

PCOS: 1935 to Now

Ricardo Azziz, M.D., M.P.H., M.B.A.

Chief Officer of Academic Health & Hospital Affairs

State University of New York (SUNY) System Administration

Research Professor, Health Policy, Management & Behavior

School of Public Health, Univ. at Albany, SUNY

The SUNY logo consists of the letters "SUNY" in a white, sans-serif font, centered within a white circular outline. The logo is positioned in the bottom left corner of the slide.

SUNY

COI

Consulting for Bayer Pharma, Fractyl, Longitude Capital, and Ansh Labs; and on the advisory board for GlobalPET Imaging

headed. The *third* day, was cold in his extremes; grew hot, and sweated; but dy'd this very day, after drinking *mead*.

A very odd case. *Phaethusa* in *Abdera*, the wife of *Pytheus*, who had had a child formerly when she was very young, upon her husband's being banish'd, miss'd her *Menses* a long time; and her joints grew afterwards painful and red. Upon this her body became *manly*, and *hairy* all over; a beard thrust out, and her voice became rough. Every thing was try'd by us that was likely to bring down her *Menses*, but all to no purpose; and not long after she dy'd².

Another of the same. The same thing happen'd in *Thasus* to *Namusias* the wife of *Gorgippus*. All the physicians that I talk'd with were of opinion, that the only hope left was in her *Menses* coming down again as they ought: But this cou'd never be brought about, tho' we try'd every thing; and she dy'd not long after³.

*Of fevers after the sweats*⁴. AFTER the *dog-days* the fevers were attended with

again, and were feverish a long time; a difficult *crisis*, and were not very thir- they ceas'd upon the *seventh* and the *ninth* upon the *eleventh*, the *fourteenth*, the *se-* the *twenty-second*.

had a *fever*, and sweated in the manner d. After taking a *smart purge*, his fever

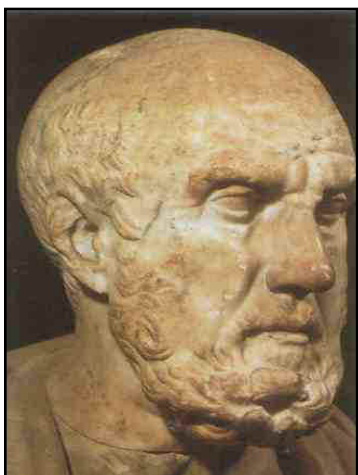
seventh, aph. the fifty-third.

ty-fifth.

ty-sixth, and with this ends the sixth book of

s the seventh book of *Epidemicks*; a book that l cases very imperfectly told, and repeated as h; but some again very well told, as we shall s of it.

was



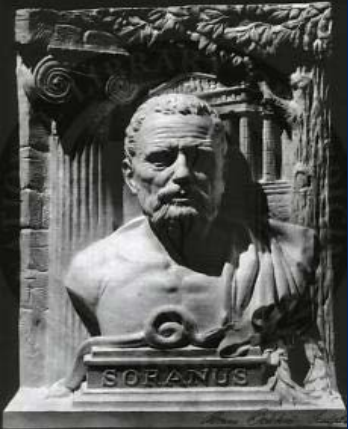
Hippocrates
(c. 460-370 BC)

HYPERANDROGENISM IN ANCIENT MEDICINE

- **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

Hippocrates. *Epidemics* Book VI, aph. 55 & 56. In Francis Clifton: *Hippocrates, upon Air, Water and Situation; upon Epidemical Diseases; and upon Prognosticks, in Acute Cases Especially*, J. Watts Pub., London, 1734

HYPERANDROGENISM IN ANCIENT MEDICINE



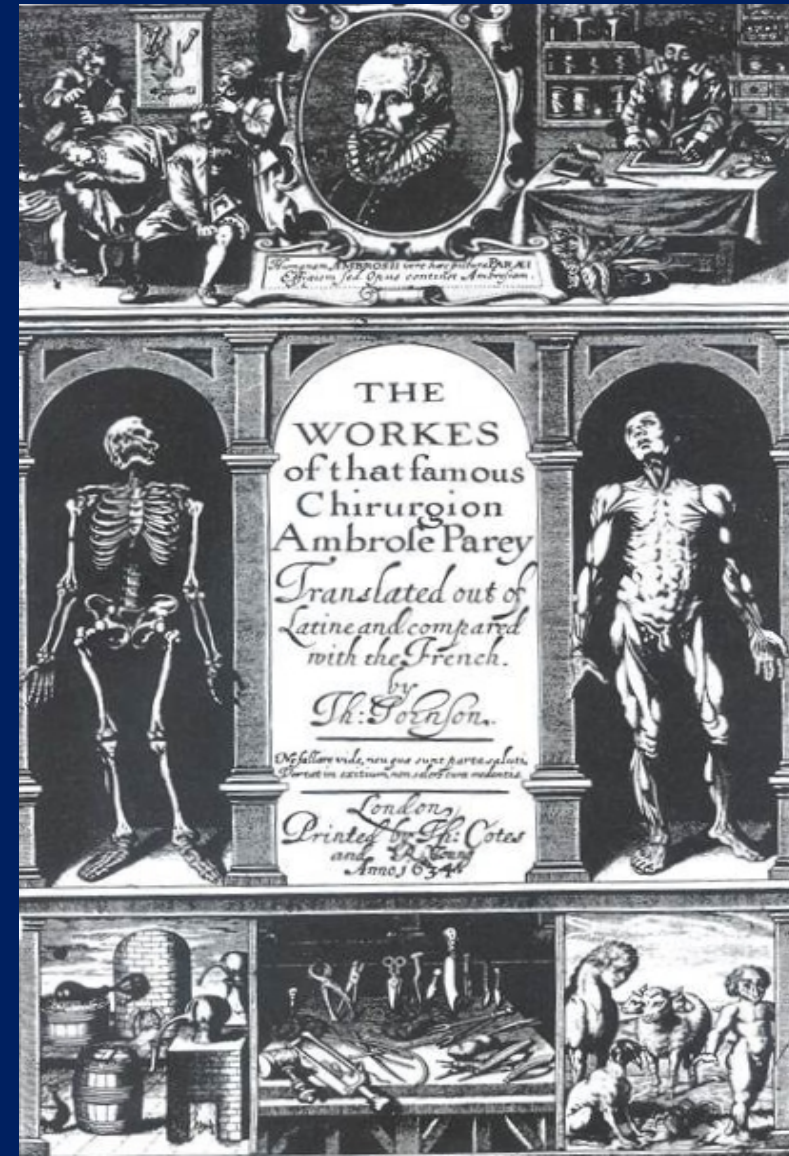
- **Soranus of Ephesus (c. 98-138 AD)**, noted that “[s]ometimes it is also natural not to menstruate at all... It is natural too in persons whose bodies are of a masculine type... we observe that the majority of those not menstruating are rather robust, like mannish and sterile women” (*Gynecology*, 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 caused 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.”*



SCLEROCYSTIC CHANGES, POLYCYSTIC OVARIES, AND THE STEIN-LEVENTHAL SYNDROME



Antonio Vallesneri (1661-1730)

- 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

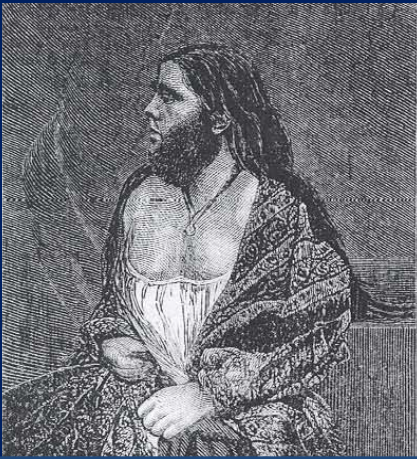
Annie Jones
as a child
("The Infant
Esau") and
as an adult
(c.1880)



PREVAILING THEORIES ON HIRSUTISM IN THE 19TH CENTURY

Hirsutism was thought to represent either:

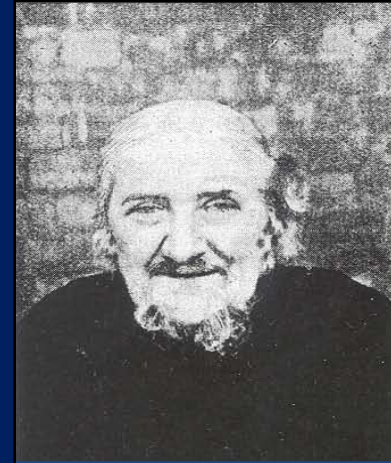
- **A normal problem of aging** (Beclard, 1815)
- **Fright of mother during pregnancy** (Chowne, 1852)
- **Intersex** (Beclard, 1815; Chowne, 1852)
- **A sign of madness or insanity** (Harris-Liston, 1894; Berillon, 1905; Bulkley & Janeway, 1908; Laignel-Lavastine, 1921)



Case reported by W.D. Chowne, 1852



Case reported by Harris-Liston, 1894

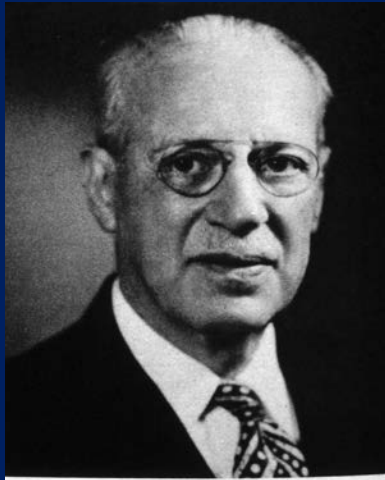


Case reported by Harris-Liston, 1894

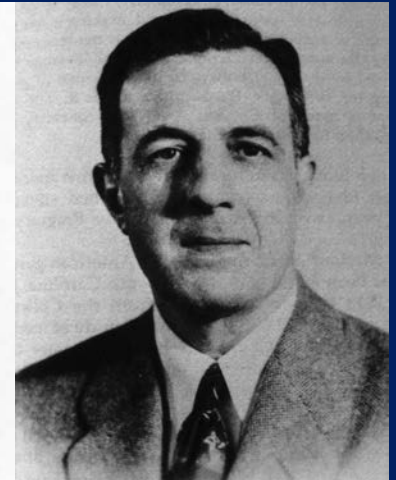
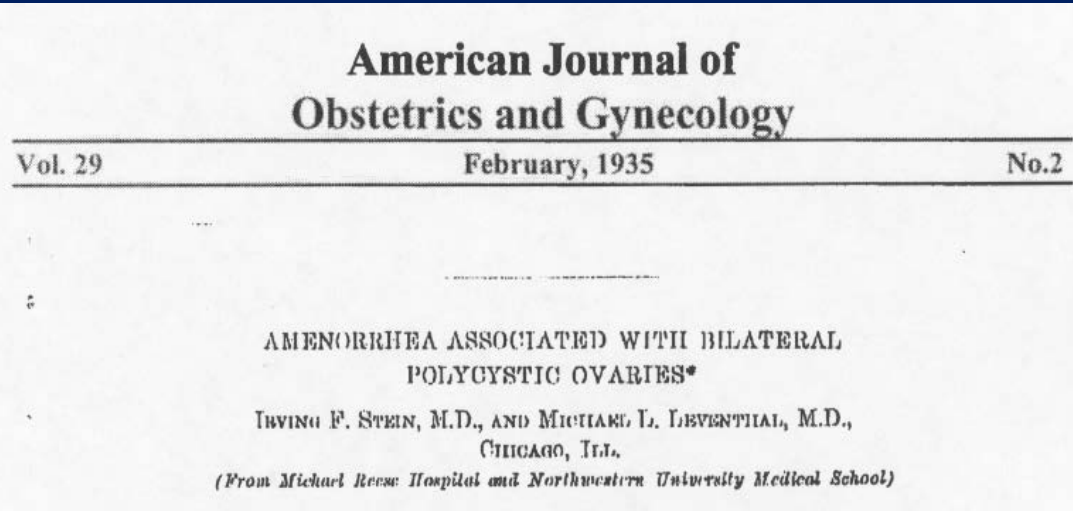


Paul-Marie Maxime Laignel-Lavastine (1875-1953)

STEIN-LEVENTHAL SYNDROME



Irving Freiler Stein (1887-1976).

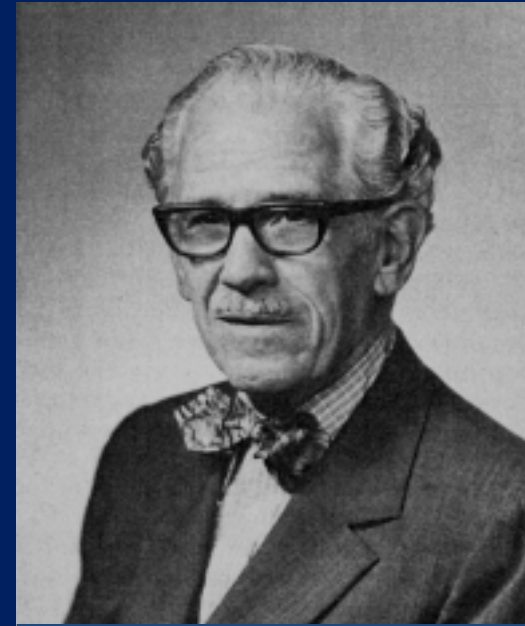


Michael Leo Leventhal (1901-1971)

- 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

THE OVARIES AS A SOURCE OF ANDROGENS

- 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



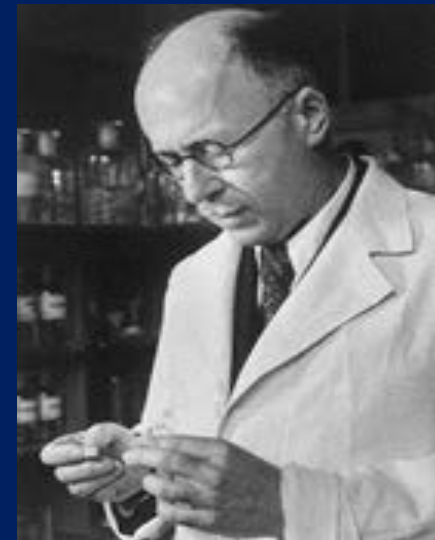
Robert Towner Hill, Ph.D.,
D. Sc.

ISOLATION OF TESTOSTERONE

- **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



Ernst Laqueur
(1880-1947)



Leopold Ruzicka
(1887-1976)



**Adolf Frederick
Johann Butenandt**
(1903-1995)

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

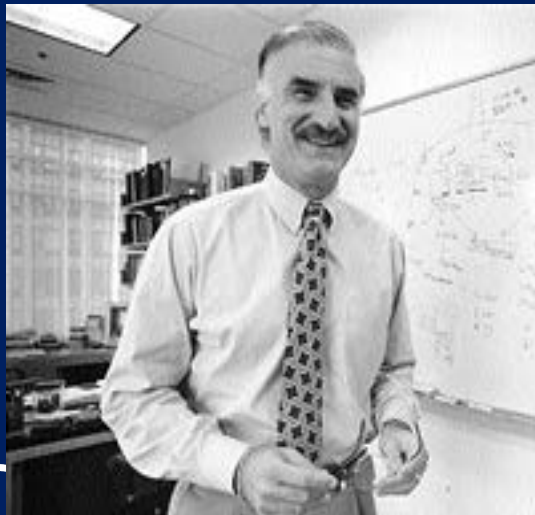
- In 1947, Kierland reported on three patients with '*benign juvenile acanthosis nigricans*' who presented with amenorrhea, hirsutism, obesity and, in the two who were surgically explored, normal adrenals



Kierland RR. *Acanthosis nigricans: An analysis of data in twenty-two cases and a study of its frequency in necropsy material.* J Invest Dermatol 9:299-305, 1947.

SYNDROMES OF INSULIN RESISTANCE AND ACANTHOSIS NIGRICANS

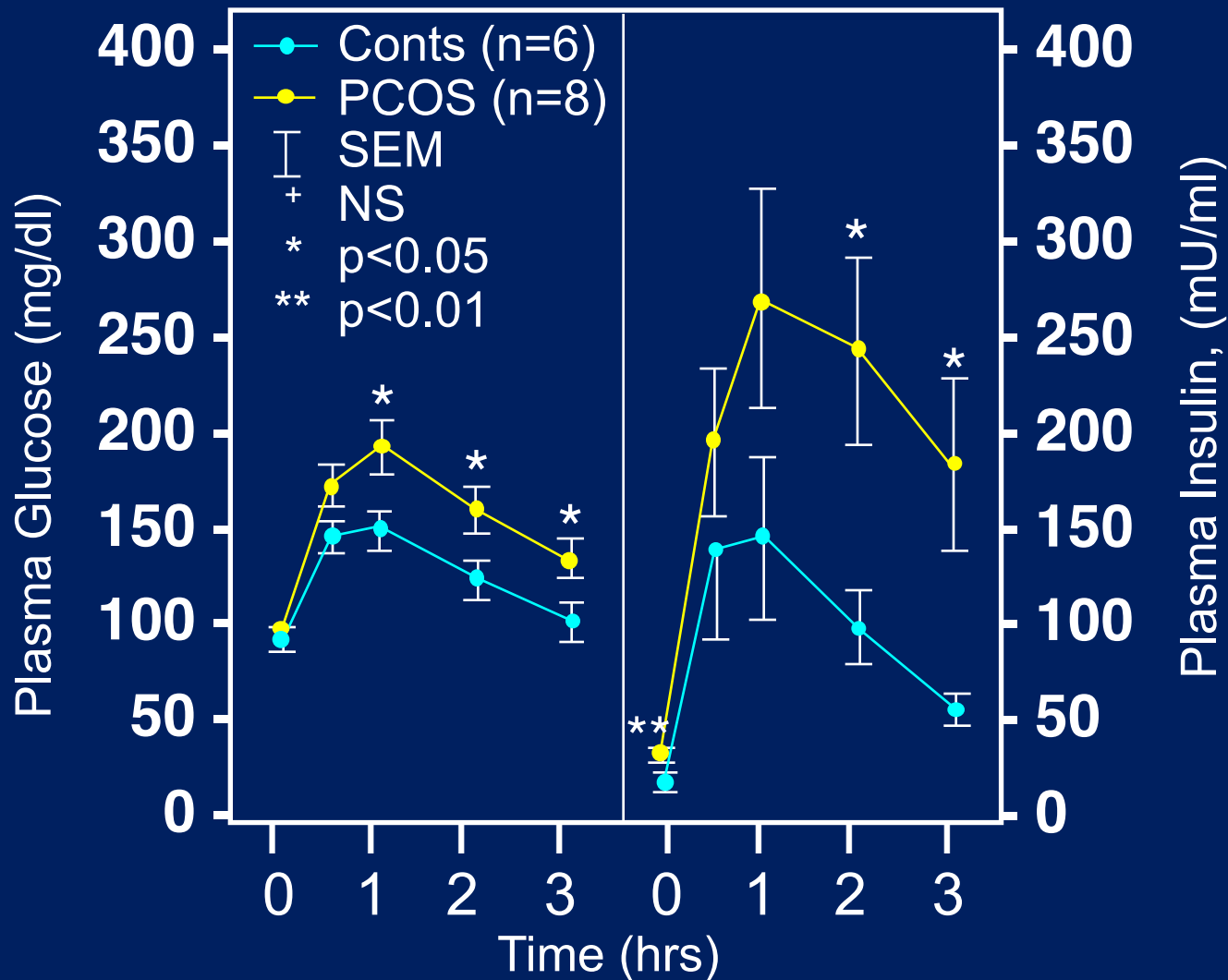
- **1976 - C. Ronald Kahn:** Reported on six patients with acanthosis nigricans, variable degrees of glucose intolerance, hyperinsulinemia, and marked resistance to exogenous insulin.



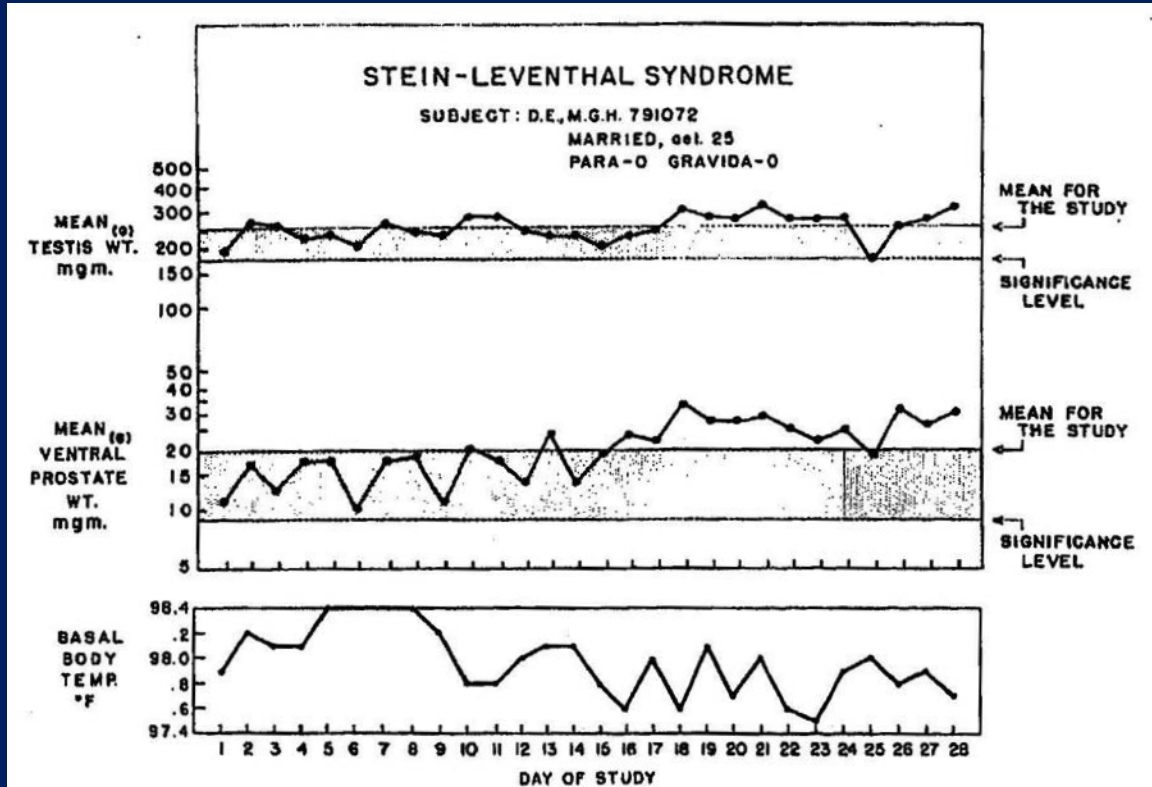
- **Suggested the term Type A for the clinical syndrome of virilization in younger women with an apparent defect of the insulin receptor.**

Kahn et al. N Engl J Med, 1976; 294:739

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



CHARACTERIZING PCOS



Janet Ward McArthur
(1914-2006)

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

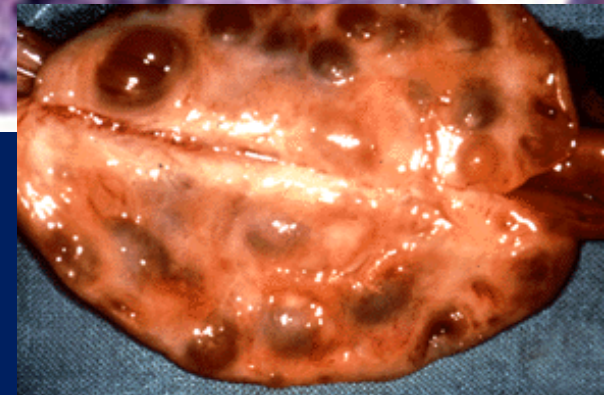
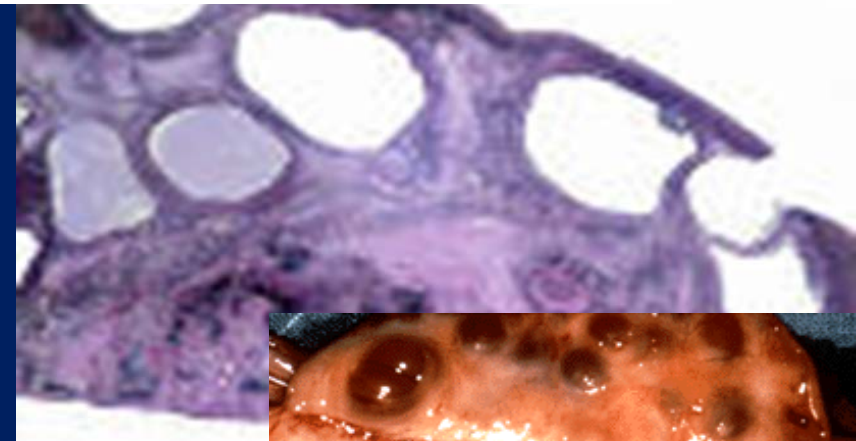
The Polycystic Ovary. I. Clinical and Histologic Features

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

The Department of Endocrinology, Southwest Foundation for Research and Education, San Antonio, Texas, and the Department of Anatomy, Medical Center, Indiana University, Indianapolis, Indiana



Joseph W. Goldzieher



Goldzieher JW, Green JA. The polycystic ovary. I. Clinical and histologic features. *J Clin Endocrinol Metab.* 1962;22:325-38.

CHARACTERIZING PCOS

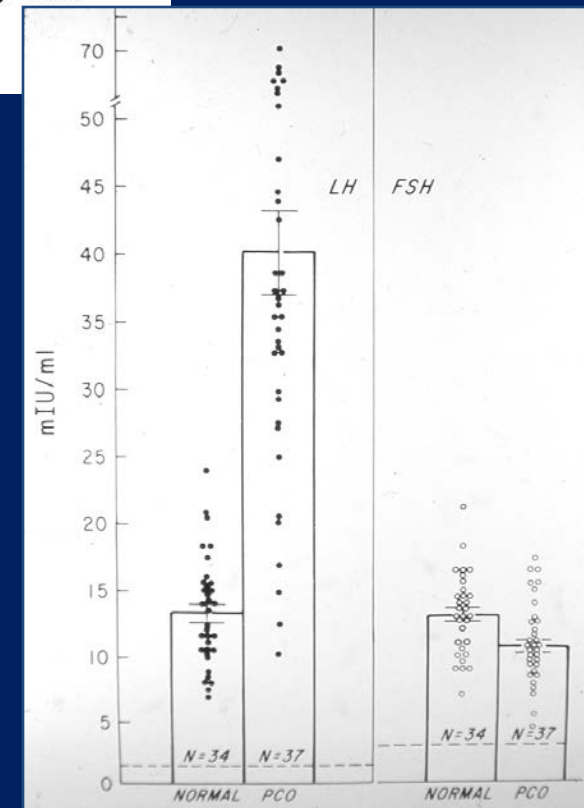
Inappropriate Secretion of Follicle-Stimulating Hormone and Luteinizing Hormone in Polycystic Ovarian Disease

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

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



Samuel SC Yen
(1927-2006)



Society for Gynecologic Investigation

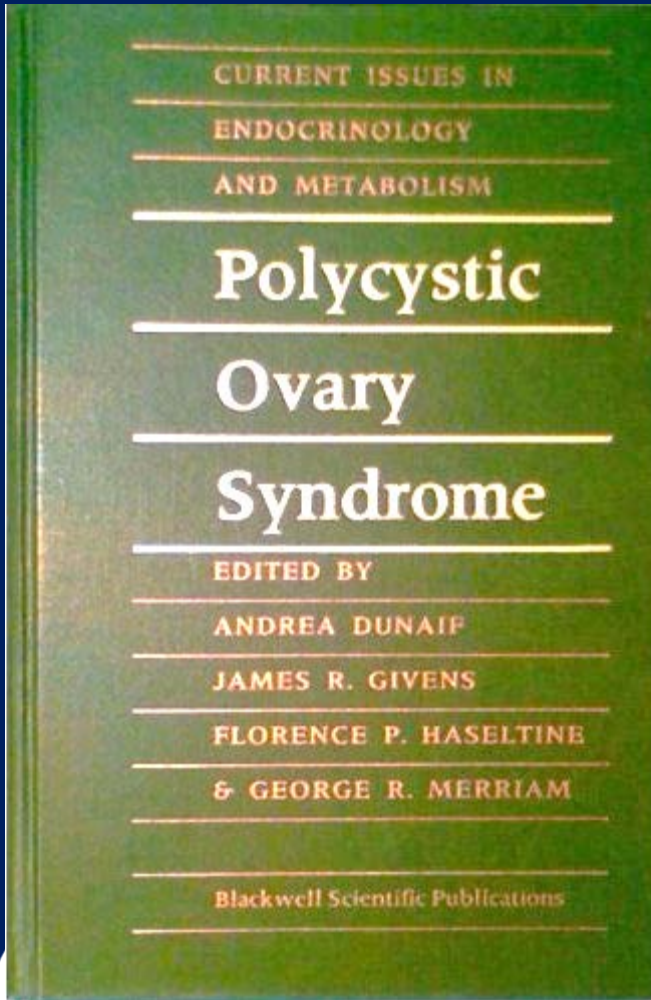
March 17-20, 1983

- *Biochemical and pathophysiological findings in women with acanthosis nigricans and androgen excess*
 - Dunaif A, Hoffman A, Scully RE, Flier JS, Levy L, Longcope C, Crowley WF
- *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

1990 NIH – NICHD PCOS Conference



1990 NIH – NICHD PCOS Conference



Polycystic Ovary Syndrome is to endocrinologists what pornography is to judges.

We can't define it but we know it when we see it!

SUNY

1990 NIH – NICHD PCOS Conference

Percent of Participants Agreeing

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

Zawadzki & Dunaif In: Dunaif A, Givens JR, Haseltine F, Merriam G eds. Polycystic ovary syndrome. Boston: Blackwell Scientific; 377-384, 1992

PREVALENCE OF PCOS IN UNSELECTED WHITE WESTERN- EUROPEAN SUBJECTS, USING THE 1990 NIH CRITERIA

Reference	Location	% PCOS in population	Mean BMI of population (kg/M ²)	% Obesity in country*
Knochenhauer et al, 1998	Birmingham, AL	4.7	24.9	32.2%
Diamanti-Kandarakis et al, 1999	Lesbos, Greece	6.8	26.7	21.9%
Michelmores et al, 1999	Oxford, UK	8.0	23.0	23.0%
Asuncion et al, 2000	Madrid, Spain	6.5	23.8	13.1%

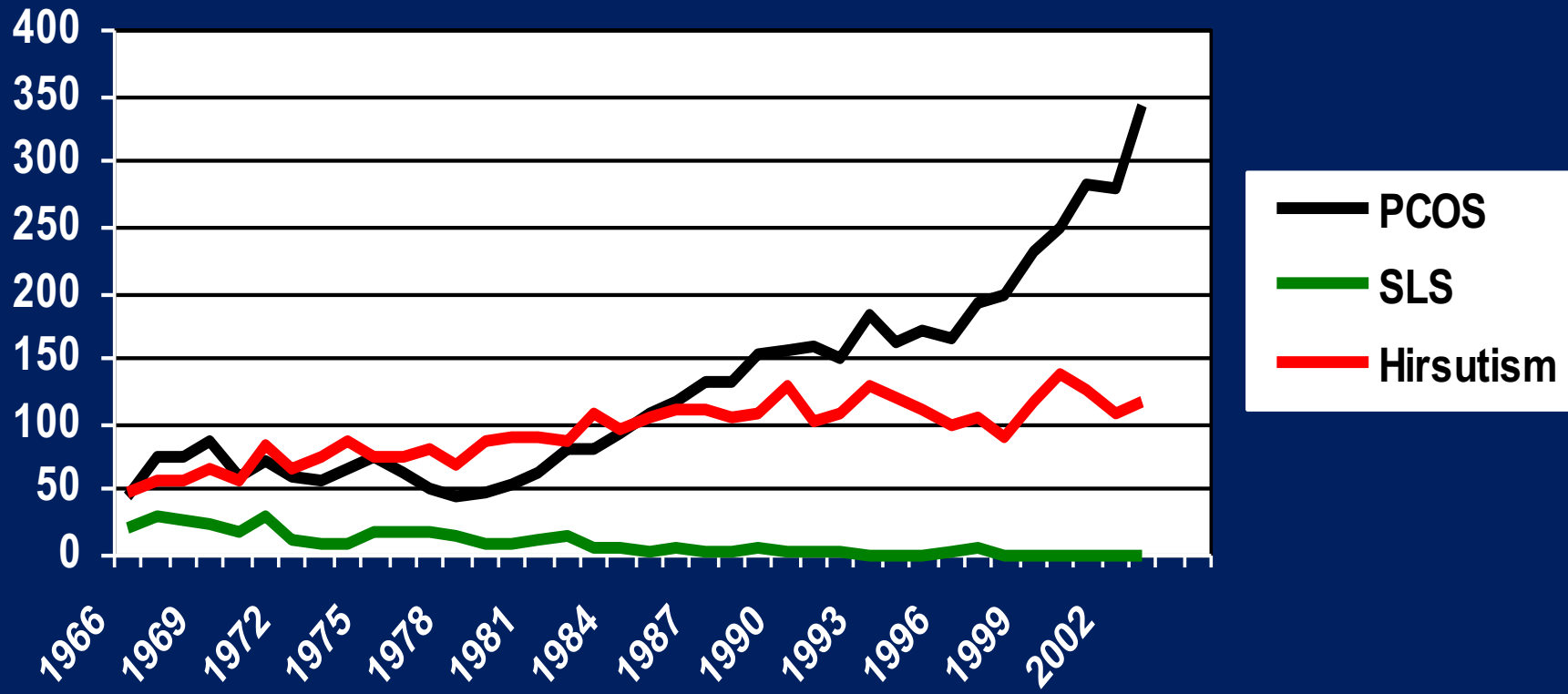
PREVALENCE STUDIES OF PCOS AROUND THE GLOBE-2015



First AES* meeting, Philadelphia, PA, 2003



NUMBER OF PUBLICATIONS ON POLYCYSTIC OVARIES, STEIN-LEVENTHAL SYNDROME (SLS), AND HIRSUTISM FROM 1966-2003, IN PUBMED



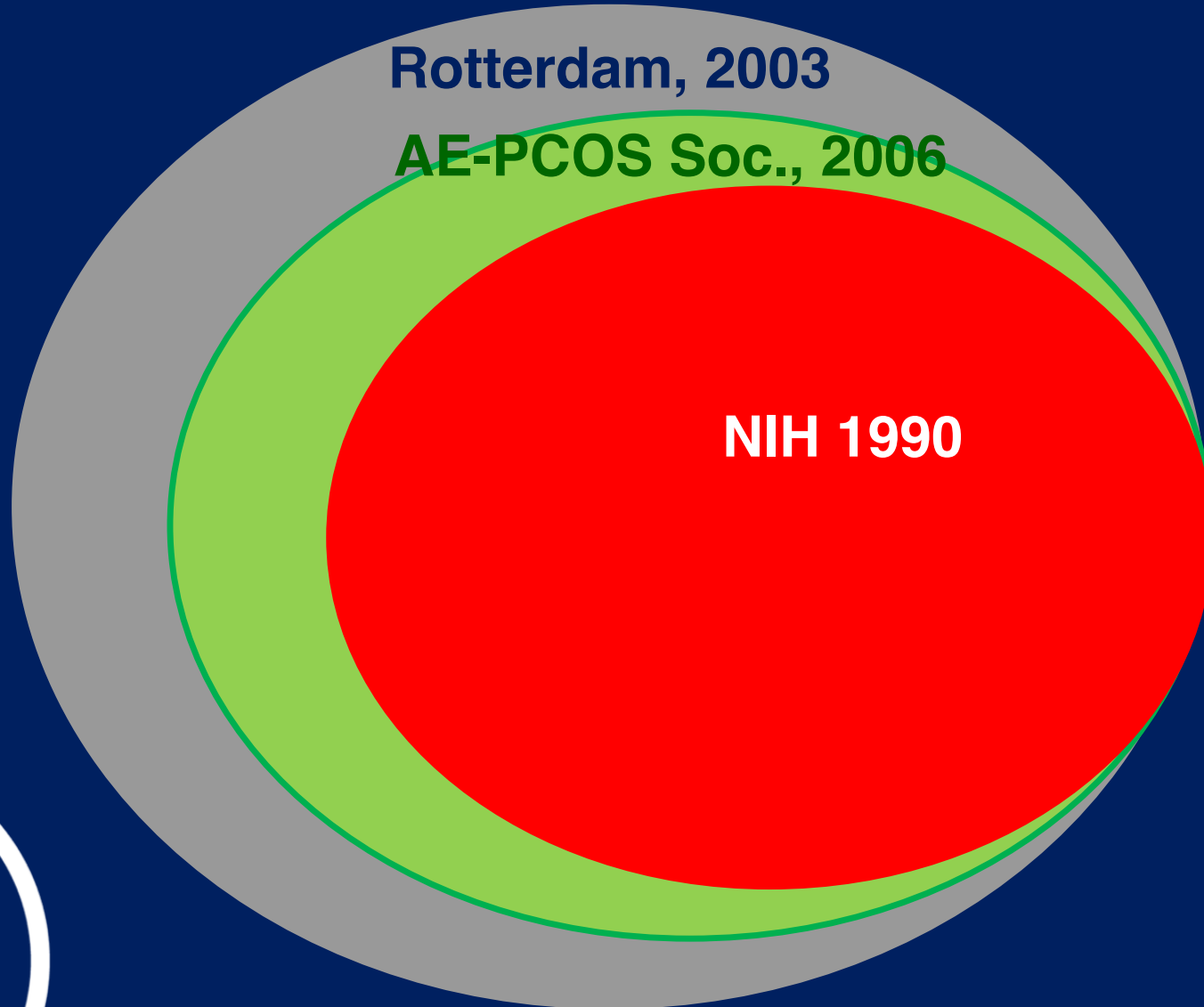
2003 Rotterdam PCOS Conference



2006 AE-PCOS SOCIETY TASK FORCE



ROTTERDAM 2003 AND AE-PCOS 2006 ARE EXPANSIONS OF NIH 1990



SUNY



NATIONAL INSTITUTES OF HEALTH

Evidence-based Methodology Workshop on Polycystic Ovary Syndrome

December 3–5, 2012



Timothy R.B. Johnson, M.D.



Pamela Ouyang, M.B.B.S.



Lorrie Kline Kaplan, CAE



Robert A. Rizza, M.D.

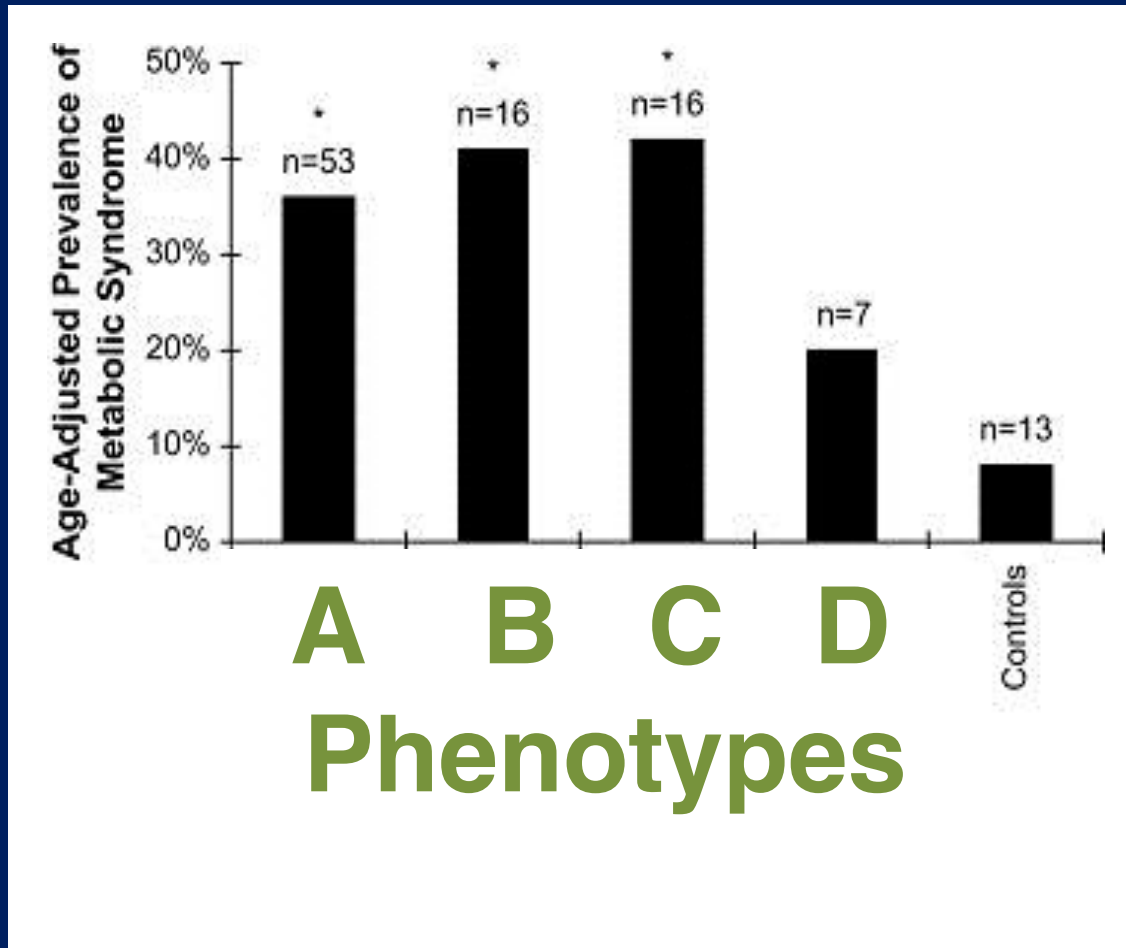
Workshop Panel Members



COMPARING THE PHENOTYPES OF PCOS BY NIH 1990, ROTTERDAM 2003, AND AE-PCOS 2006

	Phenotypes			
<i>Characteristics</i>	<i>A</i>	<i>B</i>	<i>C</i>	<i>D</i>
Hirsutism/HA	√	√	√	
Ovulatory Dysfunction	√	√		√
Polycystic ovaries	√		√	√
NIH 1990	√	√		
Rotterdam 2003	√	√	√	√
AE-PCOS 2006	√	√	√	

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 1^{ary} 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

