The Undescended testis

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John Hunter (1728–1793), Surgeon and Anatomist
When, How, and why?
Questions ??

- When to refer to surgeon?
- Bilateral impalpable testis?
- Role of US?
- Role of hormones?
- Retractile testis?
Issues

- Definitions & epidemiology
- Normal testicular development and descent
- Causes of cryptorchidism
- Consequences
- Treatment
  - Medical
  - Surgical
Definitions

- **Cryptorchid**: testis neither resides nor can be manipulated into the scrotum
- **Ectopic**: aberrant course
- **Retractile**: can be manipulated into scrotum where it remains without tension
- **Ascended**: previously descended, then “ascends” spontaneously
Cryptorchidism

• One of the most common male developmental abnormalities
• 27,000 orchidopexies annually in USA
• 89% of untreated males with bilateral cryptorchidism develop azospermia
• Lifetime risk of neoplasia 2-3%
  – 4 fold higher than average risk
Epidemiology

- Term boys: 3.4%
- 12 months: 0.8%

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Risk Factors
Hjerkvist 1989

- IUGR, prematurity
  - Incidence in premies 30%
- First-or second-born
- Perinatal asphyxia
- C-section
- Toxemia of pregnancy
- Congenital subluxation of hip
- Seasonal (especially winter)
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  – Surgical
Testicular development

- 6 wk primordial germ cells migrate to genital ridge
- 7 wk testicular differentiation
- 8 wk testis hormonally active
  - Sertolis secrete MIF
- 10-11 wk Leydig cells secrete T
- 10-15 wk external genital differentiation
Testicular descent

• 5-8 wk processus vaginalis
  – Gubernaculum attaches to lower epididymis
• 12 wk transabdominal descent to internal inguinal ring
• 26-28 wk gubernaculum swells to form inguinal canal, testis descends into scrotum
• Insulin-3 (INSL3) effects gubernacular growth
Human Testicular Development

- Genital tubercle formation
- Leydig cell activity
- Sertoli cell activity
- Germ cell migration question mark
- Mullerian duct regression
- Wolffian duct differentiation
- Male external genital differentiation and growth
- Testis descent

Gestation (weeks): 4 5 6 7 8 9 10 11 12 13 14 15 40


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• Member of the insulin/relaxin superfamily
• Highly expressed in Leydig cells
• In mice, targeted INSL3 deletion associated with bilateral cryptorchidism, abnl gubernaculum development
Germ cell maturation

- 8 wk: gonocytes (fetal stem cells)
- 15 wk: spermatogonia
- 3 mo of age: adult dark spermatogonia (adult stem cells) appear and remain – Neonatal surge in LH, FSH, T
- 4 yo: primary spermatocytes
- Puberty: spermatogenesis
It starts during the first years after birth
In normal testes, germ cell development is an active process starting in the first months of life when the neonatal gonocytes transform into adult dark (AD) spermatogonia. These cells are now thought to be the stem cells useful to support spermatogenesis. Several researches suggest that AD spermatogonia form between 3 and 9 months of age. Not all the neonatal gonocytes transform into AD spermatogonia; indeed, the residual gonocytes undergo involution by apoptosis. In the undescended testes, these transformations are inhibited leading to a deficient pool of stem cells for post pubertal spermatogenesis.

Data suggest that AD spermatogonia developmental cycle needs normal testicular hormones and the optimal scrotal temperature of 33°C.
The failure of transformation of gonocytes into AD spermatogonia leads to a **deficient pool of stem cells** for post pubertal spermatogenesis and infertility.

In undescended testes, **germ cells loss starts at 6 months of age**

It is very interesting to note that the intra-tubular **carcinoma in situ (CIS)** in the second and third decade has **enzyme markers similar to neonatal gonocytes** as placental alkaline phosphatase expression, suggesting that these cells, that fail to develop in AD spermatogonia at 3–9 months of age, are the origin of cancer in cryptorchid men.
High scrotal unilateral cryptorchid testis. The seminiferous tubules are lined by Sertoli cells and degenerated spermatogonia with some maturation to the primary spermatocyte stage (asterisk).
Biopsy specimen from a 21-year-old man with a high scrotal unilateral cryptorchid gliding testis. The tubule is lined by mature Sertoli cells only. In the Sertoli cell cytoplasm, many slender spindle-shaped Charcot-Böttcher crystals are present (arrowheads). The tunica propria is thickened (arrow).
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Development of the Reproductive System
Hypothalamus

GnRH

Pituitary

FSH

LH

Sertoli

Leydig

Germ cells

MIF

Testosterone

5α reductase

dihydrotestosterone

Androgen receptor

Post-receptor effects

Low/absent GnRH
Kallmann’s
Prader Willi

Hypopituitarism

Dysgenesis/anorchia
Testosterone biosynthetic problems

MIF deficiency/persistent Mullerian ducts

5α reductase deficiency

Androgen resistance
Abnormal gonadotropins in cryptorchidism

- Insufficient T response to hCG in 36.5% (Forest 1979)
- Blunting of LH and FSH surge at 3 mo (Gendrel 1980)
- Leydig cell hypoplasia in some undescended testes (Hadziselimovic 1986)
Defective onset of meiosis at 4-5 yo?

- Normally see increase in urinary LH and increased prominence of Leydig cells,
- Appearance of primary spermatocytes
- In cryptorchid males,
  - Low urinary LH & FSH
  - Impaired T response to hCG
  - May indicate deficiency of HP-gonadal axis as a cause of defective meiosis
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Impact on Fertility

• At bx, # spermatogonia/tubule prognostic for subsequent fertility potential
  – Bx without germ cells 33-100% risk of infertility

• Possible causes of subfertility
  – Reduction in total # germ cells (already present in 1\textsuperscript{st} year of life)
  – Defect in one or more steps in germ cell maturation
    • Defective transformation of gonocytes into Ad spermatogonia (Hadziselimovic 1986)
    • Delayed disappearance of gonocytes
## Incidence of Azospermia

Azospermia in normal population 0.4-0.5%

<table>
<thead>
<tr>
<th></th>
<th>Unilateral</th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>13.6%</td>
<td>88.6%</td>
</tr>
<tr>
<td></td>
<td>(10/73)</td>
<td>(31/35)</td>
</tr>
<tr>
<td>Medically treated</td>
<td>13.3%</td>
<td>32.0%</td>
</tr>
<tr>
<td></td>
<td>(28/210)</td>
<td>(46/142)</td>
</tr>
<tr>
<td>Surgically treated</td>
<td>13.3%</td>
<td>46.4%</td>
</tr>
<tr>
<td></td>
<td>(126/942)</td>
<td>(224/484)</td>
</tr>
</tbody>
</table>

Hadziselimovic 2001  

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Chronological development of germ cells (#/cross section)

Hadziselimovic 2001  CIP Budapest 2015
Number Ad spermatogonia/tubular cross-section from 0-9 yo

Hadziselimovic 2001

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# germ cells/tubular cross-section

Normal in 1st 6 mo, greatly decreased
Between 6-24 mo

Hadziselimovic 2001

Sperm/ejaculate (1x10^6)

If Ad spermatogonia present at orchidopexy,
Tended to have normal sperm count as adults

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Total gonocyte counts significantly higher in undescended testes, p<00005 Huff 2001
Total adult dark spermatogonia counts significantly lower in undescended testes, p<0.0005, Huff 2001
Boys < 1 yo

- Gonocytes failed to disappear
- Adult dark spermatogonia failed to appear
- Indicates defect in germ cell maturation and failure to establish an adequate adult stem cell pool
Increased risk of neoplasia

• Cortes 2001: 1638 testicular samples from 1335 patients (23% bilateral, 77% unilateral)
• Mean age @ surgery 11.7 yo (0.1-18.9 yr)
• 1 invasive germ cell tumor
• 6 carcinoma in situ
• 1 Sertoli cell tumor
• 3 neoplasms in intra-abdominal testes
• 4 neoplasms in boys with abnormal external genitalia
• 2 neoplasms in boys with known abnormal karyotype
• Risk of neoplasia 5% with intra-abdominal testes, abnormal external genitalia or abnormal karyotype  (Cortes 2001)
Thermoregulation
Countercurrent exchange
Thermoregulation

- Tunica dartos: smooth muscle in the scrotum
  - Capable of sustained contraction, elevating testes in cold environmental temperatures
- Cremaster muscle is continuous with internal abdominal oblique muscle
- Capable of short-term contraction
  - Short term elevation of testicles during fear or excitement
  - Contraction and relaxation acts as a pump on the pampiniform plexus
Scrotal testis ??.....

- Approximately 1500 species of mammals are ‘non-scrotal’
- Most of these still have a trans-abdominal migration phase
- Why is spermatogenesis still successful?
  - Some have testicles in a ‘cooler’ position
    - Eg tapir has subcutaneous testicles
  - Some have specialized cooling systems
    - Eg dolphin and vascular counter-current heat exchanger (dorsal fin and tail flukes)
  - Some have a low core body temperature
    - Eg hedgehog
  - Some we just don’t know
Whales

diaphragm

vas deferens

kidney

retractor penis muscle

testis

genital slit

penis

anus

pelvic bone
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Treatments

• Hormonal
  – hCG
  – GnRH
  – hMG
  – Combined (hCG & GnRH)

• Surgical
Hormonal Therapy

- hCG since 1930
- GnRH since 1974 (IM) and 1975 (intranasal) (Europe)
- Variable rates of success
  - hCG 0-55%
  - GnRH 9-78%
Confounding Variables in Data

• Inclusion/exclusion of retractile testes
• Variable ages of treatment
• Randomized or not
• Different dose regimens and durations
• Original testicular position not documented in all studies
• Small patient numbers
Mean success rate (%) for treatment in combined RCTs comparing hGC and GnRH with placebo. Pyorala

![Graph showing success rates](chart.png)

- # Trials: 9, 2, 11
- Testes: 472, 148, 554

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Mean success rates (%) by original location, includes both RCTs and nonRCTs after GnRH and hCG. Pyorala 1995

<table>
<thead>
<tr>
<th>Location</th>
<th># trials</th>
<th># testes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal</td>
<td>17</td>
<td>907</td>
</tr>
<tr>
<td>Inguinal</td>
<td>21</td>
<td>1430</td>
</tr>
<tr>
<td>Prescrotal</td>
<td>14</td>
<td>295</td>
</tr>
<tr>
<td>High scrotal</td>
<td>4</td>
<td>67</td>
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</table>

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Mean success rates (%) of hormonal treatment (GnRH or hCG) in combined RCTs in boys under 4 yo vs boys > 4 yo. Pyorala 1995  p=NS

<table>
<thead>
<tr>
<th></th>
<th>&lt;4yo</th>
<th>&gt;4yo</th>
</tr>
</thead>
<tbody>
<tr>
<td># trials</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td># testes</td>
<td>48</td>
<td>167</td>
</tr>
</tbody>
</table>

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• Overall success rate 19.3% (30/155)
• No significant differences between regimes
• Relapse 23.3% (7/30)
  – No significant difference between regimes
Testicular Histology Related to Fertility Outcome and Postpubertal Hormone Status in Cryptorchidism

Die Histologie des kryptorchen Hodens in Korrelation zur Fertilitätsprognose und zu Hormonergebnissen

Bibliography
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Fig. 1 Testicular histology of HIR (high infertility risk group lacking bilateral Ad spermatogonia) and UR group [with Ad spermatogonia (arrow)].
• In conclusion, infertility induced by cryptorchidism is an endocrine disease of impaired mini-puberty.
• Bilateral testicular biopsy analysis is currently the most effective method for identifying boys at risk of infertility after successful surgery for cryptorchidism.
• Patients should consider gonadotropin treatment following orchidopexy if their undescended gonads lack Ad spermatogonia and their scrotal testis have Ad germ cell counts $< 0.005$ per tubule.
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American Urological Association (AUA) Guideline

EVALUATION AND TREATMENT OF CRYPTORCHIDISM: AUA GUIDELINE

When to refer?

• refer boys with the possibility of newly diagnosed (acquired) cryptorchidism after six months to an appropriate surgical specialist.
bilateral, nonpalpable testes

- immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development (DSD).
• should not perform ultrasound (US) or other imaging modalities in the evaluation of boys with cryptorchidism prior to referral as these studies rarely assist in decision making.
+ severe hypospadias

- should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism.
Retractile Testis

• In boys with retractile testes, should **monitor** the position of the testes at least annually to monitor for secondary ascent.
Hormonal for descent

- should **not** use hormonal therapy to induce testicular descent as evidence shows low response rates and lack of evidence for long-term efficacy.
Hormonal for fertility

• 11% of those who received surgery and hormone therapy had normal morphology as opposed to none in the surgery alone group.
Time for surgery

• In the absence of spontaneous testicular descent by six months (corrected for gestational age), specialists should perform surgery within the next year.