NOTE ON
THE EFFECTS PRODUCED ON MAN BY SUB-CUTANEOUS INJECTIONS OF A LIQUID OBTAINED FROM THE TESTICLES OF ANIMALS.

By DR. BROWN-SÉQUARD, F.R.S. &c.

On the 1st of June last I made at the Société de Biologie of Paris a communication on the above subject, which was published in the Comptes Rendus of that Society on June 21st (No. 24). I will give here a summary of the facts and views contained in that paper and in two subsequent ones, adding to them some new points.
Eugen Steinach (1861-1944)

Austrian Physiologist

Unilateral Vasal Ligation for “Physical and Mental Rejuvenation”

Nominated for 6 Nobel Prizes
Before and After Advertisements

1928

Fifty-six-year-old controller before (A) and after (B) the Steinach operation. From How to Restore Youth and Live Longer, by Serge Voronoff (1928).
Famous Patients Who Underwent Steinach Procedure

WB Yeats

Sigmund Freud
Injections of Testicle Extract

Extracts obtained from bull testicles used for injection into capons (castrated roosters) by various investigators.
Capon (castrated rooster)

- Capons began demonstrating rooster behavior after injection of testicle extract
- Stimulated growth of cocks comb
Isolation of Testosterone

• 1929-Growth of capon’s coxcomb was first bioassay
• Hypothetical androgenic substance called “androkinin”
• 1931- Butenandt isolated first androgen, androsterone, from 15,000L urine from Berlin policemen
• 1935-Ernest Laqueur (Amsterdam) isolated 10mg of a more androgenic substance from 100kg bull testes- named it “Testosterone”
1935 Synthesis of Testosterone

1939 Nobel Prize awarded for Synthesis of Testosterone

Adolf Butenandt, Germany
(1903 –1995)

Leopold Ružička, Switzerland
(1887 –1976)

Butenandt, a member of the Nazi Party, rejected the award in 1939. Accepted in 1949.
Earliest T formulations

• Oral T ineffective (not water-soluble)
• 1930s- pellets, T propionate (daily injection), oral methyltestosterone
• 1950s-longer acting injections of T esters-enanthate and cypionate
• Oral methyltestosterone clinically abandoned 1980s due to liver toxicity
• 1970s- oral T undecanoate
1970s: Introduction of Hormone Radioimmunoassays (RIA)

A RADIOIMMUNOASSAY FOR PLASMA TESTOSTERONE

Shunsuke Furuyama, Darrel M. Mayes and Charles A. Nugent

From the Division of Endocrinology and Metabolism, Department of Medicine, University of Hawaii School of Medicine, Honolulu, Hawaii 96822.

Received: July 6, 1970

ABSTRACT

A simple and reliable radioimmunoassay for plasma testosterone has been developed. Antiserum against testosterone was produced in rabbits and standard curves were constructed for the assay. The sensitivity of the assay was 0.25 ng/ml and the inter-assay coefficient of variation was 3%.
REPORT ON MEDICAL PROGRESS

ENDOCRINES: THE USE OF TESTOSTERONE*

Joseph C. Aub, M.D.†

Boston

THE drug testosterone is worthy of lengthy discussion, for when its use is indicated it is powerful and of considerable value. Indeed, in my experience this is one of the most potent drugs recently introduced to medicine. Because use is a pure substitution therapy, just as is that of insulin. Testosterone does not stimulate the pituitary gland to greater activity; in large doses, indeed, it appears to inhibit temporarily this important gland. The result is that testosterone

NEJM 1940, Aub, Joseph C.

• "Use for hypogonadism in males"
• Erections occur immediately
• Prostate grows to normal size
• "Greater psychological assurance and vigor are obvious"
The Origin of the Prostate Cancer Fear

Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 22, 1941)

Carcinoma of the prostate gland is peculiarly favorable for endocrine investigation since frequent serial observations of the activity of phosphatases in serum were found to provide objective indices of activity of the neoplasm when the enzymes were increased in amount above normal. In the present paper data are given for the values of serum phosphatases in car-

METHODS AND MATERIALS

The phosphatase activity of serum was determined by the method of King and Armstrong (10) using 0.005 M disodium monophenylphosphate as substrate. The buffers used were 0.05 M barbital-sodium at pH 9.3, and 0.1 M Sörensen's citrate. HCl or Walpole's

"Cancer of the prostate is activated by androgen injections"

Huggins C and Hodges CV, Cancer Res. 1941;1:293
Androgen Hypothesis 1941-2006

• High T causes PCa
• Low T protects against PCa
• T administration in men with known PCa is like “pouring gasoline on a fire” or “feeding a hungry tumor”
Clinical Use of Testosterone in Late 1980s

• Testosterone use was RARE
• Restricted to young men with
  – Absent/atrophic testes
  – Pituitary/hypothalamic tumors
  – Klinefelter’s
  – Aplastic anemia
• Treatment options:
  – Injections (cypionate/enanthate) q 4wk
  – Oral methyltestosterone-liver toxicity
1st Evidence Challenging Androgen Hypothesis

- In early 1990s I began performing prostate biopsies in “normal” men prior to T therapy to rule out PCa
- All with low T, PSA<4.0, nl DRE
- 11 cancers in first 77 (14%) men
- Same rate as men at risk: PSA 4-10ng/ml
- Conclusion: Low T was NOT protective against PCa

Morgentaler et al, JAMA 1996
• 2004 Review of T risks, esp PCa
• No evidence for increased risk with high endogenous T or T therapy
Serum Testosterone
Prostate cancer growth/PSA
Saturation Model

Variable-dependent growth
Variable-independent growth

Morgenthaler, Eur Urol 2006
PSA AND SATURATION
Rastrelli et al, JSM 2013

- N=2967 men
- Seen for sexual dysfunction
- All with PSA<4.0
- Saturation point 8-9 nmol/L (240-250ng/dl)
T THERAPY AFTER RADICAL PROSTATECTOMY

• T therapy in 103 men after RP
  – 26 high risk (Gleason 8-10, +margins, +nodes)
• No T therapy in 49 eugonadal controls after RP
  – 15 high risk
• Mean followup 27 mo
• Biochemical recurrence in 4 (4%) T group and 8 (16%) in control group

Pastuszak et al, J Urol 2013
T Therapy in Men on Active Surveillance

- T therapy in 28 men on active surveillance
- Gleason 6 in 22, Gleason (3+4) in 6
- Comparison with 96 men with low T on active surveillance
- 3y median f/u
- No difference in progression rates between groups (10.3% vs 9.4%, p= NS)
- PSA did not increase with T therapy

Low T Associated with Worrisome Prostate Cancer Features

- Multiple studies revealed association between low testosterone levels and the following PCa features:
  - Higher grade (Gleason score)
  - Advanced stage at surgery
  - Increased risk of recurrence after surgery
  - Decreased survival

Khera et al, Eur Urology 2014
Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O’Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD
Rates of Death, MI, and Stroke in Men Treated with Testosterone

“Of 7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Among 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. **The absolute rate of events were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group**”

<table>
<thead>
<tr>
<th></th>
<th>No T (N=7486)</th>
<th>T (N= 1223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>681</td>
<td>67</td>
</tr>
<tr>
<td>MI</td>
<td>420</td>
<td>23</td>
</tr>
<tr>
<td>Stroke</td>
<td>486</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>1587</td>
<td>123</td>
</tr>
<tr>
<td>Absolute rate</td>
<td>1587/7486=21.2%</td>
<td>123/1223= 10.1%</td>
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World’s Experts Petition JAMA to Retract T Study

• Large data errors subsequently revealed
  – >1000 individuals miscategorized
  – Nearly 10% women in all-male dataset!
• Study “no longer credible” due to “gross data mismanagement and contamination”
• >160 distinguished researchers/clinicians
• 8 emeritus professors
• 9 journal editors
• From 32 countries
• 29 Medical Societies joined petition
TRT Effects on Erectile Function in Hypogonadal Men

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Standardized Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadal (19)</td>
<td>1.2 (0.7, 1.7)</td>
</tr>
<tr>
<td>Eugonadal (5)</td>
<td>0.2 (-0.2, 0.6)</td>
</tr>
<tr>
<td>Mixed Population (5)</td>
<td>0.2 (-0.1, 0.5)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.8 (0.5, 1.2)</td>
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SMD in Erectile Function (95% CI)

Effects of Testosterone Treatment in Older Men

- 790 men ≥ 65y T gel or placebo x 1y
- Additional follow-up 2nd year
- Significant improvement in:
  - Libido
  - Erections
  - Physical activity,
  - Mood
- CV events: 7 placebo, 7 T arm
- Follow-up 2nd yr: 9 placebo, 2 T arm
My Perspective
Past, Present, Future

• 1932 “Male climacteric” Brit Med J
• 1952 “Andropause”
• We have rediscovered the obvious
  – T deficiency is common, important
  – Treatment provides benefits critical to men
Paradigm Shift

• Took a generation (20y) to disabuse our simplistic notions about T and PCa
• Provides new opportunity to assess the true potential of treatment for men with T deficiency
• Challenges remain
Increasing Global Popular Demand For An Effective Treatment
The Future of T

• T deficiency will become more widely recognized as important medical condition
• Greater recognition that symptoms represent more accurate biomarker than total T concentrations
• Research into cardioprotective potential of T therapy
• Possible Rx for PCa
Patient GS After 7 Months T Therapy

- 94 yo
- Gleason 9 with bone mets
- PSA 500
- Couldn’t tolerate ADT
- Requested T therapy for cognition and strength
- T injections resulted in improved cognition, strength, appetite
- No bone pain
- Died after septic episode at 10 mo
The Future of T

• More convenient T formulations
  – New oral T formulations

• Agents that preserve fertility/testicular volume
  – SERMs
  – Long-acting hCG