Hormonal control of spermatogenesis and the hypogonadal male

Richard Anderson
Reproductive and Developmental Sciences
University of Edinburgh

ESHRE Campus, Budapest Dec 3-4 December 2009

Outline of talk

- Hormonal regulation of spermatogenesis
- Clinical initiation of spermatogenesis

- Impact of development on adult male function

The mature H-P-T axis

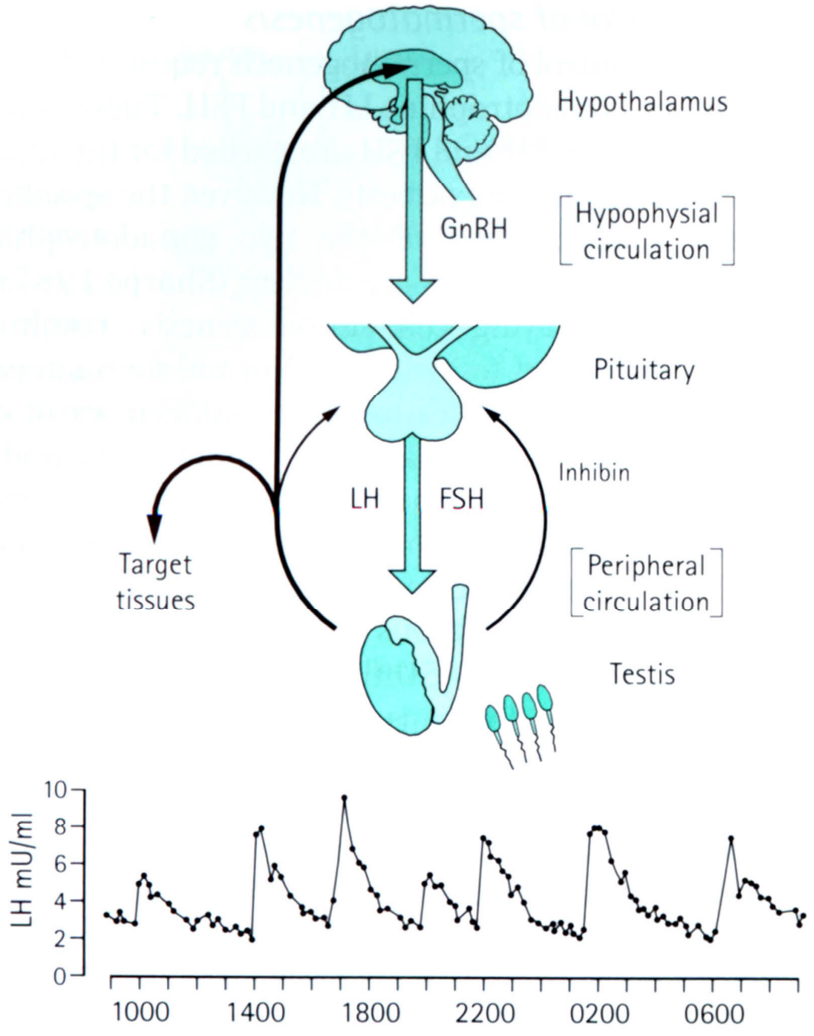
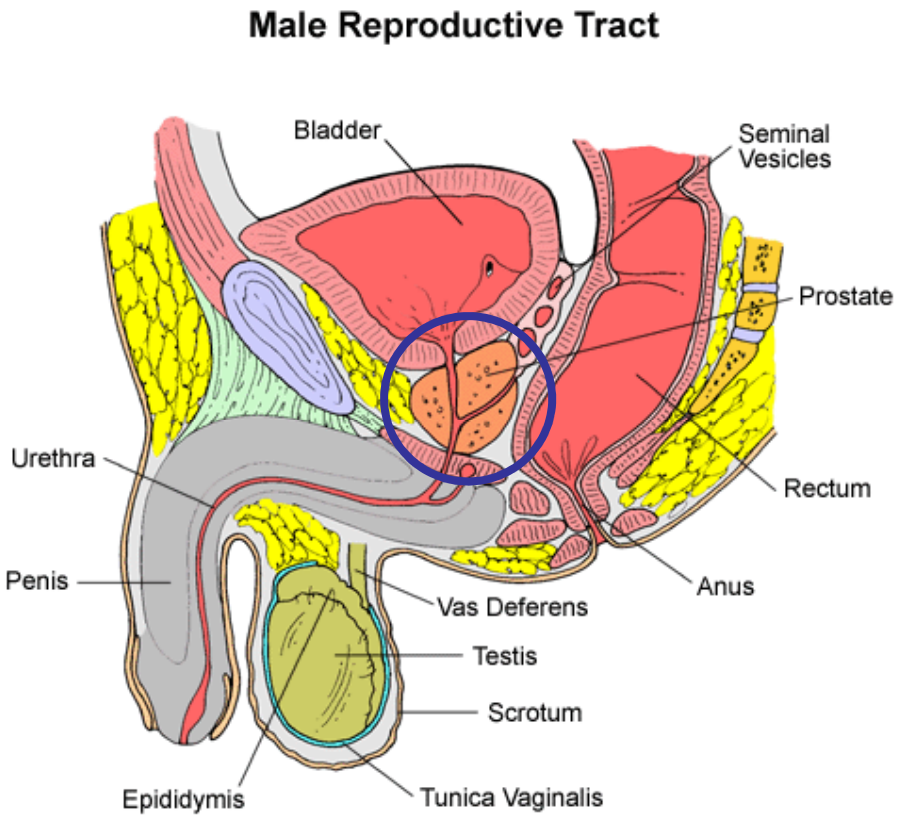


Figure courtesy of Prof Fred Wu

Testosterone metabolism

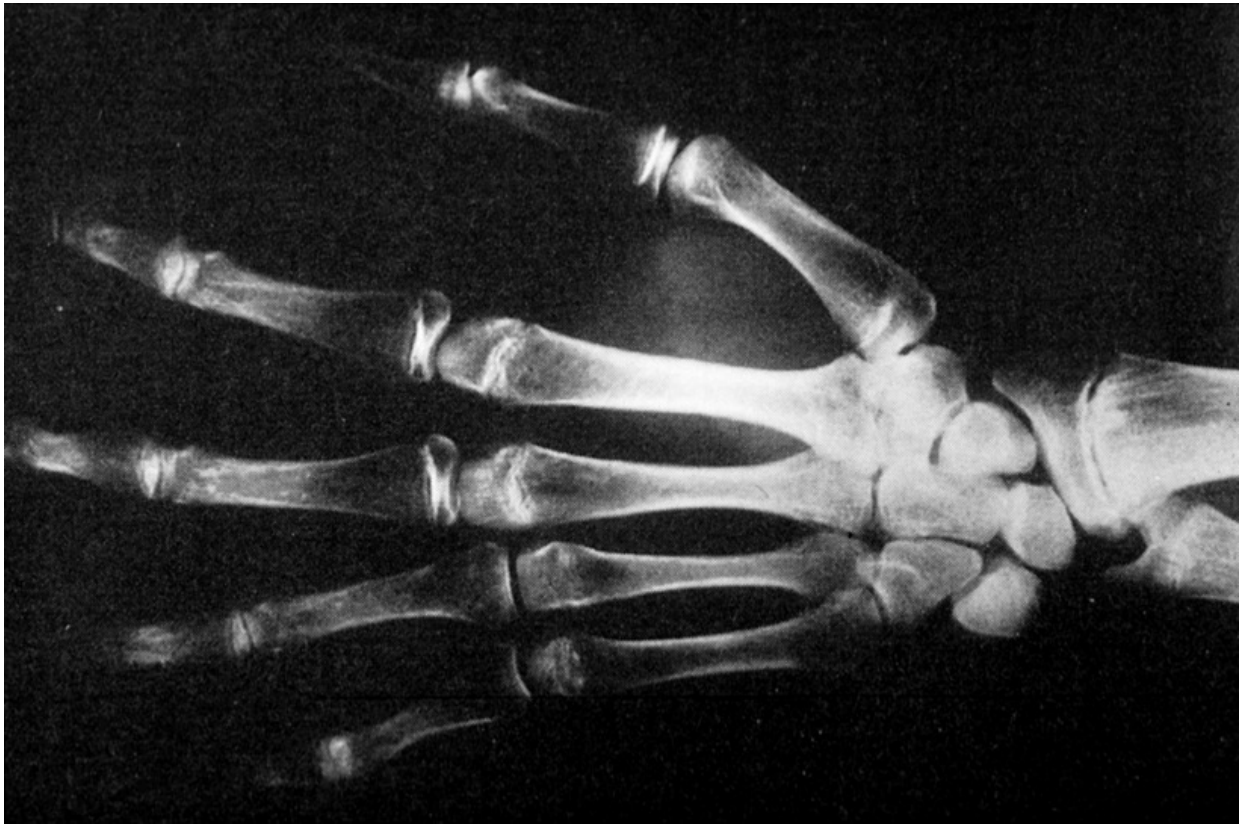


Finasteride chemoprevention study

'Use of finasteride is associated with a 25% reduction in the 7-year period prevalence of prostate cancer in men over age 55 years'

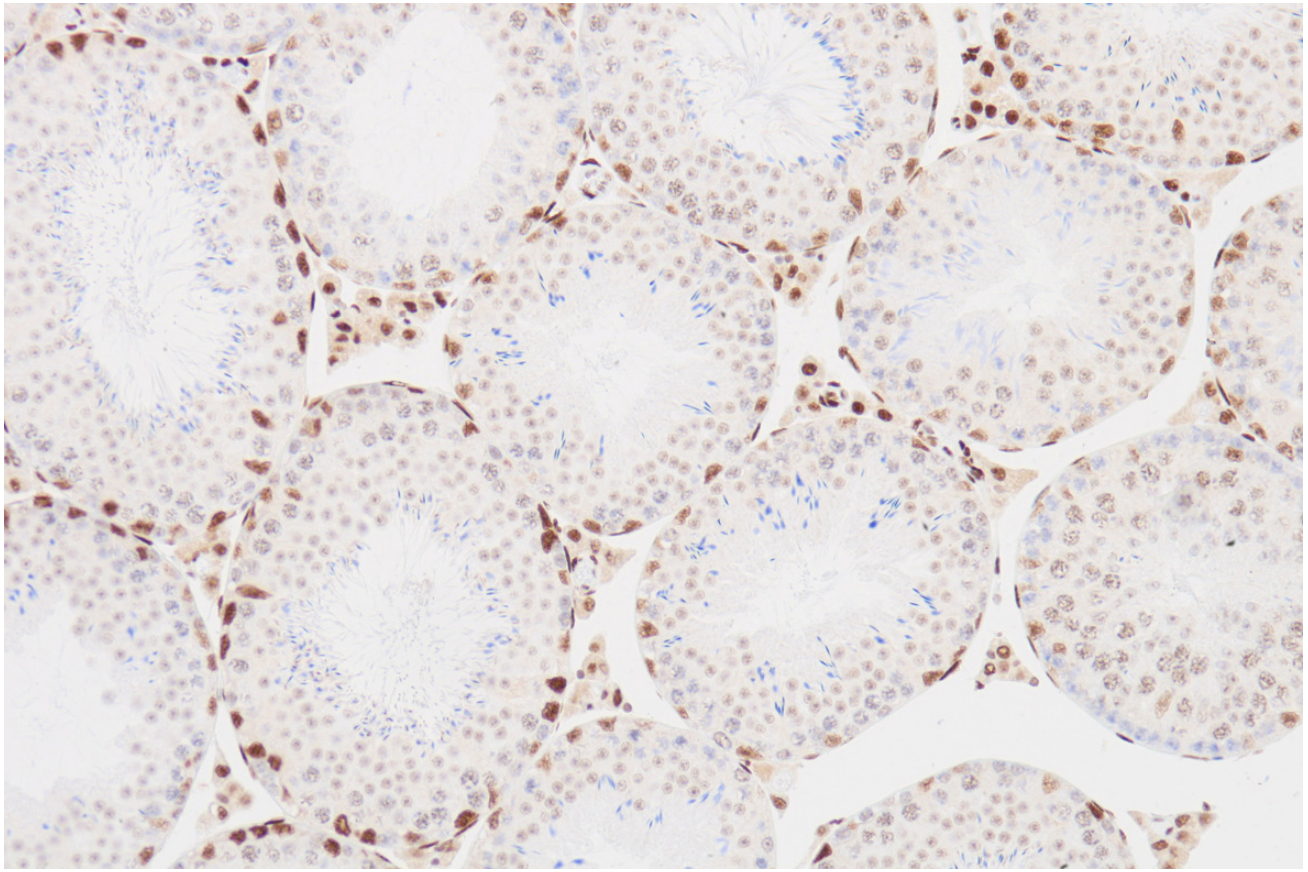
Thompson et al N Engl J Med 349 215 (2003)

The need for oestrogen: effect of aromatase deficiency



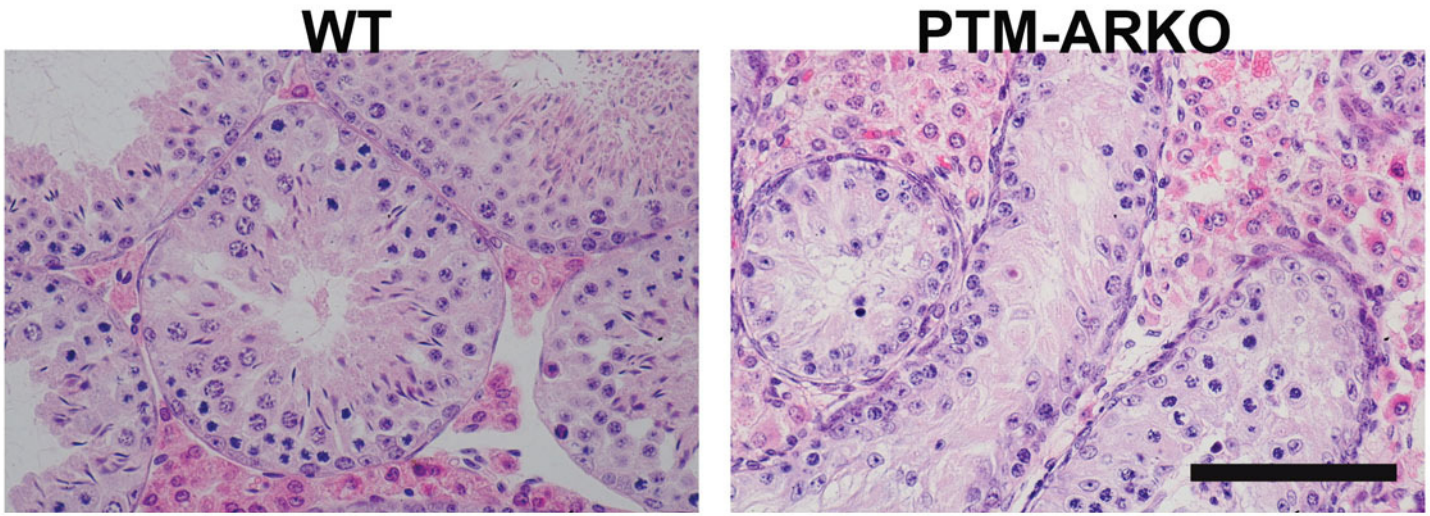
Morishima et al., 1995

Androgen action in the testis

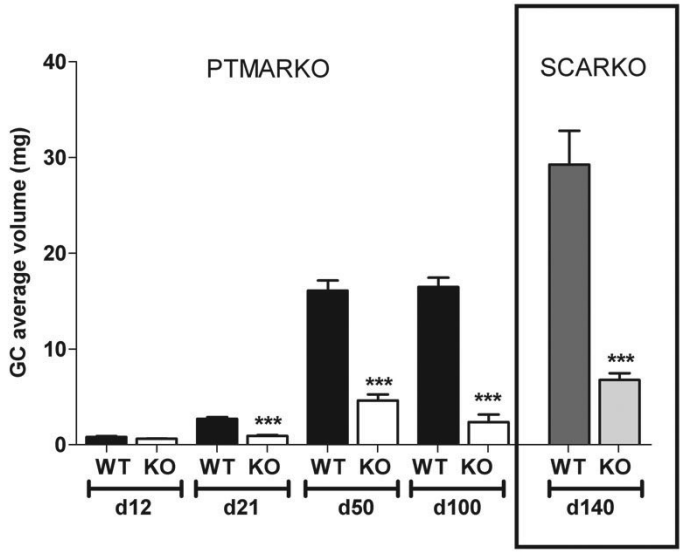


Leydig, Sertoli and PTM cells but NOT germ cells

Courtesy of Dr M Welsh



Androgen action via both Sertoli and PTM cells is essential for spermatogenesis



Welsh M et al 2009 FASEB J in press

Role of LH in adult spermatogenesis

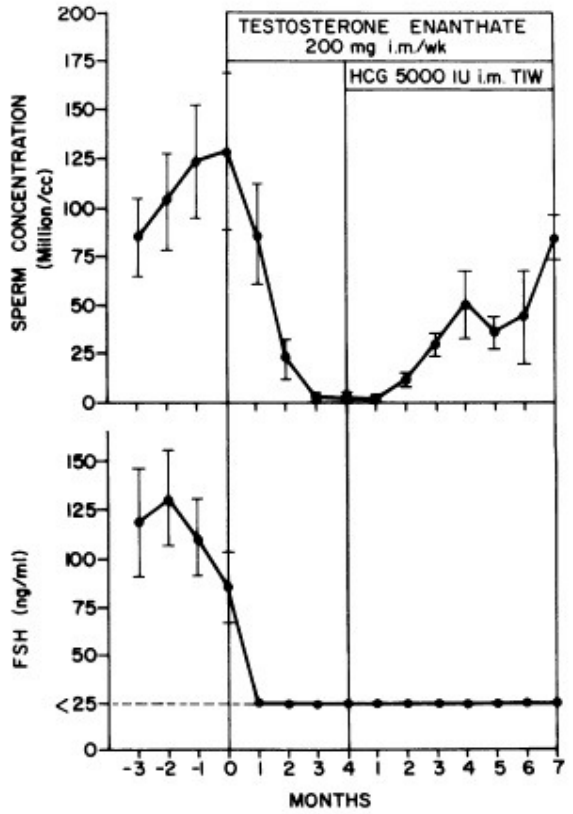


FIGURE 1 Monthly sperm concentrations and serum FSH data in five normal men during the control, testosterone administration alone, and hCG plus testosterone phases of the study (mean±SE). Note the increase in sperm concentration induced by hCG in spite of very low serum levels of FSH.

Model:
Testosterone-induced suppression

LH can restore spermatogenesis

Bremner WJ et al 1981 J Clin Invest 68, 1044

Role of FSH in adult spermatogenesis

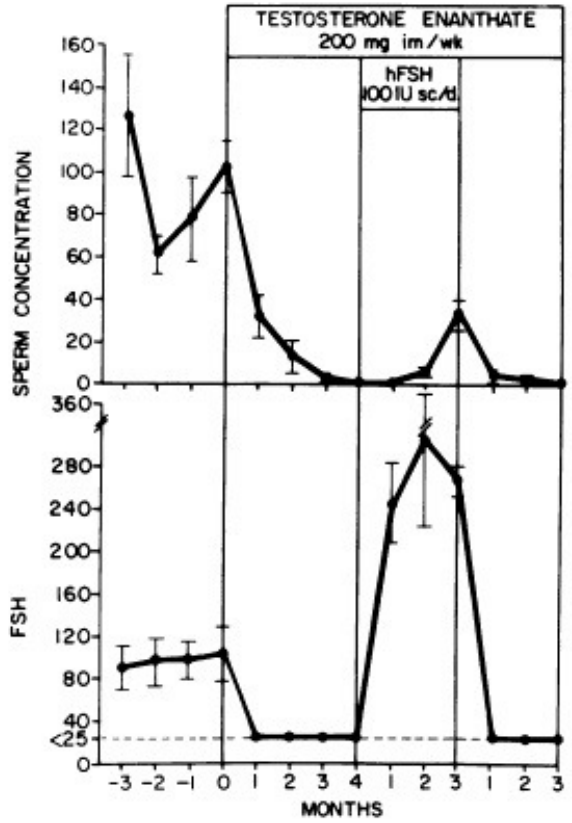
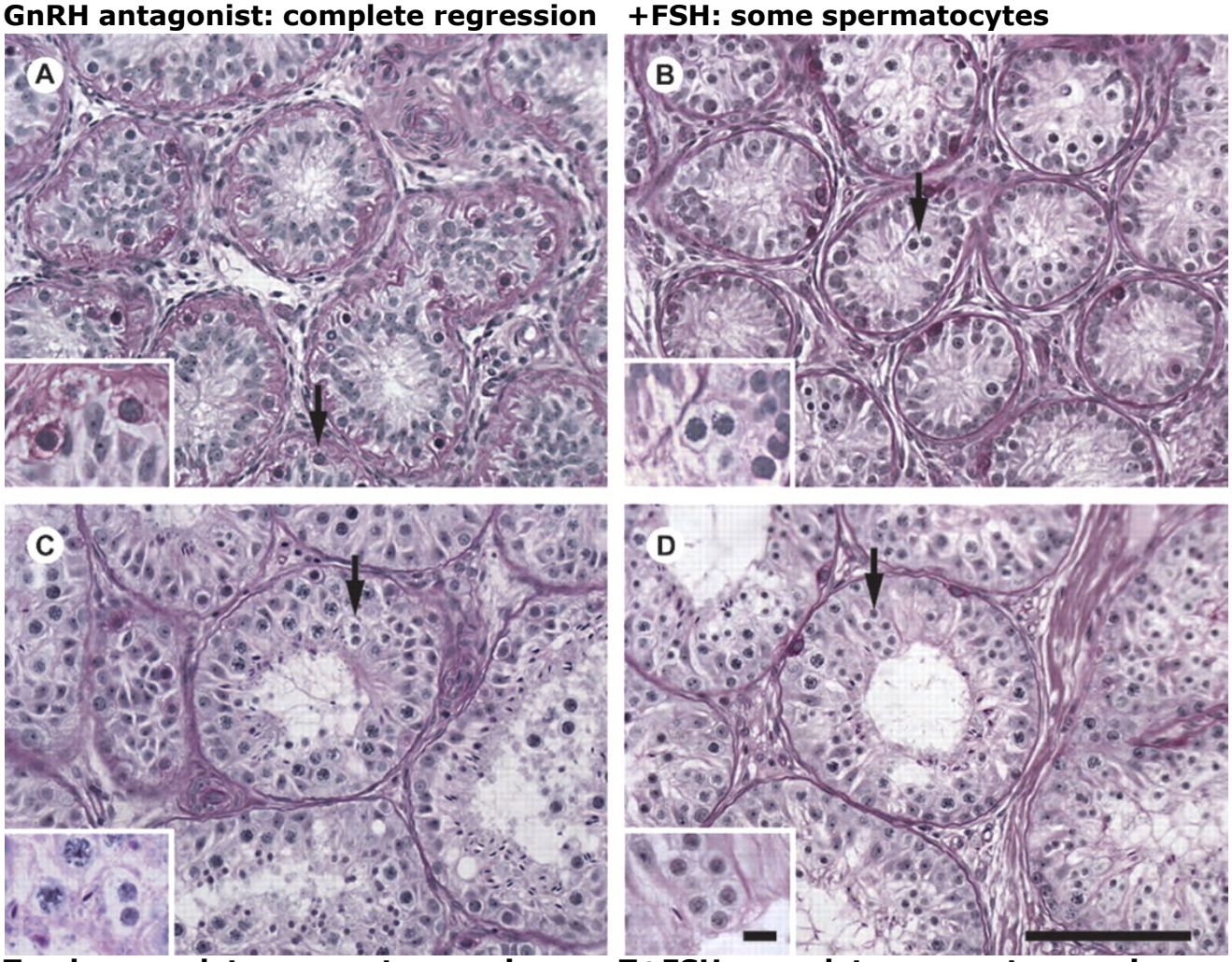


FIGURE 1 Mean monthly sperm concentrations (million per cubic centimeter) and serum FSH levels (in nanograms per milliliter) in four normal men during the control, initial T-alone, hFSH-plus-T, and second T-alone periods of the study (mean±SE). Exogenous T administration markedly suppresses sperm concentrations to severely oligospermic levels and serum FSH to undetectable levels. Note hFSH replacement at a slightly supraphysiological dosage increases sperm concentration.

FSH alone can only partially restore spermatogenesis

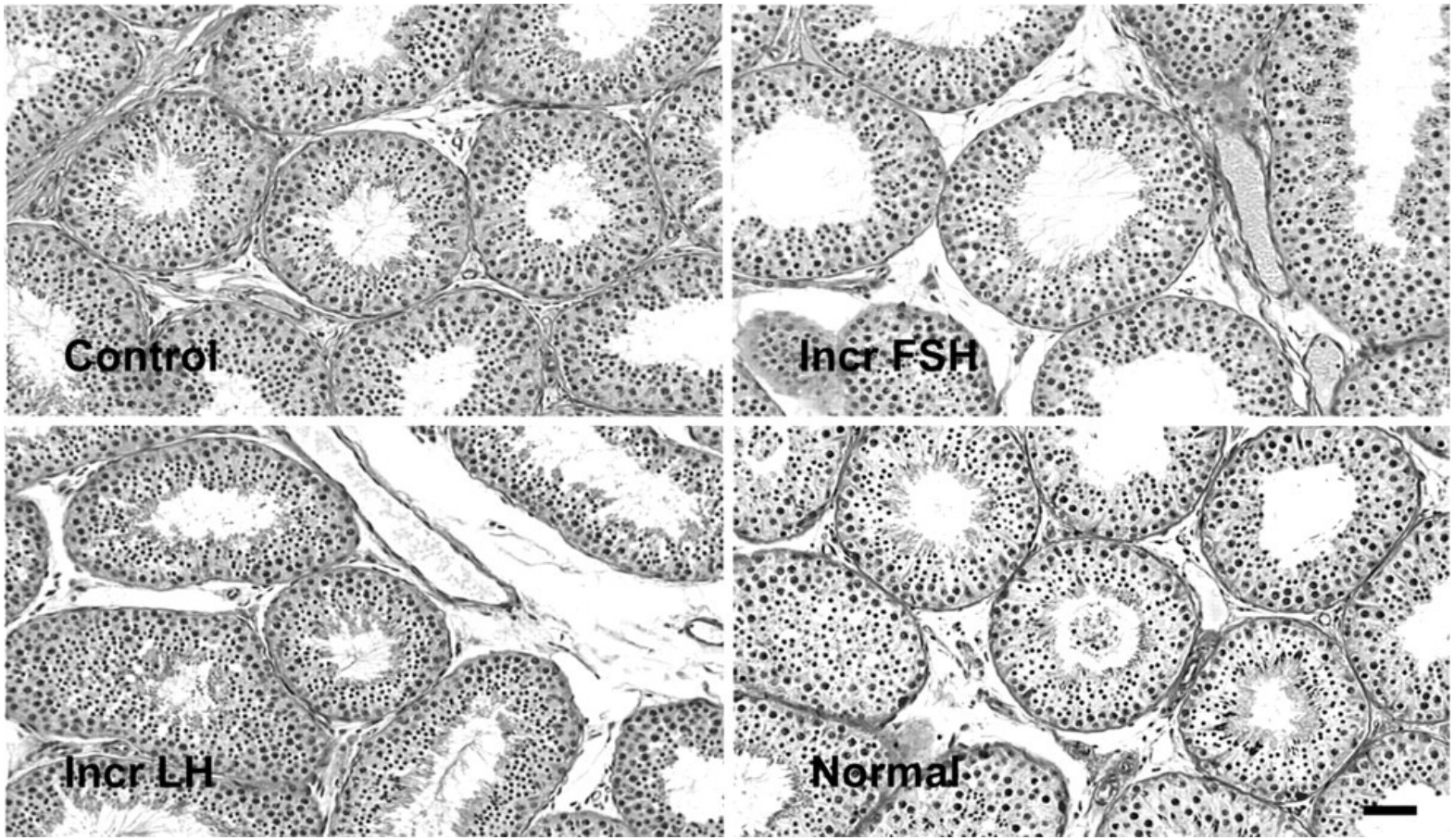
Matsumoto AM et al 1983 J Clin Invest 72, 1005

Selective testosterone/FSH replacement after GnRH antagonist in *Macaca mulatta*



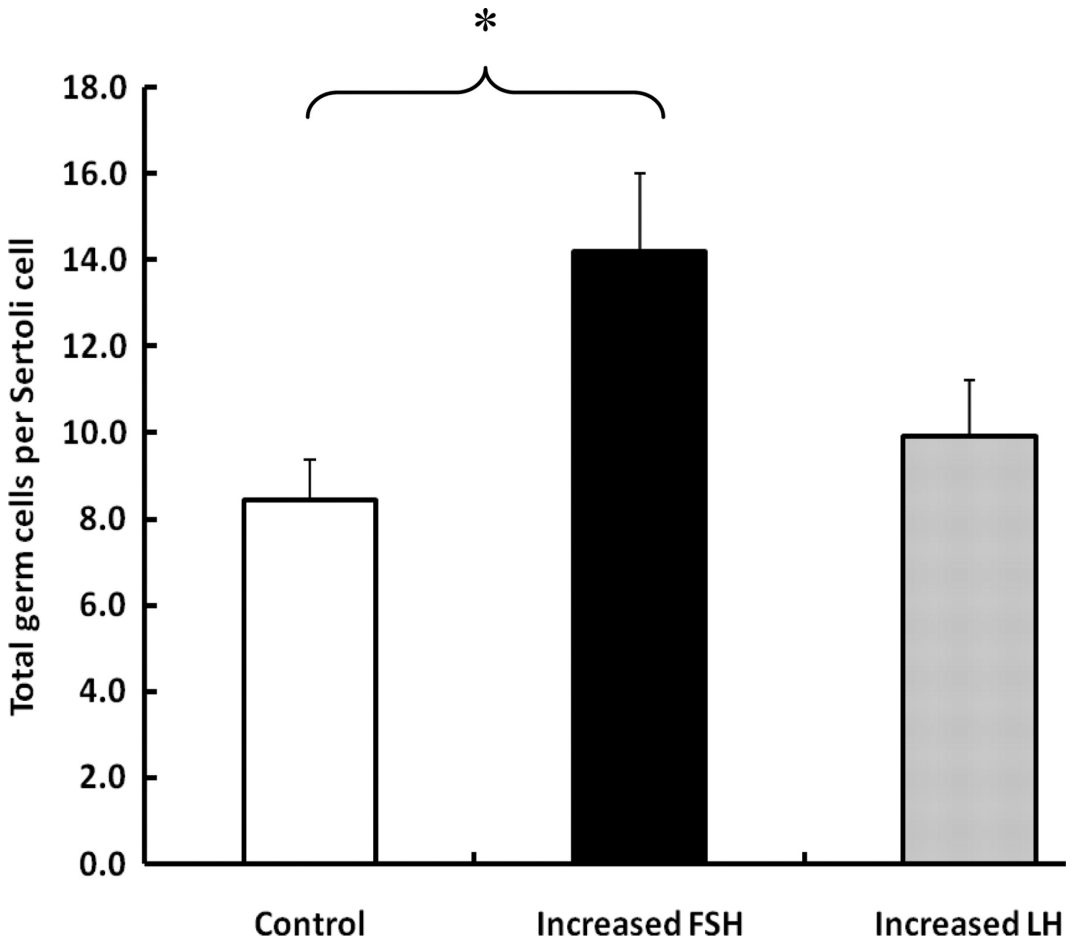
Marshall GR et al. Biol Reprod 2005;73:222-229

FSH can further stimulate spermatogenesis in primate



Simorangkir et al 2009 Hum Reprod 24, 1584

FSH increases Sertoli cell spermatogenic efficiency



'Under physiological conditions, circulating concentrations of FSH directly dictate sperm output of the primate testis by regulating the proportion of Ap spermatogonia in the growth fraction'

Simorangkir et al 2009 Hum Reprod 24, 1584

The mature H-P-T axis

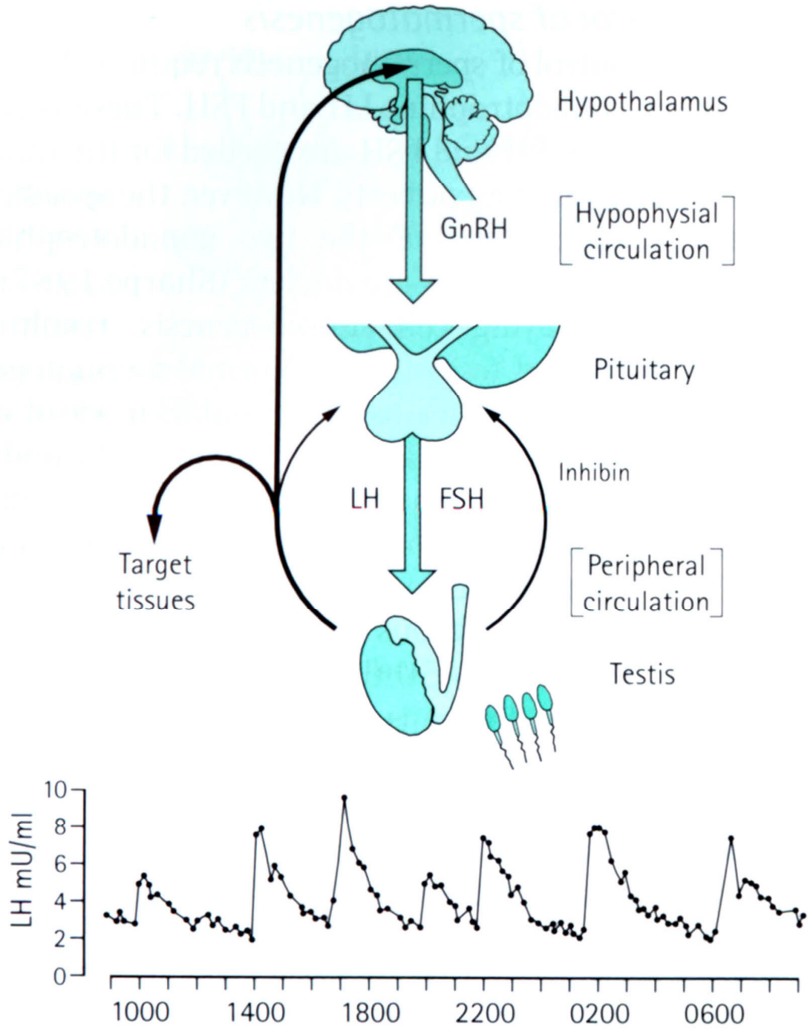
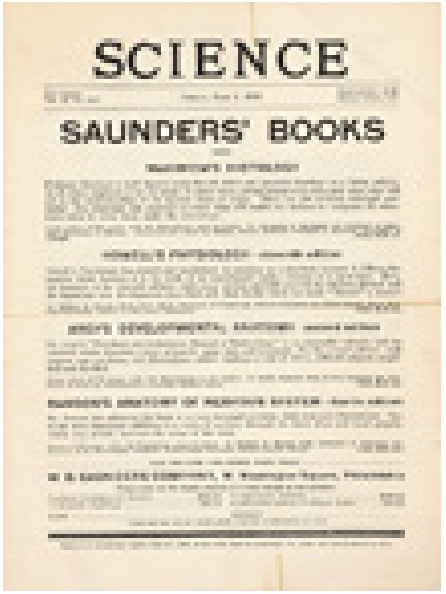


Figure courtesy of Prof Fred Wu

Inhibin: an old hormone

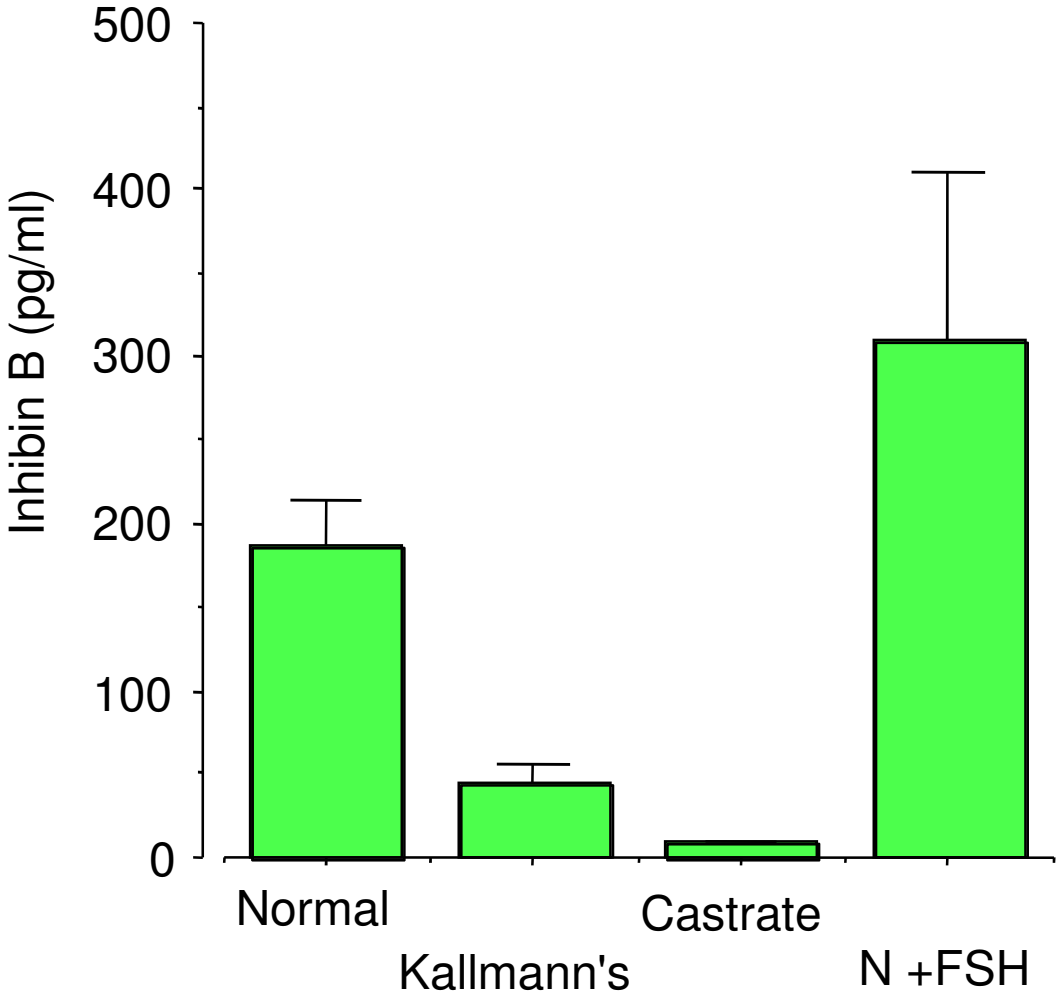

SCIENCE

SAUNDERS' BOOKS

Aqueous testis extract prevented appearance of castrate cells in rat pituitary gland

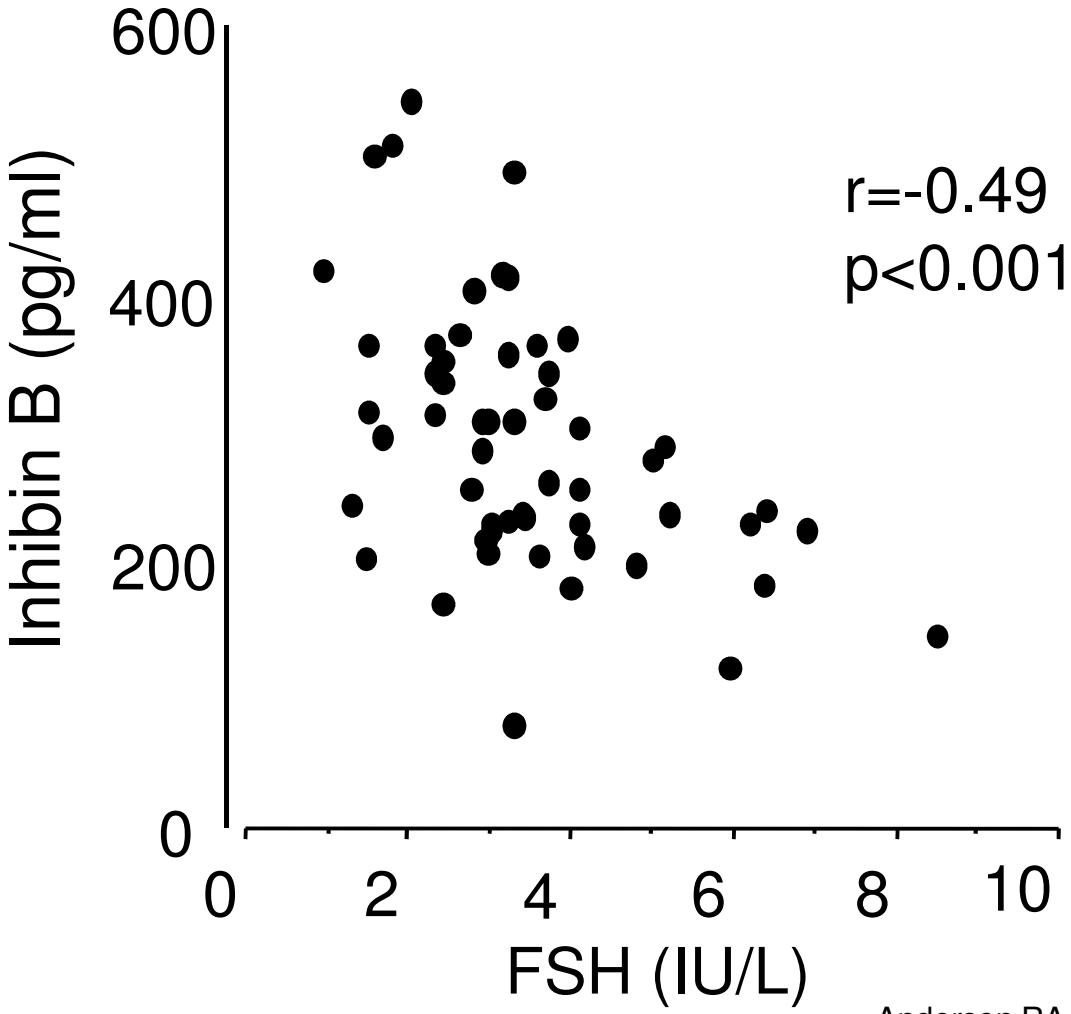
DUAL ENDOCRINE ACTIVITY OF THE TESTES
D. Roy McCullagh
Science 1 July 1932: 19-20

Inhibin B reflects Sertoli cell function



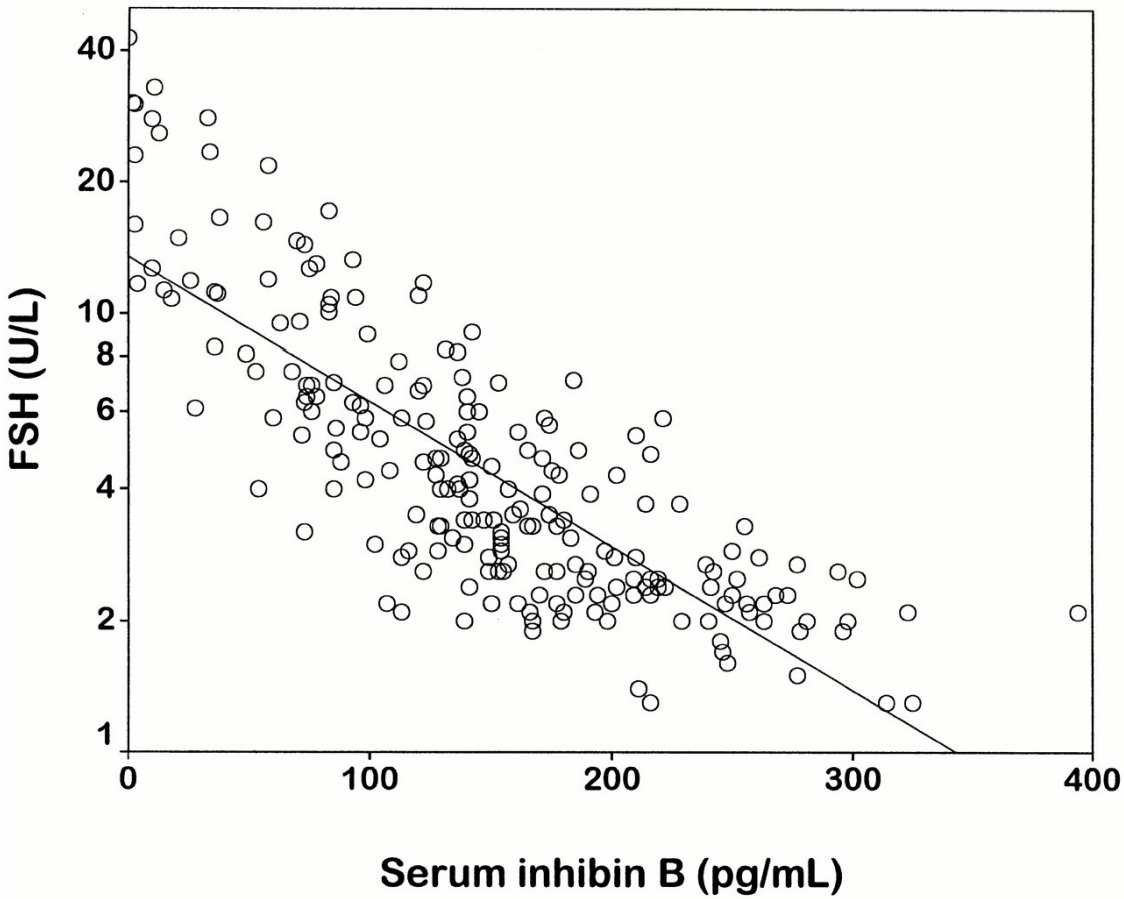
Anawalt et al., 1996

Physiologic relationship between Inhibin B and FSH



Anderson RA et al 1997 Human Reprod 12, 746

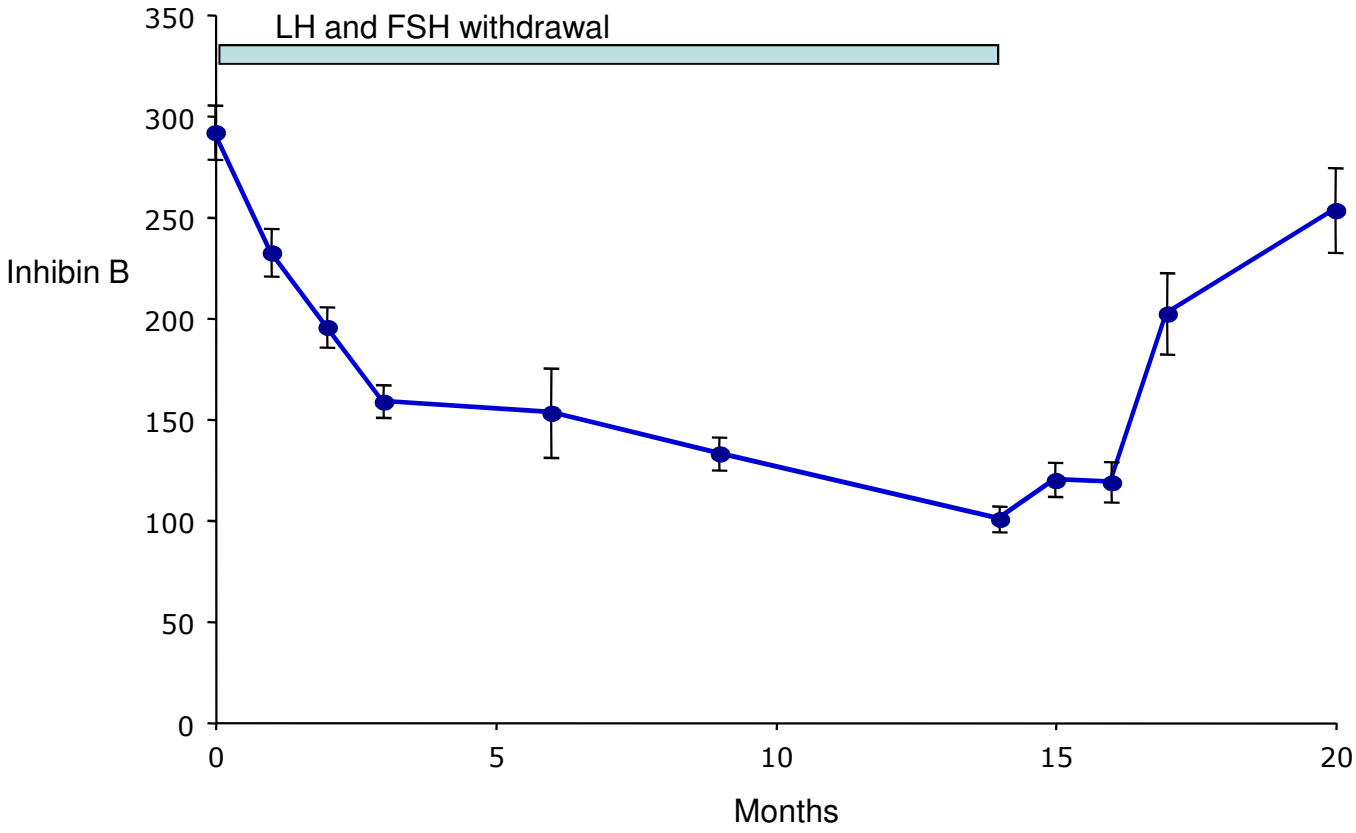
Inhibin B: infertile men



THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

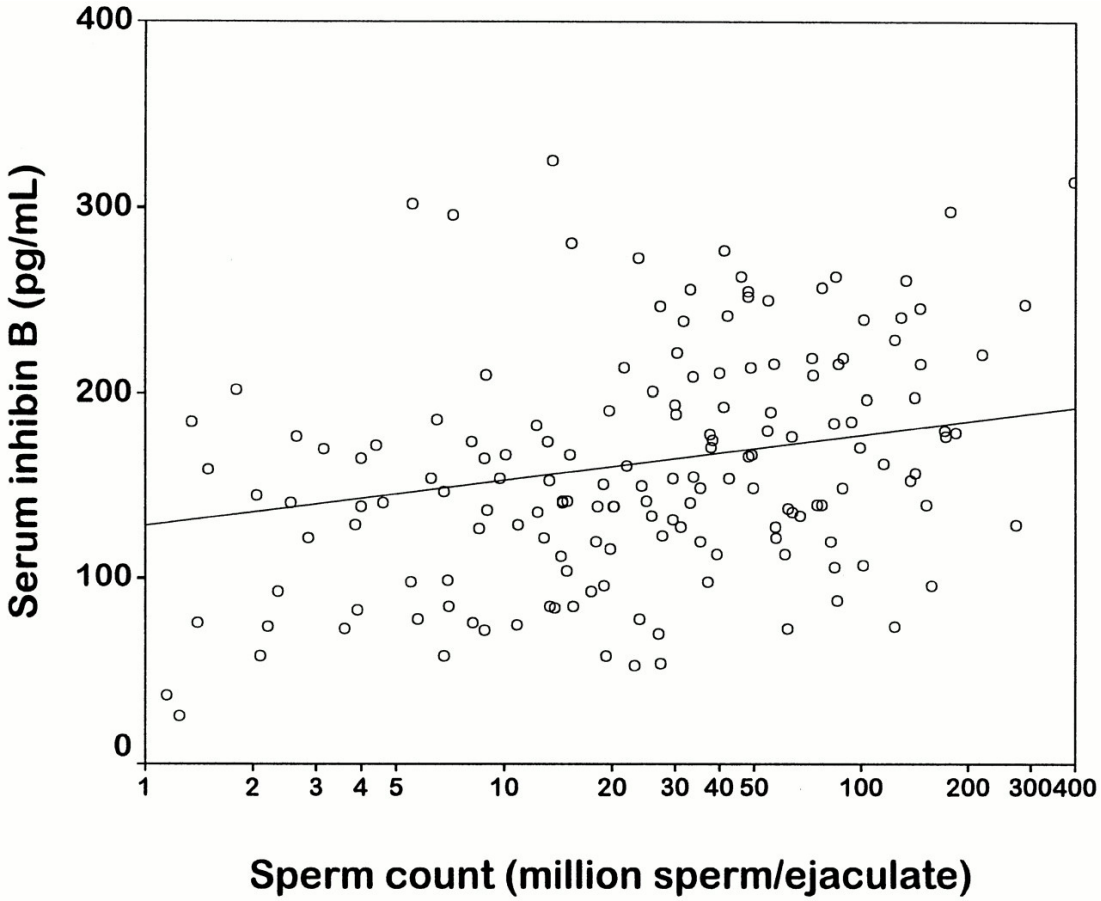
Pierik, F. H. et al. J Clin Endocrinol Metab 1998;83:3110-3114

Gonadotrophin-dependence of Inhibin B in normal men



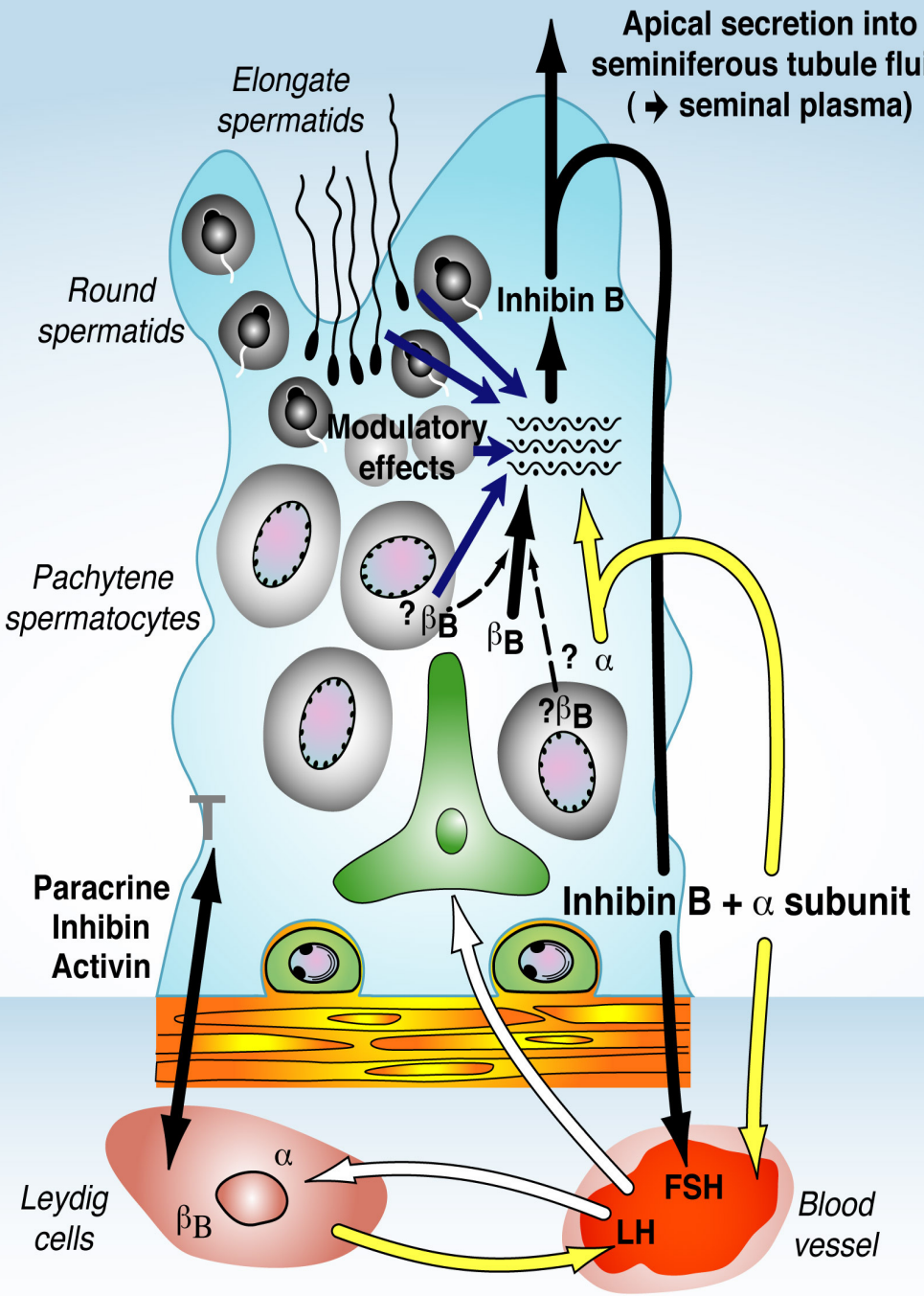
Anderson RA et al 1997 Human Reprod 12, 746

Inhibin B vs Sperm Count

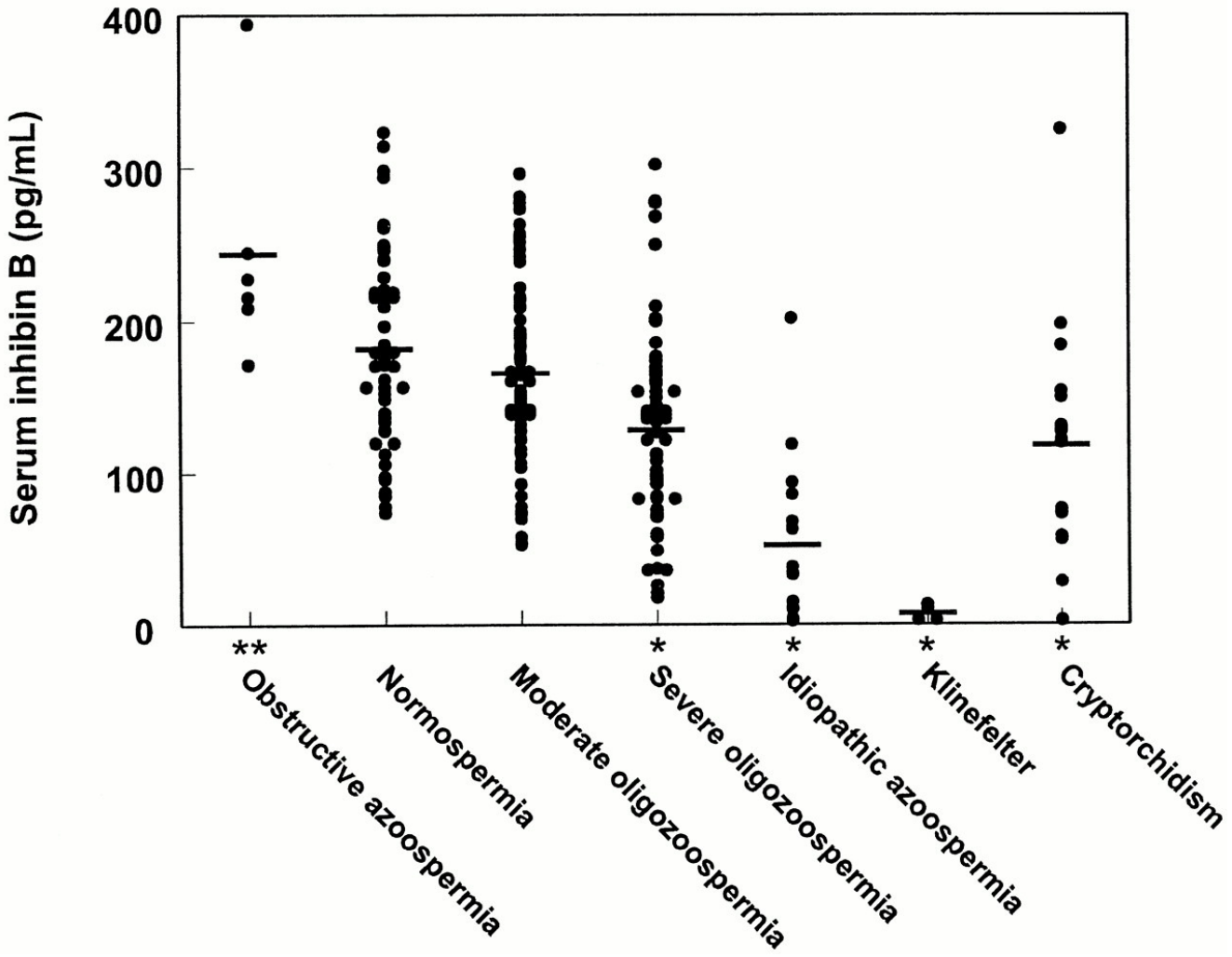


205 subfertile men r=0.54, p<0.001

Pierik FH et al. J Clin Endocrinol Metab 1998;83:3110-3114

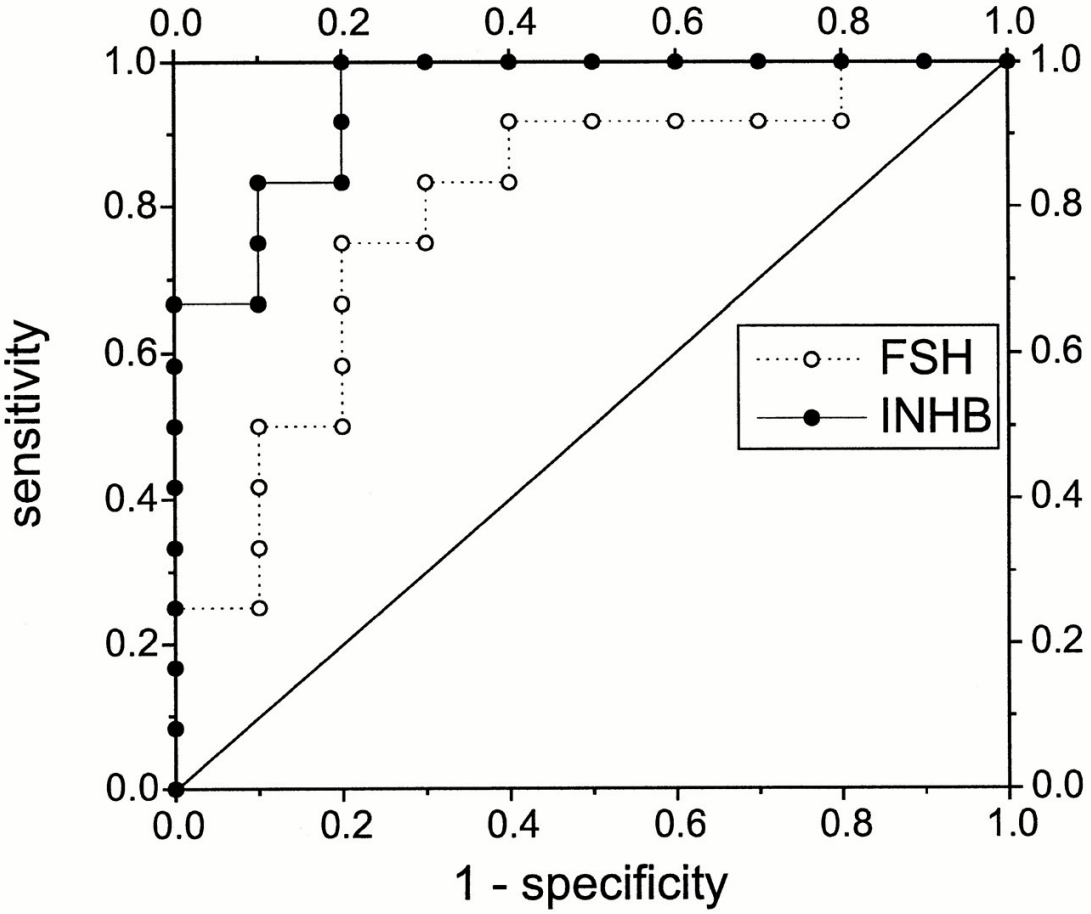

Apical secretion into seminiferous tubule fluid (➔ seminal plasma)
Elongate spermatids
Round spermatids
Inhibin B
Modulatory effects
Pachytene spermatocytes
? βB
βB
? α
?βB
Paracrine Inhibin Activin
Inhibin B + α subunit
α
βB
Leydig cells
FSH
LH
Blood vessel

Inhibin vs Spermatogenic defects



Pierik FH et al. J Clin Endocrinol Metab 1998;83:3110-3114

Inhibin B is a better predictor of abnormal spermatogenesis than FSH



Based on testicular biopsy men with azoospermia / severe oligozoospermia and Johnsen score

Pierik FH et al. J Clin Endocrinol Metab 1998;83:3110-3114

Gonadotrophin stimulation of spermatogenesis

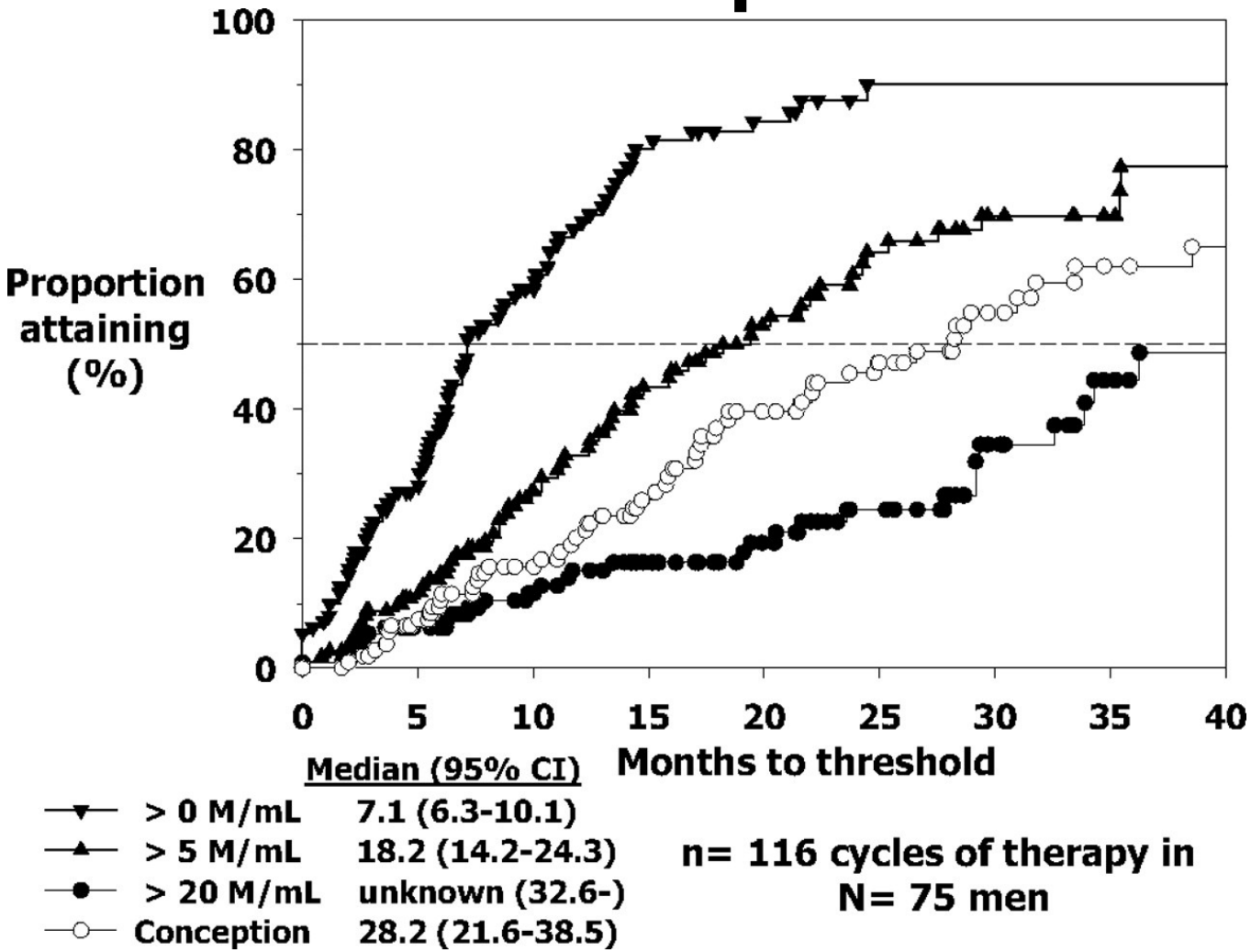
Gonadotrophin stimulation of spermatogenesis

- 75 men, 116 cycles of treatment
- Mostly IHH, 58 no spont puberty

- hCG 1500-2000IU x2/week (x3/week)
- If still azoospermia at 6 months, FSH added
- 150IU x3/week (urinary or recombinant)

Liu PY et al. J Clin Endocrinol Metab 2009;94:801-808

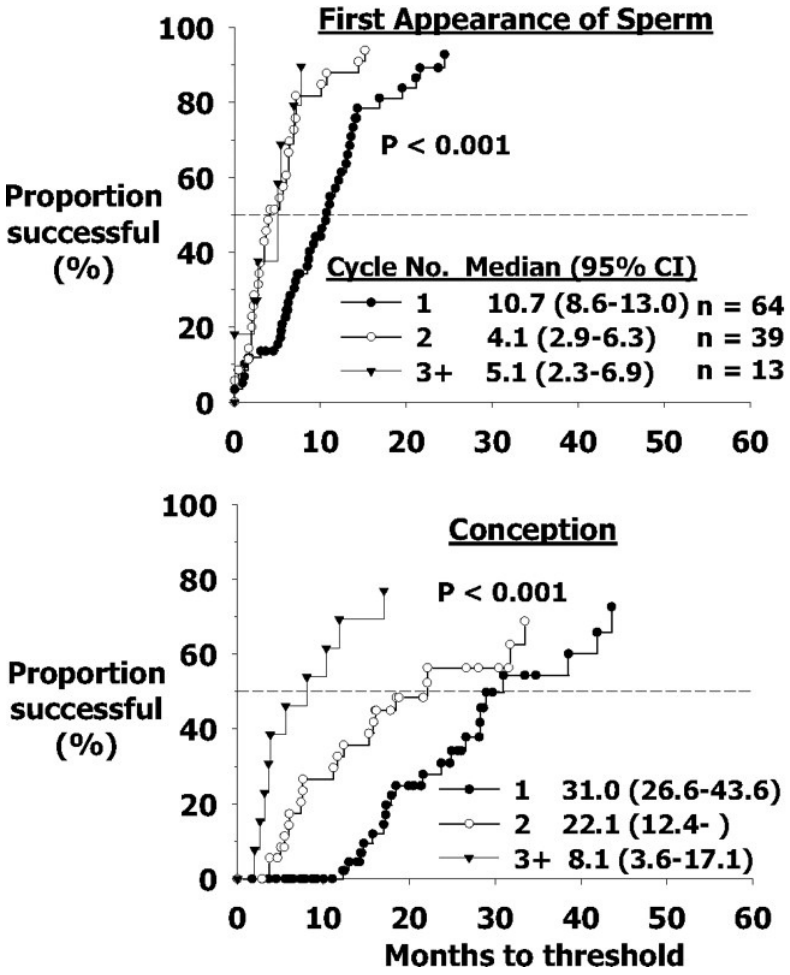
Time to spermatogenic thresholds and conception



Median at conception: 8M/ml

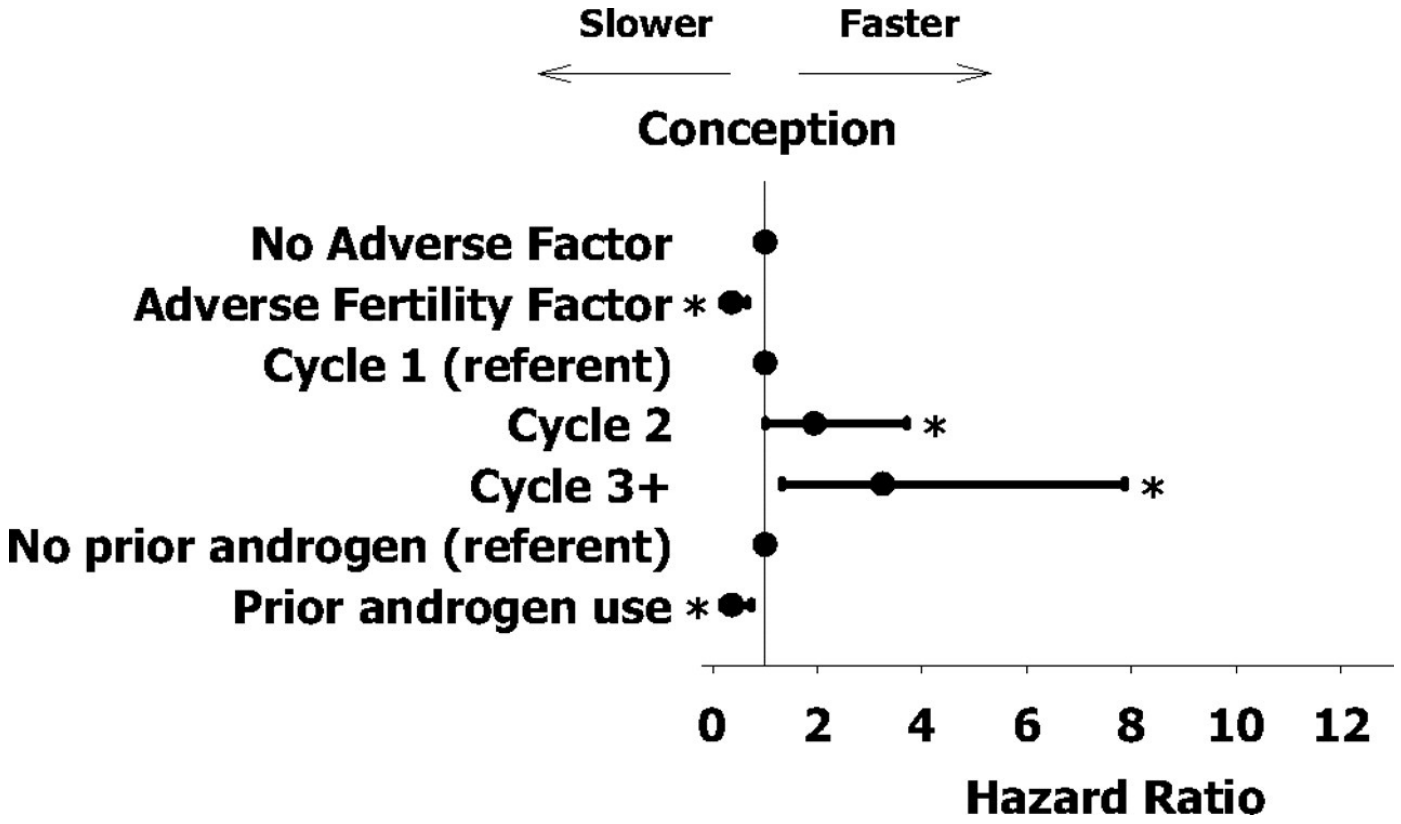
Liu PY et al. J Clin Endocrinol Metab 2009;94:801-808

Spermatogenesis by previous treatment



Liu PY et al. J Clin Endocrinol Metab 2009;94:801-808

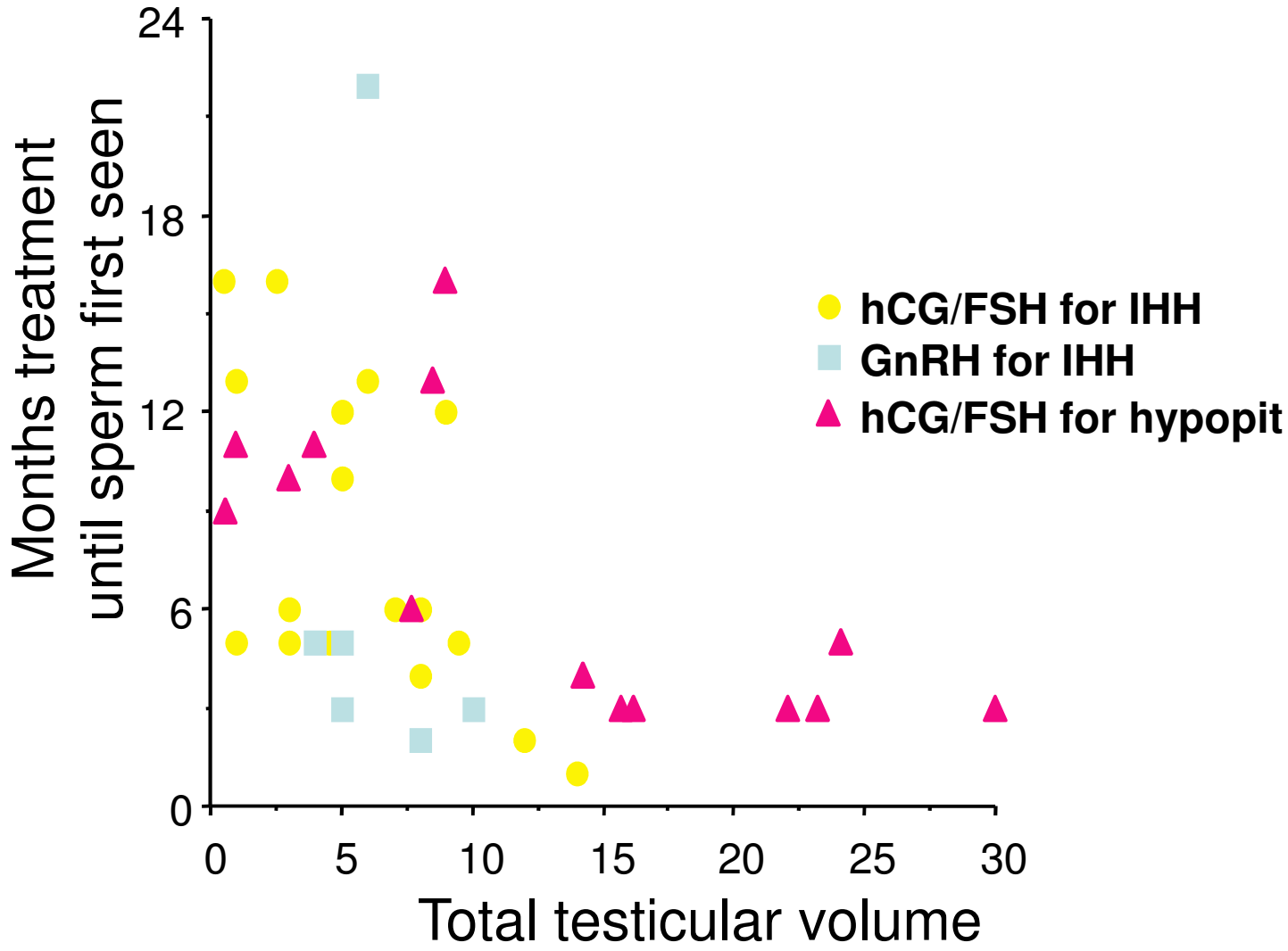
Best variables for pregnancy



Initial TV not a predictor: post-treatment TV is

Liu PY et al. J Clin Endocrinol Metab 2009;94:801-808

Predictive value of testicular volume



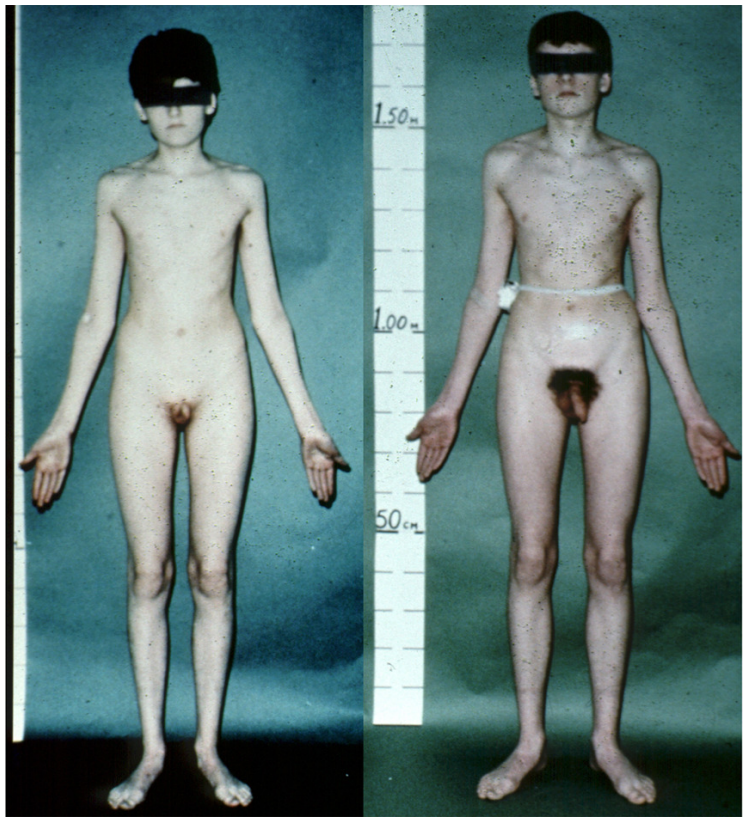
Buchter et al., 1998

Gonadotrophins for pubertal induction?

'…..slower responses after prior androgen therapy suggests that faster pregnancy rates might be achieved by substituting gonadotropin for androgen therapy for pubertal induction….'

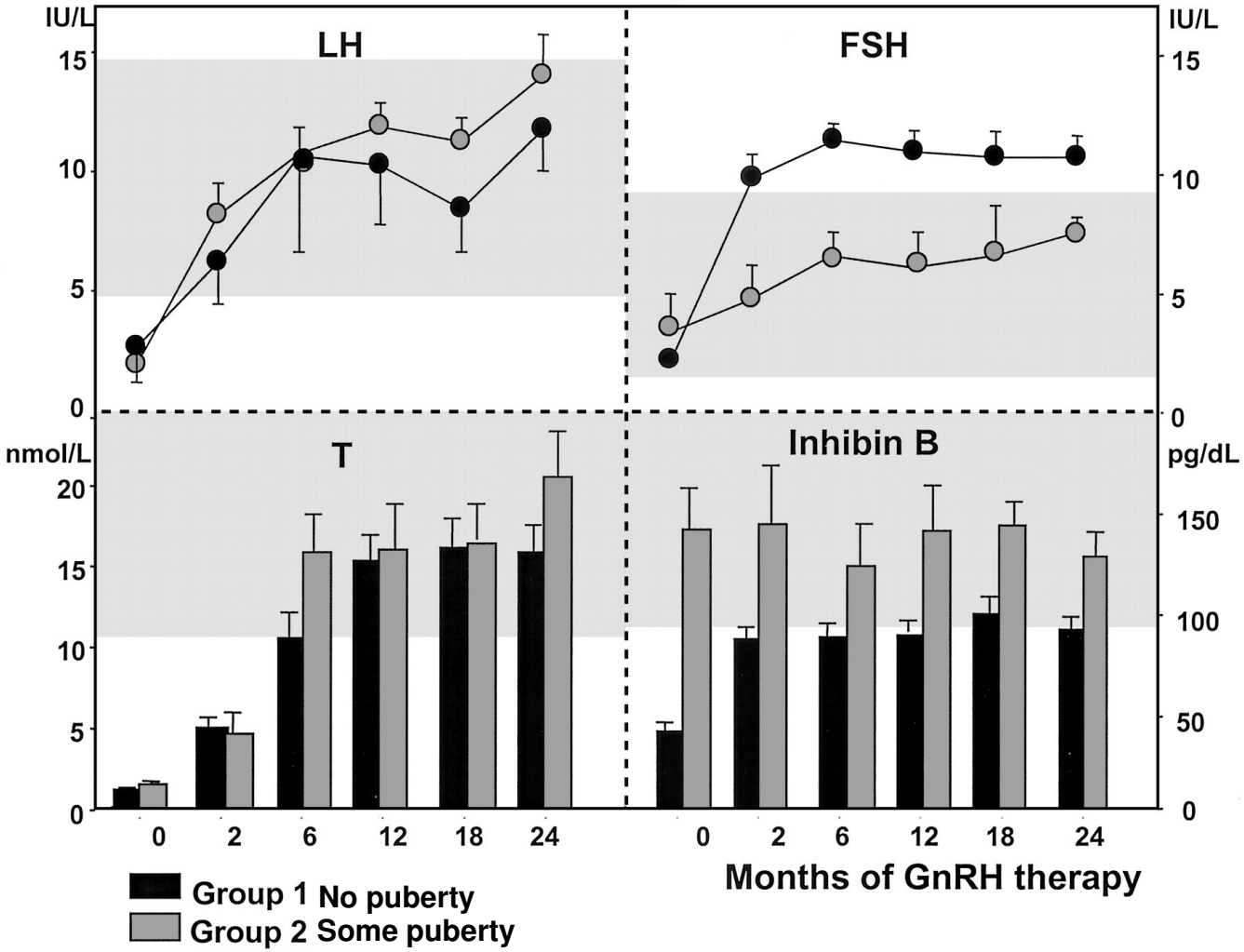
Liu et al 2009

Kallmann's syndrome pulsatile GnRH treatment



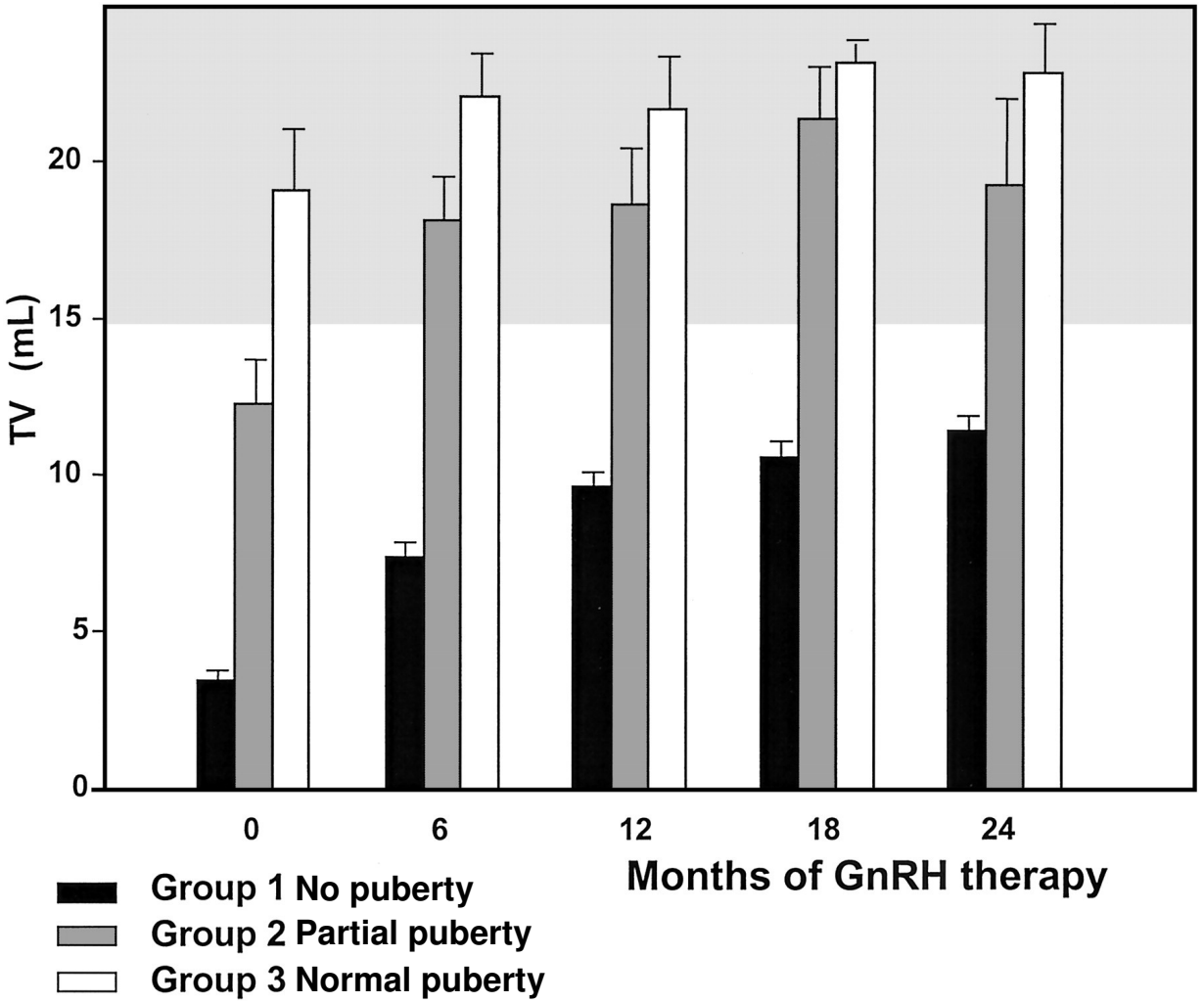
+pulsatile GnRH

Endocrine response to GnRH treatment



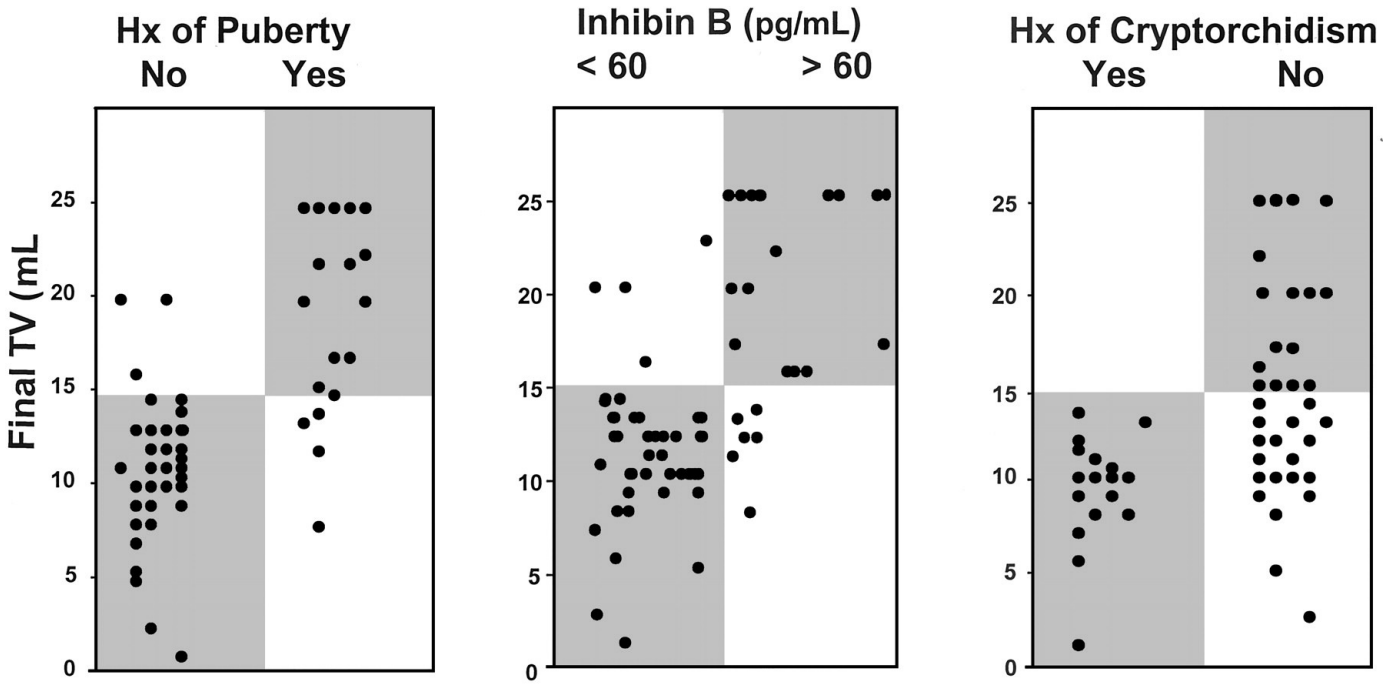
Pitteloud N et al. J Clin Endocrinol Metab 2002;87:4128-4136

Testicular response to GnRH treatment



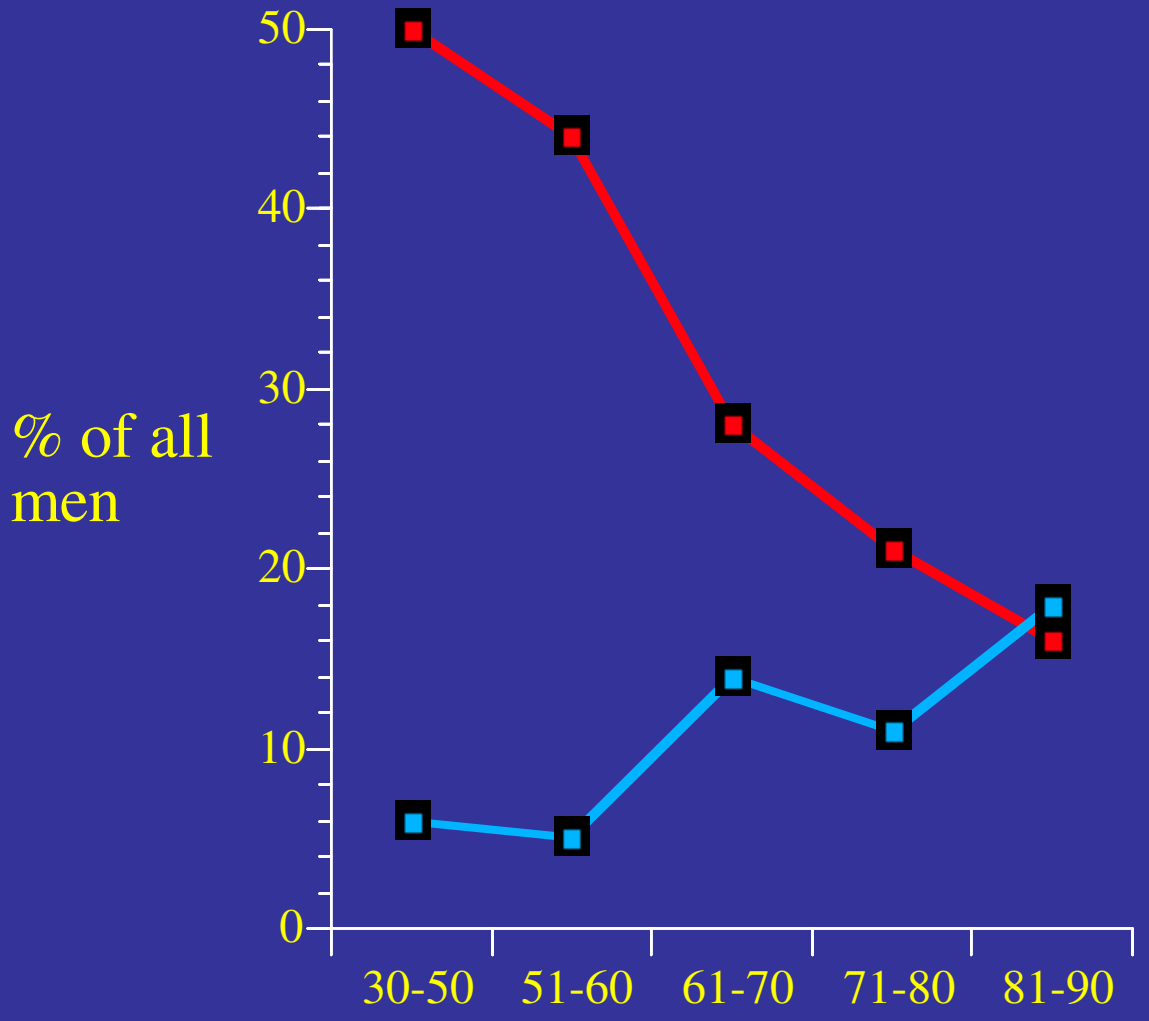
Pitteloud, N. et al. J Clin Endocrinol Metab 2002;87:4128-4136

Prediction of response to GnRH



Pitteloud N et al. J Clin Endocrinol Metab 2002;87:4128-4136

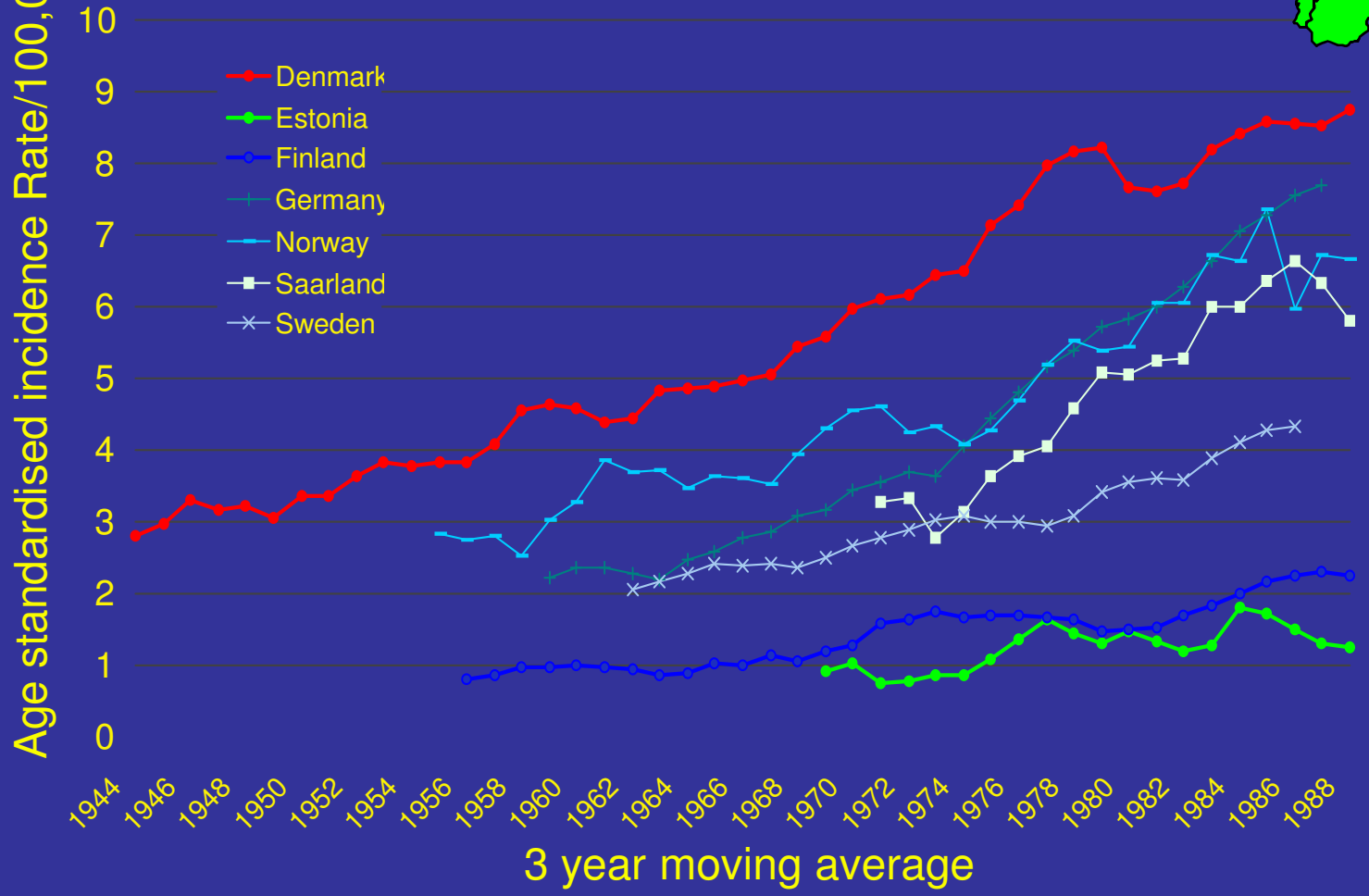
Semen Quality : 1930 - 1990



Data from Carlsen et al, Br Med J, 1992, 305 : 609-13.

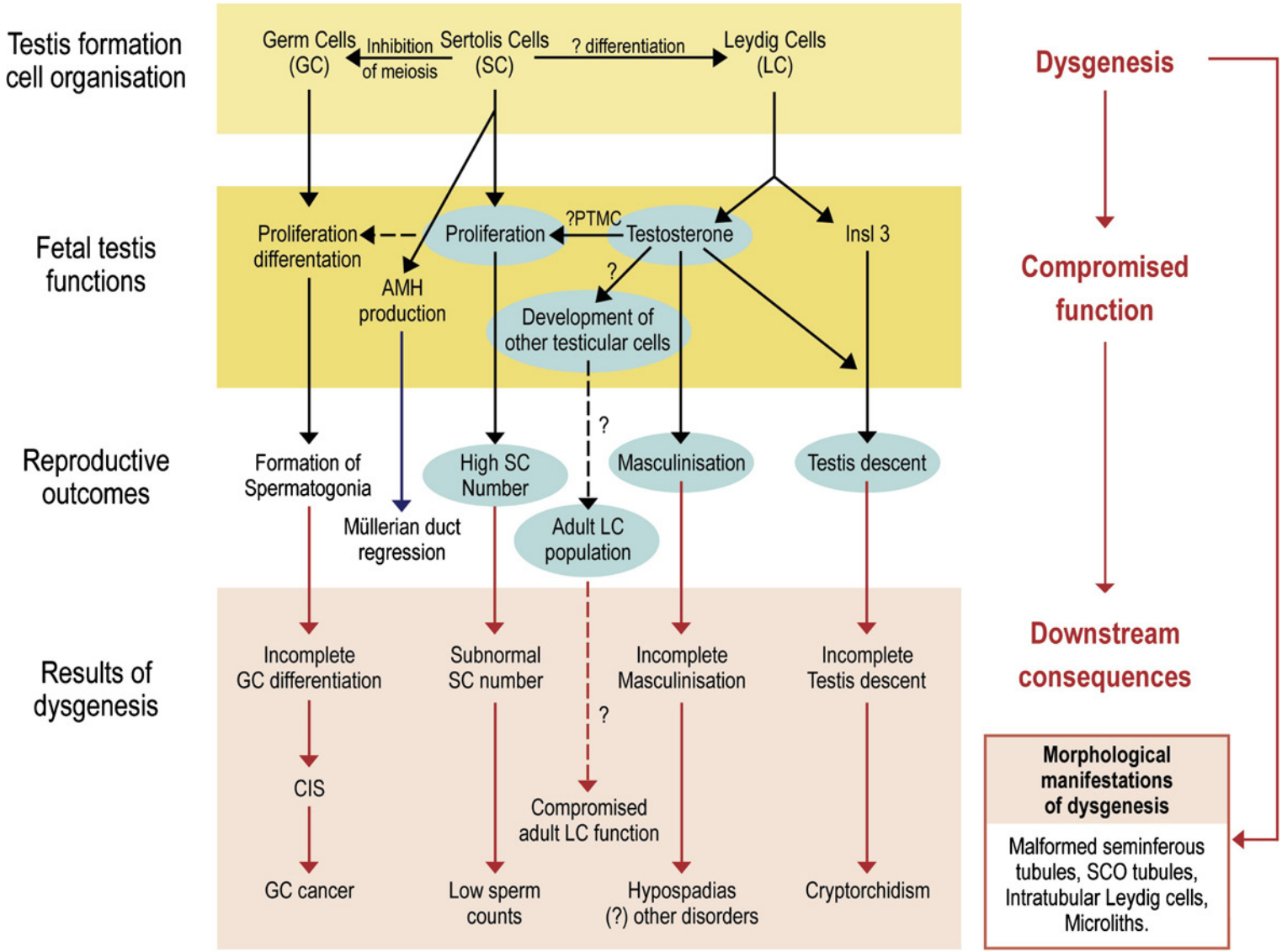
Based on data from 61 paper 1938-91, 14947 normal men.

Testis Cancer : trends in age standardised incidence



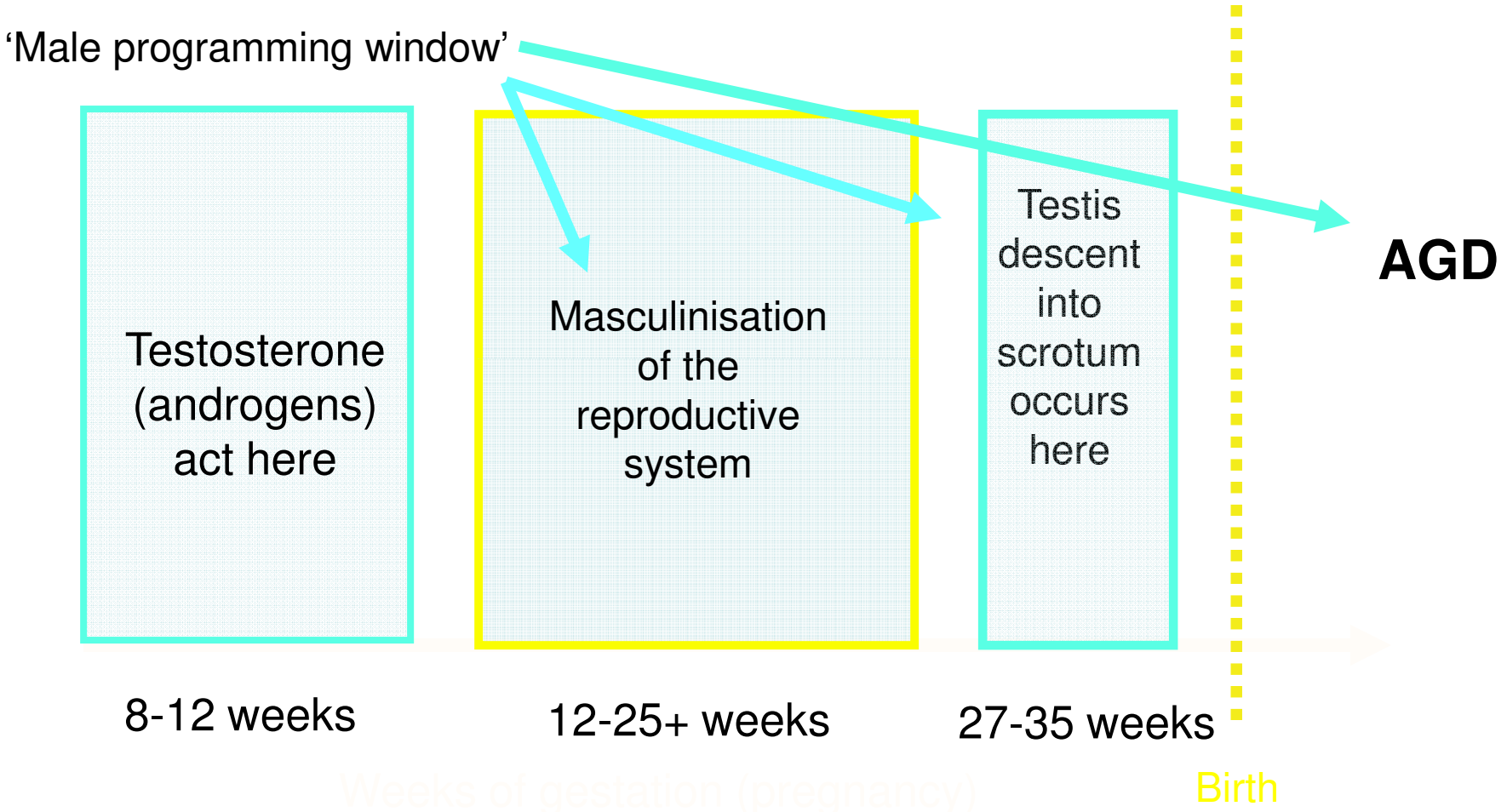
Data from Adami et al, Int J Cancer, 1994, 59, 33-38.

Fetal testicular disorder: consequences



Sharpe and Skakkebaek 2008 Fertil Steril 89, S1 e33

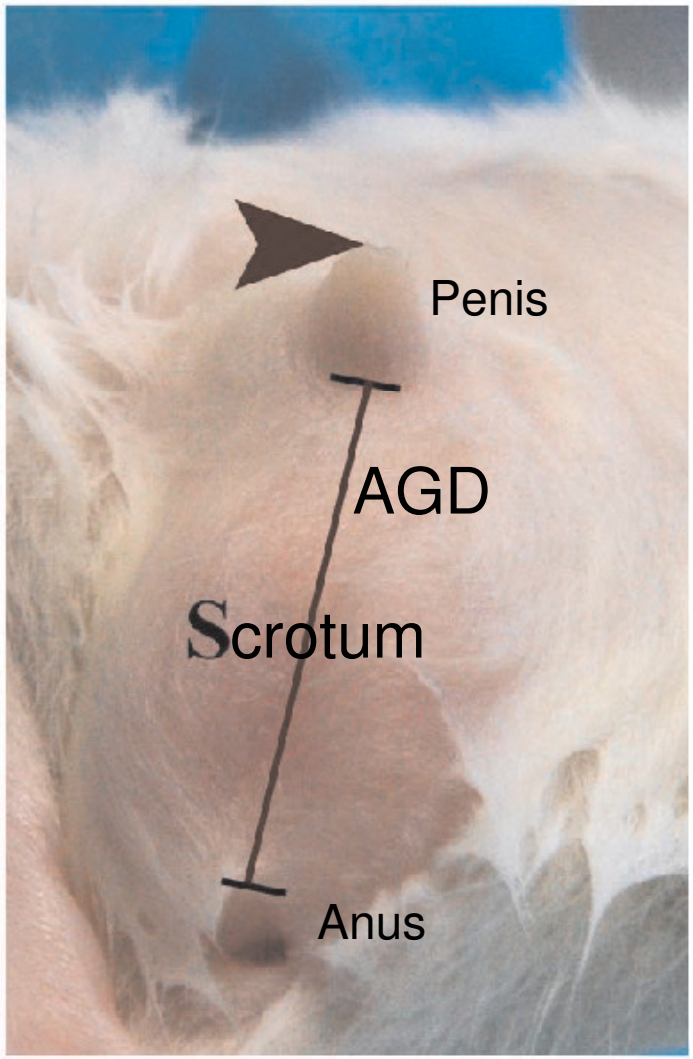
Timing of androgen action in male fetal development



Based on experimental studies in rats: M Welsh et al (2008) J Clin Invest

Anogenital distance (AGD)

- Sexually dimorphic in rats and humans; ~1.7x length in males compared with females



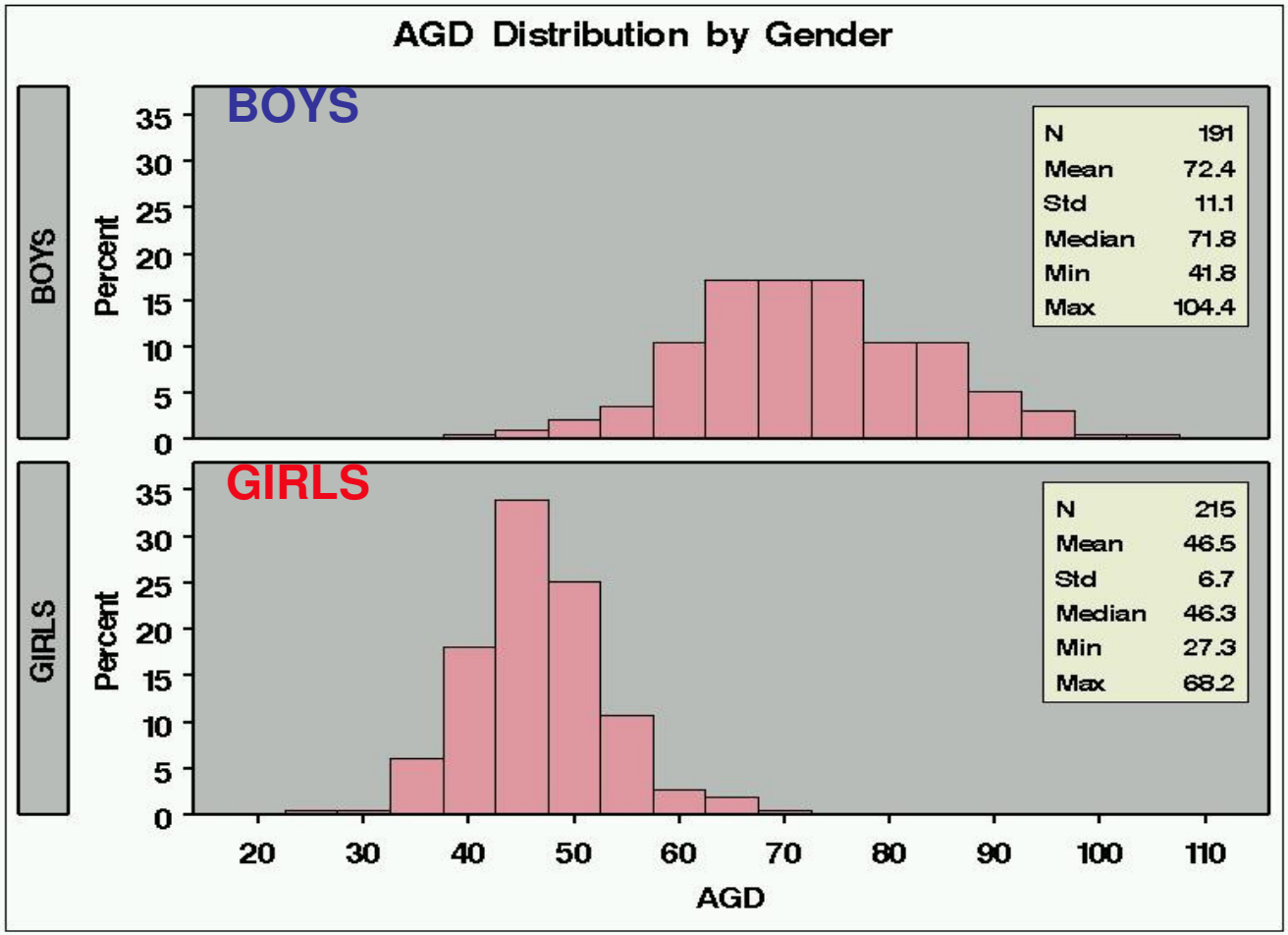
Anogenital distance in boys

A read-out of androgen action in the MPW?

- MPW probably 8-14 weeks' gestation
- AGD correlates with penis length
- Reduced AGD in hypospadias
- ?Reduced AGD in cryptorchidism

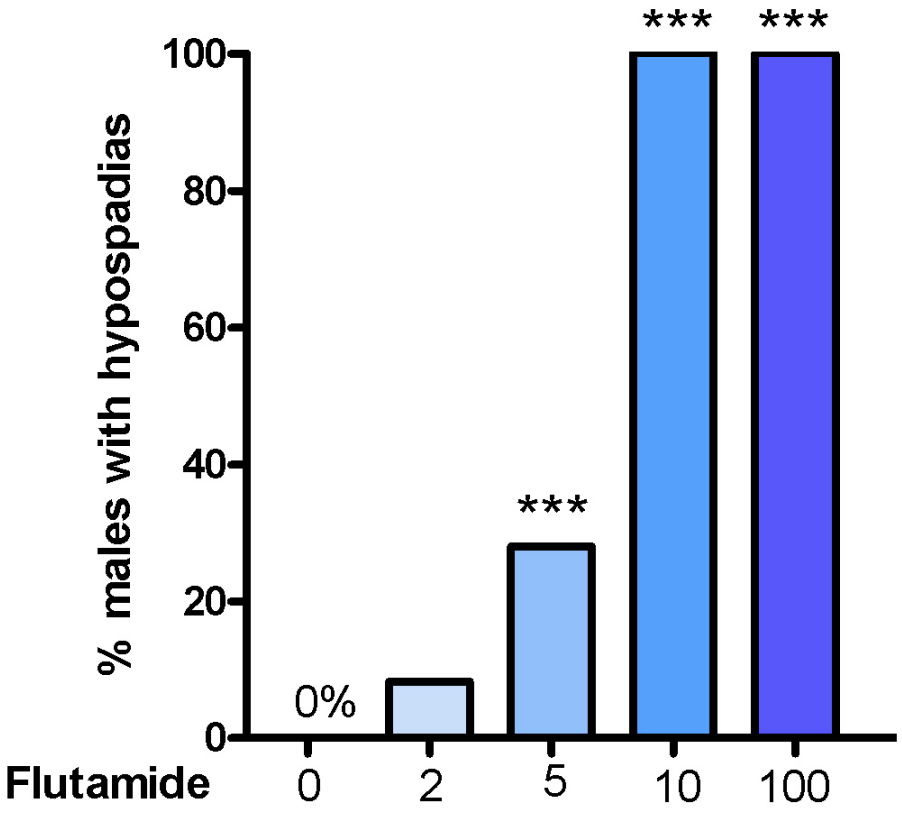
Picture courtesy of Shanna Swan

Anogenital distance (AGD) is ~1.5 times longer in boys than in girls



From Swan (2008) Environ Res

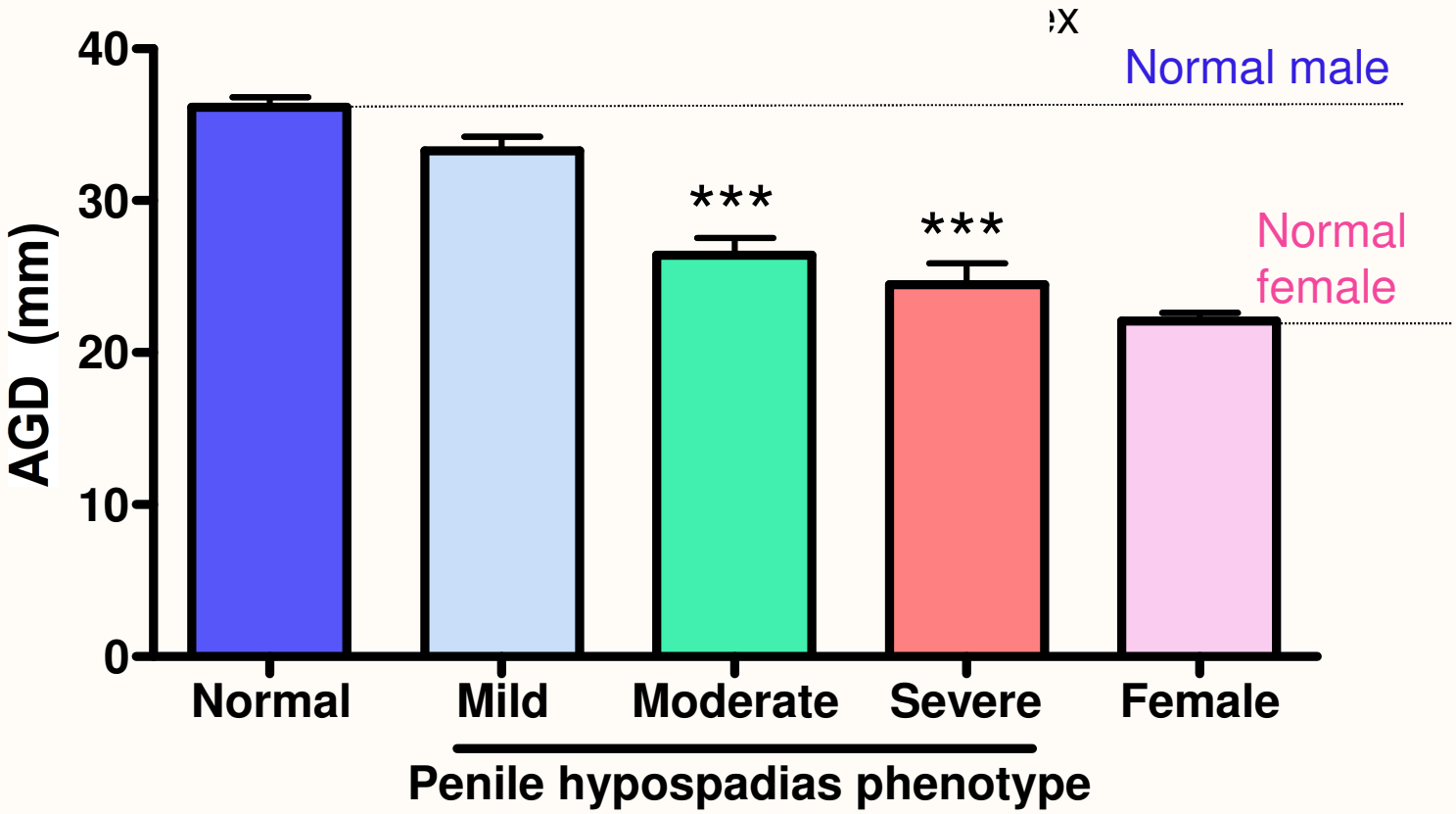
Effect of flutamide exposure within the MPW on hypospadias incidence



N= 9-20 per group

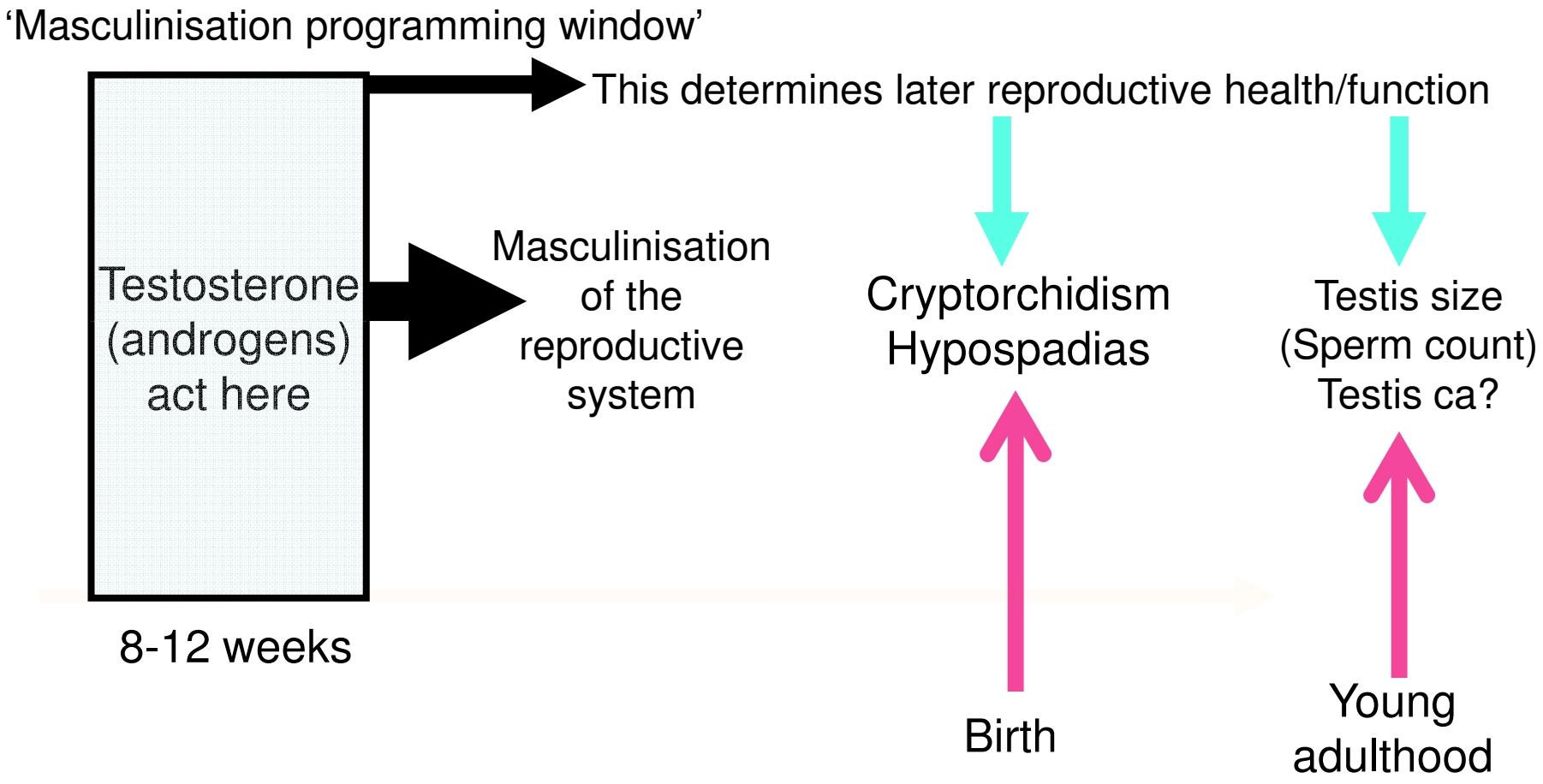
From Welsh et al (2009) Int J Androl (In Press)

Relationship between AGD and penile phenotype in adult male rats in which fetal testis function was manipulated

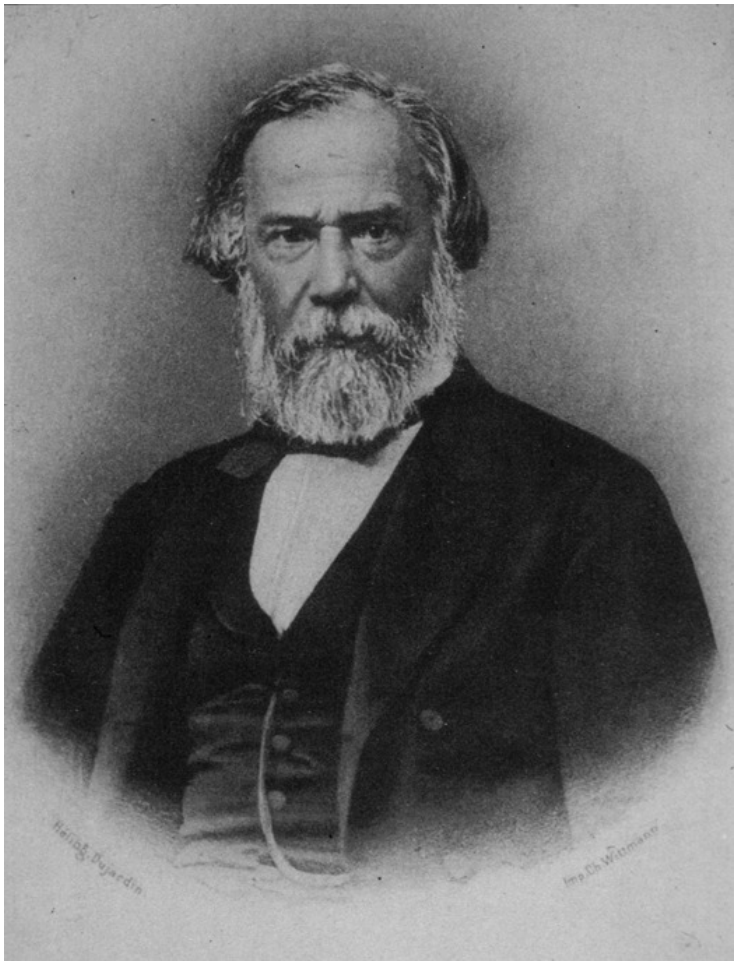


Drake et al (2009) Endocrinology

Key programming role of androgens in male development: origin of the TDS disorders?



Based on experimental studies in rats: M Welsh et al (2008) J Clin Invest



‘Increased physical strength, mental abilities and appetite’

Lancet 1889, 2, 105

Charles Edouard Brown-Sequard
1817-1896