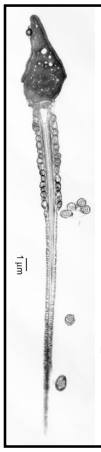

History and Background

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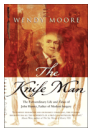
Sentinel markers in history

- Ah hoc insemination since the beginning of time.
- Storage and cryopreservation of semen.
- Organisation of treatment networks/systems e.g. CECOS.
- Transmission of HIV and eventual mandatory use of cryopreserved screened samples.
- Trends and current [anticipated] demand for donor insemination.
- Regulation/guidelines/legislation
- Use as a research tool.

- Unofficial history claims that crude attempts to artificially inseminate Juana, the wife of King Henry IV of Castile in the 1400s, was an early endeavour to artificially impregnate an infertile couple.
- Lazzaro Spallanzani transferred male dog semen into a rutting female in 1784.
- John Hunter apparently carried out the first successful experiment on humans (late 1700's). He advised a patient with severe hypospadia to collect his semen and inject it into his wife
- In 1884 Professor William Pancoast of Jefferson Medical College deposited a medical students sperm with a rubber syringe and swore everyone to secrecy. The mother was sedated and not told about the procedure.
- Ilya Ivanovich Ivanov inseminated animals in early 1900's leading to the start of the successful animal insemination industry.



Cryopreservation history on human semen (1776-1964)

[adapted from Sherman 1973 Fertil Steril 24, 397-412].

Date	Contributor	Contribution
1776	Spallanzani	Low temp. observation
1866	Mantegazza	First suggestion of frozen semen bank
1938	Jahnel	-269°C survival; storage at -79°C
1940	Shettles	Individual variation, aging and thawing
1942	Hoagland & Pincus	Vitrification principle; foam freezing
1945	Parkes	Survival better in greater volumes
1949	Polge, Smith & Parkes	Glycerol as cryoprotectant
1953-55	Sherman	Freezing rates; glycerol; preservation
1953-55	Bunge, Keettel & Sherman	First progeny from stored spermatozoa (dry ice)
1954-59	Keettel et al.,	16 births with stored sperm
1962-63	Sherman	Survival factors, banking applications, nitrogen vapour.
1964	Perloff, Steinberger & Sherman	Births with nitrogen vapour

Challenges in 1973 ……

- Why is fertility reduced by freeing?
- What is the nature of the damage at the molecular level?
- What is the ideal vehicle/cryoprotectant?
- What changes are required to the technique of freezing?
- What parameters are we to use to judge the fertilizing capacity of any given specimen?

adapted from Sherman 1973 Fertil Steril 24, 397-412

History

- Liquid Nitrogen introduced in early 1960' by Sherman and colleagues.
- By 1973 564 normal births with no increased risk of abnormality.

  – which led to :

  a. Organised sperm banks in USA

  b. CECOS (Centre d'Etude et de Conservation du Sperme Humain) established by G David in 1973. Leading the way.

CECOS led way with clinical research

Success rates of DI according to donor semen characteristics.

	# motile cells/straw x10^6		
	<5	5-10	>10
	7%	13%	15%
Cycles	513	635	341

Adapted from David *et al* 1980 Int J Androl 3, 613-9.

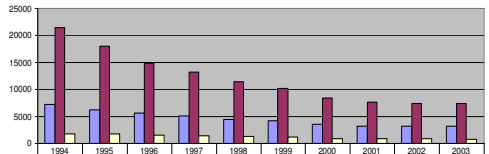
NB success rates using cryopreserved semen.

Transmission of HIV by cryopreserved semen

- 4/8 women inseminated with cryopreserved semen from a symptomless carrier of human T-cell lymphotropic virus type III (HTLV-III) were found to have antibody to the virus.
- 1 developed symptoms whilst other 3 were symptom free 3 years after insemination.
- 3 became pregnant more than a year after contact with the infected semen
- Children, who are now over 1 year of age, are in good health and do not have HTLV-III antibodies.
- Emphasize the need for a rigorous screening programme and that fresh semen should not be used in AI.
- The findings confirm the role of semen in heterosexual transmission of the virus and suggest that in women with HTLV-III antibodies pregnancy and subsequent breast-feeding does not necessarily lead to infection of the infant.

Stewart GJ, et al., (1985) Transmission of human T-cell lymphotropic virus type III (HTLV-III) by artificial insemination by donor. Lancet. 2(8455):581-3.

HFEA data

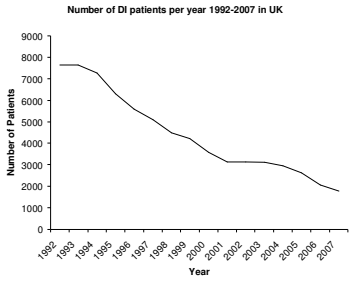


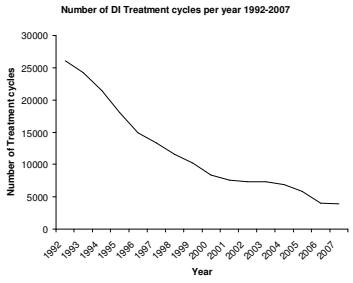
	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Number of DI patients	7243	6280	5569	5077	4462	4218	3572	3193	3149	3111
Number of DI treatment cycles	21465	17967	14871	13166	11466	10195	8352	7575	7327	7317
Total live DI babies	1836	1730	1559	1360	1233	1152	904	832	884	823

IVF and ICSI treatment cycles 36049 [incl frozen] of which 2057 donor eggs. 15854 fresh ICSI cycles. (2004)

DI 03/04 patients = 3106, cycles = 7351 births = 692

DI 05 : 2618 patients





Is DI in terminal decline ?

What is the demand for DI in the UK [minimal] ?

- Assume 1999 levels are robust ~ 10,000 treatment cycles with 2000 births [better success...].
- Currently less than 2200 treatment cycles thus 22% of demand.
- CECOS in 1991 ~2000 pregnancies.

So .. Why the continual decline?

- ICSI treatment of choice but been around since 1992 and widespread from 1994.
- 'Difficulties obtaining semen'

Long time widespread concern over number and quality of sperm donors [death by 1000 cuts]

- Traditionally challenging to recruit sperm donors
- Significantly more challenging following uncertainty over 'expenses/payment' and in particular anonymity.
- This uncertainty [and rise of ICSI] led to a number of centres not bothering to continually recruit donors which undoubtedly accentuated the problem.

How many sperm donors does the UK require?

If we assume 2000 live births pa:

- if no choice in donors = 200
- Choice
  - (factor : X6 for ethnic origin, screening) =1200

In Netherlands : 700 live births [25/donors] 901 donors in 1991

(Janssens *et al.*, 2006 Hum Reprod 21, 852-856)

The challenges of regulation

Change in anonymity – a significant variable?

- In keeping with other countries e.g. Sweden changed law in March 1985.
- Holland 2004.
- UK from April 2005.
- Preliminary evidence – but not hard objective data – was that semen donor #s would decline and be more challenging to recruit [Daniels]
- ***The UK [and DH] completely unprepared.***

Success rates ??? [non development]

- Is a [national average] 10% LBR acceptable?

Challenges [2010]

- Scientific challenges identified in 1973 remain. But we have additional ones……
- Dealing with demand [from all sources] whilst improving success and maintaining safety and confidence of the patients and public.
- Utilizing (designing) experimental data. Great research tool – female factors e.g. Age, sperm function etc.
- Informing regulatory/professional bodies in a robust, constructive and intelligent manner [pan EU level].
- Social science research on ‘families’ – pitiful at present.