

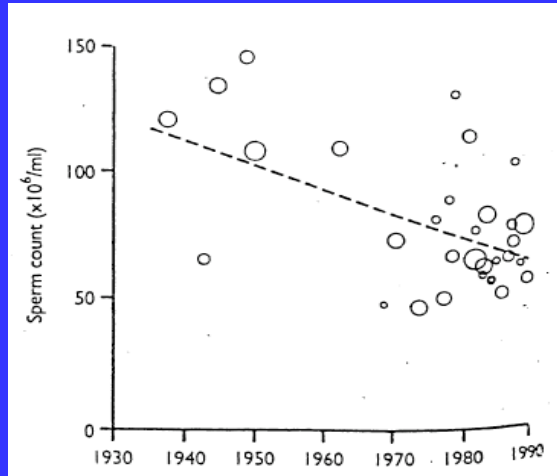
Environment and fertility: Male-mediated factors

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Carlsen et. al. 1992

- Meta-analysis of 61 studies published 1938-1991 (included 14,947 men)
- Found a significant decrease in sperm density:
 - 1940: $113 \times 10^6/\text{mL}$
 - 1990: $66 \times 10^6/\text{mL}$
 - Average decline: 1%/yr ($-0.93 \times 10^6/\text{mL}$)**

Carlsen et al. 1992



Circles proportional to log sample size



Older studies of semen quality included an (often unknown) mix of populations

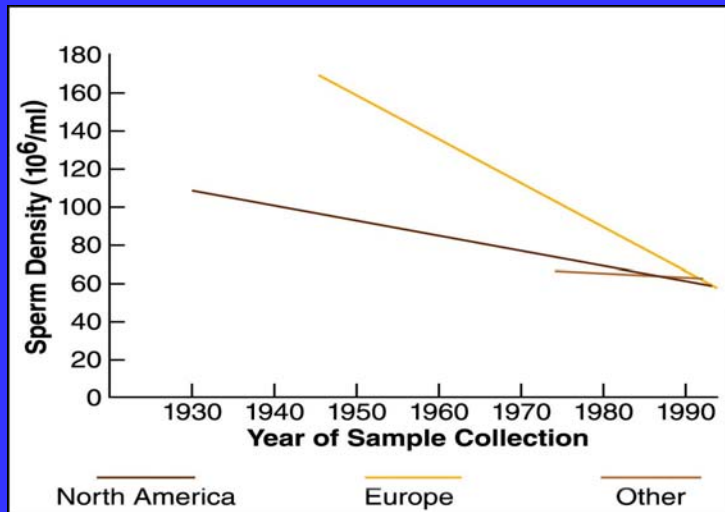
- Sperm donors
- Volunteers
- Prisoners
- Pre-vasectomy patients

Each was unlikely to be representative of the general population

Swan et al. 2000

- New literature search: 1934-1996
- Analysis included 101 studies
- North America: 44
- Europe: 34
- Other: 23

Average decline: 1%/yr ($-0.94 \times 10^6/\text{mL}$)



Swan et al. 2000

What Did We Conclude?

- **Overall** sperm density appears to have declined.
- Not explained by **obvious confounders**.
- **Rate of decline varies** geographically.
- **Mean density varies** geographically.
- Though significant, decline was not convincing

A new approach was needed

The Study for Future Families (SFF)

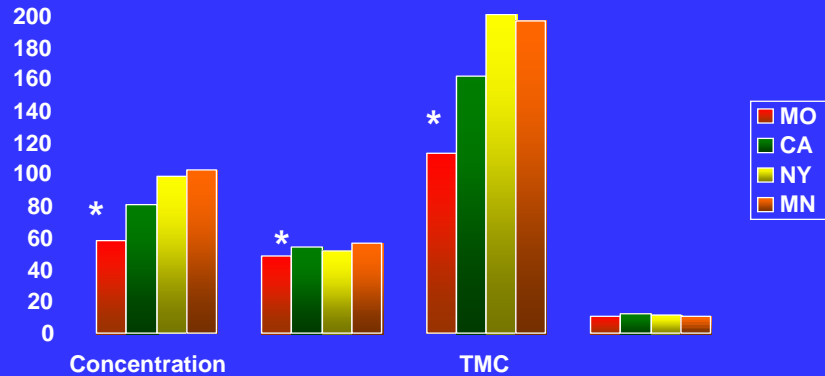


Designed to examine
geographic variation in
semen quality

- **Design**
 - Cross-sectional, multi-center
 - Pregnancy cohort study
- **Exposures**
 - Urine and serum archived for later biomarker analysis
- **Outcomes**
 - Semen quality
 - Serum hormones



Semen Quality by Center



Swan et al 2003

* P-Value for MO vs. all other centers <.001

MO – 57%

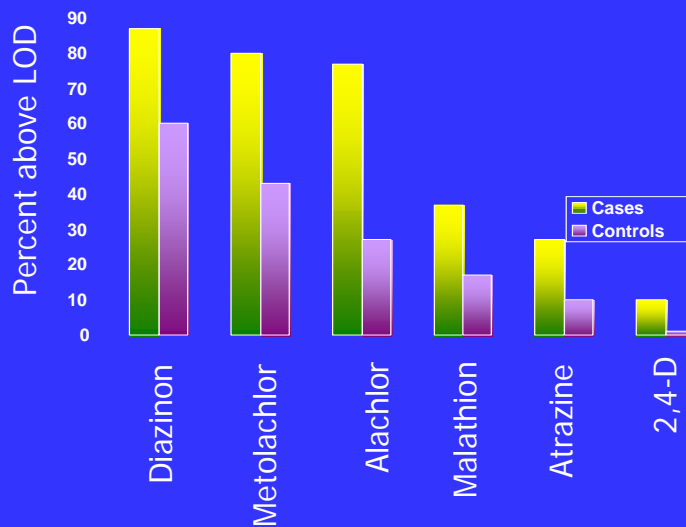
MN – 19%



Nested Case-control Study in Missouri

- **Cases:** Poor semen quality
 - Mean concentration: $32.4 \times 10^6/\text{mL}$
- **Controls:** Normal semen quality
 - Mean concentration: $72.2 \times 10^6/\text{mL}$

Pesticides Detected More Often in Cases Than Controls



Pesticide Strongly Associated with Semen Quality

Pesticide	P-value*
Alachlor	0.0003
Diazinon	0.005
Atrazine	0.02

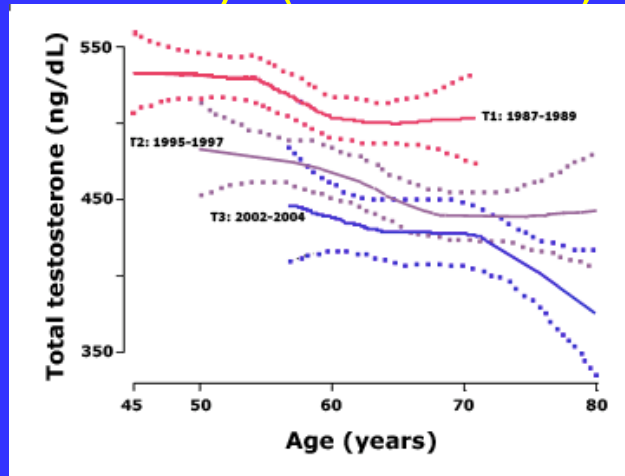
* P-value for Wilcoxon rank test comparing levels in cases and controls

A man with higher atrazine was 11X more likely to be a case than a man with low atrazine

Sperm Production Unlikely to be Effected in Isolation

- If sperm decline is real, we would expect trends in related parameters, such as steroid hormones.
- If geographic variability in semen quality is real, we would expect variability in other endpoints reflecting testicular development.

Total Testosterone: Declined 1.2% /yr (1980-2004)



Travison 2006

Example: Another possible source of geographic variation in semen quality

- Six hormones (anabolic steroids) used in production of US beef:
 - Natural steroids: estradiol, testosterone and progesterone
 - Synthetic hormones, zeranol (an estrogen), trenbolone acetate (a steroid with androgen action) and melengestrol acetate (a progestin)
- Could those hormones affect men's semen quality?

Methods

- Semen parameters in 387 partners of pregnant women related to amount of beef their mothers ate while pregnant.
- Mothers' beef consumption analyzed in relation to the son's history of previous subfertility.
- Regression analyses controlled for son's age, abstinence time, and alcohol consumption.
- Eating >1 beef meal a day = "High beef consumer"

Results

- Sons of women who ate more than one beef meal a day while pregnant vs others:
 - Sperm concentration reduced 24.3%
($p = 0.014$)
 - Percent with sperm concentration falling below "normal" ($< 20 \times 10^6/\text{ml}$) was increased three-fold 17% vs. 5.7% ($p = 0.002$)
 - History of seeing a doctor for infertility twice as frequent ($p = 0.016$).

Conclusion (1)

- Sperm concentration shows significant declines in some areas of the world.
- Semen quality shows significant geographic variation.
- This may be a “sentinel” for other adverse reproductive parameters.
- Environmental factors (such as pesticides and anabolic steroids) are suspect but not proven causes.

Conclusions (2)

Male fertility can be influenced by a mixture of exposures at different developmental stages:

- ***In utero exposures*** including environmental endocrine disruptors (e.g. phthalates, hormones in beef)
- ***Early postnatal development*** (e.g. phthalates and BPA in infant formula, breast milk, --Main et al. 2006)
- ***Adult exposure*** (e.g. pesticides, phthalates --Hauser and Duty et al. 2003-2007)