

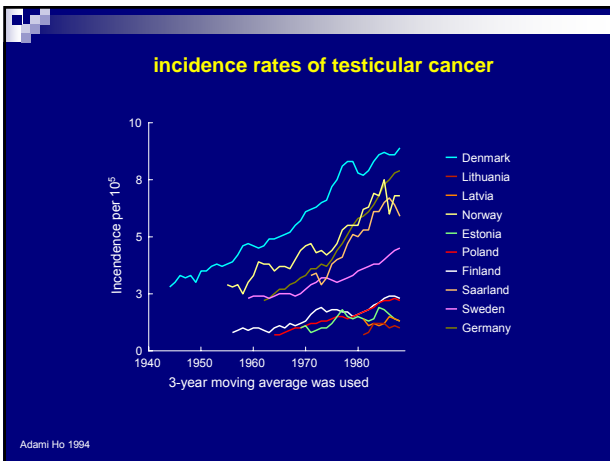
SEEDS OF CONCERN ?

Dirk Vanderschueren

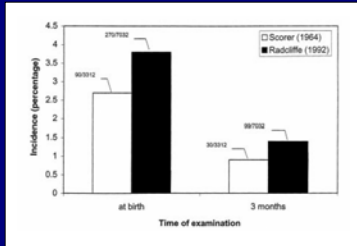
Laboratory for Experimental Medicine and Endocrinology
K.U.Leuven Belgium

Seeds of concern ?

- Incidence of testis cancer, cryptorchidism and hypospadias
- Incidence of male sperm output – subfertility
- Hypothetical model: testicular dysgenesis syndrome
- Male ageing and reproductive function
- Conclusion

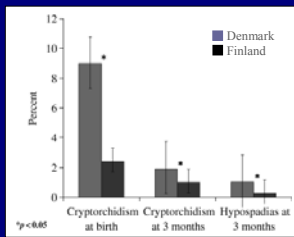


Incidence of cryptorchidism in full-term boys at birth and age of 3 months in England



Toppari J. Hum. Repr. Update 2001

Prevalence of congenital cryptorchidism and hypospadias in a prospective cohort investigation 1997–2001 from Denmark and Finland



Skakkebaek et al. Int J Andro, 2007

Incidence testis carcinoma, cryptorchidism hypospadias

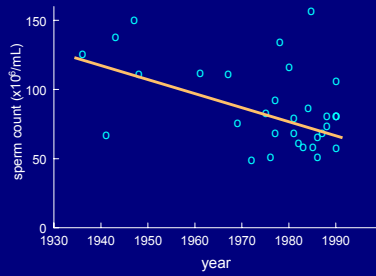
- Testis carcinoma: regional differences – increase in Denmark 2.6% per year: more dependent on birth cohort than on calendar period
- Cryptorchidism- hypospadias: regional differences – increase (lower incidence in Finland than Denmark)

Molson, 2001 Toppari, 2001

Seeds of concern ?

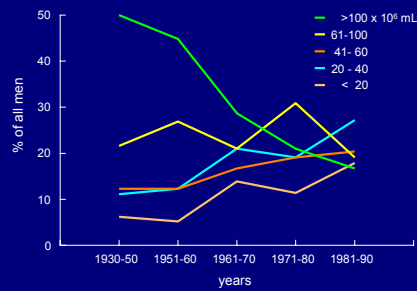
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Evidence for decreasing quality of semen during past 50 years

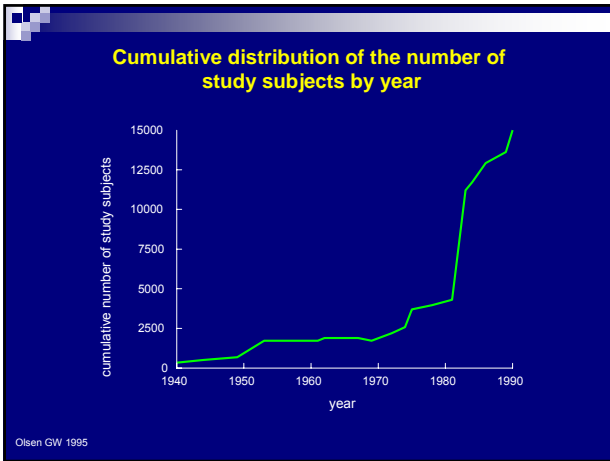


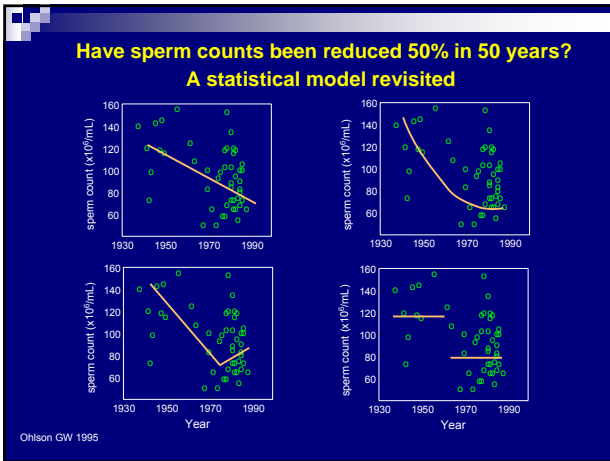
Carlsen 1992

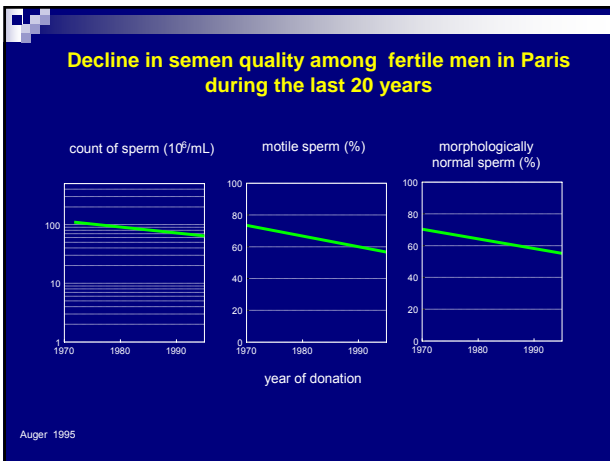
Evidence for decreasing quality of semen during past 50 years



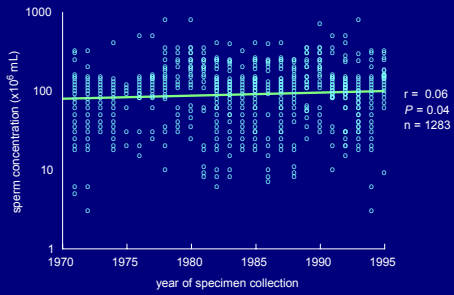
Carlsen 1992





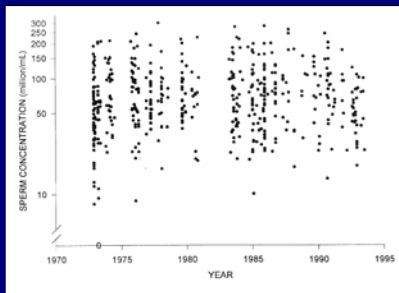


Semen analyses in 1283 men from the United States over a 25 year period: no decline in quality



Fish 1996

Data from men in greater Seattle area reveals no downward trend in semen quality



Paulsen 1996

Confounders which may influence human sperm concentration

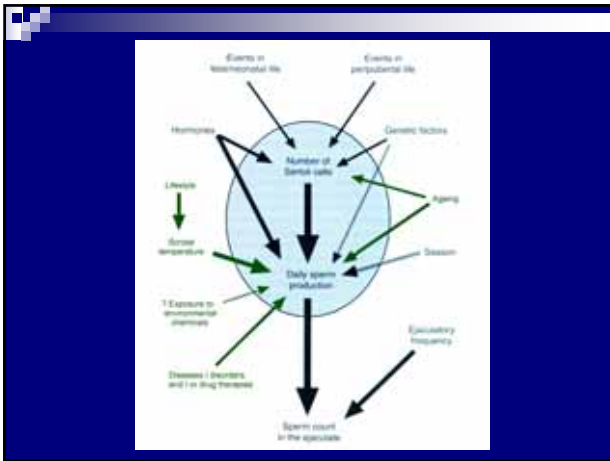
Population characteristics

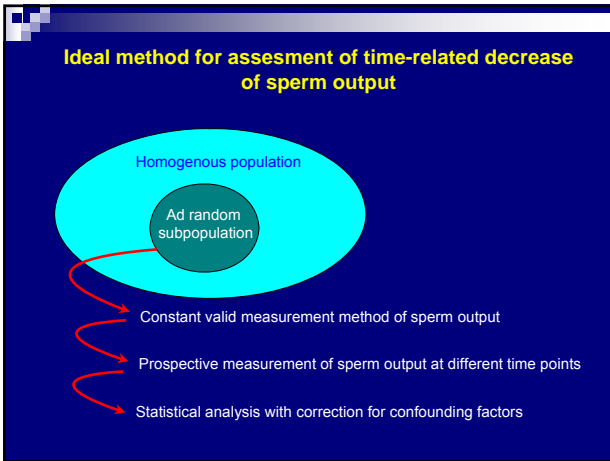
- Ethnicity
- Occupation
- Age
- Medication and diseases
- Nutrition clothing, smoking habits
- Stress
- Sexual activity

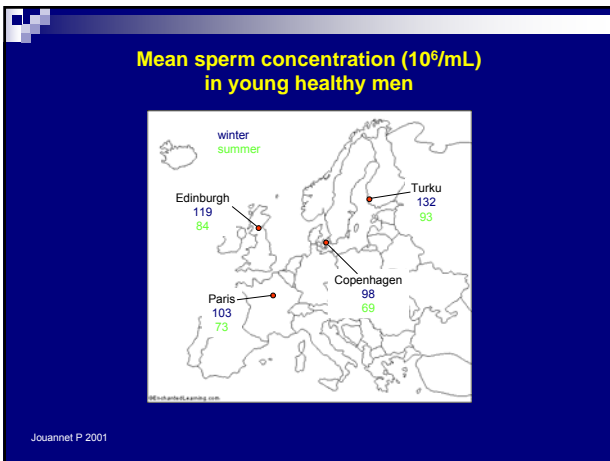
Methodology

- Mode of semen collection
- Semen analysis methods
- Number of ejaculates analysed
- Sexual abstinence delay
- Intra- and inter- technician variability
- Season at delivery of sample
- Statistical methods

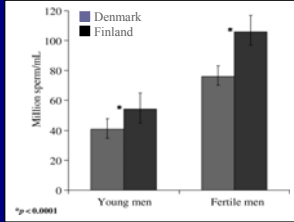
Jouannet P.2001





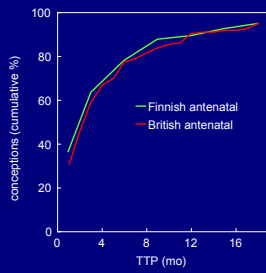


Median sperm concentration in Danish and Finnish populations



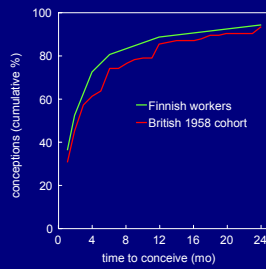
Skakkebaek et al. Int J Andro, 2007

Comparison of Time to pregnancy distributions from antenatal studies in Finland and Britain



Joffe The Lancet 1996

Comparison of TTP distributions from a Finnish occupational study and the British National Child occupational study



Joffe The Lancet 1996

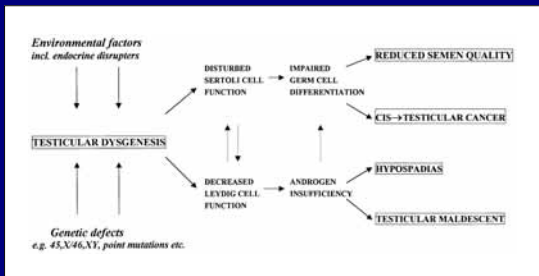
Incidence in sperm output – male subfertility

- Striking and unexplained regional differences for both sperm output - male subfertility
- Difficult to assess time –related changes in incidence of sperm output- male subfertility
- Therefore, a time-related decrease of male subfertility remains controversial

Seeds of concern ?

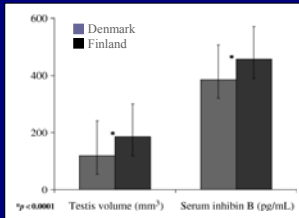
- Incidence of testis cancer, cryptorchidism and hypospadias
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The pathogenetic links between the components and clinical manifestations of testicular dysgenesis syndrome



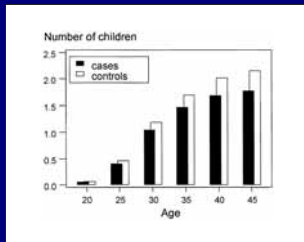
SkaKkebaek N.E. Hum. Reprod. 2001

Median testicular volume and serum inhibin B levels in 3-month-old healthy boys from Denmark and Finland



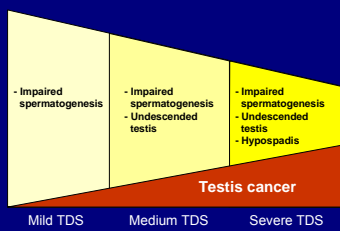
Skakkebaek et al, Int J Andro, 2007

Epidemiological evidence of decreased fertility in men who later developed testicular tumours



Skakkebaek N.E, Hum. Reprod. 2001

Illustration of the relationship between the relative frequency of various symptoms of the testicular dysgenesis syndrome (TDS)



Skakkebaek Hum. Reprod. 2001

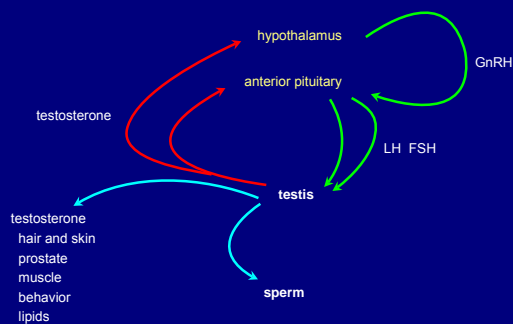
Testicular dysgenesis syndrome may explain:

- Regional differences of testicular disorders
- Association between testicular disorders
- Birth cohort effects
- Increase of incidence rates
- But difficult to prove

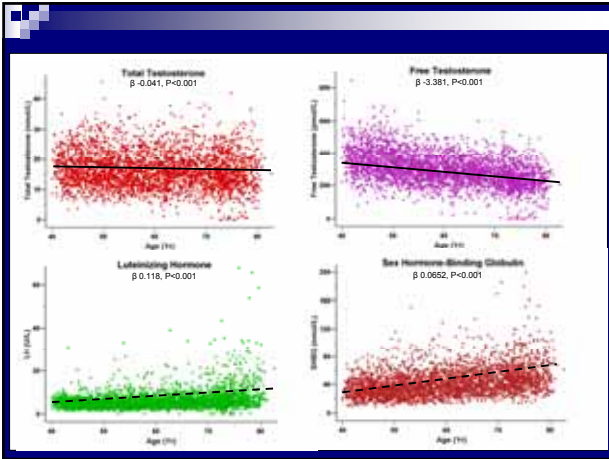
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The hypothalamic-pituitary-gonadal axis in men

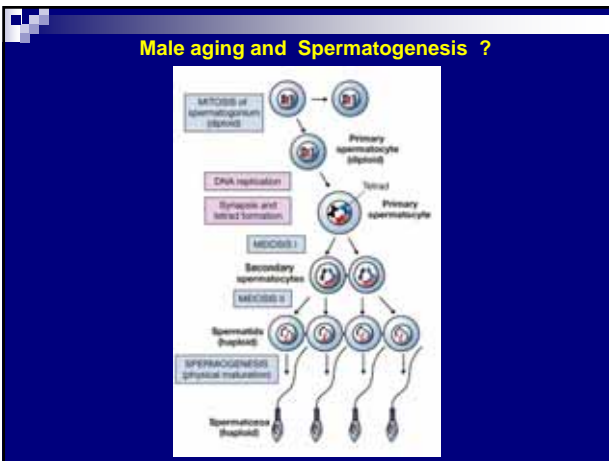


Alastair J.J.Wood, NEJM 1996



Male ageing and endocrine function

- Leydig cell function: testosterone decline 0.4 to 1.2 %/year (Kaufman 2005)
- Sertoli cell function: moderate decrease testisvolume and inhibinB/FSH ratio (Mahmoud 2003)



Male ageing and sperm output

- Sperm output: some reduction in volume and motility but no consistent decline in sperm concentration (Kidd 2001)
- Male age effect on fertility status uncertain because of confounder of female age

'Time to pregnancy and male ageing'

Older paternal age delays 'time to pregnancy' even in younger women

The effect of male age on time to pregnancy

Men's age (years)	Time to conception ≤ 6 months OR*	Time to conception ≤ 12 months OR*
≤ 24 (n = 643)	1.00	1.00
25-29 (n = 2692)	1.06	0.83
30-34 (n = 2809)	0.85	0.62
35-39 (n = 1153)	0.73	0.50
≥ 40 (n = 573)	0.72	0.51
	p < 0.0001	p < 0.0001

Ford et al., 2000

The effect of male age on time to pregnancy

	Men's age (years)	Time to pregnancy (months)
Men (n = 1932)	≤ 25	7.0
	25-30	6.9
	31-35	9.3
	36-40	11.4
	41-45	12.4
	> 45	37.2
		p < 0.001
Men with a partner < 25 years (n = 638)	≤ 25	4.6
	25-30	6.2
	31-35	6.0
	36-40	11.5
	> 40	23.2

Hassan & Killick, 2003

Spontaneous abortion and male ageing

Significant relation between spontaneous abortion after 45 years paternal age?

Andersen 2004, Slama 2005

Paternal age as the origin of autosomal dominant disorders

Disorder	Average paternal age experimental group	Average paternal age control group	Paternal age Effect *
Achondroplasia	36.8	30.4	Strong
Apert Syndrome	35.8	27	Strong
Crouzon Syndrome	33.9	28.7	Strong
Pfeiffer Syndrome	35.9	28.2	Strong
Progeria	34.1	28.7	Strong
Bilateral retinoblastoma	32.2	27	Weak
Neurofibromatosis 1	32.5	29.7	Weak

Odds Ratios and Confidence Intervals are unknown

Male ageing

- Consistent but relatively small endocrine effects
- Inconsistent also relatively small effects sperm output
- Potential effect of male ageing on time to pregnancy, spontaneous abortion and mutations

Seeds of concern ?

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Conclusion: seeds of concern ?

- Increased incidence of testis cancer, cryptorchidism and hypospadias in some regions
- Increased incidence of male sperm output – subfertility remains controversial
- Important regional differences in male sperm output – subfertility
- Hypothetical model of testicular dysgenesis syndrome
- Effect of male ageing on reproductive function seems limited but may be not fully explained by changes in sperm output or endocrine changes
