 1 ml during double-blind period.

age	placebo		LHRH	
group	total	increase	total	increase
A	38	0 (0)	39	3 (8)
B	90	4 (4)	72	5 (7)
C	85	1 (1)	84	10(12)
total	213	5 (2)*	195	18 (9)*

* increase significantly more frequent with LHRH than with placebo (chi-square test, p <0.002)

c. *Success of treatment*

Table 4.6. shows the comparative rates of success for placebo and LHRH treatment during the double-blind period (eight weeks). Figures are given for the entire study population (a) involving 252 patients with 301 undescended testes and subsequently for the study population minus drop-outs (b) involving 237 patients with 281 undescended testes. The success rate is itemized per age group for 237 patients in table 4.7., which shows testicular descent achieved with either placebo or LHRH per patient (unilateral or bilateral) and per testis. Regarding these two tables, there was no significant difference in the success rate for either placebo or LHRH. Nor was there a siginificant difference between placebo and LHRH in connection with the percentages of descent for individual patients or individual testes. Consequently, further analysis of the percentages of descent

Table 4.6. Success rates during double-blind period.

	type of treatment	patients N	testes n	complete descent: patients (N (%)) inclusive*	complete descent: patients (N (%)) exclusive**	complete descent: testes n(%)
a)						
entire study population 252 boys 301 testes	placebo	126	143	10 (8)	9 (7)	10 (7)
	LHRH	126	158	11 (9)	7 (6)	14 (9)
b)						
study population minus drop outs 237 boys 281 testes	placebo	116	130	10 (9)	9 (8)	10 (8)
	LHRH	121	151	11 (9)	7 (6)	14 (9)

* inclusive of bilateral cryptorchids in whom one testis only descended
** exclusive of bilateral cryptorchids in whom one testis only descended

Table 4.7. Itemized success rates in 237 patients, 281 testes, during the double-blind period.

		patients (N) uni-lateral	patients (N) bi-lateral	testes (n) uni-lateral	testes (n) bi-lateral	complete descent: patients (N) uni-lateral	complete descent: patients (N) bi-lateral	complete descent: testes (n) uni-lateral	complete descent: testes (n) bi-lateral
placebo	A	23	1	23	2	0	0	0	0
	B	42	5	42	10	6	0	6	0
	C	37	8	37	16	3	1*	3	1
	total	102	14	102	28	9	1	9	1
LHRH	A	20	5	20	10	0	1*	0	1
	B	39	8	39	16	1	0	1	0
	C	32	17	32	34	3	6**	3	9
	total	91	30	91	60	4	7	4	10

* only one testis descended completely
** in three patients only one testis descended completely

concerned testes only, in agreement with similar analyses in the literature, even though the patients were randomized.

Figure 4.4. is a schematic presentation of the treatment results beginning with the entire study population in the double-blind period through follow-up. Even though no placebo was given in the open study period, we continued to refer to "placebo patients" and "LHRH patients" for identification purposes. In the placebo group, 13 testes descended after one LHRH course during the open study period. In both placebo and LHRH patients together, 21 testes descended after a second LHRH course, resulting in the complete descent of 48 testes (18%)

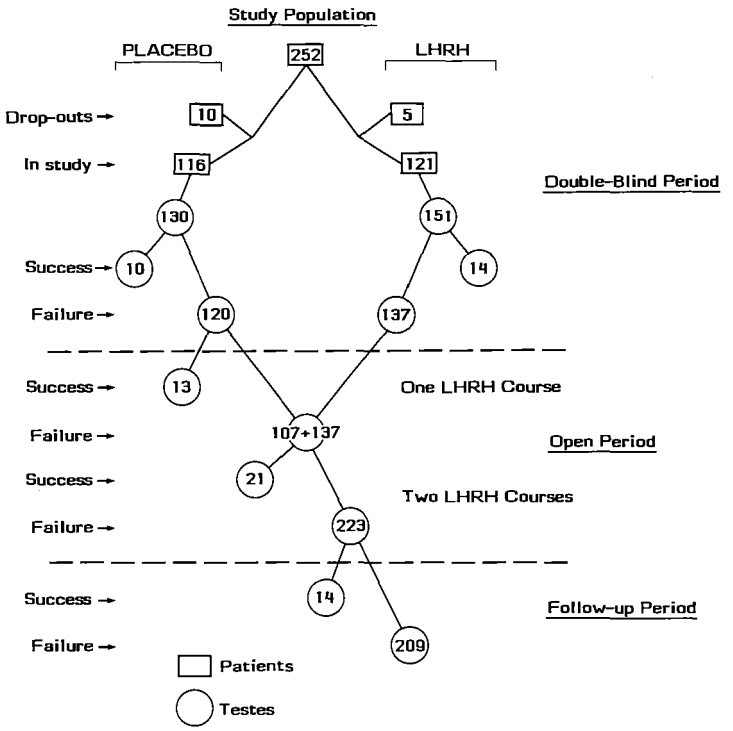


Figure 4.4. Results of treatment from start through follow-up.

Table 4.8. Final results of treatment of 237 boys (281 testes).

age group	patients (N)		testes (n)		complete descent of testes: number (%)			
					double-blind period		two LHRH courses*	late descent
	placebo	LHRH	placebo	LHRH	placebo	LHRH		
A	24	25	25	30	0 (0)	1 (3)	4 (7)	3 (5)
B	47	47	52	55	6 (11)	1 (2)	12 (12)	1 (1)
C	45	49	53	66	4 (7)	12 (18)	32 (28)	10 (9)
total	116	121	130	151	10 (8)	14 (9)	48 (18)	14 (5)

* complete descent of testes in combined placebo and LHRH groups, excluding placebo descent

after two LHRH courses (placebo descent excluded). Another 14 testes descended at a later stage during the follow-up period. These were classified as "late descent". The final results of the entire study period, including follow-up, are given in table 4.8. concerning 237 patients, 281 testes.

Figure 4.5. gives the most caudal testicular positions before and after treatment for the three age groups, excluding placebo descent. Of the 48 testes that descended completely with LHRH treatment, 36 (75%) could at least be manipulated to the scrotal entrance before treatment. The same applies to eight of ten testes (80%) that descended with placebo.

Table 4.9. gives the comparative rates of success for unilateral and bilateral cryptorchidism after two courses of LHRH treatment, excluding late descents. The percentages for complete testicular descent were identical for bilateral and rightsided unilateral cryptorchidism, while the success rate for leftsided cryptorchidism lagged far behind.

We investigated to what extent the various study factors had influenced the rates of success. For the double-blind period this involved age at treatment, type of treatment (LHRH or placebo), laterality (leftsided vs rightsided vs bilateral), and pretreatment testicular position. It appeared that the rate of success was inde-

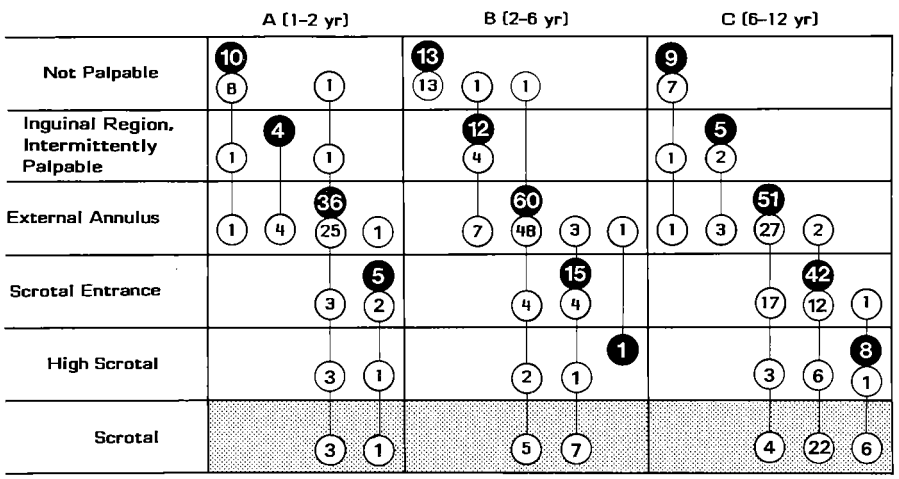


Figure 4.5. Most caudal testicular position before ● and after ○ LHRH treatment (excluding placebo descent).

Table 4.9. Success of LHRH treatment in unilateral and bilateral cryptorchidism (excluding late descents).

	patients N	testes n	complete descent of testes: number [%] right	left	both	total
unilateral right	94	94	21 [22]			21 [22]
unilateral left	90	90		8 [9]		8 [9]**
bilateral	44	87*	4 [5]	3 [3]	12 [14]	19 [22]

* one testis descended with placebo during double-blind period
** significantly lower than for right sided or bilateral cryptorchidism [chi-square test, $p < 0.05$]

pendent of age at treatment, type of treatment, and laterality ($p > 0.05$), but highly dependent on pretreatment testicular position ($p < 0.001$). For the open study period (after two LHRH courses), the factors involved age at treatment, laterality, and pretreatment testicular position. Here again, it appeared that the rate of success depended mainly on pretreatment testicular position ($p < 0.001$). There was no dependence on either age at treatment or laterality of the undescended testis ($p > 0.05$).

d. Findings in exceptional cases

The one mentally retarded patient had a late descent of testes. Despite two courses of LHRH treatment, his testes had not fully descended at the end of the study period. Surgery was postponed in view of his mental condition. Almost two years later puberty had started and both testes were in the scrotum.

One of the eight boys with small, tight scrotums, a bilateral cryptorchid, was found to have no testes at surgery. Of the remaining seven only one achieved complete descent. This was a unilateral cryptorchid and one of three boys with dysmorphisms. The other two boys with dysmorphisms did not respond to treatment.

One of three boys with hypospadias had complete testicular descent after two LHRH courses. Late descent occurred in another one, but hormonal therapy failed altogether in the third boy.

Minor adverse reactions were reported by the parents of some boys, indiscriminately for placebo or LHRH treatment during the double-blind period (table 4.10.).

Table 4.10. Adverse reactions reported during double-blind period.

	placebo			LHRH		
	A	B	C	A	B	C
more erections	0	0	1	1	1	0
epistaxis	0	0	2	1	0	0
sneezing	0	0	0	0	0	1
acne	0	0	0	0	0	1
appetite increase	0	1	1	0	0	1
headache	0	0	0	0	0	1
more aggressive	0	0	1	0	1	1

e. Follow-up period

The boys were followed for six months to three years after treatment. In group A, late descent occurred in three boys (three testes) two to six months after LHRH treatment. No return of the testis to the former, undescended position occurred in this age group. At follow-up examinations, none of the successfully treated

testes were spontaneously intrascrotal; all these testes appeared to be retractile. The testicular volume was 1-2 ml.

In age group B, late descent occurred in one boy (one testis) three months after LHRH treatment. Five patients (five testes) had a relapse 3-12 months after treatment, including one placebo descent. A repeat course of LHRH was successful in four of them. Orchiopexy was required in the remaining one. Of the 18 testes, that descended with LHRH treatment in this age group, two were spontaneously intrascrotal six months to two years later. All the others were retractile. The testicular volume was 1-3 ml.

In age group C, late descent was observed 3-20 months after LHRH treatment in seven boys (ten testes). In three patients (five testes) complete descent coincided with the start of puberty. Relapse occurred in five patients (six testes) 6-12 months after treatment. A repeat course of LHRH was successful in three of them (three testes), but failed in one patient (two testes). The parents of the fifth patient refused another course of LHRH. During the follow-up period of the successfully treated testes, totalling 43 for this group, the spontaneous position of 29 testes was in the scrotum. The other testes were retractile. In 11 boys (with 17 successfully treated testes) puberty had started. In all these boys the testes were spontaneously intrascrotal. In three boys who were successfully treated for unilateral cryptorchidism, puberty had started but the previously undescended testis remained smaller than the contralateral one. Testicular volume of the whole age group was between 2-16 ml.

f. Hormonal evaluation

The pretreatment hormonal data for cryptorchid boys and age-matched control subjects are given in table 4.11. The figures for one boy (aged 2 yrs, group B) were excluded when surgery revealed bilateral gonadal aplasia in this patient. Serum LH levels were slightly higher in cryptorchid boys than in control subjects, which was significant for basal LH in all age groups, and for peak and delta LH in groups B and C ($p < 0.05$). Serum FSH levels were identical for cryptorchids and controls. Basal and stimulated serum testosterone values in cryptorchids were similar to those in controls or even higher (basal testosterone age group B, $p < 0.05$).

Comparing the three age groups, stimulated LH values were higher in age group A than in B or C in both cryptorchids and controls. Regarding the values for basal LH, as well as basal and peak FSH, there were no differences between the three age groups in cryptorchid boys or control subjects. In patients as well as controls, basal testosterone was significantly higher in boys of age group C, than in boys of groups A or B. There were significant falls with age in peak and delta testosterone levels in both patients and controls.

Tables 4.12[a]. and 4.12[b]. give the hormonal data for cryptorchid boys only, before and after the double-blind period, enabling a comparison between a

change in values after LHRH treatment or placebo. There was a small but statistically significant decline in basal and peak LH after LHRH and placebo in age group A, while age group B showed a similarly significant decline in peak and delta LH after placebo only. A decline in peak FSH was noted after LHRH therapy in age groups B and C, while age groups A and B showed a statistically significant decline in peak FSH after placebo. Rather than an increase in basal testosterone levels after LHRH therapy, we observed a significant decrease in age groups A and B. A decrease of basal testosterone level was even found after placebo in age group B. Comparing the total results of LHRH therapy with those of placebo, there was a similar change of peak LH in all age groups and of peak FSH in groups A and B. Conversely, there was a significant difference ($p < 0.05$) in the change of peak FSH in age group C and of basal testosterone in age group A.

When the hormonal data were compared for unilateral or bilateral cryptorchidism, serum LH levels were the same in the three age groups before treatment (table 4.13[a].) as well as after treatment (table 4.13[b].). Before treatment, peak and delta FSH were significantly higher in bilateral than in unilateral cryptorchids of age group B only. After treatment, peak and delta FSH were higher in bilateral than in unilateral cryptorchids of group A as well as group B. In group C there was no difference in FSH values between unilateral and bilateral cryptorchids after treatment. Compared with pretreatment values, a significant decline of peak and delta LH was observed after treatment in unilateral cryptorchids of age groups A and B, but not in bilateral cryptorchids. Peak and delta FSH showed a decline in unilateral cryptorchids of all age groups and in bilateral cryptorchids of age groups B and C. Basal testosterone levels only declined in unilateral cryptorchids of age groups A and B. Finally, comparing the changes of hormonal values after LHRH therapy in either unilateral or bilateral cryptorchids, there was a significant difference in peak FSH values of age group A only.

Table 4.14. gives the comparative pretreatment hormonal values for boys that subsequently responded fully to two courses of LHRH treatment and for boys that had total failure of treatment (involving results of either placebo or LHRH treatment beginning with the double-blind period and on through the entire follow-up period). Regardless of age group, there was no difference in pretreatment values comparing the successfully treated boys with the nonresponders.

The final evaluation of hormonal values before and after LHRH therapy in relation to subsequent success or failure, involved a comparison of boys that had complete testicular descent after one course of LHRH with boys that had total failure of treatment (tables 4.15[a]. and 4.15[b].). Consequently, the so-called "successes" do not include patients that had complete testicular descent after two courses of LHRH, nor patients with "late" testicular descent. Before treatment, there was no significant difference in hormonal values between success and failure, except for basal LH in group A. After treatment, peak and delta FSH differed significantly between success and failure in age group C. Comparing

Table 4.11. Hormonal data in patients *before* treatment and in control subjects.

	Mean ± SEM					
	A		B		C	
	patients	controls	patients	controls	patients	controls
LH (IU/l)						
basal	2.13 ± 0.11*	1.51 ± 0.16	2.26 ± 0.13*	1.74 ± 0.11	2.63 ± 0.11*	1.97 ± 0.14
peak	9.91 ± 0.63□	8.38 ± 1.15□	7.98 ± 0.37*	6.00 ± 0.42	8.25 ± 0.31*	6.16 ± 0.61
delta	7.78 ± 0.60□	6.87 ± 1.12□	5.73 ± 0.32*	4.27 ± 0.41	5.62 ± 0.27*	4.19 ± 0.58
FSH (IU/l)						
basal	0.72 ± 0.04	0.60 ± 0.00	0.74 ± 0.02	0.65 ± 0.03	0.84 ± 0.02	0.84 ± 0.15
peak	3.97 ± 0.49	3.15 ± 0.79	3.39 ± 0.23	3.11 ± 0.47	2.72 ± 0.17	2.84 ± 0.42
delta	3.25 ± 0.49	2.55 ± 0.79	2.66 ± 0.22	2.46 ± 0.47	1.88 ± 0.17	2.00 ± 0.33
Testosterone (nmol/l)						
basal	0.10 ± 0.01	0.07 ± 0.01	0.12 ± 0.01*	0.07 ± 0.01	0.27 ± 0.03■	0.22 ± 0.03■
peak	12.67 ± 0.86●	11.73 ± 1.77○	7.10 ± 0.38●	7.99 ± 0.90○	5.45 ± 0.31●	4.51 ± 0.31○
delta	12.57 ± 0.86●	11.66 ± 1.77○	6.98 ± 0.38●	7.92 ± 0.90○	5.18 ± 0.30●	4.29 ± 0.31○
Number of boys	49	10	92	28	93	23

* significantly higher than control value ($p < 0.05$)
□ significantly higher than the same determination in groups B and C ($p < 0.05$)
■ significantly higher than the same determination in groups A and B ($p < 0.05$)
peak and delta testosterone group A > group B > group C in patients (●) and controls (○) ($p < 0.05$)
Mann-Whitney-U test

Table 4.12[a]. Hormonal data in patients *before* LHRH treatment or placebo.

	Mean ± SEM					
	A		B		C	
	LHRH	Placebo	LHRH	Placebo	LHRH	Placebo
LH (IU/l)						
basal	2.23 ± 0.17	2.03 ± 0.15	2.30 ± 0.17	2.21 ± 0.19	2.67 ± 0.15	2.58 ± 0.16
peak	10.46 ± 0.96	9.34 ± 0.80	8.52 ± 0.61	7.45 ± 0.43	8.66 ± 0.52	7.83 ± 0.34
delta	8.23 ± 0.94	7.32 ± 0.73	6.22 ± 0.55	5.24 ± 0.33	5.99 ± 0.45	5.25 ± 0.28
FSH (IU/l)						
basal	0.77 ± 0.06	0.66 ± 0.03	0.72 ± 0.02	0.75 ± 0.04	0.85 ± 0.03	0.84 ± 0.03
peak	4.68 ± 0.86	3.22 ± 0.43	3.49 ± 0.33	3.30 ± 0.32	2.85 ± 0.26	2.58 ± 0.21
delta	3.91 ± 0.84	2.55 ± 0.43	2.77 ± 0.33	2.55 ± 0.31	2.01 ± 0.27	1.75 ± 0.22
Testosterone (nmol/l)						
basal	0.13 ± 0.02	0.07 ± 0.01	0.11 ± 0.01	0.12 ± 0.02	0.28 ± 0.03	0.26 ± 0.04
peak	12.36 ± 1.35	13.02 ± 1.05	6.48 ± 0.53	7.71 ± 0.55	5.60 ± 0.40	5.28 ± 0.47
delta	12.23 ± 1.35	12.94 ± 1.04	6.37 ± 0.53	7.59 ± 0.55	5.32 ± 0.40	5.02 ± 0.46
Number of boys	25	23	46	46	47	45

Table 4.12[b]. Hormonal data in patients *after* LHRH treatment or placebo.

	Mean ± SEM					
	A		B		C	
	LHRH	Placebo	LHRH	Placebo	LHRH	Placebo
LH [IU/l]						
basal	1.98 ± 0.16●	1.79 ± 0.12●	2.39 ± 0.21	2.06 ± 0.15	3.36 ± 0.37 *	2.27 ± 0.12
peak	8.81 ± 0.92●	8.23 ± 0.82●	7.63 ± 0.36 *	6.37 ± 0.41●	8.73 ± 0.53 *	7.24 ± 0.37
delta	6.83 ± 0.84●	6.40 ± 0.75	5.21 ± 0.37	4.31 ± 0.31●	5.37 ± 0.43	4.97 ± 0.33
FSH [IU/l]						
basal	0.71 ± 0.04	0.74 ± 0.08	0.76 ± 0.03	0.72 ± 0.02	0.88 ± 0.05	0.82 ± 0.03
peak	4.67 ± 1.01	2.20 ± 0.31●	2.21 ± 0.31●	2.34 ± 0.28●	1.61 ± 0.17 *●○	2.29 ± 0.18
delta	3.96 ± 1.00	1.46 ± 0.32●	1.45 ± 0.30●	1.61 ± 0.28●	0.73 ± 0.15 *●○	1.47 ± 0.19
Testosterone [nmol/l]						
basal	0.04 ± 0.01 *●○	0.07 ± 0.01	0.07 ± 0.01●	0.07 ± 0.01●	0.25 ± 0.04	0.19 ± 0.02
Number of boys	25	23	46	46	47	45

* significantly different from placebo value [Mann-Whitney-U test, $p < 0.05$]
● significantly different from starting value [Wilcoxon matched pairs signed rank test, $p < 0.05$]
○ change after LHRH significantly different from change after placebo [Mann-Whitney-U test, $p < 0.05$]

Table 4.13[a]. Hormonal data in unilateral and bilateral cryptorchids *before* LHRH treatment.

	Mean ± SEM					
	A		B		C	
	unilateral	bilateral	unilateral	bilateral	unilateral	bilateral
LH (IU/l)						
basal	2.11 ± 0.12	2.30 ± 0.26	2.30 ± 0.14	1.98 ± 0.19	2.70 ± 0.11	2.44 ± 0.26
peak	9.94 ± 0.68	9.70 ± 1.77	7.94 ± 0.41	8.26 ± 0.89	8.06 ± 0.28	8.76 ± 0.89
delta	7.84 ± 0.65	7.40 ± 1.56	5.64 ± 0.35	6.28 ± 0.78	5.36 ± 0.24	6.32 ± 0.75
FSH (IU/l)						
basal	0.68 ± 0.02	0.97 ± 0.24	0.75 ± 0.03	0.68 ± 0.05	0.82 ± 0.02	0.89 ± 0.05
peak	3.69 ± 0.50	5.93 ± 1.76	3.14 ± 0.23	5.13 ± 0.76 *	2.72 ± 0.21	2.72 ± 0.29
delta	3.01 ± 0.51	4.97 ± 1.59	2.39 ± 0.22	4.46 ± 0.77 *	1.90 ± 0.21	1.83 ± 0.28
Testosterone (nmol/l)						
basal	0.11 ± 0.02	0.05 ± 0.01	0.12 ± 0.01	0.13 ± 0.04	0.27 ± 0.03	0.28 ± 0.06
peak	12.94 ± 0.92	10.82 ± 2.41	6.98 ± 0.41	7.94 ± 1.06	5.33 ± 0.33	5.77 ± 0.73
delta	12.83 ± 0.92	10.77 ± 2.42	6.86 ± 0.41	7.81 ± 1.05	5.06 ± 0.32	5.49 ± 0.71
Number of boys	43	6	80	12	68	25

* significantly different from unilateral value (Mann-Whitney-U test, $p < 0.05$)

Table 4.13[b]. Hormonal data in unilateral and bilateral cryptorchids *after* LHRH treatment.

	Mean ± SEM					
	A		B		C	
	unilateral	bilateral	unilateral	bilateral	unilateral	bilateral
LH [IU/l]						
basal	1.89 ± 0.10	1.87 ± 0.47	2.16 ± 0.12	2.64 ± 0.62	3.01 ± 0.26	2.29 ± 0.16
peak	8.36 ± 0.62●	9.68 ± 2.36	6.87 ± 0.31●	7.78 ± 0.51	7.76 ± 0.37	8.64 ± 0.72
delta	6.45 ± 0.58●	7.82 ± 2.03	4.69 ± 0.26●	5.13 ± 0.68	4.75 ± 0.25	6.35 ± 0.70
FSH [IU/l]						
basal	0.72 ± 0.04	0.80 ± 0.13	0.73 ± 0.02	0.80 ± 0.06	0.85 ± 0.04	0.88 ± 0.06●
peak	2.89 ± 0.49●	7.52 ± 2.46 *○	2.08 ± 0.20●	3.56 ± 0.79 *●	2.01 ± 0.15●	1.76 ± 0.25●
delta	2.17 ± 0.50●	6.72 ± 2.36 *○	1.35 ± 0.20●	2.76 ± 0.81 *●	1.17 ± 0.15●	0.89 ± 0.25●
Testosterone [nmol/l]						
basal	0.06 ± 0.01●	0.03 ± 0.01	0.07 ± 0.01●	0.06 ± 0.01	0.21 ± 0.02	0.25 ± 0.05
Number of boys	43	6	80	12	68	25

* significantly different from unilateral value [Mann-Whitney-U test, $p < 0.05$]
● significantly different from starting value [Wilcoxon matched pairs signed rank test, $p < 0.05$]
○ change after LHRH therapy in bilateral cryptorchids significantly different from that in unilateral cryptorchids [Mann-Whitney-U test, $p < 0.05$]

Table 4.14. Hormonal data *before* treatment in boys with complete descent after two LHRH courses (success) and in boys with total failure of treatment (failure).

	Mean ± SEM					
	A		B		C	
	success	failure	success	failure	success	failure
LH [IU/l]						
basal	2.70 ± 0.51	2.10 ± 0.12	2.12 ± 0.32	2.28 ± 0.15	2.64 ± 0.18	2.56 ± 0.14
peak	11.73 ± 0.74	9.69 ± 0.68	6.38 ± 0.91	8.31 ± 0.42	7.76 ± 0.72	8.35 ± 0.34
delta	9.02 ± 0.53	7.59 ± 0.65	4.26 ± 0.82	6.03 ± 0.36	5.11 ± 0.61	5.79 ± 0.29
FSH [IU/l]						
basal	0.65 ± 0.09	0.73 ± 0.04	0.71 ± 0.06	0.75 ± 0.03	0.82 ± 0.04	0.84 ± 0.02
peak	3.68 ± 1.53	4.02 ± 0.56	2.96 ± 0.66	3.49 ± 0.26	2.41 ± 0.24	2.87 ± 0.24
delta	3.03 ± 1.52	3.29 ± 0.55	2.25 ± 0.64	2.75 ± 0.25	1.59 ± 0.25	2.04 ± 0.25
Testosterone [nmol/l]						
basal	0.06 ± 0.02	0.11 ± 0.02	0.10 ± 0.03	0.11 ± 0.01	0.39 ± 0.08	0.22 ± 0.02
peak	15.50 ± 1.71	12.22 ± 0.94	5.60 ± 0.98	7.25 ± 0.43	5.50 ± 0.70	5.48 ± 0.36
delta	15.44 ± 1.71	12.11 ± 0.94	5.50 ± 0.98	7.14 ± 0.43	5.12 ± 0.65	5.26 ± 0.36
Number of boys	4	41	11	75	27	57

Table 4.15a. Hormonal data *before* treatment in boys with complete descent after one LHRH course (success) and in boys with total failure of treatment (failure).

	Mean ± SEM					
	A		B		C	
	success	failure	success	failure	success	failure
LH (IU/l)						
basal	3.50 ± 0.50	2.10 ± 0.12 *	2.30 ± 0.62	2.28 ± 0.15	2.60 ± 0.26	2.56 ± 0.14
peak	12.30 ± 0.70	9.69 ± 0.68	5.86 ± 0.83	8.31 ± 0.42	8.43 ± 1.08	8.35 ± 0.34
delta	8.80 ± 0.20	7.59 ± 0.65	3.56 ± 0.56	6.03 ± 0.36	5.83 ± 0.88	5.79 ± 0.29
FSH (IU/l)						
basal	0.70 ± 0.20	0.73 ± 0.04	0.72 ± 0.07	0.75 ± 0.03	0.79 ± 0.05	0.84 ± 0.02
peak	2.45 ± 1.45	4.02 ± 0.56	2.12 ± 0.44	3.49 ± 0.26	2.30 ± 0.29	2.87 ± 0.24
delta	1.75 ± 1.25	3.29 ± 0.55	1.40 ± 0.43	2.75 ± 0.25	1.51 ± 0.32	2.04 ± 0.25
Testosterone (nmol/l)						
basal	0.07 ± 0.04	0.11 ± 0.02	0.09 ± 0.03	0.11 ± 0.01	0.47 ± 0.11	0.22 ± 0.02
peak	17.00 ± 3.00	12.22 ± 0.94	7.18 ± 1.39	7.25 ± 0.43	6.06 ± 1.03	5.48 ± 0.36
delta	16.94 ± 3.04	12.11 ± 0.94	7.09 ± 1.40	7.14 ± 0.43	5.60 ± 0.95	5.26 ± 0.36
Number of boys	2	41	5	75	17	57

* significantly different from success group (Mann-Whitney-U test, $p < 0.05$)

Table 4.15b. Hormonal data *after* treatment in boys with complete descent after one LHRH course (success) and in boys with total failure of treatment (failure).

	Mean ± SEM					
	A		B		C	
	success	failure	success	failure	success	failure
LH [IU/l]						
basal	2.15 ± 0.65○	1.89 ± 0.12	1.68 ± 0.47	2.26 ± 0.15	2.53 ± 0.26	2.92 ± 0.31
peak	11.75 ± 3.25	8.14 ± 0.61●	7.06 ± 1.38○	7.15 ± 0.32●	8.70 ± 1.07	7.85 ± 0.41
delta	9.60 ± 2.60	6.23 ± 0.55●	5.38 ± 1.19○	4.88 ± 0.28●	6.17 ± 0.97	4.94 ± 0.28
FSH [IU/l]						
basal	0.75 ± 0.15	0.74 ± 0.05	0.74 ± 0.08	0.74 ± 0.02	0.83 ± 0.04	0.85 ± 0.04
peak	2.80 ± 1.70	3.53 ± 0.66	1.84 ± 0.55	2.39 ± 0.25●	1.67 ± 0.35●	2.21 ± 0.17 *●
delta	2.05 ± 1.85	2.78 ± 0.66	1.10 ± 0.60	1.65 ± 0.24●	0.84 ± 0.35●	1.36 ± 0.16 *●
Testosterone [nmol/l]						
basal	0.04 ± 0.02	0.05 ± 0.01●	0.07 ± 0.02	0.07 ± 0.01●	0.28 ± 0.07	0.21 ± 0.02
Number of boys	2	41	5	75	17	57

* significantly different from success group [Mann-Whitney-U test, p <0.05]
● significantly different from starting value [Wilcoxon matched pairs signed rank test, p <0.05]
○ change after LHRH therapy in success group significantly different from that in failure group [Mann-Whitney-U test, p <0.05]

values before and after treatment, peak and delta LH differed in age group A and B for nonresponders only. Peak and delta FSH differed for failure in age group B and C, and for success in age group C. The only significant differences between success and failure in the changes of hormonal values after LHRH therapy were observed in basal LH of group A and in peak and delta LH of group B.

A comparison of the hormonal values before and after treatment of boys with placebo descent, which occurred in age groups B and C only, with the values for boys with complete descent after one course of LHRH or nonresponders, revealed no significant differences.

4.3.4. Discussion

For a proper evaluation of our results, we had to ascertain whether the criteria for excluding patients from the study had been adhered to. According to the information supplied at referral for all 252 boys, none of the undescended testes had ever been seen or felt in the scrotum. As the study progressed, we felt the need to verify this information, particularly in view of the number of placebo descents. Consequently, every effort was made to trace any documentation of previous testicular positions in our patients from birth to referral. This retrospective evaluation of testicular position was carried out as a separate study (see 4.3.5.).

Approximately one third of the study population was reported to have had mumps. However, orchitis is unlikely to have occurred as none of the patients had experienced pain or redness of the scrotum.

Seventeen of the 237 boys included in the evaluation used some kind of medicine during the study. There were no signs of drug interaction or adverse reactions.

In the Netherlands, the incidence of births with a gestational age under 37 weeks or a birth weight under 2,500 g amounts to 12.3% and 10.3% respectively (Personal communication from "Stichting Informatiecentrum voor de Gezondheidszorg" regarding National Registration of Births for 1983). The difference between the study population and the general Dutch populace is only statistically significant for low birth weight (chi-square test, $p < 0.05$). The higher frequency of low birth weight in these 237 cryptorchid boys might indicate an association. However, no conclusion can be drawn as this was not a case-control study. Scorer (1964) found that 21% of boys with a birth weight of 2,500 g or less were born with undescended testes, but he noted spontaneous descent after the first three months of life in 70% of these cases. His data do not reveal a higher frequency of cryptorchidism after the first year of life in boys with a low birth weight. Villumsen and Zachau (1966) also found a higher frequency of undescended testes at birth in boys with a birth weight of 2,500 g or less. They estimated that 2.3% of premature boys versus 0.8% of full-term boys have undescended testes at the age of three years. Depue (1984) concluded from case-control studies of cryptorchidism and inguinal hernia that there was a significantly higher risk of cryptor-

chidism in case of low birth weight or shortened gestation. Nevertheless, Mau and Schnakenburg (1977) did not find an increased frequency of undescended testes in premature babies once they had reached the age of nine months. In another case-control study of the aetiology of cryptorchidism, Swerdlow et al. (1983) found only a slightly higher risk for the low-birth-weight boys. He surmised that the higher risk for boys of low birth weight and below normal gestational age might reflect the absence of maternal hormonal stimulus for descent in babies born before the normal time of testicular descent. However, this explanation would only apply to the higher frequency of cryptorchidism at premature birth, rather than to any higher frequency at a later stage.

The maternal use of oral contraceptives before and sometimes during the first weeks of pregnancy reported for our series of boys with undescended testes did not differ in frequency from the general use of oral contraceptives in the Netherlands (Van Vliet and Hofman, 1982). The study carried out by Depue (1984) did not reveal any connection between cryptorchidism and the use of oral contraceptives. Mau and Schnakenburg (1977) reached the same conclusion.

Familial incidence of cryptorchidism has been reported in the past and again more recently, suggesting that hereditary factors are involved in cryptorchidism (Corbus and O'Conner, 1922; Minehan and Touloukian, 1974; Rezvani et al., 1976; Czeizel et al., 1980; Jones and Young, 1982; Savion et al., 1984). In this respect no conclusion can be drawn regarding our study population, because the exact incidence and nature of the familial cryptorchidism reported by the parents was not investigated.

The only conclusion we dare draw from the initial clinical findings is that boys with a tight and small scrotum are not likely to respond to hormonal therapy.

Many authors report a normal prepuberal testicular volume of 1-2 ml (Schönfeld and Beebe, 1942; Rundle and Sylvester, 1962; Dooren et al., 1963; Laron and Zilka, 1969; Kleinteich, 1979). It has also been shown that testicular volume may increase from age 10-11 years (Prader, 1975; Kleinteich, 1979). Dooren and coworkers (1963) found a testicular volume of 1-5 ml in 114 boys with normally descended testes aged 10-12 years. A volume of 4-5 ml was only noted in 12% of the boys aged 11-12 years. In our boys with undescended testes we generally found normal testicular volumes before treatment. Of the 30 boys in whom we registered a testicular volume of 2.5-4 ml, 13 were 10-12 years old and therefore the testicular volume may have been normal for age. In the remaining 17 boys (aged 1-10 years) it may have been a case of compensatory hypertrophy of the contralateral, descended testis, although in a number of these boys (particularly in those aged 9-10 years) the unilateral, undescended testis also measured 2.5 ml. In the literature there is no consensus of opinion regarding the incidence of compensatory hypertrophy of the contralateral, descended testis in unilateral cryptorchidism (Laron and Zilka, 1969; Kleinteich, 1979). For our study population we estimated that the incidence of compensatory hypertrophy was at most 9% (17 of 184 unilateral cryptorchids included in the evaluation). Furthermore, the

great diversity in volume of the contralateral testis in boys with unilateral absence of testis argues against the assumption that unilateral cryptorchidism is always associated with hypertrophy of the contralateral, descended testis.

After LHRH treatment, we noted that 18 of 195 testes (9%) had increased in volume. In the age group 6-12 years this occurred in 10 of 84 testes (12%). Karpe and associates (1983) found an increase of testicular volume (< 1 ml) in a significant number of patients during LHRH therapy, while they observed no such increase in the placebo group. Dijkstra and coworkers (1986) reported an increase in the number of spermatogonia and spermatocytes in addition to an increase in the diameter of the seminiferous tubules after four weeks of pulsatile, intramuscular administration of LHRH in pigs. Hadziselimovic and coworkers (1980[b]) found no difference in spermatogonia count per tubule in testicular biopsies, taken at operation, comparing cryptorchid boys that had undergone hormonal treatment with those that had not. On the other hand, he did find evidence of stimulation of Leydig cells after LHRH treatment. He reported an increase in size and number of Leydig cells and signs of increased secretory activity. The increase in testicular volume observed in our patients after LHRH treatment is more likely to have been caused by an increase of germinal epithelium than by an increase in the number of Leydig cells, particularly in view of the fact that the tubular compartment of the testis takes up more room than the cells of Leydig (Prader, 1966). Moreover, we also found an increased volume in 5 of 213 testes in the placebo group. Success of treatment did not coincide with increase of testicular volume.

The success rate reported in the literature for LHRH nasal spray varies from 9-38% for double-blind studies and from 13-78% for open studies as shown in table 4.1. In our double-blind period, the success rate for LHRH treatment (9%) did not differ from that for placebo (8%). Two courses of LHRH treatment were required for 43% of the testes that eventually descended with this treatment and therefore the success rate for the double-blind period is not comprehensive. However, one cannot exclude a placebo effect during the open study period. Illig and coworkers (1980[a]) found that a second trial of intranasal LHRH in patients with little or no response to the initial LHRH treatment was ineffective, regardless whether it immediately followed the initial course or was given weeks or months later. The same authors reported that HCG treatment after LHRH treatment had no effect on testicular position. This is contrary to the findings of Hadziselimovic (1982) who reported that a short course of intramuscular HCG immediately following intranasal LHRH treatment, enhanced its rate of success.

Dosage and duration of treatment varied in the various studies (see 4.1.3.). In general, the choice of treatment schedule will be based on a comparison of the rates of success achieved with the various schedules. However, the rates of success may well have been influenced by other factors. In our study, the age of the patient affected the results of LHRH treatment. Our highest success rate was in the oldest age group. This contrasts with the results of several other studies in

which the greatest success was achieved in boys of 2 to 5 years (Zabransky, 1981; Hagberg and Westphal, 1982) or where there was no relation between age and descent (Happ et al., 1975; Illig et al., 1977; Pirazzoli et al., 1978; Schwarz et al., 1985). Garagorri and coworkers (1982) reported a lower success rate for HCG treatment in the younger age groups. Regarding the LHRH treatment, we wondered whether the difference in the rates of success achieved in the different age groups might be due to an age-related divergence in the resorption of the nasal spray. A separate, small-scale investigation was carried out to test this premise (see 4.3.6.).

Most authors agree that the more caudal the location of the testis before treatment, the better the result (Klidjian et al., 1985; Schwarz et al., 1985). Some authors reported a higher success rate for bilateral undescended testes (Cacciari et al., 1982; Hadziselimovic, 1982; Borkenstein et al., 1983), while others found a higher percentage of descent in cases of unilateral cryptorchidism (Illig et al., 1977; Happ et al., 1978). Our results of the logistic regression analysis indicate that the most caudal position of the testis before treatment is far more important for a successful outcome of LHRH therapy than either age of the boy or laterality of the undescended testis.

A lower testicular position (scrotal entrance and high scrotal) was far more frequent in the older age group than in the younger boys, for which we can offer several explanations. It may be that younger boys with undescended testes in relatively low positions were not referred to our outpatient clinic ("selection bias"). Or, testicular descent may continue during the entire prepuberal period. Alternatively, a previously fully descended testis may be capable of ascending to a prescrotal position, or give the impression of having ascended ("pseudo-ascent"). The second premise can only be substantiated by a longitudinal study from birth to puberty. No such study has been reported. The third premise was substantiated to some extent by Privat in 1978. She found undescended testes in boys at preschool- or school-age that had been in a scrotal position during the first years of life. Several explanations for the apparent ascent of the testes have been proposed (see 5.8.). In boys with a persistent processus vaginalis, ascent of the testis may occur with growth (Atwell, 1985). Alternatively, the traction of the cremaster muscle may be so strong at a certain point in childhood, that it is impossible to differentiate between retractile and truly undescended testes, despite skillful, repeated examination ("pseudo-ascent"). According to Karpe and associates (1983), the descent achieved with LHRH treatment might be related to reduced testicular retraction by the cremaster muscle. The results of our retrospective evaluation of previous testicular positions (see 4.3.5.) indicate that both explanations for the ascent or pseudo-ascent of the testis are feasible. Several parents of boys with one undescended and one retractile testis reported that during LHRH therapy the retractile testis seemed to be more frequently intrascrotal than before. All these findings substantiate Karpe's premise. To gain more insight, we initiated a search for binding sites or receptors for androgens,

LH and FSH or LHRH in the cremaster muscle. The preliminary results revealed LH-binding sites in the cremaster muscle of prepuberal boys and pigs.

A number of workers reported they saw no adverse reactions to LHRH treatment (Illig et al., 1977; Happ et al., 1978; Pirazolli et al., 1978; Cacciari et al., 1982; Van der Meyden et al., 1984), while others did observe a few adverse reactions, such as behavioural changes (Hagberg and Westphal, 1982; Wit et al., 1985). It is interesting to note that in our study adverse reactions were reported by the parents of some boys that had placebo!

The phenomenon of late descent was also reported by Schwarz and coworkers (1985). In their collaborative study, late descent amounted to 6% (10/171 testes), which they blamed on the diversity in clinical assessment. In our study, 14 initially nonresponding testes (5%) were either located in the scrotum or capable of manipulation into the scrotum at follow-up. In three patients complete descent coincided with the start of puberty. However, since late descent also occurred in the younger age groups, puberty offers only a partial explanation.

The recurrence of incomplete testicular descent some time after complete descent has been achieved with hormonal therapy (time lapse in our study was 3 to 12 months) has been reported by others, varying from 5-60% (Happ et al., 1978; Illig et al., 1980[a]; Zabransky, 1981; Hagberg and Westphal, 1982; Hadziselimovic, 1982; Karpe et al., 1983; Schwarz et al., 1985).

An improved position or complete descent of testes with placebo has also been reported (Illig et al., 1977; Hagberg and Westphal, 1982; Karpe et al., 1983; Klidjian et al., 1985). These observations confirm the difficulty of diagnosis and may be explained in part by the extent to which the child is able to relax at repeat examinations.

As described in chapter 3, literature data concerning pre-existing hormonal anomalies in cryptorchid boys are highly conflicting (Sizonenko et al., 1973; Job et al., 1974[b]; Lee et al., 1974; Cacciari et al., 1974; 1976; Gendrel et al., 1977; Illig and Werder, 1977; Happ et al., 1978; Sizonenko et al., 1978). Our comparative hormonal evaluation of cryptorchid boys and control subjects did not suggest a deficient hypothalamo-pituitary-gonadal axis or deficient Leydig cell function in cryptorchid boys. Mean basal and peak FSH values were the same for all cryptorchids and controls. We only found a higher mean peak FSH in bilateral cryptorchids aged 2 to 6 years. Sizonenko and coworkers (1978) correlated increased FSH response in bilateral cryptorchids to low counts of spermatogonia in both testes.

The higher stimulated LH levels observed in both cryptorchids and controls of age group A compared with age groups B and C, demonstrate maturation of the prepuberal restraint of gonadotropin production in the older boys (see 3.4.3.). The higher basal testosterone levels in boys over six years old may be due to the increase in adrenal steroids towards puberty (adrenarche). The decrease with age of peak and delta testosterone may indicate that at a younger age the testes are more responsive to a single high dose of HCG. Forest (1979) did not find a

significant difference in post-HCG levels of testosterone in prepuberal 1-12 year old boys. However, HCG stimulation in that study consisted of repeated HCG injections. Another explanation may lie in the dosage of HCG. In our study, the same dose of HCG was administered to boys of all ages, amounting to 1,500 IU. Consequently, the younger boys received a relatively higher dose. However, since the maximally stimulating dose of a single HCG injection for adult men lies between 1,500 and 6,000 IU (Forest, 1983), one may assume that in the entire prepuberal period maximal stimulation is achieved with 1,500 IU HCG.

The mode of action of LHRH treatment is still unclear. Some investigators surmised that after LHRH stimulation LH and FSH co-operate to potentiate the local action of testosterone (Illig et al., 1980[b]) or to increase local testosterone secretion and thereby testicular descent due to differentiation of epididymis and ductus deferens (Hadziselimovic et al., 1980[b]). However, we found no evidence of stimulation of the hypothalamo-pituitary-gonadal axis. There were identical, slight changes in basal and peak LH and FSH, as well as basal testosterone levels after LHRH treatment and after placebo. We wonder whether the slight differences in the change of peak FSH in group C and of basal testosterone levels in group A are of clinical significance. Several workers have reported similar findings (Pirazolli et al., 1978; Cacciari et al., 1982; Hagberg and Westphal, 1982). Others have described a fall in peak FSH levels combined with increased, decreased, or unchanged peak LH levels (Happ et al., 1978; Spona et al., 1979; Illig et al., 1980[b]; Hadziselimovic, 1982; Höcht, 1983; Karpe et al., 1983). Comparing the successfully treated boys with the nonresponders in our study, there were only small and clinically insignificant differences in the change of a few hormonal values. Therefore, this evaluation did not explain the mode of action either, nor did it provide a prognostic aid. Our failure to determine the mode of action of LHRH nasal spray prompted us to carry out an additional investigation of this aspect, towards the end of the study period (see 4.3.7.).

There is great similarity between hormonal treatment with HCG and with LHRH as far as results and contributive factors are concerned:

- For both modalities divergent percentages of testicular descent have been reported.
- For both modalities the best rate of success involved lower positioned testes. In case of impalpable testes, success is at best minimal.
- For both modalities a higher success rate has been reported interchangeably for unilateral and bilateral cryptorchidism, for younger and for older boys.
- For both modalities return of the testis to its former, undescended position has been reported.
- For both modalities the mode of action is still unclear.

Adverse reactions to hormonal treatment, particularly signs of androgenic stimulation, are more frequently reported for HCG than for LHRH. No studies have been reported of placebo-controlled HCG treatment, but the efficacy of HCG and LHRH were recently compared in a double-blind study (Rajfer et al.,

1986). In this study involving 33 boys aged 1-5 years, the frequency of testicular descent was equally low for either modality, 1 of 20 testes after HCG versus 3 of 17 after LHRH. They concluded that hormonal treatment is practically useless for truly undescended testes.

4.3.5. Retrospective evaluation of testicular position before referral

a. Introduction

In order to decide whether a boy with unilateral or bilateral cryptorchidism qualified for our double-blind, placebo-controlled study of the efficacy of LHRH nasal spray, the parents were asked a number of questions and particularly whether the undescended testis had ever been seen or felt in the scrotum. The boy was only admitted to the study if this question was answered in the negative. As the study progressed, results seemed to cast a doubt on the information supplied by the parents. Apart from the finding that the lower the initial testicular position the better the response to hormonal treatment, it emerged that some testes descended with placebo. Consequently, we felt the need for a retrospective evaluation of our patients, tracing all available documentation of testicular position from birth up till the time of referral. Collecting these data and reviewing the anamnesis was essential for answering the following questions:

- Is the anamnesis supplied by the parents correct as regards their son's previous testicular position?
- Is there a connection between the anamnestic evaluation and the result of hormonal therapy?
- Does the anamnestic evaluation provide an explanation for the testicular descent achieved with placebo?

b. Patients and methods

After obtaining parental consent, we requested information concerning our patients, regardless of treatment results, from Child Health Care institutions (well-baby clinics and school medical officers), general practitioners and any other doctors that had examined these boys at one stage or another. We specifically asked for any documentation of testicular position. The information we received was classified as follows:

response - merely indicating information was received, which was then qualified as:

positive - indicating that the cryptorchid testis or testes of that particular patient had been documented at least once as retractile or intrascrotal;

negative - indicating that the undescended testis or testes had never been documented as retractile or intrascrotal; or

unknown - indicating that no documentation concerning testicular position was available. If there was no response whatsoever, the patient concerned was also grouped in this category.

c. *Results*

Table 4.16. gives the data, often collected with great difficulty, per age group according to success or failure of treatment and classified as described above. This concerns the testicular position in 237 boys included in our final assessment. We received a response for 213 of them, supplying pertinent information regarding 195 patients. Positive information was received significantly more often ($p < 0.05$) for boys that had success with LHRH treatment (43%) than for boys with failure of treatment (17%).

Table 4.17. lists the age at which testicular position was first documented in the 195 boys for whom pertinent information was received, per age group and again

Table 4.16. Information concerning previous testicular position in 237 cryptorchid boys; number (%) of boys.

age group	treatment result	total	response	information		
				positive	negative	unknown
A	success	7	6 [86]	1 [14]	5 [72]	1 [14]
	failure	42	40 [95]	1 [2]	39 [93]	2 [5]
B	success	18	17 [94]	9 [50]*	5 [28]	4 [22]
	failure	76	64 [84]	16 [21]*	42 [55]	18 [24]
C	success	36	34 [94]	16 [44]*	13 [36]	7 [20]
	failure	58	52 [90]	13 [23]*	35 [60]	10 [17]
A + B + C	success	61	57 [93]	26 [43]*	23 [38]	12 [20]
	failure	176	156 [89]	30 [17]*	116 [66]	30 [17]
	total	237	213 [90]	56 [23]	139 [59]	42 [18]

* success significantly different from failure [chi-square test [2 x 2 table], $p < 0.05$]

Table 4.17. Age at first documentation of testicular position in 195 boys.

age group	treatment result	total		at birth		0–1 yr		1–4 yr		4–12 yr	
		pos	neg	pos	neg	pos	neg	pos	neg	pos	neg
A	success	1	5	0	0	1	5	0	0	0	0
	failure	1	39	1	5	0	34	0	0	0	0
B	success	9	5	0	1	4	1	3	1	2	2
	failure	16	42	0	6	10	33	5	2	1	1
C	success	16	13	0	0	6	1	3	4	7	8
	failure	13	35	2	1	4	22	3	3	4	9
A + B + C	success	26	23	0	1	11	7	6	5	9	10
	failure	30	116	3	12	14	89	8	5	5	10
	total	56	139	3	13	25	96	14	10	14	20

in relation to success or failure of treatment. The information concerning testicular position at birth, in the first year of life, and from age 1-4, was generally supplied by well-baby clinics or infant health centres, while the information concerning age 4-12 generally came from school medical officers. Information regarding testicular position at birth was received for a small number of boys only. Particularly for the older boys (age group C), little information was available concerning their testicular position at birth or in the first year of life.

Table 4.18. lists the information received concerning the previous testicular position in boys whose testes descended during the double-blind period. Ten boys (ten testes) had testicular descent with placebo (table 4.18[a].). Positive information was received regarding four of these boys. Unfortunately, no information was available for another four. Eleven boys (14 testes) had testicular descent with LHRH therapy (one course) as shown in table 4.18[b]. As with placebo decents, positive information was received regarding four boys, while no information was available for five of them.

At the time of writing, 170 of 176 boys that had no success of hormonal treatment have been operated upon. Table 4.19. shows the previous testicular position in these 170 boys (196 undescended testes). This table lists 62 boys in group C, while table 4.16. of this retrospective evaluation listed only 58 boys in group C with failure of treatment. The difference is due to four bilateral cryptorchids in this group who had hemi-descent with hormonal treatment. These boys were added to the success group, as mentioned before, even though their contralateral, undescended testis required surgery. In none of these four cases did we receive positive information.

Table 4.18. Information concerning previous testicular position of boys whose testes descended during the double-blind period.

a) 10 boys, whose testes descended with placebo

age group	placebo descent	information		
		positive	negative	unknown
A	0	0	0	0
B	6	2	2	2
C	4	2	0	2
total	10	4	2	4

b) 11 boys, whose testes descended with LHRH (one course)

age group	LHRH descent	information		
		positive	negative	unknown
A	1	0	1	0
B	1	1	0	0
C	9	3	1	5
total	11	4	2	5

Table 4.19 Information concerning previous position of 196 operated testes in 170 boys; number (%) of boys.

testes	age group	boys	response	information		
				positive	negative	unknown
41	A	36	36 (100)	1 (3)	33 (92)	2 (5)
82	B	72	62 (86)	15 (21)	41 (57)	16 (22)
73	C	62	50 (81)	13 (21)	38 (61)	11 (18)
196	total	170	148 (87)	29 (17)	112 (66)	29 (17)

Table 4.20. summarizes the findings at surgery of 196 undescended testes in relation to the information received concerning previous position. The information was positive for 32 (16%) of the 196 testes that required surgery. In two of these cases (concerning unilateral cryptorchids) the surgical findings invalidated the positive information received in that there was no testis! In addition, ten testes were found in a subcutaneous position on top of the aponeurosis of the external oblique muscle (superficial inguinal ectopia), while according to the positive information these testes had been documented at least once as intrascrotal or retractile. We also received positive information regarding ten testes that were located in the inguinal canal and another ten just outside the inguinal canal in the external annulus. These 20 testes were somewhat mobile in a wide open processus vaginalis. An open processus vaginalis was a frequent finding concerning 139 testes in all.

Table 4.20. Surgical findings in relation to information concerning previous position of 196 testes; number (%) of testes.

information	peroperative position of testes					←total→	processus vaginalis	
	absent	intra-abdominal	inguinal canal	external annulus	superficial inguinal ectopia		open	obliterated
positive	2 (13)	0 (0)	10 (21)	10 (15)	10 (17)	32 (16)	22 (16)	10 (17)
negative	11 (74)	8 (100)	28 (60)	36 (55)	46 (76)	129 (66)	91 (65)	38 (67)
unknown	2 (13)	0 (0)	9 (19)	20 (30)	4 (7)	35 (18)	26 (19)	9 (16)
total	15 (100)	8 (100)	47 (100)	66 (100)	60 (100)	196 (100)	139 (100)	57 (100)

d. Discussion

The response to our request for information concerning previous testicular position was very good, amounting to 90%. Unfortunately, information concerning testicular position at birth or during the first year of life was unavailable in many cases, particularly for age group C, because the early records for these boys had often been discarded. This meant that very important information was lacking, because in early infancy an undescended testis is easily distinguished from a descended one. There is practically no cremasteric reflex in a boy of that

age and therefore there is no retractility to confuse the examiner. It stands to reason that we received positive information for only two patients in the youngest age group, one with success and one with failure of treatment.

As shown in table 4.16., positive information was significantly more frequent for boys with success than for those with failure of treatment. This may indicate that a number of successfully treated testes, viz. those with positive information, should actually have been designated as descended or retractile testes, although it was definitely impossible to make such a diagnosis before treatment. It is remarkable that positive information was received regarding four of ten boys with placebo descent and four of eleven boys with descent after LHRH in the double-blind period. Pertinent information was not available for four boys in the placebo group nor for five in the LHRH group. Therefore we cannot draw any conclusions, but the similarity between the two groups is striking.

Regarding the information we received, this could not always be taken at face value. Just how dependable are these early data? In two cases we received positive information when the testes were absent! A number of times the left and right side had changed places. Sometimes it was not clear whether the testis had been truly undescended or retractile.

It seems logical that the percentage of positive information was lower for testes with failure of treatment than for the successfully treated ones. In actual fact this percentage should have been zero! The fact that this was not the case, might suggest that a number of testes that were operated upon were actually retractile. However, this is highly unlikely as none of the operated testes were ever capable of manipulation into the scrotum at repeated examinations before and during the LHRH treatment, nor at an examination under general anaesthesia before surgery was commenced. Provided the positive information supplied in these cases is correct, these testes must have ascended at one stage or another.

The occurrence of testicular ascent has previously been reported by Privat (1978) and Atwell (1985). Both authors describe boys they themselves had examined and diagnosed as having normally descended testes, whose testes at a follow-up examination years later were no longer in the scrotum nor could they be manipulated into a scrotal position. Atwell in particular, describes the surgical findings in a number of testes he operated upon personally. In these cases he consistently found a wide open processus vaginalis. Part of such a wide open vaginal process will disappear into the peritoneum as the boy grows, which may result in a relative shortening of this process whereby the testis is lifted out of the scrotum (testicular ascent is described in more detail in chapter 5).

In agreement with these data from the literature, testicular ascent may possibly have occurred in the 20 cases where we found a testis floating in a wide open processus vaginalis. It is difficult to say whether there was testicular ascent regarding the ten testes that were found in a superficial inguinal, ectopic position at surgery while the information for these testes was positive.

e. *Conclusions*

The questions that prompted this retrospective evaluation can be answered as follows:

- The anamnesis supplied by the parents was not always correct as regards their son's previous testicular position. In 56 boys of the entire study population (23%) the testis had been seen in the scrotum at least once, of which the parents were totally unaware.
- There was a connection between the anamnestic evaluation and the results of hormonal treatment. Positive information was received significantly more often for boys in whom the treatment was successful than for those in whom the treatment failed.
- Due to a lack of pertinent information, the anamnestic evaluation could not provide an explanation for the testicular descent achieved with placebo. In this respect, there was a remarkable similarity between boys whose testes descended with placebo and boys whose testes descended with LHRH in the double-blind period.

4.3.6. Serum levels of LHRH and gonadotropins after intranasal administration of LHRH

a. *Introduction*

During the double-blind, placebo-controlled study it seemed as if the reaction to hormonal treatment was less pronounced in boys of the younger age groups than in those of the oldest age group. We wondered if this could be due to a difference in absorption of the LHRH nasal spray. Therefore we decided to carry out a substudy in a small number of boys representative of the three age groups to investigate the absorption of LHRH administered intranasally, by measuring LHRH, LH and FSH serum levels in timed blood samples.

b. *Patients and methods*

Nine boys with unilaterally undescended testes were selected for age, three boys per age group (A = 1-2 yrs; B = 2-6 yrs; C = 6-12 yrs) with a similar distribution of most caudal testicular position. They were treated for four weeks with LHRH (Cryptocur®) intranasally, one puff in each nostril three times a day before meals, one puff amounting to 200 μg. If this did not result in testicular descent, they underwent a second course of treatment. On the 15th day of the initial treatment, the boys came to the outpatient clinic at midday, before their second daily dose of LHRH had been administered. An indwelling catheter was inserted and after the first blood sample was taken at 0 minutes, 400 μg of LHRH was administered intranasally as described above. Subsequently, blood was taken at 5, 15, 30 and 60 minutes.

Dr. J. Sandow of Hoechst Aktiengesellschaft, Frankfurt, measured the LHRH serum levels by radio-immunoassay without extraction. The antiserum (HF39) used in the test was developed by Nett and coworkers (1973). Detection limit of the assay: 100 pg/ml. A control experiment was carried out by measuring LHRH plasma levels likewise at 0, 5, 15, 30 and 60 minutes in three adult men who were given 100 μg LHRH intravenously. LH and FSH serum levels were also determined by radio-immunoassay, using RIA-gnost® hLH and hFSH from Behringwerke A.G. The standards employed in these kits have been calibrated for LH versus the MRC standard 68/40 and for FSH versus the MRC standard 69/104, both expressed in mU/ml. Detection limit of the assay was 2mU/ml for LH and 1 mU/ml for FSH.

c. *Results*

One boy (age group B) was excluded from the study because of poor compliance. The result of the LHRH treatment is given in table 4.21. The serum levels of LHRH, LH and FSH before and after 400 μg LHRH intranasally are depicted in figure 4.6. . Although the LHRH serum levels were low, they could be measured shortly after the LHRH administration, at 5-30 minutes in all three age groups. In age groups A and B serum LHRH was higher in the boys that did not respond to hormonal treatment. Serum LH increased markedly in two boys of age group C, but showed little response in the younger boys. There were practically no changes in serum FSH after the LHRH administration in anyone of the three age groups. For comparison, figure 4.7. shows the LHRH serum levels in three adult men before and after intravenous administration of 100 μg LHRH. In all three men the peak response occurred five minutes after LHRH administration.

Table 4.21. Results of LHRH therapy.

age group	patient	age yrs/mos	pretreatment most caudal testicular position	complete descent
A	I	1/3	external annulus	–
	II	1/8	external annulus	–
	III	1/3	scrotal entrance	+
B	I	2/9	scrotal entrance	+
	II	2/3	external annulus	–
	III	3/3	external annulus	0 *
C	I	6/11	external annulus	–
	II	8/7	external annulus	+ **
	III	7/1	scrotal entrance	+

* withdrawn from study because of poor compliance
** two LHRH courses were needed
+ = yes
– = no

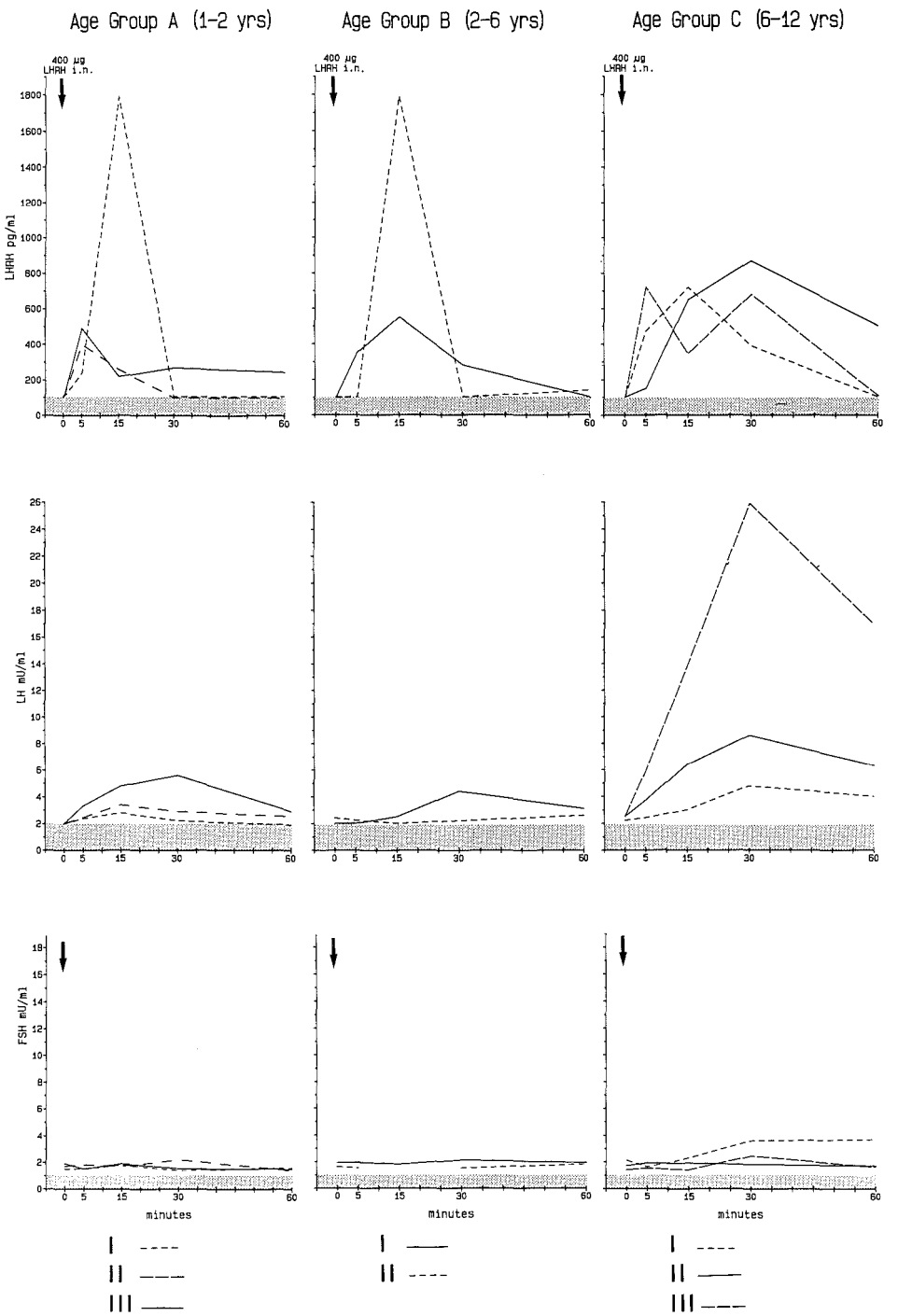


Figure 4.6. Serum levels of LHRH, LH and FSH before and after 400 µg LHRH per nasal spray in eight boys (age group A: N = 3; age group B: N = 2; age group C: N = 3).

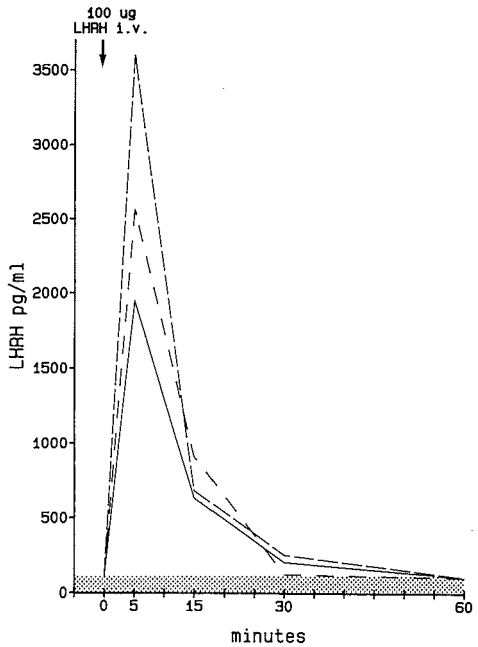


Figure 4.7. Serum levels of LHRH before and after 100 μg LHRH administered intravenously to three adult men.

d. Discussion

The auxiliary study showed that LHRH can be detected in blood 5-30 minutes after intranasal administration of 400 μg LHRH in prepuberal boys. The small number of boys did not allow for a clear differentiation between age groups, although the study did show that even in the younger age groups relatively high serum levels can be obtained, comparable to LHRH serum levels in adult men after the intravenous administration of 100 μg LHRH.

The absorption of LHRH nasal spray as well as the gonadotropin response to various doses of intranasally administered LHRH in adults is described in section 4.1.3. The absorption of LHRH nasal spray in prepuberal boys has not previously been determined, but the gonadotropin response to LHRH nasal spray in prepuberal boys was measured recently by Rajfer and coworkers (1986). They found a significant increase in serum LH levels at 30 and 60 minutes after the intranasal administration of 200 μg LHRH. Serum FSH did not change significantly. They did not measure the LHRH serum levels. To our knowledge, our study is the first one in which serum levels of LHRH as well as gonadotropins were measured in prepuberal boys after intranasal administration of LHRH.

In our limited study, a clear LH response occurred at 30 minutes after intranasal administration in age group C only, particularly in the two boys that responded

successfully to LHRH therapy. We can find no easy explanation for the fact that the response of serum LH to an intranasal dose of LHRH was most marked in boys of the oldest age group. Those boys had not yet reached the peripuberal period during which the response of gonadotropins to exogenous GnRH increases (Reiter and Grumbach, 1982). It is remarkable that in our double-blind, placebo-controlled study identical changes were observed in basal and peak levels of LH after four weeks of either LH or placebo, both administered intranasally, in all age groups. It is possible that in prepuberal boys the effect of intranasally administered LHRH on LH release is too short and therefore does not result in a lasting stimulation of gonadotropins.

No relationship could be established between serum LHRH and LH after intranasal administration of LHRH. As in studies in adult males, no response of FSH was observed after the intranasal administration of LHRH

e. *Conclusion*

This supplemental study did not reveal a difference in absorption of the intranasally administered LHRH between the three age groups which might explain the difference in success of hormonal treatment. However, a clear LH response to LHRH nasal spray was only observed in boys of age group C and these same boys responded successfully to this form of treatment.

4.3.7. Supplementary endocrinological studies before and after LHRH nasal spray treatment

a. *Introduction*

The obligatory precursor for the biosynthesis of testosterone in the testes of mammals appears to be cholesterol, which can be converted intramitochondrially to pregnenolone (figure 3.3.). The conversion of pregnenolone to testosterone can occur via several Δ 5 intermediates - involving pregnenolone (Preg), 17 α-hydroxypregnenolone (17 OHPreg), dehydroepiandrosterone (DHEA) and androstenediol (Δ 5) - as well as via several Δ 4 intermediates - involving progesterone (P), 17 α-hydroxyprogesterone (17 OHP) and androstenedione (Δ 4). According to Yanaihara and Troen (1972), the Δ 5 pathway appears to be the most significant in the human testis. In contrast, Zachmann (1972) stated that it is still controversial whether under physiological conditions the Δ 4 or the Δ 5 pathway is preferred for the biosynthesis of testosterone from pregnenolone, even though both pathways require the same enzymes, albeit in a different sequence. Forest and coworkers (1975) suggested that the prepuberal testis may also contribute to the plasma pool of metabolites of the Δ 4 pathway (Δ 4 and 17 OHP). The same group found evidence of testicular production of DHEAS in childhood (De Peretti and Forest, 1978).

The kinetics of the plasma level response of steroid hormones to a single

intramuscular injection of HCG was studied by Forest and Bertrand (1984) in normal prepuberal boys. They observed a progressive increase of plasma T with peak levels usually occurring at the 100th hour. The kinetics of dihydrostestosterone (DHT) were quite similar, although the extent of the response was modest. There was no significant change in 17 OHP or Δ 4. Toscana and coworkers (1983) likewise found an increase in plasma T and DHT, but no change in 17 OHP, Δ 4 and oestradiol (E_2), after a single dose of HCG in prepuberal boys. Untreated hypogonadotropic, hypogonadic adult men showed an almost similar reaction to a single intramuscular HCG injection, consisting of a progressive and substantial rise in plasma T, maximal at 96-120 hours, as well as a modest, late rise in E_2, but no significant change in Δ 4 or 17 OHP (Forest and Roulier, 1984). This contrasted with a biphasic T response to a single intramuscular injection of HCG observed in normal adult males; the first one after four hours and a second, delayed reaction with a more pronounced peak between 72-96 hours (Saez and Forest, 1979). Furthermore, there is ample evidence that in adult men HCG acutely stimulates the testicular aromatase, while it inhibits 17 α-hydroxylase and even more so 17,20-lyase activity, resulting in the accumulation of 17 α-hydroxylated steroids and progesterone - so-called HCG-induced testicular desensitization (Forest et al., 1979; Martikainen et al., (1980). Peak levels of E_2 and 17 OHP are obtained in adult men after one intramuscular injection of HCG, but these levels are still elevated at 72 hours (Forest and Roulier, 1984). The finding that an HCG-induced steroidogenic desensitization would occur in normal adult men and puberal boys as well as in HCG-treated hypogonadotropic, hypogonadic adult men, but not in prepuberal boys, prompted Forest to suggest that HCG-induced steroidogenic desensitization is present in patients previously exposed to a certain level of gonadotropic stimulation (Forest and Roulier, 1984).

Mercier and coworkers (1966) clearly demonstrated the existence of a separate human sex hormone-binding globulin (SHBG or TEBG = testosterone-oestradiol-binding globulin). SHBG is a beta-globulin secreted by the liver. The protein binds reversibly and with affinity the main biologically active, circulating androgen testosterone and, to a lesser extent, dihydrostestosterone and the active oestrogen oestradiol (E_2). Serum concentrations of SHBG are partially dependent on the hormonal milieu; androgens cause a reduction and oestrogens a rise in SHBG level (Anderson, 1974). The concentration of SHBG is higher in children than in adults; after the onset of puberty there is a slight fall in the female and a marked drop in the male (Anderson, 1974). Belgoroski and Rivarola (1982) suggested the use of SHBG as a parameter for the determination of gonadotropin-induced androgen secretion in prepuberal boys. They measured a decrease of SHBG concentration after five days of HCG stimulation.

These diverse findings prompted us to carry out a supplementary investigation to determine the mode of action of LHRH nasal spray in a separate series of 16 cryptorchid boys.

b. Patients and methods

Sixteen boys with either unilateral or bilateral cryptorchidism were studied with the informed consent of the parents. There were four boys in age group A (1-2 yrs), three in age group B (2-6 yrs) and nine in age group C (6-12 yrs). All 16 boys underwent an HCG test at the start and at the close of four weeks of LHRH nasal spray treatment, amounting to 200 μg in each nostril three times a day before meals. Before and three days after the intramuscular injection of 1,500 IU HCG, the serum levels of the steroid hormones T, DHT, P, 17 OHP, DHEAS and Δ 4, were determined in all three age groups. In addition, SHBG and E_2 were determined in age groups A and B only. For methods of steroid determinations see chapter 2. A second course of LHRH treatment was administered if the initial treatment was unsuccessful.

Age group matched, healthy prepuberal boys were used as control subjects. These boys had been referred to us for evaluation of their testicular position; the testes were found to be fully descended in all cases. With the informed consent of the parents, serum levels of steroid hormones and SHBG were determined before and after an HCG challenge as described above. There were seven boys in age group A, ten in age group B, and ten in age group C.

Statistical analysis of the results was carried out by means of Wilcoxon matched pairs signed rank tests and Mann-Whitney-U tests. Because of the small number of cryptorchid boys in age groups A and B, the results of these two age groups were combined for statistical analysis, regarding the cryptorchid boys as well as control subjects. This is justifiable in view of the fact that the results of hormonal evaluation of the two age groups were comparable in cryptorchids as well as controls.

c. Results

The results of the LHRH nasal spray treatment are given in table 4.22. Complete descent occurred in five unilateral cryptorchids only; in two of them after two courses of LHRH treatment.

Table 4.22. Results of LHRH nasal spray treatment in 16 boys with unilateral or bilateral cryptorchidism.

	patients (N)			complete descent (patients, N)		
age	unilateral		bilateral	unilateral		bilateral
yrs	right	left		right	left	
1- 2	2	2	0	0	1	0
2- 6	3	0	0	0	0	0
6-12	5	2	2	3*	1	0
total	10	4	2	3	2	0

* two boys needed two LHRH courses

Tables 4.23[a]. and 4.23[b]. give the median and range serum values of P, 17 OHP, DHEAS, Δ 4, T, DHT, SHBG and E_2, obtained during the HCG tests before and after the initial course of LHRH nasal spray treatment in patients of age groups A and B, in comparison with age-matched control subjects. Table 4.23[c]. gives the combined figures for age groups A and B that were used in the statistical analysis. *Before LHRH therapy*, basal and peak values of P, 17 OHP, DHEAS, Δ 4, T, DHT, E_2, and SHBG of cryptorchid boys did not differ from control values ($p > 0.05$). In cryptorchid boys as well as control subjects, peak values of T and DHT were considerably higher than basal values, while the DHEAS and Δ 4 peak values were slightly (but statistically significant) higher than basal values. In comparison with pretreatment values, the values *after LHRH therapy* showed an increase in individual peak T levels in all but one boy, although no statistical significance was obtained ($p > 0.05$). Basal T values did not change after LHRH therapy. The basal and peak values of the steroid precursors, DHT, E_2, and SHBG, did not change significantly either. In general, the basal values of the steroid precursors and DHT were low and in many cases even fell below the detection limits of the assays.

Table 4.23[d]. gives the median and range serum values of steroid precursors, testosterone and dihydrostestosterone likewise obtained during HCG tests before and after the initial course of LHRH treatment, in boys of age group C in comparison with age-matched control subjects. In these older boys, cryptorchids as well as controls, the basal and peak values of P, 17 OHP, DHEAS, and Δ 4, as well as basal T values, were significantly higher than the values found in the two younger age groups (1-6 yrs). Peak testosterone values in control subjects and peak DHT values in cryptorchids and controls were significantly lower than in the younger boys. Comparing the values for cryptorchid boys *before treatment* with control values, there was no difference in basal or peak values of P, DHEAS, Δ 4, T or DHT ($p > 0.05$). Basal and peak values of 17 OHP were slightly, but significantly higher in control subjects than in cryptorchid boys ($p < 0.05$). In cryptorchids as well as controls, peak values of T and DHT were considerably higher than basal values. In cryptorchids, peak DHEAS values were slightly, but significantly higher than basal values. In control subjects, peak Δ 4 values were slightly, but significantly higher than basal values ($p < 0.05$). In comparison with pretreatment results, the values *after LHRH therapy* showed an increase in the individual peak serum T values in all boys of this age group and this was statistically significant ($p < 0.05$). Basal T values did not change, nor was there a significant change in basal or peak values of the steroid precursors or DHT.

For the boys of all three age groups together (1-12 yrs), the increase in peak T and DHT values observed after LHRH therapy was statistically significant ($p < 0.05$).

d. Discussion

Compared with control values, basal and peak values of the steroid precursors

Table 4.23[a]. Results of HCG tests in cryptorchid boys of age group A (1-2 yrs) before and after one course of LHRH nasal spray therapy, in comparison with age-matched control subjects.

AGE GROUP A			P	17 OHP	DHEAS	Δ 4	T	DHT	E_2	SHBG
Cryptorchids (N = 4)			nmol/l	nmol/l	umol/l	nmol/l	nmol/l	nmol/l	pmol/l	nmol/l
age (yrs) mean ± SD										
1.5 ± 0.4										
	basal	median	0.9	< 1.2	0.06	< 0.35	0.06	< 0.13	13	168.9
		range	<0.5 - 1.4	<1.2 - 3.3	<0.02 - 0.12	<0.35 - 0.76	0.02 - 0.11	<0.13 - <0.13	6 - 14	125.6 - 248.0
before LHRH										
	peak	median	0.6	1.4	0.25	0.89	9.65	1.38	15	193.2
		range	<0.5 - 0.9	<1.2 - 2.2	0.17 - 0.31	0.72 - 1.04	4.90 - 14.70	1.09 - 1.58	10 - 22	101.7 - 218.0
	basal	median	0.7	< 1.2	0.09	< 0.35	0.06	< 0.13	14	165.8
		range	<0.5 - 1.3	<1.2 - 1.9	<0.02 - 0.18	<0.35 - 0.45	0.05 - 0.08	<0.13 - <0.13	9 - 18	123.9 - 247.9
after LHRH										
	peak	median	1.0	1.8	0.31	1.10	14.70	2.04	16	160.9
		range	<0.5 - 3.4	<1.2 - 4.6	0.21 - 0.46	0.90 - 1.36	7.80 - 21.00	1.18 - 2.99	13 - 20	110.2 - 241.8
Controls (N = 7)										
age (yrs) mean ± SD										
1.6 ± 0.3										
	basal	median	1.3	< 1.2	0.19	0.48	0.06	< 0.13	11	170.0
		range	1.1 - 3.0	<1.2 - 2.6	0.03 - 0.59	<0.35 - 0.80	0.03 - 0.13	<0.13 - 0.14	7 - 18	116.8 - 215.9
	peak	median	1.3	1.5	0.35	0.73	11.00	1.63	15	182.6
		range	<0.5 - 2.7	<1.2 - 2.3	0.12 - 0.45	0.52 - 0.94	6.80 - 15.00	0.85 - 1.96	9 - 24	20.1 - 188.0

Table 4.23[b]. Results of HCG tests in cryptorchid boys of age group B (2-6 yrs) before and after one course of LHRH nasal spray therapy, in comparison with age-matched control subjects.

AGE GROUP B			P	17 OHP	DHEAS	Δ 4	T	DHT	E_2	SHBG
Cryptorchids (N = 3)			nmol/l	nmol/l	umol/l	nmol/l	nmol/l	nmol/l	pmol/l	nmol/l
age (yrs) mean ± SD										
3.0 ± 1.1										
	basal	median	< 0.5	< 1.2	0.13	< 0.35	0.03	< 0.13	12	136.3
		range	<0.5 - 0.7	<1.2 -<1.2	0.06 - 0.31	<0.35 - 0.66	0.02 - 0.04	<0.13 - <0.13	6 - 13	130.3 - 138.1
before LHRH										
	peak	median	< 0.5	< 1.2	0.37	1.15	11.80	1.31	20	142.9
		range	<0.5 - 0.6	<1.2 - 1.7	0.36 - 0.48	0.97 - 1.36	3.30 - 13.00	0.57 - 1.71	9 - 31	125.7 - 180.8
	basal	median	< 0.5	< 1.2	0.18	< 0.35	0.09	< 0.13	11	176.0
		range	<0.5 - 0.8	<1.2 -<1.2	0.09 - 0.32	<0.35 - 0.55	0.02 - 0.12	<0.13 - <0.13	11 - 12	109.1 - 199.8
after LHRH										
	basal	median	1.0	1.91	0.51	1.04	19.00	1.65	18	164.5
		range	1.9 - 1.3	<1.2 - 3.4	0.43 - 1.00	0.59 - 2.02	5.10 - 28.00	1.03 - 2.44	12 - 22	127.1 - 197.1
Controls (N = 10)										
age (yrs) mean ± SD										
3.7 ± 1.2										
	basal	median	0.6	< 1.2	0.13	0.54	0.05	< 0.13	10	126.6
		range	<0.5 - 2.0	<1.2 - 3.1	0.02 - 0.49	<0.35 - 1.01	0.02 - 0.14	<0.13 - 0.30	5 - 16	80.9 - 232.5
	peak	median	0.6	< 1.2	0.31	0.89	9.85	0.92	13	135.1
		range	<0.5 - 3.0	<1.2 - 3.5	0.10 - 0.99	0.62 - 1.74	4.30 - 19.00	0.82 - 1.96	6 - 24	84.2 - 183.5

Table 4.23[c]. Results of HCG tests in cryptorchid boys of age groups A and B combined (1-6 yrs) before and after one course of LHRH nasal spray therapy, in comparison with age-matched control subjects.

AGE GROUP A + B			P	17 OHP	DHEAS	Δ 4	T	DHT	E_2	SHBG
Cryptorchids (N = 7)			nmol/l	nmol/l	umol/l	nmol/l	nmol/l	nmol/l	pmol/l	nmol/l
age (yrs) mean ± SD										
2.1 ± 1.1										
	basal	median	< 0.5	< 1.2	0.06	< 0.35	0.04	< 0.13	13	138.1
		range	<0.5 - 1.4	<1.2 - 3.3	0.02 - 0.31	<0.35 - 0.76	0.02 - 0.11	<0.13 - <0.13	6 - 14	125.6 - 248.0
before LHRH										
	peak	median	< 0.5	1.3	0.31 •	1.01 •	11.80 •	1.31 •	17	178.8
		range	<0.5 - 0.9	<1.2 - 2.2	0.17 - 0.48	0.73 - 1.36	3.30 - 14.70	0.57 - 1.71	9 - 31	101.7 - 218.0
	basal	median	< 0.5	< 1.2	0.12	< 0.35	0.07	< 0.13	12	176.0
		range	<0.5 - 1.3	<1.2 - 1.9	0.02 - 0.32	<0.35 - 0.55	0.02 - 0.12	<0.13 - <0.13	9 - 18	109.1 - 247.9
after LHRH										
	peak	median	1.0	1.9	0.43 •	1.04 •	19.00 •	1.97 •	17	164.5
		range	<0.5 - 3.4	<1.2 - 4.6	0.21 - 1.00	0.59 - 2.02	5.10 - 28.00	1.03 - 2.99	12 - 22	110.2 - 241.8
Controls (N = 17)										
age (yrs) mean ± SD										
2.9 ± 1.4										
	basal	median	1.1	< 1.2	0.14	0.52	0.05	< 0.13	10	146.7
		range	<0.5 - 3.0	<1.2 - 3.1	0.02 - 0.59	<0.35 - 1.01	0.02 - 0.14	<0.13 - 0.30	5 - 18	80.9 - 232.5
	peak	median	1.1	< 1.2	0.32 •	0.87 •	10.00 •	1.16 •	14	138.0
		range	<0.5 - 3.0	<1.2 - 3.5	0.10 - 0.99	0.52 - 1.74	4.30 - 19.00	0.82 - 1.96	6 - 24	84.2 - 188.0

• significantly higher than basal values (Wilcoxon matched pairs signed rank test, $p < 0.05$)

Table 4.23[d]. Results of HCG tests in cryptorchid boys of age group C (6-12 yrs) before and after one course of LHRH nasal spray treatment, in comparison with age-matched control subjects.

AGE GROUP C

			P nmol/l	17 OHP nmol/l	DHEAS umol/l	Δ 4 nmol/l	T nmol/l	DHT nmol/l
Cryptorchids (N = 9)								
age (yrs) mean ± SD 9.5 ± 2.1								
before LHRH	basal	median	2.2●	2.4●	0.87●	1.60●	0.16●	< 0.13
		range	1.4 - 3.1	2.4 - 2.9	0.36 - 2.80	0.35 - 3.10	0.08 - 0.64	< 0.13 - 0.64
	peak	median	1.9●	2.4●	1.28●□	1.35●	5.30□	0.39○□
		range	1.4 - 2.6	2.4 - 3.7	0.42 - 3.48	0.60 - 2.70	1.40 - 6.60	< 0.13 - 1.20
after LHRH	basal	median	1.7	2.4	1.42	1.40	0.12	< 0.13
		range	1.1 - 2.4	2.4 - 3.1	0.52 - 2.82	0.40 - 2.00	0.03 - 0.26	< 0.13 - 2.00
	peak	median	2.1	2.4	1.98□	1.95□	6.60□*	0.82□
		range	1.2 - 3.9	2.4 - 3.8	0.48 - 3.26	1.40 - 2.50	4.30 - 15.00	< 0.13 - 6.50
Controls (N = 10)								
age (yrs) mean ± SD 9.9 ± 2.0								
	basal	median	1.8●	3.7●■	1.18●	1.49●	0.13●	0.20
		range	1.1 - 3.6	2.4 - 6.0	0.58 - 5.90	0.40 - 3.90	0.05 - 0.42	< 0.13 - 0.43
	peak	median	2.2●	4.4●■	1.40●	1.75●□	4.65○□	0.50○□
		range	1.2 - 2.5	2.4 - 5.3	0.66 - 6.41	0.90 - 4.10	3.30 - 6.50	0.26 - 0.69

● significantly higher than the same determinations in younger boys (1–6 yrs) (Mann–Whitney–U test, $p < 0.05$)
○ significantly lower than the same determinations in younger boys (1–6 yrs) (Mann–Whitney–U test, $p < 0.05$)
■ significantly higher than the same determinations in cryptorchid boys (Mann–Whitney–U test, $p < 0.05$)
□ significantly higher than basal value (Wilcoxon matched pairs signed rank test, $p < 0.05$)
* significantly higher than peak value before LHRH treatment (Wilcoxon matched pairs signed rank test, $p < 0.05$)

revealed by the HCG tests performed before and after LHRH treatment, did not suggest pre-existing disorders in the testosterone biosynthesis in the cryptorchid boys. Nor did any evidence emerge of an inhibition of enzymes involved in the biosynthesis of testosterone, as a result of either the intramuscular injection of HCG or one course of LHRH nasal spray treatment.

The higher basal T and testosterone precursors observed in boys over six years old suggest an increase of adrenal steroids before puberty (adrenarche), as described by Forest (1979). The peak testosterone values were higher in younger boys (1-6 yrs) than in boys of age group C (6-12 yrs). This is in conformity with the results of the HCG test carried out in our double-blind, placebo-controlled study (see 4.3.4.), although in the auxiliary study statistical analysis showed a significance for controls only.

We did find an increase of peak testosterone values after LHRH therapy in all age groups. This may have been partly due to the HCG injection prior to treatment. This increase in peak T values supports the observations of Hadziselimovic and coworkers (1979; 1980[b]). In testicular biopsies, taken from boys with undescended testes that had undergone LHRH treatment, they found an increase in size, number and differentiation of Leydig cells, as well as recruitment of precursor cells from fibroblasts.

No significant changes of serum SHBG were found, either after HCG stimulation or after LHRH treatment, contrasting with the findings of Belgoroski and Rivarola (1982) and Dunkel (1985). In agreement with our observations, Chaussain and coworkers (1979) did not find a change in the binding capacity of SHBG after HCG stimulation in cryptorchid prepuberal boys.

In summary

The results of the HCG tests performed before and after four weeks of LHRH nasal spray therapy, support the hypothesis that LHRH treatment stimulates the Leydig cells. Under basal conditions, this stimulation cannot be detected in blood; basal serum testosterone values did not increase after LHRH therapy (see 4.3.).

We did not find any indication of a defect in the biosynthesis of testosterone in prepuberal boys with undescended testes. Nor did we find any evidence of inhibition of the enzymes involved in the biosynthesis of testosterone, either by intramuscular injection of HCG or by four weeks of LHRH nasal spray treatment.

4.3.8. Conclusions

In the double-blind period, the rate of success for LHRH treatment did not differ from that for placebo, while the results of the open study seemed to indicate that LHRH therapy does influence the position of the testis. However, the placebo effect of treatment during the open period should not be over-

looked. LHRH nasal spray may be effective in boys with incompletely descended testes that can be manipulated to the scrotal entrance.

Our hormonal data did not indicate the presence of hormonal anomalies in cryptorchid boys, although higher stimulated FSH serum values were found in bilateral 2-6 year old cryptorchids.

Nor did the hormonal data substantiate the premise that the mode of action involves activation of the pituitary-gonadal axis, although the results of the HCG test after LHRH nasal spray therapy did indicate stimulation of Leydig cells. Hormonal evaluation did not provide a diagnostic aid regarding success of hormonal treatment.

The retrospective evaluation of testicular position before referral disclosed a previous intrascrotal position or retractility of testes in more than 40% of the boys in whom complete descent was achieved. Consequently, it is feasible that the mode of action of LHRH treatment involves a decline in retractility of the cremaster muscle and that a number of the testes that responded successfully to LHRH therapy would have been spontaneously intrascrotal at puberty.

The lower success rate for LHRH treatment in the younger age groups cannot be explained by a difference in resorption of the LHRH nasal spray. The explanation may lie in the relatively small number of low testicular positions before treatment in younger boys compared to the 6-12 year olds. This indicates that only pretreatment testicular position significantly influences the rate of success.

GENERAL DISCUSSION OF HORMONAL ASPECTS AND TREATMENT OF CRYPTORCHIDISM

A (transient) deficiency of the hypothalamo-pituitary-gonadal axis would explain the pathogenesis of cryptorchidism and argue for its hormonal treatment. This hypothesis is based on the observation of relatively lower serum testosterone values during the early months of life in boys with undescended testes, compared to boys with normal or delayed spontaneous descent (Gendrel et al., 1978; 1979). The same group found peak LH values of cryptorchid boys significantly lower than those of boys with delayed spontaneous descent (Gendrel et al., 1980). In contrast, other workers found normal values for serum testosterone as well as basal and stimulated gonadotropins in cryptorchid boys during the early months of life (Davidson et al., 1981, Tapanainen et al., 1982). In view of these conflicting data we decided to study the clinical and hormonal aspects of boys born with undescended testes during the first year of life.

Clinically, we observed spontaneous, delayed testicular descent in fullterm infants. The frequency amounted to 50% for boys enrolled in the study within the first three months of life, half of whom had this spontaneous descent before they were three months old. Contrary to the reports of Scorer (1964; 1981) and Forest

and coworkers (1984), we did observe spontaneous testicular descent after the sixth month of life.

Our hormonal evaluation of boys with normal testicular descent showed a clear postnatal testosterone surge rising to peak levels at approximately two months. The values decreased again and after approximately the sixth month, the concentration of plasma testosterone had reached prepuberal levels. These data are in agreement with those of Forest et al. (1976) and Hammond et al. (1979). Comparing the cross-sectional serum testosterone values of persistently cryptorchids and boys with delayed spontaneous descent with those of control subjects, we found no significant differences. Nor did we find significant differences comparing the cross-sectional and longitudinal serum testosterone values of boys with delayed spontaneous descent with the values of boys that stayed cryptorchid. The fact that Gendrel and coworkers (1978) did not evaluate cross-sectional and longitudinal data separately, may to some extent explain the divergence between our findings and theirs. The difference in results may also be influenced by the fact that the French workers did not expect spontaneous descent after the fourth month of life, while we observed spontaneous descent even after the sixth month. A drawback of our study might be that testosterone values of persistently cryptorchid boys and of those with delayed, spontaneous descent were not measured before 80 days of age. On the other hand, we did measure these values before 80 days in control subjects and found a markedly wide range throughout the first three months. Our results are in conformity with those of Tapanainen et al. (1982) who found testosterone levels of cryptorchid infants similar to those of infants with normal testicular descent.

In our study, cross-sectional and longitudinal basal LH and stimulated LH and FSH serum values showed no significant differences from the age of 80 days through the first year of life between boys with delayed, spontaneous descent and persistently cryptorchid boys. The small number of control subjects did not allow for a definite conclusion, although the levels of basal and peak LH and FSH serum values of the controls were comparable to those of cryptorchids and boys with delayed spontaneous descent. Basal LH values were even higher for boys with delayed, spontaneous descent than for controls. The longitudinal basal and stimulated LH serum values in cryptorchids and boys with delayed, spontaneous descent showed a significant decrease from 3 to 6 and from 6 to 12 months of age. Job and coworkers (1977[b]) found lower stimulated LH serum values in cryptorchid infants compared to control subjects. However, the fact that they considered the first year of life as a whole may account for the discrepancy. In our study, we observed an age-related decrease in stimulated LH values during the first year of life. Our findings were in agreement with those of Tapanainen and coworkers (1982), who also found initially increased basal and stimulated LH levels in cryptorchid boys, which declined to prepuberal levels towards the end of the first year of life, comparable to those of boys with normal testicular descent.

Our hormonal evaluation during the first year of life did not support the hypothesis of a deficient hypothalamo-pituitary-gonadal axis in cryptorchid infants.
Spontaneous testicular descent in the first year of life occurs in 40-50% of all cases, even after the sixth month of life.
There were no hormonal differences between boys with persistent cryptorchidism and boys with spontaneous testicular descent in the first year of life.

The lack of correlations between basal or stimulated LH serum values and testosterone serum values in the first year of life favours the theory that intrinsic CNS inhibitory influences suppress the secretion of gonadotropins in childhood and that this mechanism is independent of sex steroids. A deficiency of gonadotropic and androgenic hormones has also been suggested as causal to cryptorchidism. Provided that such hormonal deficiency can be determined postnatally, our findings of normal testosterone and gonadotropin levels in cryptorchid boys during the first year of life do not support this premise. In actual fact, our results question the role of gonadotropic and androgenic hormones in testicular descent.
Our hormonal evaluation favours the theory that intrinsic CNS inhibitory influences, independent of sex steroids, suppress the secretion of gonadotropins in childhood.
Our findings did not support the premise that cryptorchidism is caused by a deficiency of gonadotropic and androgenic hormones.

The levels of testosterone, dihydrotestosterone and steroid precursors before and after HCG stimulation at the start of the second year of life were very similar for boys that stayed cryptorchid and boys with delayed spontaneous descent in the first year of life compared to boys with normal testicular descent. After HCG stimulation, a clear and identical rise of serum testosterone and DHT was found in the three groups. The steroid precursors showed no or only small increases. In conformity with the physical appearance of our boys with undescended testes, these hormonal data contra-indicate disorders in the biosynthesis of testosterone or enzyme inhibitions.
The results of the HCG tests gave no indication of disorders in the biosynthesis of testosterone in boys with undescended testes, in conformity with the physical appearance of our study population. Moreover, we found no signs of enzyme inhibition.

The results of the pilot study of LHRH nasal spray treatment for boys with undescended testes after the first year of life were encouraging; 17 out of 26 (65%) testes descended with LHRH therapy. However, in our double-blind, placebo-controlled study, the percentage of descent with LHRH treatment (9%) was not better than with placebo (8%). After two LHRH treatment courses, complete

descent was achieved for 48 out of 271 undescended testes (18%). Comparing the success rate of our double-blind period with the results of other double-blind, placebo-controlled studies in the literature (see table 4.1.), it appeared that our rate of success (9%) was similar (chi-square test, $p > 0.05$) to that of Karpe et al., 1983 (20%) and Wit et al., 1985 (17%). The success rates of the studies of Illig et al., 1977 (38%), Bertelsen et al., 1981 (24%) and Hagberg and Westphal, 1982 (28%) were significantly higher (chi-square test, $p < 0.05$) than ours in the double-blind period. Comparing the percentage of success after two LHRH courses in our study (18%) with that of other, uncontrolled studies, including our own pilot study, it appeared that the results of Pirazolli et al., 1978 (32%), Cacciari et al., 1982 (22%), Van der Meyden et al., 1984 (13%), and Rajfer et al., 1986 (18%) were comparable to ours (chi-square test, $p > 0.05$). The success rate of our pilot study (65%) was significantly higher and so were the percentages of complete descent achieved in the studies of Happ et al., 1978 (64%), Zabransky, 1981 (78%), Hagberg and Westphal, 1982 (61%), Hadziselimovic et al., 1982 (62%), Borkenstein et al., 1983 (57%), and Schwarz et al., 1985 (37%). Even when we added the placebo descents to the success group in the open study period (surmising that in an uncontrolled study these descents would have been considered as success of hormonal therapy) the comparison with the other studies did not vary.

Which factors are responsible for these divergent success rates?

Although the results of our study suggested that success of treatment was dependent on age at treatment (a lower success rate in the younger age groups) as well as laterality of the undescended testes (a lower success rate in leftsided cryptorchidism), the influence of pretreatment testicular position and success of hormonal therapy seemed paramount. From the logistic regression analysis it emerged that success of treatment was indeed highly dependent on pretreatment testicular position and not on age at treatment or laterality of the undescended testes. In our study more than 50% of the testes that could be manipulated at least to the scrotal entrance before treatment, descended after two LHRH courses. Therefore it is very likely that the treatment results will be better for a study population that includes more boys with testes in a lower, albeit undescended position. In this respect, it appeared that our own pilot study involved significantly more undescended testes that were capable of manipulation to at least the scrotal entrance before treatment, than our double-blind, placebo-controlled study (54% versus 26%). This may explain the difference in success between these two studies. Some investigators did not mention pretreatment testicular position at all (Bertelsen et al., 1981; Borkenstein et al., 1983), while others merely specified "inguinal" or "inguinal canal" without mentioning the most caudal testicular position before treatment (Illig et al., 1977; Pirazolli et al., 1978; Cacciari et al., 1982). In contrast, Happ and coworkers (1978) reported that

28 of the 36 undescended testes in their series could at least be manipulated to the scrotal neck before treatment. It is not surprising that the success rate in this study was 64%! Hadziselimovic et al., (1982) reported that in their series more than 60% of the inguinal testes responded successfully to LHRH therapy, but the most caudal testicular position before treatment was not mentioned. Some investigators (Happ et al., 1978; Van der Meyden et al., 1984) included so called gliding testes or "gleithoden" (i.e. testes that can be manipulated into the upper part of the scrotum with immediate return to the undescended position), which had been excluded by others (Karpe et al., 1983).

Success of LHRH treatment for nonscrotal testes is highly dependent on pretreatment testicular position. The diversity, or lack of description of the pretreatment testicular positions in the various study populations, complicates comparison of treatment results.

The placebo descents in our own study and in other placebo-controlled studies have demonstrated that it is impossible to exclude retractile testes with absolute certainty. Hadziselimovic et al., (1982) claimed that in his study only true cryptorchids were selected for treatment (hormonal or surgical). In testicular biopsies from all surgically treated boys he found histological changes typical for a cryptorchid gonad. However, animal studies have revealed histological changes in testes that were located extrascrotally for a certain length of time, which were reversible in many cases (Moore, 1924; Clegg, 1963; Frankenhuis and Wensing, 1979).

Inclusion of retractile testes may have influenced the percentages of success of all studies of hormonal treatment for undescended testes.

We also wondered whether our dosage schedule might have caused our lower success rate for LHRH therapy compared to other studies. It appeared that the same dosage was used in most other studies, including the studies with higher success rates. Some workers attributed higher success rates to double stimulation (administration before *and* after meals one nostril at a time), whereby the effect of the second dose is enhanced by the priming effect of the preceding dose (Illig et al., 1977; Happ et al., 1978). However, similarly good results were achieved with single, binasal LHRH administration three times daily (Hagberg and Westphal, 1982; Hadziselimovic et al., 1982; Borkenstein et al., 1983). Hadziselimovic (1983[b]) even surmised that LHRH treatment administered six times daily, leads to down regulation or exhaustion of the pituitary gland.

In our study, a repeat course of LHRH treatment enhanced the success rate. This may indicate that the success of treatment depends on duration of the therapy, although a placebo effect in the open study cannot be excluded. In most studies LHRH was administered for four weeks only and the results were the same or even better than after our second course of LHRH. A repeat course of LHRH has been called useless by some (Illig et al., 1980[a]), while others claimed high

success rates with prolonged treatment (Happ et al., 1978).
Enhancement of the rate of success after two LHRH courses in our study may indicate that success of treatment depends on duration of therapy, although a placebo effect in the open study cannot be excluded.

The mode of action of LHRH nasal spray treatment is unclear. Illig and coworkers (1980[b]) suggested that FSH has a key function in inducing testicular descent, without offering an explanation for the way in which testicular descent takes place. Hadziselimovic surmised that the epididymis has a primary role in testicular descent and that high local testosterone concentrations are necessary to induce differentiation and outgrowth of the epididymis and thereby testicular descent (Hadziselimovic et al., 1980[b]). Our observation of statistically significant differences in hormonal values before and after placebo administration indicates that factors other than LHRH treatment may influence gonadotropic release after exogenous GnRH stimulation. The results of the LHRH tests before and after LHRH therapy gave no signs of a lasting stimulation of the hypothalamo-pituitary-gonadal axis, although we did find some clinical and hormonal indications of stimulatory influences of the LHRH therapy:

- In some boys we observed an increase in testicular volume after LHRH therapy. This increase may be caused by stimulation of the germinal epithelium as found in pigs after LHRH administration (Dijkstra et al., 1986).
- In some boys we observed a rise of LHRH and LH serum levels after intranasal LHRH administration. Increase of LH serum levels in prepuberal boys after LHRH administered intranasally was also found by others (Rajfer et al., 1986). However, the results of the LHRH tests before and after LHRH treatment in our double-blind, placebo-controlled study indicated that the LH release after LHRH nasal spray is of short duration and that LHRH nasal spray treatment does not result in a lasting stimulation of gonadotropins.
- We observed a significant increase of HCG-stimulated serum testosterone values after LHRH treatment compared to pretreatment results. These findings support the testicular biopsy findings of Hadziselimovic et al. (1979), consisting of an increase in size, number and differentiation of Leydig cells and Leydig cell precursors after LHRH treatment. Animal studies have shown that in rats, LHRH may directly stimulate the activity of gonadal cells, while evidence is still lacking for a direct stimulation of human gonadal cells by LHRH (For review, see Rommerts and Themmen, 1986).

We found some clinical and hormonal indications of stimulatory influences of LHRH intranasal therapy, although we wonder whether these findings really explain the mode of action of LHRH nasal spray therapy.

Karpe and coworkers (1983) suggested that the descent occurring during LHRH treatment was the result of decreased retractility of the cremaster muscle. Our retrospective evaluation of previous testicular position indicated that a relatively

larger number of testes that descended with LHRH treatment had at one point occupied a scrotal position than of testes that failed to descend. Apart from that, the parents of some boys with unilaterally undescended testes mentioned several times that during LHRH therapy the contralateral descended, albeit retractile testis was more frequently intrascrotal. These findings suggest that LHRH therapy may have some effect on the cremaster muscle. It remains to be seen whether LHRH, LHRH-mediated LH and FSH, or testosterone influence this process. In order to gain more insight, we have initiated a study in humans and pigs to evaluate whether the cremaster muscle contains binding sites or receptors for androgens, LH and FSH or LHRH. The preliminary results reveal binding sites for LH in the cremaster muscle of humans and pigs. If the assumption of decreased cremaster retractility as a result of LHRH treatment is true, this might also explain the return of the testes to the former undescended position (relapse), frequently observed after cessation of LHRH therapy and the positive reaction to a repeat course of LHRH. Nevertheless, placebo descent, which occurs in virtually all double-blind studies, illustrates that factors other than hormonal therapy may influence the relaxation of the cremaster muscle.

We support Karpe's premise that the mode of action of LHRH therapy might be explained by a decrease in retractility of the cremaster muscle.

Our results did not indicate hormonal anomalies in cryptorchid boys. The only hormonal abnormality we could find was the relatively higher stimulated FSH levels after the first year of life in some boys with bilateral cryptorchidism. Hormonal evaluation did not provide a prognostic aid regarding success of hormonal therapy.

Our hormonal evaluation during and after the first year of life did not support the assumption that a deficiency of the hypothalamo-pituitary-gonadal axis is responsible for cryptorchidism, contra-indicating that LHRH treatment might stimulate such a deficient axis.

The hormonal data did not provide a prognostic aid regarding success of hormonal therapy.

Having compared the results of our study of LHRH treatment for undescended testes with literature data, we conclude that there is no evidence that age at treatment, laterality of the undescended testes, or frequency of LHRH administration, influence the success of LHRH therapy.

We consider LHRH spray treatment useless for undescended testes that are not palpable. Complete descent may be achieved in some cases when the undescended testis can be manipulated to the scrotal entrance. It is feasible that a number of testes that descend with LHRH treatment, would have descended spontaneously at puberty.

CLINICAL STUDIES B

CHAPTERS 5 AND 6

F.W.J. Hazebroek

CHAPTER 5.

SURGICAL ASPECTS OF CRYPTORCHIDISM

5.1. FAILURE OF TESTICULAR DESCENT

5.1.1. Aetiology of cryptorchidism

Our knowledge of the normal mechanism of testicular descent being incomplete subject to many contradictory theories, it is not surprising that our comprehension of the pathogenesis of cryptorchidism is also limited. According to Backhouse (1981) failure of testicular descent is likely to stem from one of two major causes, (1) a failure of the hormonal environment or (2) mechanical failure. Hormonal failure is usually believed to produce a state of incomplete descent, while mechanical failure leads to an ectopic testis position.

5.1.2. Hormonal failure

Cryptorchidism is frequently found in patients with abnormalities of the hypothalamo-pituitary gonadal axis. For example, Kallmann's syndrome, which is secondary to deficient LHRH secretion, and anencephaly, are both associated with cryptorchidism. Intratesticular steroid enzymatic defects, causing disorders of testosterone production, are likewise associated with a high incidence of cryptorchidism (Kogan, 1985; Farrer et al., 1985). Farrer and coworkers identified a definite defect in androgen biosynthesis in the cryptorchid testis in mice, resulting in a diminution in the intratesticular testosterone contents. They surmised that cryptorchidism exerts a deleterious effect on the ability of the Leydig cell to synthesize testosterone, which might explain to a certain extent the abnormal morphology and resultant infertility seen in boys with cryptorchidism. In disorders of androgen utilization such as 5 α-reductase deficiency and androgen insensitivity syndrome, cryptorchidism is very common (Rajfer and Walsh, 1977). The finding of atrophic Leydig cells in cryptorchid newborns (Hadziselimovic and Herzog, 1976) points to a gonadotropin deficiency as the cause of cryptorchidism. According to Job and coworkers (1974[b]), cryptorchid boys suffer from an LH deficiency which lasts till puberty, after which the condition becomes rectified (Canlorbe, 1974). In Leydig cells of young cryptorchid boys, secretion of testosterone is impaired (Gendrel et al., 1978). The premise that the LH deficiency causes

cryptorchidism due to a low testosterone level, led to treatment with gonadotropins (see chapter 4).

It is generally believed that Müllerian Inhibiting Substance (MIS) is considered to stimulate testicular descent, at least its initial stage (Donahoe et al., 1977; Hutson, 1985; Hutson and Donahoe, 1986). In the rare persistent Müllerian duct syndrome (Josso et al., 1983; Beheshti et al., 1984; Van Lanschot et al., 1985) phenotypic males have a uterus, fallopian tubes and cryptorchidism. In these cases the testes occupy the position of normal ovaries, which is consistent with the hypothesis that a deficiency of MIS prevents transabdominal descent (Hutson, 1985). Mininberg and Bingol (1973) found chromosomal abnormalities in cryptorchid testes in boys with normal karyotypes, which according to them had caused the failure to descend, because these chromosomal abnormalities inhibited a normal hormonal and histological testicular development. Their findings were not confirmed by other authors (Dewald et al., 1977).

5.1.3. Mechanical failure

John Hunter (1762) drew attention to the descent of the testis during late intra-uterine life and he described the gubernaculum as a fibromuscular cord connecting the testis to the scrotum. The discovery of this gubernaculum led to considerable controversy concerning its role in the descent of the testis. Lockwood (1888) described five so-called gubernacular tails terminating in the scrotum, at the pubic bone, in the perineum, in the femoral, and in the superficial inguinal area. Sometimes these nonscrotal gubernacular tails were strongly developed, pulling the testis out of the scrotum into an ectopic position. Lockwood's theory was questioned by Sonneland (1925), who was unable to find any embryologic or anatomic evidence for the existence of gubernacular tails. McGregor (1929) was also unable to demonstrate such a subdivision of the gubernaculum and suggested that an ectopic testicular position was due to other anatomic abnormalities. He described an orifice in the inguinal region which he called "the third inguinal ring". This ring is distal to the external inguinal ring of the inguinal canal and serves as the entrance to the scrotum. If it is absent or underdeveloped, because of an abnormal subcutaneous fascia (Scarpa's fascia), the gubernaculum which guides the testis in its descent fails to make further progress and becomes adherent to the surrounding fasciae and pubic bone, whereby the testis remains only partially descended. Charny and Wolgin (1957) stated that McGregor's theory appears acceptable for those cryptorchid testes which have passed beyond the external inguinal ring but which have either stopped short of the scrotum or have been directed into other directions. However, the theory does not take into account those testes which are located intra-abdominally or high in the inguinal canal. Browne (1938) followed by Scorer and Farrington (1971), mentioned a fascial barrier at the scrotal entrance obstructing further descent,

which was the factor responsible for the testis assuming a pubic or superficial inguinal, ectopic position.

The present concept of the structure and mode of action of the gubernaculum described by Backhouse (1965, 1981) is that of an undifferentiated mesenchymal band which paves the way for the testis and guides it to its position. He described fibrous encroachment on the gubernaculum which may similarly divert it, partly causing an ectopic testis position. To quote Backhouse:

"In the developing state, the gubernaculum must remain as an undifferentiated mesenchymatous mass into which the processus vaginalis and the cremaster muscle can grow and differentiate. It is important that as the body wall and scrotal fasciae differentiate in the fetus, the fibrous tissue and abdominal muscles not encroach on the gubernaculum. Encroachment of the developing fibrous tissue into the gubernacular mesenchyma will effectively prevent the downward growth of the processus vaginalis and the cremaster muscle at that site (figure 5.1.). In the remaining part of the gubernaculum, without invasion, their growth will occur normally. Although we have not found such invasion in human fetuses, we have observed it in pigs. Because the pig is remarkably like man with respect to the overall pattern of the process, it appears reasonable to assume that the mechanism also is similar. It is easy to recognize that the pattern observed in the pig fetus leads to the morphological pattern of the human ectopic testis, which is comparable morphologically to the essential anatomy of a pig ectopic testis.

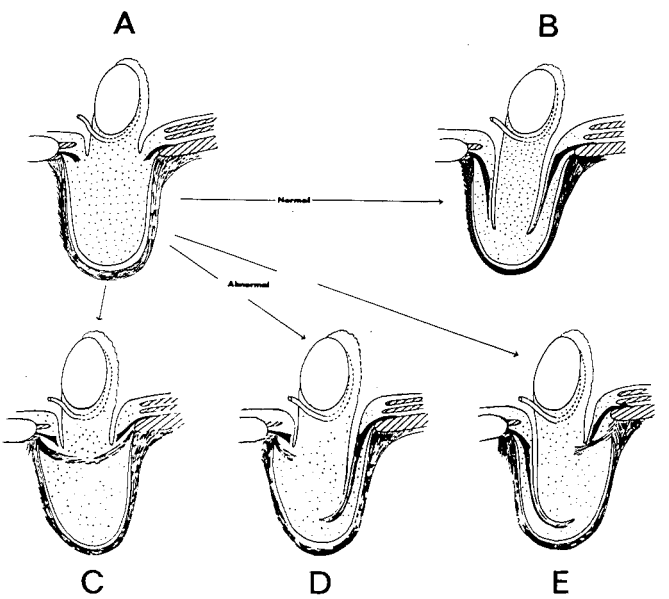


Figure 5.1. Schematic presentation of normal cremasteric muscle and processus vaginalis growth (A, B) and how this can be limited by fibrous invasion of the gubernacular mesenchyme to produce an ectopic testis (C, D and E) (Backhouse, 1982; with permission).

A small invasion of fibrous tissue at one site will set up the fibrous band shown by Lockwood to form the necessary anchor for one or another of the peripheral sites of ectopia. These peripheral sites also provide the attachments of normal fascia. As the normal cremaster and processus vaginalis develop elsewhere in the gubernaculum (and with other changes such as normal swelling), the normal descent process is limited only by the fibrous band and the deficient processus vaginalis at that point. Thus the testis is free to descend normally but only as far as the anchor point. Because of this and the pattern of development of the processus vaginalis, the testis will swing out of the normal line of descent in much the same way as a boat tethered to the bank of a stream will be carried into the shore by the current. From time to time cases are seen in which there is complete barrier across the external ring, a continuation of the abdominal wall fascia below which there may be a relatively small, wrinkled, albeit empty scrotum. Such a condition can be explained as an extension of the small fibrous invasion of the ectopic testis entirely across the gubernaculum. The distal mesenchyma may still exist as a pocket that will allow normal scrotal development, but the testis will be totally blocked in its descent."

That an increase of intra-abdominal pressure might be the primary force causing the testis to leave the abdomen and enter the inguinal canal was mentioned by Gier and Marion (1969). This theory was recently revived by Mickel in 1982. He stated that the three months delay between internal testicular descent and transit through the inguinal canal into the scrotum (external descent) is determined by the need for the abdominal wall to develop the ability to increase intra-abdominal pressure. This results from fetal movements, respiratory excursion, and increase in intestinal volume. When the abdominal wall musculature is absent, as in prune-belly syndrome, or inadequate, as in bladder extrophy or gastroschisis, inability to increase intra-abdominal pressure may result in cryptorchidism. It is obvious that intra-abdominal pressure is one of the factors, but certainly not the main factor in testicular descent.

In summary

Many theories have been proposed to explain failure of testicular descent, all of which have some merit, but no single one covers every aspect. Failure of testicular descent is likely to stem from two major causes:

- *mechanical failure* - A disturbance in the outgrowth of the gubernaculum and processus vaginalis are the main causes for the occurrence of an abnormal testicular position. Apart from that, an abnormal course of Scarpa's fascia may obstruct the path of testicular descent into the scrotum. Another mechanical factor that may inhibit normal testicular descent is the absence of intra-abdominal pressure.
- *hormonal failure* - Failure in secretion or action of gonadotropin, androgen, AMH, or another gonadal factor may play a part in the disturbance of testicular descent. It is not yet clear which hormones, nor at what time these play a part.

Consequently, hormonal failure as a cause for incomplete testicular descent raises many questions that remain unanswered.

5.2. HISTOPATHOLOGY OF THE UNDESCENDED TESTIS

5.2.1. Aetiology of histopathological anomalies in cryptorchid testes

In the eighteenth century John Hunter wrote: "When one or both testes remain throughout life in the belly, they are exceedingly imperfect and probably incapable of performing their natural function". Two centuries later Bland-Sutton (1923) stated that, in his experience: "The imperfections of the cryptorchid testis are the cause, not the consequence of its failure to reach its goal in the scrotum. Surgical efforts to preserve a retained or partially descended testis may be described as supererogation". Not every surgeon today would be so outspoken, but many have a suspicion that there is considerable truth in these words.

It remains uncertain to what degree hormonal or mechanical defects are responsible for the situation in which an otherwise normal boy has one or two testes which failed to descend. Likewise, there is no consensus concerning the observed histologic features, which may be partly or entirely based on a congenital deficiency (Sohval, 1954; Charny and Wolgin, 1957) or, alternatively, to a derangement of normal structures produced by a higher temperature in the abnormal location (Mengel et al., 1974; Hadziselimovic et al., 1975; Hedinger, 1979). A number of investigators (Moore and Quick, 1924; Harrenstein, 1928; Badenoch, 1945) have demonstrated that the temperature in the scrotum is some degrees lower than in the inguinal canal or in the abdominal cavity. Cooling experiments of abdominal testes in adult, naturally cryptorchid pigs indicate that spermatogenic arrest in abdominal testes is not due to an inborn defect, but is caused solely by maintenance of the testis at abdominal temperature (Frankenhuis et al., 1979). Hence the hypothesis that a nonscrotal position would in due course result in degenerative anomalies of the germinal epithelium because of the higher temperature. In other words, these degenerative anomalies would occur in primarily normal testes which had failed to descend sufficiently.

5.2.2. Histopathology of unilateral and bilateral cryptorchidism

Various histological studies, with divergent outcome, have been carried out to establish basic anomalies that would render the cryptorchid testis less capable of spermatogenesis. Cooper (1929) correlates the degenerative changes in cryptorchid testes with the age of the boy and with the degree of incomplete descent. Her first observation was that the younger the age at which the cryptorchid testis was examined histologically, the closer the appearance approximated normality. The second observation she made was that the further the testis had descended

the more closely it corresponded histologically to the scrotal testis of boys of the same age. Comparing biopsies taken of both the retained and the contralateral, normally descended testis, Nelson (1951) noted that in terms of the mean diameters of the seminiferous tubules, the retained testis keeps pace with its normally descended mate up till age 6 or 7, thereafter showing retardation of development. Robinson and Engle (1954) came to a similar conclusion, setting the age limit at 5 rather than 6 or 7. With increasing age he noted a lag in tubular growth, reduction in the number of spermatogonia and thickening of the peritubular connective tissue. Charny and Wolgin (1957) reported a form of testicular dysgenesis in about 20 per cent of the retained testes which they examined. Of the remainder, no sustained difference was observed between the scrotal and the retained testes up to the tenth year, the spermatogonia and Sertoli cells being similar in number in both groups. Progressive degeneration of retained testicular tissue, beginning at age 5-6, was mentioned by Hecker and Hienz (1967) and Numanoglu et al. (1969). The premise that the cryptorchid testis would remain stable to at least the fifth year of life was re-evaluated in the light of new histological data reported since 1972.

By examination of testicular weight, diameter of seminiferous tubules and spermatogonia count, Städtler and Hartman (1972) showed that gonads of prepuberal boys have a linear pattern of development. This was contrary to previous beliefs. Hadziselimovic (1981) described similar findings and noted that the seminiferous tubular diameter increased continuously up till puberty, when there is a sudden increase in the tubular diameter and the formation of lumina becomes apparent.

As mentioned before, there used to be considerable controversy regarding the age at which damage to a cryptorchid testis begins. It is now apparent that damaging influences causing morphologic changes in the cryptorchid testis begin at the end of the second year. Hösli, 1971; Mengel et al., 1974; Hedinger, 1979 believed that the spermatogonia count in seminiferous tubules (apart from tubular maturation and tubular diameter) is the crucial parameter when assessing the impairment of function of the cryptorchid testis. In their experience, the method of Mancini et al. (1964) which relies on the germ cell count of 50 transverse sections of seminiferous tubules proved to be very useful. Based on spermatogonia count as well as on qualitative examination of the ultrastructure of interstitial tissue, Mengel et al. (1974) reported several significant features. They carried out a histologic investigation of biopsy specimens of 515 retained and 237 unilaterally descended testes. Determination of spermatogonia content and tubular diameter showed that during the first and second year of life no morphologic changes occurred in the retained testes. After the second year, however, the spermatogonia count decreased significantly. Hedinger (1982) evaluated 619 unilaterally or bilaterally undescended testes of 450 boys, from several months to ten years old. His controls were normal testes of children with sudden death or children who had died accidentally. The mean spermatogonia count during the

first year of life was equal to that found in normally descended testes. A difference in spermatogonia count between descended and undescended testes was observed during the second and third year of life, stabilizing after the third year with the mean spermatogonia value of the cryptorchid testes remaining significantly lower than normal until puberty (figure 5.2.). In the same study, the mean values of spermatogonia were nearly identical for unilateral and bilateral cryptorchidism (figure 5.3.). Early, ultrastructural, morphologic changes in cryptorchid testes have been demonstrated in the second year of life (Hadziselimovic et al., 1975) and even in the first year (Mininberg et al., 1982). It remains unclear whether the underlying mechanism is a primary diminution of spermatogonia, accompanied by either atrophy of the seminiferous tubules with a secondary thickening and fibrosis, or atrophy of the germinal epithelium due to diminished vascularization caused by primary expansion of the connective tissue (Mengel et al., 1981).

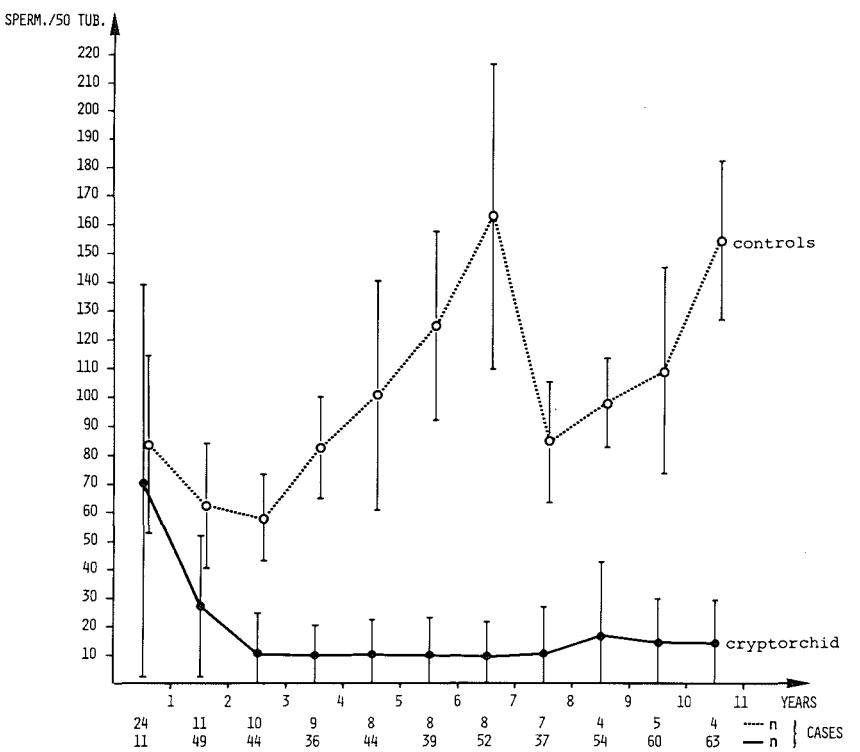


Figure 5.2. Number of spermatogonia per 50 transverse sections of seminiferous tubules in all cryptorchid testes and in normal controls, mean values per age group (Hedinger, 1982; with permission).

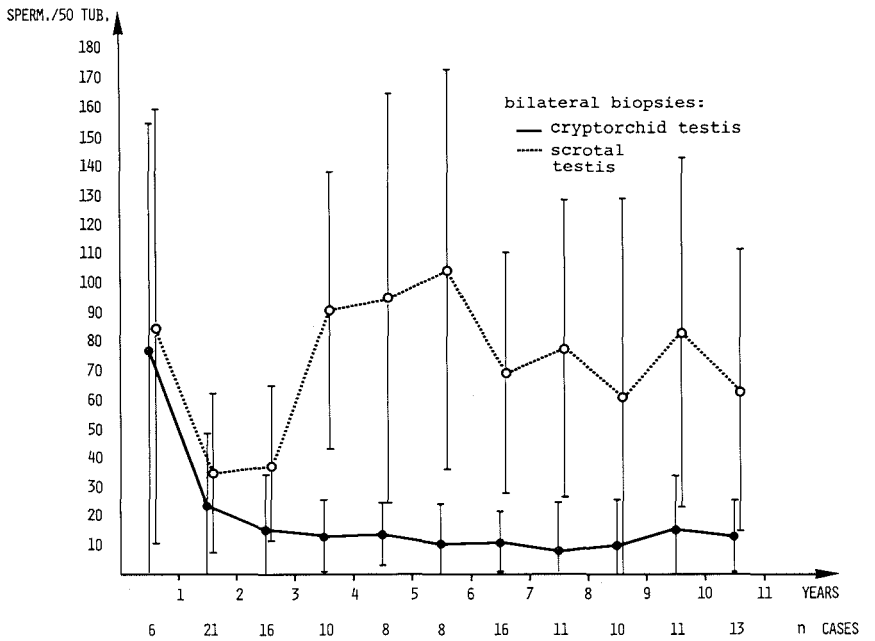


Figure 5.3. Unilateral cryptorchidism. Mean values of spermatogonia per age group in cryptorchid and scrotal testes (Hedinger, 1982; with permission).

5.2.3. Histopathology of the undescended testis as compared with the contralateral, descended testis

It is of considerable clinical interest that not only the cryptorchid testis but also the contralateral, descended testis shows morphologic changes during the early years of childhood. The morphologic changes in the descended testis in boys with unilateral cryptorchidism have been reviewed by several authors since biopsies have been routinely done on both testes. Mack et al. (1961), Hecker and Hienz (1967), Bay et al. (1968), Mengel et al. (1974), Nistal et al. (1980), Schindler (1982) and Yunis et al. (1984) found damage in the germinal epithelium of the descended testes in 25-60% of their patients with unilateral cryptorchidism. The marked divergence in outcome of the various studies shoud be interpreted in the light of the divergence in investigative criteria and not taken at face value. In 1985, Kirby and coworkers proposed the premise of damage to the contralateral descended testis. They performed bilateral testicular biopsies on 66 boys with unilateral cryptorchidism and determined the tubular fertility index (TFI = number of tubules containing spermatogonia counted and expressed as a value per 100 tubules for each testis). The results were compared with those previously

reported for a group of boys with normally descended testes (Farrington, 1969). Kirby's group found no significant differences comparing the germ cell activity of the scrotal testes in unilateral cryptorchidism with that of controls. In contrast, the mean TFI of the cryptorchid testes was significantly lower than that of control patients of all ages. In neither group was there evidence of a progressive loss of germ cell activity during childhood.

5.2.4. Histopathology of the undescended testis in relation to its position

As mentioned before, nonscrotal testes fall into three categories, (1) retractile testes, (2) incompletely descended testes, and (3) ectopic testes. This classification is not only based on the spontaneous location of the testis, but also on the testicular lesions involved. Mack et al. (1961) regarded the presence of germ cells in the seminiferous tubules as evidence of potential spermatogenesis in their series of testicular biopsies. In the normal testis, germ cells are usually found in 80 to 100% of the tubules. They assessed the number of tubules containing germ cells in 20 ectopic testes and 12 incompletely descended testes. Defective germ cells were frequent in both types, but much more so in the incompletely descended testes. The defect is present before puberty and they found no evidence of an increase with age.

Dougall et al. (1974) examined 107 testicular biopsies of boys with either unilateral or bilateral cryptorchidism. No spermatogonia were found in 6 of the 10 abdominal testes (60%), 9 of the 27 testes lying in the inguinal canal (33%), or 3 of the 69 testes lying in a superficial inguinal, ectopic position (4%).

In addition, the investigations of Farrington (1969), Scorer and Farrington (1971) and Nistal et al. (1985) have shown that, despite a deficiency of germinal cells in all cryptorchid testes, the prognosis appears best for the boy whose testes have progressed furthest along the path of descent as the germinal cell content is dependent upon the position of arrest.

5.2.5. Testicular histology after orchiopexy

Little is known about the evolution of testicular lesions in cryptorchid testes after orchiopexy. Histological proof of further differentiation of germ cells in testes brought down surgically, was obtained in seven clinical cases reported by Hecker and Hienz in 1967. In 1969 Kiesewetter and coworkers studied 29 boys with bilateral undescended testes to determine what effect scrotal placement had on the structure of the testis. Fifteen of 29 repeat biopsies (52%) after orchiopexy showed moderate or marked improvement when compared to the original biopsy. An additional 34% showed slight improvement, while in only 14% the second biopsy showed no change. Compared to the unoperated fellow, only 7 of 23 repeat biopsies (30%) after orchiopexy showed moderate or marked improvement, 39% showed slight improvement and 31% were unchanged. Unfortunately,

the criteria for improvement in Kiesewetter's study are not clearcut. In their own words, it was not always possible to quantitate exactly the improvement in the second biopsy. In this study "it was not possible to draw conclusions concerning the influence that the time between biopsies had or ultimate histologic improvement."

Diagnostic biopsies were taken by Kleinteich and Schickedanz (1977) from 74 unilateral and 78 bilateral cryptorchid testes surgically corrected two to ten years previously, as well as from 74 contralateral, descended testes. They concluded that in the surgically treated testes, the amount of extratubular connective tissue was greater than in the contralateral, descended testes, while a morphological improvement of the germinal epithelium had occurred in comparison with untreated, undescended testes of boys of the same age. In contrast, Francavilla and coworkers (1979) concluded from their study that neither spontaneous nor induced descent of the testis before puberty, seems to modify the development of the lesions which are already present in the seminiferous tubules.

Another important study was published by Nistal and coworkers in 1980. They studied a second biopsy of testes from boys whose ages ranged between 11 and 20 years, who had undergone orchiopexies with biopsies during previous years. Comparing the first and second histologic pattern, they found that 3 out of 5 high scrotal testes showing marked germinal hypoplasia in the first biopsy specimen revealed incomplete arrest of maturation at the level of the first spermatocyte stage in the second specimen, while the remaining two showed severe hypospermatogenesis in the second specimen. Of 16 testes initially located in the inguinal canal, seven showed severe germinal hypoplasia in the first biopsy specimen, while the second specimen revealed only Sertoli cells. Eight testes with marked germinal hypoplasia later showed seminiferous tubules with only Sertoli cells or isolated spermatogonia and spermatocytes. One testis with Sertoli cell hypoplasia showed only mature Sertoli cells in the second biopsy specimen. They also took second biopsies from another series of six testes, initially located intra-abdominally. One of these testes, presenting with severe germinal hypoplasia in the first biopsy specimen, showed only Sertoli cells and severe thickening of the basement membrane in the second one. In the other five, initially diagnosed as Sertoli cell hypoplasia, the second biopsy specimens all revealed that most of the seminiferous tubules contained only immature Sertoli cells. All second biopsy specimens in these testes showed variable thickening of the basement membrane. The final conclusion of this study was that testes do not show spectacular increases in germinal cell number following orchiopexy. More or less the same conclusions were drawn by Schindler and coworkers (1982). With repetitive biopsies in 12 patients they clearly showed that maturation does progress after orchiopexy, but without improvement of cellularity.

In summary

Undescended testes are histologically abnormal. This histological abnormality

may be due to both a hormonal and a mechanical disturbance caused by the nonscrotal postion of the testis (temperature influence). Based on microscopical as well as qualitative examination of the ultrastructure of undescended and descended testes, the following features are reported:

- In comparison with a normally descended testis, the undescended testis shows a normal development until approximately the second year of life.
- The same histological anomalies that are found in the undescended testis are found in 25-60% of normally descended testes.
- Although there is a deficiency of germinal cells in all undescended testes after the first year of life, the prognosis appears best for the boys whose testes have progressed furthest along the path of descent, as germinal cell content is dependent on the position of arrest.
- After complete descent achieved with orchiopexy, the previously undescended testis does not show improvement of germinal cells.

5.3. CLINICAL IMPLICATIONS OF CRYPTORCHIDISM

5.3.1. The nonscrotal testis and fertility

It has been known for a long time that there is a definite relationship between cryptorchidism and infertility. Therefore it is hardly surprising that most authors have focussed their attention on this aspect. In most studies the aspect of fertility is referred to as "fertility percentage", indicating the percentage of men out of the study population with a sperm density (or sperm count) over 20×10^6 spermatozoa/ml, which has generally been accepted as the lower limit of normal values (Freund, 1966; Scorer and Farrington, 1971).

Fertility of untreated cryptorchids

Few studies have appeared in the literature that include fertility rates for men with unilateral or bilateral undescended testes that were left untreated. The rare publications that do deal with this entity clearly show that if bilateral cryptorchidism is left untreated, this always leads to infertility (Mack, 1963; Scott, 1962; Schirren, 1966). Lipshultz (1976) studied 212 men with unilateral undescended testes that were never operated upon, and found that 142 (64%) of them were infertile.

Fertility of cryptorchids after hormonal and surgical treatment

Numerous studies have been published analyzing the incidence of infertility in cryptorchid boys after hormonal or surgical treatment. Cywes and coworkers (1981), Kogan (1983), as well as Gilhooly and coworkers (1984) compiled fertility data from the literature, concerning altogether 958 bilateral and 1273 unilateral cryptorchids, who had been treated in the prepuberal period. Only 28-40% of the

subjects with initially bilateral undescended testes appeared to be fertile, but this percentage was considerably higher (51-70%) for the men with initially unilateral undescended testis.

Very recently, Chilvers and coworkers (1986) published the results of an extensive review of the literature concerning the long-term effect of cryptorchidism on fertility. Twenty-seven papers that considered adult fertility in terms of sperm density following treatment for undescended testes were identified. Here again, it appeared that the fertility percentage after successfully treated, unilateral undescended testes (343 out of 600 or 57%) was considerably higher than that for bilateral cryptorchidism (82 out of 331 or 25%). The relatively higher fertility rate for treated, unilateral undescended testes still falls far short of the often-quoted figure of 90% fertility common among couples, for half of which the male partner may be a primary or contributing cause (WHO Statistics, 1969).

Evaluation of the results cited in the numerous retrospective studies is difficult because here again there is considerable diversity. According to Kogan (1983) and Chilvers et al. (1986) the most important factors complicating direct comparison are:

- *Composition of study population*

For some studies the patient source is not mentioned, or the series may include patients from infertility clinics, which obviously has a negative influence on the results. In most studies, the men providing semen specimens represented only a small fraction of the case series originally presenting with cryptorchidism and it is more than likely that they comprise a self-selected group whose characteristics vary.

- *Definition of fertility and methods of fertility evaluation*

Interpretation of data on fertility in published series of cryptorchid patients requires a common definition of fertility. Most studies use the accepted definition of more than 20×10^6 spermatozoa/ml by semen analysis. However, there is a further source of diversity in the various methods of semen collection and analysis (documentation of motility and morphology is seldom mentioned), duration of abstinence, number of semen specimens examined, and repetition of low sperm count. In some studies, fertility has been determined on the basis of paternity, but paternity tells very little about semen quality other than negating azoospermia (Bramble et al., 1974; Lipshultz, 1976). Apart from that, the paternity percentage of a study population may be influenced adversely by a number of men that either did not marry or may not (yet) have wanted children (Gilhooly et al., 1984). On the other hand, semen analysis alone does not provide a clear-cut distinction between fertility and sterility, while a number of so-called subfertile men may become fathers.

- *Hormonal versus surgical treatment*

Studies that include successful and unsuccessful hormonal treatment (HCG) seem to indicate that, at least in bilateral cryptorchidism, those testes that descend with HCG treatment are more fertile than those that do not (Albescu et al.,

1979[b]). For most series of boys successfully treated with HCG, subsequent semen analysis shows fertility to surpass that of surgically treated patients. It would appear then, that the method of treatment influences fertility results, while inclusion of varying numbers of patients that were either sucessfully or unsucessfully treated with hormones affects analysis of fertility results (Kogan, 1983). In this respect one should bear in mind that the testes that seemed to descend as a result of hormonal treatment may in actual fact have been retractile and therefore normal testes with potentially normal fertility, while the testes that did not respond to hormonal treatment were on the whole truly cryptorchid and more likely to be associated with abnormal anatomical structures. Regarding surgical treatment, very few authors mention the occurrence of testicular atrophy after orchiopexy in connection with fertility results. From the literature it appears that the incidence of postoperative testicular atrophy varies from 2 tot 40% (Charny and Wolgin, 1957; Gross and Replogle, 1963; Fahlstrom, 1963). A high percentage of testicular atrophy will obviously have a negative influence on subsequent fertility rates.

- *Pre-operative testicular position*

Few studies cite the pre-operative testicular position and then correlate the results of treatment with subsequent fertility. It is a wellknown fact that high inguinal or intra-abdominal testes are more difficult to bring into the scrotum and that results in terms of fertility are worse in this group. Consequently, series that include either fewer or greater numbers of patients with high-lying testes, cannot be meaningfully compared (Kogan, 1983). Apart from that, many studies fail to elucidate the criteria for excluding retractile testes. Particularly concerning the studies with large series of bilateral cryptorchids, it is not unlikely that retractile testes were included. As mentioned above, retractile testes are generally normal in development and consequently their fertility is in no way reduced (Puri and Nixon, 1977).

Age of treatment

In almost all published studies of cryptorchidism and fertility, treatment was carried out between the 4th and 14th year of life, while the results are presented as a totality for the entire group without any division for age. The question whether early treatment has a favourable effect on subsequent fertility, has not been answered convincingly. The study of Ludwig and Potempa (1975) is frequently cited in support of the premise that early treatment (orchiopexy) is conductive to subsequent fertility. However, their study carries no statistical significance as the number of patients that were under four years of age at operation amounted to no more than 15 out of 71 (21%). The aforementioned literature review of Chilvers et al. (1986) included fertility assessment in five series of bilateral cryptorchids whereby the age at operation was taken into account. They found no difference in fertility percentages related to age at treatment. In addition, the same group analyzed five similar studies concerning unilateral

cryptorchidism and found a slight (and statistically insignificant) effect of early treatment, which appeared to be entirely attributable to one of the five studies, namely the study of Ludwig and Potempa (1975).

One study that did take all aforementioned criteria into consideration is the one carried out by Schoorl (1983). His patient series consisted of 285 bilateral cryptorchids that had all undergone surgery at 11-12 years, performed by the author himself in over 85% of the cases. Schoorl drew up a classification for fertility and subfertility based on semen quality and he also looked at paternity. He obtained sperm analyses for 141 of these initially bilateral cryptorchids, revealing fertility in only 20%, subfertility in 55% and azoospermia in 25%. In 108 of these men the testes had been palpable in the inguinal region before operation; fertility fell below the lower limit in 84 (77.8%) of them, with azoospermia in 18 (16.7%). The results were much poorer for the men whose testes had been impalpable before operation (intra-abdominal or high inguinal). Altogether 29 of 33 (87.9%) were subfertile, with azoospermia in 17 (51.5%) of them, while the sperm count in the remaining 4 men (12%) just reached the lower limit (20×10^6). Schoorl's study would be an excellent basis for comparison with a similar retrospective study, involving a series of bilateral cryptorchids that had undergone surgery at an earlier age. Such a comparison would furnish conclusive evidence regarding the effect of age at treatment on subsequent fertility.

In summary

Drawing conclusions from published assessments of fertility after treatment for cryptorchidism is a precarious exercise, because comparison of results is complicated by great diversity. The main areas of diversity concern patient source, methods of fertility evaluation, lack of specification of pre-operative conditions (diagnosis, position of testis, age), etc. Schoorl's retrospective study stands out because of a very succinct recital of most of the factors that may contribute to or detract from post-orchiopexy fertility. Unfortunately, very few if any studies are comparable. No hard evidence has been furnished for the premise that early treatment favourably affects subsequent fertility, although it does seem best to treat cryptorchidism before puberty. Failure to treat cryptorchidism almost certainly leads to infertility.

5.3.2. The nonscrotal testis and malignancy

It has been known for more than a hundred years that there is a link between the nonscrotal testis and malignancy and this has been investigated extensively by many authors. A review of large series of testicular tumours described in the literature (Campbell, 1944; Wobbes et al., 1980; Martin, 1981; Whitaker, 1981) revealed that 3 to 12% of these tumours occurred in undescended testes. A testicular tumour is a very rare occurrence; the annual incidence in the Nether-

lands is estimated to amount to 2 to 3 of 100,000 men (Soebhag, 1982). However, the nonscrotal testis appears to be 10 to 48 times more prone to tumour formation than a normally descended testis (Gilbert and Hamilton, 1940; Martin, 1979; Wobbes, 1981; Welvaart and Thijssen, 1981). The tumours occurring in nonscrotal testes are mostly germ cell tumours, generally seminoma. Other tumours that may occur in the cryptorchid testis are embryonic cell carcinoma, choriocarcinoma and teratocarcinoma (Martin, 1979).

It is not entirely clear what causes this increased risk of malignant degeneration of the nonscrotal testis. According to Fergusson (1962), testicular trauma is a major cause of the occurrence of a testicular tumour. According to Cromie (1983), any correlation between trauma and tumour lies mainly in the fact that medical treatment for, say a minor trauma, will reveal the existence of a testicular tumour. Others (Ashlay and Mostofi, 1959; Hausfeld and Schrand, 1965) feel that damage to the germinal epithelium as a result of a higher than scrotal temperature, is a major cause of malignant degeneration. Hadziselimovic and Girard (1977) suggested that suppression of both the hypothalamus and hypophysis in cryptorchid boys during intra-uterine development, would result in incomplete development of not just the Leydig cells, but also the germinal epithelium, which in its turn would eventually lead to malignant degeneration.

Provided that a nonscrotal testis is a potential source of malignancy (third or fourth decade after birth), one may well wonder whether treatment of a nonscrotal testis makes sense. Would it not be better to carry out a preventive orchidectomy? To answer that question, we first have to elucidate several aspects related to the link between nonscrotal testis and malignity.

Is there a relationship between the incidence of testicular tumour and the location of the nonscrotal testis, be it in the abdomen or in the inguinal region?

Campbell (1944) described a series of 2119 nonscrotal testes, 302 (14.3%) of which were located in the abdomen and 1807 (85.7%) in the inguinal region. A tumour presented in 68 of the altogether 2119 testes, but 33 (48.5%) of these 69 tumours occurred in the initially intra-abdominal testes. This assessment seems to lead to the obvious conclusion that intra-abdominal testes are six times more prone to malignant degeneration than nonscrotal testes lying in the inguinal region. Cromie (1983) reached the same conclusion in his investigation.

Does orchiopexy reduce the risk of subsequent malignant degeneration?

No hard evidence has as yet been furnished in the literature for the assumption that orchiopexy would prevent the subsequent occurrence of a testicular tumour (Krabbe et al., 1979; Martin, 1981; Whitaker, 1981). What does happen is that bringing the testis into a scrotal position makes it more accessible to examination, enabling early diagnosis and treatment of a testicular tumour if it does occur.

Is there a relationship between age at orchiopexy and malignant degeneration?

a. *Would early treatment reduce the risk of malignant degeneration of the initially undescended testis?*

There is no definite answer to this question, although some reports do indicate that a testicular tumour is less likely to occur if orchiopexy has been carried out before the sixth year of life (Gehring et al., 1974; Martin, 1979; Pottern et al., 1985).

b. *Is there an upper age limit for orchiopexy in relation to malignant degeneration?*

Nonscrotal testes presenting with histologically obvious degenerative anomalies around puberty, will not contribute to a normal process of spermatogenesis (Nistal et al., 1980). This concerns mainly testes that have remained in a high inguinal or abdominal position until puberty and are frequently also macroscopically abnormal (smaller and softer). Examining 50 male adults a number of years after they had undergone orchiopexy around the age of puberty, Krabbe and coworkers (1979) found a carcinoma in situ in the operated testis of 4 (8%) of them. In 2 of 35 (6%) patients that underwent surgery for unilateral undescended testis after the 11th year of life, Zwierstra and coworkers (1984) diagnosed malignancy in a macroscopically normal testis (once seminoma and once carcinoma in situ). Both patients had undergone orchiopexy at a very late stage (at the age of 23 and 42 respectively) and in both cases it concerned a high-lying testis (intra-abdominal and high inguinal respectively). Based on the histological data and the relative frequency of malignant degeneration, these authors, in agreement with others (Martin and Menck, 1975; Hinman, 1979), advocate orchidectomy for unilateral cryptorchids with a high-lying testis first presenting for treatment at or even after puberty.

It is far more difficult to give guidelines for the treatment of bilateral undescended testes first presenting after puberty. Bilateral orchidectomy as a preventive measure against malignancy amounts to castration of the patient with all that entails. Consequently, there is some controversy as to the treatment of choice in these cases. There is no hard evidence for the assumption that orchidectomy coupled with hormone substitution would be preferable to bilateral orchiopexy (Martin, 1981). Individual factors, such as age of the patient, surgical possibilities, macroscopic aspect of the testes, etc. will have to indicate the treatment of choice (e.g. orchidectomy for one testis and orchiopexy for the other one). If orchiopexy is decided upon, a testicular biopsy is mandatory.

In summary

- Compared with a normally descended testis, the nonscrotal testis is more prone to subsequent malignant degeneration.
- A testis remaining in the abdomen is more prone to malignant degeneration than a testis remaining in the inguinal region.

- There is no proof that orchiopexy would prevent malignant degeneration, although there are indications that testicular tumours occur less frequently in nonscrotal testes that are operated on at an early age.
- Orchiopexy is rarely indicated if the testis has remained in the abdomen past the age of puberty; unless this condition is bilateral, orchidectomy is the treatment of choice.

5.3.3. Psychosexual aspects of cryptorchidism

Psychosexual development is undoubtedly a consequence of many influences, including biologic factors such as hormones; situational and social factors (rearing as well as imitation and identification); cognitive maturation with genital awareness and concepts of self-image; and probably more subtle innate drives as well. Gender identity, or self-concept of being male or female, is well established by the age of two to three years (Money et al., 1955; Dewurst, 1975; Ladee-Levy, 1986). Psychiatric studies have revealed that at or even before three years of age, a cryptorchid boy may become aware of the fact that his genitalia appear different from those of his friends. This awareness is not considered significant until the cryptorchid boy is exposed to peer scrutiny taking a shower in an environment such as the school locker room. An empty scrotum may be a source of considerable anxiety and embarrassment, often causing feelings of physical inferiority and concern about virility (Gross and Replogle, 1963; Smith and Lattimer, 1975).

Psychological consequences of having undescended testes

Reported psychotherapy of boys whose lack of testicular descent has contributed to a disturbance of their psychological development, often reveals that in the eyes of these boys their genitalia constitute one whole entity. At play and fantasizing, they reveal their feeling of having a defective penis in every possible way (Bloss, 1960; Schiffman, 1978). Evaluation of cryptorchid boys that did not end up at the psychiatrist or psychologist, revealed that many of them thought of their body as being damaged (Bloss, 1960; Druss, 1978). The figures that these boys drew were often equipped with long rifles, or they had long noses, or there were other phallic symbols executed in great detail (Cytren et al., 1967). These boys often suffer from irrational anxiety, while the realisation of their parents fear concerning their masculinity adds to their feelings of inferiority. They often attempt to keep their abnormal genitalia a secret from their peers, which may cause problems at sports events or other group activities involving the locker room (Meyer-Bahlburg et al., 1974; Smith and Lattimer, 1975; Ladee-Levy, 1986). This is probably due to a sense of shame. It is significant that in Dutch the genitals are commonly referred to as "shame parts".

In general, these boys do not present with real psychological problems unless there are other contributive factors, such as mental instability; family stress;

parents that doubt their son's ability to function as a man when he grows up; etc. (Finemann, 1959). The longer the boy has to live with one or two undescended testes, the bigger the risk of psychological problems (Finemann, 1959; Bloss, 1969; Manley, 1982). If psychological problems do occur, these are generally not related to specifically sexual areas, but affect other aspects of the boy's personality instead, consisting of learning problems; behavioural disturbance; anxiety; gender identity crises; etc. (Bloss, 1960; Ladee-Levy, 1986). Successful surgical correction of the undescended testes results in a rapid recovery of the psychological disturbance.

Optimal timing of orchiopexy

In determining the optimal time for surgery, one must consider the child's general reaction to hospitalization as well as the specific reaction to an operation of the genitalia. According to Manley (1982), there are several basic influences that must be considered, such as a) separation anxiety, and b) the hospital experience.

re a) *separation anxiety:*

Separation anxiety affects children of various ages (Kelalis et al., 1975; Manley, 1982). From birth to age six months there should be little concern about brief episodes of separation, but from the age of six months, the infant begins to be aware of and increasingly upset by separation from the mother. From age one to three years, separation from the mother is traumatic, particularly during the early phase of the episode. From three to six years of age, separation from the mother is more tolerable because with increasing age, the child is increasingly able to comprehend the necessity and nature of the operation.

re b) *the hospital experience:*

Much has been done to humanize children's hospitals in recent years. One aspect that can be influenced to a great extent by the physician is the preparation of the child for the hospital procedure for surgical patients. Above all, a realistic and honest explanation of what the child and his parents should expect will go a long way towards preventing any postoperative psychological disturbance. Allowing the parents to be with the child right up till the operation and immediately afterwards is important in this respect. Other benefits relate to a shorter stay in hospital or day-care surgery (Manley, 1982).

In summary

Having undescended testes may be associated with a sense of anxiety and shame. In general, an obvious psychological disturbance requiring proper care generally does not occur unless there are other contributive factors related to the child's personality or parent-child relationship. The psychological disturbance which then occurs mainly affects behavioural aspects of personality rather than sexual ones.

From a psychological or psychiatric point of view there is no optimal age at

which a child is most able to cope with the operation, because every age is beset by its own specific fears. Separation anxiety reaches a peak in the age period 6 months to 3 years and consequently, if orchiopexy has to be performed during that period (as indicated by the correct diagnosis), rooming-in or day-care surgery will do much to forestall problems connected with an operation in the first years of life. An operation at that age has the advantage that the child never reaches the point of comparison with other boys so that he will not have to go through the agony of feeling different.

5.4. ANATOMICAL ASPECTS OF CRYPTORCHIDISM

A disturbance of testicular descent is usually associated with a severe disturbance of the anatomical proportions. The location of the undescended testis appears to be directly related to any anatomical anomalies of the testis itself and particularly to any anomalies of the surrounding structures. Consequently, the anatomical anomalies often associated with a disturbance of testicular descent, should be discussed in relation to the position of the testis (incompletely descended or ectopic).

5.4.1. Anatomy of the undescended tesis

a. *The testis*

In prepuberal boys the volume of the normally descended testis varies from approximately 1-3 ml (Zachman et al., 1974; Cassorla et al., 1981; Takihara et al., 1983). The volume of the incompletely descended testis is usually small compared with the contralateral, descended testis or, in case of bilateral cryptorchidism, in comparison with the testicular volume of descended testes of boys of the same age (Scorer and Farrington, 1971; Lipshultz, 1976). These differences in volume increase with age. In case of unilateral absence of testis, or severe underdevelopment of testis, compensatory hypertrophy of the contra lateral, descended testis may occur. Compensatory testicular hypertrophy can be defined as a progressive testicular enlargement beyond the normal size for age (Laron and Zilka, 1969; Tato et al., 1979; Laron et al., 1979).

b. *Testicular absence*

Sometimes inguinal exploration for incompletely descended testes will reveal a vas deferens with testicular vessels only, ending in a tissue remnant, which appears to consist of epididymal tissue. This finding has been reported unilaterally as well as bilaterally and has been described as "the vanishing testis syndrome" (Abeyaratne, 1969). The fetal testis is of primary importance in the development of the Wolffian duct (male) and the degeneration of the Müllerian duct (female). In the absence of the testis, the female system will develop and the

Wolffian ducts will degenerate. A female system will even develop if the testes are initially present but disappear early in fetal life. If the testes disappear after a critical gestational phase (about 16 developmental weeks), a male system will persist. Consequently, in case of a phenotypic and genotypic male with proved bilateral anorchidism, we must assume that testes were present through 16 weeks of embryologic development but have subsequently vanished.

Why the fetal testis subsequently "vanishes" is obscure in most cases. Intrauterine torsion, infarction, infection or impairment of vascular supply during testicular descent have all been proposed as mechanisms (Abeyaratne, 1969; Tosi and Morin, 1976; Honoré, 1978). In these cases indentifying the testicular vessels is of the utmost importance; if these vessels accompany the vas into the inguinal canal to terminate with the vas into the knob of epididymal tissue, the presence of a separate intra-abdominal testis can safely be excluded. If, however, exploration reveals a vas deferens only in the inguinal canal or retroperitoneally at the deep inguinal ring, then the intra-abdominal presence of a testis is feasible and cannot be excluded (Lythgoe, 1961; Nowak, 1972; Levitt et al., 1978; Bergdahl and Andersson, 1981).

It is extremely rare for testis, epididymis, vas or testicular vessels to be totally absent, either unilaterally or bilaterally, in an otherwise normally developed boy. Such a rare finding is frequently associated with anomalies of the urinary tract (Bergmeyer and Meradji, 1977). As compensatory testicular hypertrophy does not solely occur in the absence of a contralateral testis, inguinal exploration is always required to trace a nonpalpable, albeit present testis (Laron and Zilka, 1969; Laron et al., 1979).

c. *Epididymis and vas deferens*

Epididymal deformities are frequently seen in association with cryptorchid testes and can vary in extent from total agenesis of the epididymis (Lazarus and Marks, 1947) to failure of union, complete or imcomplete, between the testis and the epididymis (Marshall and Shermeta, 1979; Mininberg and Schlossberg, 1983; Heath et al., 1984). The most common deformity of the epididymis is slight or gross extension in relation to the testis (Scorer and Farrington, 1971).

Occasionally, when the testis is located intra-abdominally, the epididymis dips down with the open processus vaginalis through the inguinal canal into the top of the scrotum and returns as the vas deferens into the abdomen (Moschcowitz, 1912; Fowler and Stephens, 1959; Brendler and Wulfsohn, 1967). While the functional significance of epididymal deformities is uncertain, with the exception of complete separation between testes and epididymis, the surgical implication is obvious. If the possibility of an extended or loosely attached epididymis is not considered, the descended tissue may be injured during surgical dissection. It may be mistaken for the tunica vaginalis or for an atrophic testis and as such excised, leaving a retained testis intra-abdominally. Alternatively, the testis may

be considered absent and no further exploration undertaken (Dean et al., 1952; Lythgoe, 1961; Nowak, 1972). Figure 5.4. gives an overview of the more common types of epididymal deformities (Scorer and Farrington, 1971).

Partial absence of either the epididymis or the vas deferens also occurs in association with cryptorchidism, although such anomalies are more frequently found in boys with a congenital rubella infection or cystic fibrosis (Priebe et al., 1979; Kroovand and Perlmutter, 1981; Wingerden and Franz, 1984).

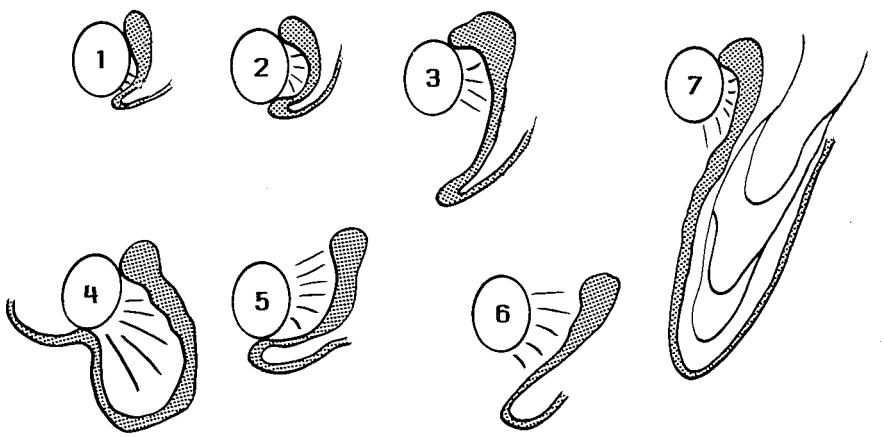


Figure 5.4. Overview of the more common types of epididymal deformities.

d. Processus vaginalis peritonei

During the descent from their retroperitoneal points of origin, the testis, epididymis and spermatic cord invaginate the posterior aspect of the processus vaginalis, thus becoming enveloped by two layers of this structure. Following testicular descent, the layers of the processus vaginalis around the spermatic cord normally close except around the testis and epididymis, where they form the tunica vaginalis. These normal conditions are found when the processus vaginalis continues to the bottom of the scrotum, but if development is arrested before this has occurred, the testis will be unable to reach its normal position and only a partial descent of the testis results. In these partially descended testes, however, the processus vaginalis usually persists as a wide open sac in which the testis is

"floating freely" (Kroovand and Perlmutter, 1981; Heath et al., 1984). This wide open processus vaginalis is a precursor of an inguinal hernia or hydrocele (Curtis and Staggers, 1960).

Traversing the inguinal canal, the processus vaginalis sometimes persists at the level of the annulus internus to such an extent as to cause folds in the peritoneum, frequently resulting in adhaesions. According to Hunter (1926), the peritoneal folds that remain after closure of the processus vaginalis, may well lead to the type of inguinal hernia that is not readily apparent (figure 5.5.).

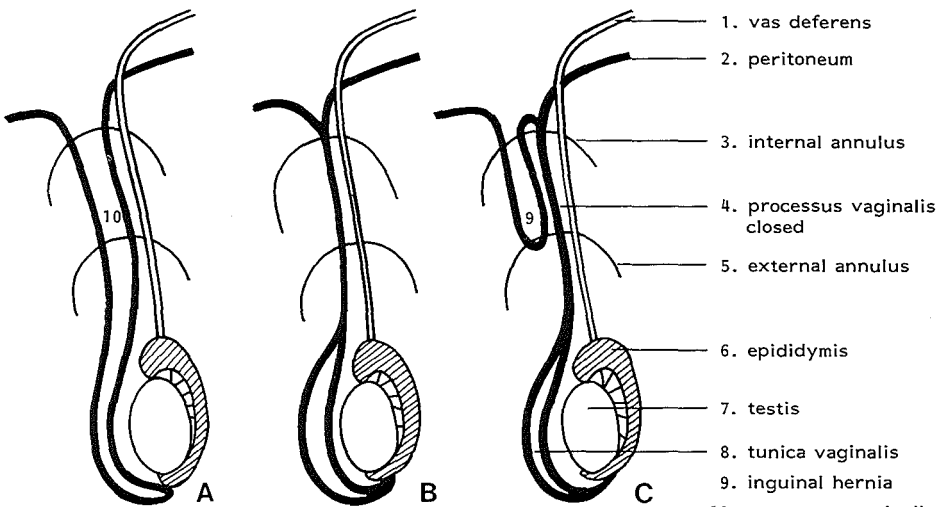


Figure 5.5. Diagram illustrating various types of hernial sacs
a. wide open processus vaginalis
b. closed processus vaginalis
c. excess of peritoneum in which case the funicular portion may become completely obliterated.

e. *The scrotum*

In case of unilaterally undescended testis, the scrotum is generally normal although on one side somewhat flattened compared with the other half containing a normally descended testis. An underdeveloped scrotum, poor in rugae, is uncommon and if it does occur this is usually associated with high-lying (inguinal or abdominal) testes, or with atrophic or absent testes. In these cases, there is usually an endocrinologic disturbance often associated with genetic or dysmorphic syndromes.

5.4.2. Anatomical anomalies in relation to ectopic testes

a. *Introduction*

Considerably fewer anatomical anomalies of testes and surrounding structures

are found in case of ectopic testes as compared with the incompletely descended testes described above. The ectopic testis and epididymis are generally normal with the processus vaginalis generally closed. The spermatic cord, likewise, is generally of normal or near-normal length. In these cases any and all anomalies are usually related to the mechanical failure that has obstructed the path of descent of an otherwise normally developed and descending testis (McGregor, 1929; Backhouse, 1982[a]).

b. Anatomical anomalies in relation to truly ectopic testes

True ectopia (perineal, peno-dorsal testis, etc.) rarely occurs. In case of ectopia, a developmental disturbance of the gubernaculum (see 1.3.2. and 1.4.2.) may cause the testis to descend into, for example, the perineum, as shown in figure 5.6. At operation, the testis is capable of being brought down to the scrotum once the fascial barrier preventing descent, has been dissected (Backhouse, 1982[a]).

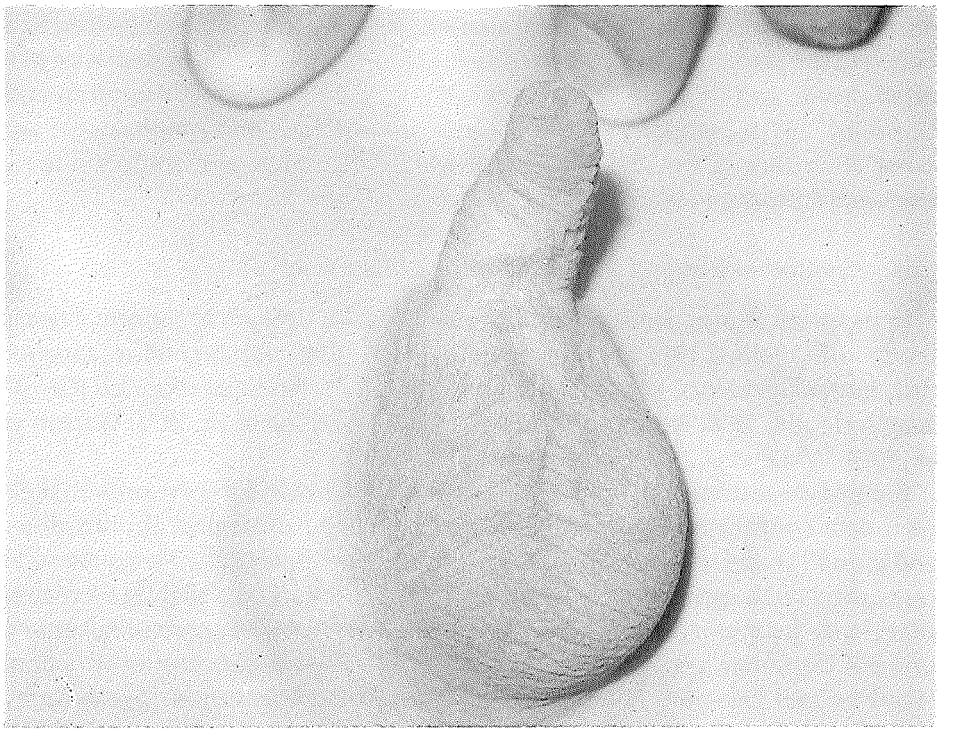


Figure 5.6. Perineal ectopic testis in a one year old boy.

c. *Anatomical anomalies in relation to superficial inguinal, ectopic testes*

This abnormal position finds the testis in the superficial inguinal pouch (see 1.4.1.a.). To arrive there, it has turned sharply upwards and outwards upon leaving the external annulus of the inguinal canal. This is due to an abnormal attachment of Scarpa's fascia to the pubic bone and scrotal entrance, preventing passage of the gubernaculum and testis into the scrotum. The anatomy of this area has been fully described by McGregor in 1929. Sprawling almost like a tent to shelter the testis in its abnormal position in the superficial inguinal pouch, Scarpa's fascia can be clearly identified in these cases right down to the pubic bone. At that level, its abnormal attachment to the pubic bone narrows the scrotal entrance, blocking gubernaculum and testis (Browne, 1938; Jones, 1966; Scorer and Farrington, 1971; Flach, 1977). In these cases, the gubernacular remnants generally present as a fibrous cord extending to the pubic bone.

5.4.3. Associated anatomical anomalies

a. *Cryptorchidism and anomalies of the abdominal wall*

Bilateral cryptorchidism is a common feature of several anomalies involving the abdominal wall. In the so-called prune belly syndrome, bilateral undescended testes are frequently located in the abdomen. The syndrome is characterized by a defect of the abdominal wall musculature, giving it the wrinkled appearance of a dried prune, and multiple severe anomalies of the urinary tract (Hendren and Ginsburg, 1981). Exstrophy of the bladder, gastroschisis and omphalocele are other anomalies of the abdominal wall with which bilateral cryptorchidism is frequently associated (Kaplan et al., 1986).

b. *Cryptorchidism and anomalies of the urinary tract*

In the general population, the incidence of major urological abnormalities is less than 2% (Felton, 1959; Leary et al., 1972). In boys with cryptorchidism, a higher than normal incidence of urinary tract malformations has been reported (Grossman and Ririe, 1968; Farrington and Kerr, 1969; Donahoe et al., 1973; Watson et al., 1974; White et al., 1973; Tveter and Fjaerli, 1975).

Bergmeyer and Meradji (1977) reviewed the literature in comparison with their own data concerning cryptorchidism and associated urological abnormalities and found 13 cases with a major abnormality in 579 patients (2.2%). Five of these 13 cases required surgical intervention. There appeared to be a slightly increased prevalence for minor abnormalities such as duplication of the upper urinary tract, ureteral dilatation, renal malrotation and uretero-pelvic junction obstruction. Hendren and Ginsburg (1981) routinely carried out intravenous pyelography (IVP) in all boys with bilateral cryptorchidism. Others advocate limiting an IVP or other radiologic investigations to boys with undescended testes that have urolo-

gic symptoms or congenital abnormalities outside the urinary tract (Watson et al., 1974; Tveter and Fjaerli, 1975; Bergmeyer and Meradji, 1977).

c. Cryptorchidism and abnormal paratesticular structures

Persistence of Müllerian duct structures may be revealed by chance at surgery (frequently at operation for inguinal hernia). A uterus, vagina, and Fallopian tubes may be found in combination with a vas deferens and undescended, frequently intra-abdominal testes (Snow et al., 1985; Van Lanschot et al., 1985).

d. Cryptorchidism and ambiguous genitalia

Cryptorchidism is frequently found in infants with ambiguous genitalia (Visser, 1982). Adrenogenital syndrome, mixed gonadal dysgenesis, feminizing testes syndrome, and true hermaphroditism are intersex disorders in which cryptorchidism is combined with other genital abnormalities. Drop and coworkers (1984) published a comprehensive description of ambiguous genitalia and all that this entails.

5.5. THE HISTORY OF ORCHIOPEXY

5.5.1. Conventional orchiopexy

Surgical placement of an incompletely descended testis into the scrotum was first attempted by Rosenmerkel in 1820. The first work of merit in this line was done by Schüller in 1881. He recognized the processus vaginalis as the chief factor hampering the natural course of the testis down to the scrotum. In 1899, Bevan first described division of the processus vaginalis with extended funicolysis. Four years later, he published the results of an improved technique (Bevan, 1903). Bevan's technique was based on principles that govern orchiopexy to this day (figure 5.7.). In 1909, Torek described a new technique which is essentially the same as Bevan's, but the testis is fixed to the fascia on the inner surface of the thigh for two or three months. The testis is then released from the thigh in a second procedure. Davison (1911) recommended division of the deep epigastric vessels to permit the cord to pass in a more direct line to the scrotum. Ombredanne (1927) perfected Bevan's technique, adding fixation of the testis by placing it in the opposite scrotal compartment. La Roque (1931) introduced the principle of retroperitoneal dissection to free the cord structures. Cabot and Nesbit (1931) introduced the use of a rubber band attached at one end to a testicular suture and at the other end to the inner surface of the thigh, by means of adhesive tape, in order to maintain the new position of the testis. Refining the fixation technique by positioning the testis between the tunica dartos and the scrotal skin was recommended in 1932 by the Dutch surgeon Schoemaker (figure 5.8.). Gross (1953) advocated extended retroperitoneal dissection freeing the vas down to the

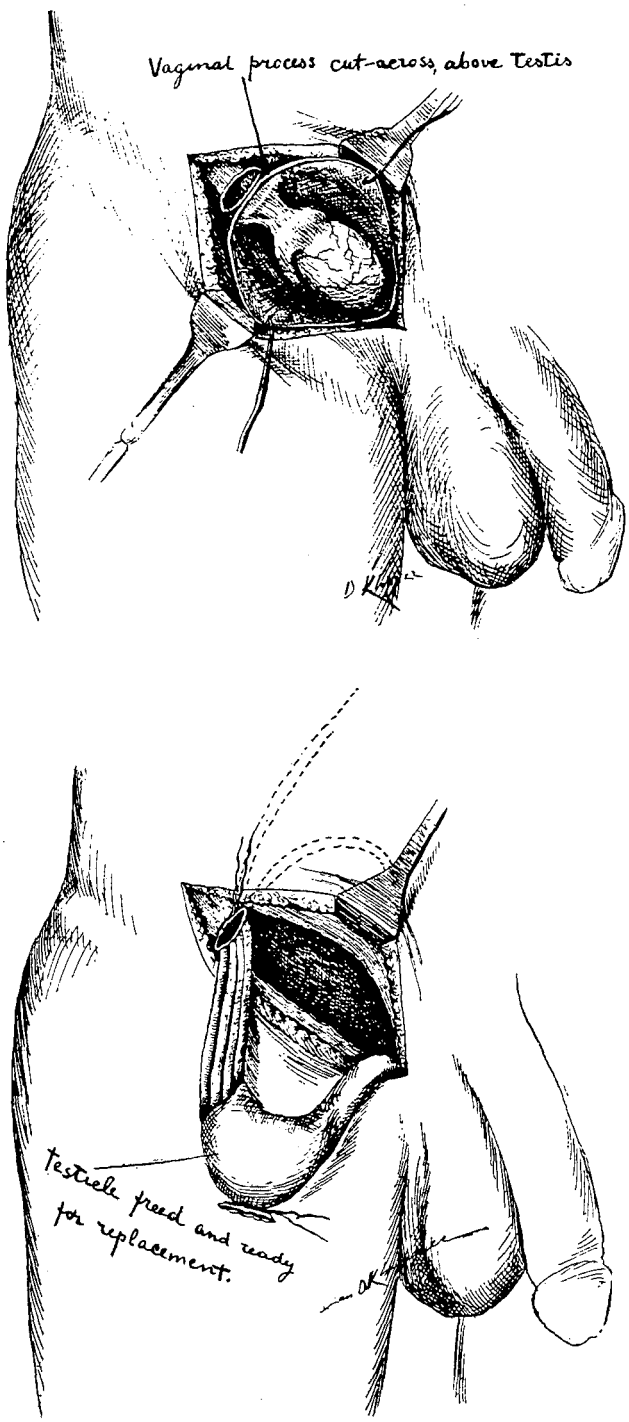


Figure 5.7. Original drawings of the first publication of orchiopexy (Bevan, 1903; with permission).

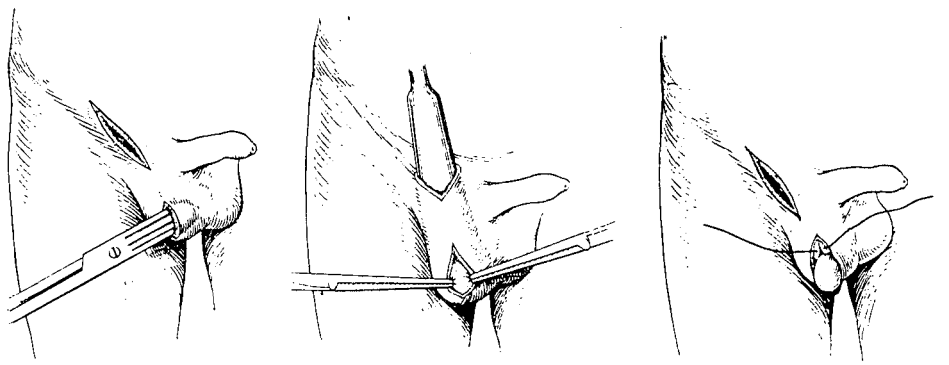


Figure 5.8. Original drawings of the Schoemaker orchiopexy (Schoemaker, 1932; with permission).

base of the bladder and the vessels up to the inferior pole of the kidney. Prentiss and coworkers (1960) further shortened the distance from the deep inguinal ring to the scrotum by transplanting the cord structures to the medial end of the posterior wall of the inguinal canal. Their report affirmed the mathematic principle that the shortest distance between two points is a straight line. Another new anchoring technique, the window septopexy, was described by Welch in 1972. His surgical technique consists of anchoring the orthopic testis permanently to a window in the elastic membrane that divides the scrotal compartments. Saha (1978) introduced "cordopexy", a technique which is based on fixation of the spermatic cord and not the testis. All these modifications of the original technique designed by Bevan depend on two main factors, mobilization and fixation, while it has become evident that undue traction or fixation of the testis with tension on the cord vessels will contribute to testicular atrophy and loss of function. Table 5.1. gives the results of conventional orchiopexy.

A revised approach to the inguinal region using diverse incisions was described by Lipton, as well as by Chambless and Florence in 1961. They advocated either a tranverse or a midline preperitoneal approach to the imcompletely descended testis. Both procedures incorporated many technical principles common to conventional inguinal orchiopexy and the incision originally described for inguinal hernia by Cheatle (1921) and Henry (1936). This approach afforded excellent

Table 5.1. Results of conventional orchiopexy; number (%) of testes.

authors	clinical results	
	operations	success
Gross and Replogle [1963]	1767	1537 [87]
Daum et al. [1969]	295	264 [89]
Scorer and Farrington [1971]	125	96 [77]
Cywes et al. [1981]	587	457 [78]
Lynch et al. [1982]	233	193 [83]
Thorup et al. [1984]	695	572 [82]
Total	3702	3119 [84]

exposure of the high-lying testis and allowed extensive dissection of spermatic vessels and vas deferens. Furthermore, their approach gave adequate exposure for bilateral orchiopexy at one and the same operation. Good results of this midline preperitoneal approach are described by Hunt and coworkers (1981). They recommended a more frequent use of this operation technique. Jones and Bagley (1979) described another modification of the standard orchiopexy. They used a high inguinal incision combined with an abdominal extra- and retroperitoneal approach using a muscle-splitting incision. Exploration of the retroperitoneal area enables extensive mobilization of the testicular vessels and vas deferens.

5.5.2. Staged orchiopexy

The majority of incompletely descended or ectopic testes can be brought down into the scrotum with the conventional orchiopexy procedure, but in some cases the length of the spermatic cord is not adequate to reach the scrotum. A "staged orchiopexy" is one where the testis is mobilized to its maximum extent at the first operation and fixed at a site as distal as possible, usually outside the external inquinal ring or at the pubic tubercle. After at least one year, a second operation is performed involving inguinal and retroperitoneal dissection. Staged orchiopexy for the treatment of the high-lying testis was first described by Snyder and Chaffin in 1955 and has since been advocated by many other surgeons (table 5.2.).

Most surgeons encounter difficulty in the dissection of the testis and cord during the second procedure. In 1975 Corkery described a technique to protect the testis and the spermatic cord at the first-stage operation by temporarily encasing these structures in silastic sheeting. This allows for a safer second-stage procedure by preventing adherence of the testis and cord structures. The role of the staged orchiopexy is controversial. Redman (1976) sees no rationale for a staged procedure. In his highly critical review he suggested that a successful second stage is most likely an indication of inadequate dissection during the first stage and that there is no documentation of further elongation of the spermatic cord after operation.

Table 5.2. Results of staged orchiopexy; number (%) of testes.

authors	clinical results		
	operations	success	follow-up in years after second stage
Snyder and Chaffin [1955]	7	6 [86]	not mentioned
Gross and Replogle [1963]	24	24 [100]	not mentioned
Persky and Albert [1971]	13	9 [69]	not mentioned
Firor [1971]	32	30 [94]	not mentioned
Corkery [1975]	6	5 [83]	not mentioned
Zer et al. [1975]	41	32 [78]	2-10
Kiesewetter et al. [1981]	40	33 [82]	1-24
Steinhardt et al. [1985]	12	10 [83]	"adequate"
Total	175	149 [85]	

5.5.3. Orchiopexy with testicular vessel transection

The concept of testicular vessel transection was first described by Bevan in 1903. He recommended dividing all the structures of the spermatic cord, except the vas deferens and its associated deferential artery and vein, in case the internal spermatic vessels were too short to permit scrotal placement. Because of the poor results with this procedure, it quickly fell into disfavour. Interest was renewed by Fowler and Stephens in 1959. They observed that in patients with high-lying testes, the vas deferens was often elongated, frequently extending down through the external inguinal ring and then looping back to rejoin the testis. The testicular vessels are short, but the vas deferens and its companion vessels are long. Using peroperative angiography, they demonstrated vascular collateral anastomoses between the vasal and the spermatic arteries. Under such anatomical conditions, high ligation and division of the main vascular pedicle to the testis may be feasible, allowing the testis to be placed in an intrascrotal position. To assure the adequacy of blood supply from the vasal artery, Fowler and Stephens recommended temporary occlusion of vessels followed by incision of the tunica albuginea of the testis which should observed for fresh bleeding. Although the Fowler-Stephens procedure is particularly applicable in case of a high-lying testis with a long vas, several authors used this procedure with high-lying testes without a long loop vas deferens (table 5.3.). Analysis of the various results demonstrates that the procedure must be decided upon early in the course of dissection, since retroperitoneal dissection damages the perivasal circulation, which forms the collateral blood supply. In the normal testis, the division of the main spermatic vessels does not necessarily lead to testicular atrophy, provided the collateral channels in the cord and scrotum are left undisturbed.

Table 5.3. Results of Fowler-Stephens procedure; number (%) of testes.

authors	clinical results		
	operations	success	long loop vas present
Moschcowitz [1910]	22	21 [95]	not mentioned
Mac Collum [1935]	5	0 [0]	no long loop vas
Fowler and Stephens [1959]	12	8 [67]	7 long loop vas [5 success]
Brendler and Wulfsohn [1967]	5	5 [100]	no long loop vas
Clatworthy et al. [1972]	32	24 [75]	all long loop vas
Datta et al. [1977]	3	3 [100]	no long loop vas
Gibbons et al. [1979]	27	22 [81]	not mentioned
Total	106	83 [78]	

5.5.4. Microvascular orchiopexy

The short vascular pedicle of the intra-abdominal or high-lying, inguinal testis poses a major surgical problem. Staged orchiopexy and reliance on the vessels of

the vas deferens for testicular vascularization (Fowler-Stephens procedure) have not given consistently satisfactory results. The last ten years have seen a general advance in the clinical application of microsurgery. With the improvement of microvascular techniques, testicular autotransplantation has become feasible. In 1976, Silber and Kelly reported successful autotransplantation of an intra-abdominal testis in a child with prune belly syndrome and since then testicular autotransplantation has gained in popularity. Using a surgical microscope, the intra-abdominal testis is transplanted to the scrotum with re-anastomosis of the divided testicular vessels to the inferior epigastric artery and vein. Subsequently, many authors have described their experience with this technique and the overall results demonstrate the feasibility of such microvascular surgical orchiopexy (table 5.4.). The rationale of this new operation is based on the assumption that the restoration of an optimal vascular supply represents the best guarantee for a possible functional recovery of the testis.

Table 5.4. Results of microvascular orchiopexy; number (%) of testes.

authors	clinical results		
	operations	success	follow-up period in months
Silber and Kelly [1976]	1	1 [100]	?
Silber [1978]	1	1 [100]	8
Romas et al. [1978]	4	4 [100]	6-15
MacMahon et al. [1980]	8	6 [75]	6-48
Martin and Salibian [1980]	2	2 [100]	3-12
Rossignol et al. [1981]	1	1 [100]	12
Wacksman et al. [1982]	7	6 [86]	6-36
Silber [1982]	5	5 [100]	>6
O'Brien et al. [1983]	11	6 [54]	12-72
Giuliani and Carmignani [1983]	5	5 [100]	>3
Upton et al. [1983]	10	6 [60]	>6
Garibyan and Hazebroek [1984]	9	8 [89]	9-18
Bianchi [1984]	10	8 [80]	1-24
Shioshvili [1985]	6	6 [100]	2-12
Total	80	65 [81]	

5.5.5. Neonatal transabdominal orchiopexy

In patients with prune belly syndrome, one expects intra-abdominal testes lacking the potential for spontaneous descent. Woodard and Parrott (1978) demonstrated that the testis of prune belly patients can be brought down into the scrotum with their vascular pedicle intact, by means of a transabdominal, transperitoneal orchiopexy carried out during the first weeks of life, either in conjunction with urinary tract reconstruction or as a primary procedure. The cord is mobilized transperitoneally to the origin of the spermatic vein and artery, after which the testis is passed through the abdominal wall at the site of the external inguinal ring and into the scrotum. The results achieved in these patients support the view that orchiopexy, performed very early in life, offers the best chance of obtaining viable testes in the scrotum.

5.5.6. Orchiopexy procedures applied in the Sophia Children's Hospital

At the Sophia Children's Hospital the surgical procedure for undescended testes has since long consisted of funiculolysis followed by orchiopexy with testis fixation in a subcutaneous pouch after Schoemaker. Staged orchiopexy, the Fowler-Stephens procedure, and neonatal transabdominal orchiopexy are carried out on occasion. From 1981, microvascular orchiopexy has become one of our standard procedures. An extensive description of all these surgical procedures and their fields of application is given in chapter 6.

CHAPTER 6

SURGICAL TREATMENT OF UNDESCENDED TESTES

6.1. INTRODUCTION

The hormonal studies described in chapters 3 and 4 have demonstrated unconditionally that surgical intervention is the only therapeutic modality for the majority of truly undescended testes. Retractile testes generally do not require any treatment (see below), while *all* undescended testes that are impalpable, require surgical therapy. Incompletely descended testes that are capable of manipulation to at least the scrotal entrance, may descend with hormonal treatment. A great deal depends on the diagnostic findings. It is essential that the diagnostic examination of boys with any form of testicular nondescent is carried out by someone with anatomic insight and with expertise in the examination of infants and children (Spitz, 1983).

6.2. MANAGEMENT OF THE RETRACTILE TESTIS

The retractile testis differs from the normally descended testis in that it is a great deal more mobile. It can readily be pulled out of the scrotum over the bar of the pubic bone by the active cremaster muscle (cremasteric reflex). Farrington (1968) studied the position and retractility of the testes of 594 boys in the age range of 0 to 16 years. He found that the cremasteric reflex cannot be provoked before the age of two weeks, while the reflex contraction of the cremasteric muscle only reaches sufficient strength to withdraw the testis from the scrotum at the age of six months. Retractility reaches its peak around the age of six years, whereupon it begins to decline. Around puberty the cremasteric reflex disappears altogether.

Once over the pubic bone, the testis floats freely into the superficial inguinal pouch (Browne, 1938; Scorer, 1962; Johnston, 1965; Flach, 1977). From the superficial inguinal pouch, where it can reside for lengthy periods, the retractile testis can be manipulated into a stable intrascrotal position, while it is also capable of descending spontaneously at any time. The retractile testis is never found in front of the pubic bone as that is not a stable position. Apart from its hypermobility, the retractile testis is entirely normal. Figure 6.1. is a schematic presentation of the retractile testis.

During the period under study (October 1982 to April 1985) a total of 660

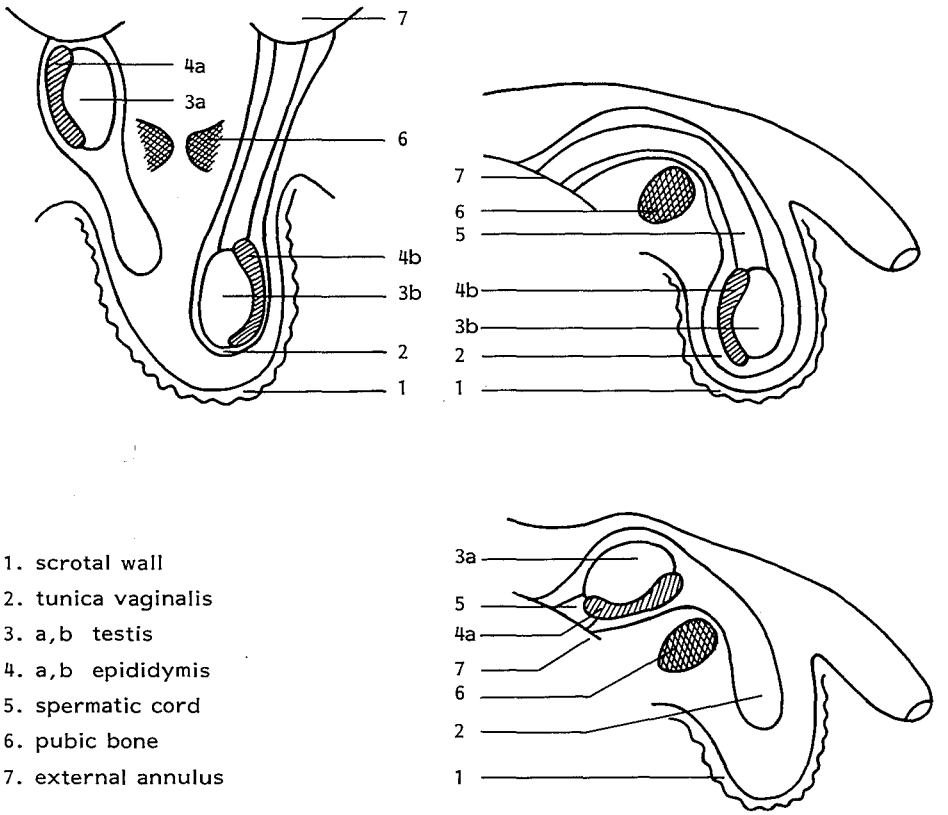


Figure 6.1. Schematic presentation of the retractile testis.

prepuberal boys with either unilateral or bilateral undescended testes were referred to us for treatment (figure 6.2.). In 217 of them (33%) we diagnosed retractile testis, generally at the very first examination, though sometimes only after repeated examinations. It is important to note that all 660 boys had previously been examined by their general practitioner and/or school physician and referred with a diagnosis of undescended testis. None of the boys in whom we diagnosed a retractile testis were operated upon; they were just told to come back for annual checkups.

In the group of boys with retractile testes, there were 24 whom we first saw when they were 10-11 years old. In 20 of them we found both testes in a scrotal position around age 12 with the cremasteric reflex no longer capable of withdrawing the testis from the scrotum. For the other boys the duration of the follow-up was too short at the conclusion of the study period to allow for an examination at the age of puberty.

It is generally assumed that retractile testes do not require treatment as these testes will be permanently intrascrotal around puberty. However, some authors

Figure 6.2. Division between boys with retractile testes (n = 217) and boys with undescended testes (n = 443) in different age groups.

have described previously retractile testes that were in a permanent nonscrotal position after a number of years, requiring surgical intervention (Villumsen and Zachau, 1966; Privat, 1978; Atwell, 1985). Atwell suggested a possible cause for this testicular ascent. In a number of cases where the testis had ascended, he would find an open processus vaginalis at operation. It seemed feasible that in the course of further growth of the abdominal wall, for example, this open processus vaginalis had gradually become part of the peritoneum thereby lifting up the testis (figure 6.3.).

We did not (yet) see permanent ascent of a testis diagnosed as retractile, but here again we must stress that the follow-up period never exceeded two years. In this connection it is interesting to note that 5 of 443 boys in whom we diagnosed incompletely descended testes had been examined years before by an experienced paediatric surgeon, who diagnosed retractile testes (three bilateral, two unilateral). In one of these five boys, the right testis was palpable in the external inguinal ring though incapable of manipulation down to the scrotum, while the left testis had assumed a high scrotal position. At operation of the right testis, we found a wide open processus vaginalis with adhesions and folds of connective tissue at the transection of processus vaginalis to peritoneum. This might well account for the ascent of the testis as it was lying in a processus vaginalis which no longer extended down to the scrotum (figure 6.4[a]. and 6.4[b].). The aetiology of these peritoneal adhesions is not clear.

In conclusion, we can safely say that retractile testes generally require no treatment, although a regular checkup, preferably once a year, up to the age of puberty is imperative. We have found that a simple explanation of the need for

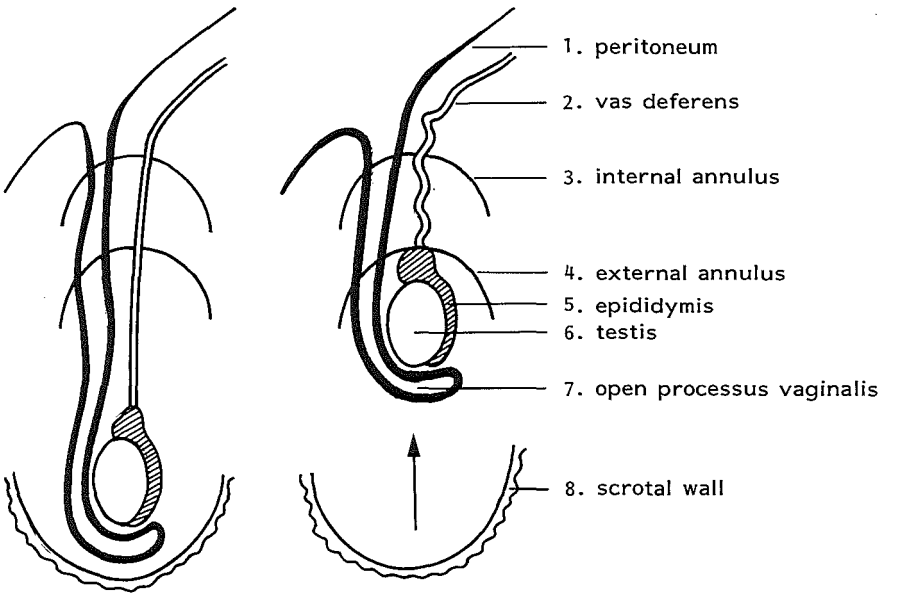


Figure 6.3. Schematic presentation of open processus vaginalis becoming part of the parietal peritoneum with resultant shortening of the cord and testicular ascent (Modified from Atwell, 1985).

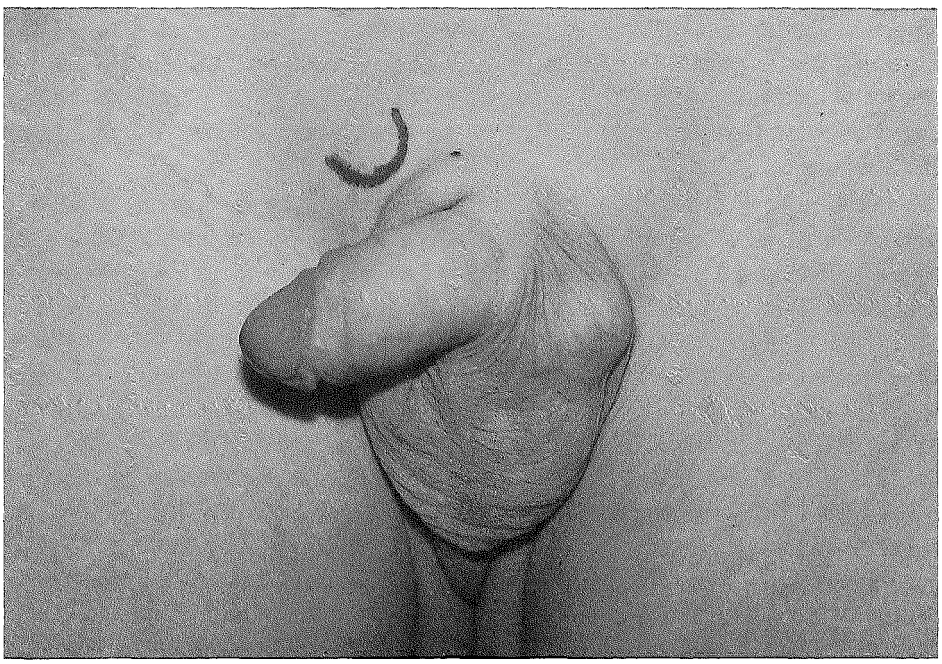


Figure 6.4[a]. Spontaneous testicular position in a 10 year old boy with previously descended testes. Line indicates position of right testis.

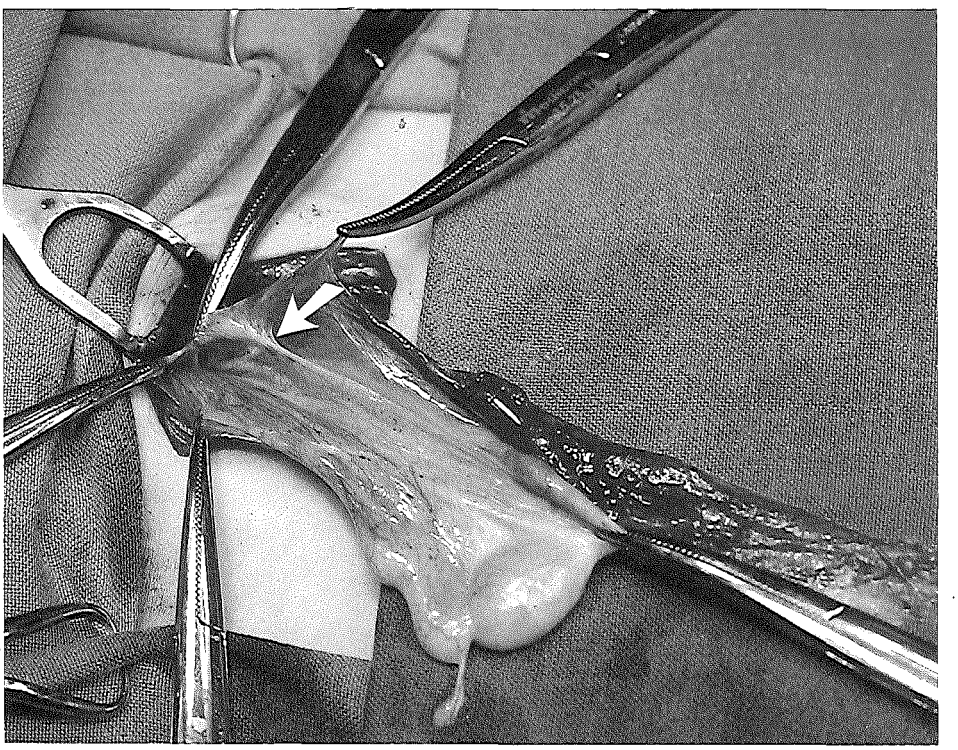


Figure 6.4[b]. Exploration of the right inguinal canal revealed wide open processus vaginalis with adhesions and folds (arrow) of the peritoneum.

such regular checkups will prevent any anxiety the boy or his parents may feel when told to come back once a year.

6.3. SURGICAL MANAGEMENT OF THE IMPALPABLE TESTIS

6.3.1. Introduction

The impalpable testis by the simplest definition is a testis that is not palpable by the examiner. Testes are impalpable when they are lying intra-abdominally or high in the inguinal canal and never emerge through the external inguinal ring, or when they are atrophic or absent (Browne, 1938). In a review of the literature, Levitt and coworkers (1978) reported that the incidence of impalpable testes is approximately 20 per cent of the undescended testis populations.

The surgical management of the palpable testis has since long been a routine surgical procedure, but for the nonpalpable testis the surgical management

remains controversial. Hinman (1979) advocates removal of high-lying testes (orchidectomy), while Redman (1980) argues for treatment (orchiopexy). The reason for these completely opposing views lies in the fact that impalpable testes differ in some ways from either descended or palpable, undescended testes. For example, impalpable testes are often comparatively smaller and histologically divergent (Mack, 1961; Nistal et al., 1980). A partial or completely separated epididymis, as described in the previous chapter (5.4.1.c.) is a frequent finding. If there is total separation of epididymis and testis in bilaterally undescended, high-lying testes, this condition greatly reduces the chances of fertility, which are limited anyway in boys with such an abnormal testicular position (Scorer and Farrington, 1971; Marshall and Shermeta, 1979; Kroovand and Perlmutter, 1981; Heath et al., 1984) (see 5.3.1.). With intra-abdominal or high-lying, inguinal testes, there is an increased risk of carcinoma in situ or even a real germ cell tumour (see 5.3.2.). Bringing the impalpable testis to the scrotum frequently involves a technically complicated surgical intervention due to the large distance that often has to be bridged, while the functional and cosmetic result is rather poor (Gibbons et al., 1979; Smolko et al., 1983).

This chapter describes the author's own experience with the treatment of boys with unilaterally or bilaterally undescended testes that are lying intra-abdominally or high in the inguinal canal. The results are compared with literature data. The following questions will be dealt with:

- What are the indications for treatment of impalpable testes?
- How should impalpable testes be treated?

6.3.2. Diagnostic evaluation of the impalpable testis

In deciding what type of diagnostic examination is required before surgical intervention for impalpable testis is initiated, one should distinguish between unilateral and bilateral impalpable testis. Hormonal evaluation is essential in boys with bilateral impalpable testes, to ensure the presence of testicular tissue. Normal basal serum gonadotropins - FSH and LH - and an appropriate increase in serum testosterone over basal values after stimulation with HCG (1,500 IU) denote functioning testicular tissue and mandate further therapy. In contrast, elevated basal levels of FSH and LH in association with failure of testosterone elevation over basal levels after HCG stimulation, denote an absence of functioning testicular tissue. These endocrine findings in a normal phenotypic male subject with a normal 46 XY karyotype without palpable Müllerian structures on rectal examination, establish the diagnosis of congenital bilateral anorchism or vanishing testis syndrome (see 5.4.1.b.). Surgical exploration is not necessary for confirmation of this syndrome. Hormonal evaluation is pointless in boys with unilateral impalpable testis. The presence of one normally descended testis with normal hormonal function, makes it impossible to determine whether this is a

case of anorchia or vanishing testis, or rather an existing testis which is merely not palpable.

The last decade has witnessed an incrasing emphasis on evaluations to ascertain pre-operatively the position of the impalpable testis. The inference is that when the testis is impalpable pre-operatively, a fruitless exploration of the inguinal canal may herald a frustrating search for an elusive gonad. Selective gonadal arteriography and venography have been proposed to localize the position of impalpable testes pre-operatively as an aid in surgical management (Domellöf et al., 1978; Rubin and Gershater, 1981; Pommerville et al., 1982; Khan et al., 1982). However, these examinations are definitely not recommended as routine diagnostic procedures, because both arteriography and venography are invasive examinations with an inherent risk of complications (lesion of femoral artery or vein), while the interpretation of the images achieved remains difficult due to anatomical variations of the testicular vessels (Harrison, 1949). The information gained from these procedures must therefore be seen in the light of their limited accuracy and invasive nature. Computerized tomography and ultrasonography are not very invasive procedures, which are easy to reproduce. However, these methods are not very dependable for visualizing the impalpable testis (Green, 1985; Malone and Guiney, 1985; Wright, 1986). In contrast, laparoscopy has been found to demonstrate intra-abdominal testes accurately and to visualize the spermatic vessels and vas deferens entering the inguinal ring (Scott, 1982; Lowe et al., 1984; Boddy et al., 1985; Manson et al., 1985). Laparoscopy will also demonstrate blind-ending vessels within the abdomen (Silber and Cohen, 1980). However, laparoscopy is certainly invasive, while the findings are often difficult to interpret despite the fact that it is not a difficult procedure for an expert surgeon to perform.

The main argument against performing any one of these diagnostic examinations routinely lies in the fact that surgical exploration will still be required. None of these methods are capable of providing conclusive evidence of testicular absence, so that at least in these cases surgery could be circumvented (Sheldon, 1986). Besides, this would only involve a small percentage of the impalpable testes, as surgery generally does reveal a testis, albeit sometimes an atrophic one. Table 6.1. gives a summary of literature data concerning 337 impalpable testes.

Table 6.1. Peroperative position of 337 impalpable testes; number (%) of testes.

authors (year)	total of testes	peroperative position			
		absent	intra-abdominal	inguinal canal	outside ing. canal
Redman (1980)	114	6 (5)	19 (17)	84 (74)	5 (4)
Smolko et al (1983)	80	17 (20)	44 (56)	15 (19)	4 (5)
Rajfer et al (1983)	8	1 (12.5)	1 (12.5)	2 (25)	4 (50)
Malone and Guiney (1985)	14	2 (14)	7 (50)	5 (36)	0 (0)
Manson et al (1985)	17	1 (6)	5 (29)	9 (53)	2 (12)
Wright (1986)	104	29 (28)	34 (33)	34 (33)	7 (6)
Total	337	56 (17)	110 (33)	149 (44)	22 (6)

Surgery revealed testicular absence in only 56 (17%) of these cases, which means that regardless of the type or invasiveness of pre-operative diagnostic examinations, surgical intervention was definitely required in 281 cases, amounting to 83%. In actual fact this percentage is even higher, because the 56 cases of testicular absence included a number of so-called vanishing testis whereby testicular vessels and vas deferens do reach the inguinal canal through the annulus internus, but neither laparoscopy nor venography can provide conclusive evidence for or against the presence of a testis in the inguinal canal. This means that surgical exploration remains mandatory. A primary surgical approach to the impalpable testis has the added advantage that in most cases a surgical exploration will provide both diagnosis and therapy, because orchiopexy can generally be performed rightaway. Consequently, surgical exploration is the only correct method of diagnostic evaluation of the impalpable testis.

Hormonal treatment of the impalpable testis is pointless, as demonstrated extensively in chapter 4. Therefore, we agree with Levitt et al. (1978) and Redman (1980), that an inguinal skin incision is the simplest, most cosmetic and most direct approach in most cases of impalpable testes. The degree of exposure is striking. The retroperitoneal space can be visualized from the base of the bladder to just below the lower pole of the kindney. The peritoneum may be opened widely for intraperitoneal exploration. The following conditions may be revealed:

- Extensive extraperitoneal and intraperitoneal exploration demonstrate the absence of either testicular or funicular structures. This finding is very rare (Levitt et al., 1978).
- There is only a blind-ending vas deferens, in which case intraperitoneal exploration is still required to exclude a higher-lying testis (Kogan et al., 1986).
- Testicular vessels with a vas deferens are located in the inguinal canal or at the level of the annulus internus; these structures usually end in a tissue remnant consisting of epididymis (Kogan et al., 1986). This is a case of "vanishing testis" (see 5.4.1.b.).
- The testis is located intra-abdominally or high in the inguinal canal, in which case there is often a partial or complete separation of testis and epididymis, while the testis is obviously smaller and softer than the contralateral, descended testis.

The surgical possibilities depend on the explorative findings. If the exploration reveals testicular absence, provided this is a case of "vanishing testis", a scrotal orchiopexy will have to be performed on the contralateral testis, in order to prevent torsion of this solitary testis. This operation is not indicated in case of unilateral anorchia.

Indications for orchidectomy are not easy to define. Unilateral testicular atrophy associated with anatomical abnormalities of epididymis and vas deferens may be such an indication, whereby the extent of the abnormality and the ultimate length of the testicular vessels will be the deciding factors. If the testis is

incapable of being brought to the scrotum, e.g. because of insufficient funicular length, orchidectomy may be indicated to prevent the development of carcinoma. Bilateral orchidectomy to prevent malignant degeneration is obviously unacceptable. In boys with two impalpable testes, all attempts should be made to conserve hormonal function. Sparing hormonal function is paramount and should even prevail over the wish to achieve a scrotal position should this be feasible. In case of bilaterally impalpable testes, it may be necessary to leave at least one testis in a subcutaneous position without damage to the vascularization, to ensure normal hormonal function. In case of unilateral impalpable testis, the mentality and age of the boy also play a part in a decision for or against orchidectomy.

It is essential that all possibilities are fully discussed with the boy and his parents, before surgery takes place. Surch pre-operative consultation should include mention of a testicular prosthesis in case orchiopexy is not feasible. It is generally advisable not to insert a prosthesis before the age of puberty. A testicular prosthesis of adult dimension can then be inserted rightaway and, what's more important, the motivation will come from the boy himself and not merely from the parents.

Fortunately, it appears that the majority of the impalpable testes are capable of being brought well into the scrotum (Gross and Jewett, 1956; Redman, 1980; Wright, 1986). Table 6.2. gives the results of surgical treatment of impalpable testes carried out by the author. Between April 1982 and April 1985, a total of 68 prepuberal boys with 84 impalpable testes were operated upon. Eighteen testes (22%) appeared to be absent, while 38 testes (45%) could be placed in a scrotal position with a standard orchiopexy after Schoemaker (see 6.5.3.d. for a description of this technique). A special surgical technique was required for 28 testes (33%), involving orchidectomy in two cases, but succeeding in a scrotal position for another 18 testes. (The number of cases listed for the staged procedure only include cases where both first and second operation were carried out by the author). In the following paragraphs the special surgical techniques will be dealt with extensively, as well as the indications for such techniques and the subsequent results.

Table 6.2. Results and type of surgical correction of 84 impalpable testes in 68 prepuberal boys; number of testes (number of boys).

surgical procedure						
exploration testis absent	standard orchio-pexy	Fowler-Stephens	staged incl.orchi-dectomy	micro-vascular	postoperative condition/position of testis	total
18	0	0	2	0	no testis	20
0	0	3	0	3	atrophic testis	6
0	0	0	2	0	outside ing. canal	2
0	8	2	2	4	high scrotal	16
0	30	4	0	6	low scrotal	40
18 [18]	38 [26]	9 [8]	6 [4]	13 [2]	total	84 [68]

6.4. SPECIAL SURGICAL PROCEDURES FOR IMPALPABLE TESTES

For a number of impalpable testes, particularly the intra-abdominal ones, a scrotal position can only be achieved by means of a special surgical technique. The author's own experience with a number of these techniques and the results are presented below, with reference to the literature.

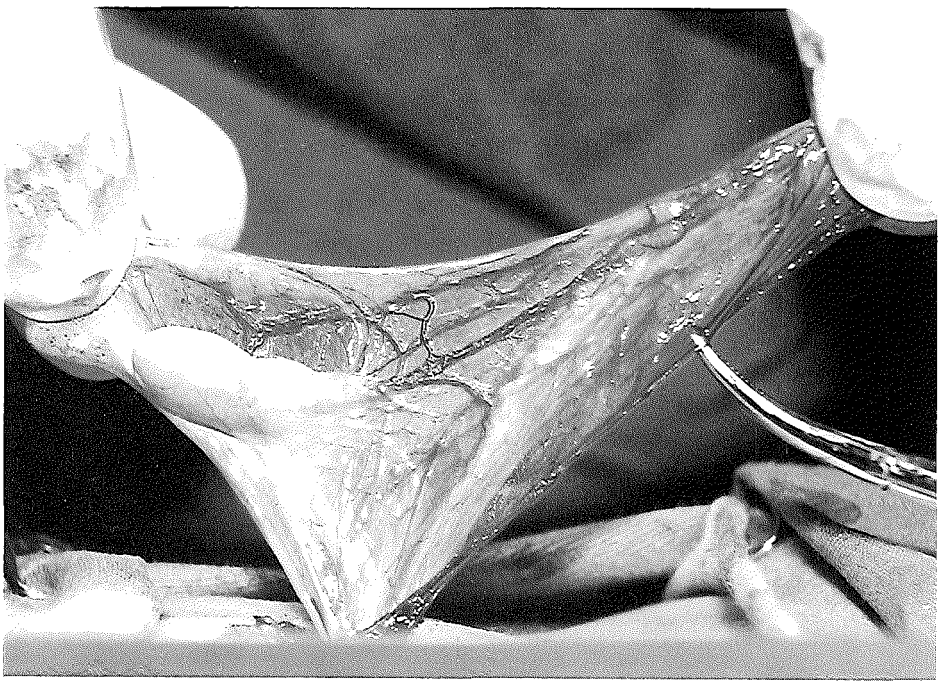
6.4.1. Experience with Fowler-Stephens procedure

a. Introduction

The principle of orchiopexy with testicular vessel transection (Fowler-Stephens procedure) has been dealt with in chapter 5 (5.5.3.). A special anatomical situation must be present to permit a satisfactory performance of this technique. In such a situation, the testis itself is usually located in the abdomen or high in the inguinal canal, while the epididymis and vas deferens often extend caudally past the annulus externus ("long loop vas and epididymis"). Although the main vascular pedicle to the testis is short, a secondary vascular loop emerges from the deep epigastric vessels with a lot of branches entering the posterior wall of the open processus vaginalis. This vascular network creates a rich collateral circulation for the testis (figure 6.5.). Following localization of the testis, vas and epididymis, the spermatic vessels are mobilized high through the posterior peritoneum without disturbing the medial blood supply along the vas. A bulldog clamp temporarily occludes the spermatic vessels high above the testis and sometimes a number of the collateral vessels are ligated. The colour of the testis is observed for several minutes and a small incision may be made in the tunica albuginea of the testis to aid assessment of the adequacy of the collateral blood supply (figure 6.6.). Provided the circulation appears intact, the testicular vessels are ligated high above the testis and a wide tongue is created of medially based peritoneum containing the vas and the perivasal collateral blood supply.

b. Results of Fowler-Stephens procedure

In the period April 1982 - April 1985, nine intra-abdominal or high-lying, inguinal testes were brought into the scrotum by the author applying the Fowler-Stephens procedure. Table 6.3. lists the results of these operations. There were six cases with an obvious "long loop" vas deferens and epididymis with extensive collateral vascularization. In the other three cases there was no "long loop" vas or epididymis, but the epididymis was almost completely separated from the testis. The results of these nine operations clearly demonstrate that a "long loop" anatomy, coupled with adequate collateral circulation between vas deferens, epididymis and testis, is essential for the persistence of a good testicular vascularization. Only one of the six testes with this anatomical structure appeared to have become atrophic after at least six months had elapsed. In contrast, two of the



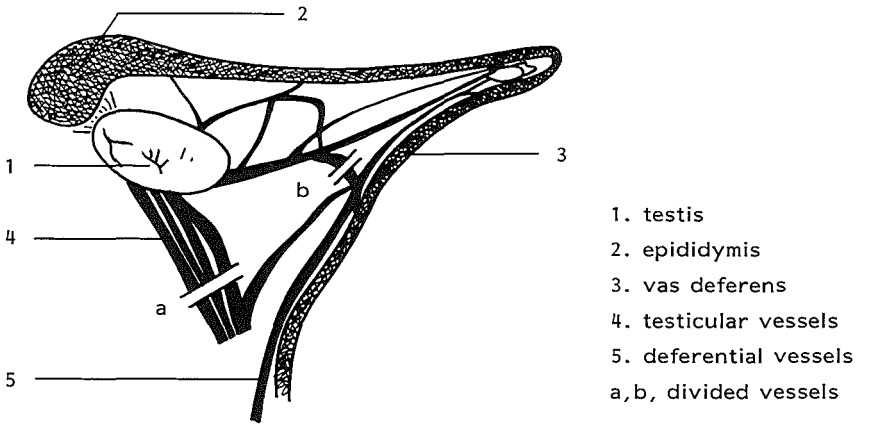


Figure 6.5. Peroperative photograph of "long loop" vas, showing collateral circulation between testicular and vasal vascularization.

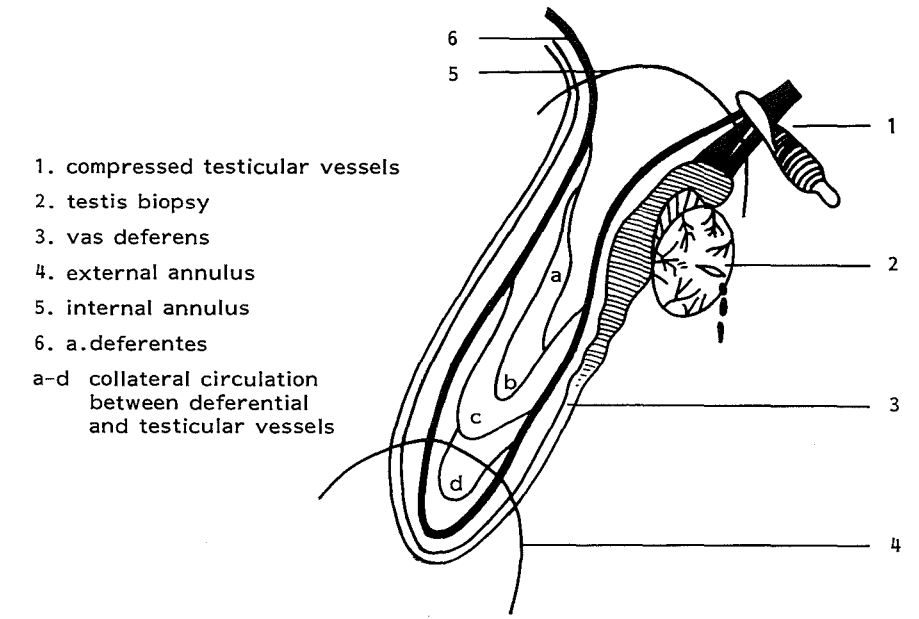


Figure 6.6. Schematic presentation of Fowler-Stephens procedure. After compression of the testicular vessels, several collateral vessels (a, b, c, d) across the major long loop of the vas deferens can usually be divided. Provided bleeding is continuous, it is safe to divide the testicular vessels whereby adequate length can be achieved.

Table 6.3. Results of Fowler-Stephens procedure; number of testes (number of boys).

anatomical structure	total	results >6 months postoperative		
		normal testis		atrophic testis
		high scrotal	low scrotal	
"long loop" vas and epididymis	6 (5)	1 (1)	4 (3)	1 (1)
normal vas and epididymis	3 (3)	1 (1)	0 (0)	2 (2)
Total	9 (8)	2 (2)	4 (3)	3 (3)

three testes without a "long loop" anatomy had atrophied as a result of insufficient vascularization. In conclusion, the Fowler-Stephens procedure proved a good surgical technique for the high-lying, impalpable testis associated with a "long loop" vas deferens and epididymis.

c. *Discussion*

The concept of dividing the vascular pedicle of the testis is not new, having been performed by Bevan as early as 1903. Bevan considered it a "radical but perfectly safe" procedure, and noted no evidence of interference with testicular

position. In 1910, Moschcowitz described the long loop vas variant with transection of the vessels as a safe procedure for undescended testes. Over the years, this procedure fell into disrepute because of poor long-term results (MacCollum, 1935). Interest in the maneuver of testicular vessel division was revived by Fowler and Stephens in 1959. They ligated the spermatic vessels in 12 patients with high-lying undescended testes and obtained good anatomic results in 8 of them. There seem to be two reasons for the present success with this procedure in contrast to the poor experience in the past. The first of these lies in the recognition of anastomoses between the vasal and spermatic arteries within the spermatic cord and in the region of the epididymis. The second reason lies in the current practice of high ligation of the spermatic vessels, above the point where they diverge from the vas, avoiding damage to collateral channels.

In 1972, Clatworthy and coworkers reported their experience with the Fowler-Stephens procedure in 32 patients. These patients could be divided into two groups. In the first group, a premeditated Fowler-Stephens procedure resulted in an 85% success rate (18 of 21). All 7 high inguinal testes survived, while only 3 of 14 intra-abdominal testes atrophied. In the second group of patients, the Fowler-Stephens procedure was carried out after an attempt to bring the testis down by mobilizing the cord had failed. The success rate for this group was much lower, amounting to 54% (6 of 11). Their results exemplify the fact that the cord should not be dissected before spermatic vessel division.

Datta and coworkers (1977) achieved a satisfactory intrascrotal position of the testes by dividing the spermatic vessels in three boys with unilateral undescended testes. They recommended a postoperative scrotal scan to determine the adequacy of testicular circulation. Gibbons and coworkers (1979) stressed the importance of creating a wide pedicle of peritoneum on either side of the vas to preserve the precariously delicate vasal structure.

d. Indications for Fowler-Stephens procedure

Most authors that reported their experience with the Fowler-Stephens procedure concluded that its performance must be "premeditated" and not a "salvage" attempt. This is something which we can wholeheartedly agree. Analysis of our own results demonstrate that for a successful outcome it is essential that the decision to carry out the Fowler-Stephens procedure is taken early in the course of dissection, since retroperitoneal dissection damages the perivasal circulation. The "long loop" anatomy must be present, because this means there is a good collateral circulation so that the testicular vessels may safely be divided. The decision to divide the testicular vessels must be taken before further mobilization of processus vaginalis and peritoneum is initiated, to prevent damage to the testicular vascularization. In the absence of a "long loop" vas deferens and epididymis, there is a very real risk that division of the testicular vessels will result

in testicular atrophy and consequently, the Fowler-Stephens procedure should not be carried out.

6.4.2. Experience with staged procedure

a. *Introduction*

Judging from literature data, one would say that the results of the planned, staged orchiopexy are not disappointing. Table 5.1. (see 5.5.2.) shows that 149 of 175 (85%) staged operations performed by various authors were successful in that the undescended testis could be brought into the scrotum at the second operation.

b. *Results of staged procedure*

In the period April 1982 - April 1985, a second-stage procedure was carried out 15 times in ten prepuberal boys. In six boys (nine testes) the initial operation was carried out elsewhere by another surgeon, resulting in seven testes in a subcutaneous position outside the inguinal canal and two testes in the inguinal canal. In the other four boys (six testes), both operations were carried out by the author, with the first operation resulting in six testes lying in a subcutaneous position outside the inguinal canal. In all cases, the second operation was carried out at least 12 months after the first one. Table 6.4. gives the final results of these 15 staged operations (6 of them were also listed in table 6.2.). Ten testes were successfully brought into a high or low scrotal position. In one bilateral cryptorchid, neither testis was capable of being brought into the scrotum even at the second operation. Both testes were affixed in a subcutaneous position outside the inguinal canal. Microvascular testis transplantation may still be carried out in this boy at a later stage. Three boys had one testis each removed at the second-stage operation, because these testes were considerably smaller than the contralateral, descended testes and could not possibly be brought to the scrotum without severe traction to the testicular vessels.

c. *Discussion*

Dividing the boys that underwent staged procedures into two groups, with the boys that had both operations performed by the author in one and the remainder

Table 6.4. Results of 15 "second-stage" testicular operations; number of testes (number of boys).

first stage operation	total	orchi-dectomy	outside ing.canal	high scrotal	low scrotal
performed elsewhere	9 [6]	1 [1]	0 [0]	1 [1]	7 [4]
performed by author	6 [4]	2 [2]	2 [1]	2 [1]	0 [0]
Total	15 [10]	3 [3]	2 [1]	3 [2]	7 [4]

in the other group, has a marked effect on the results. For the group of boys that underwent the first operation elsewhere, the results seem to be much better. Eight of nine undescended testes first explored by another surgeon could be brought into the scrotum at the second operation. At this second operation, it always proved possible to carry out extensive retroperitoneal mobilization of the funiculus coupled with dissection of the processus vaginalis and thereby gain sufficient funicular length for a scrotal fixation of the testis without undue traction. In this respect it must be stressed that at the first operation of these high-lying testes the funiculus was obviously only partially mobilized if at all! We may safely assume that a second operation would not have been necessary if extensive funicular mobilization had taken place at the initial exploration. In contrast, in the six cases where both operations were carried out by the author, the first operation involved maximal retroperitoneal funicular mobilization and medialization. The results illustrate clearly that the gain in funicular length at the second operation is minimal. Not a single testis could be brought low into the scrotum. Two testes had to be left in a subcutaneous position outside the inguinal canal and orchidectomy was carried out twice (against one orchidectomy in the other group). Scarring with connective tissue formation around the testis and funiculus generally complicated the freeing of these structures and effectively inhibited any gain in funicular length.

A critical evaluation of the published series of successful staged procedures frequently show that patient selection or the extent of funiculolysis at the first operation were largely responsible for the success of the second operation. For example, it appears that a number of the second-stage procedures described by Persky and Albert (1971) were carried out in patients with an iatrogenically undescended testis secondary to an earlier operation for inguinal hernia. It stands to reason that dissection of the funiculus would return the testis to the scrotum in these cases. Firor (1971) goes so far as to describe retroperitoneal dissection of the funiculus as something that is only required at the second operation! In 1975 Corkery introduced a new technique whereby the funiculus is wrapped in a fellow sheet following funicolysis at the first operation, to prevent the formation of connective tissue around the funiculus and thereby simplify the second operation. However, for all six patients he operated on in this way, Corkery describes the teflon sheet as enveloping, apart from the testis itself, only the part of the funiculus that lies in the inguinal canal and not the retroperitoneal part of the funiculus. Consequently, it seems likely that the gain in funicular length achieved at the second operation, was the result of retroperitoneal funicular mobilization first carried out at that second stage. In their report of 60 staged procedures, Kiesewetter and coworkers (1981) describe as many as 28 second-stage operations of initially intrascrotal testes that had returned to a subcutaneous position in the inguinal area in the course of time. Here again, we wonder if the first operation included sufficient funiculolysis.

d. Indications for a staged procedure

Good results of a second-stage procedure are generally due to incomplete funiculolysis being carried out at the first operation. In our group of patients that had both operations performed by the author, the initial procedure did involve maximal retroperitoneal funiculolysis. In those cases the second operation provided practically no gain in funicular length and therefore the results were disappointing. Although these results are based on a small number of patients, we believe with Redman (1976) that "there is still no proof that later surgical manipulation of the testis allows the spermatic cord structures to resume again their elongation for the testicular descent".

In summary

A staged procedure is only indicated in case of an acquired high position of the testis, generally secondary to improperly executed, surgical correction of inguinal hernia; or incomplete mobilization of the funiculus at the initial surgical exploration. If the testis can be manipulated past the annulus externus all the way to the scrotal entrance before the second operation, there is a particularly good chance that this second operation will succeed in bringing the testis low into the scrotum. If the first operation involved extensive funiculolysis without this resulting in sufficient funicular length to bring the testis into the scrotum, then a "second-stage procedure" is pointless, unless this procedure involves autotransplantation of the testis employing microsurgical, vascular anastomoses (see 6.4.3.).

6.4.3. Experience with microvascular orchiopexy

In recent years, reports of orchiopexy with revascularization of the autotransplanted testis have appeared in the literature with increasing fequency (table 5.3., see 5.5.4.). In 1984, we published our own results with the microvascular technique and its application for the high-lying, undescended testis. The full text is reproduced below, with permission from the publishers.

a. MICROVASCULAR SURGICAL ORCHIOPEXY IN THE TREATMENT OF HIGH-LYING UNDESCENDED TESTES

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Summary

Extensive laboratory experiments in animals have led us to believe that autotransplantation of the testis in the human is feasible. To date, nine of our patients (aged 4-13 years) with undescended intra-abdominal testes have undergone autotransplantation. Using a microvascular surgical technique to anastomose the testicular vessels to the inferior epigastric vessels, it has been possible to place the testis in a scrotal position in every case. No postoperative complications have been noted. Follow-up varied from 9 to 18 months and no atrophy of the testis was observed in this period. Doppler investigations on all of the transplanted testes continue to demonstrate good arterial flow. The aim of surgery on the undescended testis is not only to increase the chances of fertility and to diminish the possibility of malignant transformation but also, more importantly perhaps, to prevent possible abnormal psychosexual development in the child.

Introduction

Approximately 9% of impalpable testes are located intra-abdominally or are absent (Scorer and Farrington, 1971). In 5% of such cases conventional surgical methods will not enable the testis to be brought into the scrotum. Several operative techniques to solve this problem have been reported. Some of the better known are staged orchiopexy and division of the spermatic vessels (Fowler and Stephens, 1959). Although good results have been achieved with these techniques, the number of abortive attempts leading to testicular atrophy is considerable. A review of our cases 6 months after division of the spermatic vessels revealed that testicular atrophy was present in 50%.

In 1976 Silber and Kelly described autotransplantation of an intra-abdominal testis using a microvascular surgical technique. Subsequently, other authors have also reported success using this method (Giuliani and Carmignani, 1983; O'Brien et al., 1983; Upton et al., 1983). Interest in organ and tissue transplantation has increased dramatically and microsurgical techniques have advanced so rapidly that it is now possible to anastomose blood vessels with a diameter of 0.5 mm (Acland, 1972; Hayhurst and O'Brien, 1975). These developments prompted us to attempt experimental microvascular orchiopexy in dogs. The results were reviewed by histological examination of the testes, plasma testosterone levels and patency of the anastomoses by angiographic studies (Garibyan, 1981). Having obtained sufficient technical expertise and continued success with the autotransplanted canine testis, we carried out the procedure in the human.

Patients and methods

Nine patients with unilateral intra-abdominal testes (age range 4-13 years) were operated upon. A higher than normal inguinal incision was made to avoid injury

to the epigastric vessels. Depending on the position of the testis, it was approached either intraperitoneally or retroperitoneally. The testis, epididymis, vas deferens and testicular vessels were first inspected and the vessels dissected free of the surrounding structures to the level of the lower pole of the kidney. The epigastric vessels were then isolated and the vein and artery cleanly divided under the operating microscope. Thereafter the testicular vessels were divided as high as possible and ligated proximally. The testicular artery and vein were anstomosed to the respective epigastric vessels under the microscope, avoiding any tension on the anastomoses. When great disparity in diameter between two vessels existed, spatulation of the end of the smaller vessel facilitated proper tension-free approximation. The diameter of the testicular vein varied from 0.8 to 1.4 mm and that of the artery from 0.5 to 0.9 mm. An end-to-end anastomosis was carried out under the operating microscope using a magnification of x5 and a zoom magnification of x25. A BV-6 or BV-4 needle and 10/0 atraumatic, interrupted, monofilament nylon sutures were used. The arterial anastomosis was completed first in order to limit the warm ischaemia time to a minimum. In order to obtain an intrascrotal testis it was sometimes necessary to mobilise the vas deferens, together with the surrounding peritoneum, as far as the posterior aspect of the bladder. The testis was fixed in the usual manner in a subcutaneous pouch as shown in figures 6.7. and 6.8. (figures 1 and 2 in original article). Details of the patients are summarised in table 6.5. (the only table in the original article). In seven patients the inguinal canal had been explored before the testis was transplanted and the testis identified as lying proximal to the inguinal ring or intra-abdominally. In the other two patients laparoscopy was undertaken before transplantation and the presence of the testis confirmed. Operating time varied from 2½ to 4 h and the warm ischaemia time varied from 30 to 40 min. Postoperatively, patients were kept in bed for a day and thereafter were gradually mobilised. Prophylactic antibiotics were not administered and no wound infections or other complications occurred. Hospitalisation varied from 5 to 7 days.

Results

Using this technique all testes could be brought into the scrotum. During the follow-up period, lasting from 10 to 18 months, no atrophy of the testis was encountered on clinical examination. However, in two patients a high scrotal testis was present because of a short vas deferens and in one patient residual induration of the spermatic cord persisted for as long as 6 months postoperatively. The testicular vessels are regularly checked by the Doppler flow technique and normal pulsations have been recorded to date.

Discussion

The procedure of testicular autotransplantation with microvascular anastomo-

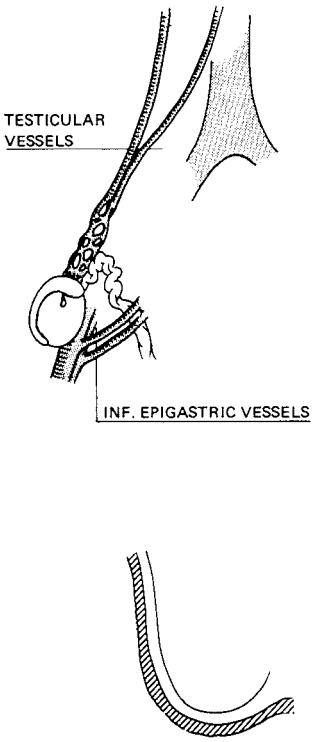


Figure 6.7. Diagram of a high-lying undescended testis.

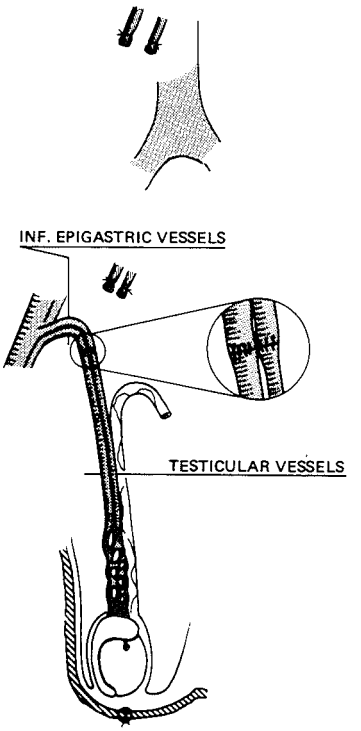


Figure 6.8. Diagram of a testicular autotransplantation.

sis is feasible and, while the immediate results appear to be good, the long-term results are still awaited. Our experience has convinced us that this procedure has a greater potential for success than vascular pedicle division or a staged orchiopexy. Microvascular techniques require considerable training and expertise. Consequently, testicular autotransplantation will probably have to remain for the foreseeable future a prerogative of specialised surgical centres.

The aim of surgery on the undescended testis is not only to increase the chances of fertility at a later date and to diminish the possibility of malignant transformation but also, more importantly perhaps, to prevent possible abnormal psychosexual development in the child. Several publications on the psychological effects of cryptorchidism on young children and pre- and post-pubertal adolescents with untreated non-descended testes have revealed that these patients suffer from psychological symptoms and disorders such as hyperactivity, learning difficulties, accident proneness, indecision, fear, immaturity, depression, passivity, a poor self-concept and confusion about body image and psychosexual identity (Blos, 1960; Yazmajian, 1966; Cytryn et al., 1967; Manley, 1982). The chances of emotional instability are greatly increased with the absence of a father figure as a suitable object of identification, if the mother is dominant or if the

Table 6.5. Results of testicular autotransplantation.

Patient no.	*Age at operation (years)*	*Side*	*Operation time (hours)*	*Follow-up location and condition of the testis*	*Doppler control of testicular vessels*	*Remarks*
1	$5\frac{2}{12}$	R	4	18 months normal	++	Unsuccessful conventional exploration 2 years previously
2	11	R	4	15 months normal	++	Long loop vas
3	$12\frac{8}{12}$	R	$3\frac{1}{2}$	$14\frac{1}{2}$ months high scrotal normal	++	Unsuccessful conventional exploration 3 years previously
4	$6\frac{7}{12}$	R	4	$12\frac{1}{2}$ months normal	++	
5	$11\frac{3}{12}$	R	3	12 months indurated sperm. cord	+	
6	$9\frac{8}{12}$	L	3	12 months normal	++	
7	$9\frac{3}{12}$	L	$2\frac{1}{2}$	11 months high scrotal normal	++	
8	$3\frac{5}{12}$	L	3	$10\frac{1}{2}$ months normal	++	
9	$10\frac{4}{12}$	R	$2\frac{1}{2}$	10 months normal	++	Contralateral atrophic testis after earlier orchiopexy with ligation of testicular vessels

parents try to hide their fears about the future development of their son under a cloak of secrecy and false pretences.

In view of the profound impact that cryptorchidism may have on an individual patient, medical intervention appears to be indicated about the third year of life, before the condition exercises its pathogenic influence and the child becomes aware of his anatomical aberration by comparison with his peers, and before the external genitals play a major part in the enhancement of body image and psychosexual identity.

When treatment of cryptorchidism takes place at a later age, almost inevitably a combination of anatomical correction and intensive psychotherapy is required (Blos, 1960).

Thus, restoration of normal anatomy in every case of cryptorchidism deserves the highest priority and in order to achieve this goal every improvement in surgical technique in the treatment of the undescended testis deserves to be implemented.

b. Recent evaluation of the results of microvascular orchiopexy

In the period 1982 - 1985, microvascular orchiopexy was carried out on 13 testes in 12 patients, including the patients mentioned above. Among the additional three boys, there was one with bilateral intra-abdominal testes. Initially, we limited the performance of microvascular orchiopexy to boys with unilateral high-lying testis. We first wanted to acquire sufficient expertise with this new modality, before tackling the bilateral condition. In this first attempt, the boy underwent two separate operations, one for each high-lying testis, with an interval of eight months.

A follow-up examination of all 12 boys was carried out in April 1985. The clinical results of the 13 autotransplantations are given in table 6.6. In patient number 5, residual induration of the spermatic cord persisted for six months postoperatively (table 6.5., see 6.4.3.a.), which may have been secondary to a haemorrhage in the funicular region. This testis was now obviously atrophic. In patients 4, 8 and 11, the transplanted testis had likewise atrophied. Regarding patient number 2, the transplanted testis was well palpable 19 months postoperatively, but obviously lagged behind in growth compared with the contralateral, normally descended testis. The transplanted testis of patient number 12 had a volume of 2 ml about six months postoperatively, but at the follow-up examination 12 months later, the volume appeared to be reduced to approximately 1 ml, even though the testis was still palpable high in the scrotum. This reduction in testicular volume is a clear sign of partial atrophy. Discounting this testis, 4 of 13 transplanted testes (31%) have become completely atrophic.

A closer look at the group of patients whose testes eventually atrophied after transplantation, clearly shows a connection between the occurrence of testicular atrophy and age at operation. With only one exception, all patients that were operated on under the age of seven years, suffered at least partial testicular atrophy. In the testes that had atrophied completely, pulsations in the testicular vessels were not longer audible, and therefore it seems likely that a disturbance of the circulation caused this testicular atrophy. The results also show that the transplanted testis may atrophy after some time has elapsed, i.e. longer than a year after the operation, as happened in patients 4 and 8. Consequently, it is no mere coincidence that the published series of microvascular testis transplantation with a long follow-up period (MacMahon et al., 1980; O'Brien et al., 1983; Upton et al., 1983) show a lower rate of ultimate success than the series with a shorter follow-up period (Martin and Salibian, 1980; Shioshvili, 1985).

c. Indications for microvascular orchiopexy

Long-term studies following microvascular testis transplantation are still lacking and therefore the indications for this intervention can only be given with reservations. At this stage, the "success" of this rather new modality can only be judged from the postoperative position, volume and consistency of the trans-

Table 6.6. Results of testicular autotransplantation including recent operations.

patient no.	age at operation (years)	side	operation time (hours)	follow-up location, condition of the testis	Doppler control of testicular vessels	testis volume (ml) R	L	remarks
1	5 5/12	R	4	32 months low scrotal normal	+ +	2	2	
2	11	R	4	19 months low scrotal normal	+ +	3	11	R testis small, well palpable
3	12 8/12	R	3 1/2	29 months high scrotal normal	+	2–3	3	
4	6 7/12	R	4	26 months – atrophic	–	<1	2	atrophic testis after >12 months
5	11 3/12	R	3	26 months – atrophic	–	2–3	<1	atrophic testis after indurated sperm. cord
6	9 8/12	L	3	12 months low scrotal normal	+ +	2–3	2–3	after 12 months patient "lost" for follow-up
7	9 3/12	L	2 1/2	25 months high scrotal normal	+ +	3	3	
8	3 5/12	L	3	22 months – atrophic	+	2	<1	atrophic testis after 15 months
9	10 4/12	R	2 1/2	23 months low scrotal normal	+ +	2	2–3	
10	12	R	3	18 months low scrotal normal	+ +	6	?	bilateral intra-abdominal testes R testis operated first
10	12 8/12	L	2 1/2	10 months high scrotal normal	+	6	3–4	L testis small compared to R one
11	4 10/12	L	3	8 months – atrophic	–	2	<1	atrophic testis after 3 months
12	5	R	3 1/2	12 months high scrotal	+ +	1–2	2	after 6 months: R testis 1 ml

planted testis. The author's own experience with this operation and follow-up examination coupled with the aforementioned literature data, suggest the following indications for the performance of microvascular orchiopexy:

1. *Bilateral high-lying testes* - Microvascular orchiopexy is primarily indicated for patients with bilaterally undescended testes that are incapable of being brought to the scrotum with conventional orchiopexy. The alternative would be bilateral orchidectomy, which is obviously unacceptable. The two testes

should never be transplanted at one and the same operation, because of the risk of testicular atrophy. If this occurs in the one testis that is transplanted, the contralateral, also high-lying testis can still be treated "conservatively" (e.g. affixing the testis in a subcutaneous position outside the inguinal canal) in order to prevent castration of the patient.

2. *Second-stage operation* - A second indication for this modality concerns the "second-stage operation" whereby the previously operated testis is still incapable of being brought to the scrotum. This depends on the extent of funiculolysis carried out at the first operation. If the funiculus has not been completely mobilized at the initial operation, a high funiculolysis at this second stage usually results in sufficient funicular length to achieve intrascrotal testis fixation without undue tension to the spermatic cord. However, microvascular anastomoses may still be required in some cases to achieve a scrotal position of the testis, for example when the mobilization of the funiculus at the first operation has been so complete that no further gain in length can possibly be obtained at the second operation.
3. *Unilateral high-lying testis* - Indications for microvascular transplantation of the unilateral high-lying testis are very limited. If exploration reveals a testis that clearly lags behind in growth compared with the normally descended, contralateral testis, or if there are obvious, macroscopic signs of a loss in continuity between the testis and the epididymis, orchidectomy will be the proper treatment. If the macroscopic appearance of testis and epididymis is normal, particularly regarding testicular shape and size, then microvascular transplantation is justified. The psychosexual aspect is important and the situation should be weighed carefully and individually for each patient.
4. *Age at operation* - Microvascular testis transplantation should at best not be carried out before the age of seven years (or even later in a boy that is small for size) when the diameter of the testicular vessels is such that the chance of a successful anastomosis is good. The ultimate results of testicular transplantation carried out at an early age, have been poor and there seems to be no pressing indication for an early performance. Histological investigation has revealed that any abnormalities that are present when the boy is two years old remain unchanged practically up till the age of puberty (Hedinger, 1982).

In summary

If a standard orchiopexy carried out at an early age results in insufficient funicular length to bring the testis to the scrotum without causing tension (this is particularly rare at an early age), then the testis should be fixed in a subcutaneous position to be followed by microvascular testis transplantation when the boy is at least seven years old. It is imperative that a boy who has undergone autotransplantation of one or both testes be followed for an extended period of time, at

least until a few years have elapsed after the onset of puberty. Regular checkups (1-2 times per year) are particularly essential in the peripuberal period, because in those years it will become apparent whether the growth of the transplanted testis is normal. If the growth of the transplanted testis lags behind in the presence of a normal contralateral testis, the abnormal testis had best be removed, whereupon a prosthesis may be inserted. Obviously such a decision can only be taken after extensive consultation with the boy and his parents.

6.5. SURGICAL TREATMENT OF CRYPTORCHID BOYS AFTER UNSUCCESSFUL HORMONAL TREATMENT (LHRH NASAL SPRAY)

6.5.1. Introduction

Our double-blind, placebo-controlled study of the efficacy of LHRH nasal spray revealed a rate of success of only 18% for this hormonal treatment (see chapter 4). Consequently, the intranasal administration of LHRH seems to have a limited role in the treatment protocol for boys with undescended testes. Surgical treatment, consisting of orchispexy following funiculolysis, will still be required in most cases. Several workers (Illig et al., 1977; Hadziselimovic, 1982; Karpe et al., 1983; Van der Meijden, 1984; Schwartz et al., 1985; Wit et al., 1985) have reported their findings at operation of boys that were treated unsuccessfully with LHRH. Only some of these authors (Karpe et al., 1983; Van der Meijden et al., 1984; Schwartz et al., 1985) ascribed the failure of hormonal treatment to the anatomical anomalies they found at surgery. Provided these anatomical anomalies are not too extensive, surgical treatment will usually be successful, resulting in a stable intrascrotal position of the testis.

In the last few decades several publications have appeared concerning the functional results and complications of surgical treatment of cryptorchidism. Some large studies, notably those carried out by Gross and Replogle (1963), Daum et al. (1969), Cywes et al. (1979), and Lynch et al. (1982), include a follow-up period of 10-20 years after orchiopexy usually performed when these boys were over six years old. However, the recommendation of recent years has increasingly been to treat boys with undescended testes at an earlier age, preferably after the second year of life. As this treatment will generally involve surgery, more insight is required into the results and complications of orchiopexy carried out in younger children.

The foregoing prompted a prospective study aiming to answer the following questions:

1. Would surgery reveal anatomical anomalies in the boys whose testes did not descend despite two courses of LHRH nasal spray, which would explain the failure of hormonal treatment?

2. What is the postoperative course after orchiopexy and what postoperative complications may occur?
3. What are the obvious results, as regards position and volume of the testis, immediately after orchiopexy and four months later?
4. Would age at orchiopexy influence the answers to questions 2 and 3?

6.5.2. Patients and methods

The study population included none other than boys from our double-blind, placebo-controlled study of the efficacy of LHRH nasal spray in whom this treatment had failed. During the study period (August 1983 - April 1985) 170 cryptorchid boys underwent surgery. Divided into the same three age groups as for the hormonal study (table 6.7.), there were 36 boys in group A (1-2 years), 72 in group B (2-6 years) and 62 in group C (6-12 years). There were 144 unilateral cryptorchids (69 rightsided, 75 leftsided) and 26 bilateral cryptorchids (table 6.8.).

The definitive protocol for this study was based on the evaluation of data from our pilot study (see 4.2.), which included registration of the most relevant normal and abnormal anatomical findings at orchiopexy. Various criteria played a part in the protocol. Significant differences were determined with the chi-square test.

Table 6.7. Age division for 170 boys undergoing surgery after unsuccessful LHRH therapy.

		mean age and standard deviation	
age group	boys	at admission	at surgery
A (1-2 yrs)	36	1.5 ± 0.3	2.1 ± 0.4
B (2-6 yrs)	72	4.1 ± 1.1	4.6 ± 1.4
C (6-12 yrs)	62	8.5 ± 1.5	9.2 ± 1.5
Total	170	5.2 ± 3.0	5.8 ± 3.1

Table 6.8. Laterality of cryptorchidism in 170 operated boys; number (%) of boys per age group.

	boys		A	B	C
unilateral R	69	(41)	10	31	28
unilateral L	75	(44)	21	31	23
bilateral	26	(15)	5	10	11
total	170	(100)	36	72	62

a. *Registration of most caudal testicular position immediately preceding surgery*

Immediately preceding the operation, the patient was examined under general anaesthesia and the most caudal position achieved with manipulation was defined as described in chapter 2 (2.3.2.b.):

- *testis impalpable;*
- *testis intermittently palpable* (emergent inguinal position);
- *testis palpable outside inguinal ring;*
- *testis palpable in scrotal entrance;*
- *testis palpable high in scrotum.*

If the testis proved capable of manipulation into a stable scrotal position, albeit high, the operation was cancelled.

b. Registration of peroperative testicular position

Location of testis at operation was defined as follows:

- *testis absent*: this could be a case of true anorchia whereby intraperitoneal exploration might reveal a blind-ending vas deferens or a funicular remnant, usually lying in the inguinal canal or just inside the annulus internus ("vanishing testis");
- *intra-abdominal testis*: the testis lies cranial to the annulus internus of the inguinal canal and is only located after opening the peritoneum;
- *testis in inguinal canal*: the testis lies caudal to the annulus internus, but cranial to the external annulus of the inguinal canal;
- *testis in external annulus*: the testis lies in or just outside the annulus externus and is located at exploration of the subcutaneous tissues caudal to the still unopened inguinal canal;
- *testis in superficial inguinal, ectopic position*: the testis is lying on the aponeurosis of the external abdominal muscle under the subcutaneous fascia of Scarpa and is located at exploration of the subcutaneous tissues outside the inguinal canal.

Scrotal entrance is not a stable testicular position, merely the result of testicular manipulation towards the scrotum. Consequently, no testis would be found in the scrotal entrance at operation.

c. Registration of anatomical findings

Processus vaginalis peritonei - the appearance of the processus vaginalis was defined as follows:

- wide open - the testis can move freely in the open processus vaginalis, ranging from the most caudal position to intra-peritoneal;
- slightly open - there is an open communication between the peritoneal cavity and that part of the processus vaginalis immediately surrounding the testis which always remains open, the tunica vaginalis;
- closed - the processus vaginalis has been obliterated and instead of an open communication between peritoneal cavity and tunica vaginalis, there is merely a fibrous band alongside the funiculus.

Epididymis - description of the epididymis was based on a modification of the

combined classification of Scorer and Farrington (1971), Marshall and Shermeta (1979) and Heath et al. (1984):

- epididymis absent;
- normal epididymis, caput and tail are firmly attached to the testis;
- partial separation of epididymis, the epididymis extends more than twice the length of the testis, the head is normally attached, but the tail may be unattached;
- complete separation of epididymis, there is a macroscopical, total separation of the head of the epididymis and the testis, while the tail is lying free;
- long-loop epididymis and vas deferens, the epididymis and vas are extended in a caudal direction (sometimes reaching the scrotum), while the testis is located in the inguinal canal or in the abdomen.

Vas deferens - regarding the vas deferens, registration focused on any disruption of vaso-vasal or vaso-epididymal continuity.

Testicular volume - after opening the tunica vaginalis, the volume of the testis was measured and registered in ml with a Prader orchiometer (see 2.3.1.) using the following scale: 1, 1, 1½, 2, 2½, 3 and > 3 ml.

Gubernacular remnant - a gubernacular remnant was identified during surgery by pulling funiculus, testis and epididymis gently in a cranial direction at a point where these structures are still surrounded by the tunica vaginalis. If this traction resulted in an obvious shrinking of scrotal skin, an identifiable gubernacular remnant was registered.

Cremaster muscle - we decided against a systematic description of the course of the cremaster muscle. The pilot study had revealed such a wide divergence in size and course of the individual cremasteric fibres that classification was hardly feasible.

d. Surgical procedures and registration of results

All operations were carried out by one and the same surgeon (F.H.). If there was a chance that no testis would be found at surgery, the boy and his parents were so informed beforehand. They were also told rightaway that if this suspicion proved correct, no testicular prosthesis would be inserted at this operation, as this could always be done at a later stage, even after the onset of puberty. Depending on the findings at operation, one of the following procedures was carried out:

- *orchidectomy or excision of funicular remnant;*
- *funiculolysis and orchiopexy,* consisting of:
- *standard orchiopexy with fixation of testis in a scrotal pouch* (Schoemaker technique as described under 6.5.3.d.), or

- *subcutaneous fixation of testis outside the inguinal canal,* or
- *orchiopexy with transection of the testicular vessels* (Fowler-Stephens technique as described under 5.5.3. and 6.4.1.), or
- *microvascular testis transplantation* (Silber technique as described under 5.5.4. and 6.4.3.).

All stitching was done with resorbable sutures. The inguinal incisions were closed intracutaneously with continuous sutures, while the scrotal incisions were closed transcutaneously with interrupted sutures.

Special forms, specifically designed for this purpose, were used to register surgical findings and results related to type of surgical intervention performed in each individual patient. A sample form is included in the appendix to chapter 2.

e. *Registration of postoperative complications*

Only complications that occurred within the first two weeks after operation were registered as postoperative complications.

Wound infections - these were divided into three subsets:
- redness and swelling of the wound, no pus visible;
- pus visible in the wound;
- other complications (haematoma, dehiscence, etc.).

Duration of hospital stay - for a standard orchiopexy, hospital stay usually lasted from admission on the day before the operation to discharge on the morning after. The number of times that a longer stay in hospital was required was duly registered. For a "nonstandard" orchiopexy, the duration of hospital stay varied and as such was not included in the evaluation.

f. *Registration during follow-up period*

All surgical patients were recalled for a follow-up examination at least four months after the surgical intervention. This examination served mainly to register testicular volume and position, enabling a comparison with the peroperative registration of these parameters.

6.5.3. Results

a. *Most caudal testicular position immediately preceding surgery*

Not one single testis of this study population was capable of manipulation into a stable scrotal position at the final pre-operative examination under general anaesthesia. Consequently, all 170 boys (with 196 undescended testes) underwent surgical intervention, during which no evidence was found of any effect of the earlier hormonal treatment. The most caudal position achieved immediately preceding the operation is listed per age group in table 6.9.

Table 6.9. Most caudal position of testis before operation; number (%) of testes per age group.

	A + B + C	A	B	C
not palpable	29 [15]	7 [17]	15 [18]	7 [10]
emergent inguinal	9 [4]	2 [5]	4 [5]	3 [4]
external annulus	115 [59]	28 [68]	55 [67]	32 [44]
scrotal entrance	39 [20]	4 [10]	7 [9]	28 [38]
high scrotal	4 [2]	0 [0]	1 [1]	3 [4]
Total	196 [100]	41 [100]	82 [100]	73 [100]

b. *Peroperative testicular position*

Table 6.10. gives the testicular position found at operation per age group. The testis was absent in 15 cases, including seven cases of (unilateral) true anorchia, and eight "vanishing testes". Regarding the testes that were present, there was a lack of even distribution for the three age groups as far as location was concerned. Group A had a higher percentage of testes in the inguinal canal than either B or C (34% vs 26% or 16%), while there were comparatively more testes in a superficial inguinal, ectopic position in group C, than in either A or B (40% vs 27% or 24%). In contrast, the testes located in the annulus externus, outside the inguinal canal, did not show a clear difference between the age groups. The number of testes located intra-abdominally was too small for a comparison between age groups, although group C had by far the lowest percentage.

Table 6.10. Peroperative testicular position; number (%) of testes per age group.

	A + B + C	A	B	C
anorchia	7 [4]	2 [5]	3 [4]	2 [3]
funicular remnant	8 [4]	2 [5]	4 [5]	2 [3]
intra-abdominal	8 [4]	2 [5]	5 [6]	1 [1]
inguinal canal	47 [24]	14 [34]	21 [26]	12 [16]
external annulus	66 [34]	10 [24]	29 [35]	27 [37]
superficial inguinal ectopia	60 [30]	11 [27]	20 [24]	29 [40]
Total	196 [100]	41 [100]	82 [100]	73 [100]

c. *Anatomical findings*

Processus vaginalis - table 6.11. lists the condition of the processus vaginalis found at operation per age group. There were significant differences between the three groups. A wide open processus vaginalis was found far more frequently in age groups A and B (54% and 56%) than in group C (26%). The processus vaginalis was obliterated in 47% of the testes in group C, but a closed processus vaginalis was significantly less frequent in the younger age groups (17% in A and 20% in B).

Epididymis - as shown in table 6.12.a., an abnormal epididymis was significantly more frequent in the groups A and B (58% and 56%) than in group C (25%).

Table 6.11. Condition of processus vaginalis in relation to number (%) of undescended testes per age group.

	A + B + C	A	B	C
wide open	87 [44]	22 [54]	46 [56]	19 [26]
slightly open	52 [27]	12 [29]	20 [24]	20 [27]
closed	57 [29]	7 [17]	16 [20]	34 [47]
Total	196 [100]	41 [100]	82 [100]	73 [100]

Table 6.12[a]. Condition of epididymis in relation to number (%) of undescended testes per age group.

	A + B + C	A	B	C
absent	15 [8]	4 [10]	7 [9]	4 [5]
normal	93 [47]	13 [32]	29 [35]	51 [70]
abnormal	88 [45]	24 [58]	46 [56]	18 [25]
Total	196 [100]	41 [100]	82 [100]	73 [100]

Table 6.12[b]. Type of epididymal anomaly in relation to number (%) of undescended testes per age group.

	A + B + C	A	B	C
absent	15 [8]	4 [10]	7 [9]	4 [5]
normal	93 [47]	13 [32]	29 [35]	51 [70]
partial separation	66 [34]	20 [49]	34 [41]	12 [17]
complete separation	12 [6]	3 [7]	5 [6]	4 [5]
long loop	10 [5]	1 [2]	7 [9]	2 [3]
Total	196 [100]	41 [100]	82 [100]	73 [100]

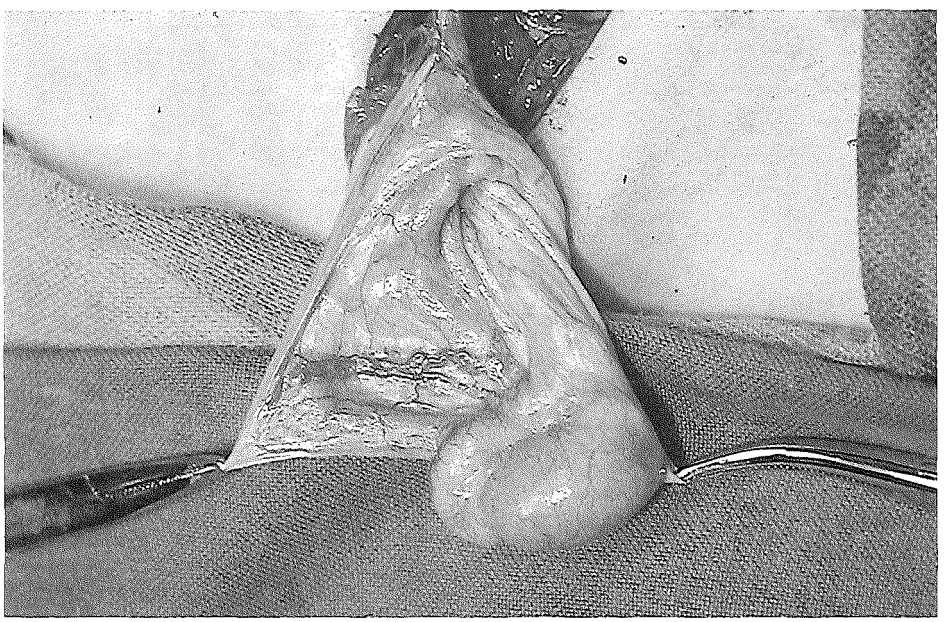


Figure 6.9. Epididymal deformities. Relation between testis and epididymis: normal.

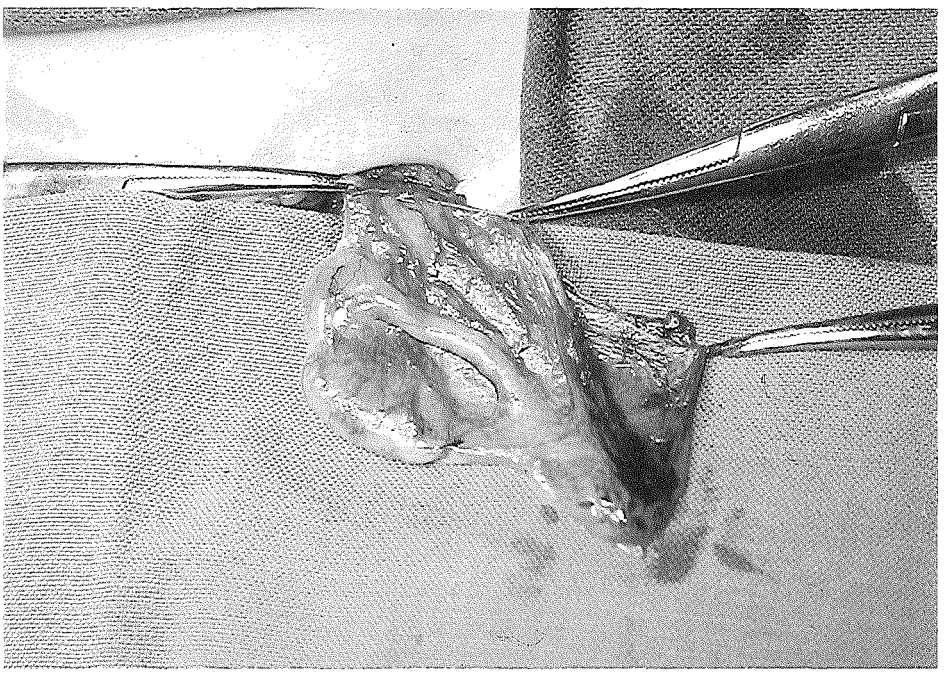


Figure 6.10. Epididymal deformities. Relation between testes and epididymis: partial separation.

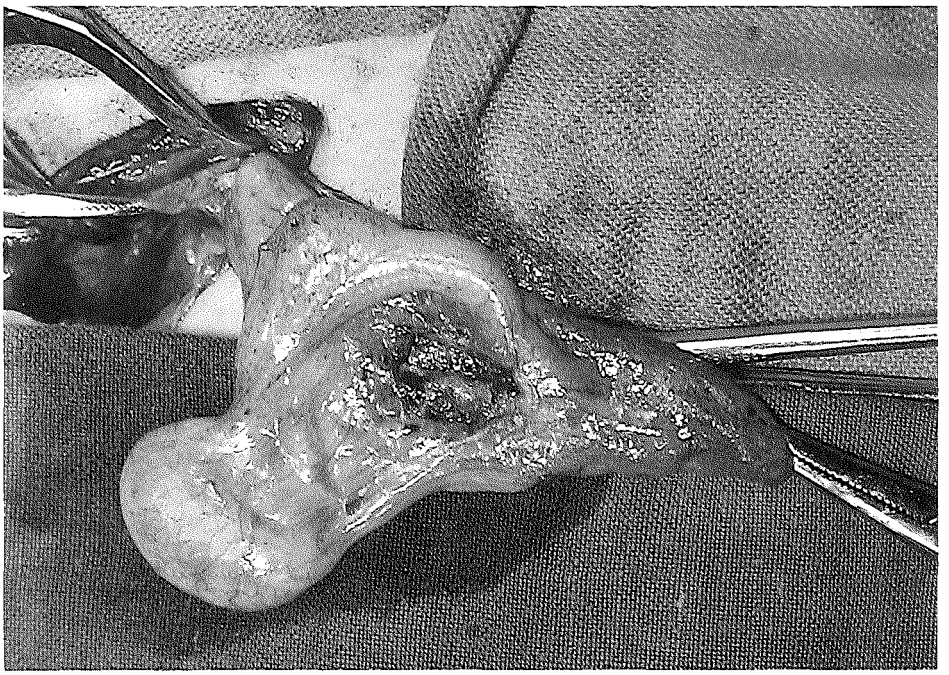


Figure 6.11. Epididymal deformities. Relation between testis and epididymis: complete separation.

Table 6.12.b. shows the diversity of epididymal abnormalities found at surgery, to some extent depicted in figure 6.9., 6.10. and 6.11.

Vas deferens - no disruption of vaso-vasal or vaso-epididymal continuity was ever found.

Testicular volume - a testicular volume exceeding 2 ml was comparatively more frequent in group C than in the groups A and B (table 6.13.). Markedly divergent testicular volumes as seen in compensatory testicular hypertrophy, were never registered.

Gubernacular remnant - here again, age group C differed from the other two age groups; the percentage of an identifiable gubernacular remnant amounted to 45% in age group C, against 22% in group A and 24% in group B (table 6.14.).

Table 6.13. Testicular volume; number (%) of testes per age group.

	A + B + C	A	B	C
absent	15 [8]	4 [10]	7 [8]	4 [5]
< 1 ml	9 [4]	4 [10]	3 [4]	2 [3]
1 ml	17 [9]	7 [17]	9 [11]	1 [1]
1.5 ml	90 [46]	23 [56]	46 [56]	21 [29]
2 ml	55 [28]	3 [7]	14 [17]	38 [52]
2.5 ml	10 [5]	0 [0]	3 [4]	7 [10]
Total	196 [100]	41 [100]	82 [100]	73 [100]

Table 6.14. Presence of gubernacular remnant in relation to number (%) of undescended testes per age group.

	A + B + C	A	B	C
identifiable	62 [32]	9 [22]	20 [24]	33 [45]
not identifiable	134 [68]	32 [78]	62 [76]	40 [55]
Total	196 [100]	41 [100]	82 [100]	73 [100]

Cremaster muscle - a clear distinction of individual fibres of the cremaster muscle was only possible if the testis had passed the inguinal canal. While these fibres could usually be distinguished surrounding a testis in the annulus externus, they were particularly conspicuous in case of superficial inguinal ectopia. The cremasteric fibres surrounding such a testis were markedly divergent in size and fanned out over the tunica vaginalis along the distal part of the funiculus. A systematic registration of these fibres was not feasible because of dissimilarity in course as well as development.

d. Surgical procedures and rates of success (table 6.15.)

Except for a strongly developed vena cremasterica, there were no particular

Table 6.15. Results of operation in relation to procedure; number (%) of undescended testes per age group.

	A + B + C	A	B	C
anorchia no therapy	7 [3.5]	2 [5]	3 [4]	2 [3]
excision funicular remnant	8 [4]	2 [5]	4 [5]	2 [3]
standard orchiopexy high scrotal	46 [23]	15 [36]	18 [22]	13 [18]
standard orchiopexy low scrotal	130 [66]	20 [49]	55 [67]	55 [75]
Fowler Stephens high scrotal	2 [1]	0 [0]	1 [1]	1 [1]
testis fixation outside inguinal canal	2 [1]	2 [5]	0 [0]	0 [0]
microvascular testis transplantation	1 [0.5]	0 [0]	1 [1]	0 [0]
Total	196 [100]	41 [100]	82 [100]	73 [100]

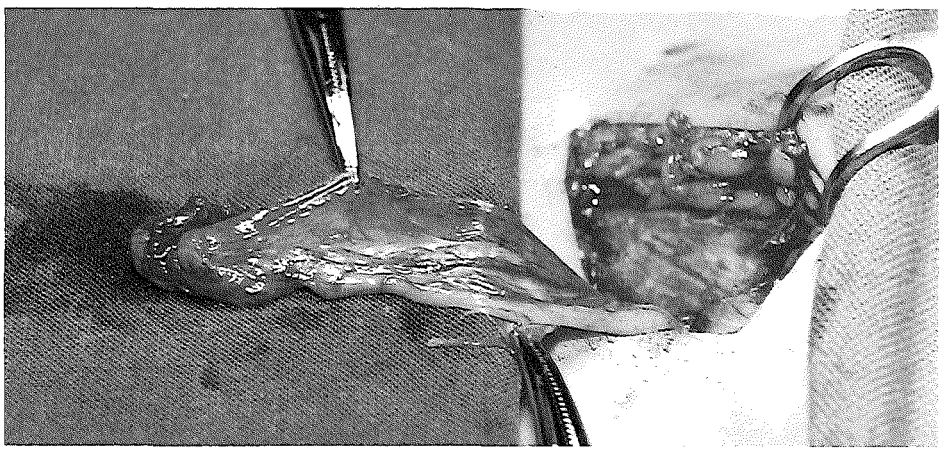


Figure 6.12. Macroscopical aspect of funicular remnant.

features that either facilitated or complicated operation. Orchidectomy was never performed. In the seven cases of true anorchia, surgery merely consisted of extensive intraperitoneal and extraperitoneal exploration. A funicular remnant was identified and excised in the eight cases where the testis had vanished. Figure 6.12. is a macroscopic presentation of such an excised funicular remnant. The vas deferens and testicular vessels ended blindly in these tissue remnants. Microscopically, the remnants consisted mainly of epididymis and connective tissue with calcifications, in the absence of any testicular tissue. These histological findings support the hypothesis that a "vanishing testis" is secondary to torsio testis occurring at a very early age, possibly even antenatally. In order to prevent torsion

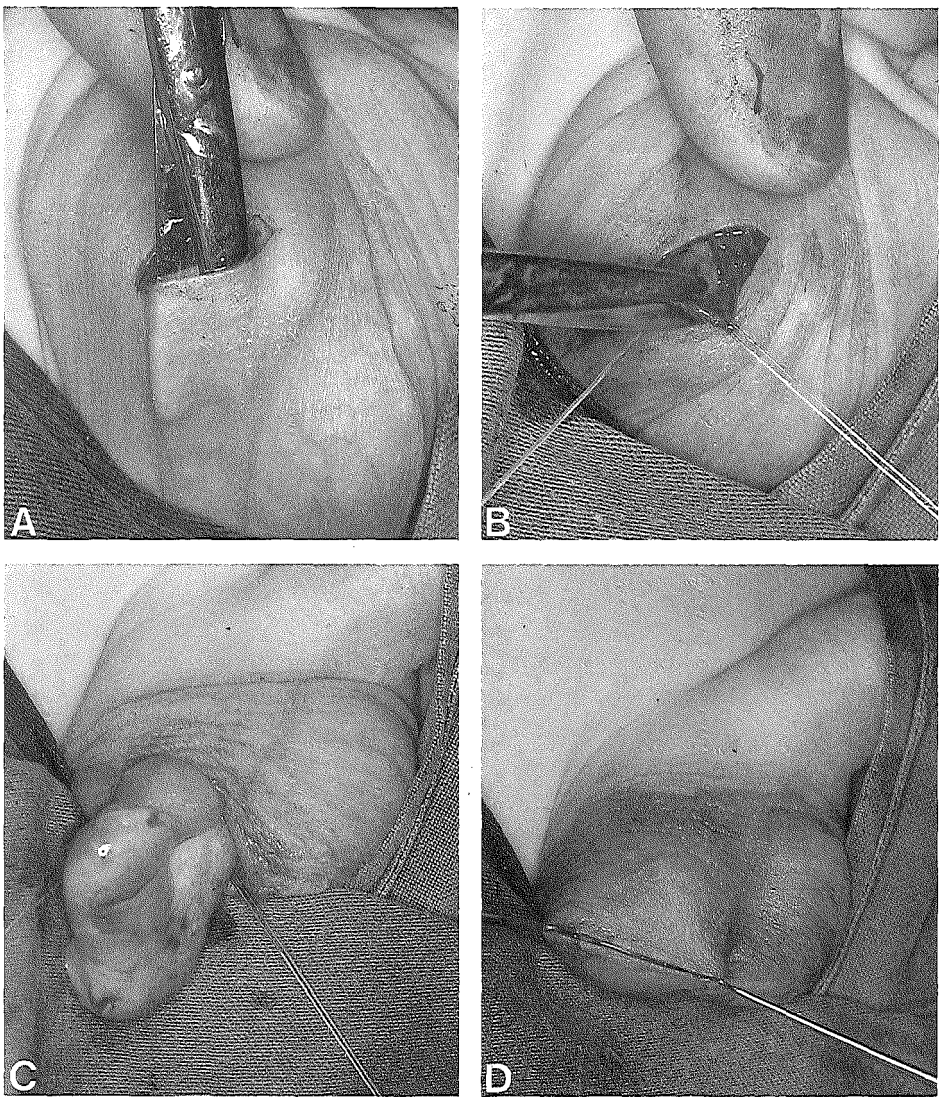


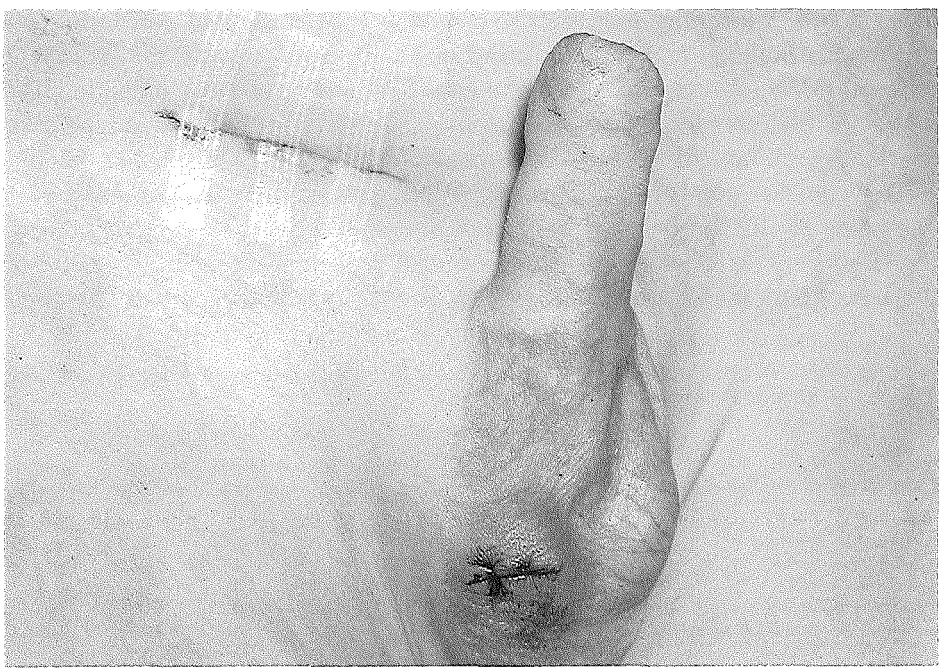
Figure 6.13. Standard orchiopexy after Schoemaker.

A. After routine orchiopexy via an inguinal approach, a scrotal pouch is created between the tunica dartos and the scrotal skin.
B. With two catgut retentionsutures the tunica dartos is secured and a small incision is then made between these sutures, so that the assisting finger becomes visible. A clamp is passed through this opening which pushes the finger away and then becomes visible in the wound.
C. This clamp carefully takes hold of the tunica albuginea of the testis. Subsequently the testis is pulled down through the scrotal opening.
D. After the catgut retentionsutures are stitched to the membranous layer covering the testis, two small one-pronged retractors are placed in the corners of the scrotal wound and the testis is placed in the space between the tunica dartos and the scrotal skin.
E. The scrotal skin is closed with a few thin catgut sutures. Closure of the fascia of the inguinal canal and the subcutaneous fascia with polyglycolic acid sutures. The skin of the inguinal incision is closed with a continuous intracuticular polyglycolic acid suture.

of the single remaining testis, the contralateral, fully descended testis was attached to the tunica dartos (window orchiopexy) in all eight boys.

In the 181 operations that did reveal a testis, the funiculus was first dissected free from the processus vaginalis, to obtain sufficient funicular length for an intrascrotal fixation of testis. This was followed by funiculolysis, which was generally extensive and except for the ectopic testes reached a high retro-peritoneal level. In case the testis was ectopic, there were obvious fibrous connections (gubernacular remnants) between on the one hand tunica vaginalis and caudal epididymis, and on the other hand pubic bone and scrotal entrance. Dissection of these fibrous connections, together with Scarpa's fascia and cremasteric fibres usually sufficed. If the processus vaginalis had not been obliterated, this also had to be dissected. Dissection of the cremasteric fibres added very little to the length of the funiculus.

A standard orchiopexy with fixation of the testis in a scrotal pouch according to Schoemaker (figure 6.13.) was performed on 176 testes (89% of total number), resulting in a low scrotal position for 130 testes (66%) altogether. A non-standard technique was required in three cases, twice consisting of Fowler-Stephens procedure and once of microvascular testis transplantation, all resulting in a high scrotal position. In one three year old bilateral cryptorchid, it proved impossible to get sufficient funicular length to achieve a scrotal position for either testis and therefore these testes were affixed subcutaneously outside the inguinal canal. Further descent would be attempted at a second-stage operation some time in the future.



6.5.4. Relationship between peroperative testicular position and other findings

By means of cross-sectional tables, we looked for any relationship between the peroperative testicular position and the diverse findings. For clarity's sake, we did not differentiate per age group in these cross-sectional tables.

a. *Peroperative testicular position in relation to most caudal position immediately preceding operation (table 6.16.)*

Cross-referencing the most caudal testicular position immediately preceding operation with the position found at surgery, supplied information regarding the mobility of these undescended testes. It appeared that the 47 testes located in the inguinal canal were rather mobile; 3 testes had even been capable of manipulation to the scrotal entrance, while 30 had been palpated in the annulus externus preceding surgery. These 30 testes were found to be lying very close to the annulus externus, which explains the pre-operative finding. The remaining 14 testes were located high in the inguinal canal, approximating the annulus internus and these testes had at best been intermittently palpable. The tunica vaginalis of all 47 testes ended at the level of the annulus externus.

Of the 66 testes located in the annulus externus, 51 had not been capable of descending further than this exit of the inguinal canal before the operation. Thirteen of these testes had been manipulated to the scrotal entrance and two even high into the scrotum. For 52 testes the distal part of the tunica vaginalis was found at the level of the pubic bone. In 12 cases it extended towards the scrotum, although never reaching deep into the scrotum. The 60 testes that were located in a superficial inguinal, ectopic position appeared to be very mobile; for 25 of these testes mobility extended to the scrotal entrance. The scrotal entrance itself was never obstructed in these cases; it appeared that the tunica vaginalis enveloping the rather mobile testis was the hampering factor. This was due to the fact that the tunica vaginalis ended at best right at the scrotal entrance over the os pubis, never extending to the bottom of the scrotum. Regarding the remaining 35 ectopic testes, surgery revealed a narrowing, sometimes even an actual obstruction, of the scrotal entrance. This was caused by Scarpa's fascia, which was stretched

Table 6.16. Peroperative testicular position in relation to most caudal position before operation; number of testes.

		most caudal testis position before operation				
peroperative testicular position	total	not palpable	emergent inguinal	external annulus	scrotal entrance	high scrotal
anorchia	7	7	0	0	0	0
funicular remnant	8	7	1	0	0	0
intra-abdominal	8	7	0	1	0	0
inguinal canal	47	8	6	30	3	0
external annulus	66	0	2	49	13	2
superficial inguinal ectopia	60	0	0	35	23	2
Total	196	29	9	115	39	4

tautly across the os pubis in its superficial course, leaving no room for the subcutaneously located testis to move to the scrotum. Instead of being continuous with the tunica dartos, which would be the normal course, Scarpa's fascia frequently ended at least partially at the os pubis, causing an obstruction or at least a narrowing of the scrotal entrance. This anatomical anomaly was frequently found in association of another abnormality, viz. a gubernacular remnant extending like a cord from the epididymis and testis to end on the os pubis or in the scrotal entrance also hampering testicular descent.

The registration of a most caudal position outside the inguinal canal (in the annulus externus) for one of the eight testes located intra-abdominally, was obviously based on a faulty observation.

b. Peroperative testicular position in relation to condition of processus vaginalis (table 6.17.)

Four of eight testes located intra-abdominally were associated with a wide open processus vaginalis which extended into the inguinal canal. No such extension was found in the other four cases. All 47 testes located in the inguinal canal were floating rather freely in a wide open processus vaginalis, the most caudal part of which was always found at the level of the annulus externus. As mentioned in section 6.5.3.c., there was a clear correlation between age and frequency of this testicular position: age group A > B > C. Over half (35 of 66) the testes located outside the inguinal canal, in the annulus externus, were also surrounded by a wide open processus vaginalis. In the remaining 31 cases the processus vaginalis had at least partially been obliterated. With one exception, all testes that had passed the inguinal canal and were located in a superficial inguinal, ectopic position, were associated with a slightly open or completely obliterated processus vaginalis. A slightly open processus vaginalis was particularly frequent in age group A; the processus vaginalis was either slightly open or completely obliterated in age group B, while in age group C the processus vaginalis was always obliterated.

Table 6.17. Peroperative testicular position in relation to condition of processus vaginalis; number of testes.

peroperative testicular position	total	processus vaginalis: wide open	processus vaginalis: slightly open	processus vaginalis: closed
anorchia	7	0	0	7
funicular remnant	8	0	8	0
intra-abdominal	8	4	0	4
inguinal canal	47	47	0	0
external annulus	66	35	19	12
superficial inguinal ectopia	60	1	25	34
Total	196	87	52	57

c. *Peroperative testicular position in relation to condition of epididymis*

As mentioned in section 6.5.3.c., anomalies of the epididymis were often noted. The frequency in relation to testicular position (table 6.18.) amounted to six out of eight (75%) intra-abdominal testes, 40 out of 47 (85%) testes located in the inguinal canal, and 37 out of 66 (56%) testes located in the annulus externus. In contrast, only five out of 60 (8%) testes in a superficial inguinal, ectopic position were associated with an abnormal epididymis.

Table 6.18. Peroperative testicular position in relation to condition of epididymis; number of testes.

		epididymis				
peroperative testicular position	total	absent	normal	partial separation	complete separation	long loop
anorchia	7	7	0	0	0	0
funicular remnant	8	8	0	0	0	0
intra-abdominal	8	0	2	4	0	2
inguinal canal	47	0	7	26	6	8
external annulus	66	0	29	31	6	0
superficial inguinal ectopia	60	0	55	5	0	0
Total	196	15	93	66	12	10

d. *Association of abnormal epididymis and open processus vaginalis*

It appeared that an abnormal epididymis was often associated with a wide open processus vaginalis (table 6.19.). This association was found most frequently when the testis was located in the inguinal canal.

Table 6.19. Condition of epididymis in relation to condition of processus vaginalis; number of testes.

		processus vaginalis		
epididymis	total	wide open	slightly open	closed
absent	15	0	8	7
normal	93	12	34	47
partial separation	66	53	10	3
complete separation	12	12	0	0
long loop	10	10	0	0
Total	196	87	52	57

e. *Peroperative testicular position in relation to testicular volume (table 6.20.)*

Relatively the largest testicular volume (2 ml and over) was registered for testes lying outside the inguinal canal. These testicular locations (annulus externus and superficial inguinal ectopic) were most frequent in age group C.

Table 6.20. Peroperative testicular position in relation to testicular volume; number of testes.

peroperative testicular position	total	testicular volume: absent	<1 ml	1 ml	1.5 ml	2 ml	2.5 ml
anorchia	7	7	0	0	0	0	0
funicular remnant	8	8	0	0	0	0	0
intra-abdominal	8	0	2	1	4	1	0
inguinal canal	47	0	3	5	32	7	2
external annulus	66	0	3	5	37	18	1
superficial inguinal ectopia	60	0	1	6	17	29	7
Total	196	15	9	17	90	55	10

f. Peroperative testicular position in relation to gubernacular remnant (table 6.21.)

With one exception, a gubernacular remnant was only identifiable if the testis had passed the inguinal canal. For 61 out of 126 testes located outside the inguinal canal, it proved possible to mobilize a distinct gubernacular remnant.

Table 6.21. Peroperative testicular position in relation to gubernacular remnant; number of testes.

peroperative testicular position	total	gubernacular remnant: identifiable yes	no
anorchia	7	0	7
funicular remnant	8	0	8
intra-abdominal	8	0	8
inguinal canal	47	1	46
external annulus	66	22	44
superficial inguinal ectopia	60	39	21
Total	196	62	134

g. Peroperative testicular position in relation to success of surgical intervention

Table 6.22. shows the relationship between peroperative testicular position and result of diverse surgical procedures. Excluding the 15 cases where surgery revealed absence of testis, all but two testes became intrascrotal. These two testes (see section 6.5.3.d.) had been intra-abdominal. The remainder of the intra-abdominal testes were successfully fixed in the scrotum, once requiring dissection of testicular vessels (Fowler-Stephens procedure) and once requiring microvascular transplantation. All 47 testes located in the inguinal canal were fixed in a predominantly low scrotal position. Dissection of testicular vessels was required for one of these testes, resulting in a high scrotal position. The majority (50 of 66) of the testes located outside the inguinal canal, in the annulus externus, were successfully placed in a low scrotal position without causing funicular traction.

For the remaining 16 testes, the result was a high scrotal position. The result was even better for the testes located in a superficial inguinal, ectopic position; a low scrotal position was achieved in all but five of these testes.

Table 6.22. Peroperative testicular position in relation to surgical procedure and results; number of testes.

peroperative location of testis	total	surgical procedure and result: exploration only	excision funicular remnant	standard orchiopexy: high scrotal	standard orchiopexy: low scrotal	Fowler-Stephens: high scrotal	microvasc. transpl.: high scrotal	fixation outside inguinal canal
anorchia	7	7	0	0	0	0	0	0
vanishing testis	8	0	8	0	0	0	0	0
intra-abdominal	8	0	0	3	1	1	1	2
inguinal canal	47	0	0	22	24	1	0	0
external annulus	66	0	0	16	50	0	0	0
superf. ing. ectopia	60	0	0	5	55	0	0	0
total	196	7	8	46	130	2	1	2

6.5.5. Postoperative course

a. *Wound-related complications*

Complications in connection with wound healing occurred in 9 of the 170 (5%) operated boys (table 6.23.). Three boys, two with a one-sided operation, one two-sided, had excessive swelling of the wound which was red and painful. Even so, wound healing proceeded normally. Wound healing was disturbed in six cases, secondary to wound dehiscence in one boy, and to wound drainage in five other boys. Wound drainage was required because of an abscess in three of these boys and to haematoma in the other two. All these wound-related complications occurred in the inguinal incisions. The scrotal incisions all healed without disturbance.

Table 6.23. Wound-related complications; number of testes per age group (number of boys).

Wound related complications	A + B + C	A	B	C
Redness and wound swelling	4 (3)	1	1	2*
Pus visible in wound	3 (3)	2	1	–
Haematoma	2 (2)	1	1	–
Wound dehiscence	1 (1)	–	–	1
Total	10 (9)	4	3	3

* in one boy

b. *Duration of hospital stay*

All but two of the 170 boys that underwent a testicular operation left the

hospital, in an ambulatory condition, the day after the operation. The longer hospital stay of the other two boys was caused by wound-related complications. Dehiscence of the wound occurred in one of them, while the other one developed haematoma on one side and therefore it took longer for him to be ambulatory. However, both boys were released from hospital within four days after surgery.

6.5.6. Follow-up period

Within the study period it was possible to re-examine 141 (83%) of the 170 boys, from four to ten months after the operation. All but the boys in whom surgery had revealed an absence of testis, were recalled for a checkup. Figure 6.14. gives, side by side, the position of the testis achieved at operation and the position noted at least four months postoperatively. At this follow-up examination, it appeared that 5 (4%) of the 114 testes that were surgically placed low in the scrotum, had now assumed a position high in the scrotum, while one testis was no longer in the scrotum, but palpable in the inguinal region instead. It was even more remarkable, that 25 (51%) of the 46 testes placed high in the scrotum at orchiopexy, were now obviously low in the scrotum. The two testes affixed outside the inguinal canal, remained well palpable in that same position.

With the aid of Prader's orchiometer, the volume of the operated testes was measured at the follow-up examination and compared with the peroperative registration (figure 6.15.). Three (2%) of the 162 testes appeared to have become atrophic. A slight increase of testicular volume was noted in 15 testes, which can hardly be significant in view of the fact that at follow-up the volume was measured through the scrotal skin, which was not the case at operation.

While neither the boys nor their parents were asked specifically what they thought of the hospital stay or the operation, it was remarkable that many of them told us of their own accord that they had gone through the whole experience with little discomfort. Particularly regarding the boys that were still very young at operation, the parents said that they had often been hard put to curb their son's activity when he came home from the hospital!

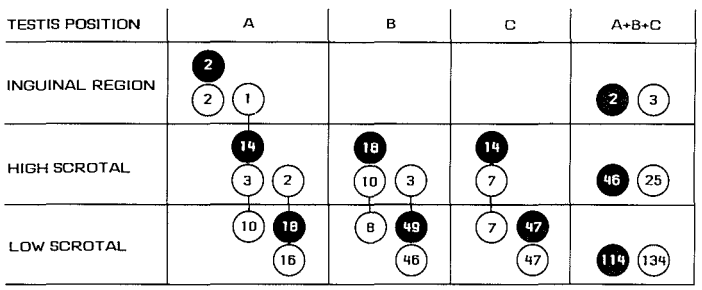


Figure 6.14. Follow-up findings; testicular position immediately after ● and 4-10 months after ○ orchiopexy; number of testes per age group.

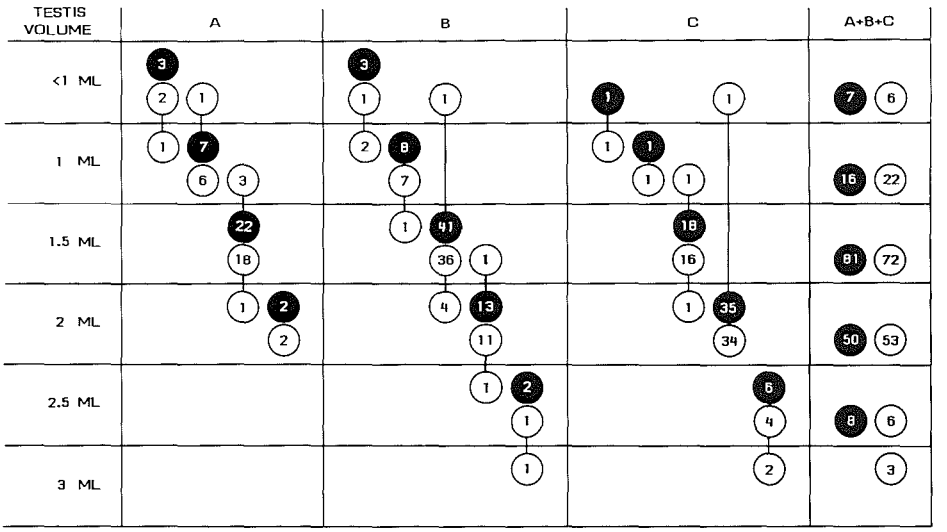


Figure 6.15 Follow-up findings; testicular volume immediately after ● and 4-10 months after ○ orchiopexy; numer of testes per age group.

6.5.7. Discussion

We found various anatomical anomalies that might explain the failure of testicular descent and which might also account for the failure of hormonal treatment. These anomalies can be summarized as follows:

1. An underdeveloped processus vaginalis extending no further than the annulus externus. This was found in 55 of the 196 testicular operations, concerning 47 testes in the inguinal canal and all eight intra-abdominal testes. The associated epididymal anomalies and the lack of obliteration of the processus vaginalis often found in these cases, demonstrate a true disruption of the developmental process of testicular descent.
2. Testes lying in the annulus externus or on top of the inguinal canal in association with:
   - a mechanical obstruction (gubernacular remnant or abnormal course of Scarpa's fascia); this was the case in 35 of the 60 testes found in a superficial inguinal, ectopic position;
   - a tunica vaginalis ending cranial to the scrotal entrance; the tunica vaginalis of 52 of the 66 testes located in the annulus externus ended at the distal level of the os pubis.

If we include the 15 explorations revealing the absence of a testis, then we come to a total of 157 of the 196 testicular operations (80%), whereby anatomical anomalies were found that would explain the failure of testicular descent, let alone failure of LHRH treatment. It is difficult to find an answer to the question which now arises, whether the other 39 operations were justified. Would these 39 testes have descended of their own accord at the onset of puberty? The retrospective evaluation of previous testicular position (see 4.3.5.) revealed that some of these testes had at one point been observed in a scrotal position. However, this information was received *after* the operation had been carried out, while none of these testes could possibly have been described as retractile at the pre-operative examination. Even under general anaesthesia, these testes could not be manipulated into a stable scrotal position. That finding certainly justified surgery!

6.5.8. Conclusions

The questions posed in the introduction may be answered as follows:

1. In 80% of the testicular operations, surgery revealed anatomical anomalies that explain the failure of LHRH treatment. The most common of these anomalies was incomplete development of the processus vaginalis, in that it did not extend into the scrotum, and an abnormal course of the subcutaneous fascia of Scarpa, which caused partial or complete obstruction of the scrotal entrance, preventing testicular descent into the scrotum. The latter anomaly was often found in association with a gubernacular remnant which also formed an obstruction to testicular descent.
2. For most of our 170 patients the postoperative course was uncomplicated. Wound-related complications occurred in 10 of the 196 operations carried out (5%), usually secondary to infection. The wound-related complications had no effect on subsequent position or volume of the testis (Infection of the wound never caused testicular atrophy).
3. In 179 of the 196 operations the testis could be placed in either a high (49) or low (130) scrotal position. At the follow-up examination (4-10 months postoperatively), it appeared that two per cent of the operated testes had atrophied. Approximately half the number of testes that had been affixed high in the scrotum were found in a low scrotal position at follow-up.
4. The age at which orchiopexy was carried out did not influence the operative results as regards position or volume of testis, postoperative complications, or the incidence of testicular atrophy. Particularly where the younger boys were concerned, neither the boys nor their parents had experienced any hardship in connection with the operation.

GENERAL DISCUSSION OF SURGICAL ASPECTS AND TREATMENT OF CRYPTORCHIDISM

REGARDING RETRACTILE TESTES

The consensus of opinion is that retractile testes do not require any treatment, because these testes assume a permanent intrascrotal position around puberty. Consequently, no follow-up would be required for a boy with a retractile testis (Woolley, 1979; Schoorl, 1982; Hirasing et al., 1982; Snick, 1984). However, there are clear indications that this supposition is not always correct. Villumsen and Zachau (1966), Privat (1978) and Atwell (1985) all noted that some testes that had been in a scrotal position, albeit retractile, were no longer in the scrotum after a number of years. Wyllie (1984) reported that 42 testes out of 100 that he himself had diagnosed as retractile, did require surgery five years later when a follow-up examination revealed that these testes had ascended. He also found that the volume of 27 of these 42 testes had decreased. He did not mention the surgical findings. Atwell was the only one to describe a possible cause of this testicular ascent. In a number of cases where the testis had ascended, he would find an open processus vaginalis at operation. It seemed feasible that in the course of further growth of the abdominal wall, for example, this open vaginal process had gradually become part of the peritoneum thereby lifting up the testis.

Boys with retractile testes do not require treatment, but they should be followed until puberty as their retractile testes may fail to assume a permanent scrotal position.

REGARDING IMPALPABLE TESTES

Impalpable testes are testes that are either located in the abdomen or in the inguinal canal. Histologically, these testes are generally more markedly divergent from normally descended testes than the undescended testes that have passed the inguinal canal. In contrast, hormonal function of the impalpable testis is usually normal. In case of bilateral impalpable testes, the presence of testicular tissue should first be ascertained by means of an HCG test, before surgical exploration is initiated.

Hormonal treatment of impalpable testes is pointless.

An immediate surgical approach has the advantage of having a diagnostic as well as a therapeutic function. Orchiopexy can generally be carried out at the initial surgical exploration. Inguinal exploration is clearly preferable to various nonsurgical, but frequently invasive, diagnostic evaluations that have been proposed in the literature, for the following reasons:

Inguinal exploration enables a more efficient examination of the anatomical

structures, while the peroperative findings enable a justified decision for orchiopexy or orchidectomy.
Inguinal exploration is much more economical than, for example, CT-scanning, angiography or laparoscopy, because these procedures generally do not render an inguinal exploration dispensable.

The impalpable testis can generally be brought into the scrotum with a standard orchiopexy, provided the funiculus is extensively mobilized and medialized. A special surgical technique is seldom required.
Orchiopexy with transection of the testicular vessels (Fowler-Stephens procedure) is only indicated in the presence of a "long loop" vas deferens and epididymis.

Sometimes orchiopexy has not resulted in a scrotal position of the testis, requiring a second operation. It may be that the initial operation did not include (sufficient) retroperitoneal mobilization of the funiculus. In that case the second operation should include extensive funiculolysis, which generally results in a scrotal position of the testis.
A second-stage, conventional orchiopexy is only indicated if there is uncertainty regarding the extent of the funiculolysis carried out at the first operation.

If the first operation did include adequate retroperitoneal mobilization without resulting in a scrotal position of the testis, then the second-stage procedure should involve autotransplantation of the testis.
A second-stage procedure is pointless, unless microvascular techniques can be employed to transplant the testis at the second operation.

Employing these microvascular techniques is also indicated in case of bilateral impalpable testes, whereby it is essential to operate one testis to begin with. Once that operation has proved successful, the same procedure should be carried out on the contralateral high-lying testis. If the first operation has resulted in testicular atrophy, then the contralateral testis should be left in an undescended (subcutaneous inguinal) position.
In case of bilateral impalpable testes, hormonal function should always prevail over the achievement of a scrotal position of the testis.
In agreement with the literature, we had relatively poor results with autotransplantation of the testis in very young boys. When the boy was under seven years of age at the time of operation, the autotransplanted testis seemed more prone to atrophy.
It is safer to carry out a microvascular orchiopexy after the seventh year of life.

No clear indications can be given for orchidectomy. Such an intervention requires an individual approach; there are no general guidelines. A combination of various factors, such as psyche and age of the patient, extent of testicular

atrophy, continuity of epididymis and testis, length of the testicular vessels, will indicate whether orchidectomy should be performed.
There are no guidelines for the decision to carry out an orchidectomy, but bilateral orchidectomy should be avoided at all cost.

If orchidectomy has taken place, a testicular prosthesis may be inserted. Here again, there are no guidelines, although it seems preferable to wait until the boy has reached puberty. An adult-sized prosthesis can then be inserted rightaway and the boy himself can be involved in the decision.

The treatment protocol for prepuberal boys with impalpable undescended testes is schematically presented in figure A.

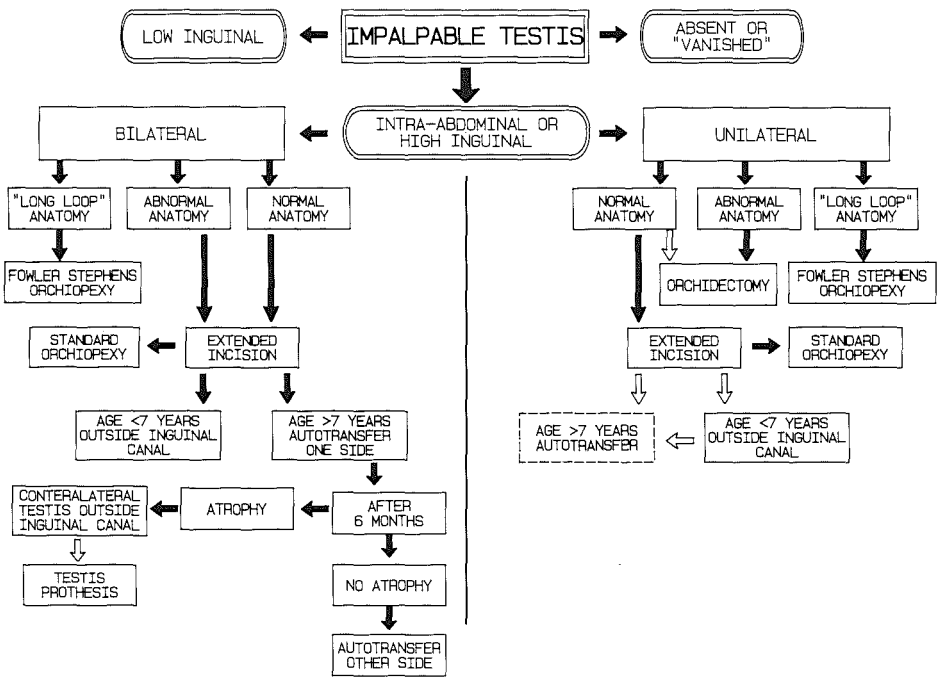


Figure A. Schematic presentation of surgical protocol for boys with impalpable testes.

REGARDING SURGICAL TREATMENT OF UNDESCENDED TESTES IN GENERAL

The anatomical anomalies found in this study should be viewed in the light of the normal process of testicular descent (chapter 1). Even though the mystery surrounding testicular descent has not been cleared up completely, several factors have been established. The epididymis plays a major part in testicular descent as demonstrated extensively by Hadziselimovic (1983[c]), Mininberg and Schlossberg

(1983), while the important role of hormonal influences has also become obvious (Wensing et al., 1980; Hadziselimovic, 1982). In his embryological study, Backhouse 1981) demonstrated that testicular descent can only proceed without disruption if the processus vaginalis extends into the scrotum (see 1.3.2., figure 1.5.).

Testicular descent requires ingrowth of the processus vaginalis into the gubernaculum, which is a mesenchymal mass filling the scrotum.

Once the testis has descended, the gubernaculum goes into regresssion (Wensing et al., 1980). The actual descent of the testis occurs during the last few months of fetal development. It is unlikely that this process would repeat itself after birth under influence of hormonal stimulation. For this reason, it is not likely that an undescended testis, particularly one located in the annulus externus with incomplete extension of the processus vaginalis, would assume a scrotal position as a result of LHRH treatment. Depending on the age of the child, the testis would have to traverse a distance of 4-8 cm caudally to reach the scrotum (Scorer and Farrington, 1971), while the development of the processus vaginalis and responding gubernaculum regression would have to occur anew. In laboratory animals with undescended testes, no such extension of the processus vaginalis nor gubernacular reaction was ever noted as a result of LHRH treatment (Wensing and Colenbrander, 1986).

Considering the important part played by the epididymis in testicular descent, it is not surprising that epididymal anomalies are often found in boys with disruption of testicular descent. In our patient series, epididymal anomalies amounted to 45%, which correlates well with the incidence of 32-66% reported for other studies (Marshall and Shermeta, 1979; Mininberg and Schlossberg, 1983; Heath et al., 1984.). Heath and coworkers found a wide open processus vaginalis in association with 21 of their 28 cases of epididymal anomalies (75%). In our series this amounted to 88% (75 of 88 cases).

The fact that the processus vaginalis remains open does not necessarily imply a disturbance of testicular descent.

Completely descended testes may be associated with various forms of hydrocele, which may be secondary to local anatomical relations (e.g. wide annulus externus). Noting and documenting epididymal anomalies at orchiopexy is essential in connection with fertility disorders that may appear later, possibly due to the lack of attachment between testis and epididymis. Microsurgical repair of the disrupted continuity between testis, epididymis and vas deferens may be required to improve the potential for fertility and in that case a record of anatomical structures will be invaluable (Heath et al., 1984).

In case of bilaterally undescended testes, it is particularly important to document the extent of attachment between testis and epididymis to facilitate subsequent surgical repair that may be required to enhance fertility.

Another aspect that warrants further discussion is the uneven distribution of the

diverse testicular positions found at operation. In age group A (1-2 years), we found significantly more testes in the inguinal canal than in the older boys (A > B > C), while a superficial inguinal, ectopic location was significantly more frequent in age group C (6-12 years) than in the younger boys (A < B < C). Age group B was obviously the intermediary between A and C as far as peroperative testis location was concerned. There are various possible explanations for the divergence in testicular position related to age group:

1. The divergence may be due to the manner of patient selection. The patients were not randomly assigned to diverse age groups; classification was subject to the pattern of referral of the general practitioners.
2. A testis which is at best intermittently palpable will be noticed at an earlier age. Consequently, chances are that referral will take place at a relatively young age. This may be the reason that so many testes were found in the inguinal canal in age group A.
3. It may well be that a testis which is initially located low in the inguinal canal, is pushed out of the inguinal canal and permanently into the annulus externus as a result of a toughening of the abdominal wall in the course of further development (possibly followed by obliteration of the processus vaginalis). This may explain the number of testes that are initially located in the inguinal canal but assume a lower position with passage of years. In these cases an incomplete development of the processus vaginalis would prevent complete descent into the scrotum.
4. A superficial inguinal, ectopic testicular position was found in all three age groups secondary to a partial or complete obstruction at the level of the scrotal entrance. The fact that this testicular position was found more frequently in age group C than in the younger boys may be due to the following reasons:
   - a testis which is initially located in the annulus externus may, in the course of a few years, be "pushed" out and on to the inguinal canal as a result of growth of the abdominal wall on the one hand and the abnormal anatomical relations of Scarpa's fascia cranio-lateral from the annulus externus on the other hand (figure B). This would explain the increased number of testes located in a superficial inguinal, ectopic position in the older age group.
   - a retractile testis is often located in the "subcutaneous inguinal pouch". It might well be that a testis with a tendency to move to this "pouch" may eventually find the way to the scrotum blocked. As a result of further growth of the various structures in the course of time, the scrotal entrance may have become relatively more narrow making passage less easy. Alternatively, the distal part of the tunica vaginalis of this initially retractile testis may to some extent have collapsed, as a result of which the testis (which has meanwhile also increased in size) cannot return to the scrotum through the tunica vaginalis. This premise furnishes an explanation for the apparent ascent of the testis.

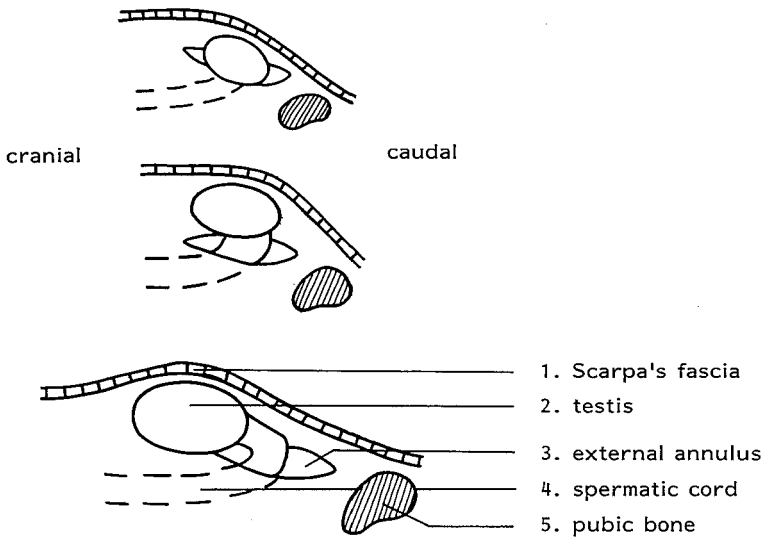


Figure B. Path of testicular ascent from external annulus into a superficial inguinal, ectopic position.

5. The occurrence of testicular ascent as a result of the extension of the processus vaginalis which has become continuous with the peritoneum, may also furnish an explanation for more testes being found subcutaneously outside the inguinal canal in age group C.

Few studies reported in the literature include a description of peroperative testicular position. Thorup and coworkers (1984) registered the peroperative testicular position in a number of boys that underwent surgery at various ages. In agreement with our study, he also found more testes in a superficial inguinal, ectopic position in the older boys, but he did not suggest an explanation for this finding. Privat (1978), Wyllie (1984) and Atwell (1985) described the ascent of initially intrascrotal testes.

The ultimate aim of surgical treatment, a scrotal position for the undescended testis, was achieved in this series of operations with few exceptions. Excluding the 15 absent testes, 179 of 181 undescended testes were successfully affixed high or low in the scrotum. This rate of success corresponds with similar good results of other large series of orchiopexies reported in the literature (Gross and Replogle, 1963; Daum, 1969; Cywes et al., 1979; Mengel and Hecker, 1979; Lynch et al., 1982; Thorup et al., 1984). A standard orchiopexy was carried out in most cases. It would actually be better to talk of orchiofunicolysis followed by orchiopexy, rather than just orchiopexy, to illustrate the essential step preceding the fixation of the testis in the scrotum, consisting of mobilization of the funiculus (Molenaar, 1982). Particu-

larly for testes located in the inguinal canal or higher, extensive mobilization of the funiculus is essential for a sufficient gain in length. If the testis is located subcutaneously, outside the inguinal canal, funiculolysis up to the annulus internus will usually result in sufficient funicular length for testis fixation in the scrotum without traction (Prentiss, 1960; Odiase et al., 1982). This procedure is shown schematically in figure C.

A correctly executed orchipexy includes adequate funiculolysis, whereby the funiculus is first teased free from the processus vaginalis and then mobilized as far as possible retroperitoneally to, enable a medial replacement and to gain enough funicular length for the testis to be affixed inside the scrotum.

The number of infections and other wound-related complications amounted to only five per cent (10 out of 196 operations). A close scrutiny of these complications does not lead to stringent, preventive measures. Infection of the wound had no effect on the vitality of the testis, as the follow-up examination never revealed atrophy of a testis whereby wound healing had been complicated. Altogether, testicular atrophy amounted to two per cent (3 out of 163), corresponding with 2-3% reported by other workers (Snijder and Chaffin, 1955; Gross and Jewitt, 1956;

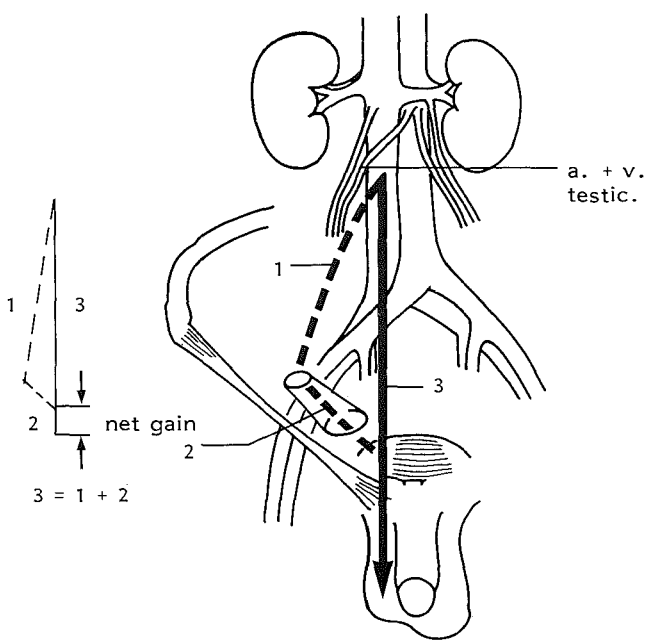


Figure C. Schematic presentation of orchiopexy including funiculolysis.

Hecker, 1976; Mengel, 1979). Wound infection and other wound-related complications occurred in all age groups, so that there could not have been a connection with e.g. urine or faeces contamination which would be a frequent occurrence in the younger age group.

None of the patients, nor their parents, experienced any hardship connected with the operation or the hospital stay. This was particularly so for the younger boys. Coupled with the good results of the operation in the younger boys, this shows that:

A standard orchiopexy may safely be carried out at a very young age.

Regarding the technical aspect of the operation, the younger the child, the more difficult the surgical intervention (Scholtmeijer, 1983).

For our patient series, the age at which surgery was carried out had no effect on the results. Our conclusion regarding the safety of performing orchiopexy in young infants is justified, despite the fact that our follow-up period was rather short (4-10 months). It remains to be seen whether the fertility of boys that underwent surgery at a very young age, is better than that for boys that were operated on when they were older.

No evidence has emerged from the literature indicating that surgery at a very young age would enhance the potential for fertility.

Orchiopexy in a very young child demands a great deal of surgical expertise. The funicular structures are very vulnerable at an early age, while the processus vaginalis is frequently wide open and very thin, complicating its required dissection from a long stretch of the funiculus without damage to the testicular vessels and the vas deferens.

The results of these series of operations have meanwhile occasioned a change in our protocol. We feel confident in reducing the duration of hospital stay to a minimum. Boys with an undescended testis that is well palpable are even undergoing surgery on a day-care basis. Rather than causing any problems, this seems to enhance recovery.

Orchiopexy requires only a short stay in hospital. Recovery will proceed much better at home.

We have also learned from these studies that the inability to place a testis low in the scrotum at surgery, is no cause for concern. Follow-up examination revealed that a number of testes that had been affixed high in the scrotum, had assumed a low scrotal position of their own accord.

A testis placed high in the scrotum at surgery may subsequently assume a low scrotal position of its own accord.

Finally, it is important to mention that, in case exploration reveals a "vanished

testis", the contralateral testis should be affixed on the tunica dartos to prevent torsion of that single remaining testis. This is because the possibly antenatal occurrence of torsio testis may have caused the vanishing of the "undescended" testis (Abeyaratne et al., 1969). At contralateral exploration in 13 boys with a unilateral vanished testis, Harris et al. (1982) found an abnormally loose attachment between testis and epididymis (bell-clapper deformity) in 11 of these boys. This anatomical anomaly is associated with an increased risk of torsio testis (Bellinger, 1985). Window orchiopexy, as described by Morse and Hollobaug in 1977, is a good technique for affixing the solitary testis transscrotally.

In case of a "vanished" testis, the contralateral testis should be affixed on the tunica dartos to prevent subsequent torsion of that single remaining testis.

CHAPTER 7

GENERAL CONCLUSIONS AND GUIDELINES FOR THE FUTURE

7.1. INTRODUCTION

As outlined in the first chapter of this dissertation, we have carried out a joint endocrinological and surgical investigation of the entity of cryptorchidism. The paediatrician and the paediatric surgeon have each argued their case and now the time has come for the summing up. WHY did we carry out such an extensive review of the literature? HOW did we apply literature data to our clinical studies? And finally, WHEN did we begin to find answers to the questions that embodied our motivation?

An extensive review of the literature was required in the first place to enable presentation of a clear profile of the anatomy, physiology, and pathophysiology of testicular descent. Secondly, a critical study of the literature would throw light on the implications of a disturbance of testicular descent indicating the need for, and possibly the type of treatment. Lastly, the data gleaned from the literature would form a basis for comparison with out findings. Coming through a maze of agreement and, at times, disagreement with the literature, we finally saw our way clear to translate our findings into a protocol for nonscrotal testes as well as proposals for the future.

7.2. WHY SHOULD CRYPTORCHIDISM BE TREATED?

Boys with unilateral or bilateral undescended testes should be treated for the following reasons:

- There is a definite connection between a disturbance of testicular descent and infertility. The risk of infertility is that much greater if both testes are undescended. The location of the undescended testis also influences the potential for fertility. Intra-abdominal testes have far less chance of fertility than, for example, testes lying subcutaneously in the inguinal region.
- Normal anatomical relations of the genitalia are extremely important for an undisturbed psychosexual development of the boys concerned.
- A testicular tumour, albeit a rare occurrence, is more frequently found in an undescended than in a normally descended testis. Bringing the testes into a scrotal position renders the previously undescended testis more accessible for

examination, instantly revealing a tumour that might occur just the same, which could then be treated without delay.

7.3. HOW SHOULD CRYPTORCHIDISM BE TREATED?

Before any kind of treatment can be initiated, the proper diagnosis has to be made. To reach the proper diagnosis, the cryptorchid boy has to be examined at least twice, following the procedure described in chapter 2. The type of treatment depends to a large extent on the diagnostic findings. The results of our study of the efficacy of LHRH nasal spray show that this hormonal treatment may be successful for undescended testes that have emerged from the inguinal canal, although a placebo effect cannot be excluded. It appeared that the rate of success was highest for low-lying testes capable of manipulation to the scrotal entrance or even lower, at physical examination. In our patient series such low testicular positions were most prominent in boys with an age range of 6 to 12 years. LHRH therapy seemed to be least successful in the younger boys, which may be due to the fact that a low testicular position was relatively less frequent in the younger age groups. Our dosage schedule for LHRH administration consisted of: one puff (200 μg) in each nostril three times a day before meals for a period of four weeks; four weeks respite; another four weeks of LHRH administration if required. Data on lengthy follow-up periods for LHRH treatment being scarce, we feel the successfully treated boys should have regular checkups, say once a year, until they have reached puberty.

If hormonal treatment is indicated, we feel LHRH is preferable to HCG treatment, for the following reasons:

- The administration of LHRH nasal spray is less invasive and therefore less burdensome for the child than the intramuscular HCG injection.
- With LHRH nasal spray there are fewer side effects during treatment.
- The percentage of success is similar for either modality.

We have no personal experience of HCG treatment following unsuccessful LHRH therapy. However, comparing the results of these two modalities as well as the factors contributing to the success of either modality (see chapter 4), the chances of HCG treatment succeeding where LHRH therapy has failed seem very slim.

Our patients that did not have testicular descent with LHRH therapy underwent surgical treatment. In most cases, surgery revealed anatomical anomalies which had prevented testicular descent and would account for the failure of hormonal treatment. This fact also argues against any attempt to achieve testicular descent with HCG treatment after failure of LHRH therapy.

There are cases where hormonal treatment of any kind is doomed to fail, demonstrating clearly the paramountcy of a proper diagnosis. The child should be examined by someone with an anatomic insight of the inguinal region, not

only to distinguish between a retractile and a truly undescended one, but even more so to differentiate:

- an ectopic testis, which always lies subcutaneously and is therefore palpable. Hormonal treatment is pointless; ectopic testes have to be surgically corrected.
- a testis that is intermittently palpable; lying in the inguinal canal this testis will emerge with gentle manipulation. This testis needs surgical intervention.
- a testis that will not emerge from the inguinal canal, remaining impalpable; this testis may lie high in the inguinal canal or intra-abdominal and always requires surgical treatment.

We feel the method of choice for locating the impalpable testis is inguinal exploration. This method has the advantage that orchiopexy can generally follow immediately upon location of the testis at the same operation. Special surgical procedures may be required in some cases, for example, if inguinal exploration reveals an intra-abdominal testis, microvascular orchiopexy may be required. Our results indicate that this type of operation had best be carried out after the seventh year of life.

Naturally, all these operations should only be carried out by surgeons that are familiar with dissection of the fragile structures in the inguinal region of young children; in other words, paediatric surgeons or paediatric urologists.

7.4. WHEN SHOULD CRYPTORCHIDISM BE TREATED?

A proper diagnosis is an essential element in determining the time of treatment. It is also important to have complete medical records of the patient; documentation of previous testicular positions should be available (supplied by well-baby clinics and school medical officers, etc.). These data together with the age of the boy will decide the timing of treatment.

Boys referred for unilateral or bilateral undescended testes before the second year of life

Provided a definite diagnosis has been reached, the best time for initiating treatment is when the boy is approximately two years old. There is no real proof that early treatment is the best course of action, but there are a number of factors that argue against suspension of treatment:

- The younger the child, the easier it is to diagnose truly undescended testes, because the retractility of the cremaster muscle is less pronounced. In other words, the shorter the interval between birth and moment of referral, the less likely the chance of a retractile testis being diagnosed as undescended. Apart from that, documentation of previous testicular position, e.g. at birth, is more likely to be available, the younger the child.

- Delayed, spontaneous descent is extremely unlikely to occur after the first year of life.
- After the second year of life, obvious histological changes occur in the germinal epithelium of the undescended testis. It is not yet known to what extent these changes are reversible.
- Early placement of the testis in the scrotum reduces the negative effect that a higher temperature may have on potential fertility.
- There are indications that testicular tumours occur less frequently in initially nonscrotal testes that are operated on at an early age.
- Early treatment is also preferable from a psychological point of view, because the anomaly in the genital region will have been corrected before the boy himself discovers that he is *"different"*. This reduces the risk of a disturbance of the boy's psychosexual development.

Boys that are referred for unilateral or bilateral undescended testes after the second year of life

If the boy is over two years old (but still prepuberal) upon referral, there are few pressing reasons for initiating immediate treatment. Histological investigation of the germinal epithelium of undescended testes at various stages of development, has revealed that the changes are not progressive. The reduction in the number of spermatogonia per tubule stabilizes after the second year of life and no further decrease is likely to occur (see figures 5.2. and 5.3.). Consequently, the timing of treatment for the age period past two years to puberty, can be adapted to personal circumstances, such as scholastic achievement; family situations; the extent to which the boy and his parents are able to cope, psychologically, with his physical abnormality.

Suspending treatment will provide more time to ensure that the proper diagnosis has been reached. In this age period it may be difficult to differentiate between a retractile and a truly undescended testis.

Regardless of the time of referral, microvascular orchiopexy had best be carried out after the seventh year of life (see 7.3.).

7.5. PROTOCOL FOR THE TREATMENT OF NONSCROTAL TESTES

Based on the results of our studies, we have drawn up a protocol for the treatment of boys with nonscrotal testes. This protocol is schematically presented in page 333 (foldout), which requires some elaboration.

During the *diagnostic phase*, the boy should be examined several times (at least twice) by the same examiner, following the proper procedure as defined in chapter 2. A number of questions have to be answered before proceeding on to the *treatment phase*. Following the treatment phase, or if treatment can be

dispensed with, a decision has to be taken regarding the *follow-up phase*. The questions that have to be answered are:

1. Is the testis truly undescended or retractile? A testis that can be manipulated into a stable scrotal position is retractile. Although the retractile testis requires no treatment, we feel that a follow-up phase is essential. The boy should have an annual checkup until he reaches puberty, because testicular ascent may occur.
2. If the testis is truly undescended, the question arises whether there are other, associated anomalies. The cryptorchid boy requires a complete workup. In case of chromosomal or dysmorphic syndromes, treatment of cryptorchidism will depend on the prognosis for this associated anomaly. Life expectancy will play an important part in the decision. In case of inguinal hernia, surgical treatment is indicated for both unilateral and bilateral undescended testes.
3. If the cryptorchid boy is otherwise normal, the question is whether there are any signs of the onset of puberty. If so, surgical treatment should be carried out without delay, regardless of laterality of the undescended testis.
4. If the cryptorchid boy is prepuberal, the question concerns the treatment of choice. The *most caudal position* to which the testis can be manipulated figures very prominently in this decision. Impalpable testes cannot be manipulated and always require surgery. In case of bilateral impalpable testes, an HCG test has to be carried out before surgery is initiated. A positive test indicates functioning Leydig cells, excluding a total absence of testicular tissue. In case of intermittently palpable, or ectopic testes, surgical treatment is also indicated. If the testis has emerged from the inguinal canal and can be manipulated to a lower position, hormonal treatment may be considered (preferably consisting of LHRH nasal spray). If this hormonal treatment fails to induce complete testicular descent, surgical treatment should be carried out without too much of a delay.

A follow-up phase is required for all successfully treated boys, regardless of type of treatment. For the boys that had complete testicular descent with hormonal treatment, this is necessary because experience with LHRH nasal spray is still short-lived. For the surgically treated boys, this is necessary to assess short-term as well as long-term results of the operation.

We have not come to a definite decision regarding the expediency of a repeat course of LHRH nasal spray in case of a "relapse". If the undescended testis did assume an intrascrotal position or at least became retractile with hormonal treatment but has subsequently returned to its undescended position, suspension of treatment until puberty seems justified.

The schematic presentation of the treatment protocol does not include any indication of timing of treatment. This aspect has been dealt with extensively in section 7.4. The extent to which previous documentation of testicular position

should play a part in the treatment protocol will be discussed in the next section, dealing with proposals for the future.

In summary

If the boy is under two years old at referral, treatment should take place around age two. If he is over two years old, there is no urgency and treatment may be suspended, subject to personal circumstances. For a boy that is over two years old, it is more important to allow sufficient time for a proper diagnosis.

7.6. PROPOSALS

Our clinical studies may have answered the questions that motivated our investigation, but in the process our findings have raised new questions, such as: Should all prepuberal boys with undescended testes be treated or would a "wait-and-see" approach be the wiser course in some cases?

Consideration of previous documentation of testicular position enables differentiation between testes that have never had a scrotal position and testes that have at one point been intrascrotal or at least retractile, even though the present position is definitely nonscrotal. At this point in time, we are unable to state categorically one way or the other whether the latter group of testes should be treated, or whether it would be better to wait and see if these testes will assume a scrotal position of their own accord after the onset of puberty.

Our retrospective evaluation of previous testicular positions (see 4.3.5.) has revealed positive information for a large number (43%) of boys that had complete testicular descent with LHRH treatment. In other words, their undescended testes had at one point been documented as intrascrotal or retractile. This percentage was very much lower (17%) in the group of boys that did not have testicular descent with hormonal treatment. Considering the fact that the majority of the success group consisted of boys whose undescended testes could be manipulated to at least the scrotal entrance, it may well be that anyone of this group, given positive information, need not have been treated. Extensive, longitudinal investigation would be required to settle this issue conclusively. Consequently, we have been conducting another clinical study from the beginning of 1985, whereby boys with undescended testes that can be manipulated to the scrotal entrance and whose history reveals previous documentation of a scrotal position or retractility of the undescended testis, are not treated but followed closely until the age of puberty. At the time of writing, there are some slight indications that this "wait-and-see" approach is correct, but it is definitely too early to draw any conclusions.

The results of LHRH therapy coupled with those of the retrospective evaluation have shown that a large percentage of success concerns testes that have previously been retractile or intrascrotal, whereby subsequently a (transient?) ascent has occurred. This has raised the question whether the LHRH therapy affects the

cremaster muscle. To investigate this aspect, we have recently started an investigation of the feasibility of binding sites in the cremaster muscle for LHRH, gonadotropins, or androgens.

In conclusion, we want to stress the paramountcy of a proper physical examination and consequently the proper diagnosis, amidst all questions that may remain unresolved concerning cause and effect of undescended testes. Proper examination and diagnosis, coupled with proper documentation of this diagnosis, may prevent needless treatment. As early as 1938, Sir Denis Browne said it all in his inimitable, tongue-in-cheek way:

"There are few conditions upon which more contradictory diagnosis and advice can be obtained from the medical profession than those which fall into the vague and elastic category of "undescended testicle". I know a parent who was told that her son's testicles:

a. Needed immediate operation if he were not to be practically a eunuch (A surgeon of great experience).
b. Should be left for five years to see what happened (Another reputable surgeon).
c. Should be treated by hormone injections (A physician).
d. Should on no account be operated upon, as the operation invariably failed (The family general practitioner).
e. Were normal (Myself).
f. Were held up owing to a displaced vertebra (An osteopath.).

it is hardly necessary to say that the last diagnosis and the treatment that followed are now held responsible for the present obviously satisfactory condition of affairs."

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CURRICULUM VITAE

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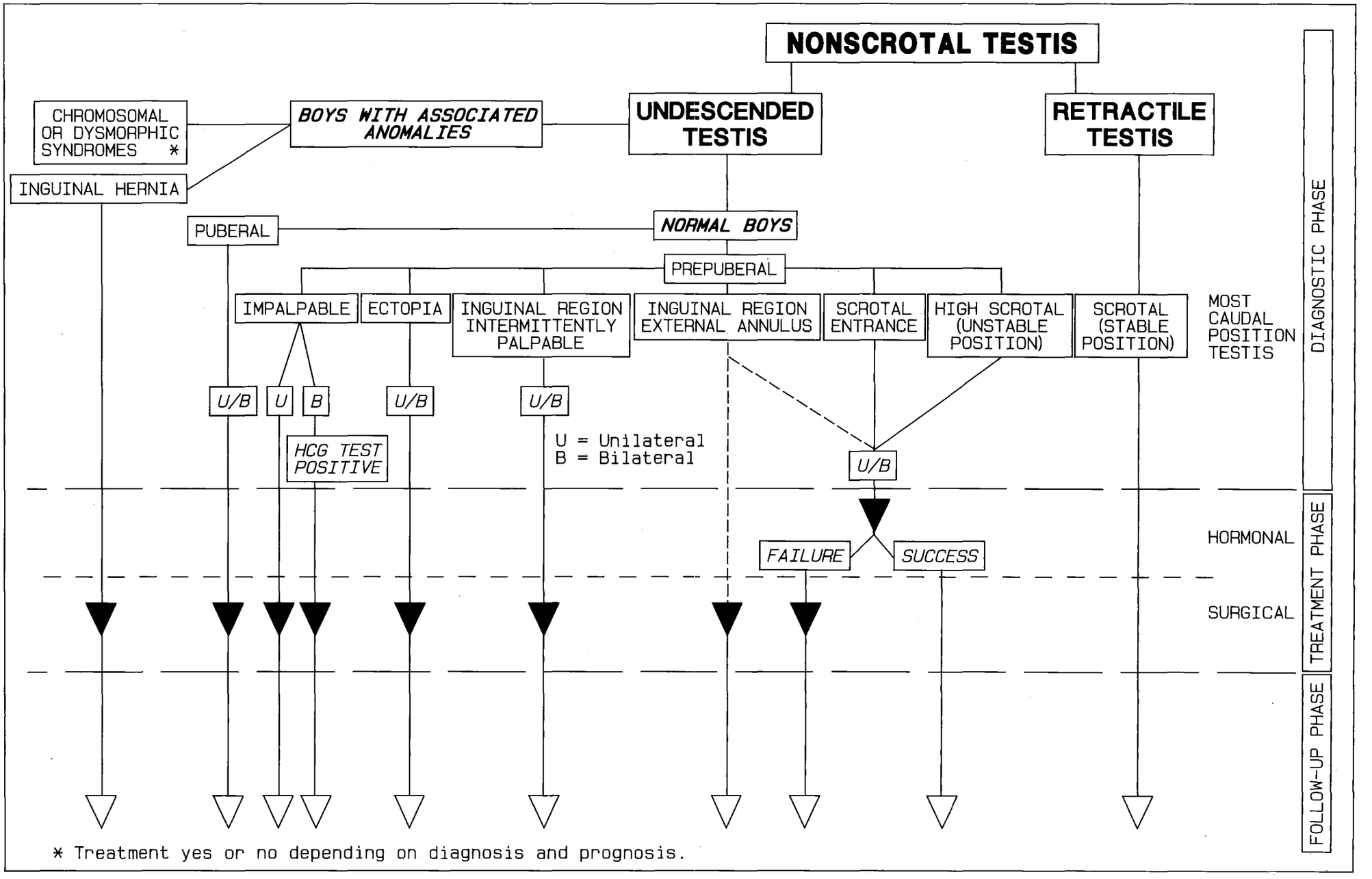
NONSCROTAL TESTIS
CHROMOSOMAL OR DYSMORPHIC SYNDROMES *
INGUINAL HERNIA
BOYS WITH ASSOCIATED ANOMALIES
UNDESCENDED TESTIS
RETRACTILE TESTIS
PUBERAL
NORMAL BOYS
PREPUBERAL
IMPALPABLE
ECTOPIA
INGUINAL REGION INTERMITTENTLY PALPABLE
INGUINAL REGION EXTERNAL ANNULUS
SCROTAL ENTRANCE
HIGH SCROTAL (UNSTABLE POSITION)
SCROTAL (STABLE POSITION)
MOST CAUDAL POSITION TESTIS
U/B
U
B
U/B
U/B
HCG TEST POSITIVE
U = Unilateral
B = Bilateral
U/B
HORMONAL
FAILURE
SUCCESS
SURGICAL
DIAGNOSTIC PHASE
TREATMENT PHASE
FOLLOW-UP PHASE
* Treatment yes or no depending on diagnosis and prognosis.

EXPLANATION OF PATIENT GROUPS, AGE PERIODS AND SYMBOLS IN FIGURES AND TABLES

Group I : boys that stayed cryptorchid in the first year of life

▲ unilateral

△ bilateral

Group II : boys with spontaneous testicular descent in the first year of life

■ unilateral

□ bilateral

⧈ hemi-descent (descent of one testis in case of bilateral cryptorchidism)

Group III : boys born with normally descended testes

○ control subjects

Age period X : approximately 3 months of age, range: 80–126 days

Age period Y : approximately 6 months of age, range: 169–236 days

Age period Z : approximately 12 months of age, range: 330–410 days