Male Infertility

Tim Hargreave

Urological Surgeon, Edinburgh

What is male fertility?

The ability to produce and deliver by normal sexual intercourse an ejaculate containing spermatozoa with the capability of causing conception in the partner at the normal rate of 20% per month

What is male fertility?

We now have the ability to produce pregnancies using assisted conception technology at a rate that exceeds the normal conception rate of 20% per month

Overcoming male fertility problems?

Bypassing natures safeguards against faulty conceptions?

5 x Increase (0.39 – 1.94%) in de novo chromosome abnormalities in ICSI babies

Ref	Fetuses	De novo		Inherited
		Sex	Autosomal	
Testart 1996 Human reprod 11	115	-	-	5
Van Opstal 1997 Human Reprod 12	71	6	3	-
Govaerts 1998 Human Reprod 13	101	-	1	3
Loft 1999 Human Reprod 14	209	-	6	1
Van Gold 1999 J Assit Reprod	57	1	-	1
Wennerholm 2000 Human Reprod 15	149	-	2	2
Bonduelle 2002 Human Reprod 17	1473	9	14	19
All ICSI	2175	16 (0.74%)	26 (1.2%)	31(1.42%)
Newborn	94465	131(0.14%)	232 (0.25%)	

Van Steirteghem in Current Practices in assisted repro
WHO 2002 adapted by TBH TBH04

Genetic abnormalities

Chromosome abnormalities (XXY commonest)

CBAVD

Translocations

Y microdeletions

Environment and occupation

Hormone disrupters

Toxic substances Heavy metals e.g. Lead pesticides etc

Fertile

Subfertile

Infertile

Lifestyle

Food – obesity, lipids

Alcohol, drugs

Clothing

Warm baths

Stress

Diseases

Varicocele

Infections (chlamydia)

Antisperm antibodies

Acquired damage

Iatrogenic

Systemic

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

Sterile fully fertile

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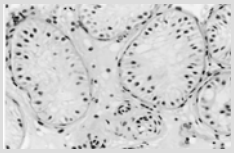
What is male sterility in 2007 ?

- Absence of testicles
  - Agenesis
  - Castration
    - Social
    - Medical
    - criminal
- Sertoli cells only
  - Spermatozoa can be obtained in approx 40-60% of men with an azoospermic ejaculate including those with XXY



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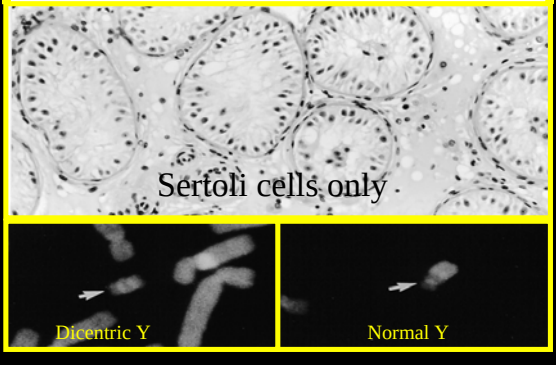
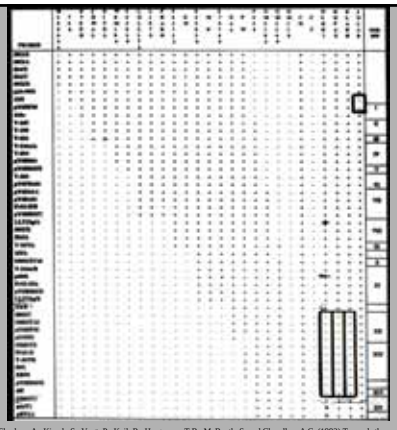
Short arm dicentric Y in a sterile man
Chandley et al 1986 Hum Genet 73:350





Ma, K., Sharkey, A., Kirsch, S., Vogt, P., Keil, R., Hargreave, T.B., McBeath, S. and Chandley, A.C. (1992) Towards the molecular localisation of the AZF locus: Mapping of microdeletions in azoospermic men within 14 subintervals of interval 6 of the human Y chromosome. Human Molecular Genetics 1, 29-33.

Non obstructive Azoospermia

Should we centrifuge the sample?

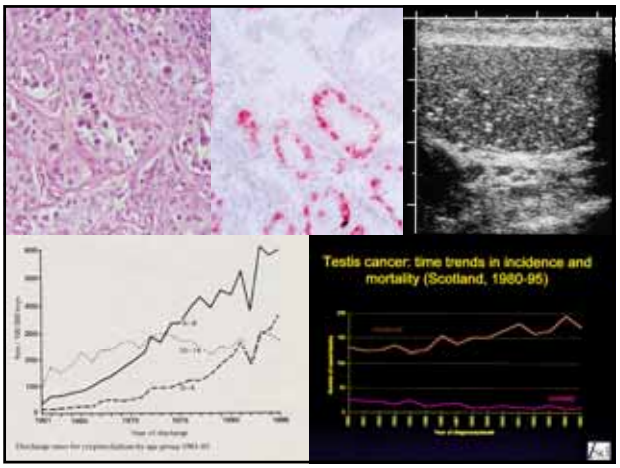
- 50/55 (91%) UK IVF clinic centrifuge semen for men with azoospermia
- 19/87 men who attended unit at Oxford has sufficient sperm recovered after centrifugation and careful examination of the sperm pellet to enable ICSI without the need for surgical sperm retrieval (PESA / TESA etc)

Swanton A Itani A McVeigh E Child T Azoospermia: is sample centrifugation indicated? A national survey of practice and the Oxford experience. In: Fertil Steril (2007 Aug) 88(2):374-8

Outcome of testicular sperm recovery and ICSI in patients with non- obstructive azoospermia with a history of orchidopexy.

Vernaeve V, Krikilion A, Verheyen G, Van Steirteghem A, Devroey P Tournaye H 2004 Hum Reprod 19:2307

- 79 men with non- obstructive azoospermic men and a history of orchidopexy.
- Testicular spermatozoa were recovered in 41 patients (52%).
  - The mean age at orchidopexy of the patients was:-
    - Sperm recovered - 10.6 years [95% c.i. 7.3-13.8]
    - No spermatozoa found 15.5 years (95% c.i.11.3-19.8)
- No differences were observed in the fertilisation rate, implantation rate and pregnancy rate between the orchidopexy group and a comparison group with unexplained azoospermia.



Induction of meiosis?

- Kalejs M et al. Upregulation of meiosis-specific genes in lymphoma cell lines following genotoxic insult and induction of mitotic catastrophe. In: BMC Cancer (2006) 6:6
- Matsui Y Hayashi K. Epigenetic regulation for the induction of meiosis. In: Cell Mol Life Sci (2007 Feb) 64(3):257-62
- Inai T et al. Interplay between chromatin and trans-acting factors on the IME2 promoter upon induction of the gene at the onset of meiosis. In: Mol Cell Biol (2007 Feb) 27(4):1254-63
- Downs SM Chen J. Induction of meiotic maturation in mouse oocytes by adenosine analogs.In: Mol Reprod Dev (2006 Sep) 73(9):1159-68
- Sedmikova M et al. Induction and activation of meiosis and subsequent parthenogenetic development of growing pig oocytes using calcium ionophore A23187. In: Theriogenology (2003 Dec) 60(9):1609-20

Fertility after death

If we become able to programme cells to undergo meiotic division then this will open the door to fertilisation using cells from other parts of the body and if so there may be no such thing as male sterility even after death!

Kaguya

Mouse created without father Scientists turn egg cell into surrogate sperm. Nature *21 April 2004*

Kaguya shows that imprinting normally blocks parthenogenesis

Reduced Fertility

Challenges

•To identify specific fertility defects and correct them

• To predict the fertility potential so that treatment is cost effective

Infertility is a couple problem

The urologist should have some understanding of female problems

Male partner	Female Partner
• History • Physical examination • Ultrasonography • Semen Analysis • Endocrine	• Significance of female age • History of problems that may cause Fallopian tube occlusion • Understanding of – ovulation induction – interaction between male and female fertility

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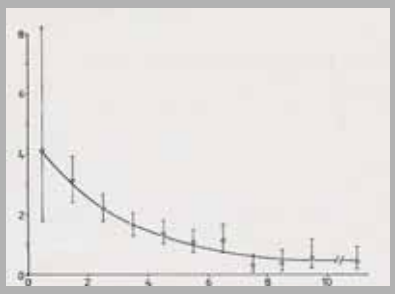
Couples who have been trying for a long time have a poor chance of spontaneous conception irrespective of test results

% chance
of conception
per month



Years trying without use of contraception

Data from Fertility Clinic WGH Edinburgh

Examination of the man

The urologist is likely to be the only doctor who examines the man

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

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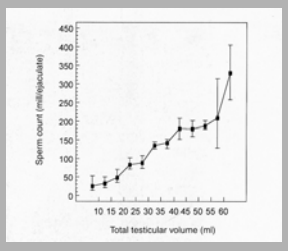
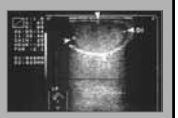
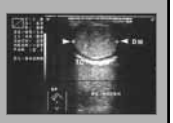
TESTICULAR VOLUME

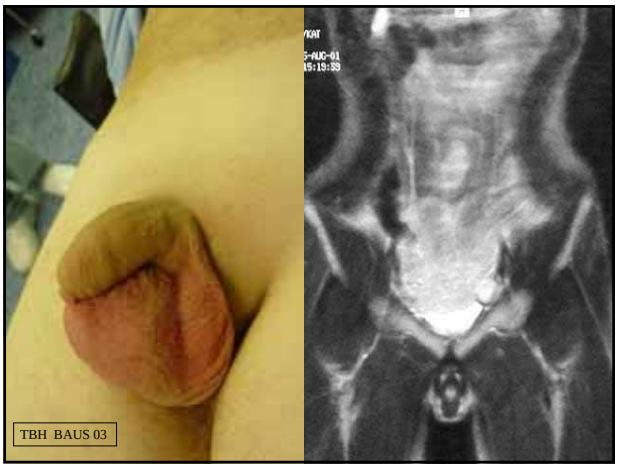




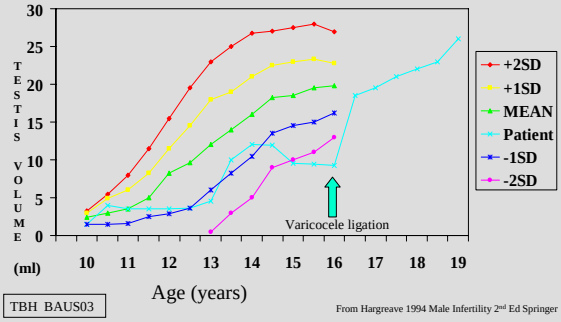


ml = a x b x c x 0,52
cutpoint = 15 ml (both testicles)

Weidner Eurep 05



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



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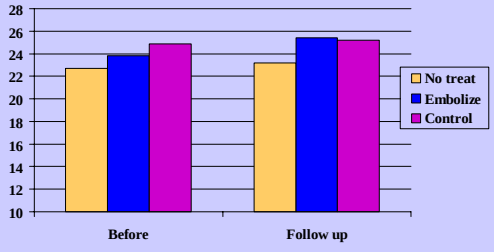
From Hargreave 1994 Male Infertility 2nd Ed Springer

Effects of varicocele treatment in adolescents: a randomised study
Laven et al 1992 Fertil Steril 58:756

Right testis vol (ml) before and after treatment



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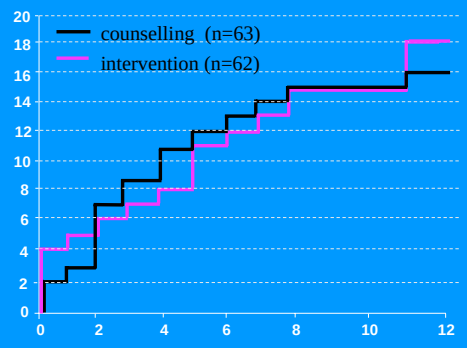
Cumulative pregnancy rates over 12 months in couples with varicocele treated by intervention (ligation or embolization) or counselling alone



Nieschlag et al 1998

Varicocele

- Treatment of adolescent varicocele restores testicular growth in those with unilateral testicular hypertrophy
- Treatment of varicocele improves semen
- Treatment of varicocele for couples does not improve pregnancy rates (met-analysis)

Treatment recommendations Adolescents

- Treatment is recommended for adolescents who have progressive failure of testicular development documented by serial clinical examination
- Treatment is probably recommended for adolescents with ipselateral testicular atrophy. Further clinical studies are needed with long-term follow up.

EAU guidelines 05

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 very rare except after severe injury e.g. Paraplegia, Pelvic fracture

Predicting fertility potential from semen analysis

– Strict morphology
– Sperm function tests

– Study of the whole ejaculate
– Study of swim up or other selected sperm
– Centrifugation

Poor Quality sperm

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

Poor fertility *(Hull et al 1985)*

High rates of DNA damage *(Irvine et al 2000)*

High rates of aneuploidy

High rates of pregnancy loss

High rates of birth defects

Compared to viviparous vertebrates

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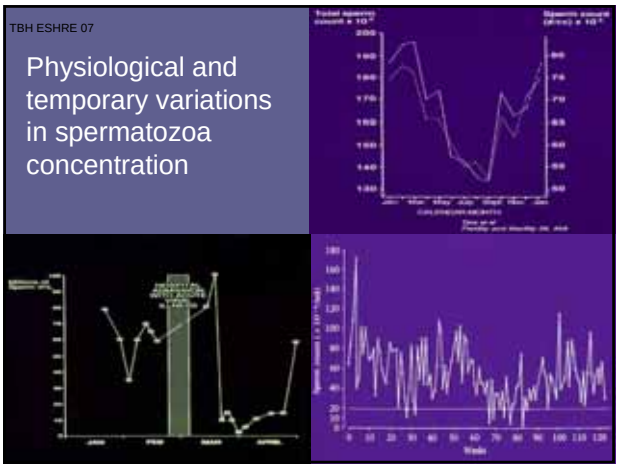
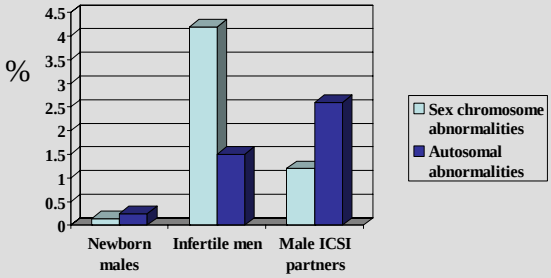
Physiological and temporary variations in spermatozoa concentration



Genetic tests

- Klinefelters syndrome XXY and variants
- Translocations
  - Balanced
  - unbalanced
- CBAVD and CF gene mutations
- Y microdeletions – Y genes
  - AZFc variable phenotype
  - AZFa and AZFb azoospermia

Prevalence of chromosome abnormalities in various male populations



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

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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

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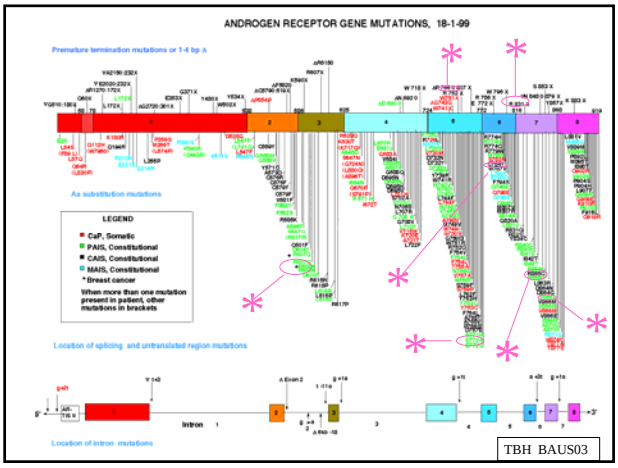

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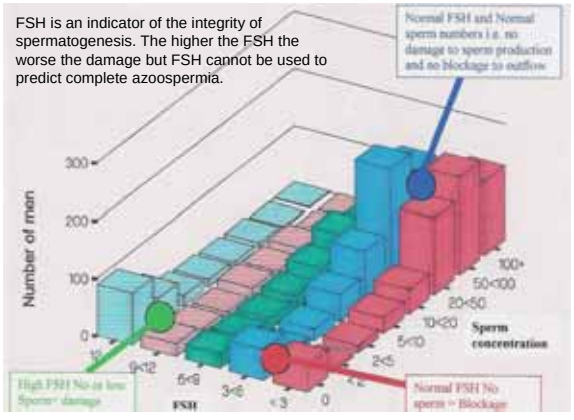

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Molecular tests

- Not yet in routine clinical practice
- One of the research challenges is to identify defects that are causative and specific
- It is likely that many abnormalities will simply reflect damaged metabolic processes common to all damaged tissues.

Proteomics and Spermatogenesis

- Huo R et al Differential expression of glucose-regulated protein 78 during spermatogenesis. In: Cell Tissue Res (2004) 316:359
- Govin J et al Post-meiotic shifts in HSPA2/HSP70.2 chaperone activity during mouse spermatogenesis. In: J Biol Chem (2006) 281:37888
- Zhu YF et al Proteomic analysis of effect of hyperthermia on spermatogenesis in adult male mice. In: J Proteome Res (2006) 5:2217
- Chu DS et al Sperm chromatin proteomics identifies evolutionarily conserved fertility factors. In: Nature (2006) 443:101
- Huang SY et al Developmental changes of heat-shock proteins in porcine testis by a proteomic analysis. In: Theriogenology (2005) 64:1940

Automated molecular techniques will bring down the cost of testing and make it practical to perform many molecular tests on blood or sperm samples to identify defects known to be associated with reduced fertility.

Sperm banking

Adolescents more likely to produce sperm if not accompanied by mother !

Bahadur et al Human reproduction 17:2654-2656

Live birth with sperm cryopreserved for 21 years prior to cancer treatment:

Case report G. Horne, A.D. Atkinson1, E.H.E. Pease, J.P. Logue, D.R. Brison and B.A. Lieberman

Department of Reproductive Medicine, St Mary's Hospital, Manchester M13 0JH and Department of Clinical Oncology, Christie Hospital, Manchester, UK Human Reproduction, Vol. 19, No. 6, 1448-1449, June 2004

Advances in cancer treatment have led to significant improvements in the likelihood of reaching remission and long-term survival for men. Chemo- and radiotherapy-induced infertility are significant treatment side effects. Cryopreservation before the start of treatment enables sperm to be stored, thereby preserving the man's potential fertility. Here, we describe the successful use (with ICSI) of sperm cryopreserved prior to cancer treatment, for a total of 21 years. We believe this to be the longest period of sperm cryopreservation, resulting in a live birth, so far reported in the literature.

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Seager technique - The First European baby

Veterinary technique adapted for Humans

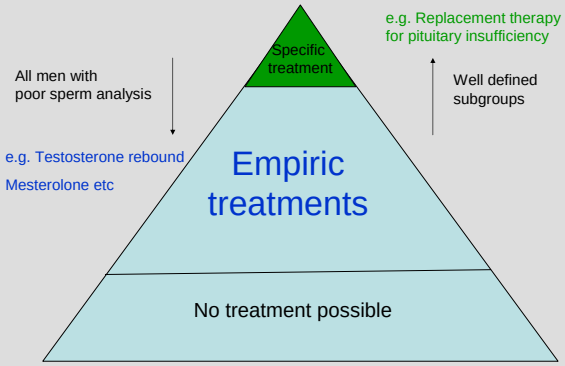
TBH electro - ejaculating a Gorrilla

Permission given for photo TBH

Fertility problems as a consequence of Urological procedures

- Orchidopexy and hernia repair in infancy *be careful of the vas*
- Epididymal cysts *be careful of bilateral cysts in young men*
- Pelvic surgery *advise about sperm recovery*
- Renal transplantation *may damage the vas*

Treatment for male fertility problems 1900 - 1980



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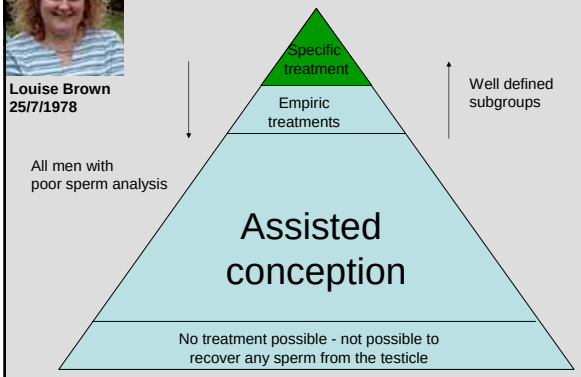
Treatment for male fertility problems 1980 – 200?

Louise Brown 25/7/1978



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IVF - ICSI for male factor infertility is an admission of failure to be able to treat the underlying male problem

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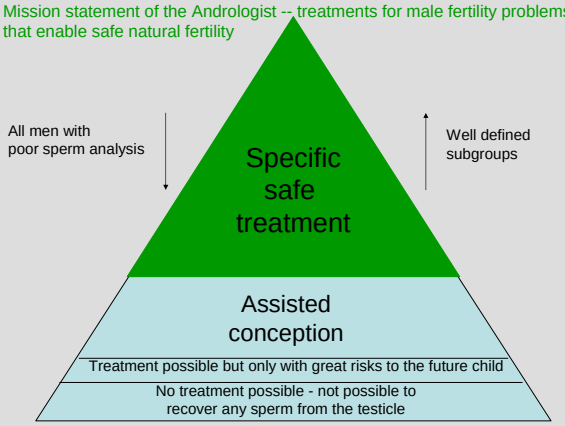
Mission statement of the Andrologist -- treatments for male fertility problems that enable safe natural fertility



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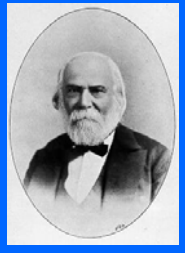
Irrational belief

therapy with Testicular Extracts



Brown - Séquard

Increased physical strength, mental abilities and appetite by self-injection of animal testicle preparations

Don't let women prefer dildo to you ! Megadik will bring you to your sexual dreams! You just have to trust this excellent preparation! Soon you'll be the only one girls will want! Megadik is your real cure!

Research treatments to improve spermatogenesis

- Molecular therapy for specific defects
  - Not very practical as most men with poor spermatogenesis have multiple molecular defects i.e. there is not a single lesion that accounts for the disorder
- Gene transfer research
  - Gene Therapy
    - Altering the germline
    - Supporting the germline
- Transplant therapy
  - Repopulating the testis with germ cells
  - Transplant between individuals
  - Stem cells
  - Into animals

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AOCA 04

Interspecies transplantation of germ cells

Donor	Recipient	colonisation	proliferation	Reference
Mouse	Infertile mouse	Yes	Yes	*1994 Brinster, Avarbock PNAS 91:11287* Proof of concept of germ cell transplant
Rats Hamsters	Nude Mice	Yes	Yes	*1996 Clouthier, Avarbock, Maika, Hammer, Brinster Nature 381:418* Proof of concept of xenotransplant of germ cells
Rabbits Dogs	Nude Mice	Yes	No	*1999 Dobrinski, Avarbock, Brinster Biol Reprod 61:1331*
Boars Bulls Stallions	Nude Mice	Yes	No	*2000 Dobrinski, Avarbock, Brinster Mol Reprod Dev 57:270*
Primates	Nude Mice	Yes	No	*2001 Nagano, McCarrey, Brinster Biol Reprod 64: 1409*
Rat with retroviral vector	Nude Mice	Yes	Yes	*2002 Orwig, Avarbock, Brinster Biol Reprod 67:874* Proof of concept of germline modification
Humans	Nude Mice	Yes	No	2002 Nagano, Patrizio, Brinster Fertil Steril 78:1225 First human germcell xenotransplant

PUTS A NEW MEANING INTO BEING AFRAID OF MICE!

Male Infertility

Tim Hargreave, Urological Surgeon, Edinburgh

Senior Fellow, Dept of Oncology, Edinburgh University

Chair, Scientific and Ethical Review Group UNDP / UNFPA / WHO / World Bank Special programme of Research, Development and Research Training in Human Reproduction. WHO, Geneva.

Co-editor “Andrology for the Clinician” (Published Springer 2006)

Y Micro-deletions as a cause of male infertility were first identified in my patients

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