PCOS: 1935 to Now

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Hippocrates described two women on the Island of Cos who were notable for their beards (‘Epidemics’, Aphorisms 55 and 56)

– Both demonstrated sudden cessation of their periods & died not soon after
Soranus of Ephesus (c. 98-138 AD), noted that “[s]ometimes it is also natural not to menstruate at all... It is natural too in persons whose bodies are of a masculine type... we observe that the majority of those not menstruating are rather robust, like mannish and sterile women” (Gynecology, Book I. Art. 23 and Book I. Art. 29)

Maimonides (1135-1204 AD) wrote that “…there are women whose skin is dry and hard, and whose nature resembles the nature of a man. However, if any woman’s nature tends to be transformed to the nature of a man, this does not arise from medications, but is causes by heavy menstrual activity” (Fin Liber Comm. Epidemirum VI, 8)
HYPERANDROGENISM IN ANCIENT MEDICINE

• Ambroise Pare (1510-1590): Noted that “Many women, when their flowers or tearmes be stopped, degenerate after a manner into a certaine manly nature, whence they are called Viragines, that is to say stout, or manly women; therefore their voice is loud and bigge, like unto a mans, and they become bearded.”
In 1721, Antonio Vallisneri (1661 - 1730) described the case of a young married pleasant woman, moderately obese and infertile, with two larger than normal ovaries, bumpy, shiny and whitish, just like pigeon eggs.
Annie Jones as a child ("The Infant Esau") and as an adult (c.1880)
PREVAILING THEORIES ON HIRSUTISM IN THE 19TH CENTURY

Hirsutism was thought to represent either:

- A normal problem of aging (Beclard, 1815)
- Fright of mother during pregnancy (Chowne, 1852)
- Intersex (Beclard, 1815; Chowne, 1852)
- A sign of madness or insanity (Harris-Liston, 1894; Berillon, 1905; Bulkley & Janeway, 1908; Laignel-Lavastine, 1921)
STEIN-LEVENTHAL SYNDROME

• 1935 - Stein & Leventhal reported on 7 cases in which “amenorrhea was associated with the presence of bilateral polycystic ovaries”
  – Three were obese
  – Five hirsute (one obese) and one thin acneic

• Wedge resection resulted in two pregnancies, and regular cycles in remaining
Early in 1935, Dr. Robert Towner Hill was transplanting ovaries into the ears of castrated male mice to observe the development of these glands.

When the procedure did not yield the desired results, Dr. Hill abandoned the project, and left for a summer research post in Missouri, leaving the mice to be cared for at Yale.

Returning for the fall semester, Dr. Hill found the mice flourishing and the ovary implants still in place – The mice were sacrificed and carefully autopsied.

To his surprise, he discovered that the prostate and seminal vesicles in all animals were of normal size and weight; apparently they had been maintained by male-like hormones from the ovaries.
Ernst Laqueur and colleagues isolated 15 mg of crystalline testosterone in early 1935, using several tons of steer testes.

Later that year (1935) Ruzicka and Butenandt were able to, in the same manner although independently of each other, synthesize testosterone from trans-dehydro-androsterone.

- Both Butenandt and Ruzicka were awarded the Nobel Prize for Chemistry for 1939 for their work on sex hormones and related steroids.
MEASURING TESTOSTERONE

• Initial assessment of androgen levels in pathologic conditions was made by measuring the concentration of 17-ketosteroids in urine.

• Early attempts at measuring testosterone in the circulation utilized extraction with ether, chloroform, and/or benzene, followed by paper and/or column chromatography, and quantification by either colorimetry or fluorometry, directly or after enzymatic conversion to estrogen.

• This was followed by the development of double-isotope derivative methods, gas chromatography with electron capture detection, or competitive protein-binding techniques.
MEASURING TESTOSTERONE

- Using these techniques, between 1963 and 1965 various investigators demonstrated elevated levels of androgens in women with hirsutism and/or PCO.
- In 1959, the first RIA was developed by Yallow & Berson for insulin.
- In 1969, Guy Abraham reported the development of the first RIA for the quantitation of a steroid (estradiol), after organic solvent extraction and chromatography of serum.
- In 1970 the first RIA for testosterone was reported by Fukayama, Mayes & Nugent at the U. of Hawaii.
ACHARD-THIERS SYNDROME OR ‘DIABETIC BEARDED WOMAN’ SYNDROME

• 1921- Achard & Thiers in a meeting of l’Académie Nationale de Médecine the 19th of July, 1921 report on a case of a postmenopausal woman with marked by diabetes mellitus and hirsutism, deep masculine voice, facial hypertrichosis, obesity, hypertrophy of the clitoris, and hypoplasia or adenoma of the adrenal cortex

ACANTHOSIS, AMENORRHEA, AND OBESITY

- In 1947, Kierland reported on three patients with ‘benign juvenile acanthosis nigricans’ who presented with amenorrhea, hirsutism, obesity and, in the two who were surgically explored, normal adrenals.
SYNDROMES OF INSULIN RESISTANCE AND ACANTHOSIS NIGRICANS

• 1976 - C. Ronald Kahn: Reported on six patients with acanthosis nigricans, variable degrees of glucose intolerance, hyperinsulinemia, and marked resistance to exogenous insulin.

- Suggested the term Type A for the clinical syndrome of virilization in younger women with an apparent defect of the insulin receptor.

GLUCOSE AND INSULIN LEVELS IN PCOS AND WEIGHT-MATCHED CONTROLS DURING OGTT

In 1958-1959, Janet McArthur and colleagues at MGH, described elevated urinary levels of interstitial cell-stimulating hormone (ICSH), subsequently known as LH.
CHARACTERIZING PCOS

The Polycystic Ovary. I. Clinical and Histologic Features

JOSEPH W. GOLDFZIEHER, M.D. AND JAMES A. GREEN, PH.D.¹

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CHARACTERIZING PCOS

Inappropriate Secretion of Follicle-Stimulating Hormone and Luteinizing Hormone in Polycystic Ovarian Disease

S. S. C. YEN, P. VELA, AND J. RANKIN

Department of Reproductive Biology, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106

Biochemical and pathophysiologial findings in women with acanthosis nigricans and androgen excess

Insulin resistance in nonobese patients with polycystic ovarian disease
- Chang RJ, Nakamura R, Judd H, Kaplan S

Effects of insulin on ovarian steroidogenesis in cultured porcine theca
- Barbieri RL, Ryan KJ, Makris A
Polycystic Ovary Syndrome is to endocrinologists what pornography is to judges.

We can’t define it but we know it when we see it!
### 1990 NIH – NICHD PCOS Conference
Percent of Participants Agreeing

<table>
<thead>
<tr>
<th>Definite or Probable</th>
<th>%</th>
<th>Possible</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperandrogenemia</td>
<td>64%</td>
<td>Insulin Resistance</td>
<td>69%</td>
</tr>
<tr>
<td>Exclusion of Other Etiologies</td>
<td>60%</td>
<td>Perimenarchal Onset</td>
<td>62%</td>
</tr>
<tr>
<td>Exclusion of CAH</td>
<td>59%</td>
<td>Elevated LH/FSH</td>
<td>55%</td>
</tr>
<tr>
<td>Menstrual Dysfunction</td>
<td>52%</td>
<td>PCO by Ultrasound</td>
<td>52%</td>
</tr>
<tr>
<td>Clinical Hyperandrogenism</td>
<td>48%</td>
<td>Clinical Hyperandrogenism</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Menstrual dysfunction</td>
<td>45%</td>
</tr>
</tbody>
</table>

# Prevalence of PCOS in Unselected White Western-European Subjects, Using the 1990 NIH Criteria

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>% PCOS in Population</th>
<th>Mean BMI of Population (kg/M²)</th>
<th>% Obesity in Country*</th>
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</thead>
<tbody>
<tr>
<td>Knochenhauer et al, 1998</td>
<td>Birmingham, AL</td>
<td>4.7</td>
<td>24.9</td>
<td>32.2%</td>
</tr>
<tr>
<td>Diamanti-Kandarakis et al, 1999</td>
<td>Lesbos, Greece</td>
<td>6.8</td>
<td>26.7</td>
<td>21.9%</td>
</tr>
<tr>
<td>Michelmore et al, 1999</td>
<td>Oxford, UK</td>
<td>8.0</td>
<td>23.0</td>
<td>23.0%</td>
</tr>
<tr>
<td>Asuncion et al, 2000</td>
<td>Madrid, Spain</td>
<td>6.5</td>
<td>23.8</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

*OECD 2007 Factbook
PREVALENCE STUDIES OF PCOS AROUND THE GLOBE-2015
First AES* meeting, Philadelphia, PA, 2003

*Now AE & PCOS Society
NUMBER OF PUBLICATIONS ON POLYCYSTIC OVARIRES, STEIN-LEVENTHAL SYNDROME (SLS), AND HIRSUTISM FROM 1966-2003, IN PUBMED
2003 Rotterdam PCOS Conference
2006 AE-PCOS SOCIETY TASK FORCE
ROTTERDAM 2003 AND AE-PCOS 2006 ARE EXPANSIONS OF NIH 1990
NATIONAL INSTITUTES OF HEALTH

Evidence-based Methodology Workshop on Polycystic Ovary Syndrome
December 3–5, 2012

Workshop Panel Members

Timothy R.B. Johnson, M.D.
Pamela Ouyang, M.B.B.S.
Lorrie Kline Kaplan, CAE
Robert A. Rizza, M.D.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirsutism/HA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ovulatory Dysfunction</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Polycystic ovaries</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NIH 1990</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotterdam 2003</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>AE-PCOS 2006</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
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</tbody>
</table>
HYPERANDROGENISM IN PCOS IS ASSOCIATED WITH RISK OF METABOLIC SYNDROME

Age-adjusted prevalence of MS is higher in all hyperandrogenic phenotypes of PCOS, compared to the non-hyperandrogenic PCOS phenotype and to controls.

PCOS: PROGRESS 1935 TO NOW

- Presentation, Definition & Criteria of PCOS
- Prevalence & Epidemiology of PCOS
- Morbidity of PCOS
- Heritability & Genetics of PCOS
- Pathophysiology of PCOS, including defects in:
  - Insulin action, subacute inflammation, and ovarian follicular development
  - Less so on CNS/Hypothalamic/pituitary/gonadotropin function, adrenal and ovarian steroidogenesis, insulin metabolism, adipose tissue function, dietary, appetite and nutrition
- Treatment of PCOS
  - Ovarian suppression, anti-androgens, insulin sensitizers, ovulation induction, and, less so, life-style modification
- Education & Awareness – Limited
ANDROGEN EXCESS AND PCOS: A MINIBIOGRAPHY

- Androgen Excess (AE) & PCOS are ancient disorders, recorded in the annals of medicine for almost 2500 years
- Recognition of an actual medical cause dates to the 17th century
- Adrenal dysfunction was considered the primary cause of AE in women through the middle of the 20th century
- While sclerocystic ovaries & menstrual dysfunction, and hyperandrogenism & menstrual dysfunction, were recognized separately in the 18th century, it was not until Stein & Leventhal’s report in 1935 that these became intertwined into one syndrome
- 1935 represented a water-shed year due to the isolation and synthesis of T, the recognition that the ovaries could produce T, and the report by Stein & Leventhal
- Today PCOS is recognized as similarly and highly prevalent across a wide variety of races and geographies
THANK YOU