Reproductive Hormones and Aging
in humans and animal models
the need for more and bigger datasets

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Outline

• Reproductive Hormones: a primer
• How they affect the body (emphasis on aging)
• How they change with age
• Recent hormone-dependent findings relevant to Geroscience
• Knowledge gaps
Key natural sexual steroids:

- Progestins -- 21 carbon
  - Female
- Androgens -- 19 carbon
  - Male >> Female
- Estrogens -- 18 carbon
  - Female >> Male

*countless pharmacologic derivatives*
Steroid Receptors

Estrogens: Erα & ERβ

Androgens: AR

Progestins: PR, GR1, GR2
Steroid Receptors

Knowledge gap:
Post 70’s, absence of characterization of effect of aging on detailed advances in hormone receptor signaling pathways

Sex Hormones Don’t Just act on Reproductive Targets
(i.e., receptors are everywhere)
Estradiol and Testosterone Across the Lifespan

Nature Reviews | Genetics

Mehmet Tevfik Dorak, in *Principles of Gender-Specific Medicine (Third Edition)*, 2017
Knowledge gaps:
estrone?, estriol?, progesterone?, dihydrotestosterone?
Sex Hormone Actions Relevant to Aging
Organizational (e.g., neuronal)
Activational Organizational Dysorganizational

Nature Reviews Genetics

Mehmet Tevfik Dorak, in Principles of Gender-Specific Medicine (Third Edition), 2017
Examples of the data we need
Plasma estradiol declines profoundly in **women** and increases in **men** (at least in Tromso, Norway)

- **n=1952**
- **n=1555**
Plasma estradiol declines profoundly in women and increases in men (at least in Tromso, Norway)

Knowledge gap:

Effects of genetics, race, ethnicity, socioeconomic status?

Bjornerem et al JCEM 2004
Plasma Testosterone declines progressively with age in largely Caucasian, socioeconomically advantaged males

n=890

S Mitchell
Harman, MD, PhD

Marc
Blackman, MD
Profound Individual Variation

Total Testosterone

Free Testosterone

n=890


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Profound Individual Variation

Knowledge Gap: The basis for and significance of this variation to healthspan and lifespan of this variation.

n=890
Finding a Mouse Model

(to probe the role of sex hormones in aging)
Criteria

• genetically heterogeneous
• models human aging demographics
• models reproductive hormonal changes
• statistically powered to probe variation and its implications.
UM-HET3 – genetically heterogeneous 4-way cross

[BALB/cByJ X C57BL/6J] X [C3H/HeJ X DBA/2]

Courtesy R. de Cabo

Petrov et al. 2004

Richard Miller, MD, PhD
UM-HET3 mice exhibit similar early/midlife male-specific mortality increase as humans

Humans

Mice

Death Rate

Mortality Hazard

0.100
0.010
0.001
0.000
0 25 50 75 100
Age (Years)

1e-02
1e-04
0 500 1000
Age (Days)

Females
Males


n = 3690

Catherine Cheng PhD

Jonathan Gelfond, MD PhD

( HumanMortality Database )
What underlies the increased male mortality hazard in early/mid adulthood?

**Humans**

![Graph showing death rate and age for humans](HumanMortality Database)

**Mice**

![Graph showing mortality hazard and age for mice](Cheng, Gelfond, Diaz, Strong, Nelson, Aging Cell (2019))

Hypothesis:
Post-pubertal testicular steroids increase male mortality

![Diagram showing mortality hazard over age (days) for females and males with a spotlight on testosterone.]
**Hypothesis:**
Pre-pubertal castration will increase male survival

![Graph showing survival of pooled controls with castration prepubertally]
A few, among many, important unanswered questions

1. Mechanisms and tissue targets of androgen-induced excess male mortality.
2. Roles of androgens in age-specific mortality and declining healthspan in late life.

3. Roles of androgens/estrogens during the organizational phase on healthspan and longevity
4. Roles of estrogens (estradiol/estrone/estriol) on healthspan and longevity
5. Genetic, ethnic, racial variation on age-related changes of reproductive hormones

6. Effects of aging on hormone receptor / signaling cascades and target tissue sensitivity to reproductive hormones.
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