Testosterone and the Modern Masquerade of Rejuvenation

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University of Hong Kong, Hong Kong, August 2015

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Testosterone and the Modern Masquerade of Rejuvenation

- Ageing & rejuvenation: the importance of history
- Revival of rejuvenation as disease mongering
- Age-specific population profile of androgen status
- Ageing & co-morbidities: impact on androgen status
- “Andropause”/”Low T” a fiction in search of a definition
- Misguidance of “Guidelines”
- Global epidemic of testosterone mis-/overuse
The Importance of Knowing History

“Those who can’t remember the past are condemned to repeat it”
Santayana (1863-1952)

“The past is not dead, it is not even past”
Faulkner 1897-1962

“History repeats itself first as tragedy, then as farce”
Marx (1818-1883)

Modern Androgen Pharmacology
A Faltering History

• Ancient recognition that the testis is responsible for virilisation and fertility of men & male animals

• Pre-history of Androgen Pharmacology
  • Folk belief: ageing = loss of “manliness” => testis failure
  • Fountain of Youth (16th C)
  • Rejuvenation Quackery Era (late 19th/early 20th C)
    Brown-Sequard, Steinach & Voronoff
Pre-History of Androgen Pharmacology

• 1889-1930’s Era of Rejuvenation Quackery

Charles Edward BROWN-SEQUARD 1817-1894
Testis extracts

Eugen STEINACH 1861-1944
Vas ligation

Serge Samuel VORONOFF 1866-1951
Testis grafts
Pre-History of Androgen Pharmacology

Brown-Sequard’s Testis Extract

“Each dog testis crushed in 2.3 mL of water…… filtered through a Pasteur filter…… injected 1.0 mL subcutaneously……”

Charles Edward Brown-Sequard (1889)

Calculation: If aqueous extract 100% effective, need 500-10,000 dog testes -> 1 day’s T for a human (5 mg/day)

Replication: Extracted T from dog testes, ~30,000 dog testes/day (Cussons A et al, 2002)

“The Pentacle of Rejuvenescence” (BMJ editorial, 1889)

“…recalls the wild imagings of medieval philosophers in search of an elixir vitae…”

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Locomotor Ataxia, Neurasthenia...

AND OTHER NERVOUS DISEASES.

EXTRACTS OF ANIMAL ORGANS.

GRAY MATTER, TESTICLE EXTRACT.

Prepared at the New York Biological and Vaccinal Institute, according to the method of Professor Brown-Sequard.

If the treatment of Locomotor Ataxia, Neurasthenia, and other nervous diseases with “Extracts of Animal Organs,” has not obtained in America the great favor that it enjoys in Europe, it is chiefly owing to the numerous unreliable preparations of so-called “Extracts” which have been placed on the market.

Physicians desirous to try the injections of fresh and reliable extracts, may obtain them from the New York Biological and Vaccinal Institute, at the following prices:

TESTICLE EXTRACT, 1 vial, 25 c.c. $2.50
GRAY MATTER, 2.50
SPECIAL SYRINGE, 3 c.c. 2.50

Literature sent on application.

NEW YORK BIOLOGICAL AND VACCINAL INSTITUTE,
Pasteur Institute Building, 1, 3, 5 and 7 West 97th Street, New York, N.Y.

Advert for organ extracts, Bulletin of the Pasteur Institute, New York, 1897
• Ancient recognition that the testis is responsible for virilisation and fertility of men & male animals

• Pre-history of Androgen Pharmacology
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  • Fountain of Youth (16th C)
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    Brown-Sequard, Steinach & Voronoff

• 1935 birth of Modern Androgen Pharmacology with the Nobel Prize-winning characterization of testosterone
  • Lacquer (Dutch), Butenandt (Germany), Ruzicka (Swiss) teams
  • Crystallization (testis), purification (urine) & chemical synthesis
Age-Specific Population Centiles Across the Lifespan
Australian males and females from birth to 100 years of age

123,900 consecutive blood samples over 7 years requesting serum testosterone
Single testosterone immunoassay & laboratory
Data trimmed by 2%, smoothed age-specific centiles deduced by GAMLSS modelling

Male (n=58,374)

Features
- Neonatal surge followed by childhood quiescence
- Peak around age 20 followed by gradual decline till mid 30’s
- Stable between 35 and 70 years of age – decline <0.1% per year
- Marked decline after 70 years of age

Handelsman, Sikaris, Ly, unpublished
• Neonatal surge followed by childhood quiescence
• Peak age 20, gradual decline till mid 30’s
• Relatively stable 35 to 70 years – decline <0.5% per year
• More marked decline after 70 years of age

Biochemical Definition of Rare Disease
Reference ranges/95% CIs do NOT define a disease

**Hyponatremia**
Population reference range: serum sodium 135 – 145 mmol/l (SD ~2.5 mmol/l)

<table>
<thead>
<tr>
<th>Serum Sodium (mmol/l)</th>
<th>SDs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>135 - 145</td>
<td>-2 to +2</td>
</tr>
<tr>
<td>Mild</td>
<td>130 - 134</td>
<td>-4 to -2</td>
</tr>
<tr>
<td>Moderate</td>
<td>126 - 129</td>
<td>-6 to -4</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;125</td>
<td>&lt;6</td>
</tr>
</tbody>
</table>


**Renal Anemia**
Population reference range: hemoglobin 140 – 180 g/l (SD ~10 g/l)

<table>
<thead>
<tr>
<th>Hemoglobin (g/l)</th>
<th>SDs</th>
<th>Outcome of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>140 - 180</td>
<td>-2 to +2</td>
</tr>
<tr>
<td>High target</td>
<td>120 - 150</td>
<td>-2 to +0.5</td>
</tr>
<tr>
<td>Low Target</td>
<td>95 - 115</td>
<td>-4.5 to -2.5</td>
</tr>
</tbody>
</table>

Palmer et al, Ann Intern Med 2010
Significance of the Decline in Testosterone with Age?

- Andropause hypothesis
- Barometer of Health hypothesis

**Non-Specific Symptoms**

Healthy Man Study

**Objective:**
- To develop reference ranges for serum T, DHT & E₂ in healthy older men
- To quantify the impact of common covariables
- To estimate & partition within-person variability

**Healthy men, ≥ 40 yr, excellent health**
- Observational, repeated measures
- 9 serum samples per man over 3 months
- Serum T, DHT & E₂ (LC-MS)
- Mixed model ANOVA with covariates
- Covariates: age, fasting, obesity, smoking
Healthy Man Study

- **Participants**: 325 men >40 yr, **excellent health**, 2 centres
- **Samples**: >99% scheduled samples collected
- **Age**: 60±11 yr (40-97), **BMI**: 26.6±3.2 (19.5-42.7)

![Scatter plot showing serum testosterone levels by age](image1)

**Covariate Effects**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Effect (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yr)</td>
<td>2.0 (ex) - 1.0 (non)</td>
</tr>
<tr>
<td>Fasting</td>
<td>0.5 (ex) - 0.5 (non)</td>
</tr>
<tr>
<td>BMI (per SD)</td>
<td>1.5 (ex) - 1.5 (non)</td>
</tr>
<tr>
<td>Smoking (vs smoking)</td>
<td>-2.0 (ex) - 2.0 (non)</td>
</tr>
</tbody>
</table>
Healthy Man Study

- Testosterone
  - Decade (years): 40-50, 50-60, 60-70, 70-80, 80+
  - nmol/L: 0, 5, 10, 15, 20, 25, 30, 35, 40

- DHT
  - Decade (years): 40-50, 50-60, 60-70, 70-80, 80+
  - nmol/L: 0, 1, 2, 3, 4, 5

- Estradiol
  - Decade (years): 40-50, 50-60, 60-70, 70-80, 80+
  - pmol/L: 0, 50, 100, 150, 200, 250

- LH
  - Decade (years): 40-50, 50-60, 60-70, 70-80, >80
  - IU/L: 0, 5, 10, 15, 20

- FSH
  - Decade (years): 40-50, 50-60, 60-70, 70-80, >80
  - IU/L: 0, 5, 10, 15, 20, 50

- SHBG
  - Decade (years): 40-50, 50-60, 60-70, 70-80, >80
  - nmol/L: 0, 20, 40, 60, 80, 120, 130

Andropause hypothesis

Symptoms

Barometer of Health hypothesis

Disease

1. Andropause hypothesis

2. Barometer of Health hypothesis
Sexual Function and Hormones in Men over 70 years: CHAMP Study

- Population-based study
- 1705 men, >70 yr
- Baseline, 2 & 5 yr data
- Sexual function questionnaire
- Steroid assays by LC-MS
- Papers in JCEM (5), JBMR

- Decrease in sexual activity over time associated with a significant, minor fall (~10%) in serum T
- RCT → 60% decrease in serum T does NOT reduce sexual activity
- => ↓sexual activity causes ↓ androgen status

EMAS study Wu et al, NEJM 2010
Observational study: population-based, multi-centre
- 3369 men, aged 40-79 yr, from 8 European cities

Endpoints:
- Physical, Psychological & Sexual symptoms
- Single serum T (MS) and calculated “free” T
- Correlate symptoms with T levels (split sample)

Findings:
- Physical & psychological symptoms: no relationship

False negatives 40-50%
False positives 25-50%
Odds ratio (95% CI)

- Observational study: over-interpreted as cause & effect
- Low serum testosterone due to reduced sexual activity, not reverse
- Proposed definition uses only single testosterone measurement
- Requires MS steroid assays, not available clinically
- Relies on inaccurate formula to calculate “free” testosterone

Disease mongering & pathologising/medicalising of ageing: making a “diagnosis” for a “hormone deficiency” does not bypass need for proper placebo-controlled RCT evidence
Social cues & stress
Photoperiod
Weather
Food
Negative feedback
Endogenous metabolic cues
Non-Gonadal Disorders
Ageing
Chronic Disease
Obesity
Surgery
Trauma
Malnutrition
Cytokines

Classical Hypogonadism
(Pathological)

Infertility &/or Androgen deficiency

Pseudo-Hypogonadism
“Sick Eugonadal” Syndrome
(Functional)

Adaptive response of a healthy reproductive system to disease
Not a deficiency state
Pharmacological treatment requires proof of efficacy & safety

Klinefelter’s Syndrome

Major underdiagnosis
Klinefelter’s syndrome (47 XXY) - most frequent single cause of AD

- Characteristic = very small testes
- Prevalence ~152 per 100,000 births (prospective birth surveys)
- Diagnosis ~40 per 100,000 lifetime (European registry data, 4300 KS)
- Life expectancy - normal (71.4 vs 73.5 yr, Danish national registry)

Implications
- Major (~75%) under-diagnosis of KS
- Most men go through life without a full genital examination by a doctor
The Andropause Racket

**Are You Getting Enough?**

*What Every Man Should Know About Testosterone*

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**National PBS Prescriptions for Androgens**

![Graph showing units vs. years for different testosterone sources: Injectable Testosterone esters and Oral Testosterone undecanoate.](source:image)

- **Introduction Authority Requirement**
- **Introduction ESA/PBS Criteria**
- **Company Marketing Campaign**

Source: PBS
T prescribing criteria

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>Europe</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>2005/9</td>
<td>2006/10</td>
<td></td>
</tr>
</tbody>
</table>

CLINICAL COMPONENT

Pathological basis

- Recognised
- Eliminated
- Eliminated

HORMONAL CONFIRMATION

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TT &gt; 8 nM</th>
<th>TT &gt; 12 nM</th>
<th>TT 8-12 nM</th>
<th>Nil</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment &quot;trial&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>TT &lt; 8 nM</td>
<td>TT &lt; 8 nM</td>
<td>TT &lt; 10.4 nM</td>
<td></td>
</tr>
</tbody>
</table>

REGULATORY STATUS

| Governs 3rd party subsidy | Nil | Nil |
### T prescribing criteria

<table>
<thead>
<tr>
<th></th>
<th>Australia 2015</th>
<th>Europe 2005/9</th>
<th>USA 2006/10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL COMPONENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological basis</td>
<td>Recognised</td>
<td>Eliminated</td>
<td>Eliminated</td>
</tr>
<tr>
<td><strong>HORMONAL CONFIRMATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>TT &gt; 6 nM</td>
<td>TT &gt;12 nM</td>
<td>Nil</td>
</tr>
<tr>
<td>Treatment &quot;trial&quot;</td>
<td>Nil</td>
<td>TT 8-12 nM</td>
<td>Nil</td>
</tr>
<tr>
<td>Treatment</td>
<td>TT &lt; 6 nM</td>
<td>TT &lt; 8 nM</td>
<td>TT&lt;10.4 nM</td>
</tr>
<tr>
<td><strong>REGULATORY STATUS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Governs 3rd party subsidy</td>
<td>Nil</td>
<td>Nil</td>
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### Conclusions

1. Testosterone (T) replacement for disease-related "classical hypogonadism" supported
2. T treatment for age-related hypogonadism NOT supported
3. Age-related hypogonadism NOT established as a disease
4. Safety and efficacy of T treatment NOT established for age-related hypogonadism
5. Biological plausibility for CV safety signals but data weak due to study limitations
6. Labelling changes required for testosterone products to reflect these interpretations
7. Vote: Need to revise current indications? Yes 20, No 1, Abstain 0
8. Vote: Sponsors required to conduct CV risk study? Yes 20, No 1, Abstain 0

### FDA Action (March 2015)

1. Label changes – safety & efficacy for age-related hypogonadism not established
2. Male hypogonadism defined as primary or secondary pathological disorders
3. Requires 2 morning serum T measurements on different days
4. Extra warning on increased risk of myocardial infarction and stroke
Androgens & Male Ageing
Summary of Key Issues

<table>
<thead>
<tr>
<th>Does blood T decline with age?</th>
<th>Not in healthy older men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In unselected men, modest, gradual &amp; inconsistent decline &amp; due to co-morbidities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Does testosterone reverse any functional features of ageing?</th>
<th>Not so far</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Focus on co-morbidities, not ageing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If so, is it safe?</th>
<th>Not proven, doubt on CV safety, Placebo-controlled RCT required</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Diagnosis of androgen deficiency in older men?</th>
<th>Not currently justified Guidelines promote over-use</th>
</tr>
</thead>
</table>

US Institute of Medicine 2004 Report - Conclusion
• Inadequate efficacy to justify a major placebo-controlled RCT
• Recommend series of short/medium term efficacy studies
• Definitive answers still far away

Testosterone Use and Misuse
• “Andropause”/“Low T”/“LOH” is a fiction in search of a definition. Not a disease or deficiency state but a functional state (pseudo-hypogonadism, “Sick Eugonadal” Syndrome)
• Testosterone deficiency is a clinical diagnosis with a pathological basis, and confirmed by hormone assays - not the other way around
• Age effects on androgen status are mediated via effects of co-morbidities (obesity, CVD, organ failure, depression etc)
• Distinguish pathological disorders from functional low T states
• Classical disease mongering: Inventing a “diagnosis” for a “hormone deficiency” to justify wider evidence-free treatment
• Marketing-friendly “Guidelines” obscuring that distinction promote excessive testosterone prescribing
• Need for accurate measurement of testosterone and other steroid by mass spectrometry - steroid immunoassay era of 20\textsuperscript{th} C is ending
• “Free” testosterone should be consigned to science fantasy
Age
+
Non-specific symptoms
+
Low serum testosterone

= “Andropause/Low T”

**Unicorn Syndrome:**
An invented entity given a memorable name creates a new “reality”
Free Hormone Hypothesis

- Long-standing but unproven & controversial hypothesis
  Based on outdated 1970’s pharmacological drug & receptor theory
  Assumes Unbound (“free”) fraction is more biologically active
  SHBG bound T is a biologically inert buffer,
  T transfer by passive diffusion in all capillaries - equally & fully

- Theory: why would “free” fraction favour bioactivity over metabolism?
- Empirical:
  (a) SHBG not inert buffer
  (b) SHBG polymorphisms
  (c) Experiment of Nature
- Practice: Laborious, inaccurate & minimal evaluation

“Free Hormone” Industry: Ad Hoc assays

- Direct measurement
  - direct “free analog” immunoassay
  - “free” testosterone (equilibrium dialysis)
  - “bioavailable” testosterone (ammonium sulphate precipitation)

- Calculations based on TT & SHBG immunoassays
  - Empirical
    - Free Androgen (Testosterone) Index (TT/SHBG %)
    - Non-linear empirical equations
  - Equilibrium binding formula-based
    - “Law of Mass Action”

Minimal evaluation of validity - yet treated as if axiomatic
Free Testosterone: Laboratory Assay vs Calculations

Centrifugal Ultrafiltration

Equilibrium Dialysis

3975 serum samples
RPAH & Andrology Australia
Sartorius et al Ann Clin Biochem 2009

2160 serum samples
Harbor-UCLA (Wang, Swerdloff)
Ly et al, Clin Endo 2010

Equilibrium binding/Mass Action formulae ~40% positive bias
Empirical equations consistently less biased
Confirmed by two other independent groups

Equilibrium binding theory
Empirical equations
Ly et al, 2005, 2009 & 2010
## Equilibrium Binding Equations to Calculate “Free” Testosterone

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Fact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding is at equilibrium</td>
<td>True in circulation - False during capillaries unloading</td>
</tr>
<tr>
<td>SHBG binding affinity fixed &amp; uniform</td>
<td>&gt;5 fold range in binding affinity estimates used</td>
</tr>
<tr>
<td>Population polymorphisms in binding affinity</td>
<td>Population polymorphisms in binding affinity</td>
</tr>
<tr>
<td>Stoichiometry – 1 steroid per homodimer</td>
<td>False – 1 steroid per monomer, 2 per homodimer</td>
</tr>
</tbody>
</table>

### Charts

- **Men**
  - Vermeulen Standard Formula
  - Vermeulen Correct Stoichiometry
  - Free Androgen Index

- **Women**
  - Vermeulen Standard Formula
  - Vermeulen Correct Stoichiometry
  - Free Androgen Index

Handelsman, Sikaris, Ly, unpublished
“Free” Testosterone Studies

Key Findings

- Underlying theory badly flawed and implausible
- Widely used equilibrium binding formulae (Vermeulen, Sodergard) over-estimate actual “free” T measurements
- Errors due wrong assumptions: incorrect SHBG-T stoichiometry & arbitrary steroid binding affinity constants
- Simple empirical formula for “free” T using TT & SHBG assays more accurate vs equilibrium dialysis reference method
- “Free androgen (T) index”- invalid for men, inaccurate for women

Focus on the real issue - do such derived T measures add any useful information to valid T measurements?

“Free Hormone” Industry: Ad Hoc assays

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Focus on the real issue - do such derived T measures add any useful information to valid T measurements?
The Mismeasure of Testosterone

- Direct testosterone (& estradiol) immunoassays are inaccurate with method-specific bias vs mass spectrometry (MS) reference methods
- Original steroid immunoassays used extraction, chromatography and authentic tracers (triplet validity criteria) to overcome non-specificity due to cross-reacting steroids and metabolites and matrix effects
- Modern simplified assay formats sacrifice validity for high throughput in multiplex platforms and single tube kits
- Inaccuracy (bias) & non-specificity worst at low steroid concentrations
  - Testosterone acceptable for eugonadal men
    NOT reliable in children, women & hypogonadal men
  - Estradiol acceptable in pre-menopausal women (ovulation induction, IVF)
    NOT reliable in children, men, post-menopausal women
- Bench-top MS steroid assays are increasingly available and combine high sensitivity with reference level specificity
Conclusions

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2. Testosterone treatment for age-related hypogonadism NOT supported
3. Age-related hypogonadism NOT established as a disease
4. Safety and efficacy testosterone treatment NOT established for age-related hypogonadism
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Male Sexual Function Has A Low Threshold For Testosterone

Common study design: Depot GnRH analog to suppress endogenous T + add-back dose-range of testosterone

50-60% reduction in serum T has no effect on male sexual function

Age-Specific Population Centiles

58,374 consecutive blood samples over 7 years requesting serum testosterone
Single testosterone immunoassay & lab
Smoothed age-specific centiles with 2% data trim deduced by GAMLSS modelling

Handelsman, Sikaris, Ly, J Steroid Biochem Mol Biol

- Neonatal surge followed by childhood quiescence
- Peak age 20, gradual decline till mid 30's
- Stable 35 to 70 years – decline <0.3% per year
- Marked decline after 70 years of age
Klinefelter’s Syndrome

- 47 XXY (+ mosaic & variants) 1:650 male births
- Most frequent cause of classical hypogonadism
- **Characteristic feature = very small testes**
  - Phenotype = congenital androgen deficiency
  - Eunuchoidism, poor virilization, gynecomastia
  - Delayed or incomplete puberty
  - Male infertility (azoospermia)
  - Neurobehavioural defects
  - Increased cancer susceptibility

Implications

- Major (~75%) under-diagnosis of KS
- Missed diagnosis or atypical phenotype?
- Most men go through life without a full genital examination by a doctor
Testosterone Use and Misuse

- Testosterone deficiency is a clinical diagnosis with a pathological basis, and confirmed by hormone assays - not the other way around
- Age effects on androgen status are mediated via effects of co-morbidities (obesity, CVD, renal or liver failure, depression)
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