

# The Capital Region of Denmark

REGION

## Male reproduction and reproductive disorders.

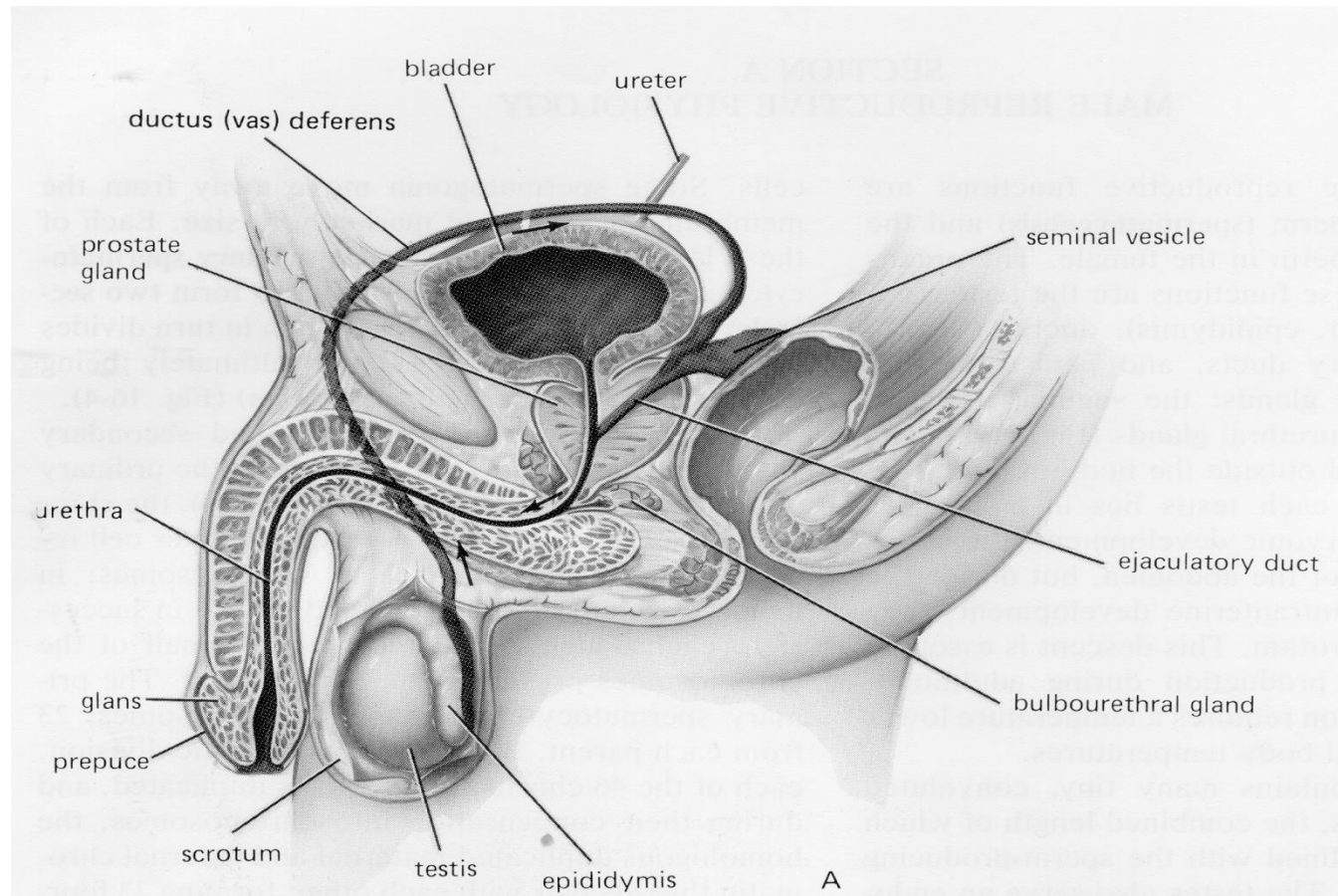
Elisabeth Carlsen  
The Fertility Clinic  
Rigshospitalet  
Copenhagen

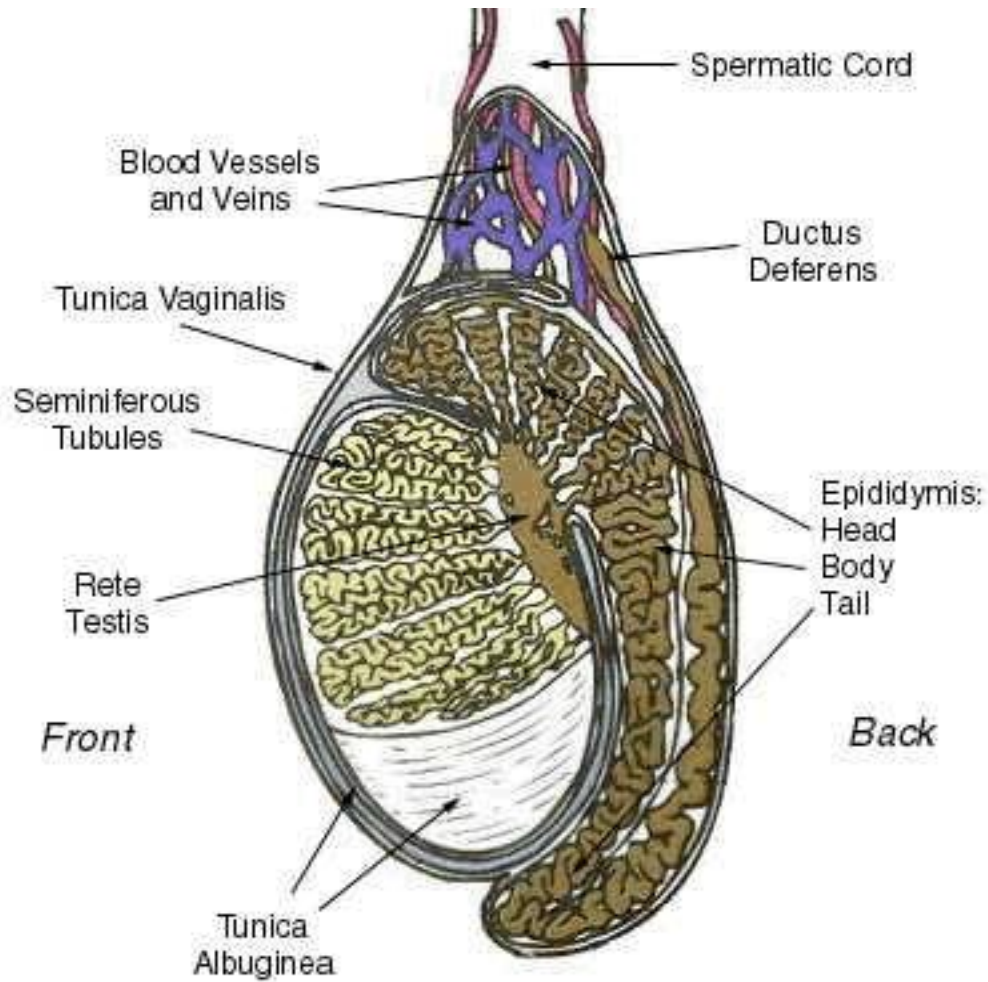
NILS January 2015

# Disposition

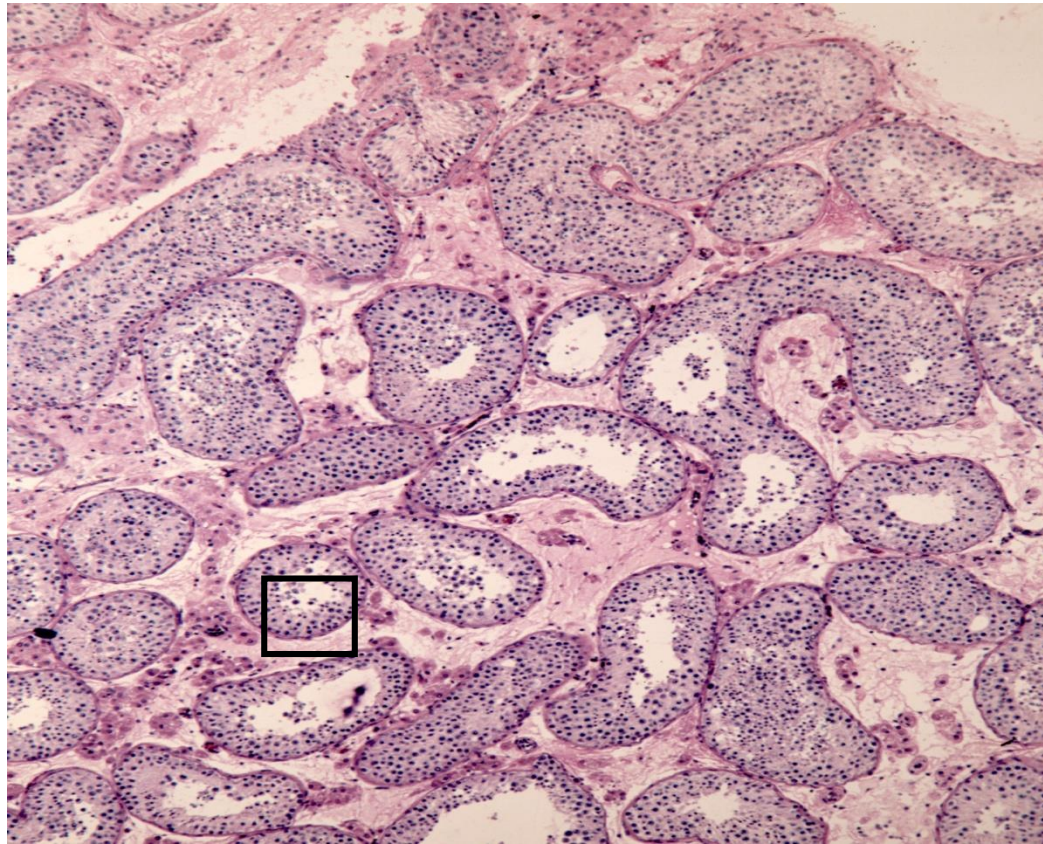
- Anatomy and physiology
- Spermatogenesis
- Reproductive hormones
- Semen analysis
- Male infertility
- Work up for male infertility

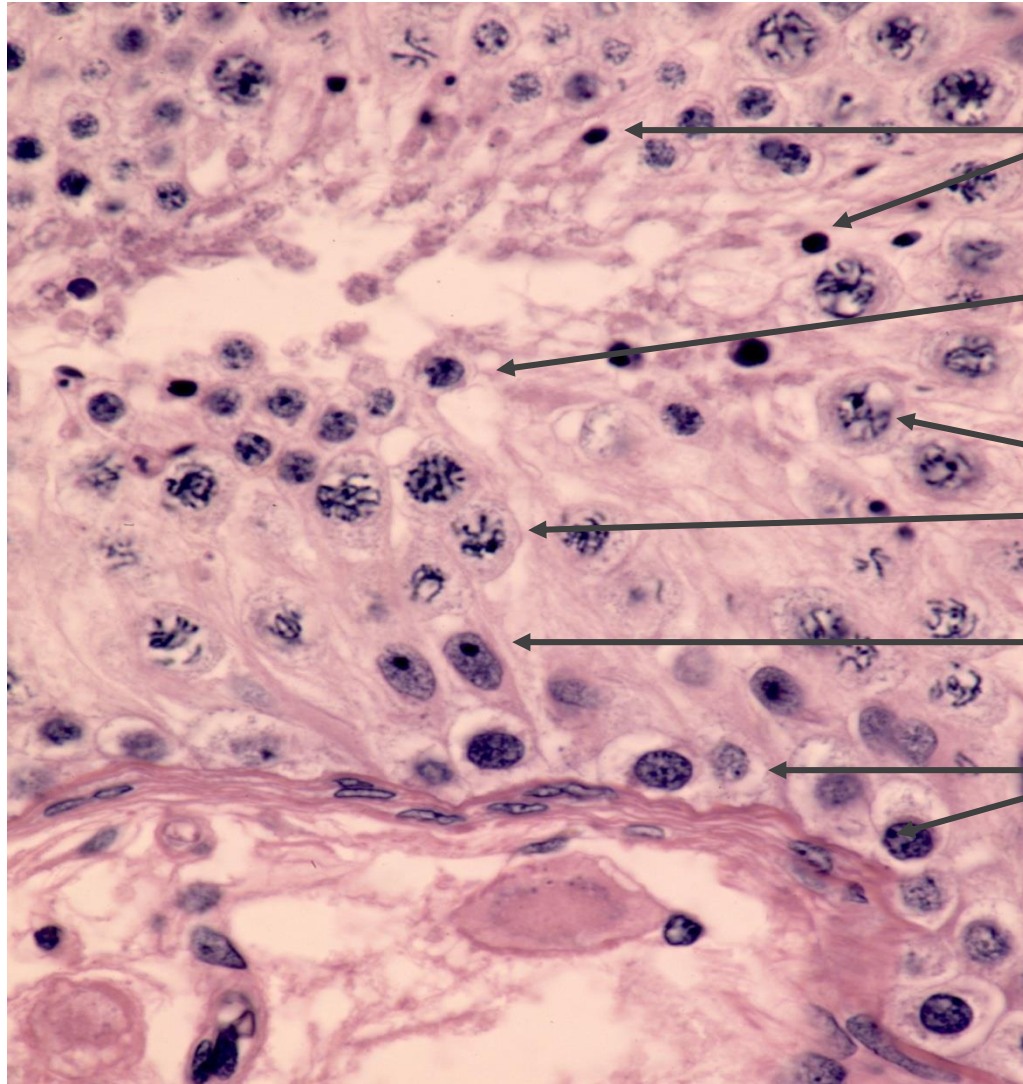
# Male reproductive system





# Cross-section of the testis





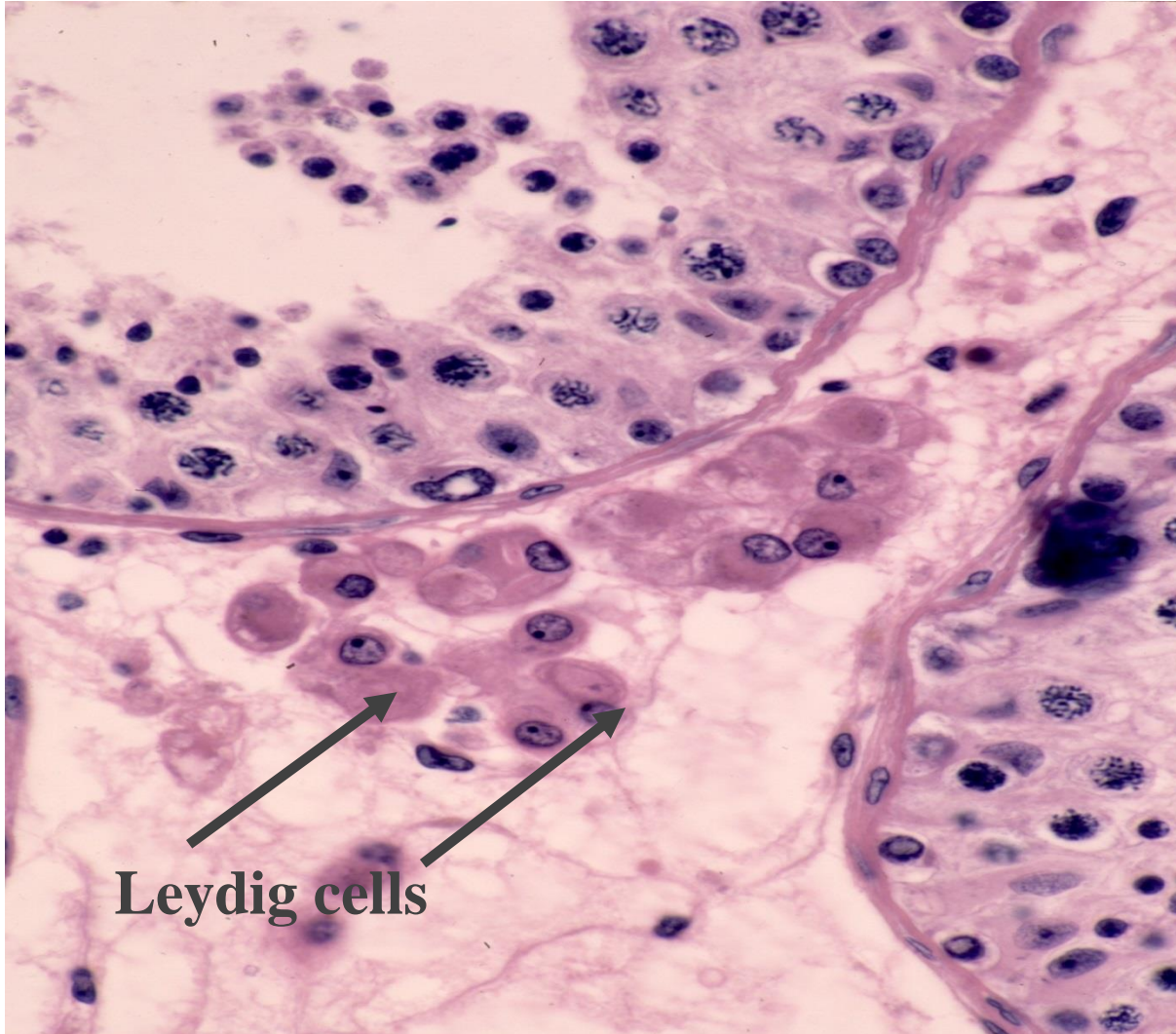
Spermatid

Secondary  
spermatocytes

Primary  
spermatocytes

Sertoli cells

Spermatogonia



# Spermatogenesis

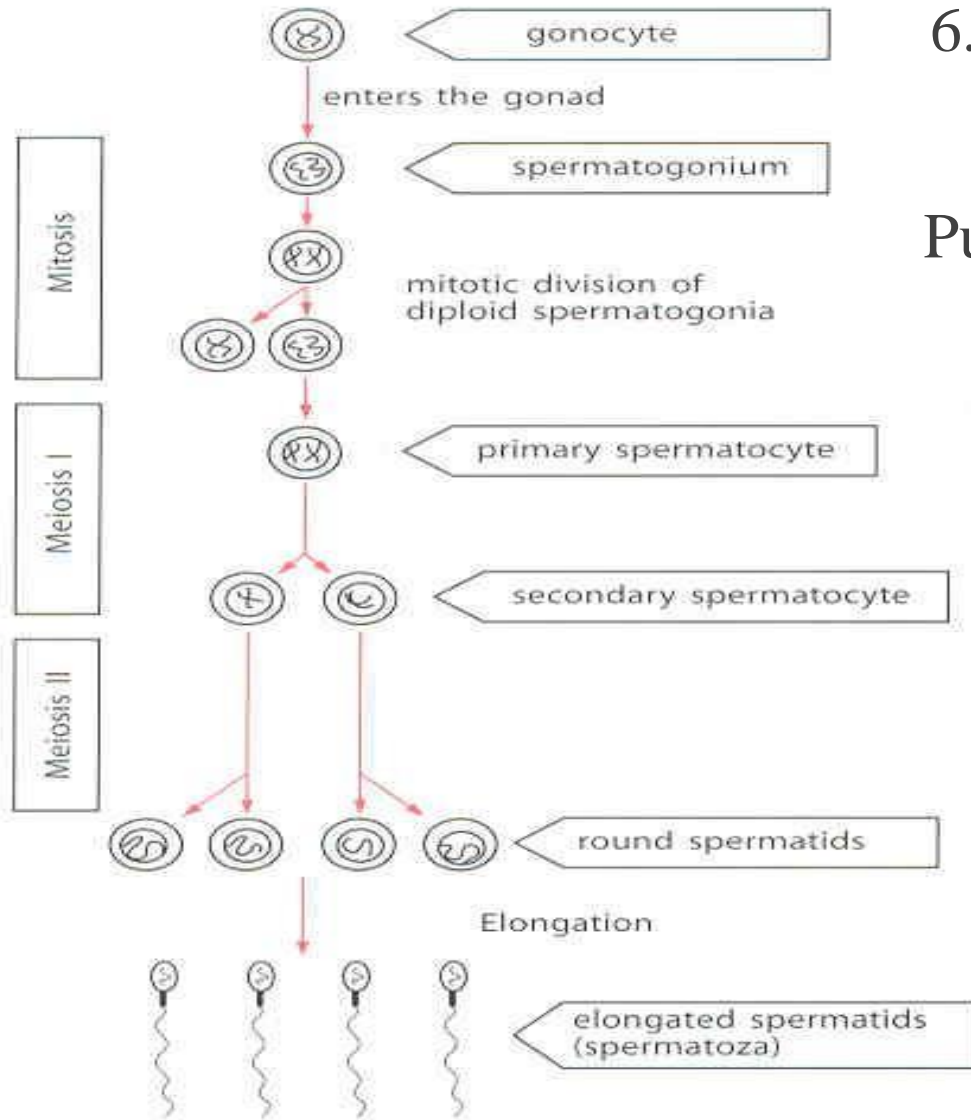
The process where the mature spermatozoa is formed achieving:

- 23 chromosomes by meiotic division and exchange of genes between homologous chromosomes (crossing over)
- the right shape to fertilize the ovum (spermiogenesis).

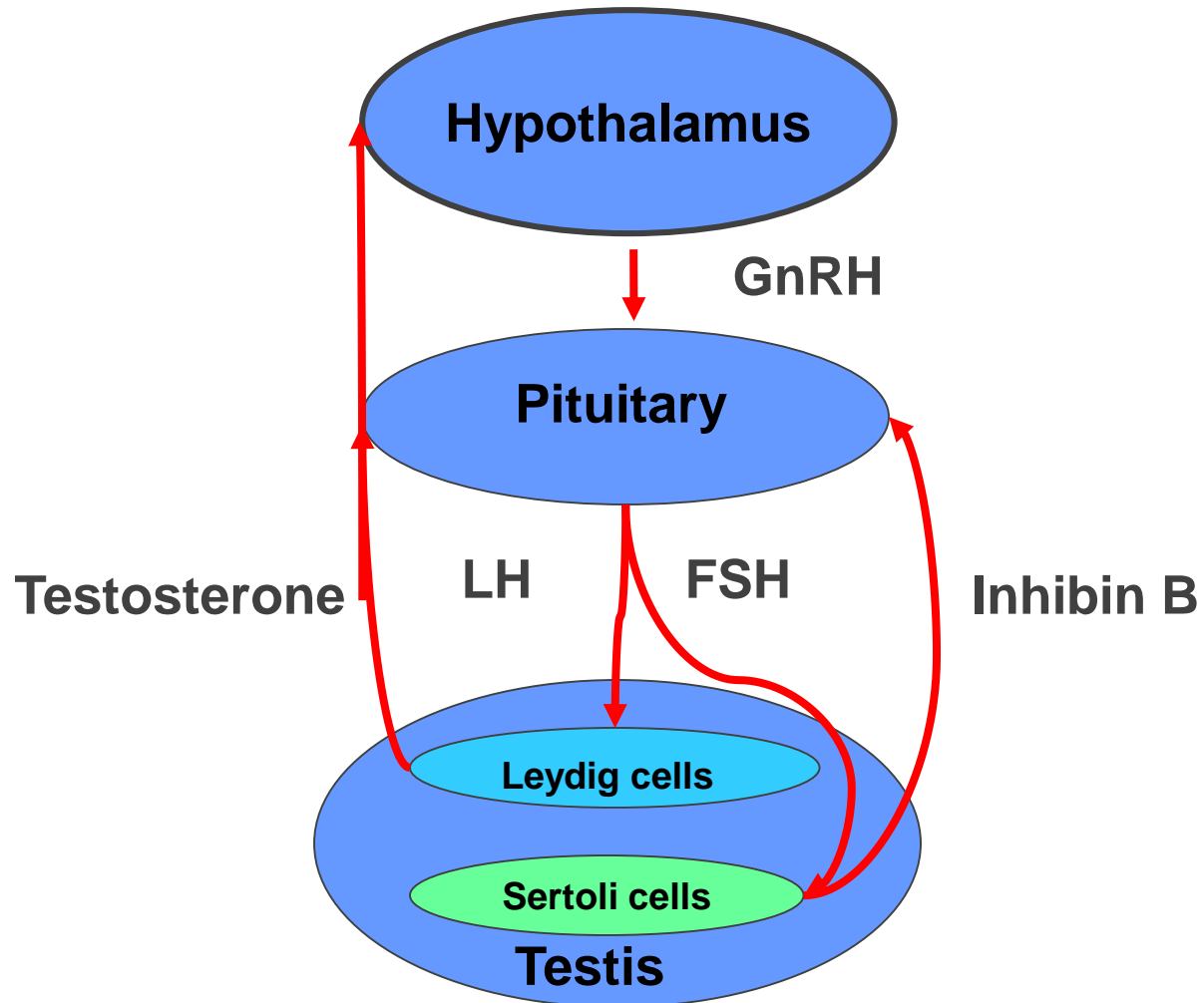


6. week

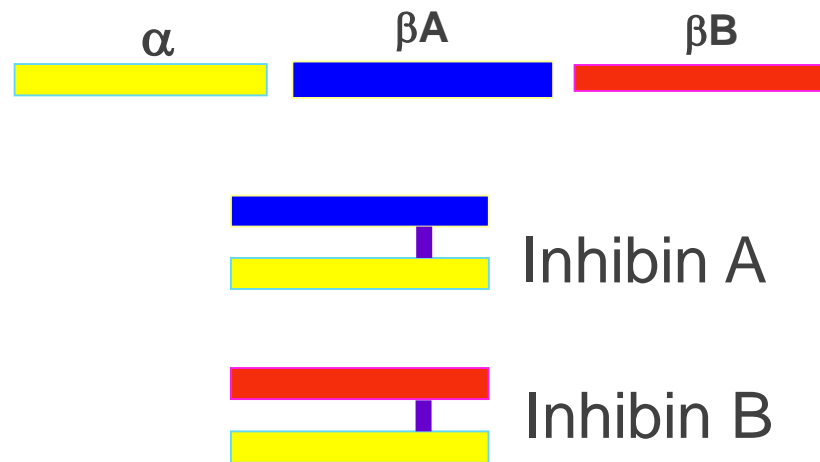
Puberty



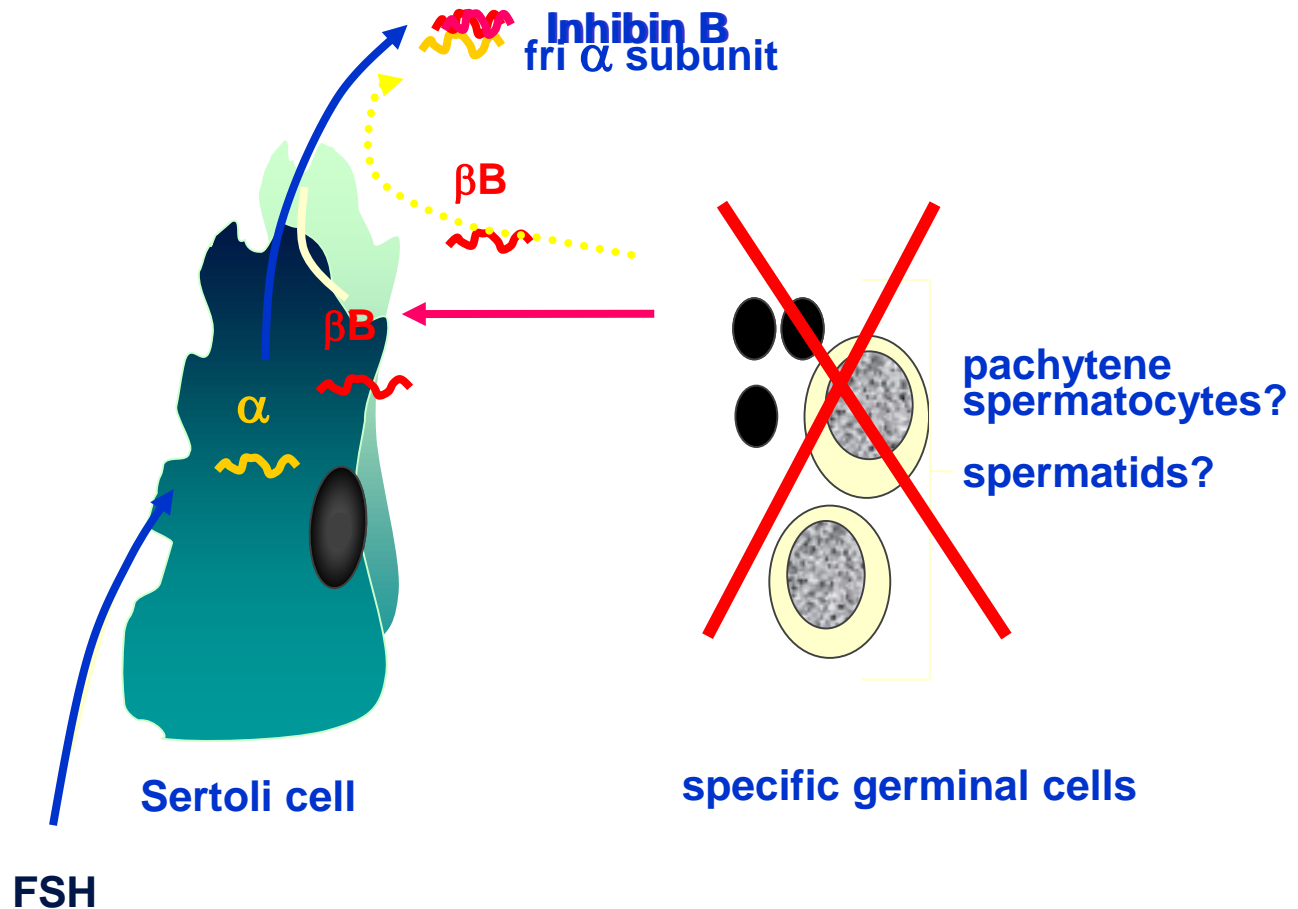
# Hypothalamic-pituitary-gonadal axis



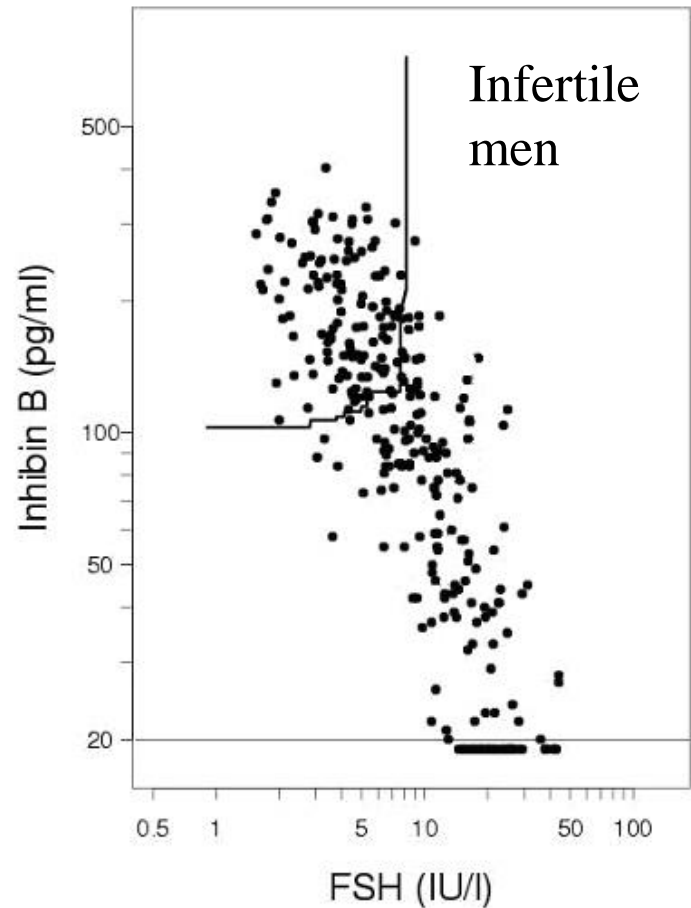
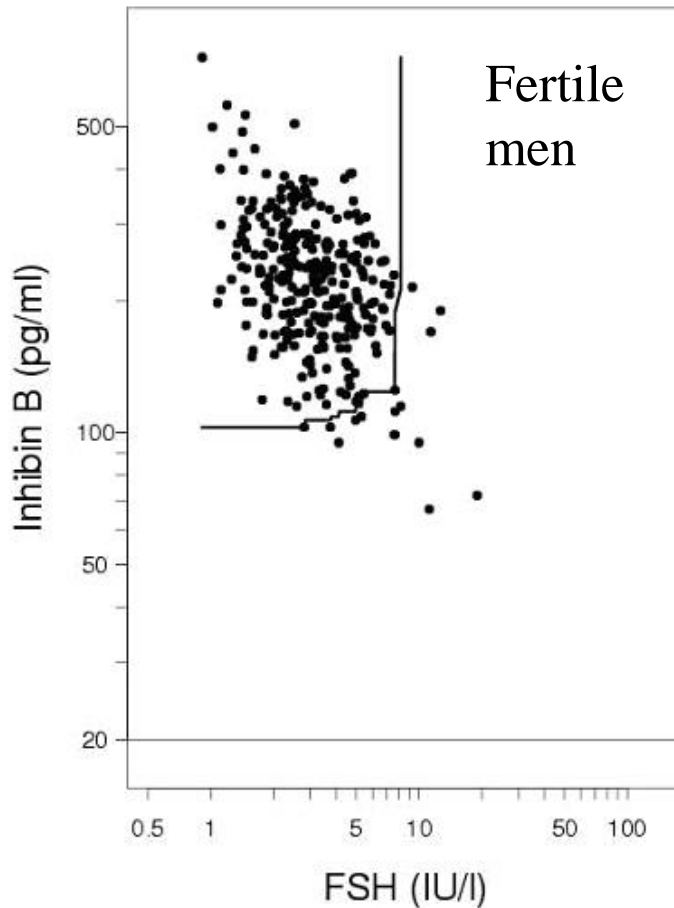
## Inhibin subunits



# Regulation of Inhibin B production by germinal cells in the adult man



# Markers of spermatogenesis

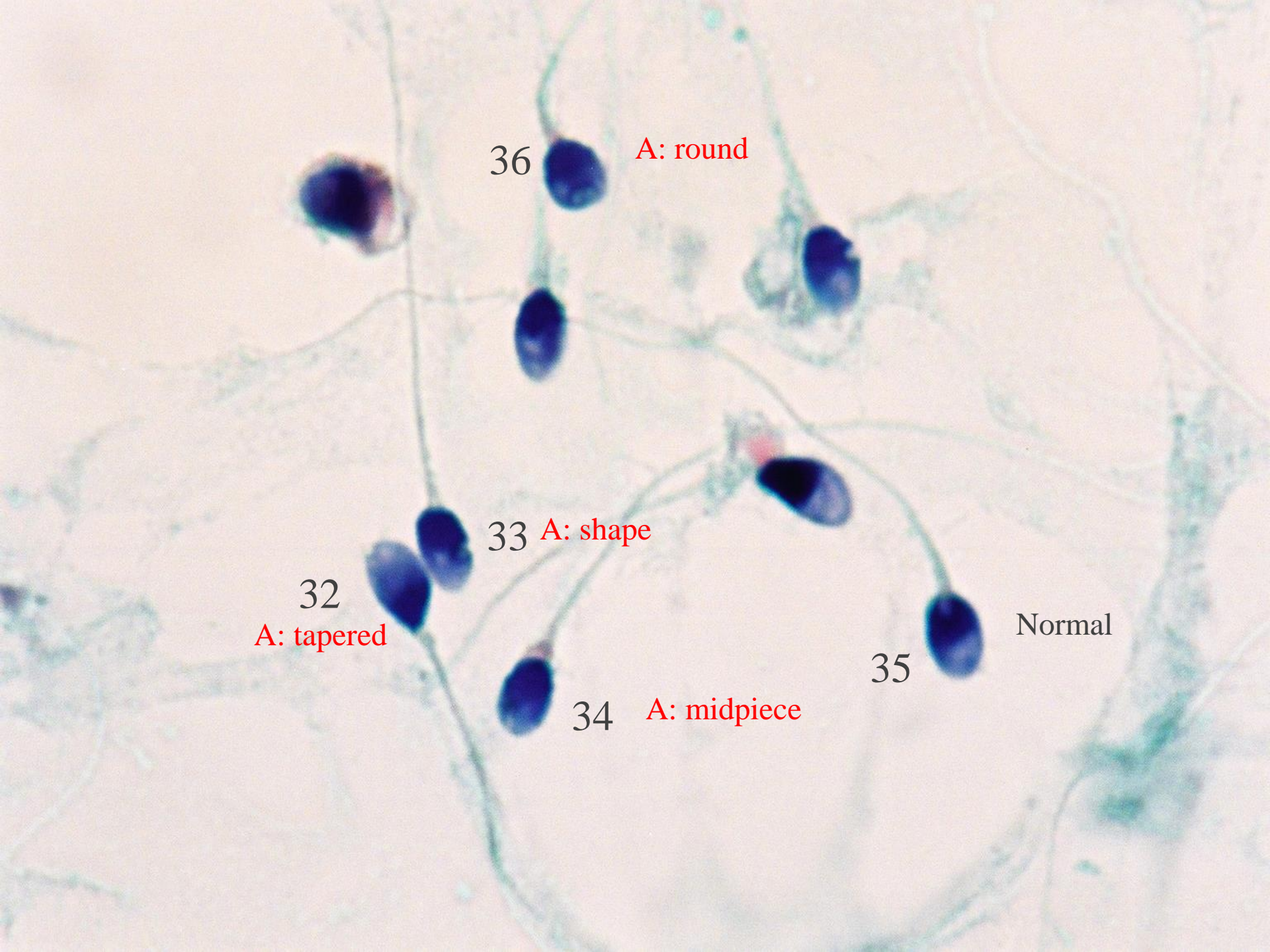


## Cut-off values for semen parameters WHO laboratory manual (2010)

- Volume 1,5 ml
- Sperm concentration 15 mill/ml
- Total sperm count 39 mill
- Motile 40%
- Progressive motile 32%
- Morphology 4% (strict criteria)
- Vitality 58% viable

## Definitions

- Azoospermia: no sperm cells in the ejaculate
- Oligozoospermia:  $< 15$  mill/ml in the ejaculate
- Astenozoospermia:  $> 40\%$  immotile sperm cells
- Teratozoospermia:  $< 4\%$  morphologically normal sperm cells



36

A: round

33

A: shape

32

A: tapered

34

A: midpiece

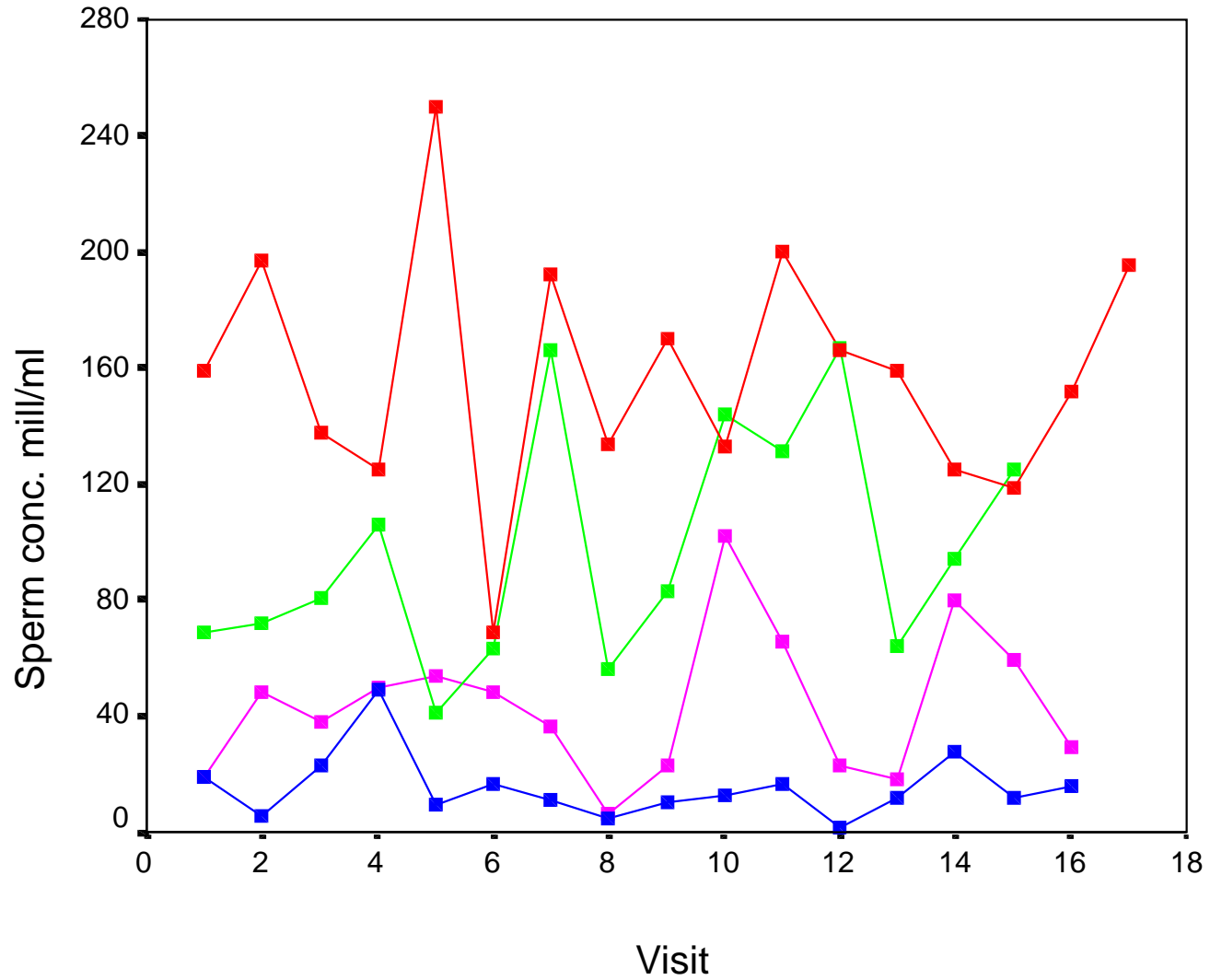
35

Normal

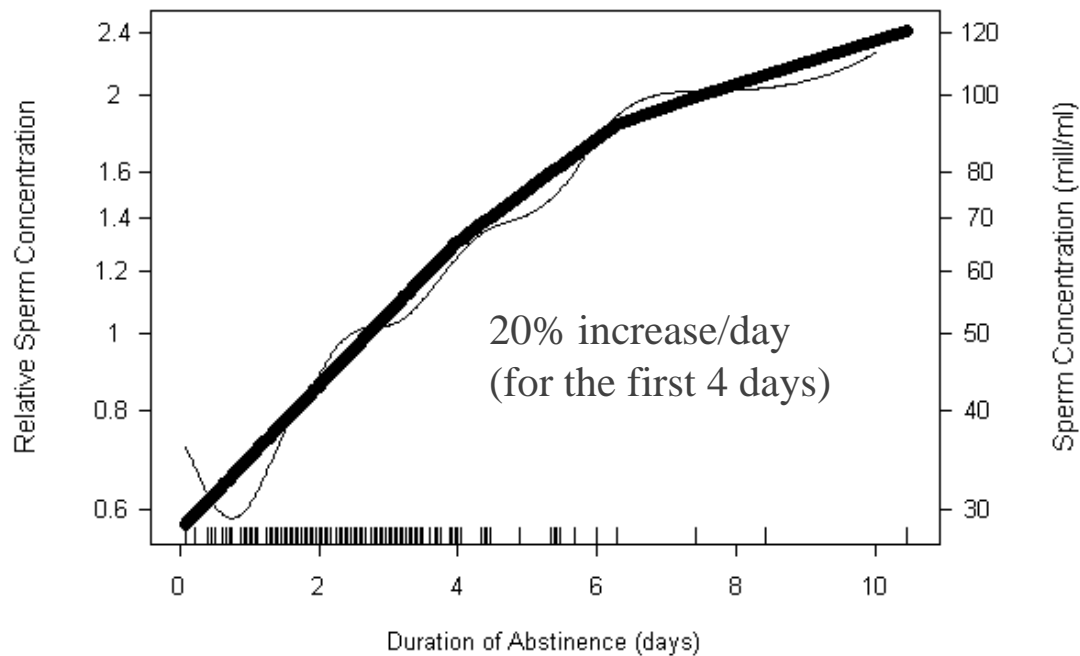


## Intra-individual variations in semen quality

- Evaluation of monthly semen samples during 17 months from 27 men (median age 24,4 y)
- Intra-individual variation:
  - Sperm concentration 61,9%
  - % immotile sperm cells 30,7%
  - % normal sperm cells 10.4%



# Effect of duration of abstinence on sperm concentration

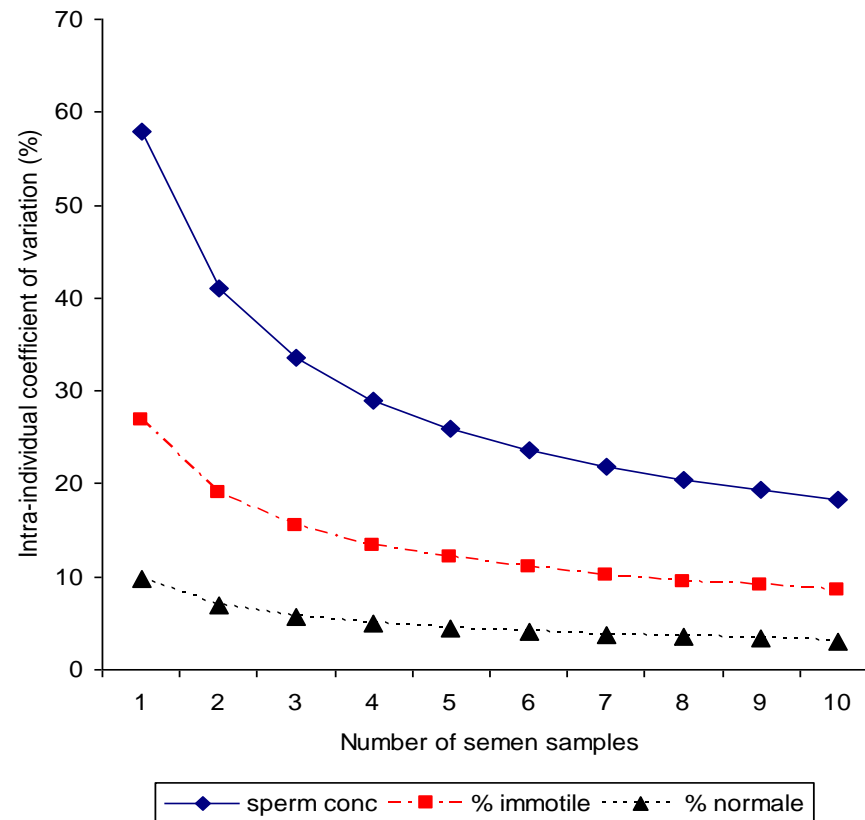


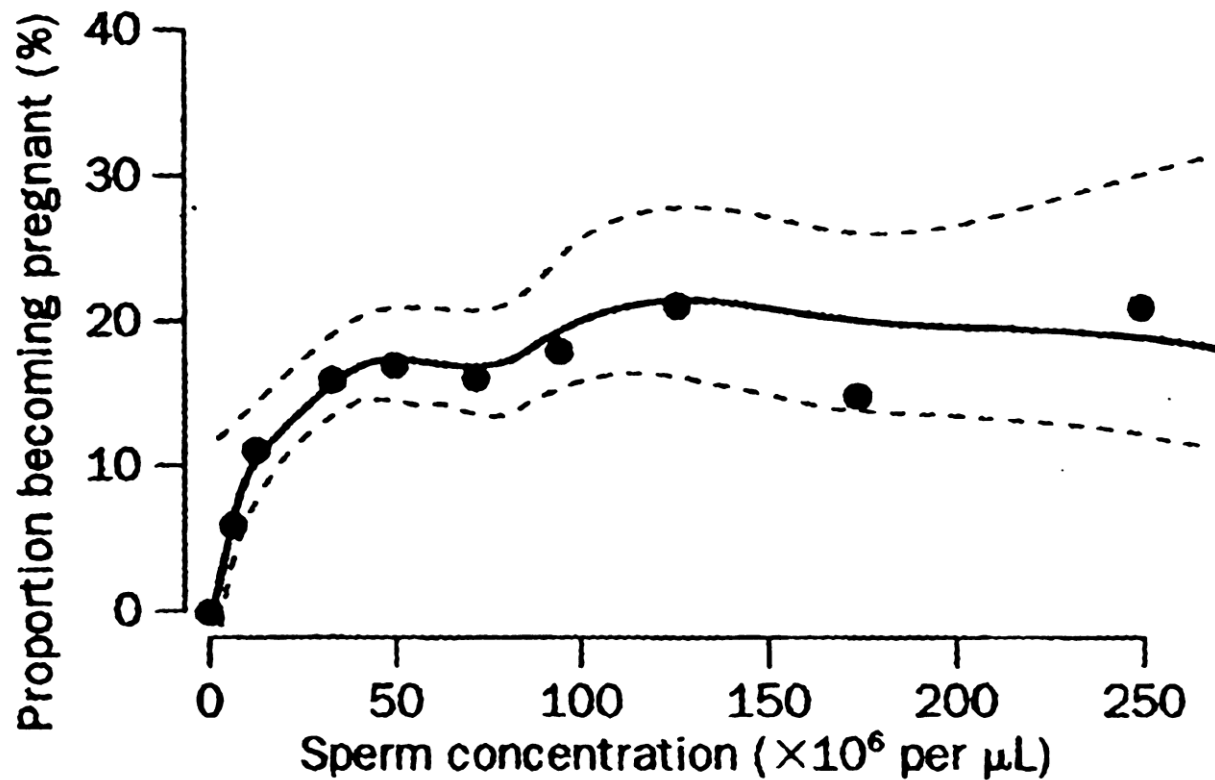
## Effect of fever on semen quality

	Fever during mitotic proliferation (day -80 to -57)	Fever during meiotic division (day -56 to -33)	Fever during spermiogenesis (day -32 to -9)	Fever during sperm maturation (day -8 to 0)
<b>Sperm concentration</b>	5.5 (-21.7; 42.0) p=0.726	<b>-32.6 (-49.9; -9.2)</b> <b>p=0.010</b>	<b>-35.0 (-50.5; -14.6)</b> <b>p=0.002</b>	-0.3 (-38.7; 51.9) p=0.877
<b>% normal spermatozoa</b>	-2.8 (-7.5; 2.2) p=0.269	-4.3 (-9.0; 0.6) p=0.084	<b>-7.4 (-11.6; -3.0)</b> <b>p=0.001</b>	-1.4 (-8.7; 6.6) p=0.730
<b>% immotile spermatozoa</b>	2.7 (-10.5; 17.9) p=0.702	-6.4 (-18.7; 7.7) p=0.355	<b>20.4 (6.0; 36.8)</b> <b>p=0.004</b>	2.0 (-17.5; 26.1) p=0.856

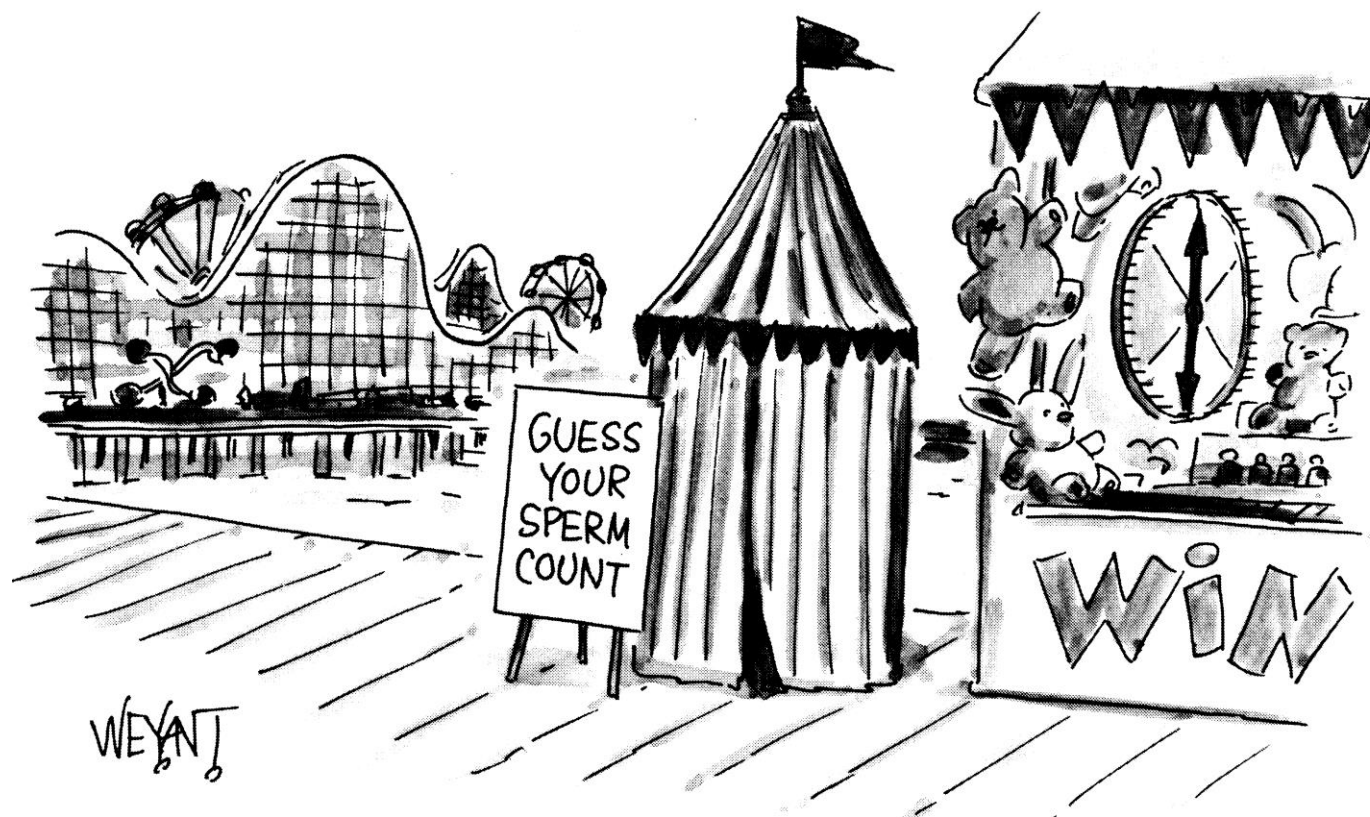
% and 95% confidence interval

# Intra-individual variation in semen parameters: effect of multiple semen samples





Bonde et al. Lancet (1998) 352: 1172-77.



## Male infertility causes

- Compromised spermatogenesis
- Obstruction
- Ejaculatory dysfunction
- Other causes



## Compromised sperm production

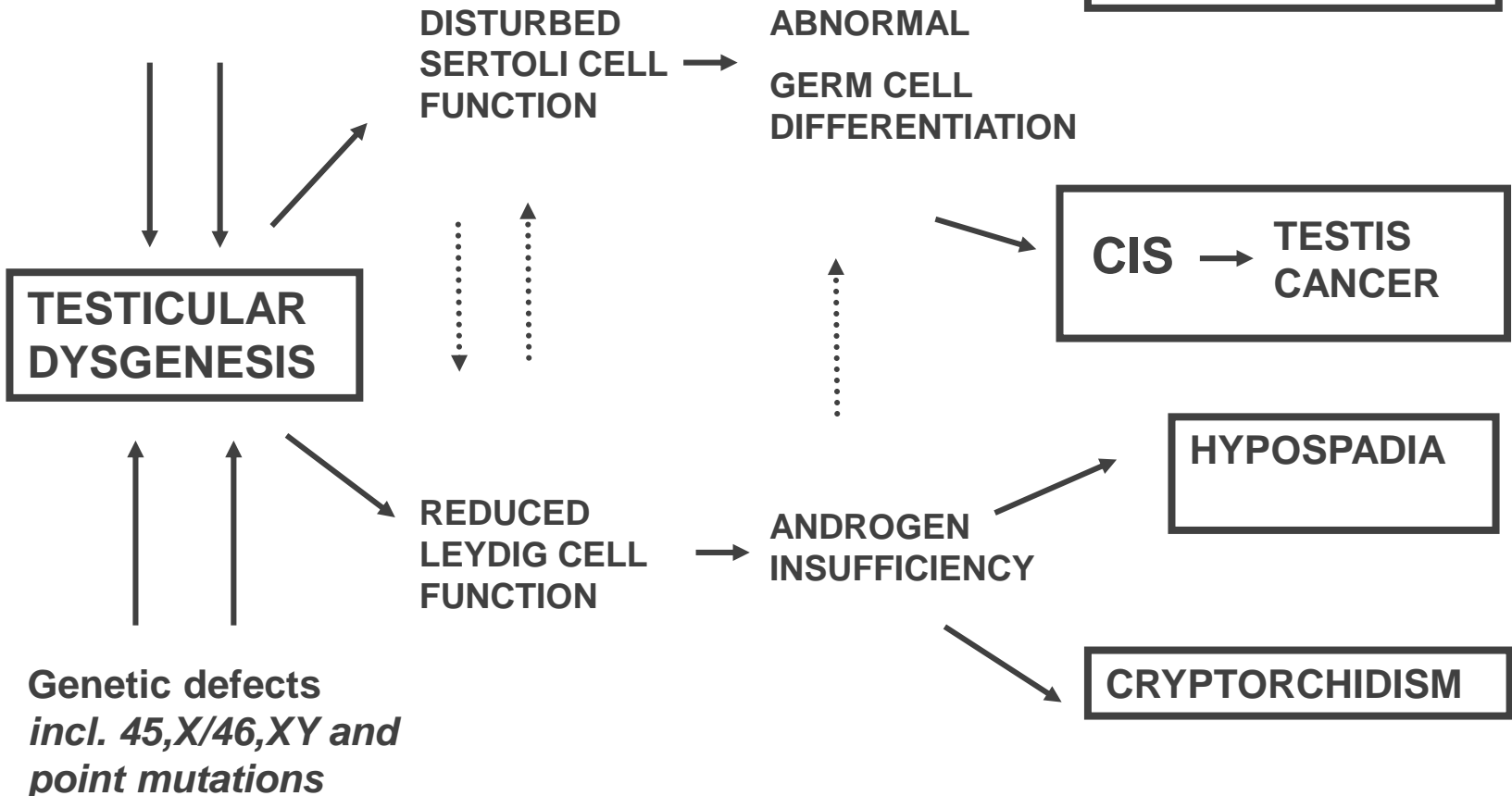
- Hormonal problems
  - Defect in GnRH release (Kallmann's syndrome)
  - Pituitary tumors or hemochromatosis
- Testicular dysfunction
  - Idiopathic
  - associated with cryptorchidism
- Genetic disorders
- Acquired disorders
  - Trauma/orchitis
  - Torsion of the testis
- Exogenous factors

## Testicular dysgenesis syndrome (TDS)

- Reduced semen quality
  - Compromised sperm production
  - Spermatogenic arrest
  - Sertoli cell only syndrome
- Cryptorchidism
- Cancer testis/ Carcinoma in situ testis (CIS)
- Hypospadias

# Testicular Dysgenesis Syndrome

Environmental factors  
*i.e. hormone-disturbing  
chemicals*



## Genetic disorders

- Klinefelter Syndrome (47, XXY)
- Chromosomal translocations
- Androgen receptor gen mutations
- Y chromosome microdeletions

## Klinefelter syndrome (47,XXY)

- 0,2% of newborn boys
- *11% of men with non-obstructive azoospermia*
- small testes < 5 ml and often azoospermia
- Decreased virilisation
- hypergonadotropic hypogonadism

## Autosomal translocations

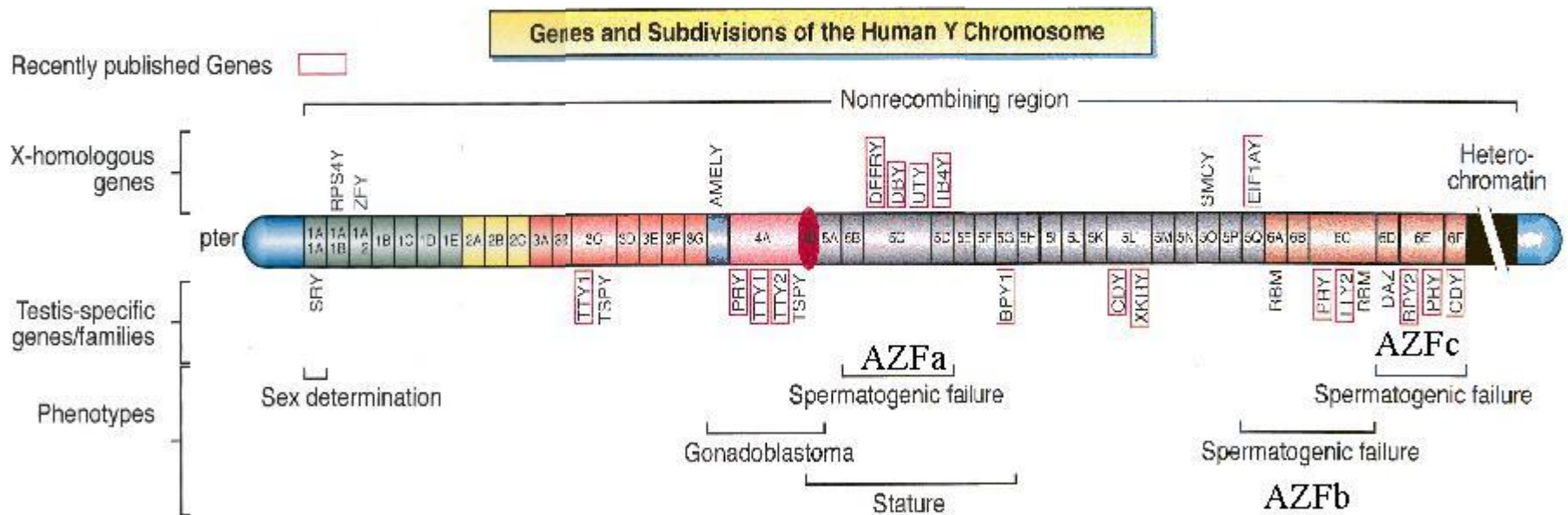
- 0,5-1% of men with oligo-azoospermia
- Robertsonian/reciprocal
- Balanced/unbalanced embryos
- PGD (preimplantation gene diagnostic)

## Y chromosome microdeletions

- Frequency:
  - *10% of men with non-obstructive azoospermia and 6% of men with severe oligozoospermia (ESHRE Capri Workshop Group, Hum Reprod Update 2007)*
- Localization:
  - 3 AZF regions on Yq: AZFa, AZFb and AZFc
  - Newer modifications of the original classification including b2/b4 and gr/gr

# A Functional Map of the Y Chromosome

(from Lahn & Page 1997, Science 278:675)



Note: contrary to this figure, an X-homologue of RBM has recently been described (Nat Gen July 1999)



## Exogenous causes

- Irradiation of the testis
- Medicine
  - Salazopyrine
  - Cytotoxic drugs
  - Anabolic steroids

## Obstructions of sperm ducts

- Previous genital infections
  - Chlamydia, gonorrhoea
- Urogenital surgery
  - Vasectomy, reconstructive surgery
- Congenital aplasia of sperm ducts
  - Cystic fibrosis or cystic fibrosis gen mutations

## CFTR-mutation

(cystic fibrosis transmembrane conductance regulator)

- Absent development of seminal duct (vas deferens) and seminal vesicle
- Azoospermia and a small semen volume
- Fertility treatment ICSI/TESA
- Female carrier?

## Ejaculatory dysfunction

- Retrograde ejaculation
  - Neuropathy in diabetes
  - Previous prostatic surgery and other pelvic surgery
- Anejaculation
  - Neuropathy
  - Spinal cord injury

## Andrological examination

- Clinical examination
  - history
  - objective examination
  - ultrasound scan of the testis
- Laboratory tests
  - semen samples
  - hormone analyses
  - genetic analyses
- Diagnostic testicular biopsy in certain cases

- History
  - Previous maldescensus
  - Infections/surgery
  - Previous conceptions
  - Symptoms
  - Medication
- Objective examination
  - Testicular size
  - Ducts and epididymis
  - Ultrasound scan



## Laboratory tests

- Semen analysis
  - Urine analysis for retrograde ejaculation
  - Diagnostic swim-up or gradient centrifugation
- Hormone analysis
  - Inhibin B / FSH
  - LH
  - Testosterone
- Genetic analysis
  - Karyotype
  - Y chromosome microdeletion analysis

## Genetic tests

- Routine tests in azoospermia and severe oligozoospermia and whenever ICSI is indicated:
  - Karyotype
  - Y chromosome microdeletion test
- When indicated
  - CFTR mutation analysis



## Treatment of male infertility

- Elimination of environmental and lifestyle factors
- Medical treatment
- Surgical treatment
- Assisted reproduction

# Flowchart

