

# What should the clinician ask and look for in the initial consultation?

**ESHRE Campus Course, Thessaloniki, Greece, 1-3 October 2009**  
**Reproductive andrology: linking laboratory to clinical practice**

## Tim Hargreave

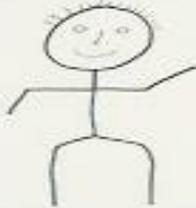
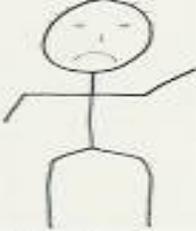
School of Clinical Science, Edinburgh University, Scotland UK

Chair, Science and Ethics Review Group  
UNDP, UNFPA, WHO, World Bank, Human Reproduction Program, WHO, Geneva

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# Infertility is a couple problem

www.urologyedinburgh.co.uk

	 Very good fertility	 Poor fertility	 Blocked Fallopian tubes
 Very good fertility			X
 Poor sperm count			X
 No sperm in ejaculate	X	X	X

# History taking male partner of an infertile marriage

- Duration of involuntary infertility
- Previous marriage/ previous children
- Previous investigations/ treatments for infertility
- History of illness / disease
- High fever
- Infections (STI / epididymitis / urethral discharge etc)
- Treatments or drugs
- Trauma
- Hazards at work
- Penis erection and ejaculation problems
- Psychological problems

## Genetic abnormalities

Chromosome abnormalities  
(XXY commonest)

CBAVD

Translocations

Y microdeletions

## Lifestyle

Food – obesity, lipids

Alcohol, drugs

Clothing

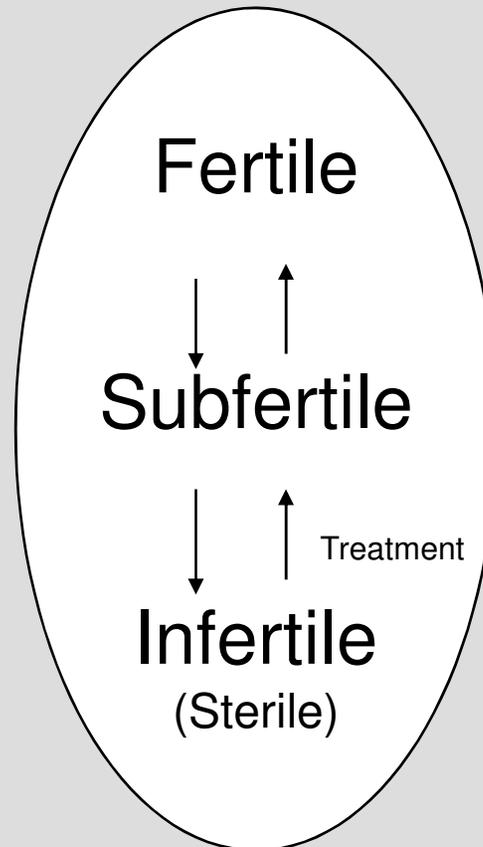
Warm baths

Stress

## Environment and occupation

Hormone disruptors

Toxic substances Lead etc



## Diseases

Varicocele

Infections (chlamydia)

Antisperm antibodies

Acquired damage

Iatrogenic

Systemic

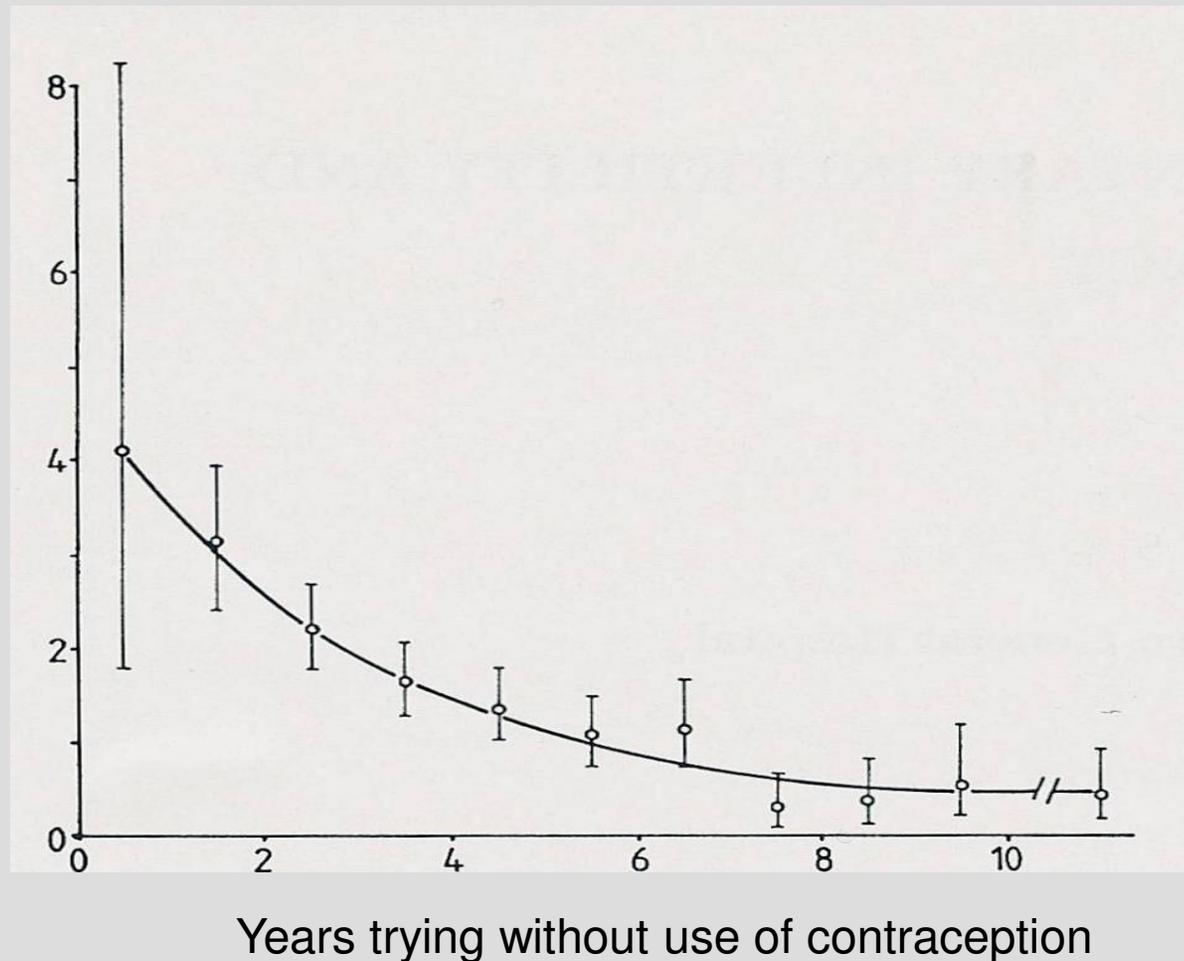
Adpated from Comhaire and Mahmoud 2006  
in Andrology for the Clinician Eds Schill et al Springer pp33

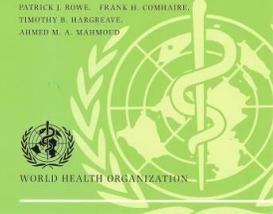
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Couples who have been trying for a long time have a poor chance of spontaneous conception irrespective of test results

% chance  
of conception  
per month





# WHO Manual Definitions

- Infertility is defined as no conception after at least 12 months of unprotected intercourse. (85% of couples achieve pregnancy within this time).
- Primary male infertility – This is when a man has never impregnated a woman
- Secondary male infertility – This is when the man has impregnated a woman irrespective of whether she is his current partner. 
- Duration of involuntary infertility – This is defined as the number of months during which the couple have been having sexual intercourse without the use of contraception



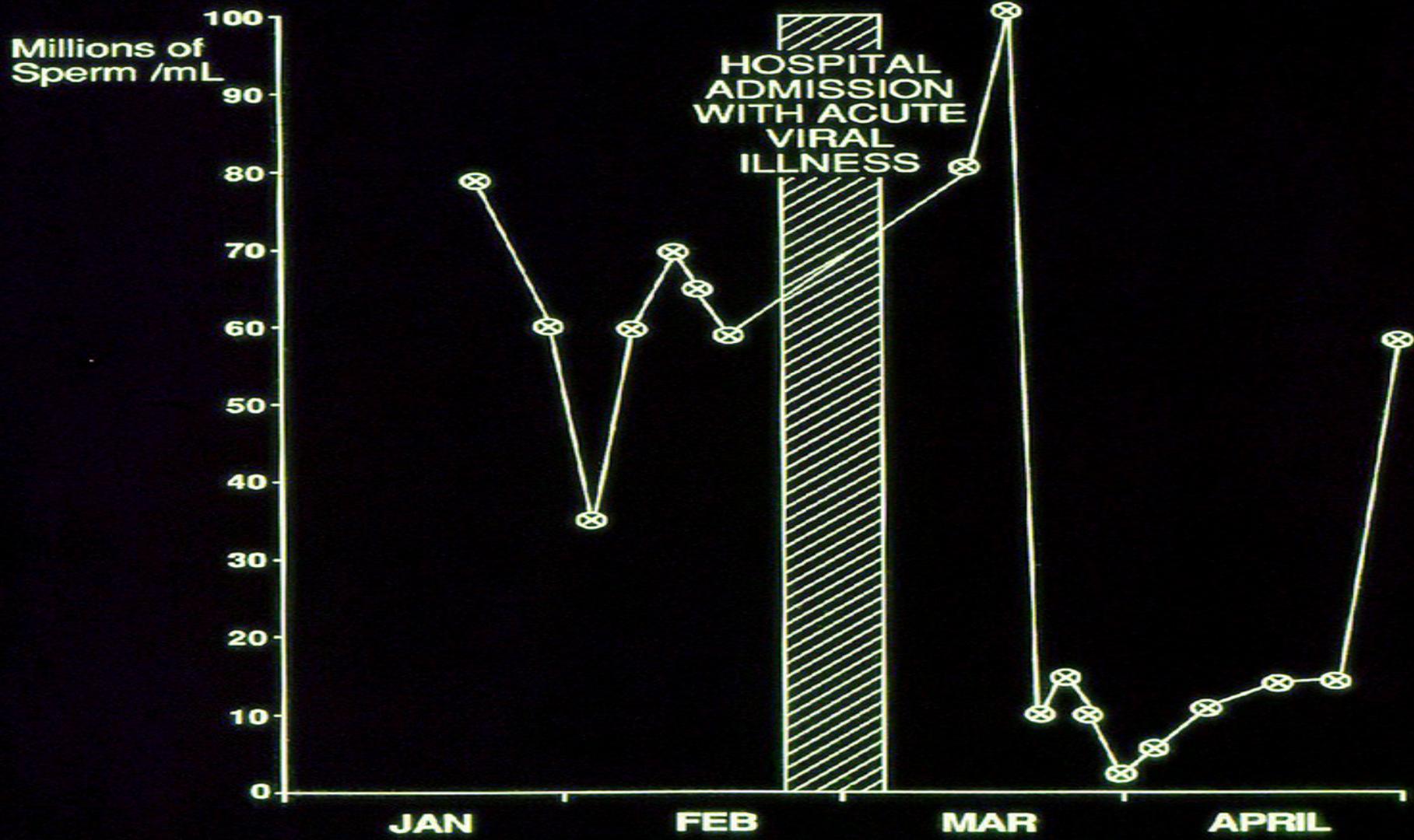
*But you may not find out about this if current partner present when you ask!!*

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# Treatments that may affect fertility

- Cancer chemotherapy (radiotherapy)
  - Testis cancer (*Sperm concentration often low prior to treatment but some spermatogenesis may be preserved*)
  - lymphoma
  - bone sarcoma (*often severe permanent damage and little recovery*)
  - Alkylating agents particularly damaging
- 5 ASA instead of salazopyrine for colitis
- Immunotherapy (organ transplantation)
- Anti-infective drugs (*Nitrofurantoin, colchicine*)

Monday August 17, 2009 UK A £2.3 million campaign has been launched to make drug driving as much of a no-no as getting behind the wheel after drinking.

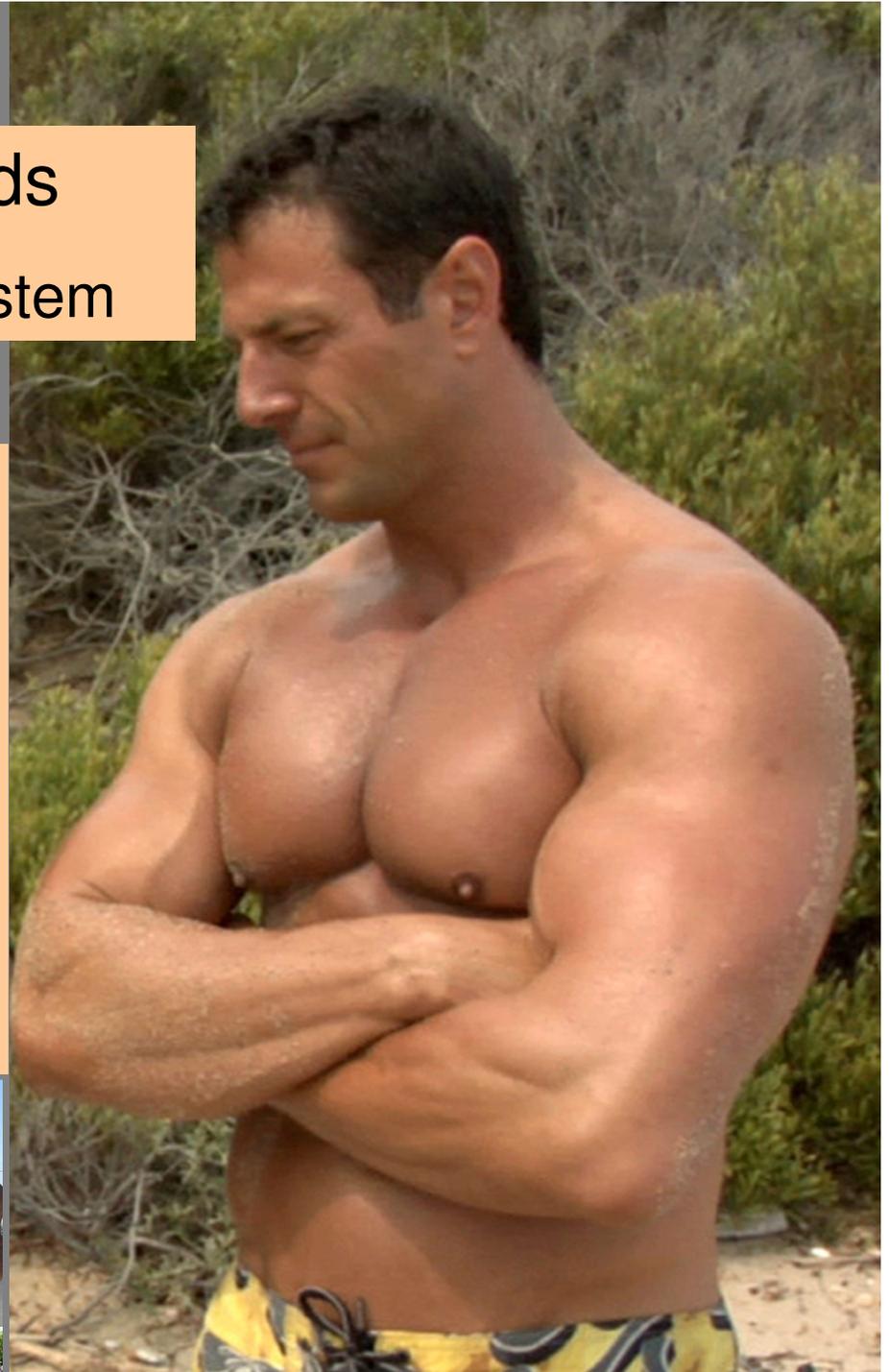


Official figures also show that more than 11,000 under-16s - legally too young to drink - received help with their addiction to cannabis, heroin, alcohol and other drugs. Daily Mail 7<sup>th</sup> July 2009

## Abuse of Anabolic steroids

### Effect on male reproductive system

- *Increased desire*
- *decreased potency*
- *Gynaecomastia (irreversible and may require surgery)*
- *Atrophy of the testes*
- *reduced or absent spermatogenesis*



# History taking male partner of an infertile marriage

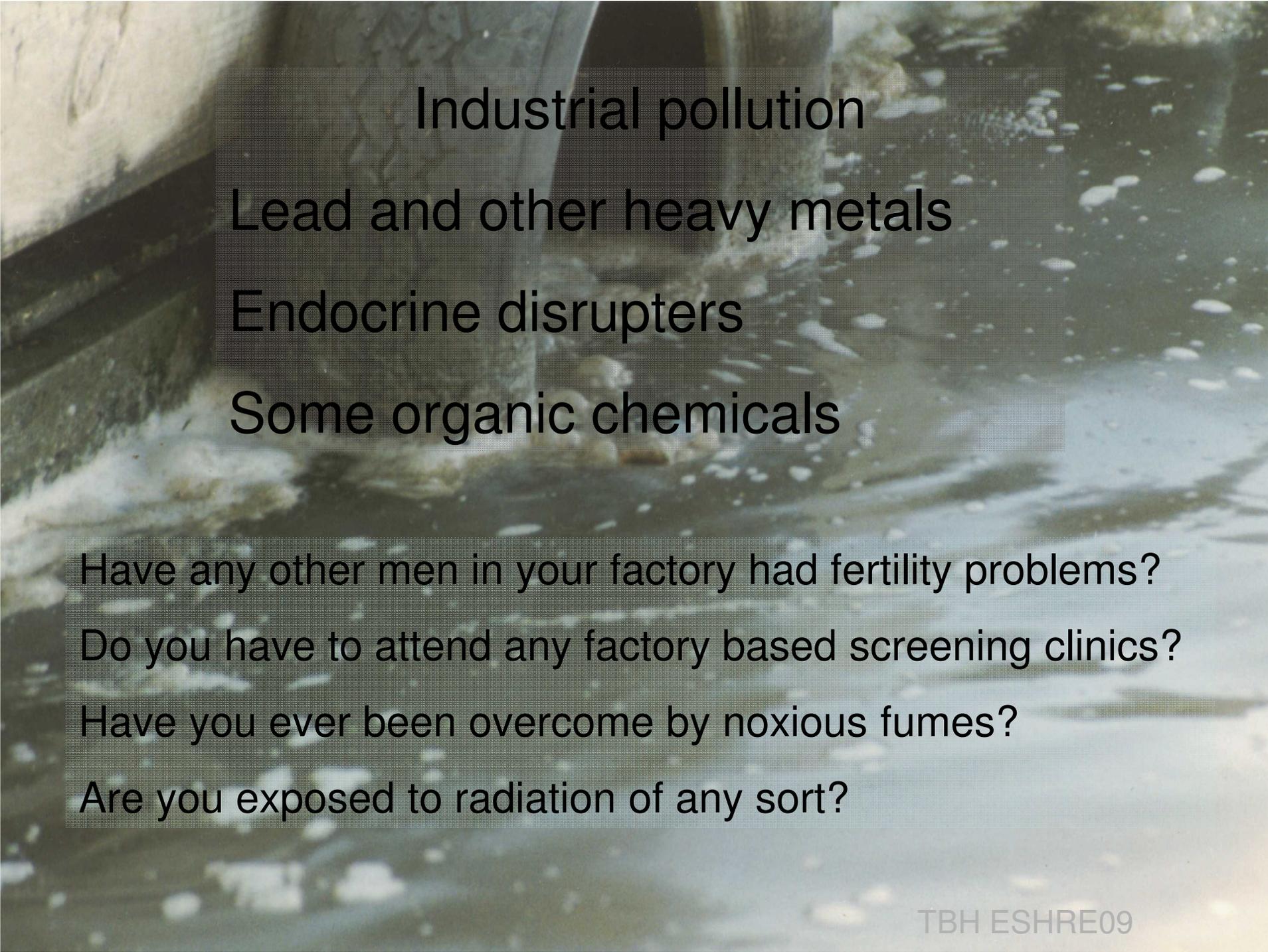
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Industrial pollution

Lead and other heavy metals

Endocrine disruptors

Some organic chemicals

Have any other men in your factory had fertility problems?

Do you have to attend any factory based screening clinics?

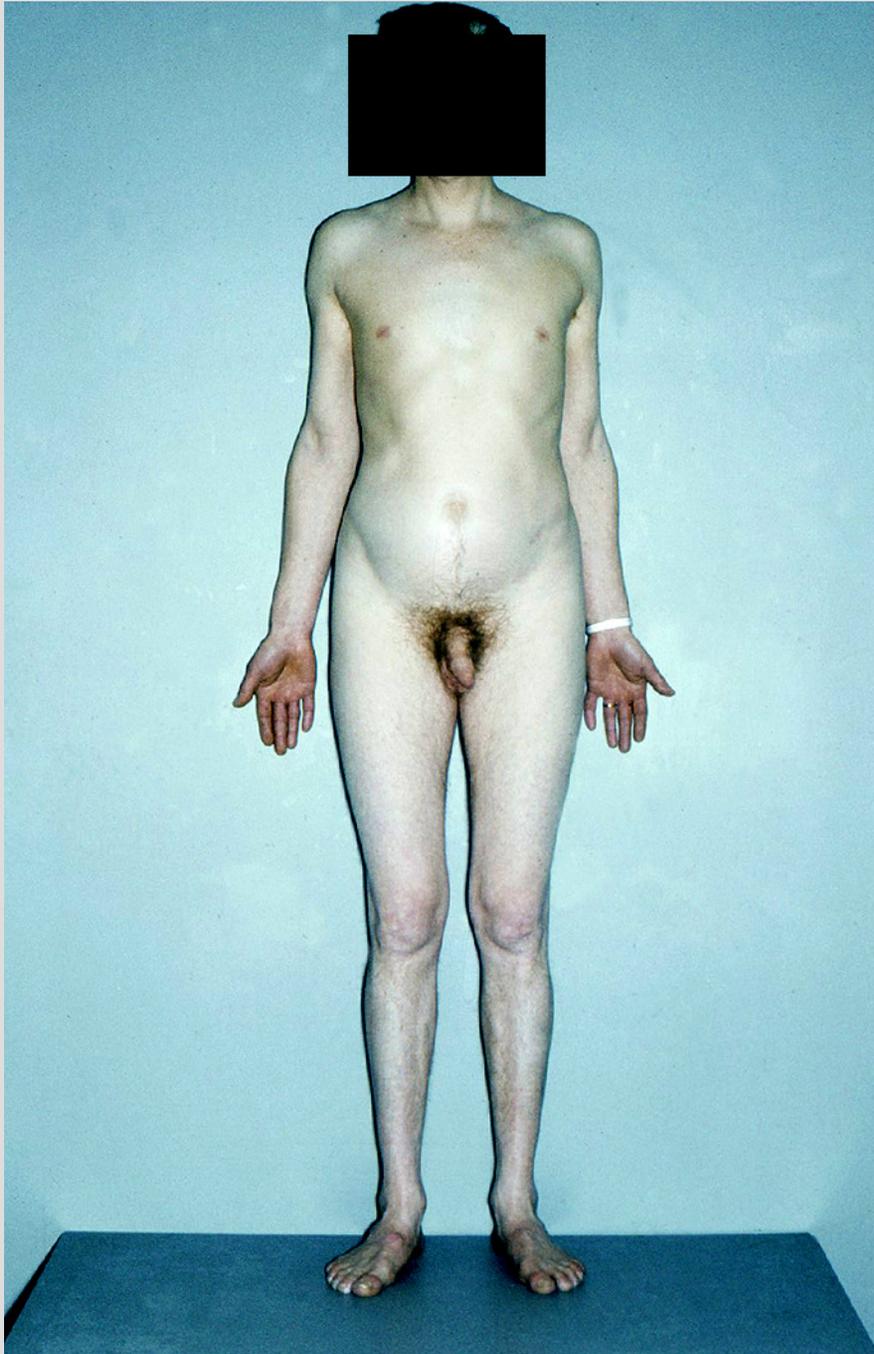
Have you ever been overcome by noxious fumes?

Are you exposed to radiation of any sort?

# Examination of the man

*You may be the only doctor who examines the man*

- General virilisation
- Penis and foreskin (phimosis and balanitis)
- Testes position, size and consistency (hernia, hydrocele, epididymal cyst) (Ultrasound)
- Congenital absence of the vas deferens (low volume ejaculate)
- Varicocele
- (Prostate)

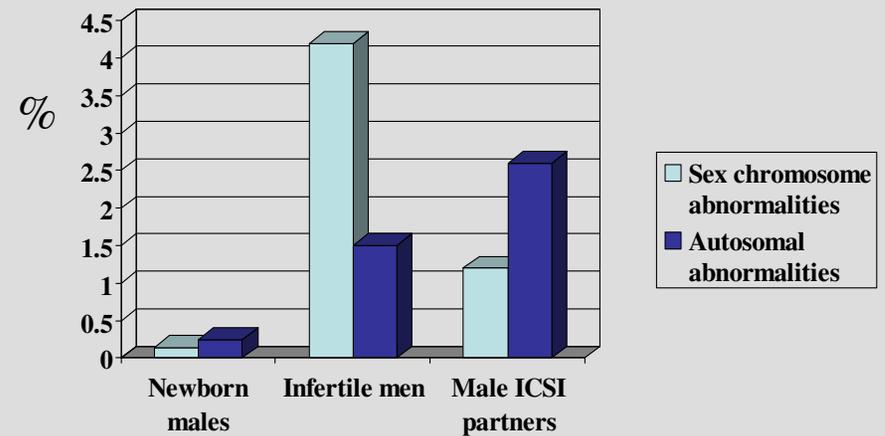


Scanty body hair

Small **firm** testes

Long arms and legs (late epiphyseal closure)

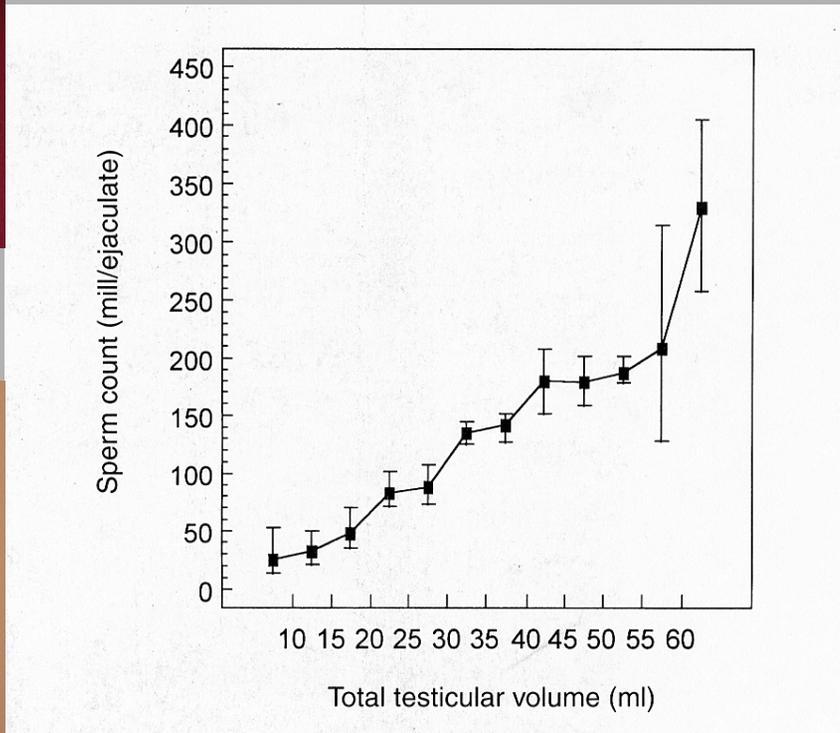
### Prevalence of chromosome abnormalities in various male populations



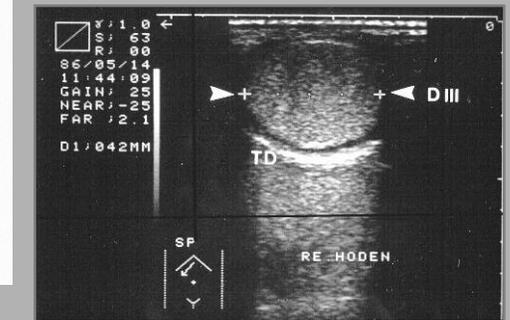
*Van-Assche et al 1996, Johnson 1998, Peschka et al 1999*

# TESTICULAR VOLUME

Prader orchimeter



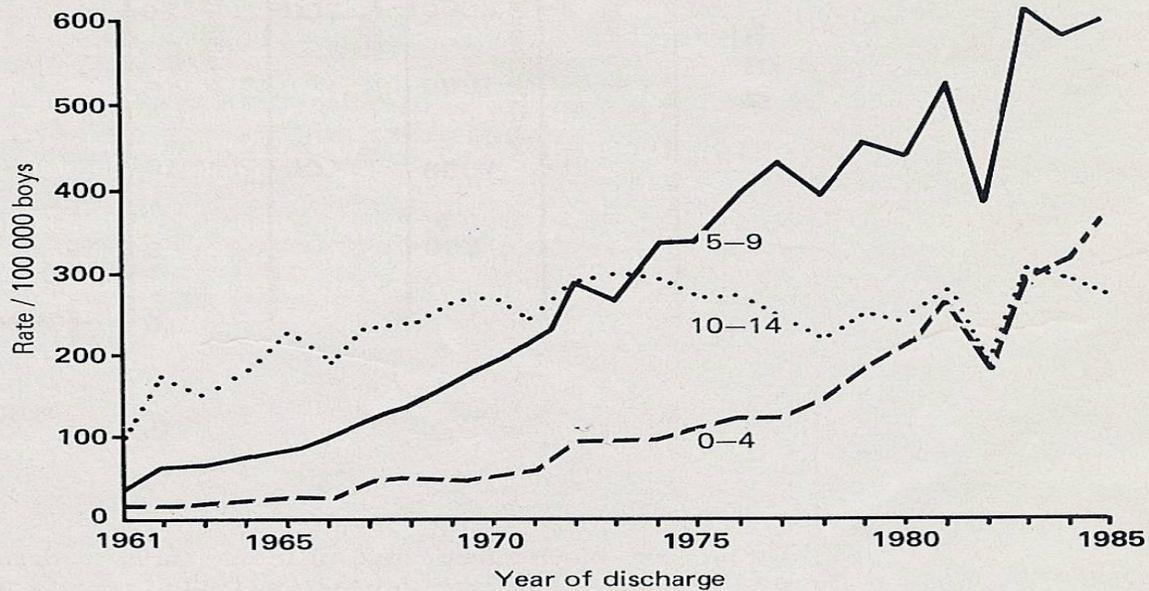
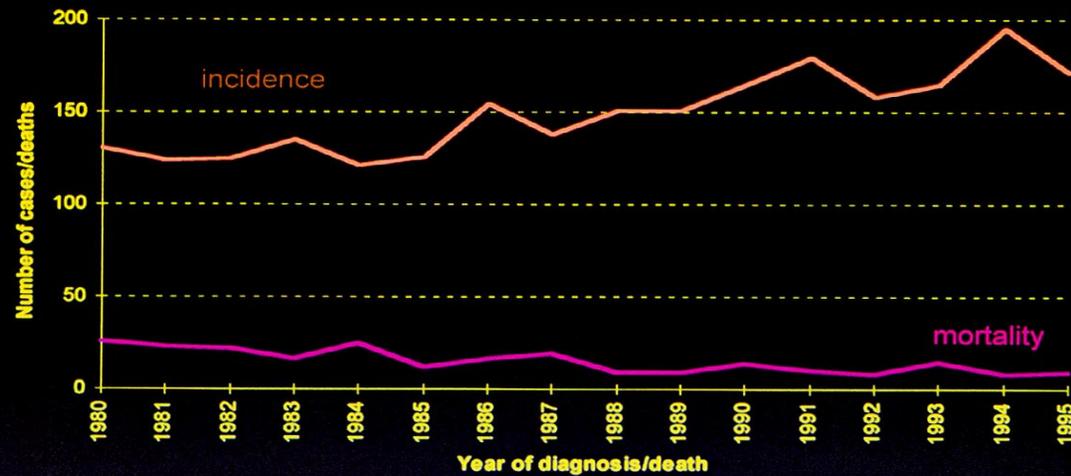
$ml = a \times b \times c \times 0,52$   
 cutpoint = 15 ml ( both testicles )





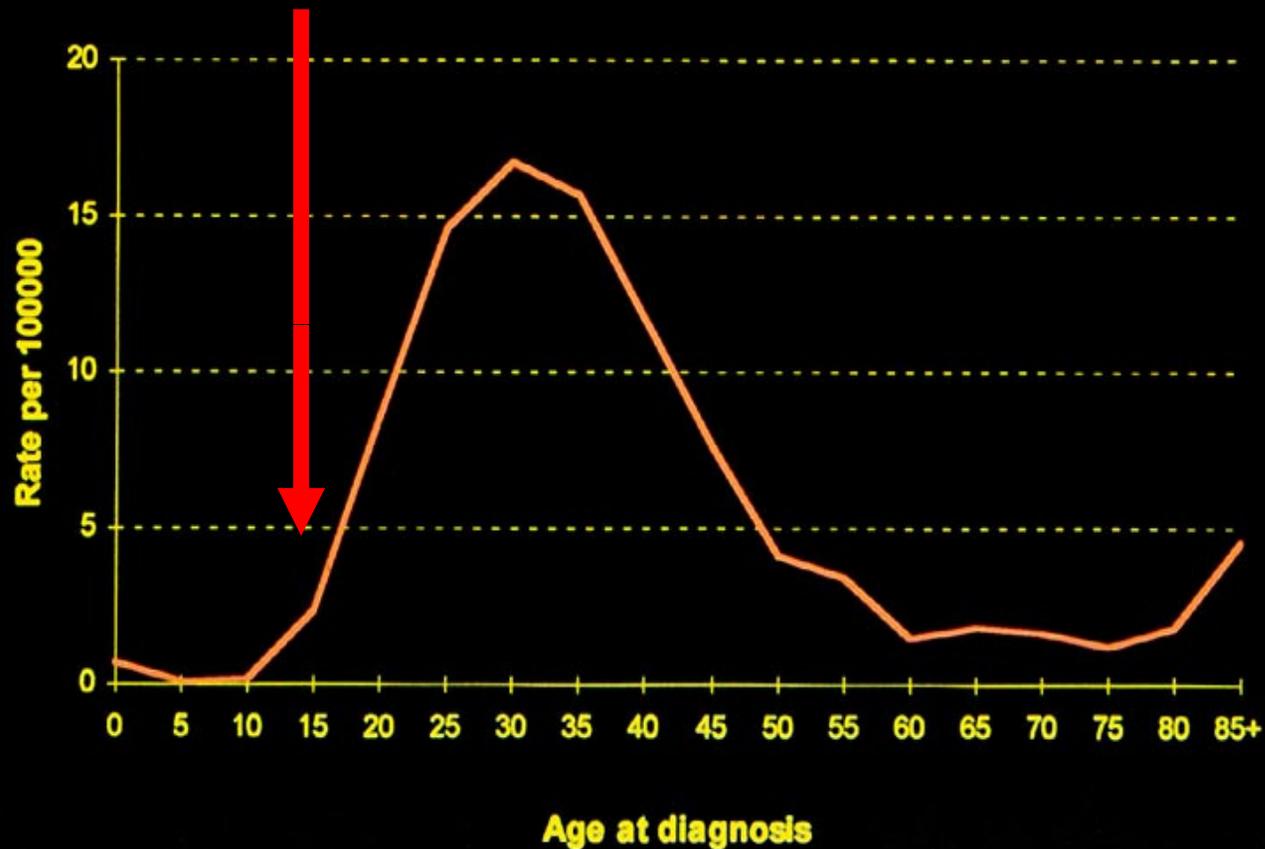
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## Testis cancer: time trends in incidence and mortality (Scotland, 1980-95)



Discharge rates for cryptorchidism by age group 1961-85.

# Testis cancer: incidence by age (Scotland, 1986-95)

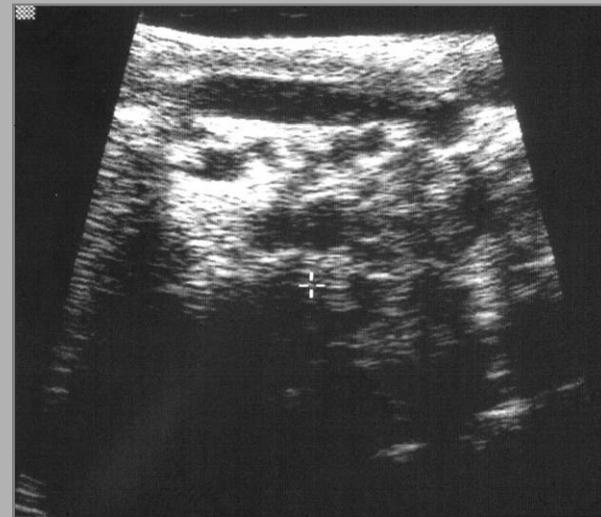


# SCROTAL ULTRASOUND

Testicular volume  
Epididymal cysts



Testis localisation  
Varicocele assessment

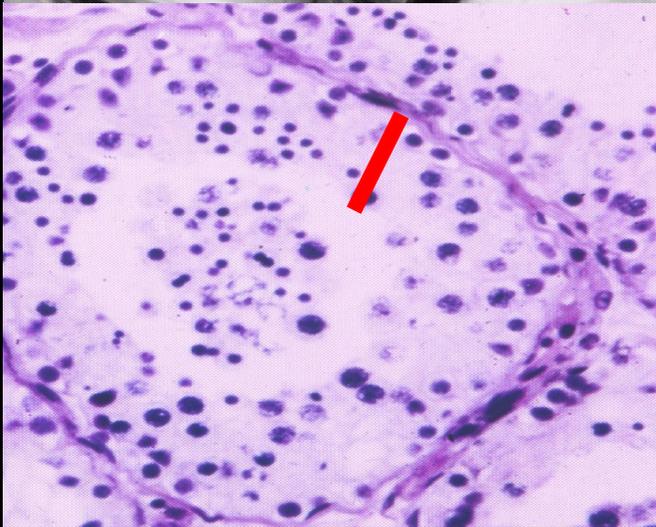


# Why I still recommend looking for varicocele

- Varicocele is associated with deterioration in semen measurements and these improve after treatment
- Pregnancy rate data in question  
*(Cochrane analysis has been criticised. Current large Netherlands study shows positive effect. Atlantic divide!)*
- Evidence that there is catch up testicular growth after varicocele treatment in younger men

**BEFORE**

**AFTER**

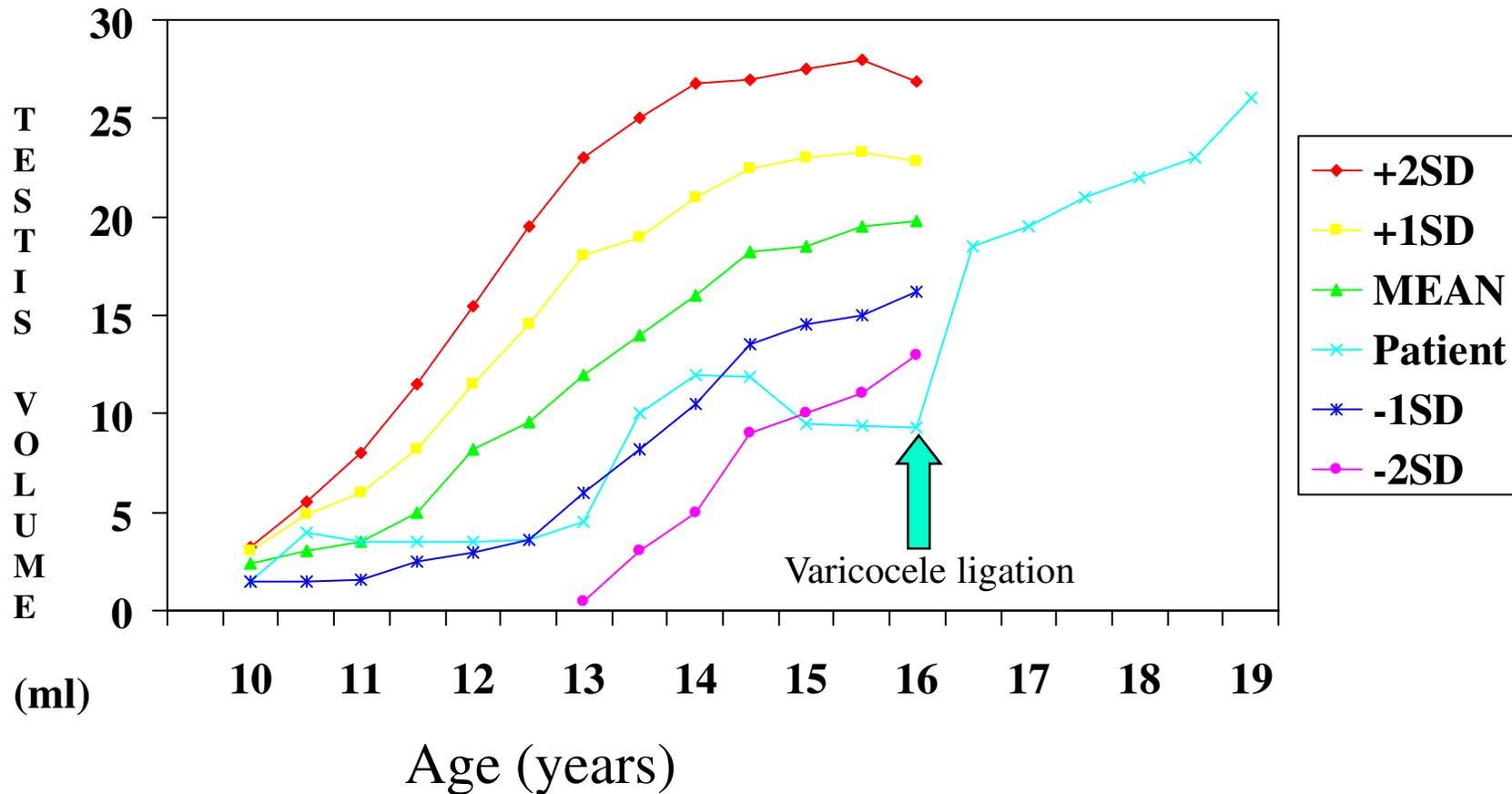


*Azoospermia*

*27,000,000*

*five children then vasectomy*

# Testicular growth in an adolescent boy before and after varicocele ligation. He was one of 91 boys in a MRC longitudinal growth study



How accurate is clinical examination for varicocele?  
Liakatas and Hargreave BJU

		Doctor A		
		Large	Small	None
Doctor B	Large	10	4	
	Small	1	5	
	None	3	24	84

# Diagnosis of varicocele

- Clinical examination unreliable  
(inter-observer error)
- Doppler ultrasound  
*(Reflux continuous, intermittent with or without  
Valsalva) (Get patient to blow against hand.  
Distinguish from cremaster movement)*
- Thermography
- Nuclear imaging

Does the foreskin retract?



# Penile Deformity

- Rare in younger men
- Associated with congenital abnormality
  - Hypospadias
  - Unilateral failure of development of genital tubule
- Commoner in older men
- Often little to find on examination of the flaccid penis
- Examination of erect penis
  - Digital (polaroid) photographs
  - Prostaglandin injection



Penile erection problems as a cause of infertility are rare except after severe injury e.g. Paraplegia, Pelvic fracture

Examination of the erect penis is essential if the man says he has an erectile deformity



Photographs or intracorporeal injection of 10-20 Micrograms prostaglandin

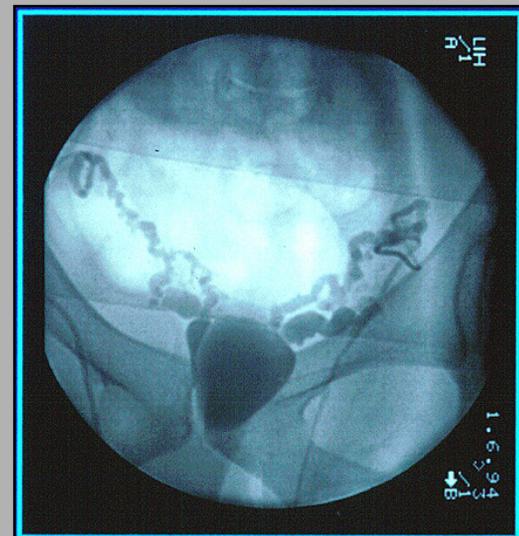
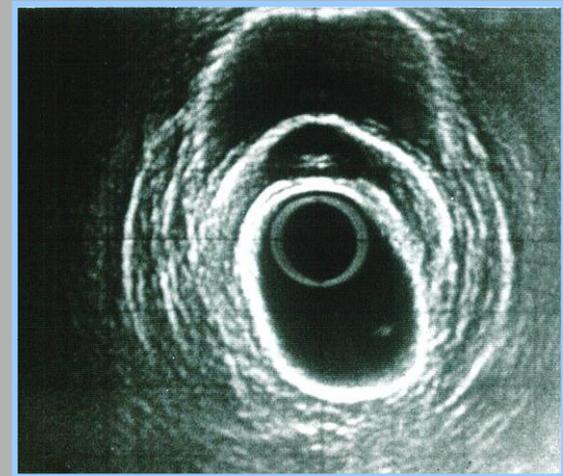
# TRUS

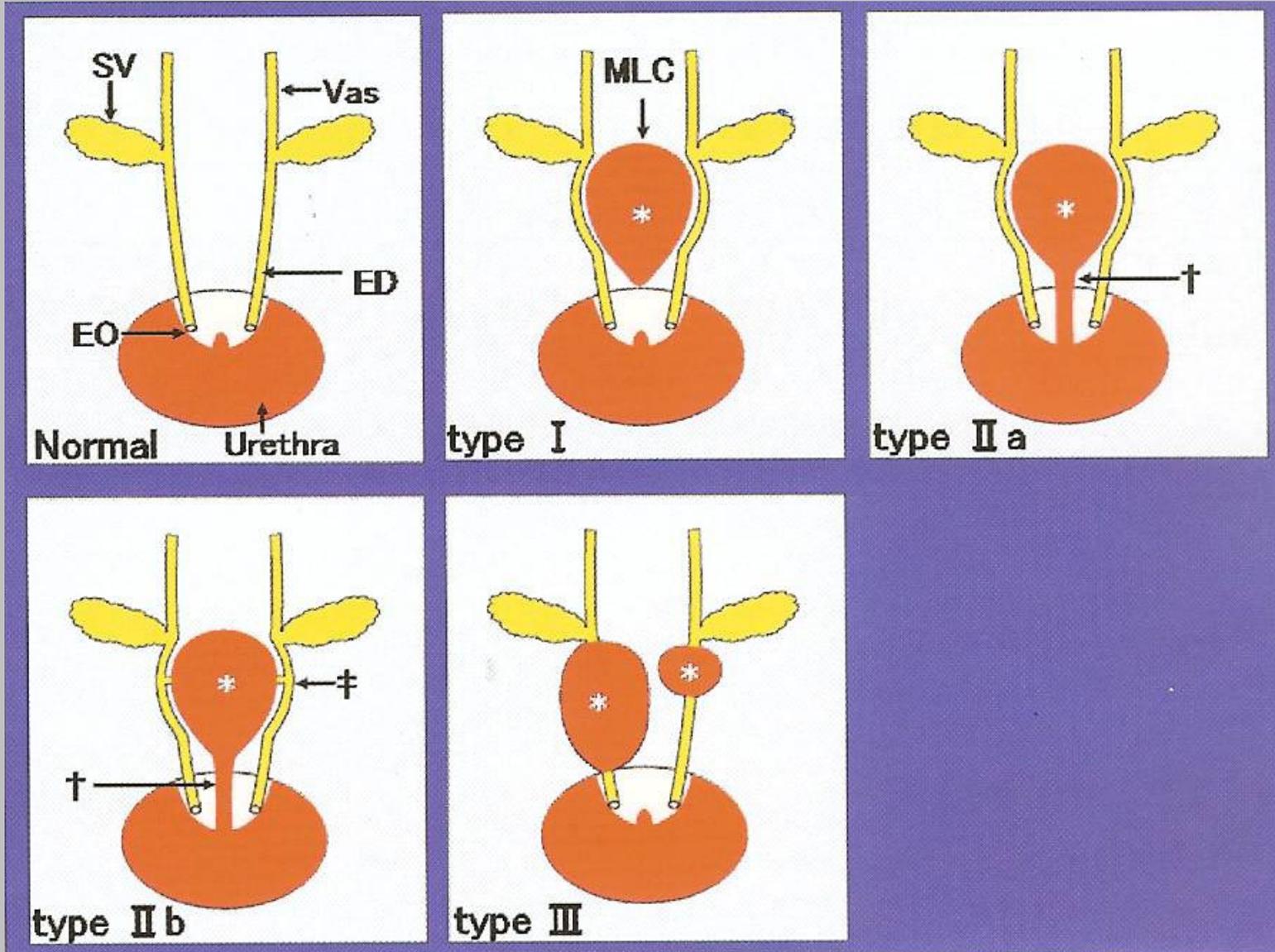
All patients with low volume ejaculate and palpable vasa deferentia

## Ejaculatory duct obstruction

- ✓ Low semen volume (<1.0 ml)
- ✓ Acidic seminal pH
- ✓ Negative or low semen fructose

Possible use of Tc 99m sulphur colloid scintigraphy. Injected into seminal vesicles at TRUS. Measurements before and after ejaculation. *Orhan et al 2008 urology 71:672*





Midline cysts of the prostate – types defined by dye injection

*Furuya et al 2008 BJUI 102, 475-478*

# Vas present?

- Not always easy to feel vas
- High index of suspicion if semen volume less than 1ml
- It is often worth re-examining the man especially if semen sample shows low volume
- Most cases of unilateral absence of the vas are nothing to do with CFTR and associated with ipsilateral renal abnormalities and with normal sperm production in the opposite testicle

# CFTR Mutations in CBAVD

The more mutations that are screened the higher the percentage of men found to have mutations

Country	No		%	No		No Mutations tested
	Patients	Mutations		Both alleles	Delta 508	
Israel	47	18	38	2	7	9
Israel	40	19	48	5	6	16
England	35	20	57	5	15	5
USA	63	40	63	6	25	12
Spain	30	22	73	3	9	13
USA	49	40	81	0	32	>10
Europe, USA	67	44	66	16	28	23
Scotland	30	21	70	6	19	14

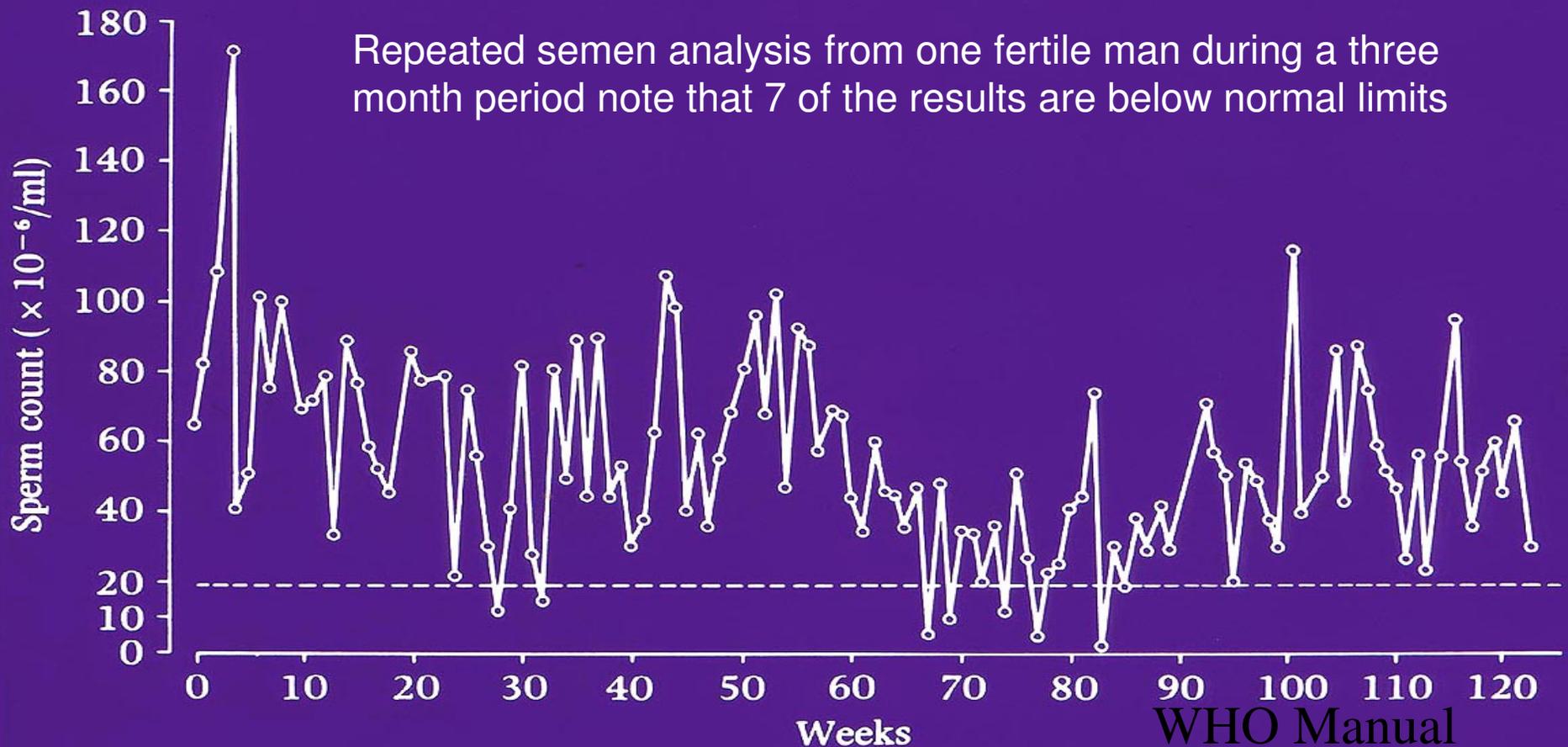


## Normal values of semen variables – WHO Manual

*\* New WHO Manual to be published 2009 Values may change*

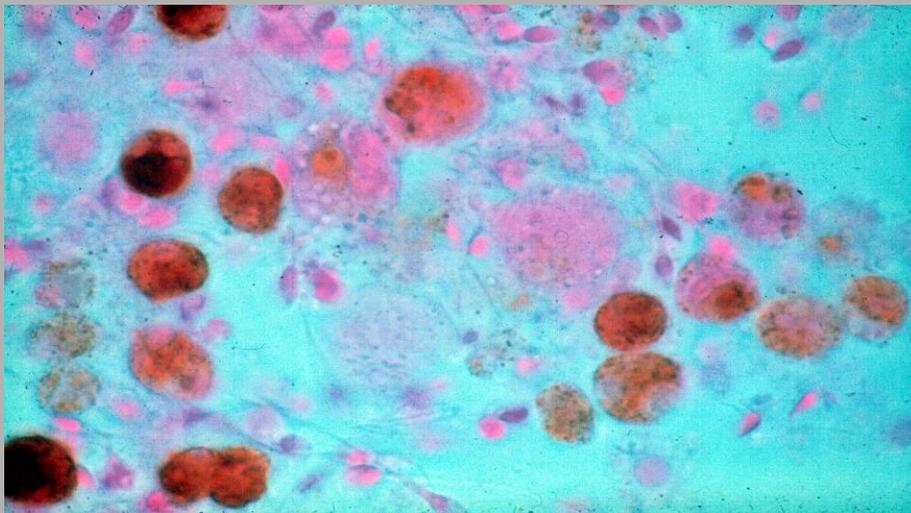
Measurement	Normal value	Comment
Sperm concentration	>20millions per ml	Predicts spontaneous pregnancy
Motility	50% with forward progression 25% with rapid progression	Predicts spontaneous pregnancy
Morphology	30% or more with normal forms	Predicts IVF / ICSI pregnancy
White cells (peroxidase)	< 1 million per ml	Poor correlation with infection
Immunobead	Fewer than 20% sperm with adherent beads	

Do not rely on a single semen analysis. If semen analysis is abnormal then repeat it. There is variation from day to day and month to month depending on sexual frequency, summer temperature, recent febrile illness etc



# LEUKOCYTOSPERMIA

WBC >  $1 \times 10^6$  / ml  
Peroxidase Staining



- cut- point under debate
- mostly derived from the epididymis
- only associated with bacterial infections in 20 %
- high rate of spontaneous resolution in the infertile men



# Poor Quality sperm



Fertile men have upto 85% abnormal sperm forms in ejaculate (Strict criteria) WHO 1999

Poor fertility (*Hull et al 1985*)

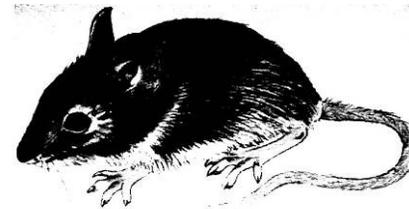
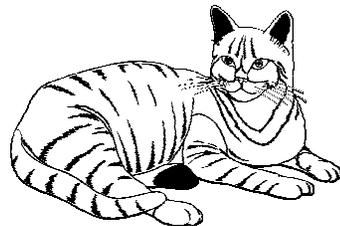
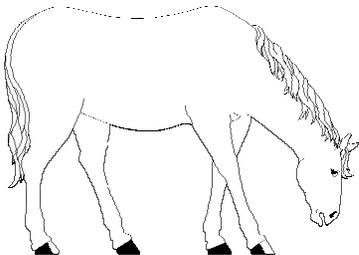
Higher rates of DNA damage in infertile men (*Irvine et al 2000 but no measurable effect on outcome of ICSI Nicopoulos et al 2008 BJUI 101:1553*) and older men (*Wyrobek AJ et al 2006 P N A S 103:9601*)

High rates of aneuploidy

High rates of pregnancy loss

High rates of birth defects

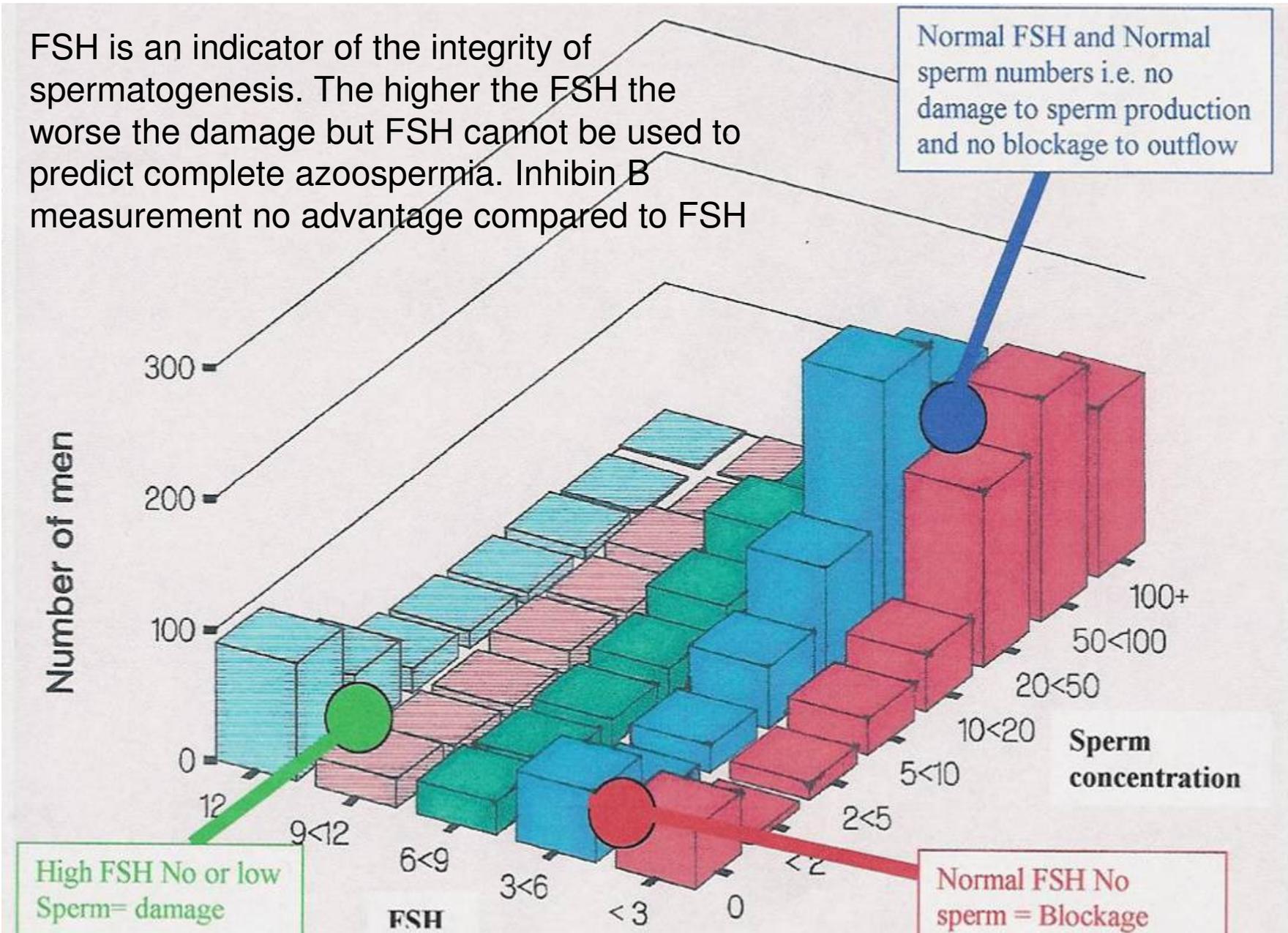
## Compared to viviparous vertebrates



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FSH is an indicator of the integrity of spermatogenesis. The higher the FSH the worse the damage but FSH cannot be used to predict complete azoospermia. Inhibin B measurement no advantage compared to FSH

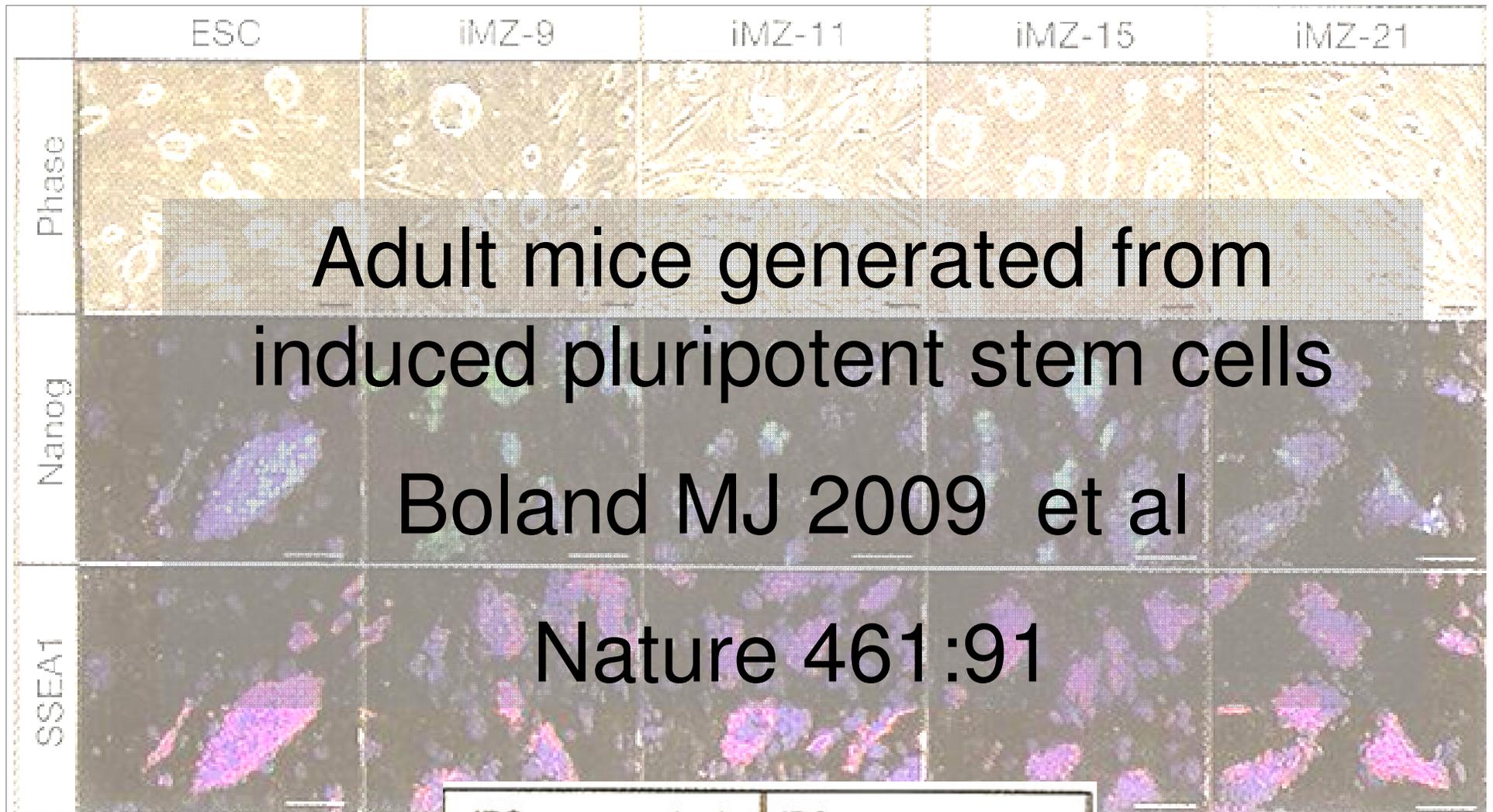


# Chromosome and genetic abnormalities.

Testing should be done prior to assisted conception

Abnormal results may impact on the future child

Test	Abnormality	Comment
Chromosome analysis (Karyotype)	47XXY Klinefelters Translocations Others	Commonest Abnormal karyotype
Specific gene screening	CFTR in men with CBAVD	Test partner as well
Y Microdeletions	AZFc Variable phenotype Complete AZFc Oligo – azo Partial AZFc (gr/gr, b2/b3) often found in fertile men	May predispose to children with complete AZFc ( <i>J Med Genet</i> 44:437) ??Turners syndrome and sexual ambiguity ( <i>Lancet</i> 360:1222)
	AZFa and b associated with azoospermia	Sperm recovery not worthwhile



Adult mice generated from induced pluripotent stem cells

Boland MJ 2009 et al

Nature 461:91

