Male infertility

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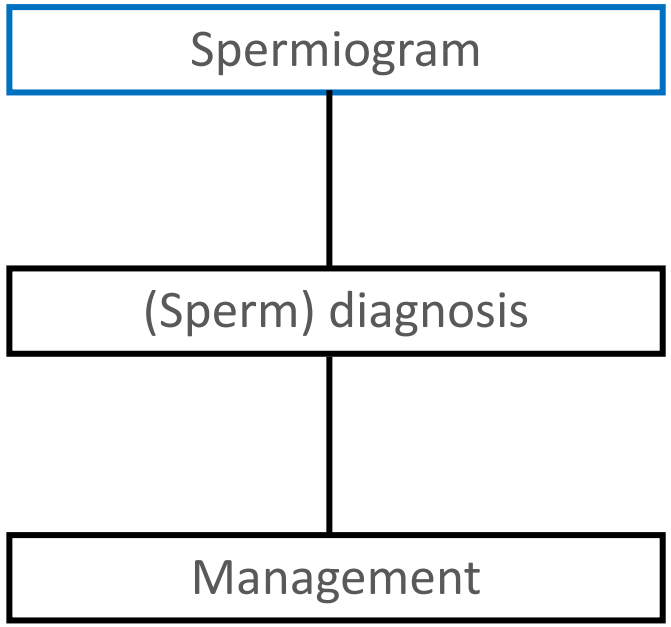
Conflict of interests

- During the last three years, I have received research, educational and travel grants from scientific societies and pharmaceutical companies.
- I am currently or have been:
  - President, Hellenic Society of Andrology (2013 - 2017)
  - President-Elect, European Menopause and Andropause Society (2019 - 2021)
  - Secretary General, European Academy of Andrology (2014 - 2018)
  - Director, Training Centre European Academy of Andrology (2013 - 2019)
  - Member of the Executive Board, Hellenic Society of Endocrinology (2011 - 2013)
  - Member of the Executive Board, Hellenic Society of Climacteric and Menopause (2013 - 2019)
  - Associate Editor, Human Reproduction (2009 - 2013)
  - Associate Editor, Hormones (2012 - 2019)
  - Member of the Editorial Board, Andrology (2012 - 2019)
  - Member of the Editorial Board, Maturitas (2015 - 2019)
  - Member of the Editorial Board, Metabolism (2015 - 2019)
  - Member of the Editorial Board, Journal of Endocrinological Investigation (2014 - 2019)
  - Associate Editor, Human Reproduction Open (2017 - 2019)
  - Associate Editor, Human Andrology (2017 - 2019)
- None of the above can be considered as a conflict of interest for today's lecture.

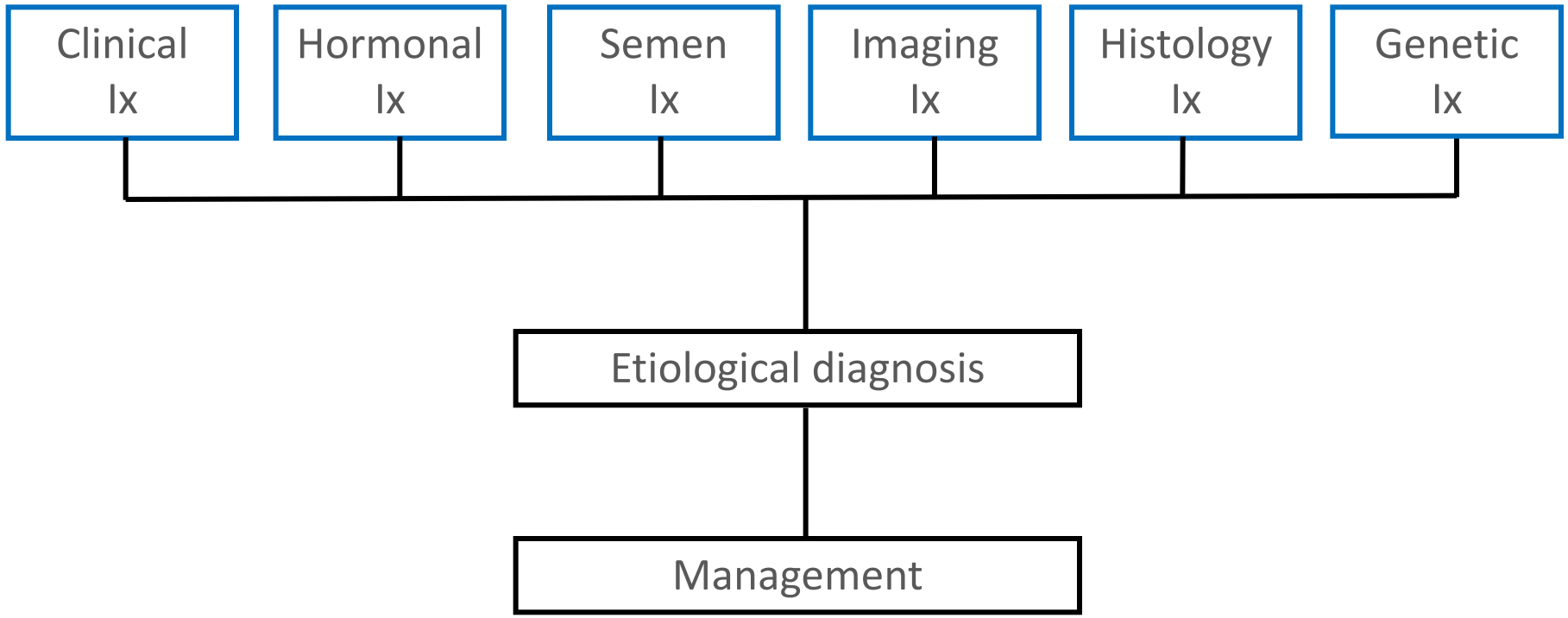
Aims

- Evaluation and etiologic approach of male infertility
- Selection of the optimal management method

Diagnostic approach



Diagnostic approach



Causes of male infertility

Cause	Prevalence (%)
Idiopathic infertility	32
Varicocele	17
Endocrine causes	9
Infections	9
Cryptorchidism	8
Sexual dysfunction	6
Systematic diseases	5
Anti-sperm antibodies	4
Testicular tumors	2
Obstruction	1
Other causes	7

Behre HM, et al. Klinik der Gegenwart 1994, 22:1

Diagnostic evaluation

- Clinical
- Hormonal
- Seminal
- Imaging
- Histologic
- Genetic

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Clinical evaluation

- History
  - Primary or secondary infertility, duration of infertility, mumps, cryptorchidism, trauma, surgical procedures, infections, recent febrile episodes, chemotherapy or radiotherapy, medications, family history of infertility, cystic fibrosis, mental retardation, female factor
- Clinical evaluation
  - Testicular size, secondary sexual characteristics, presence and consistence of epididymides and vas deferens, varicocele, digital examination

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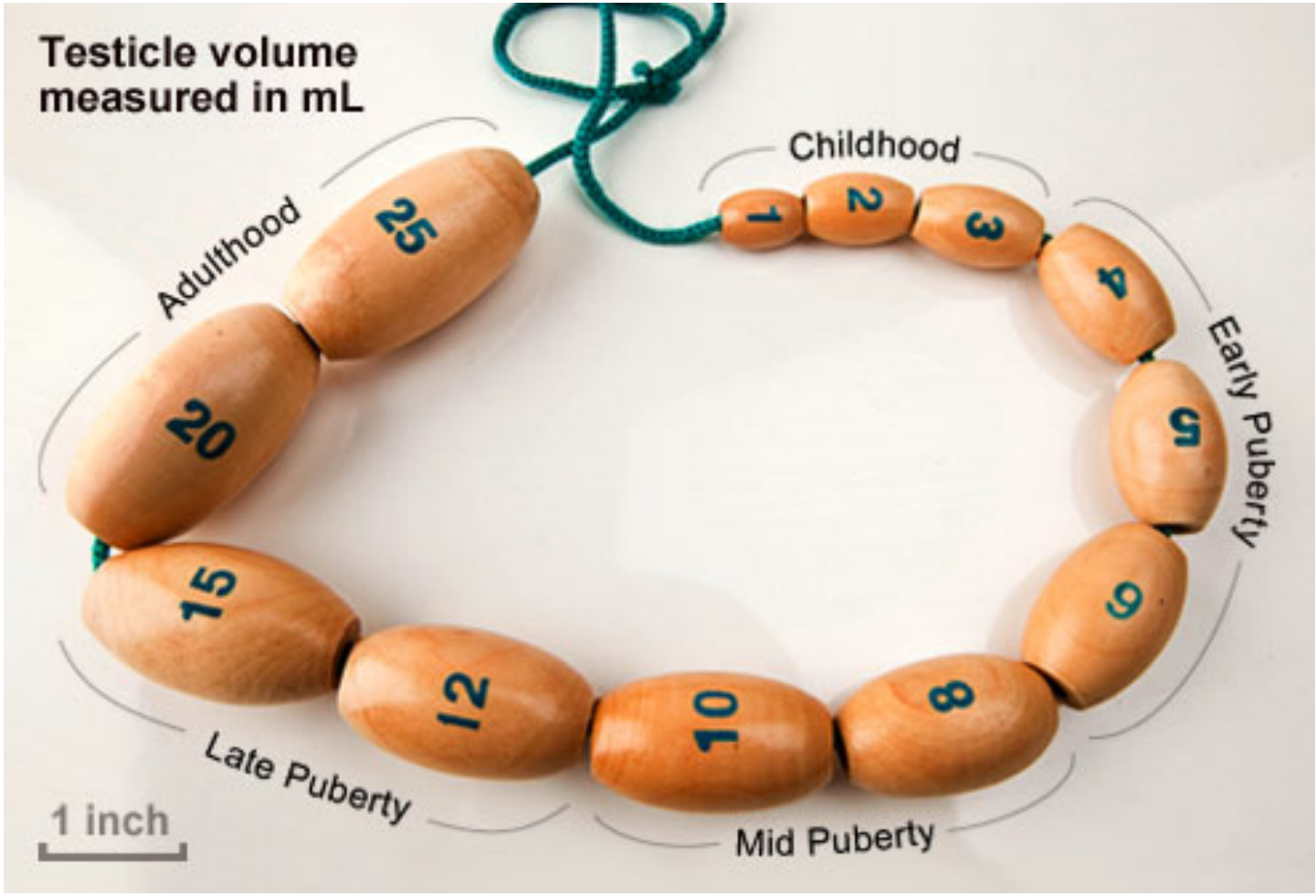
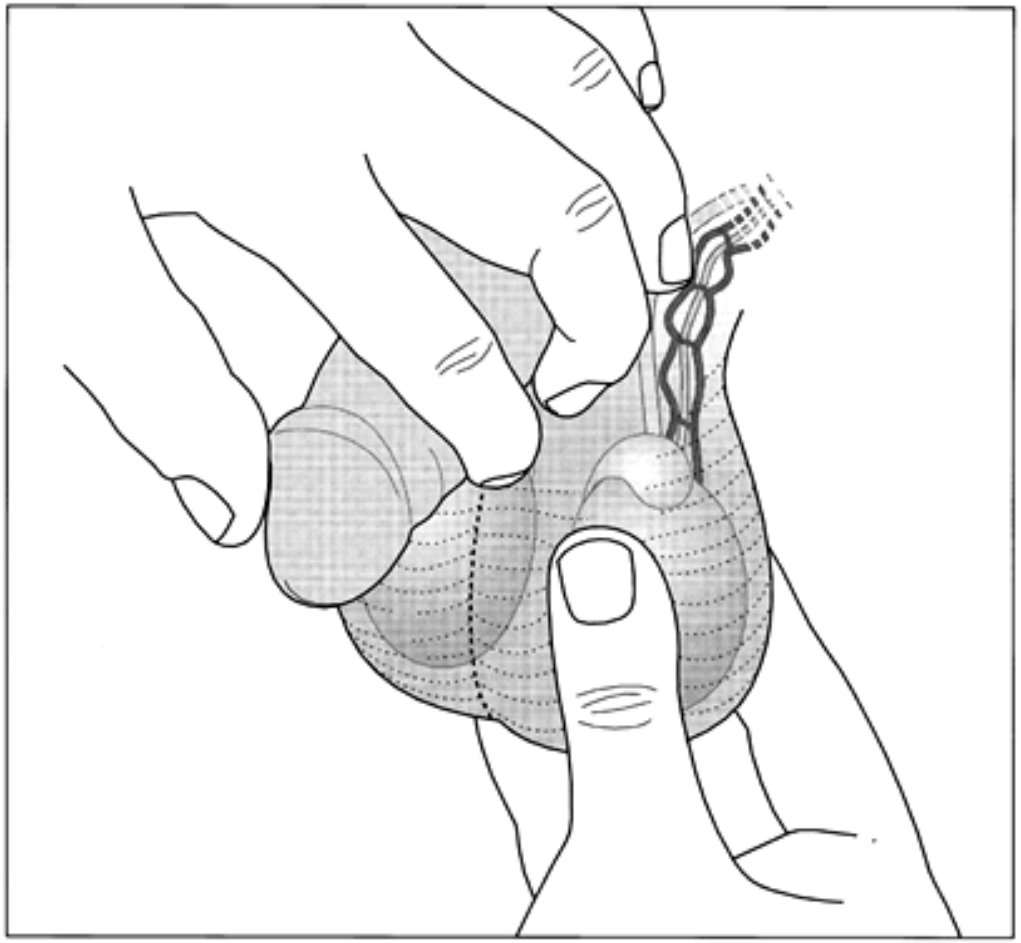
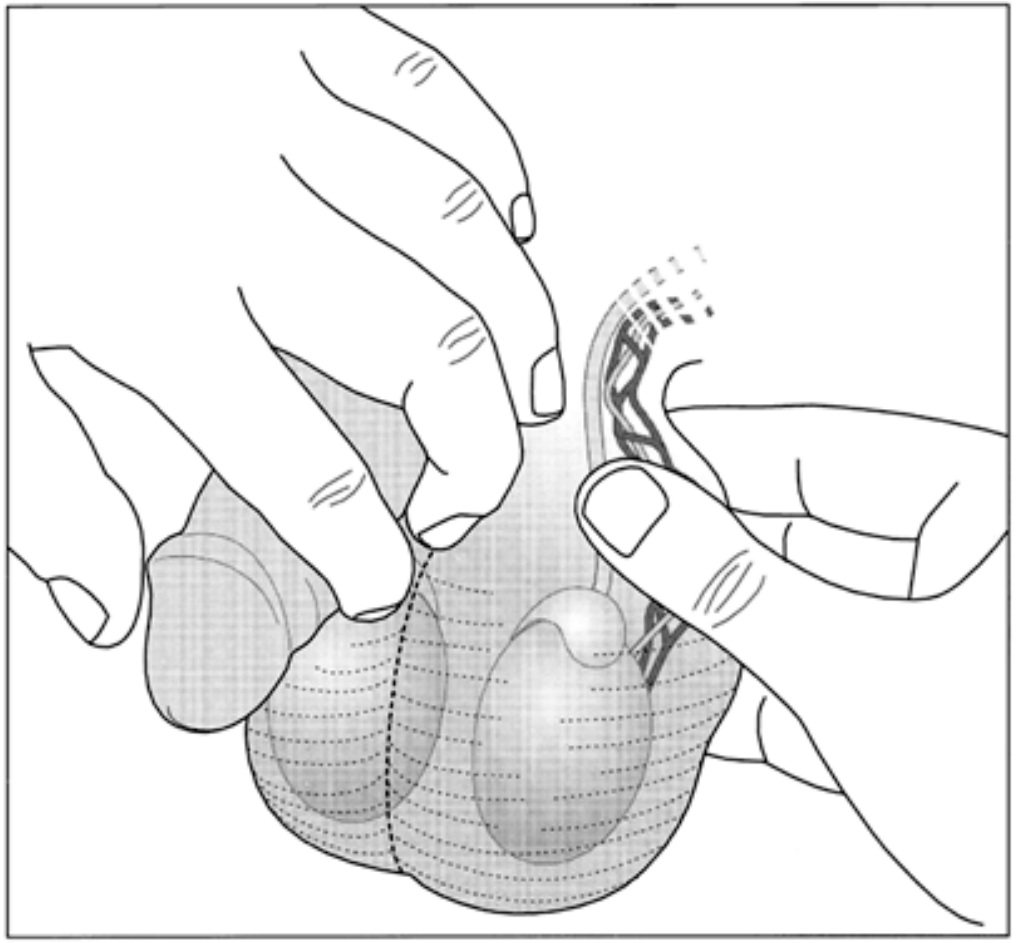
Clinical evaluation



Clinical evaluation





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Hormonal evaluation

- FSH
- LH
- Testosterone, total
- Prolactin
- Thyroid evaluation
- Inhibin B (Inh B)
- Anti-Müllerian hormone (AMH)

FSH

- Differential diagnosis between central (hypothalamus, pituitary) and peripheral (testicular) failure
- Variation <10%
- Strong correlation with:
  - Testicular histology
  - Sperm count
  - GnRH stimulation

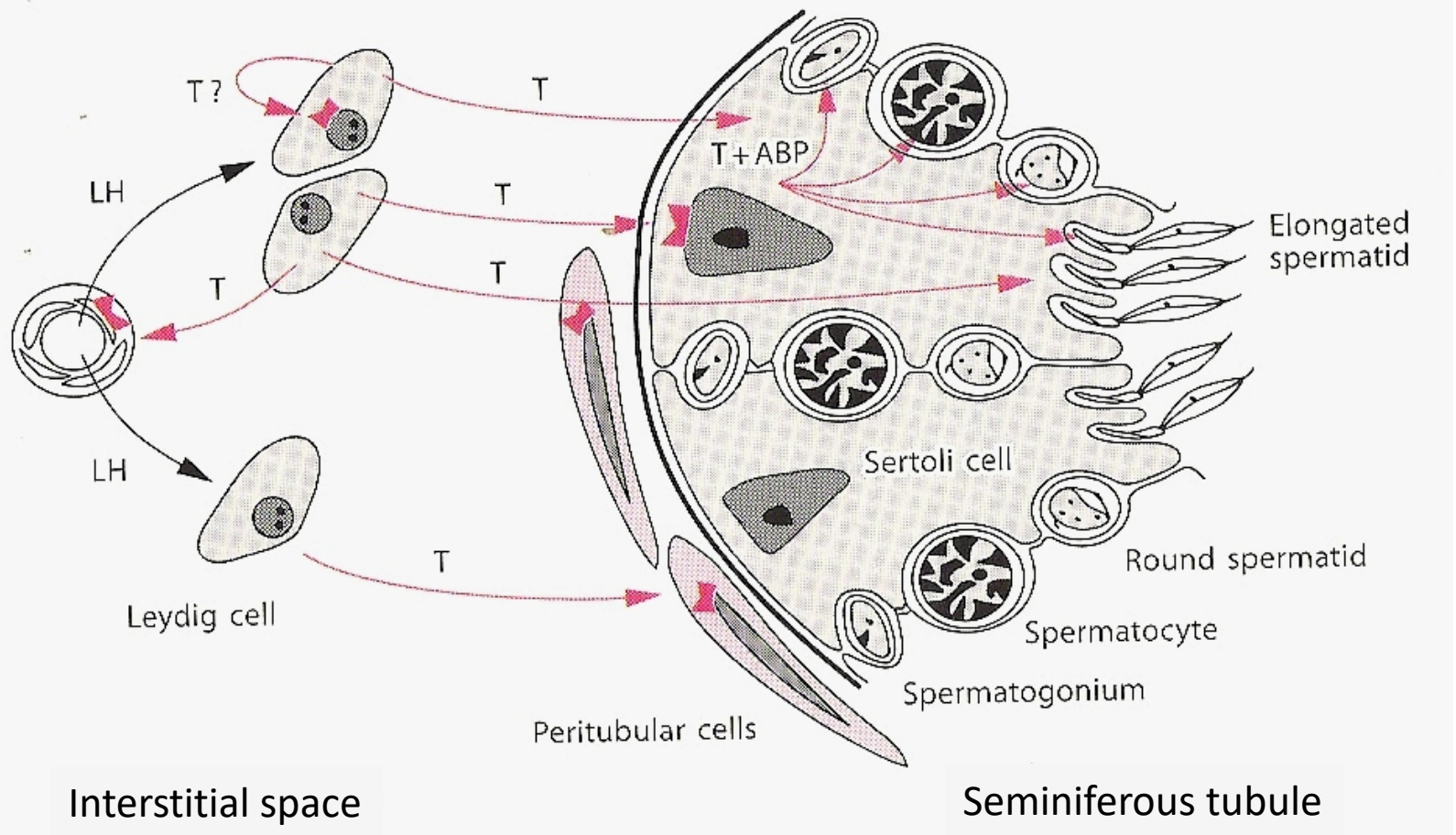
Inh B

- TGF-β family glycoprotein
- Exclusive Sertoli cell product
- Endocrine action:
  - FSH inhibition
- Paracrine effects
- Positive correlation with sperm count and testicular size
- Prognostic factor for TESE

AMH

- TGF-β family glycoprotein
- Sertoli cell product
- Endocrine action:
  - Müllerian duct reversal
- Paracrine and autocrine actions
- Prognostic factor for TESE

Testicular histology



Nieschlag E, Behre HM. Andorlogy, 1997

Diagnostic evaluation

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Semen reference ranges

- Liquefaction
  - < 60 min
- Appearance
  - Non-translucent
- Viscosity
  - Filaments < 2 cm
- pH
  - > 7.2
- Volume
  - > 1.5 ml
- Concentration
  - > 15 millions/ ml
- Motility
  - > 40 (a + b + c)
  - > 32 (a + b)
- Normal morphology
  - > 4%

Cooper TG, et al. Hum Reprod Update 2010, 16:231

Semen reference ranges

Table II Distribution of values, lower reference limits and their 95% CI for semen parameters from fertile men whose partners had a time-to-pregnancy of 12 months or less

	N	Centiles										
		2.5	(95% CI)	5	(95% CI)	10	25	50	75	90	95	97.5
Semen volume (ml)	1941	1.2	(1.0–1.3)	1.5	(1.4–1.7)	2	2.7	3.7	4.8	6	6.8	7.6
Sperm concentration (10^6/ml)	1859	9	(8–11)	15	(12–16)	22	41	73	116	169	213	259
Total number (10^6/Ejaculate)	1859	23	(18–29)	39	(33–46)	69	142	255	422	647	802	928
Total motility (PR + NP, %)*	1781	34	(33–37)	40	(38–42)	45	53	61	69	75	78	81
Progressive motility (PR, %)*	1780	28	(25–29)	32	(31–34)	39	47	55	62	69	72	75
Normal forms (%)	1851	3	(2.0–3.0)	4	(3.0–4.0)	5.5	9	15	24.5	36	44	48
Vitality (%)	428	53	(48–56)	58	(55–63)	64	72	79	84	88	91	92

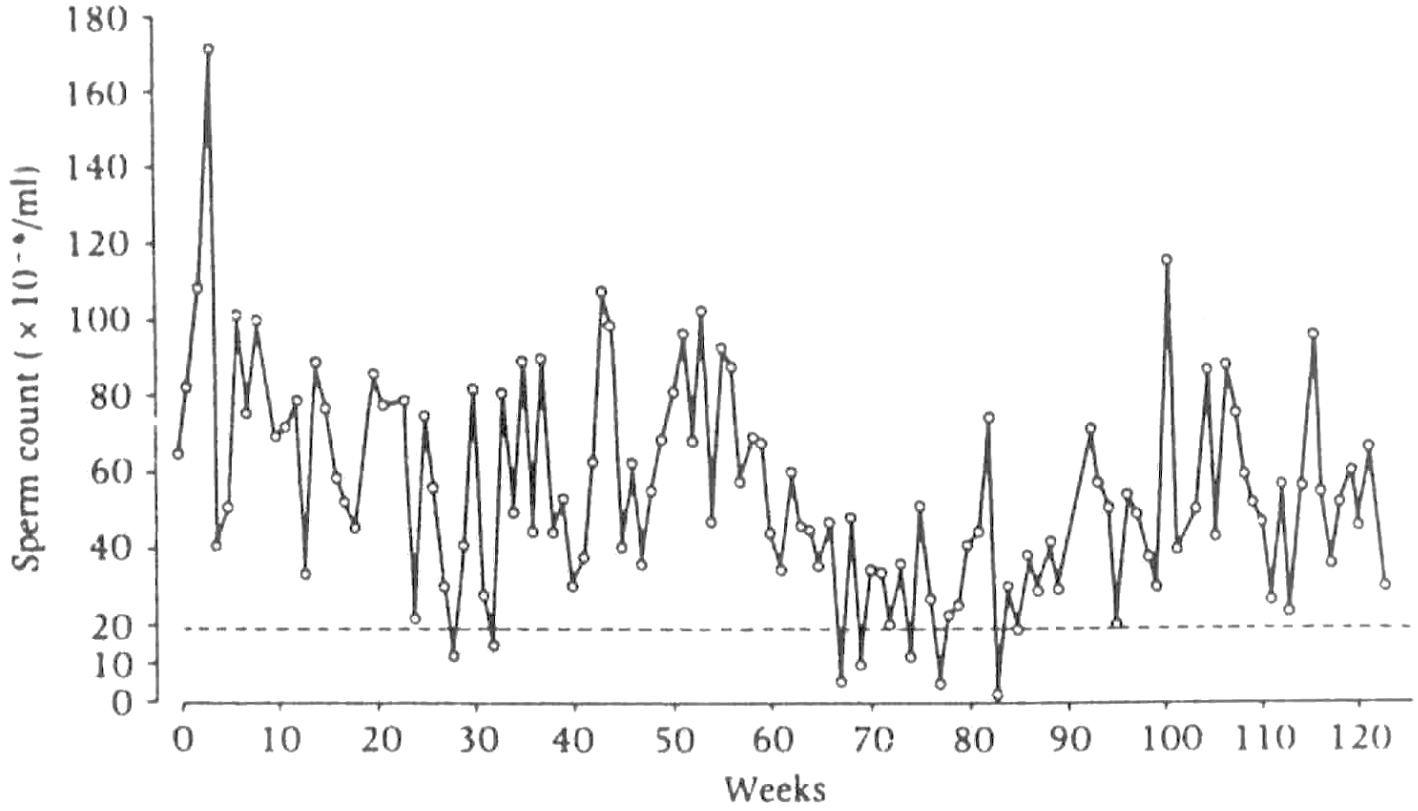
*PR, progressive motility (WHO, 1999 grades a + b); NP, non-progressive motility (WHO, 1999 grade c).
The values are from unweighted raw data. For a two-sided distribution the 2.5th and 97.5th centiles provide the reference limits; for a one-sided distribution the fifth centile provides the lower reference limit.

Cooper TG, et al. Hum Reprod Update 2010, 16:231

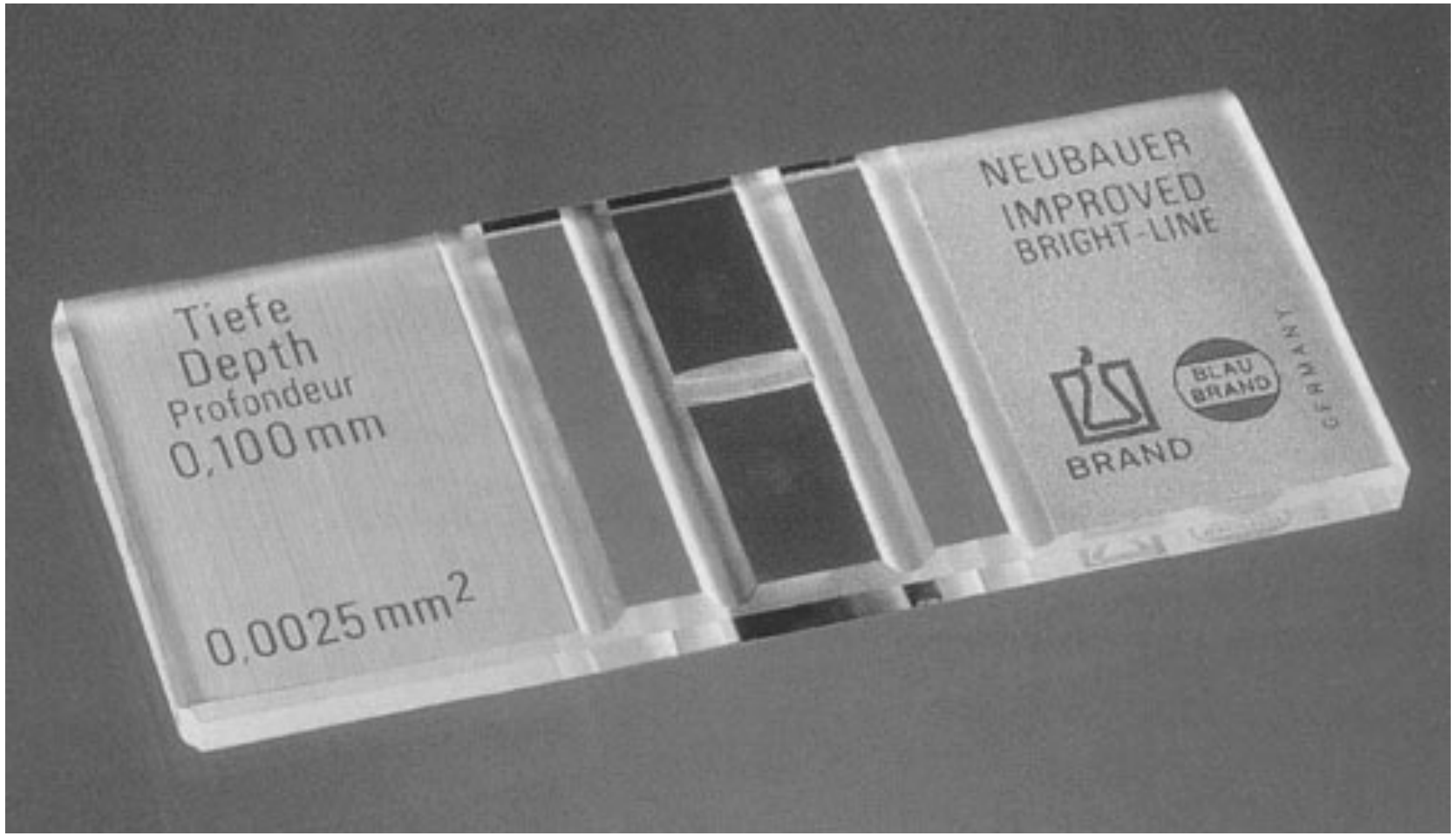
Definitions

- Oligo-astheno-teratozoospermia
  - Low sperm number – motility – morphology
- Azoospermia
  - No presence of sperm, even after centrifugation of semen
  - Transient – permanent
- Cryptozoospermia
  - No presence of sperm, after the initial inspection
  - Presence of sperm, after centrifugation of semen
- Aspermia
  - No presence of semen

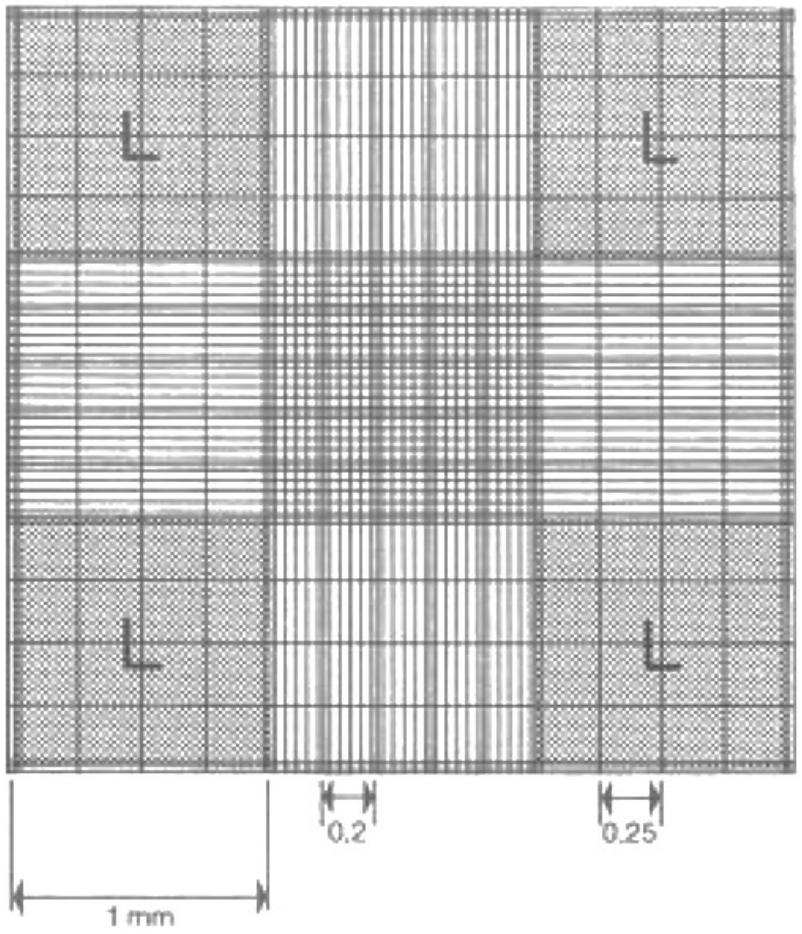
Sperm concentrations



Concentration

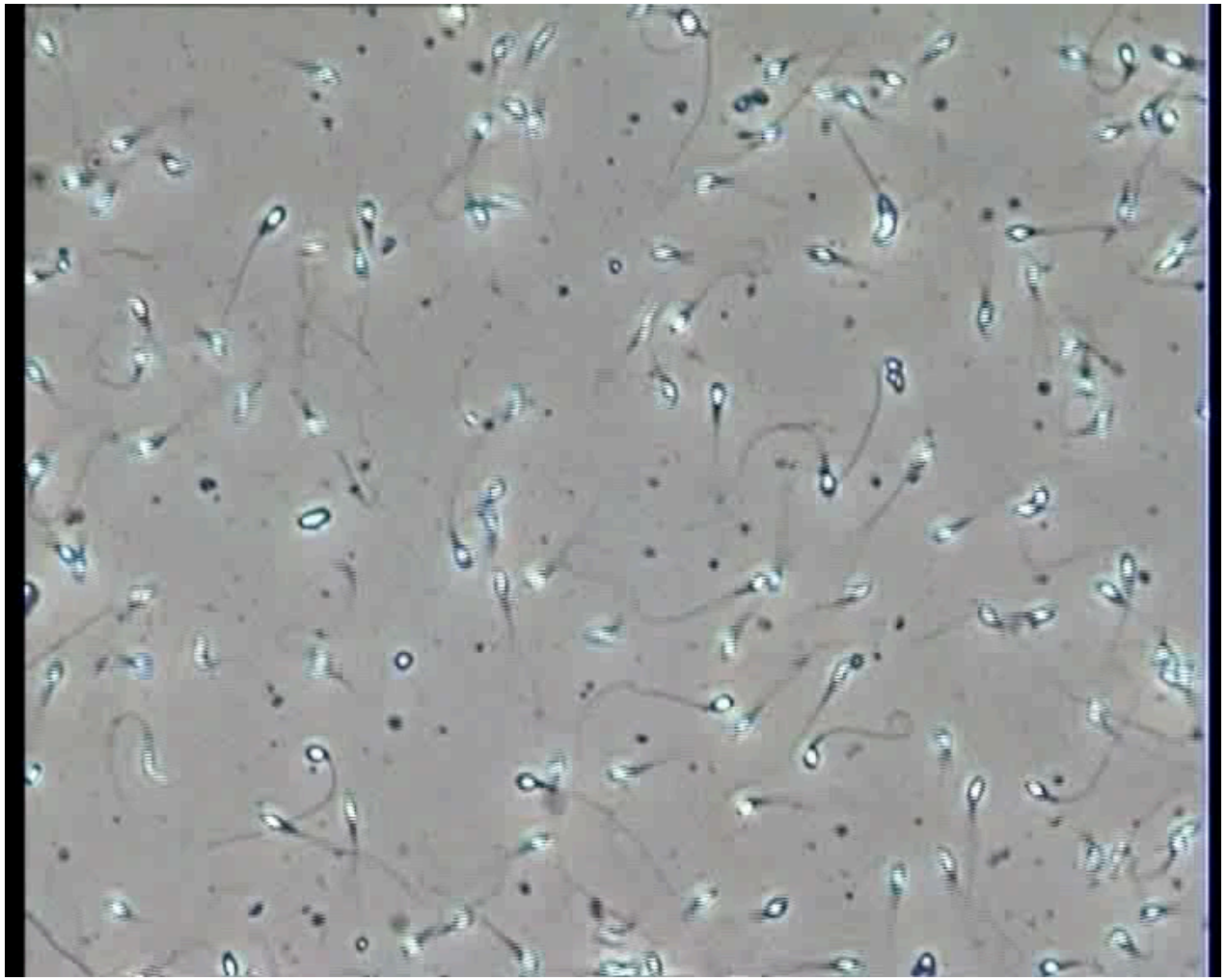


Concentration



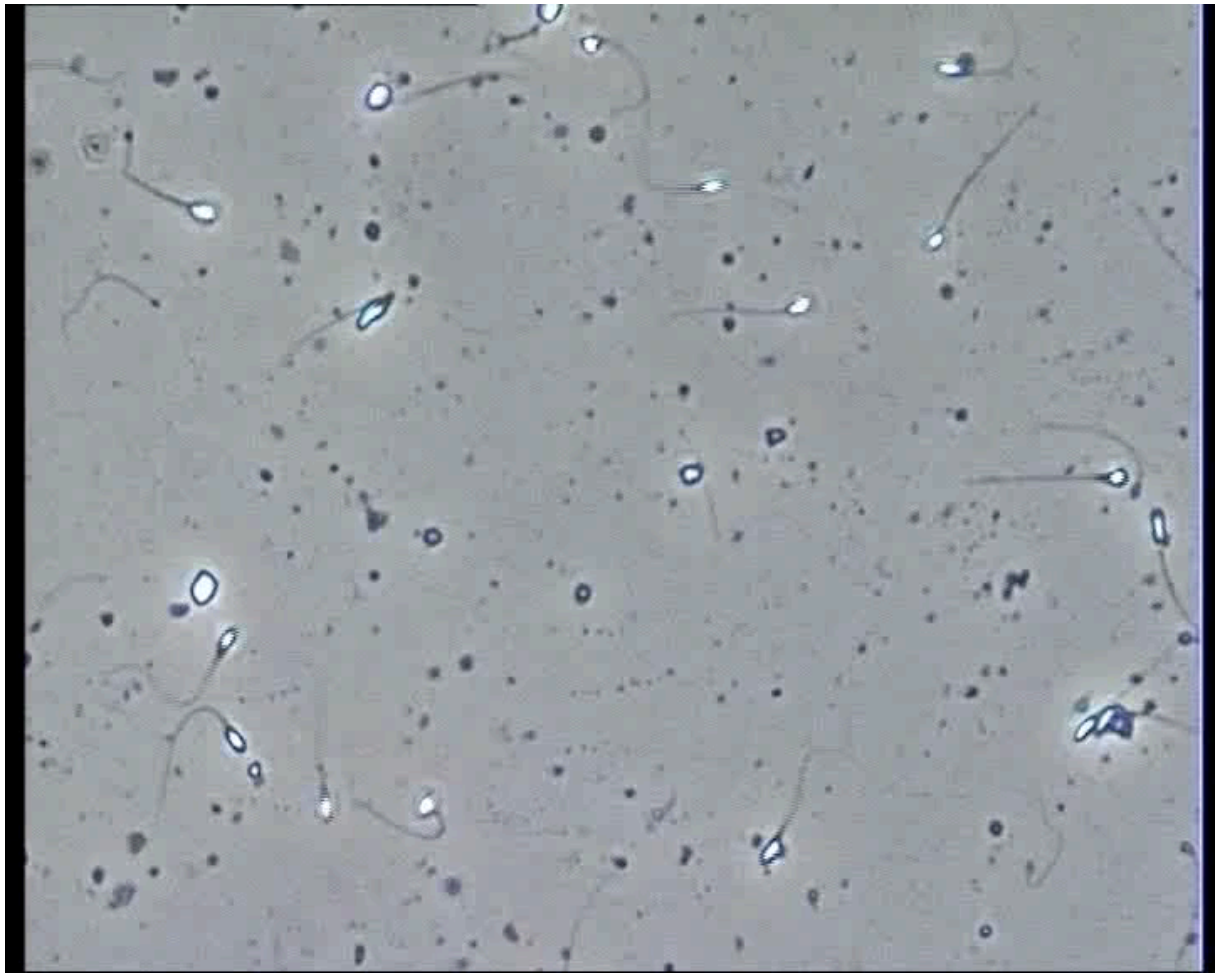
Concentration

Motility



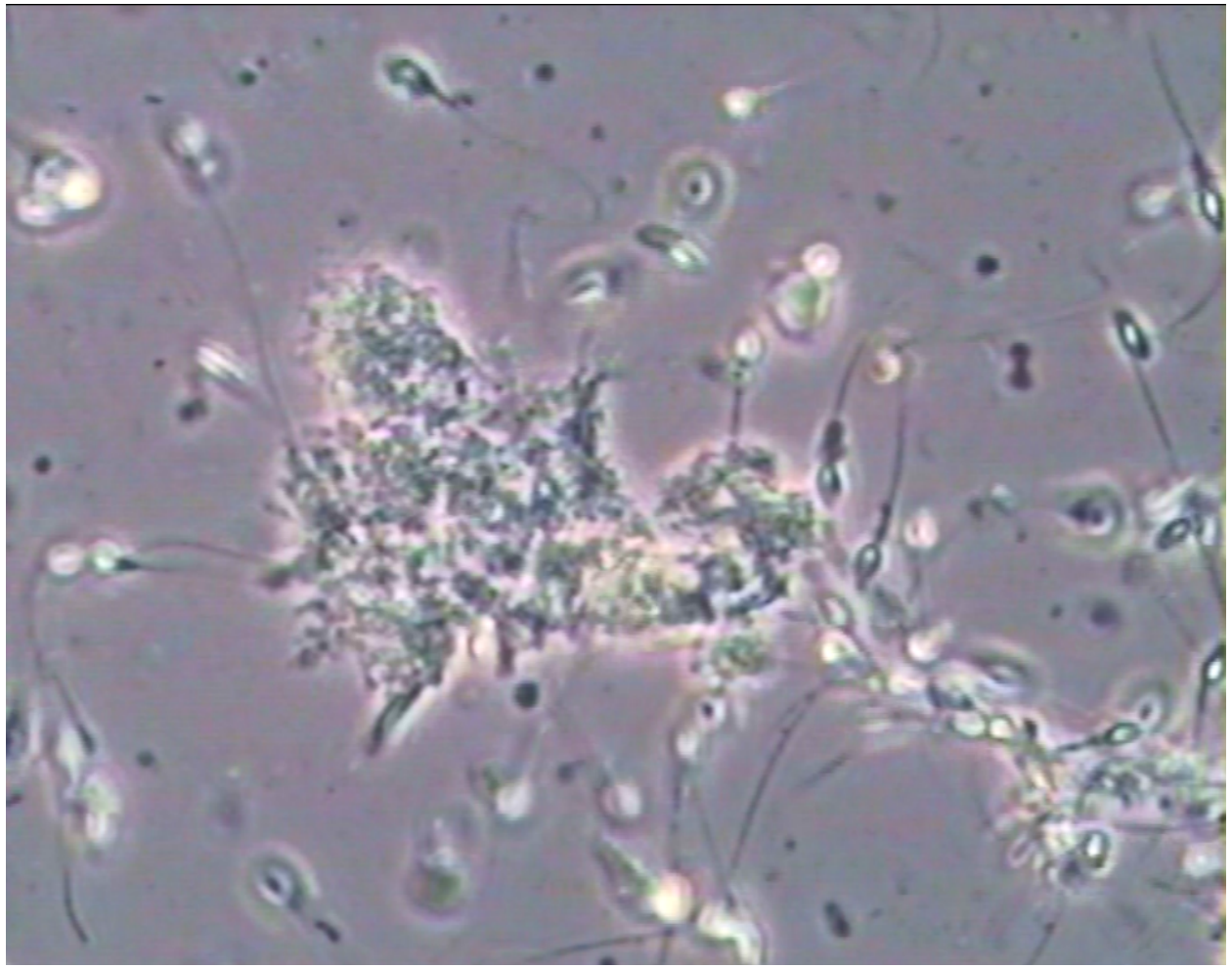
Specimen 524

Motility

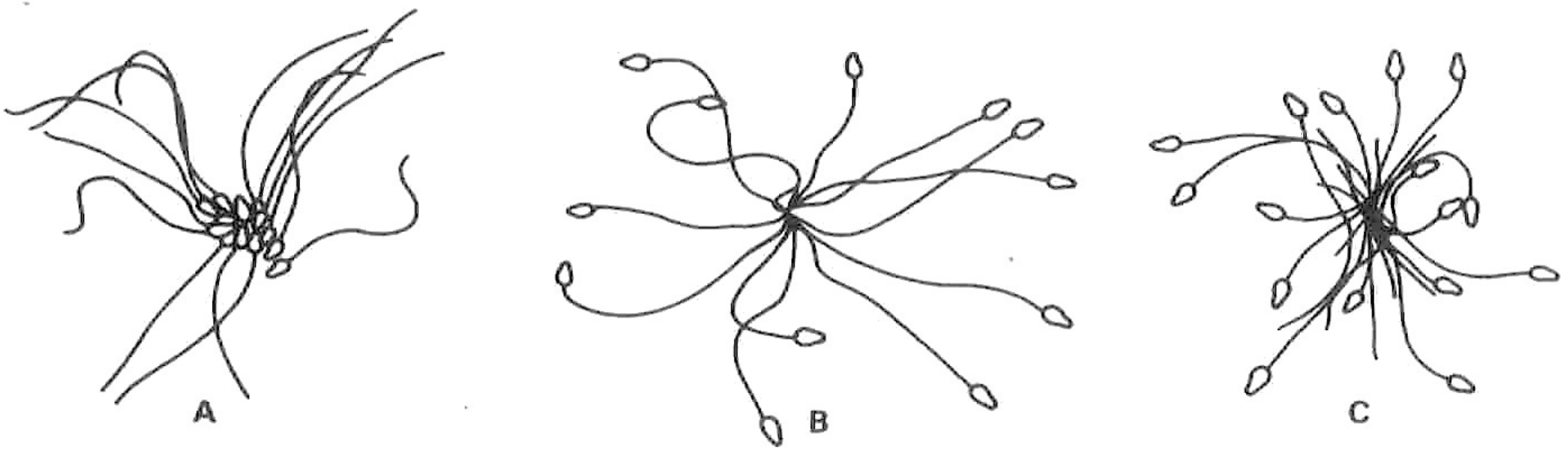


Specimen 623

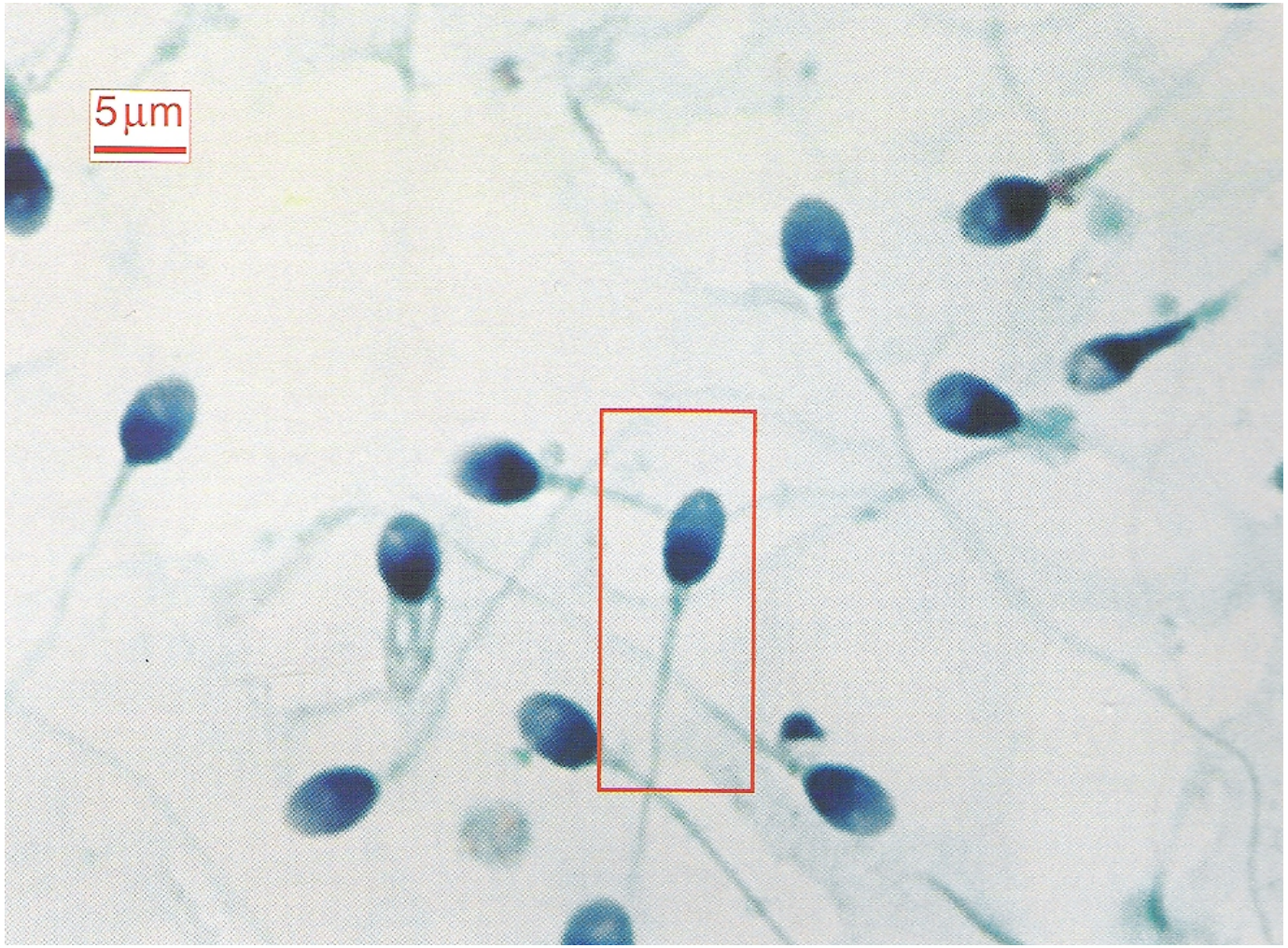
Aggregations



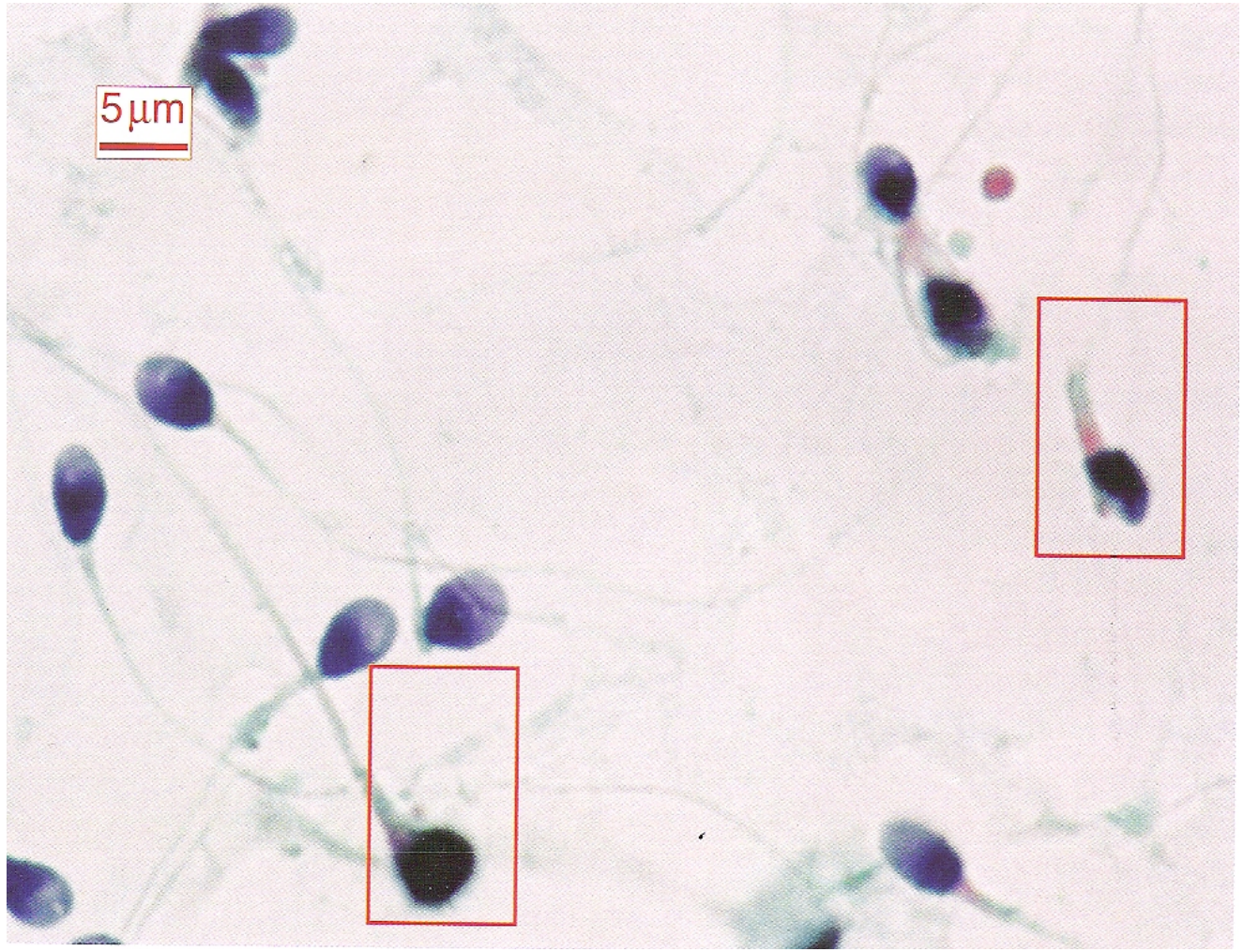
Agglutinations



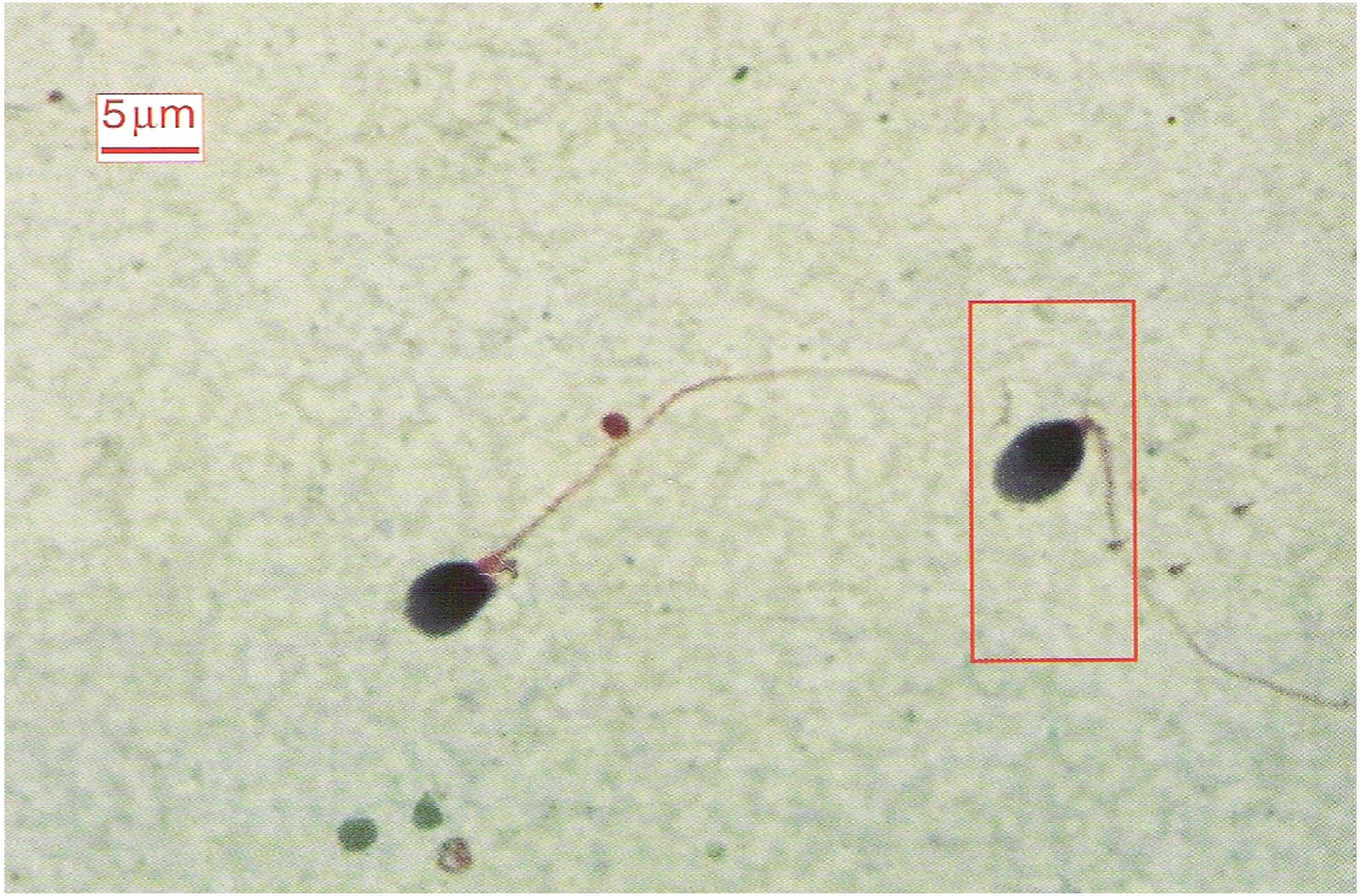
Normal sperm



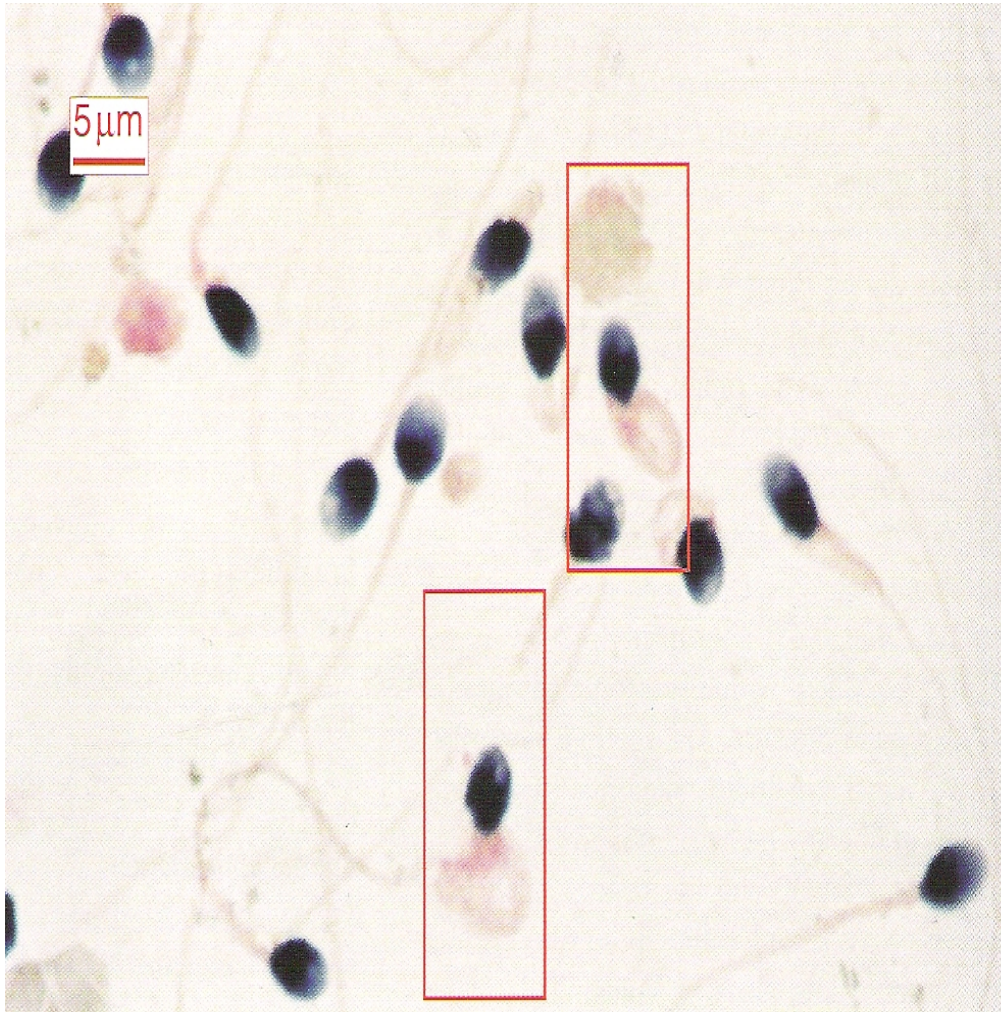
Head defect



Neck defect



Tail defect



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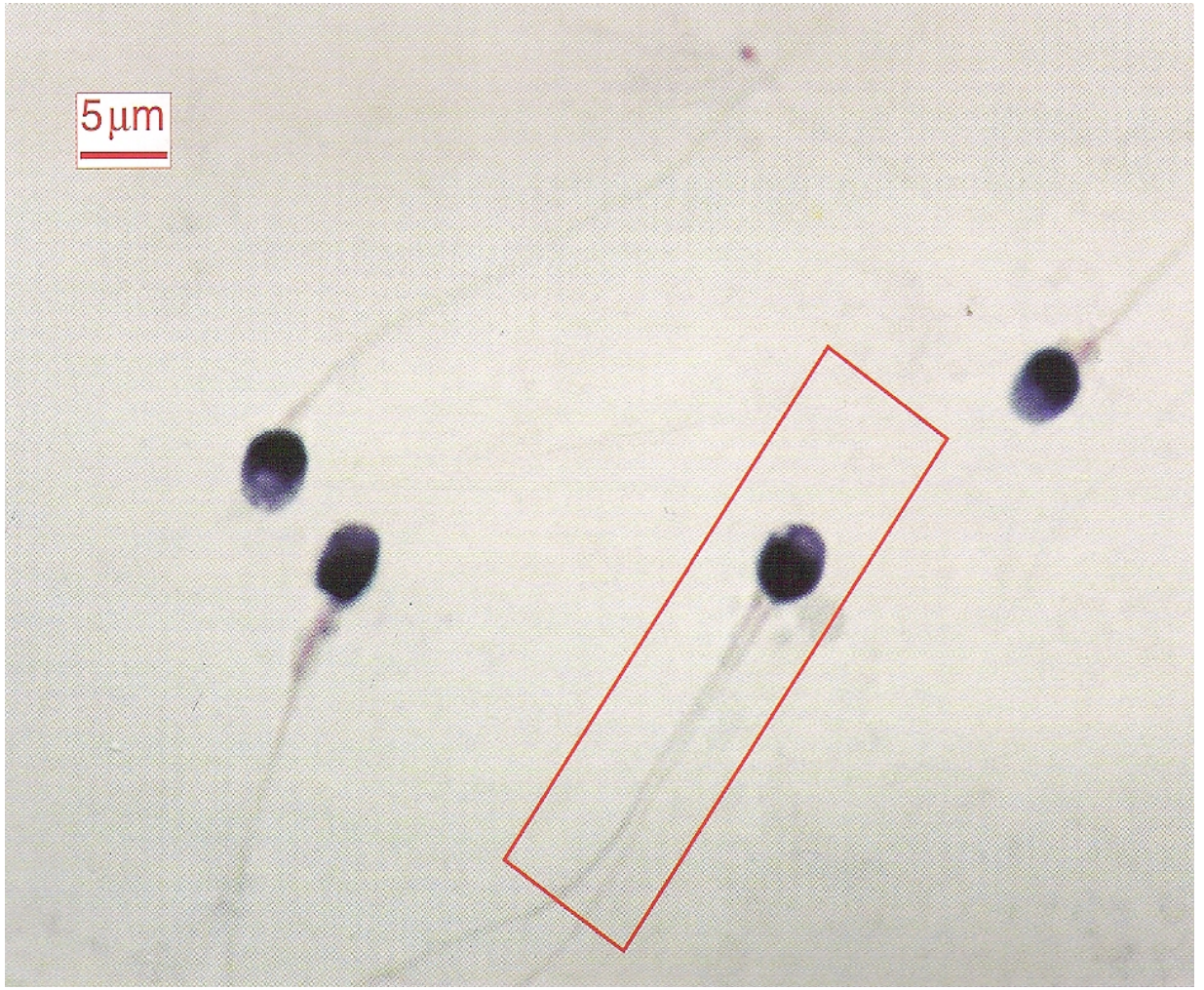
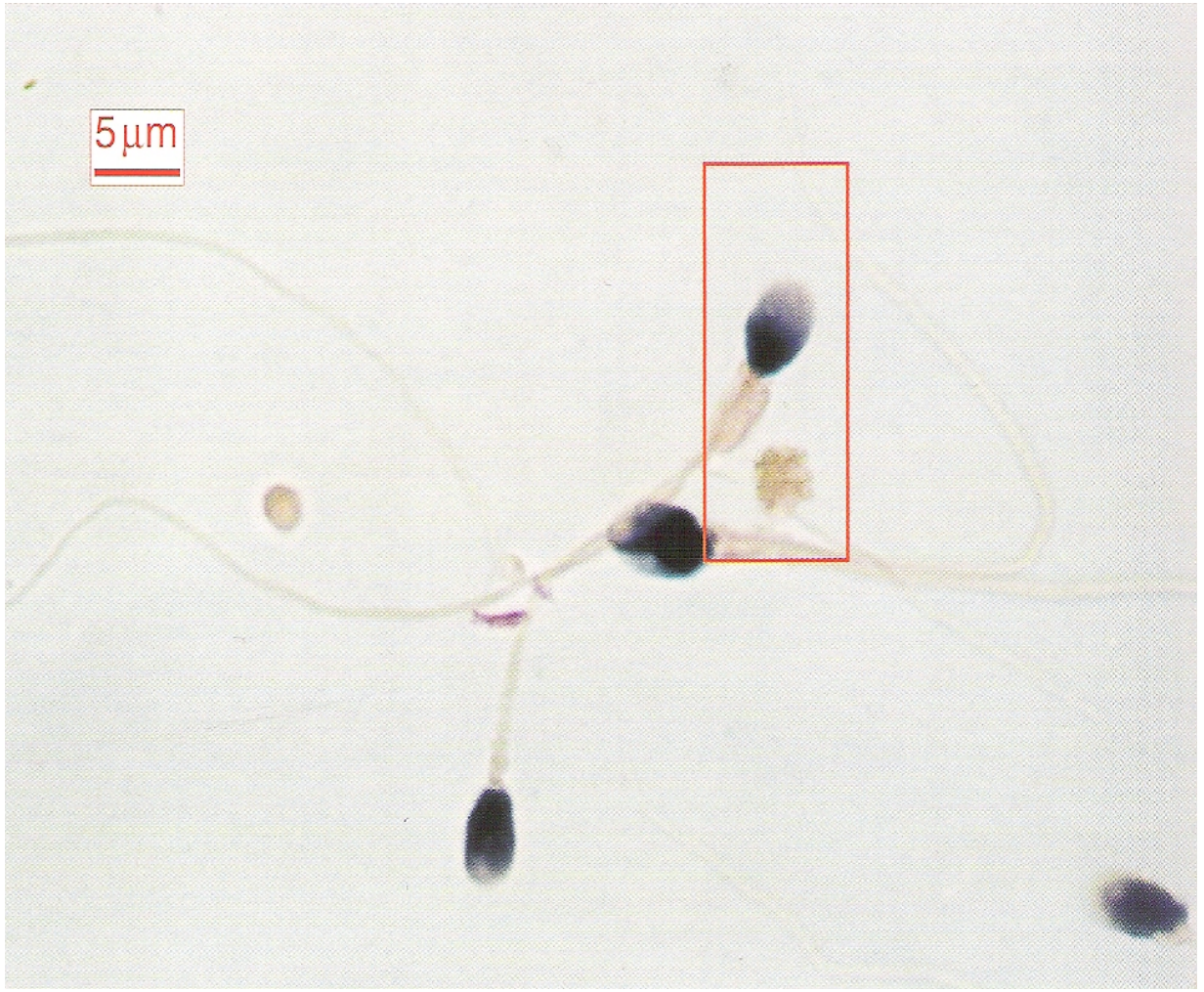


Cytoplasmic residual



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0

N/A

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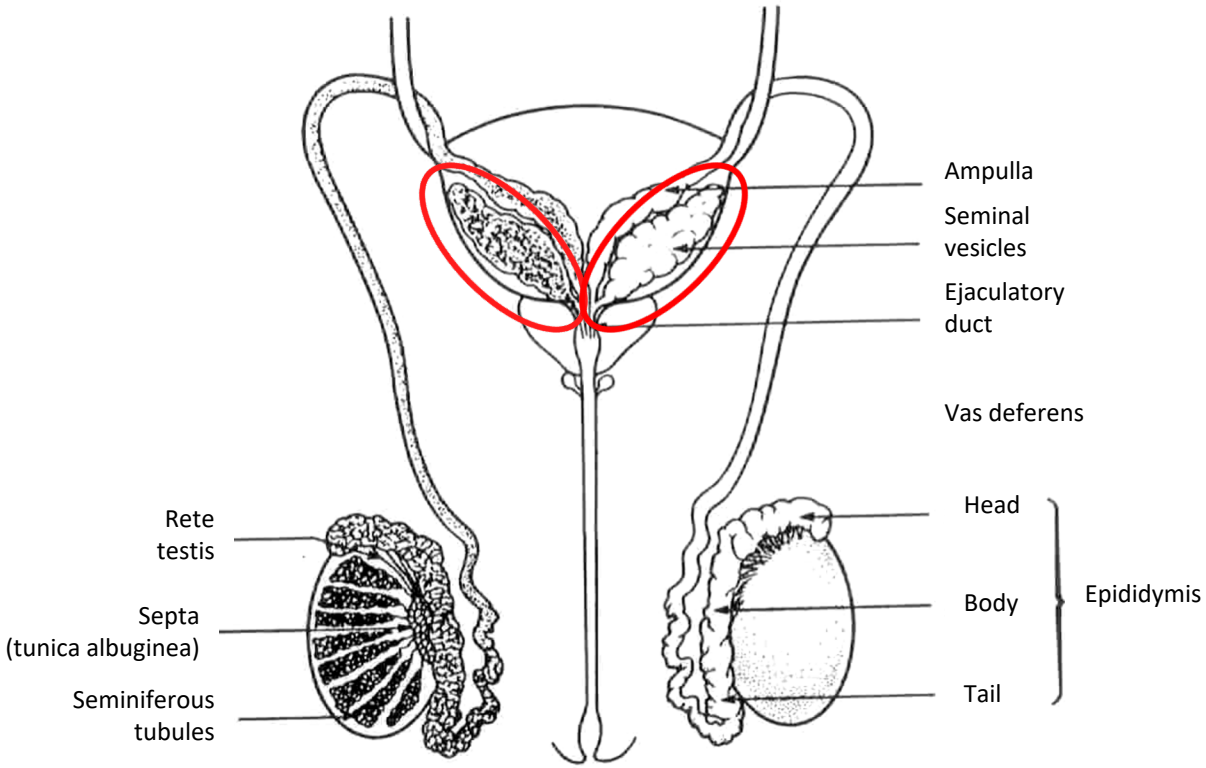
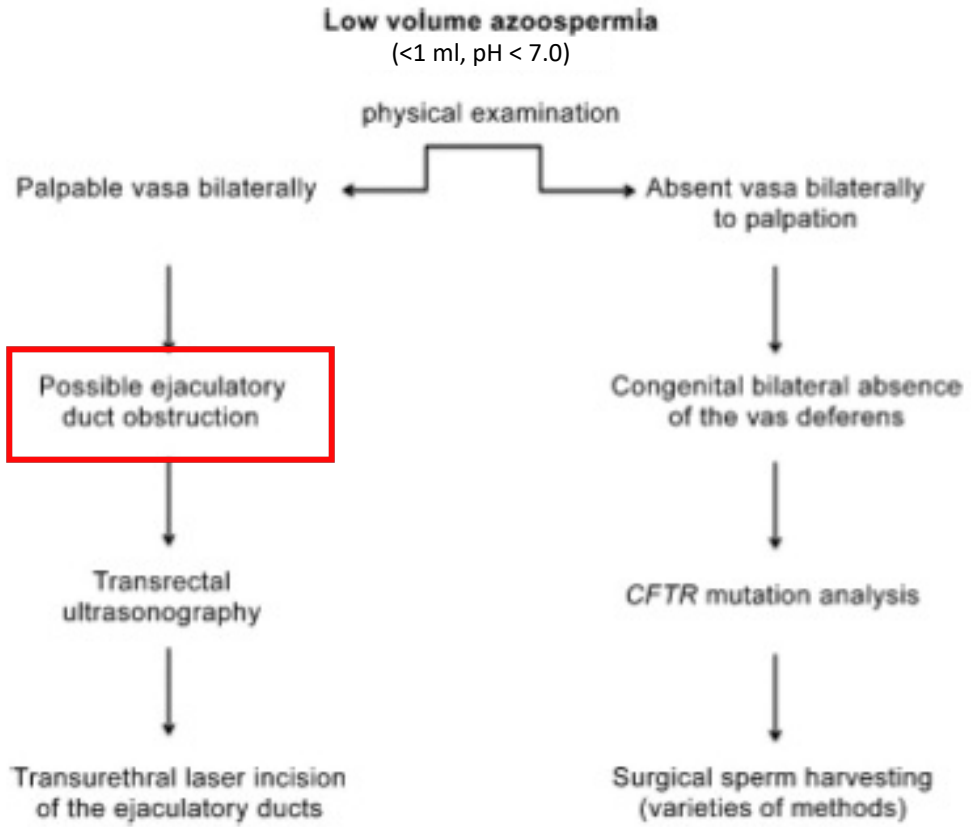
Cooper TG, et al. Hum Reprod Update 2010, 16:231

Anatomy of male reproductive system

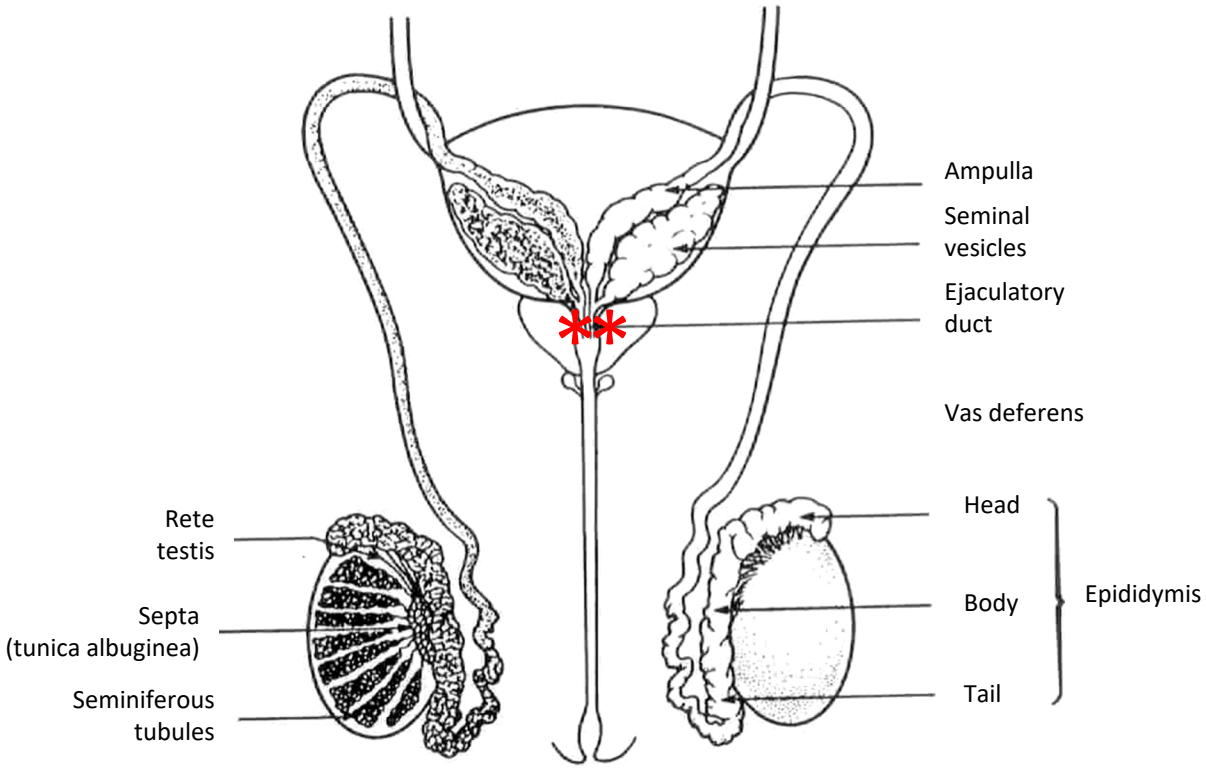


Diagnostic algorithm



Oates R. Asian J Androl 2012, 14:82

Anatomy of male reproductive system



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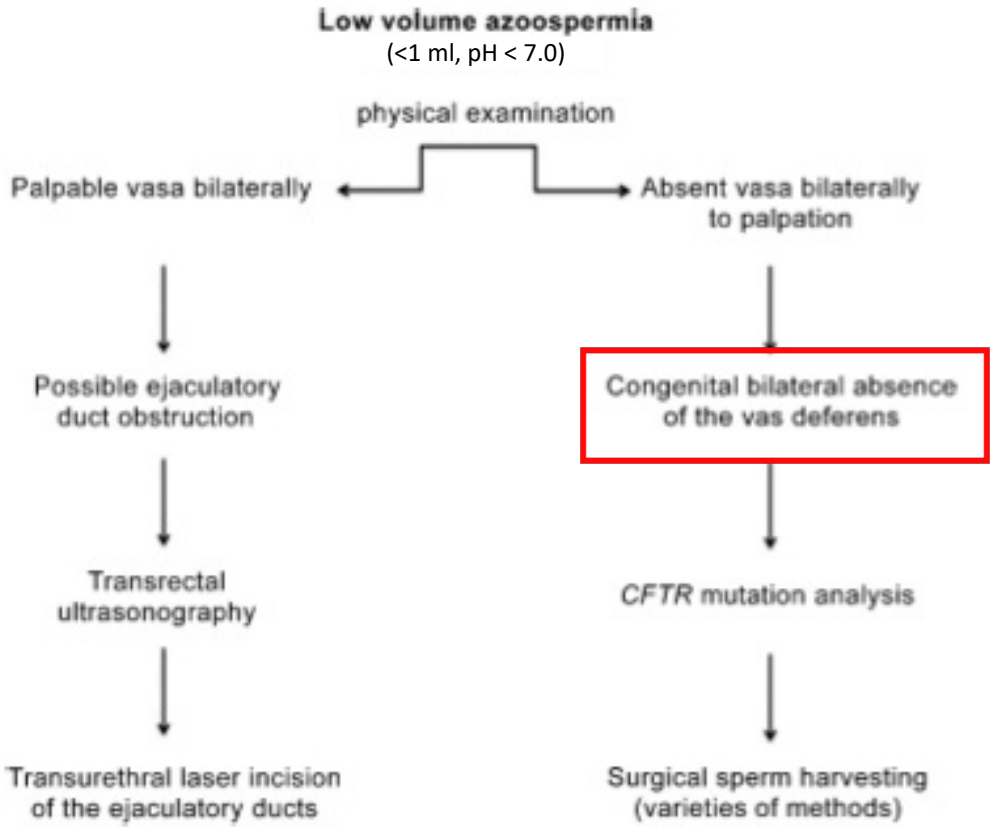

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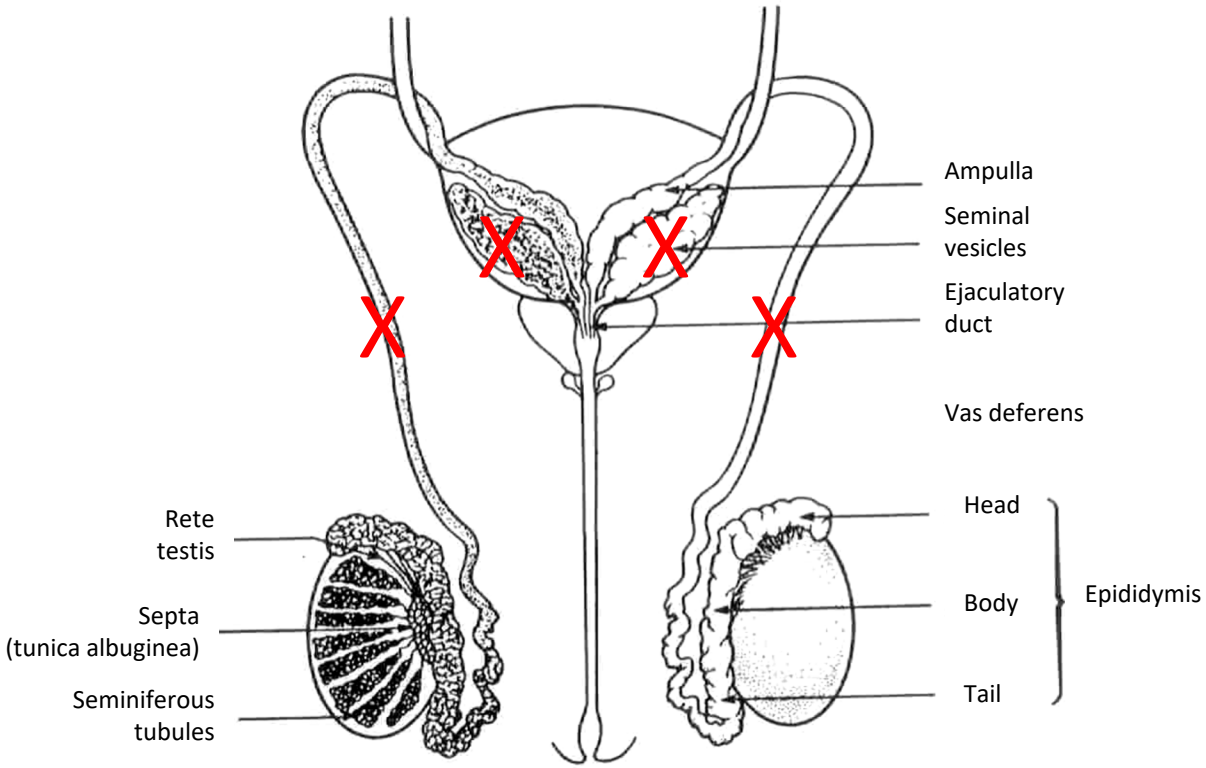

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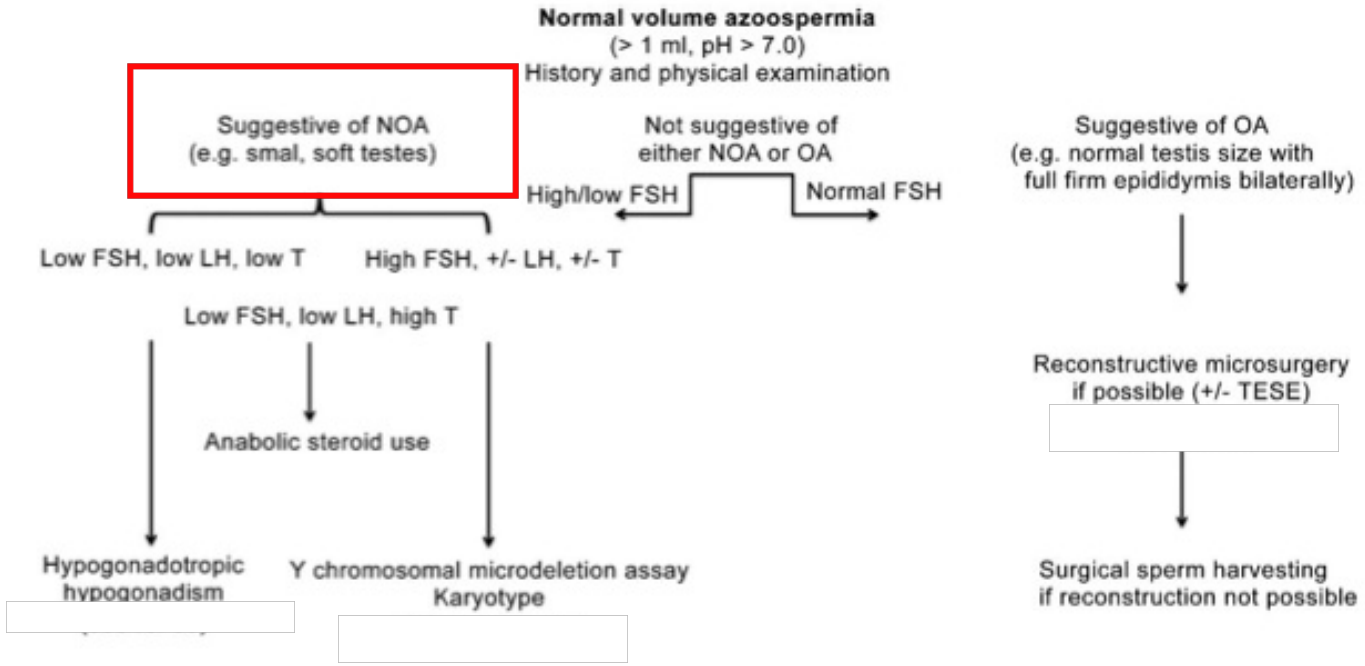

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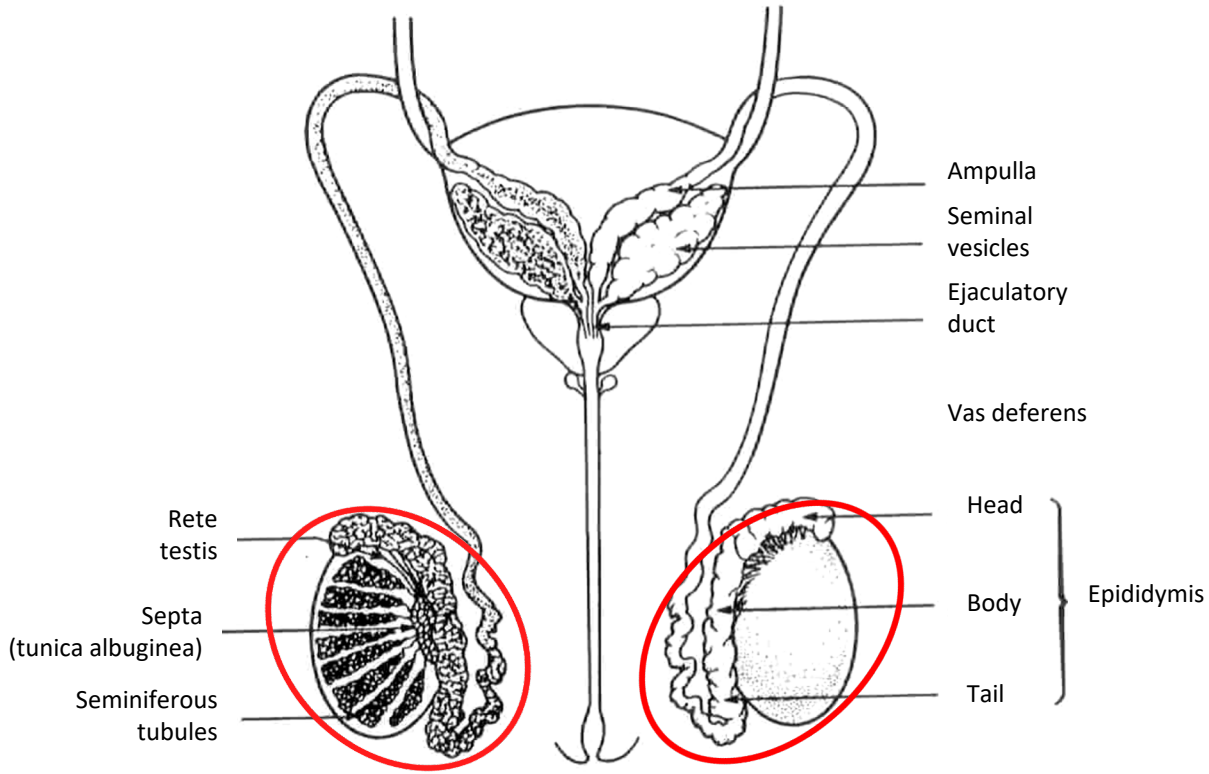

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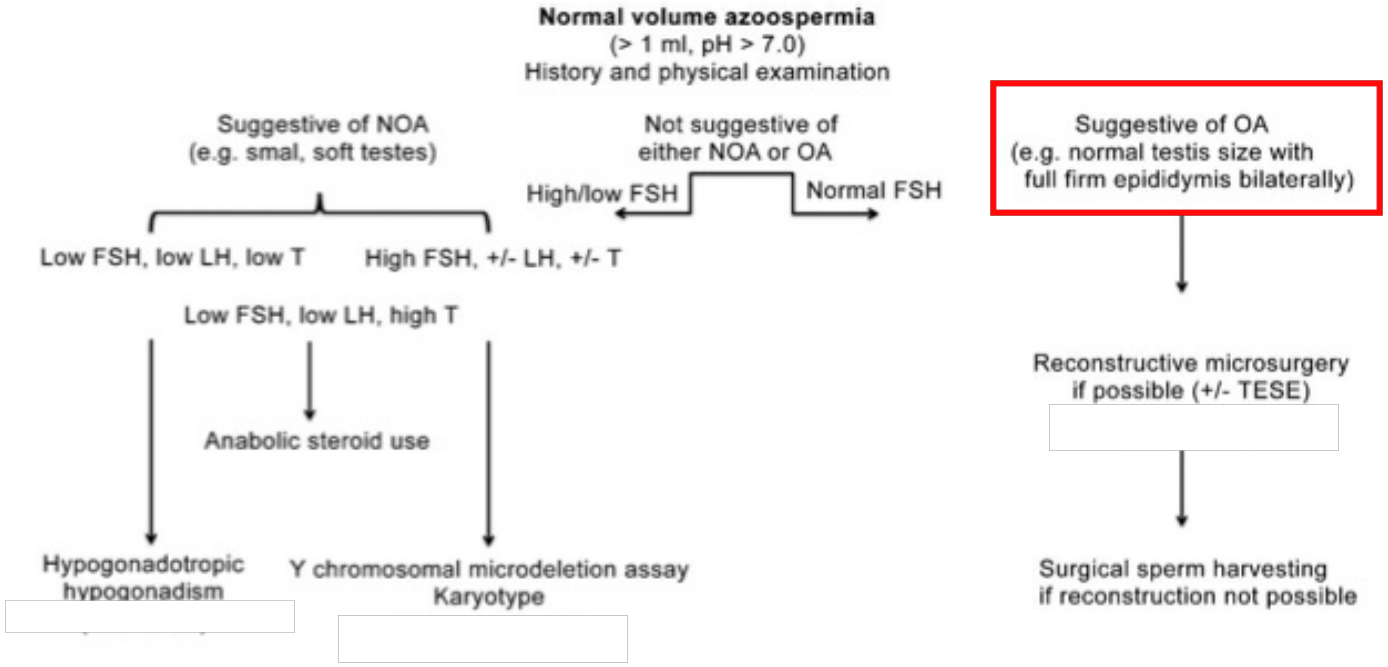

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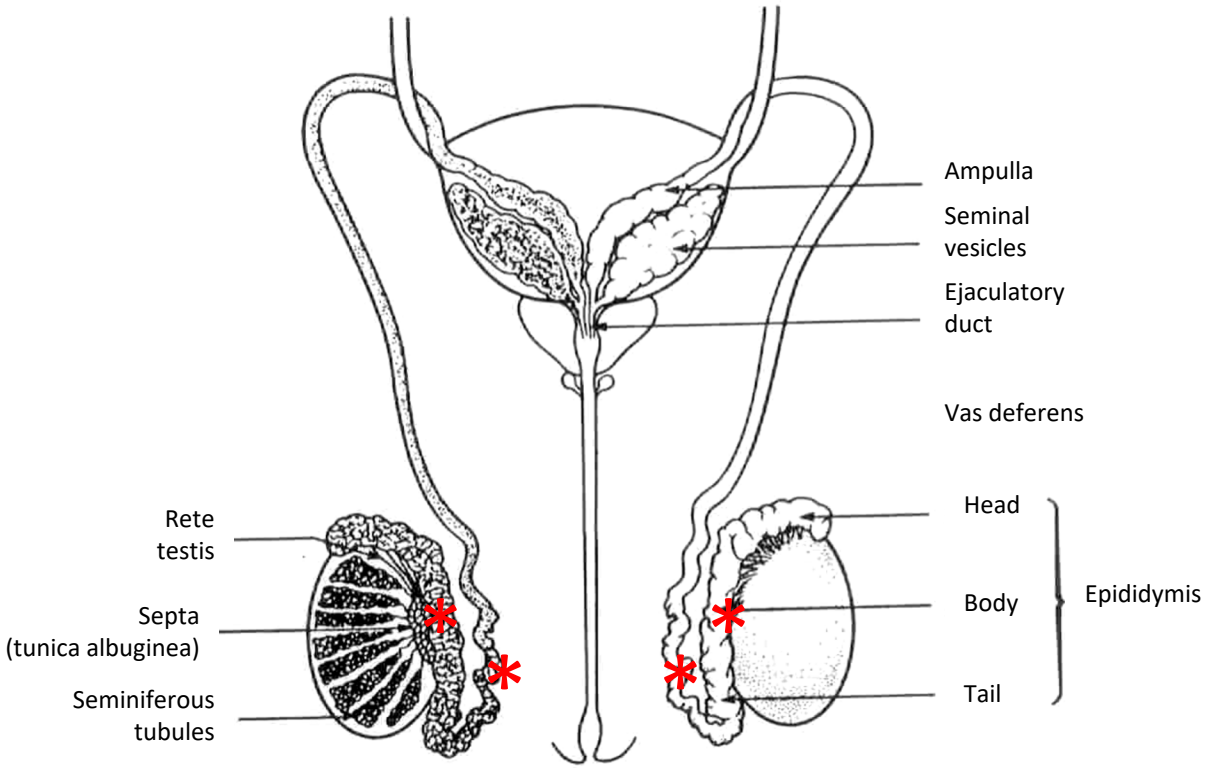
Anatomy of male reproductive system



Semen evaluation

- Spermiogram
- Biochemical evaluation of seminal plasma
- Semen culture
- Immunological evaluation
- Acrosome rection
- Sperm DNA fragmentation
- Functional tests

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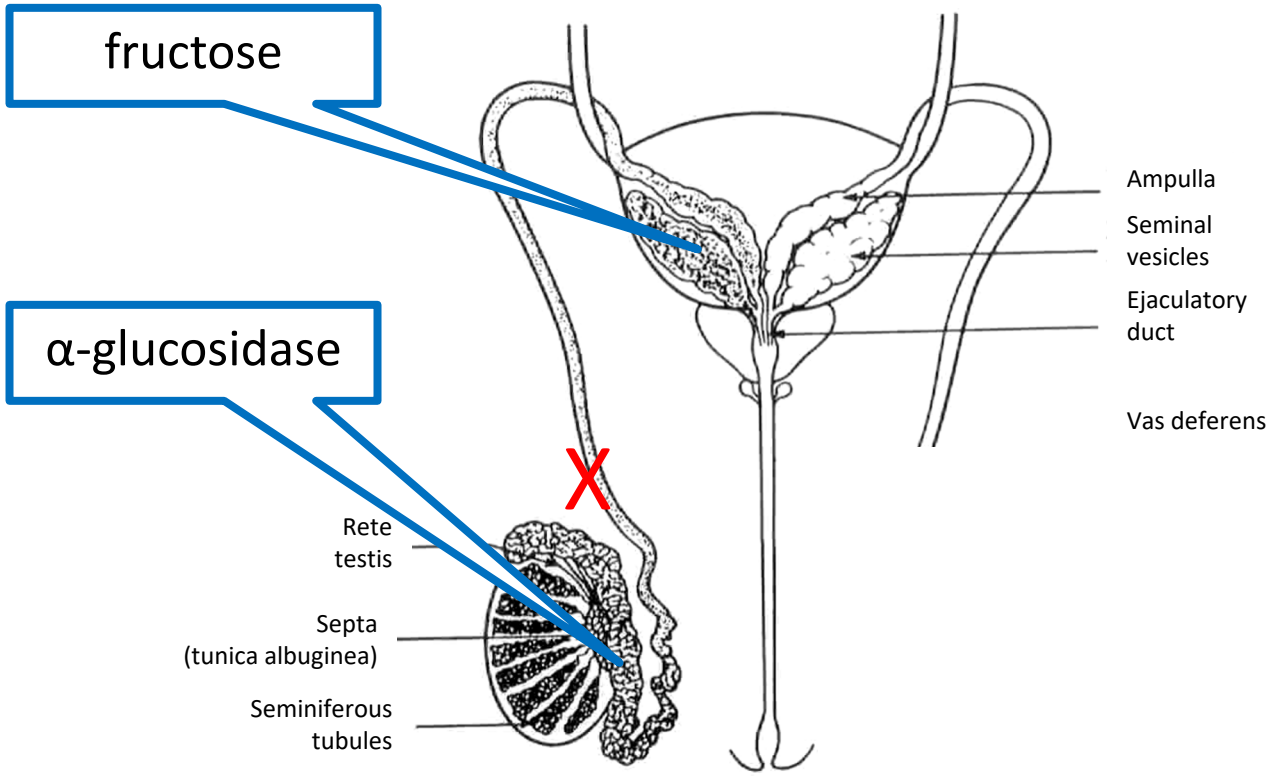

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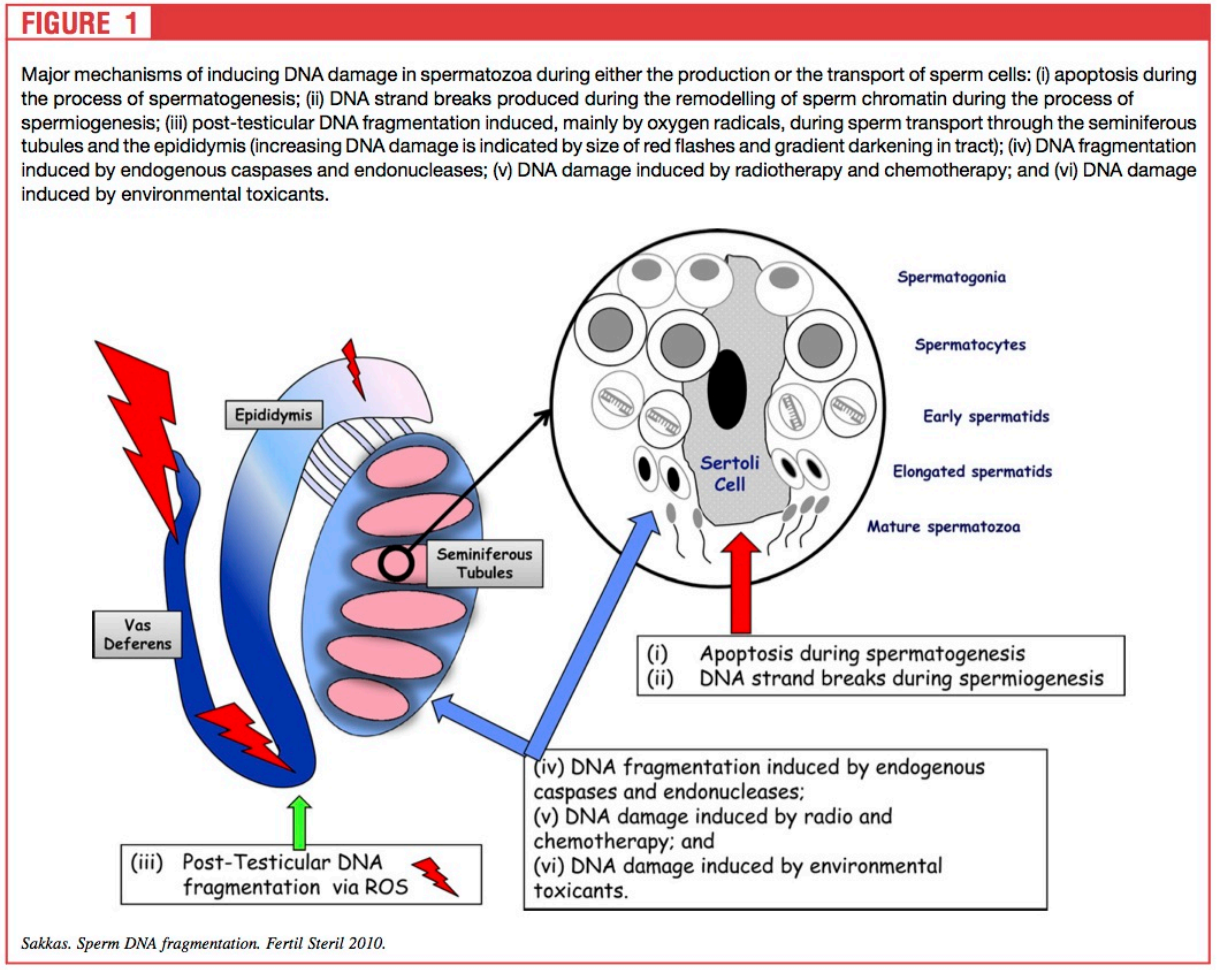
Pathophysiology

- Mechanisms
  - Oxidative: Reactive Oxygen Species (ROS)
  - Anti-oxidative: Antioxidant Scavenging Systems (ASS)

- Oxidative stress in male reproductive system results in sperm membrane damage and sperm DNA fragmentation

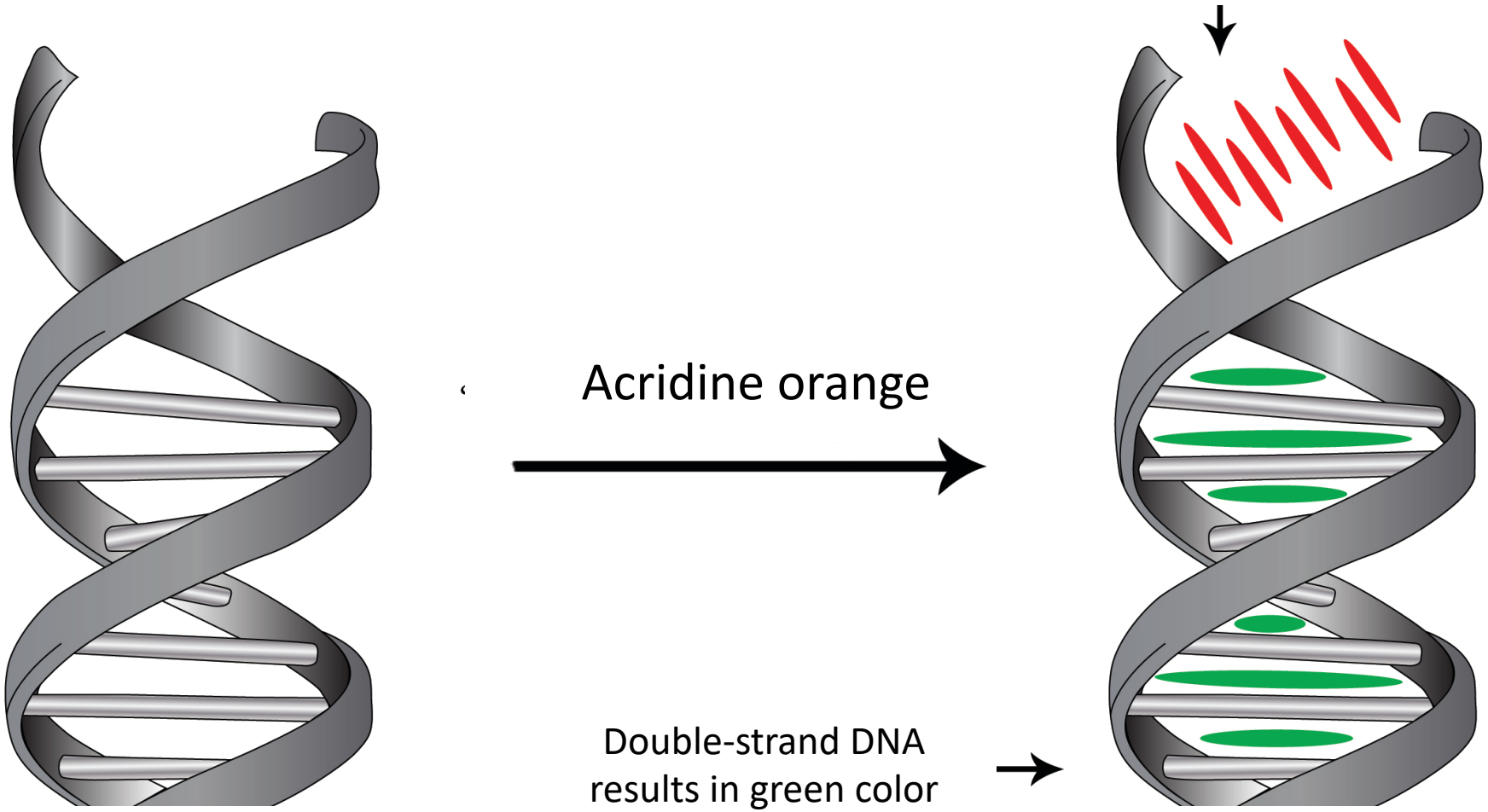
Agarwal A, et al. Reprod Biomed Online 2004, 8:616

Oxidative stress



Sakkas D, et al. Fertil Steril 2010, 93:1027

Sperm DNA fragmentation

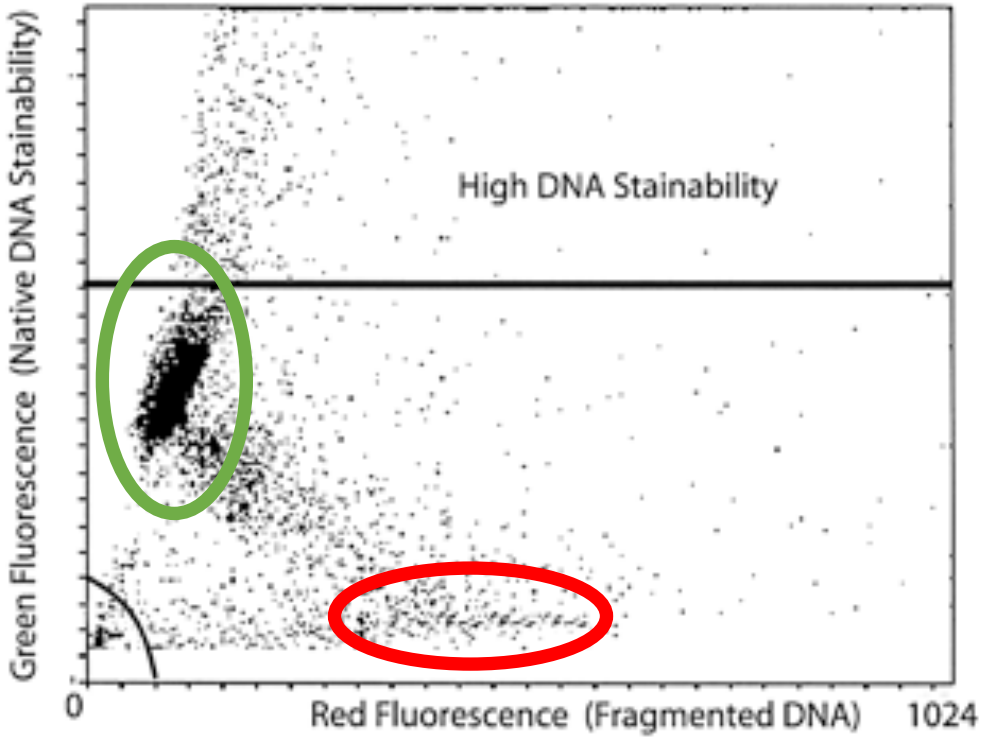


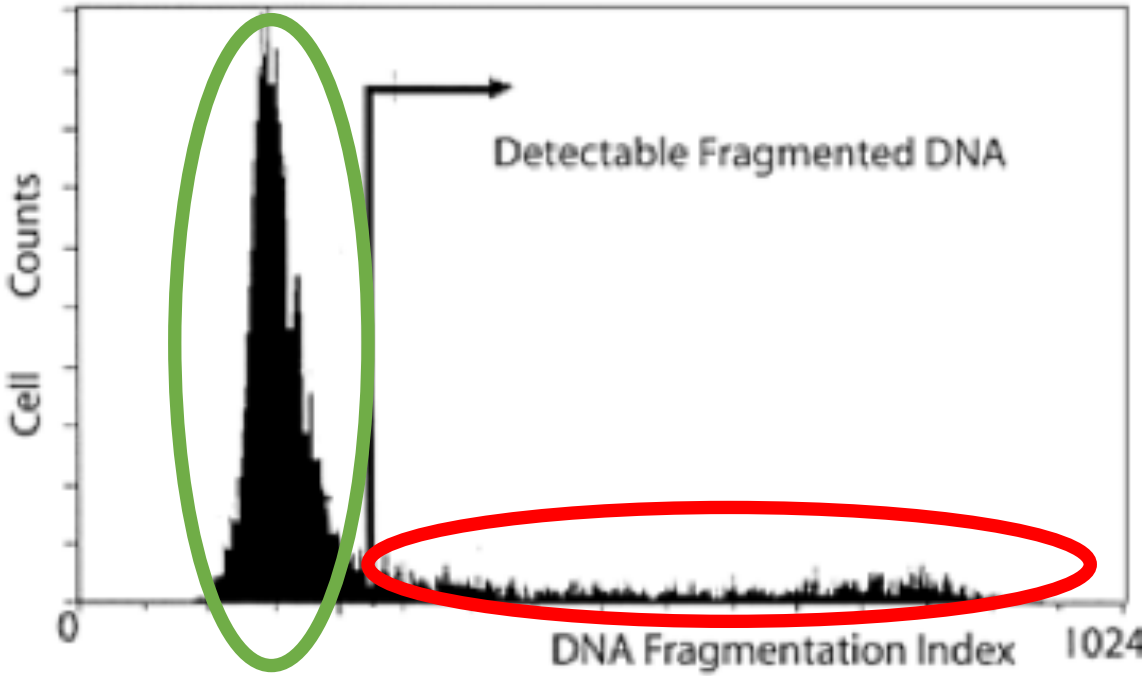
Kantartzi P-D. PhD thesis, AUTh, 2012

Evaluation methods

- Direct
  - COMET
  - TUNEL
  - NT
  - DBD-FISH
- Indirect
  - SCSA
  - AOT
  - Halosperm

Flow cytometry





Anti-oxidative substances

- Glutathione and vitamin E — Bhardwaj A, et al. Asian J Androl 2000, 2:225
- Free or total carnitine, α-glycosidase — Zopfgen A, et al. Hum Reprod 2000, 15:840
- Carnitine and acetyl-carnitine — Vicari E, et al. Hum Reprod 2001, 16:2338
- Selenium and vitamin E — Keskes-Ammar L, et al. Arch Androl 2003, 49:83
- Zinc and folid acid — Wong WY, et al. Fertil Steril 2002, 77:491

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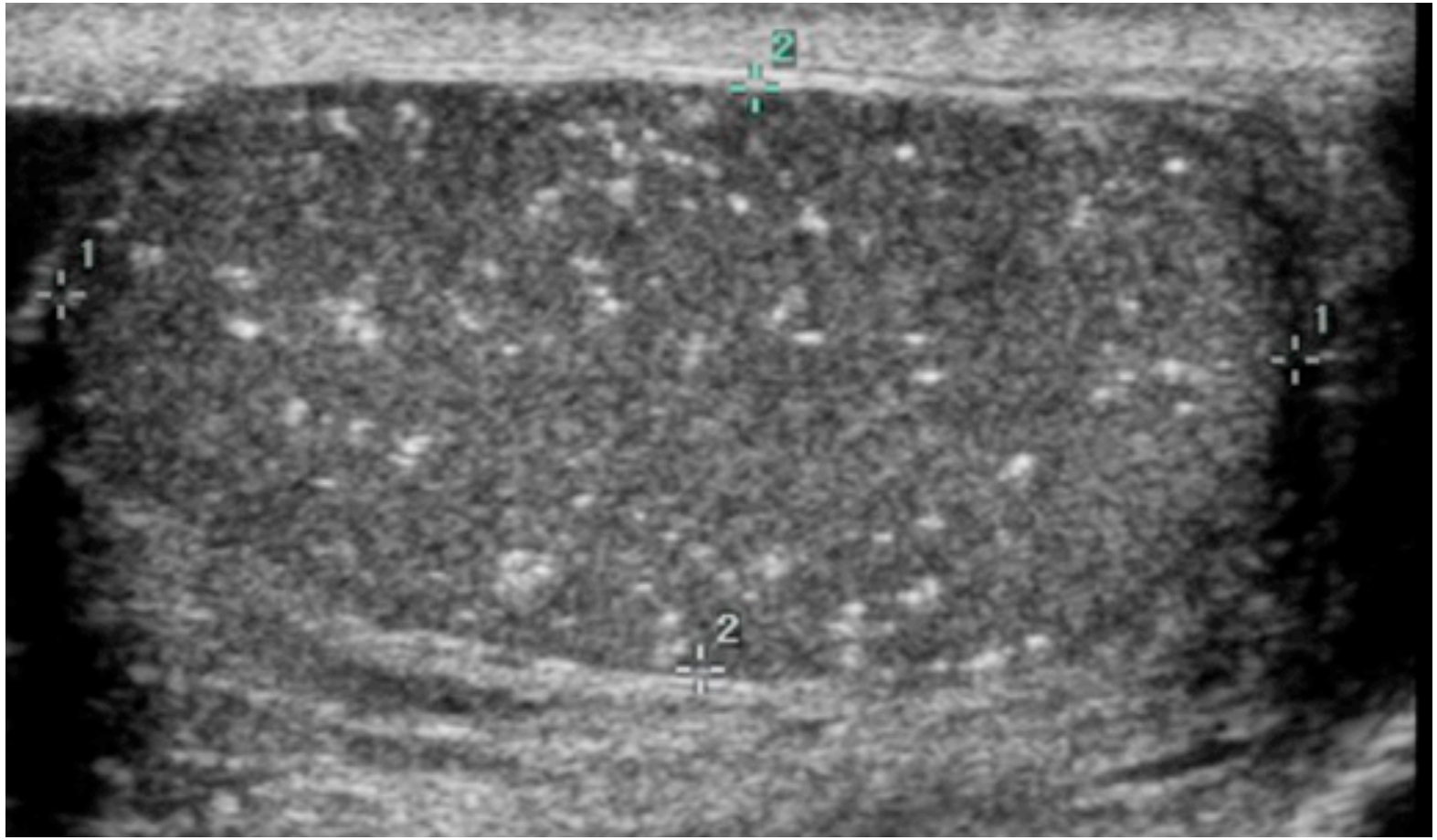
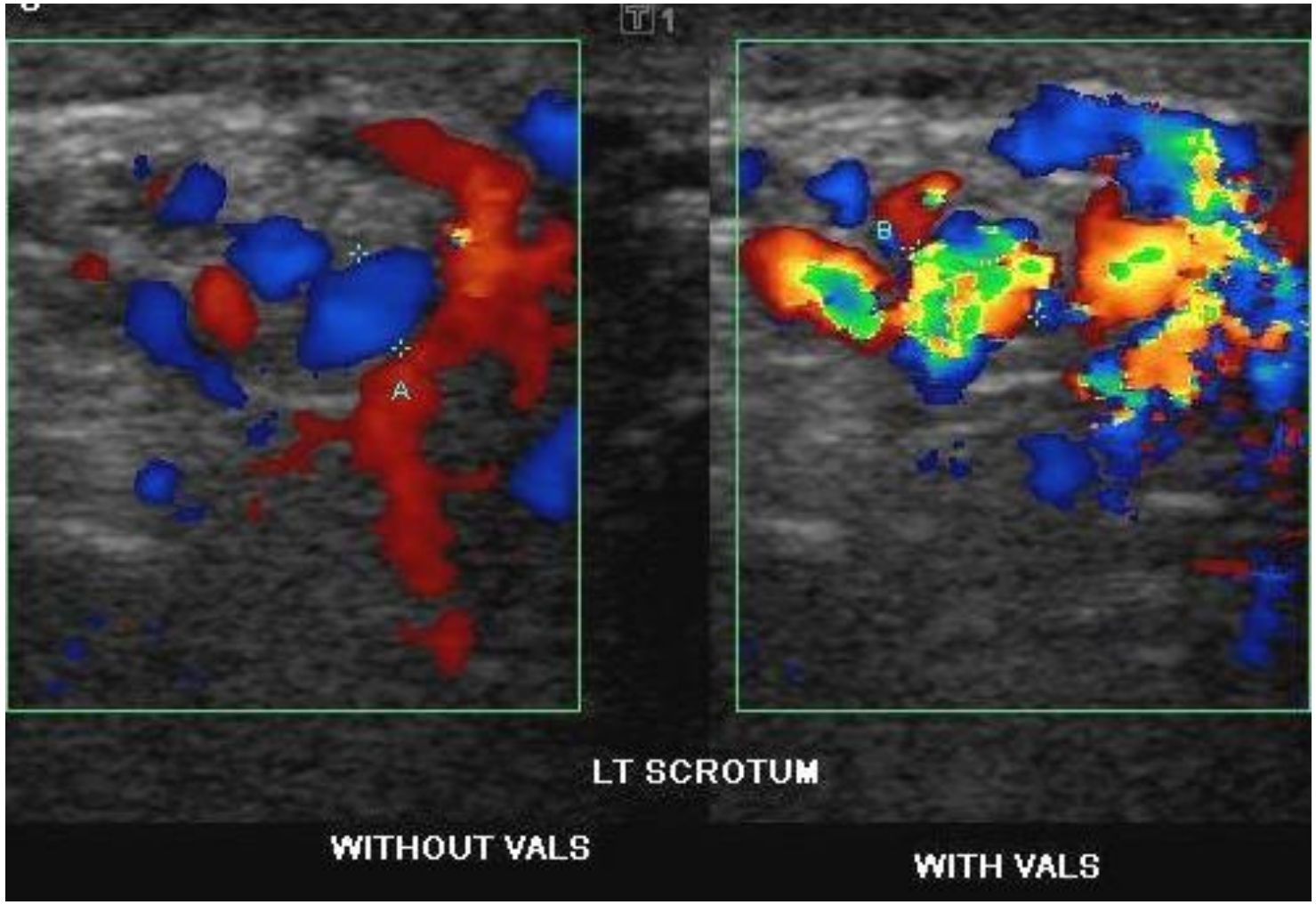
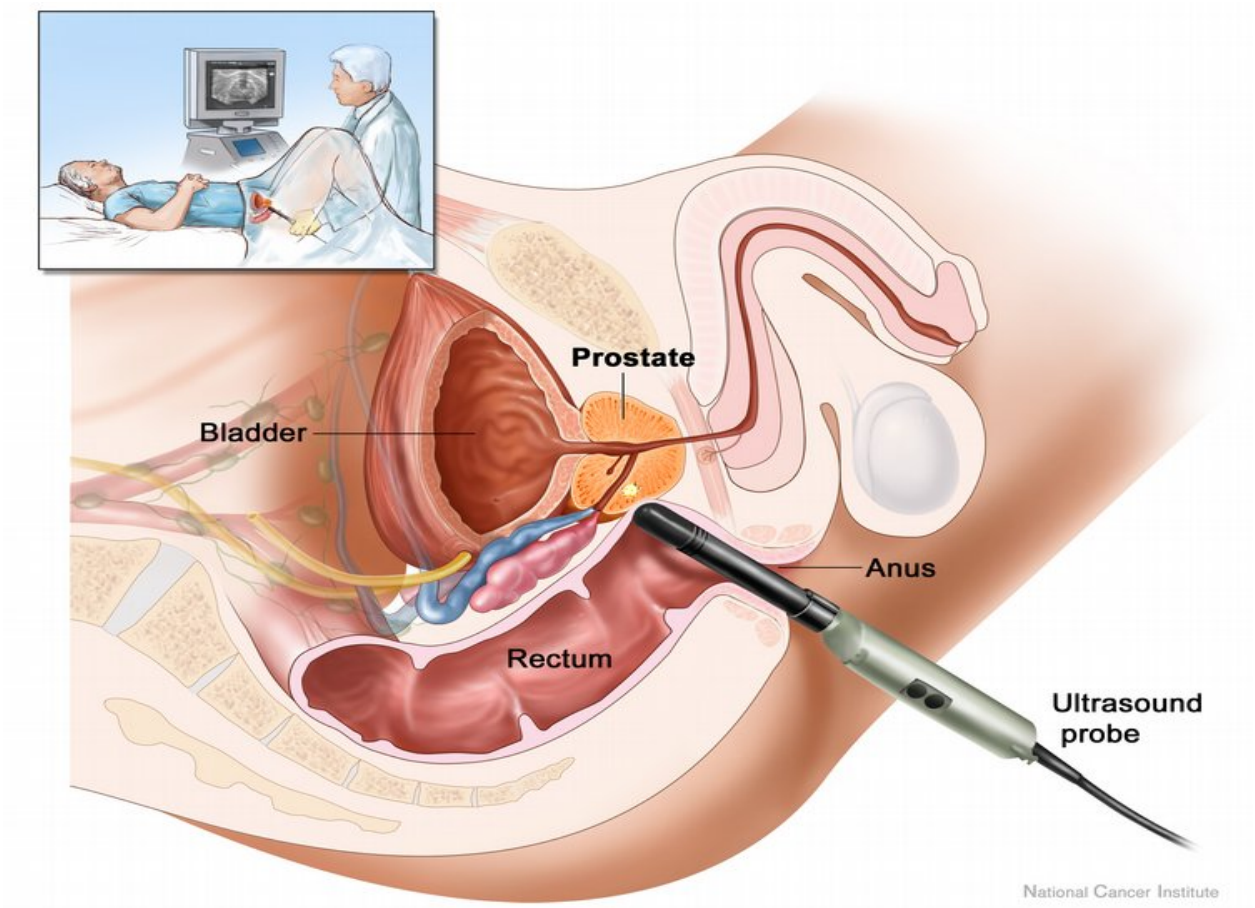
Testicular ultrasound



Testicular Triplex



Transrectal ultrasound



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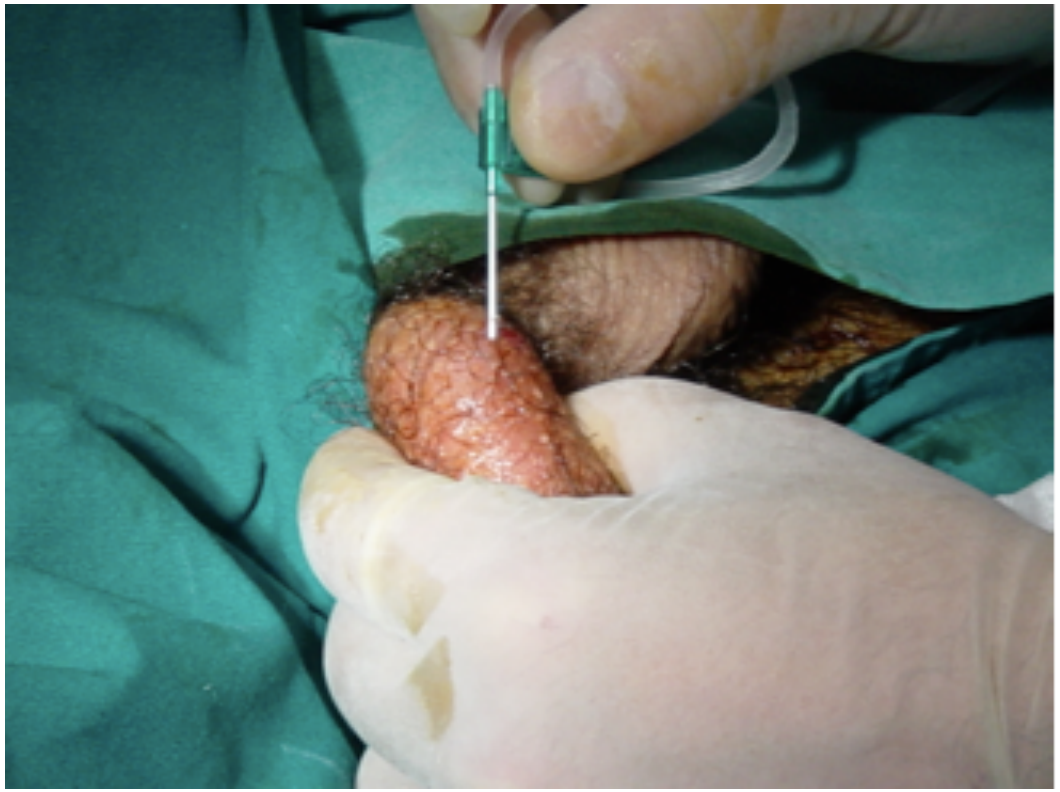
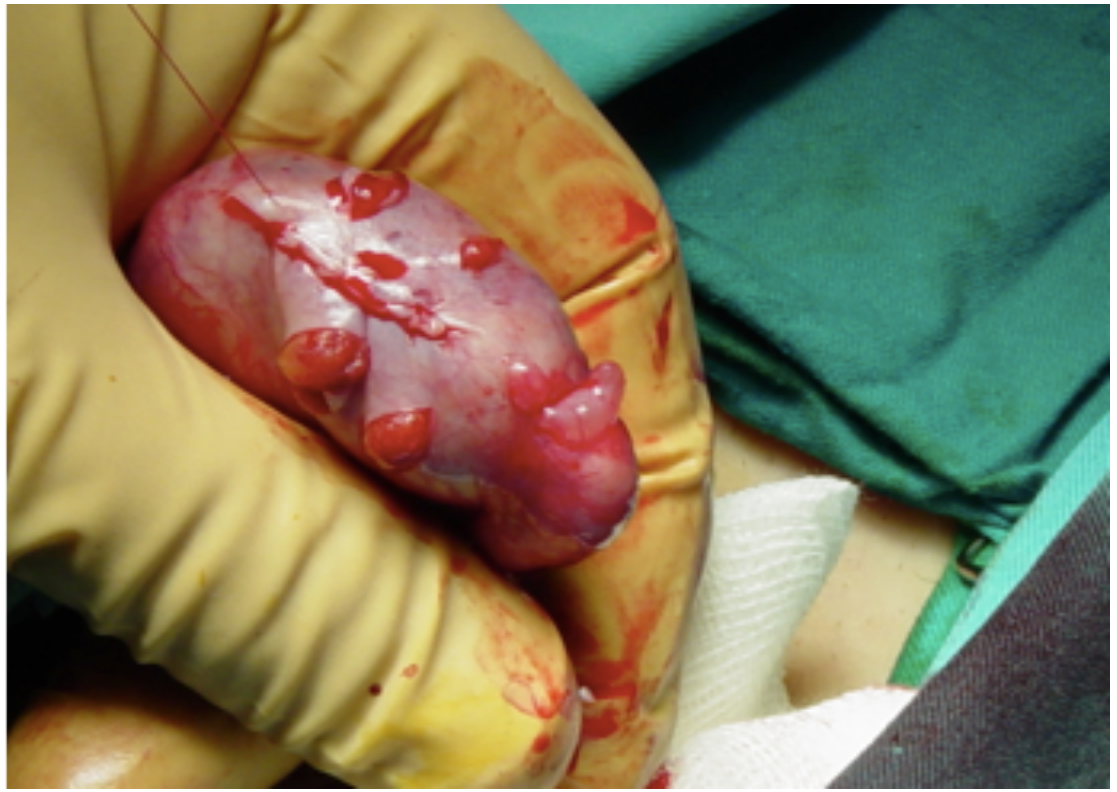
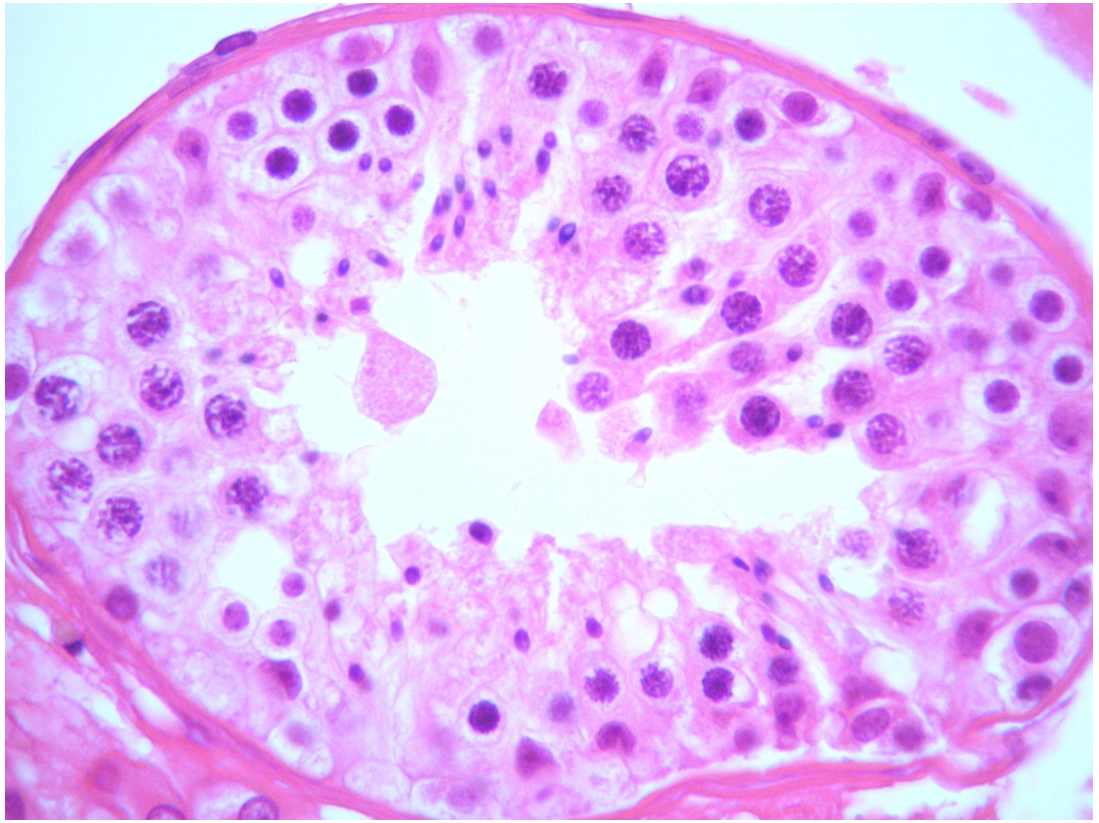
Testicular FNA and TESE

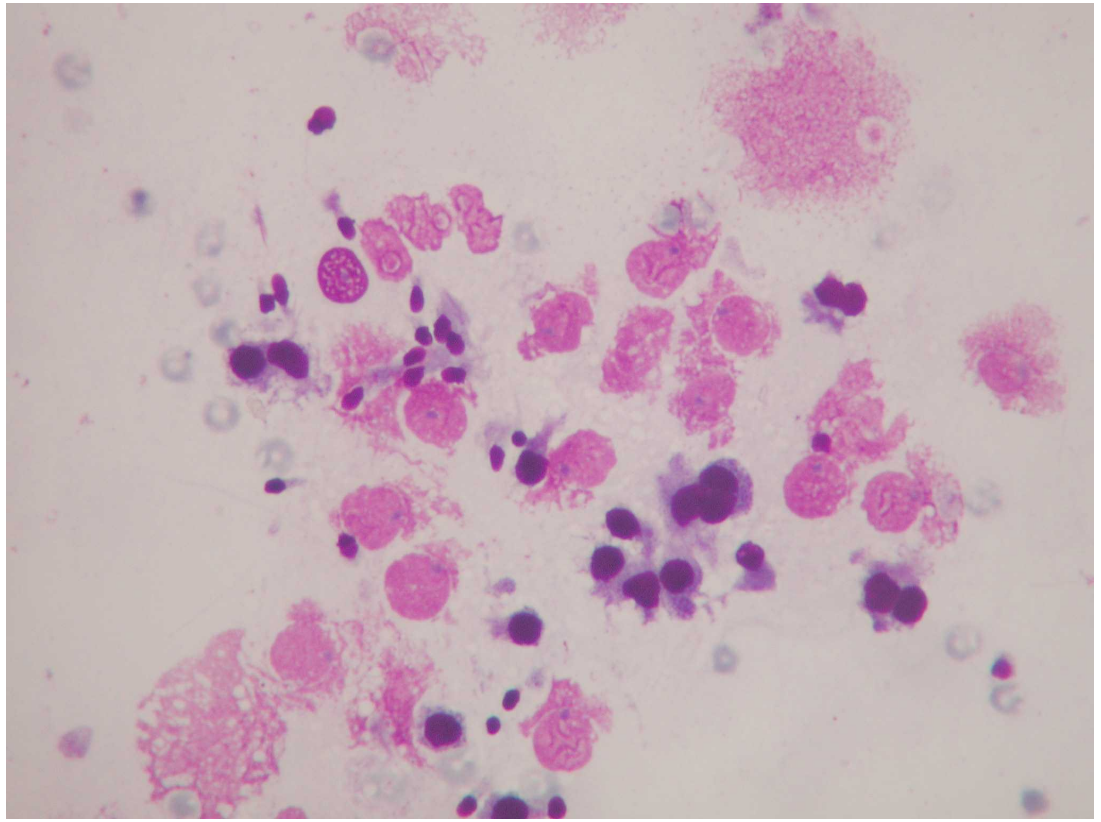




Normal spermatogenesis

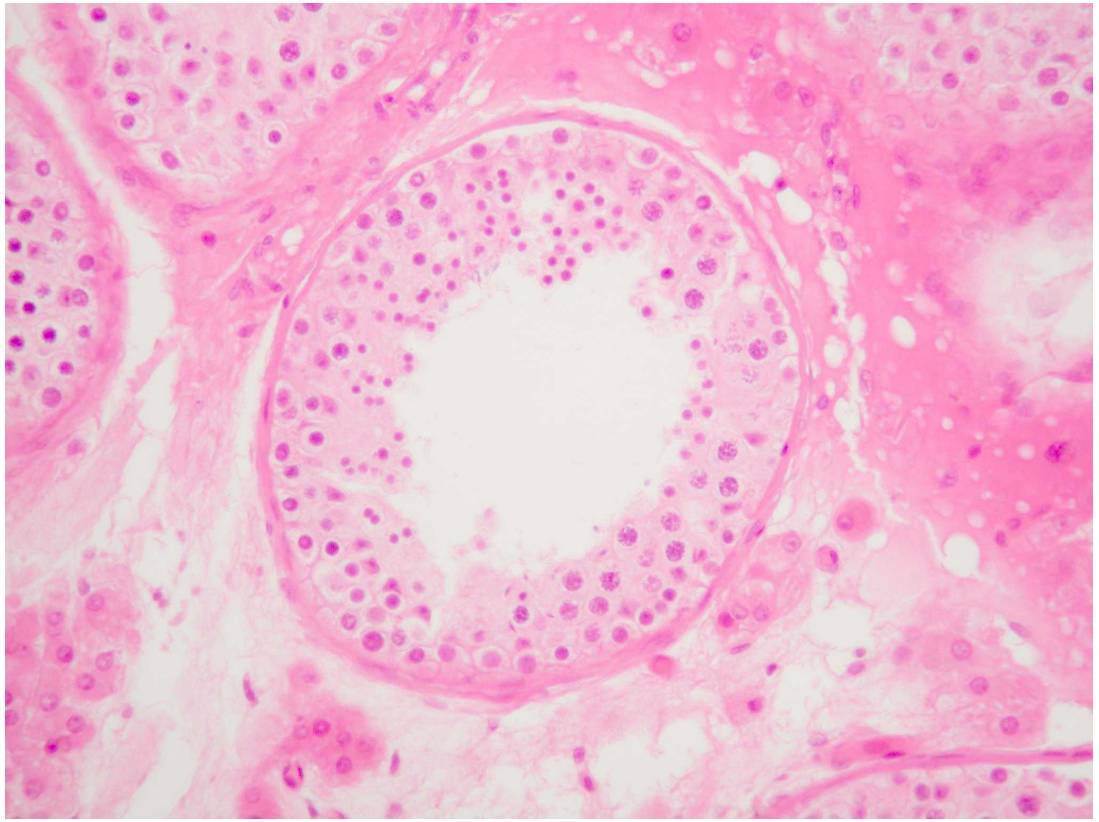


TESE

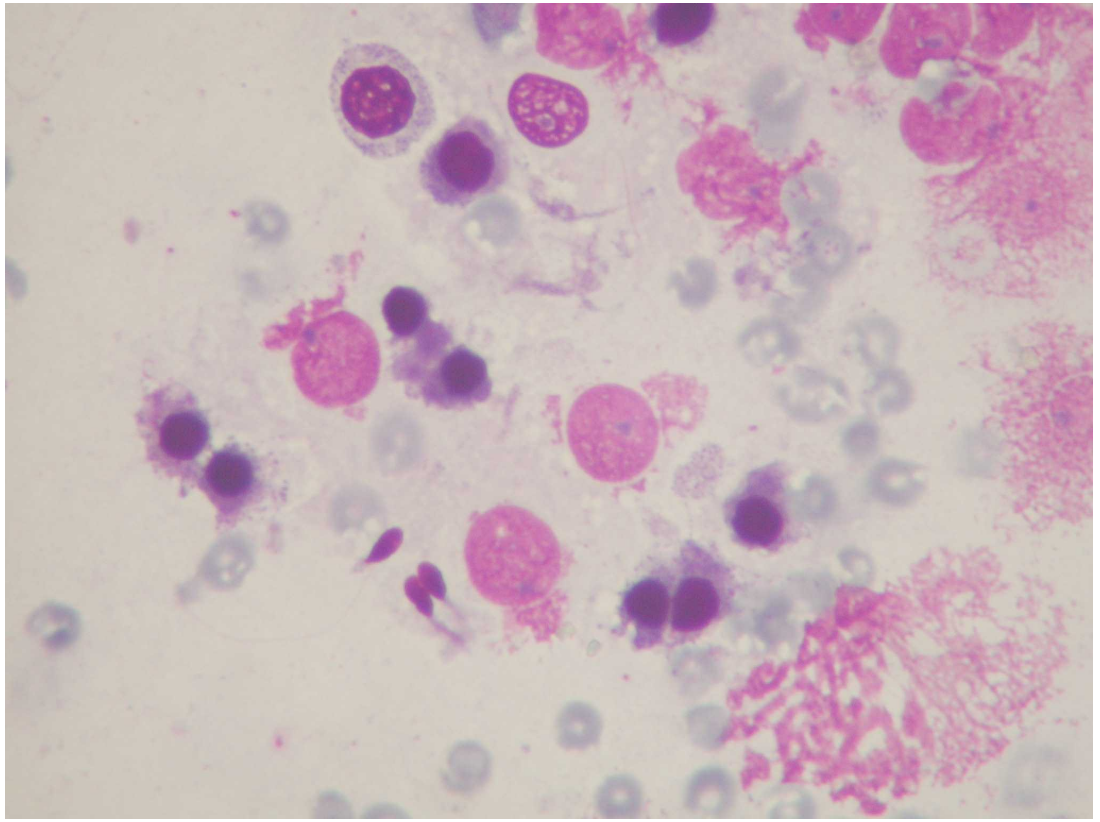


FNA

Hypospermatogenesis

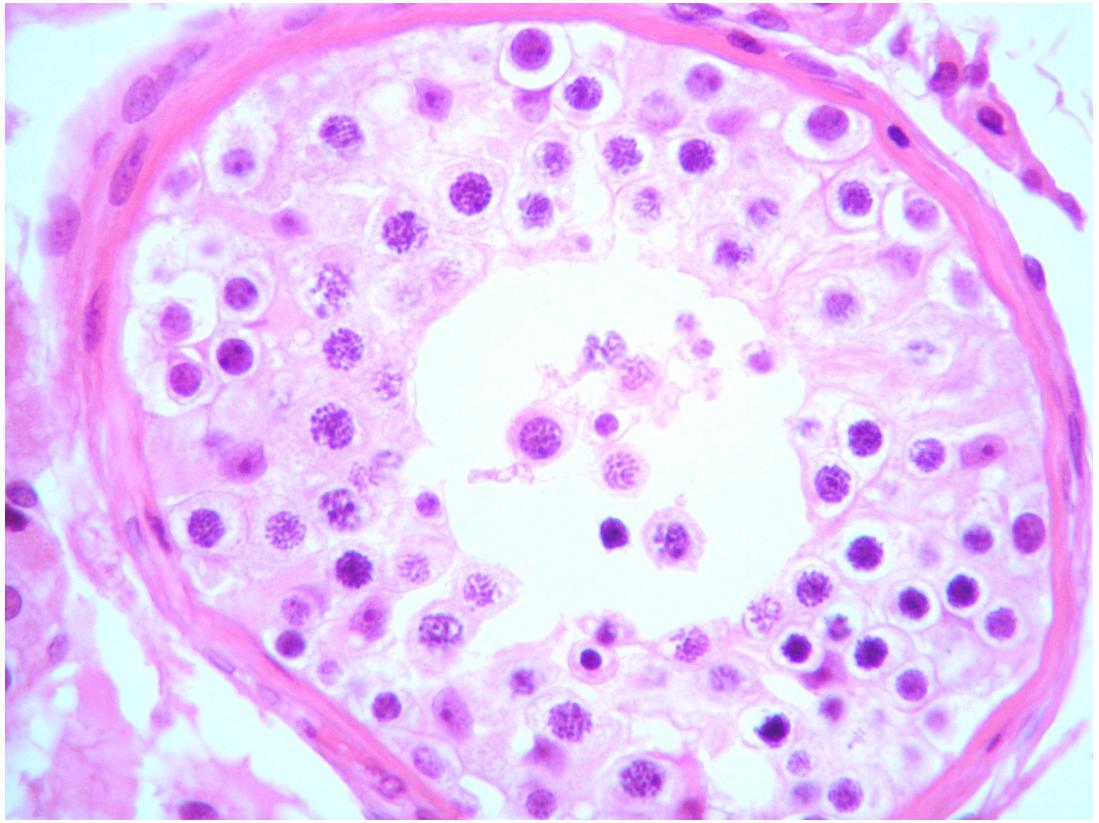


TESE



FNA

Spermatogenesis arrest



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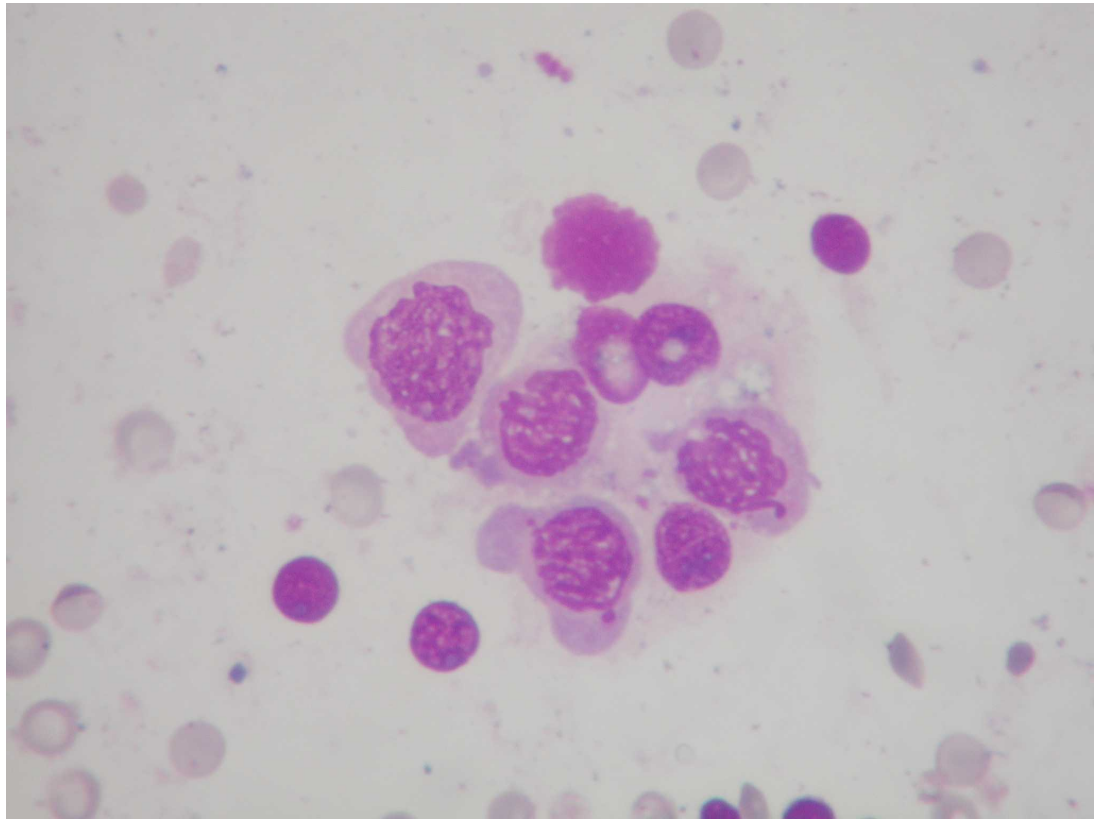
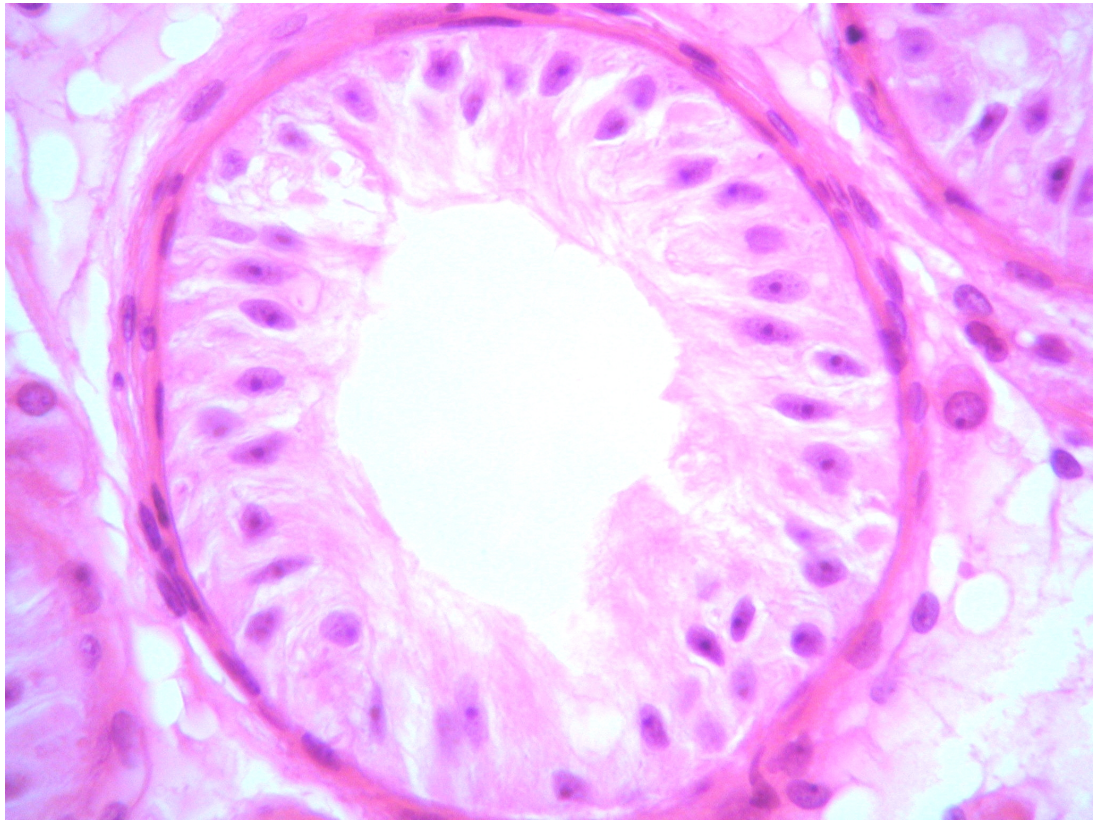
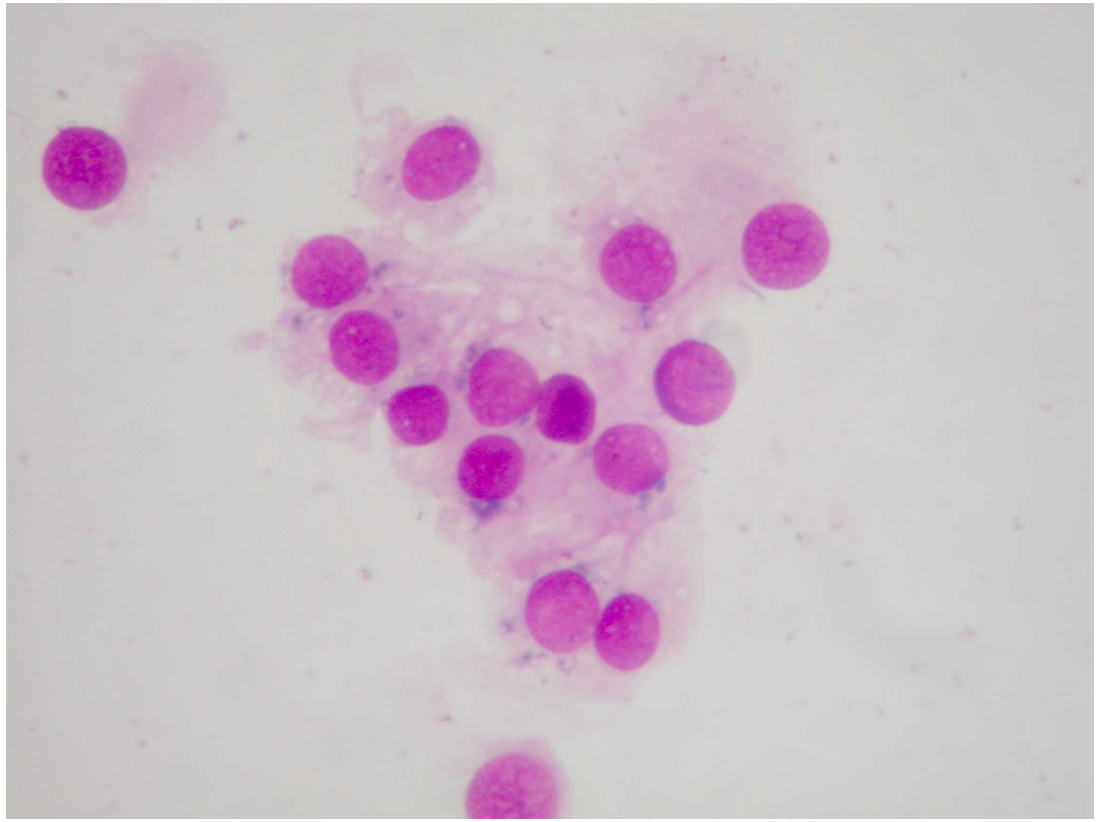


FNA

Sertoli cell-only syndrome

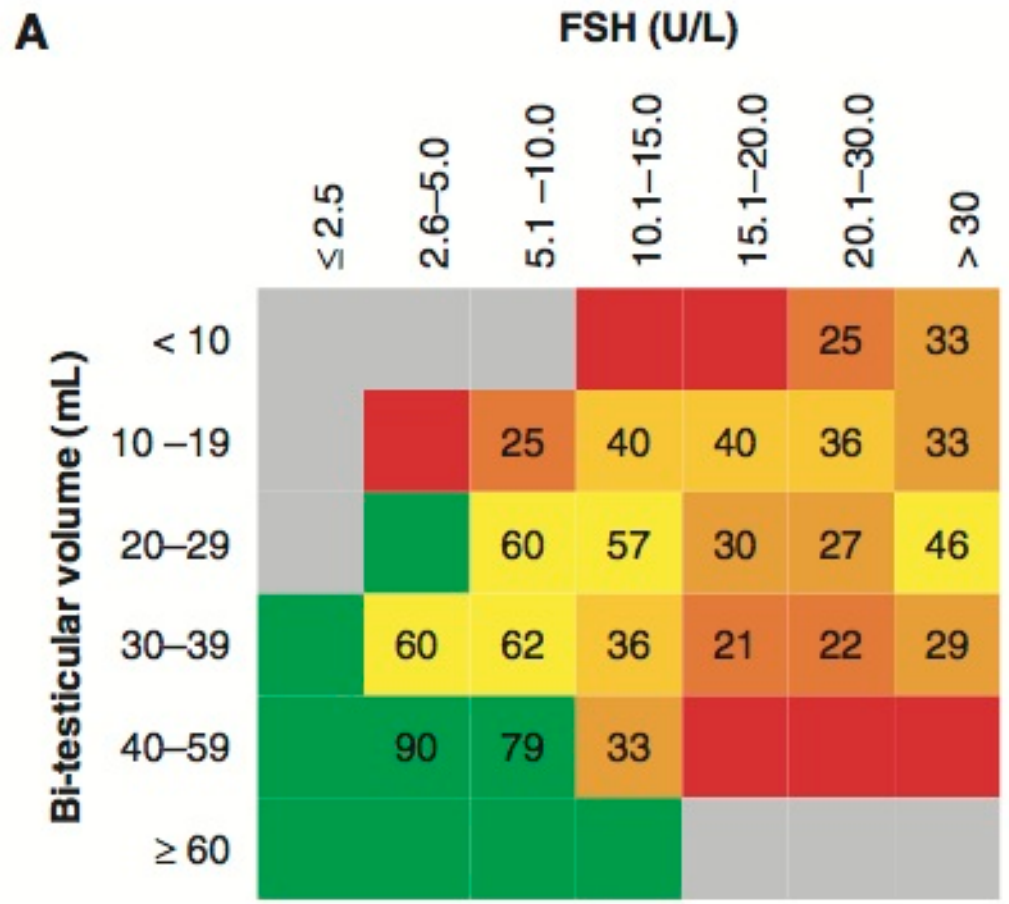


TESE



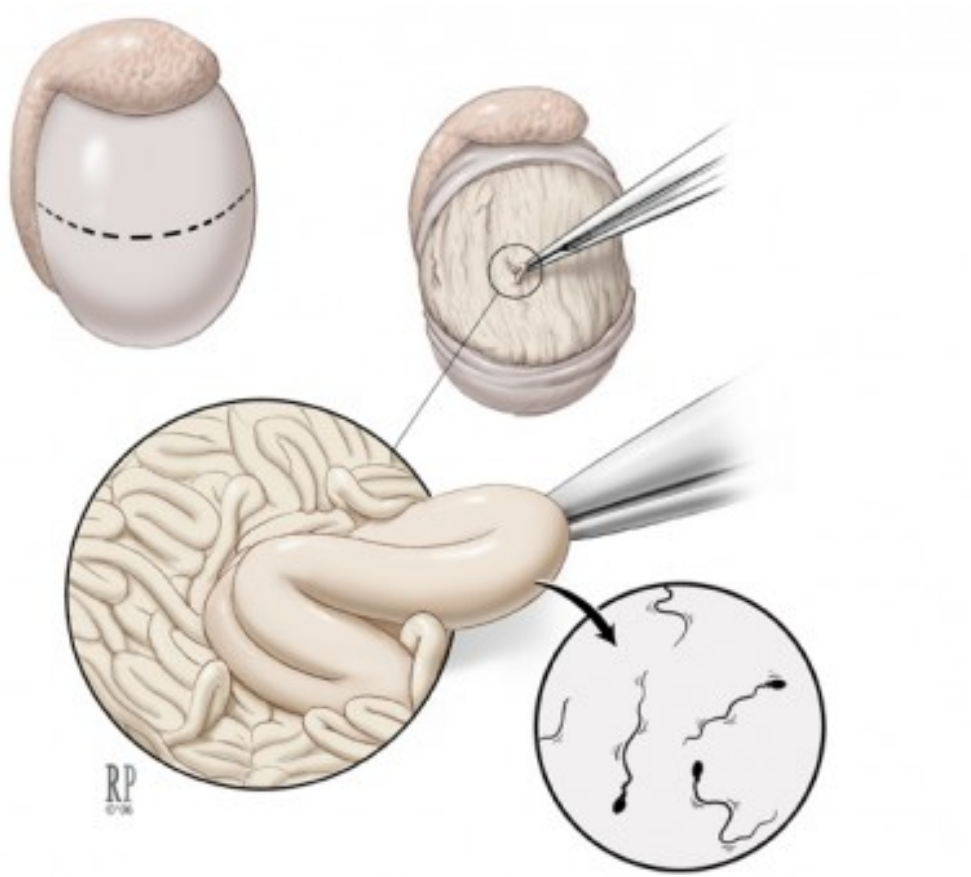
FNA

Prognosis of testicular extraction



Tuettelmann F, et al. Int J Androl 2010, 34:291

microTESE

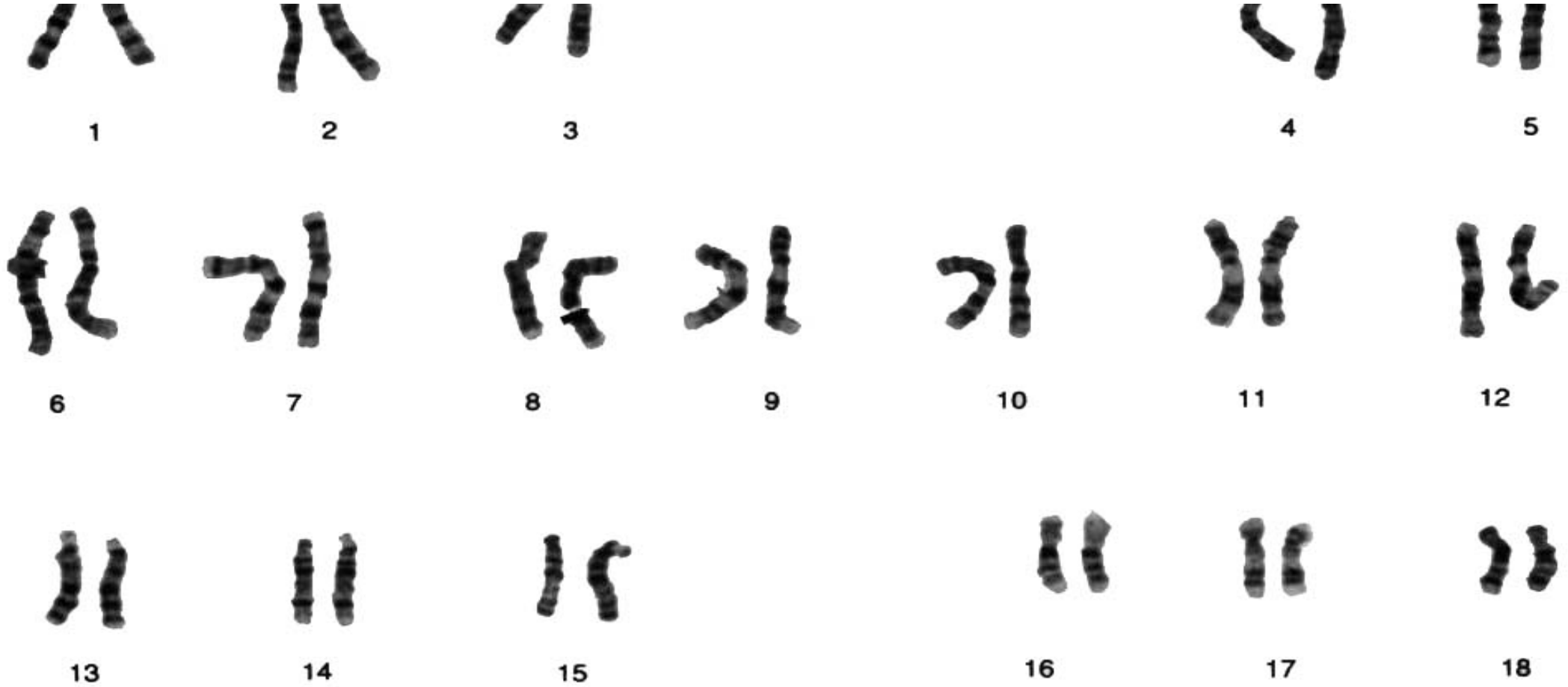


Sperm cryopreservation

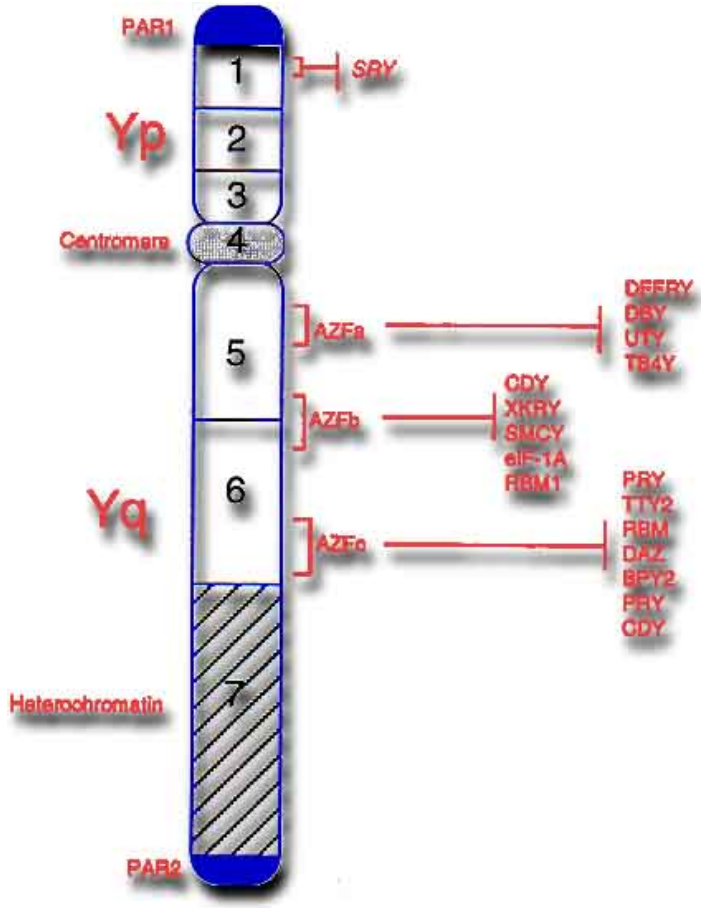
Diagnostic evaluation

- Clinical
- Hormonal
- Seminal
- Imaging
- Histologic
- Genetic

Karyotype



Yq microdeletions



- Three main areas Yq

Vogt PH, et al. Hum Mol Genet 1996, 7:933

- Azoospermia / severe OAT: 3%

Osterlund C, et al. Int J Andr 2000, 23:225

Cystic fibrosis

- Congenital bilateral agenesis of vas deferens (CBAVD)

Claustres M, et al. Hum Mutat 2000, 16:143

- Obstructive azoospermia

Jarvi K, et al. Lancet 1995, 345:1578

- Congenital bronchiectasis

Girodon E, et al. Eur J Hum Genet 1997, 5:149

- Chronic pancreatitis

Sharer N, et al. N Eng J Med 1998, 339:645

Genetics of male infertility

Human Reproduction, Vol.25, No.6 pp. 1383–1397, 2010
Advanced Access publication on April 8, 2010 doi:10.1093/humrep/deq081

human reproduction

ORIGINAL ARTICLE *Andrology*

Evaluation of 172 candidate polymorphisms for association with oligozoospermia or azoospermia in a large cohort of men of European descent

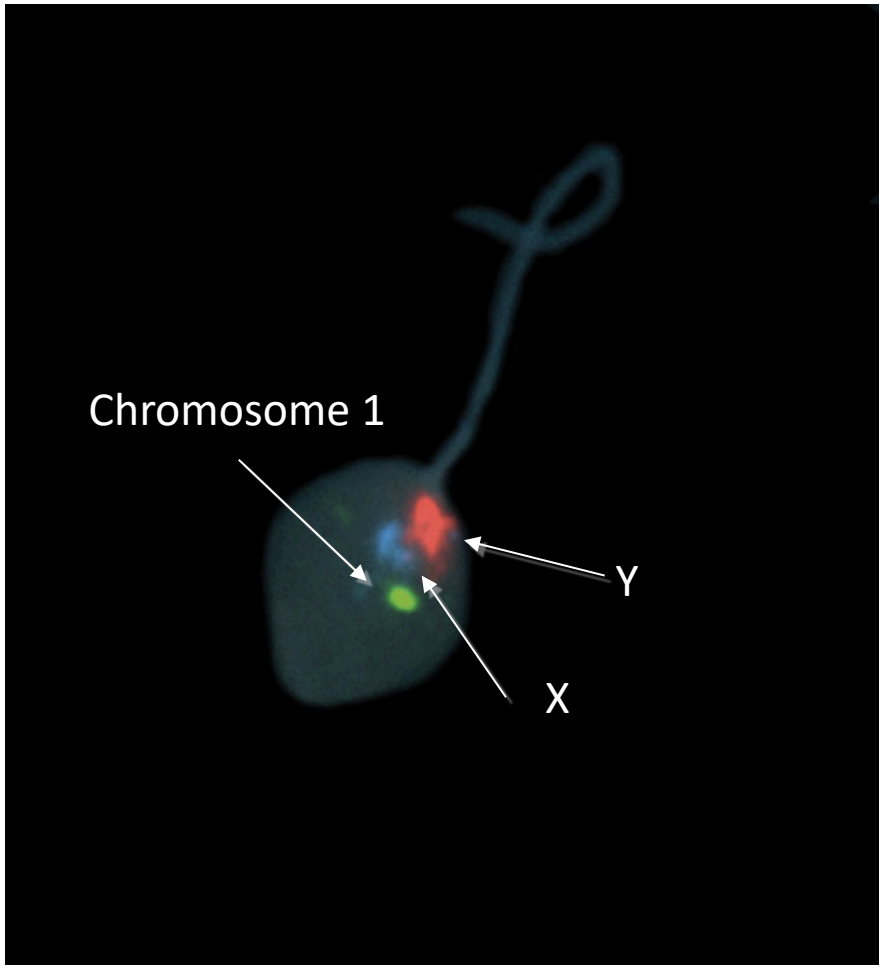
Kenneth I. Aston [1], Csilla Krausz [2,3], Ilaria Laface [2], E. Ruiz-Castané [3], and Douglas T. Carrell [1,4,5,*]

[1]Andrology and IVF Laboratories, University of Utah School of Medicine, Salt Lake City, UT, USA [2]Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy [3]Andrology Service, Fundació Puigvert, Barcelona, Spain [4]Department of Surgery, Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, UT, USA [5]Department of Physiology, University of Utah School of Medicine, Salt Lake City, UT, USA

*Correspondence address. E-mail: douglas.carrell@hsc.utah.edu

Submitted on January 26, 2010; resubmitted on March 2, 2010; accepted on March 9, 2010

Sperm FISH



Sperm disomy: 24,XY

Aims

- Evaluation and etiologic approach of male infertility
- Selection of the optimal management method

Male infertility - 1

Etiology

- Kallmann syndrome
- Prolactinoma
- Hyperthyroidism
- Hypothyroidism

Etiologic approach

- Gonadotropins
- Dopamine agonists
- Anti-thyroid drugs
- L-thyroxine

Male infertility - 2

Etiology

- Infections
- Varicocele
- Obstruction

Oriented approach

- Antibiotics
- Surgery
- Microsurgical approach

Male infertility - 3

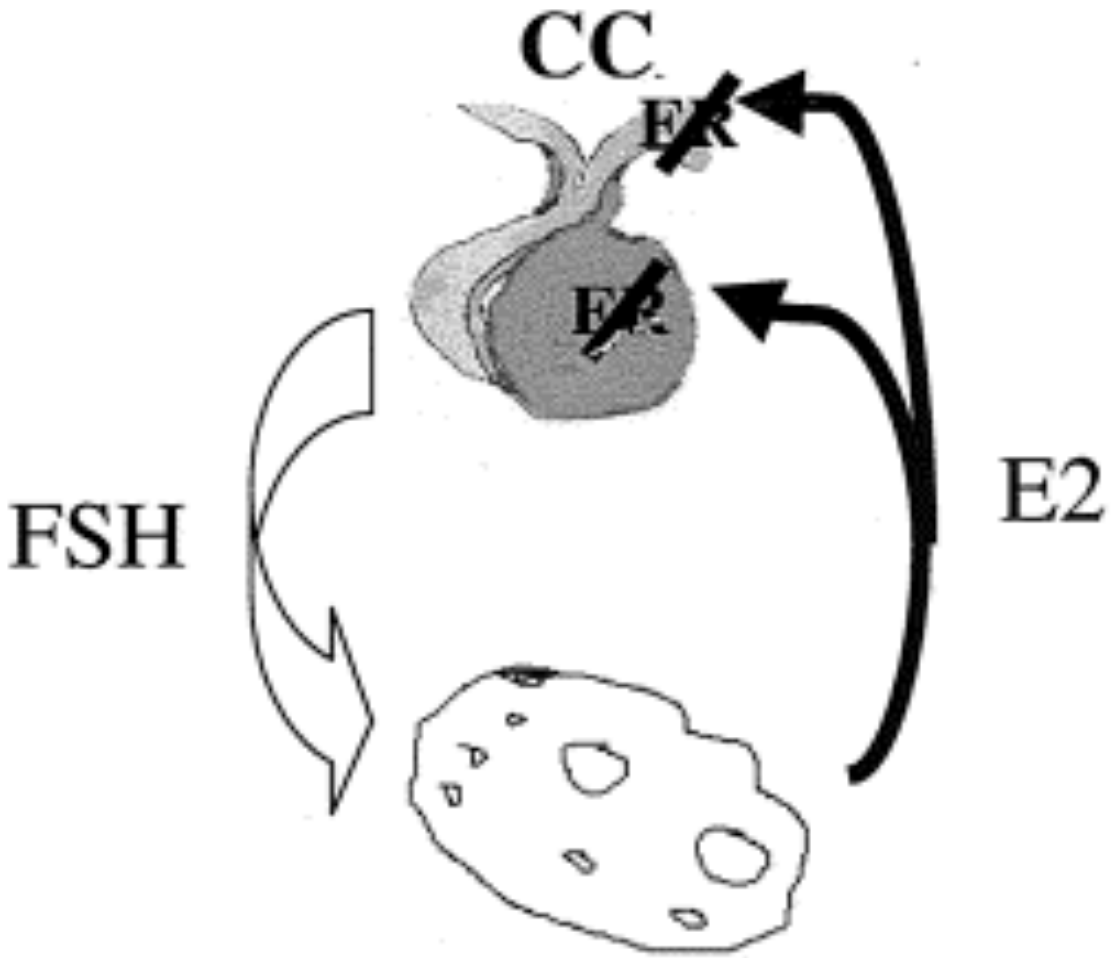
Etiology

- Idiopathic infertility

Empirical approach

- Citric clomiphene / tamoxifen
- Gonadotropins
- Testosterone
- Anti-oxidants / Vitamins
- Insemination (IUI)
- ICSI

Citric clomiphene



Casper R. Fertil Steril 80:1336, 2003

Testicular dysgenesis

Human Reproduction Vol.16, No.5 pp. 972–978, 2001

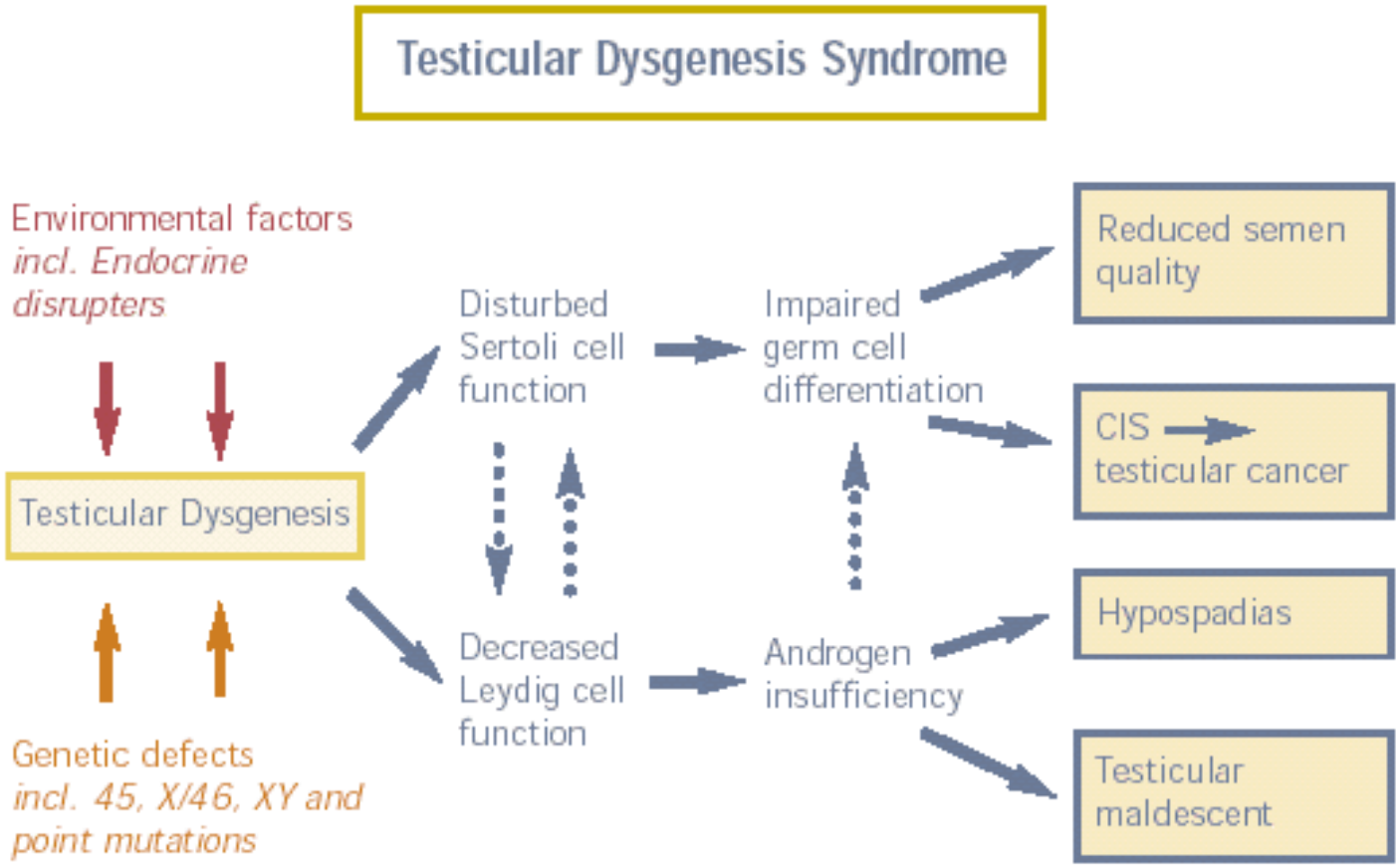
OPINION

Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects

N.E.Skakkebæk[1], E.Rajpert-De Meyts and K.M.Main

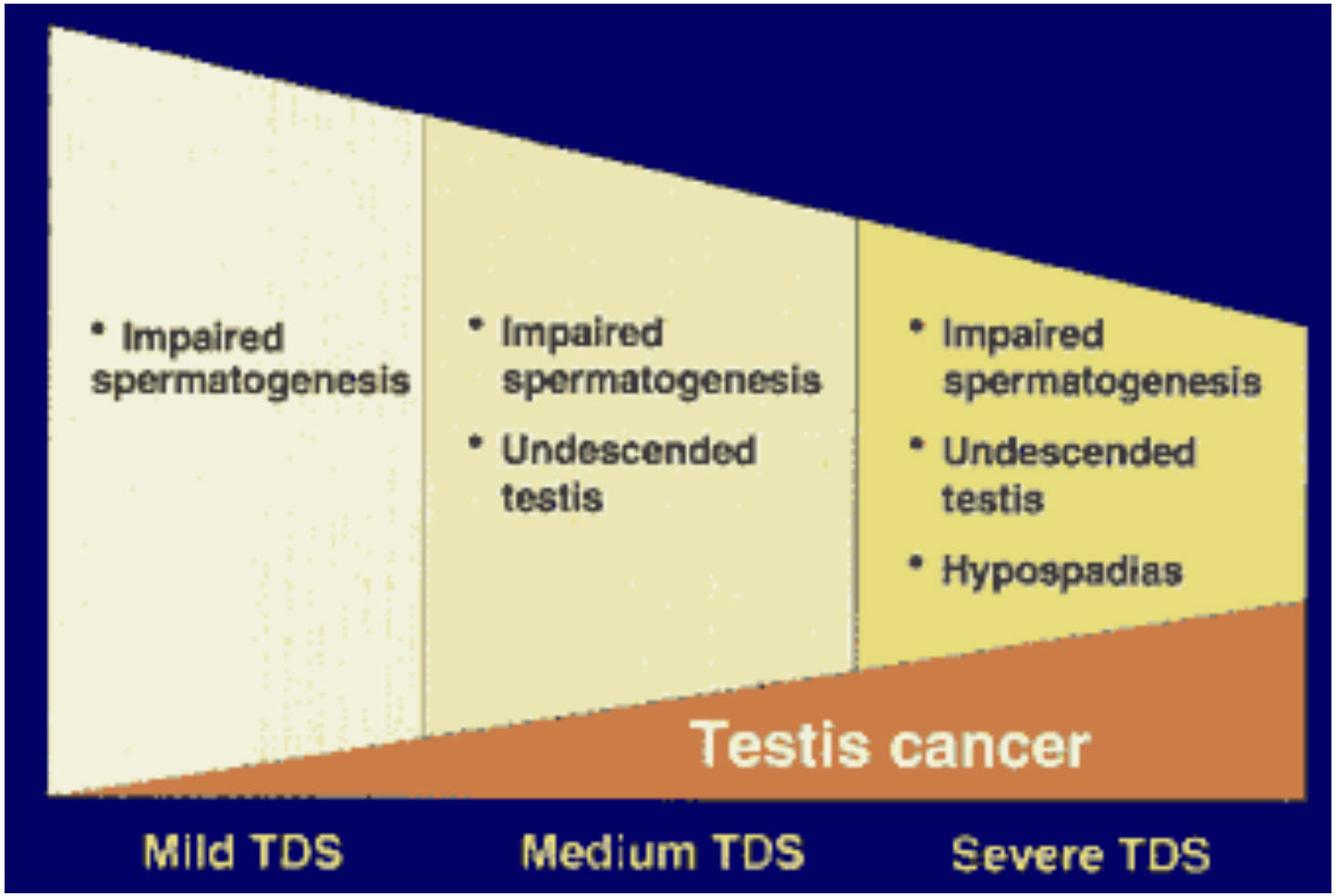
Department of Growth and Reproduction, Copenhagen University Hospital, Copenhagen, Denmark

Testicular dysgenesis



Skakkebaek NE et al. Hum Reprod (2001) 16:972

Testicular dysgenesis



Skakkebaek NE et al. Hum Reprod (2001) 16:972

Male infertility

- Application of modern diagnostic methods for the etiologic diagnosis of the cases
- Appropriate evaluation of the patients and their classification into subgroups to select the cases for the application of the optimal therapeutical approaches

Unit of Reproductive Endocrinology
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Professor emeritus J. Papadimas

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P. Poulakos (endocrinologist)
P. Iliadou (endocrinologist)
C. Dimopoulou (endocrinologist)
E. Kintiraki (endocrinologist)
S. Paschou (endocrinologist)
P. Anagnostis (endocrinologist)
I. Litsas (endocrinologist)
G. Kanakis (endocrinologist)
G. Mintziori (endocrinologist)
A. Mousiolis (endocrinologist)
E. Billa (endocrinologist)
K. Papadimitriou (endocrinologist)
V. Harizopoulou (midwife)
E. Tsirou (dietician)
E. Taousani (midwife)
D. Savvaki (physical education)
N. Athanasiadi (dietician)
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