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A Brief History of Androgen Excess

Ricardo Azziz

SUMMARY

Male-like hair growth and masculinization of women and the ambiguity of genders has fascinated mankind for millennia, frequently appearing in mythology and the arts. The earliest reports of androgen excess, beginning 400 years BC, focused on the appearance of male-like hair growth and features in women, often accompanied by menstrual cessation. The first etiologies identified as a cause of androgenization in the female were adrenal disorders, primarily adrenocortical neoplasms, but also eventually adrenal hyperplasia. The first report of a patient with nonclassic adrenal hyperplasia (NCAH) was made in 1957. The Achard–Thiers syndrome, which was originally reported in 1921 and was felt to primarily affect postmenopausal women, included the development of diabetes mellitus, hirsutism, and menstrual irregularity or amenorrhea in conjunction with adrenocortical disease. Androgen production by the ovary was not recognized until the early 1900s, with the first case of a patient with glucose intolerance, hirsutism, and ovarian pathology reported by Tuffier in 1914. As early as the mid-18th century, the presence of sclerocystic or multicystic ovaries was recognized, although this pathology was felt to be primarily associated with pelvic pain and/or menorrhagia. It was not until the seminal report of Drs. Stein and Leventhal of 1935 that the association of polycystic ovaries and amenorrhea, and possibly obesity and/or hirsutism, was noted. Subsequent investigations have elucidated the ovarian source of the androgens the gonadotropic abnormalities, the insulin resistance, and the high prevalence of the disorder, currently known as the polycystic ovary syndrome (PCOS). This syndrome was initially treated by ovarian wedge resection, but subsequent ovulatory therapies, including clomiphene citrate, menopausal gonadotropins, and most recently insulin sensitizers, have replaced this surgery as the treatment of choice for fertility improvement in PCOS. Notwithstanding, laparoscopic ovarian drilling retains a place in our current therapeutic armamentarium for these patients.

Key Words: History; hirsutism; adrenal hyperplasia; polycystic ovary syndrome; androgen-secreting neoplasms; Stein and Leventhal; Achard and Thiers.

1. INTRODUCTION

The earliest reports of androgen excess, beginning around 400 BC, focused on the appearance of male-like hair growth and features in women, often accompanied by menstrual cessation. Two other pathologies were then recognized, beginning in the late 17th and early 18th centuries, including adrenal pathologies and sclerocystic ovaries. These seemingly separate and disparate observations only begin to converge in the 20th century into the disorders we recognize today. The burgeoning research interest in androgen excess disorders can be indirectly determined from a survey of PubMed, the database managed by the National Center for Biotechnology Information, for articles published in scientific journals relating to the most common androgen excess disorders (Fig. 1). For example, in 1980 there were 69 articles published referencing "polycystic ovary syndrome" or "Stein–Leventhal syndrome"; in 1990 this number had more than doubled to 169, and in the year 2000 more than 241 articles were published on the subject.

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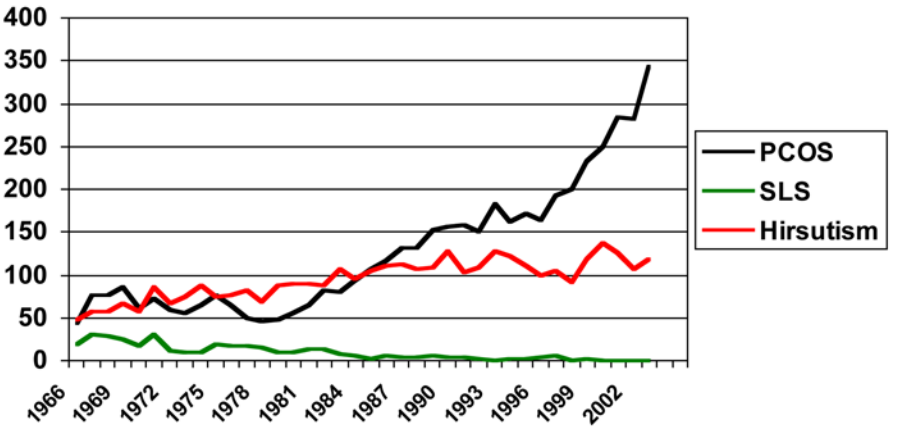

Fig. 1. Number of publications on polycystic ovaries and polycystic ovary syndrome (PCOS), Stein–Leventhal Syndrome (SLS), and hirsutism from 1966 to 2003 in PubMed.

In this chapter we briefly review the development of the study and treatment of androgen excess disorders with a historical perspective. This will not only illuminate how medical knowledge develops, but may assist us in placing this disorder, and in particular its definition, in perspective. In general, I will limit myself to studies published before 1980.

2. BACKGROUND

2.1. Hyperandrogenism in Mythology and the Arts

Male-like hair growth and masculinization of women, and the ambiguity of genders, has fascinated mankind for millennia. Hapi (or Hapy), god of the Nile, was described as an obese bearded man with the breasts of a woman *(1)*. Pharaoh Maatkare Hatshepsut of Egypt (1473–1458 BC), one of only two female pharaohs, was reported to be hirsute, although it would appear that she actually wore a false beard and dressed like a man primarily to emphasize her role as pharaoh and ruler. The Venus Barbata, the bearded cross-dressing Venus, was called on to repel unwanted husbands and suitors. A fresco in Pompei (painted sometime before the 97 AD eruption of Mount Vesuvius) depicts the toilet of Hermaphrodite with what appears to be a bearded woman assisting in the event *(2)*, although some investigators believe that it is a man dressed in eastern style (Dr. John Clarke, Professor of Art History, University of Texas at Austin, personal communication). The early medieval legend of St. Willegefortis (i.e., *virgo forte*, or strong virgin), or Uncumber, is described as growing a beard to ward off an unwanted suitor in order to remain chaste for God (and for which her father rewarded her by having her crucified) *(3)*. The fable about a bearded female pope, who later bore the name of Johanna (Joan), was first noted in the middle of the thirteenth century *(4)*.

Artists of all times have been fascinated by the hirsute woman. The most famous of these portraits is that of Magdalena Ventura de Los Abruzos, "La Mujer Barbuda" (1631, currently in the Hospital de Tavera, Toledo, Spain), by the Italian painter José (Jusepe) de Ribera. This portrait depicts Magdalena, who had arrived in Naples at 52 years of age from Acumulo in the region of Los Abruzos, alongside her second husband and a nursing child in arms. Apparently, after three miscarriages at the age of 37, she began to experience increasing hair. The Duke of Alcalá, then Viceroy of Naples, was so taken by her case that he commissioned Ribera to paint the woman and have her history recorded in the painting. Other important portraits include that of Brigida del Rio "La Barbuda de Peñaranda" (1590, currently in the museum El Prado), by the Spanish painter Juan Sánchez Cotán (ca. 1560–1627); Eugenia Martinez Vallejo "La Monstrua' Vestida," by Spanish painter J. Carreño De Miranda (1614–1685, currently in the museum El Prado); the portrait of Rosina Margerita Mullerin or Rosine-

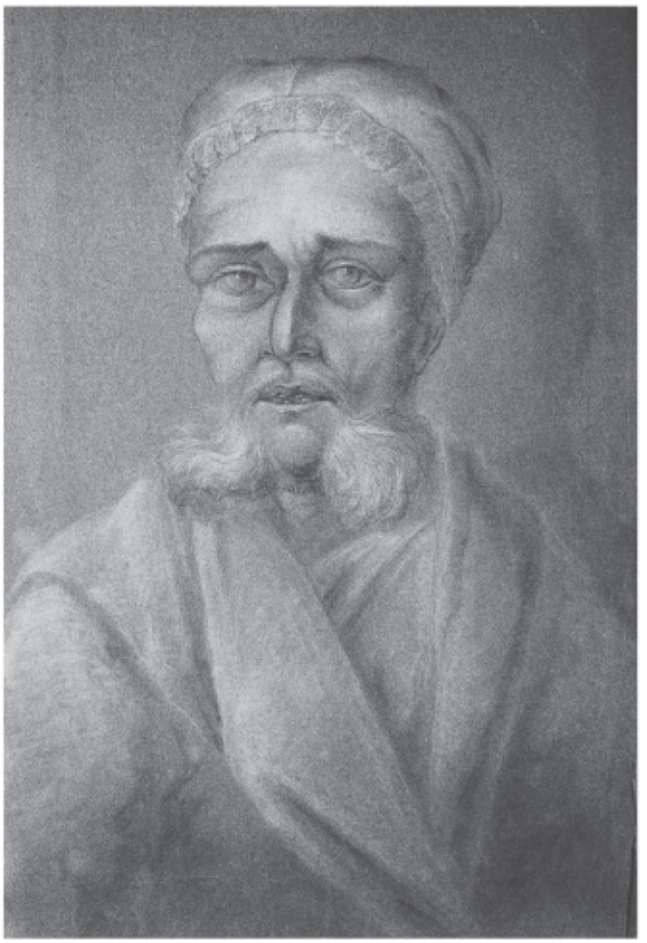

Fig. 2. Portrait of Rosina Margerita Mullerin (or Rosine-Marguerite Müller), daughter of a servant to the court of the Saxonian elector Johann-Georg III, who died in 1732 (chalk, unknown artist, currently in the Kupferstich-Kabinett, Dresden, reproduced with permission).

Marguerite Müller (Fig. 2); Margret Halsebner of Basel or "The Woman with Two Beards" (or "Portrait of Old Woman With a Beard"), by Willem Key (~1515–1568; stolen in 1972 from the Suermondt Museum, Aachen; copy made by Anthonis Mor van Dashorst, ~1517–1577, currently in the Alte Pinakothek, Munich) (Fig. 3); and that of Helene Antonia of Liege (Belgium), depicted in an engraving by Johannes Loselius (~late 16th century).

Shakespeare referred to hirsute women in Macbeth (c.1607) when he wrote about three sisters:

> You should be women and yet
> Your beards forbid me
> To interpret that you are so

In "Don Quixote" (1615) Cervantes tells the tale of the bearded Countess Trifaldi (La Dolorosa, or the Distressed One), where the giant Malabruno, in revenge for the death of his first cousin, the Queen Maguncia, casts a spell on the Countess Trifaldi and her friends, making their faces hairy and bearded. In response, the lady Dolorosa laments *(5)*: ". . . where, I ask, can a duenna [female chaperon] with a beard go to? What father or mother will feel pity for her? Who will help her? For, if even

Fig. 3. "Old Woman with a Beard," by Anthonis Mor van Dashorst (c.1517–1577; currently in the Alte Pinakothek, Munich, reproduced with permission), copy of a portrait of Margret Halsebner of Basel, or "The Woman with Two Beards," by Willem Key (c.1515–1568; stolen in 1972 from the Suermondt Museum, Aachen).

when she has a smooth skin, and a face tortured by a thousand kinds of washes and cosmetics, she can hardly get anybody to love her, what will she do when she shows a countenance turned into a thicket?"

Hyperandrogenized women have frequently been held as a curiosity for all to view. Caufield recounts the story told by one D. George Sagari describing the case of the 22-year-old Augustina Barbara, daughter of Balthazer Ursler (or Ulster), whose whole body and face was covered by yellowish hair, including "a thick beard that reached her girdle"; he noted that her husband had married her ". . . merely to make a shew of her, for which purpose he traveled into various countries . . ." *(6)*. The famous Julia Pastrana, the "Nondescript" or Bearded and Hairy Lady, a 23-year-old of Mexican origin, attracted throngs of gawkers during her tour of Britain in 1857 *(7)*. However, it is likely that neither of these cases represented women solely with hyperandrogenism, as they appeared to suffer far more extensive hair growth and, at least in the case of Pastrana, facial distortion *(8)*.

Between 1840 and 1940, freak museums, circus sideshows, and carnivals were popular entertainment and frequently exhibited famous bearded ladies such as Annie Jones, Lady Olga, Clementine Delait, Madame Devere, and Princess Gracie *(9,10)*. By the early part of the century, entertaining and extensive descriptions of a multitude of hirsute or bearded women and their history, true or invented, had been published *(11,12)*. Even now, our fascination with bearded women continues. A contemporary news article presents the biography of Jennifer Miller, circus artist, performance artist, juggler

and clown, and founder and director of Circus Amok *(13)*. Ms. Miller, by her mid-20s, had grown a full beard, although she was not sure what made it grow. Once, she said, "a doctor told me I had high progesterone."

2.2. Hyperandrogenism in Ancient Medicine

As early as the fifth century BC, Hippocrates (~460–~370 BC) described two separate cases of women who become generally hairy with beards and whose bodies assumed a masculine appearance; both became amenorrheic and died at an early age *(14)*:

> *Phaethufa* in *Abdera*, the wife of *Pytheus*, who had a child formerly when she was very young, upon her husband's being banfh'd, iffs'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 to no purpose; and not long after she dy'd.
>
> The same thing happn'd in *Thasus* to *Namufias* the wife of *Gorgippus*. All physicians that I talk'd with were of the 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 after.

Maimonides (1135–1204) noted that *(15)*:

> Just as there are men whose nature resembles the nature of women, and their skin is fair and soft, similar to the body of a woman, so too 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*)

The famous French surgeon and obstetrician Amboise Paré (1510–1590), in his "Concerning the Generation of Man" *(16)*, described affected women, noting:

> 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.

Notably, these early physicians clearly noted the association of menstrual irregularity and the development of hirsutism and masculine features. Clinical interest in the hirsutism continued in the ensuing centuries, as evidenced by the proliferation of portraits (*see* Figs. 2–4) recording the appearance and lives of these unfortunate women. Of note, during the late 19th century and early part of the 20th century, hirsutism in women was often ascribed to a number of conditions, including mental disorders *(12,17,18)* or hermaphroditsim *(19–21)*.

2.3. Adrenocortical Disorders

The first case describing androgenization of a female related to an adrenal disorder, most likely an adrenocortical carcinoma, appears to be that reported by Henry Sampson in 1697 *(22)*:

> *Hannah Taylor* was born in *Crouched Fryars June* 12 1682. She was till three Years old very sickly, lean and not able to go alone; but about *Bartholomewtide*, 1685. she began to grow strong and fat, which increased till the time of her Death: She was also a very forward Child of Understanding, had her *Pubes* grown thick and long, as also Hair under her Arm-pits, and Downyness upon her Chin, unusual with those of her Sex, except in some aged Persons. . . . She had a Face as big and broad as any fat grown Woman of 20 Years . . . the left Kidney (where was the seat of her Misery) exceeding large, and double the bigness of that on the right side. . . . The Testicles* were large, but smooth and white, without protuberances or shew of eggs.

The case appears to be also the earliest illustration of the effect that adrenal androgens may have on the ovaries. In 1905, Bulloch and Sequiera reported on an 11-year-old girl with almost identical

*Following Galen, the ovaries were termed female testis or testicles.

findings to that described by Sampson, which they diagnosed as having suffered from a left suprarenal carcinoma *(23)*. In addition to reviewing all similar prior cases, they make the then-novel observation that the "cortex of the suprarenal gland is probably connected in some way with the growth of the body and the development of puberty and sexual maturity."

De Crecchio in 1865 described the case of Giuseppe Marzo, who lived like a man and upon his death was found to have female reproductive organs and massively enlarged suprarenal (adrenal) capsules, essentially being the first report of virilizing congenital adrenal hyperplasia *(24)*. The Danish pathologist Johannes Andreas Grib Fibiger, recipient of the 1926 Nobel Prize for Physiology or Medicine, went on to describe a similar case *(25)*, followed by Debre and Semelaigne *(26)* and von Gierke *(27)*, such that the adrenogenital or adrenal virilizing syndrome became known as the Fibiger–Debré–von Gierke syndrome, a term that was in use until the early 1960s. Because previous treatment with various analogs of androgens (including 17-ethyl-testosterone, 17-vinyl-testosterone, 17-methylandrostenediol, and 17-methylandrostanediol) in an effort to block the effect of excess androgens in these patients had been unsuccessful, Lawson Wilkins and colleagues went on to describe the first successful treatment of a patient with congenital adrenal hyperplasia using intramuscular injections of cortisone crystals in aqueous solutions administered every 6 hours for 15 days in 1950 *(28)*, which was confirmed the following year *(29,30)*. Subsequent analysis of urinary steroids suggested that the likely biosynthetic defect was 21-hydroxylase deficiency *(31,32)*. Cloning of the active 21-hydroxylase gene (CYP21B or CYP21) and an associated pseudogene (CYP21B or CYP21P) confirmed the genetic etiology of the syndrome as a single gene mutation *(33)*.

The first report of a patient with nonclassic (also called nonclassical, late-onset, adult-onset, attenuated, acquired, cryptic, mild, partial, or postmenarchial) adrenal hyperplasia was made by Decourt et al in 1957 *(34)*; the following year these investigators reported on six cases and suggested that the disorder was the result of defective 21-hydroxylation *(35)*. The diagnosis of this disorder by adrenocorticotropic hormone stimulation test was suggested in 1979 by various investigators *(36–38)*. However, not until the Val 281Leu mutation was reported in nine patients with similar human leukocyte antigen (HLA) haplotypes (i.e., HLA-B14, DR1), establishing the molecular genetic basis of the disorder *(39)*, was NCAH confirmed as its own distinct entity.

2.4. Insulin Resistance, Glucose Intolerance, and Hyperandrogenism

At a session of the Société Medicale des Hôspitaux de Paris on July 19, 1921, Professor Emile Charles Achard, with the assistance of Dr. Joseph Thiers, presented the case of a 71-year-old woman who presented with poor health, incontinence, facial hair, and a history of glycosuria *(40)*. Although this is considered to be the first report documenting an association between glucose intolerance and hyperandrogenism, we should note that a number of other investigators had previously made this observation (*see* refs. *18* and *40*). Second, the patient described was not glycosuric at the time of her exam and remained so despite the ingestion of 100 g of glucose. Finally, the investigators noted on autopsy normal ovaries, evidence of chronic pancreatic, and hyperplastic and pigmented adrenals and ascribed the cause of the disorder, probably correctly, to the adrenal. The Achard–Thiers syndrome, as the disorder later became known, was felt to primarily affect postmenopausal women and included the development of diabetes mellitus, hirsutism, menstrual irregularity or amenorrhea, accompanied by suprarenal (adrenocortical) disease *(41–43)*. Hence, this syndrome does not refer to patients with insulin resistance and ovarian hyperandrogenism, but primarily to patients with adrenocortical pathology, notably carcinoma, glucose intolerance, and virilization. The hypercortisolism present may account for the high prevalence of psychiatric abnormalities observed in hirsute and amenorrheic women diagnosed at the time *(18)*.

In fact, the first case of a patient with glucose intolerance (i.e., glycosuria), hirsutism, and ovarian pathology appears to have been reported by Tuffier in 1914 *(44)*. This physician described a woman with virilization, glycosuria, bilateral adrenal hypertrophy, and a right ovarian mass the size of a walnut, possibly a luteoma; the glycosuria resolved after removal of the ovarian tumor. In 1947

Kierland reported on three patients with acanthosis nigricans who also presented with amenorrhea, hirsutism, obesity, and, in the two who were explored, normal adrenals *(45)*. Subsequent investigators continued to report on the association of metabolic abnormalities, hirsutism, and menstrual dysfunction, acanthosis nigricans, and frequently ovarian stromal hyperthecosis, in the absence of adrenocortical pathology.

In 1976 Kahn and colleagues described six patients with acanthosis nigricans and variable degrees of glucose intolerance, hyperinsulinemia, and marked resistance to exogenous insulin *(46)*. After the study, they divided these women into two unique clinical syndromes: type A, a syndrome in younger females with signs of virilization or accelerated growth, in whom the receptor defect may be primary, and type B, a syndrome in older females with signs of an immunological disease, in whom circulating antibodies to the insulin receptor are found. Women with the type A insulin resistance syndrome were later referred to as suffering from the hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN) syndrome, a term still used today *(47)*.

2.5. The Stein–Leventhal Syndrome

As described earlier, Sampson, in his description of the autopsy findings of Hannah Taylor, observed that, in addition to the suprarenal tumor, the ovaries were large, smooth, white, and without protuberances, like eggs *(22)*. In 1721 Antonio Vallisneri (1661–1730) described the case of a young married infertile peasant woman, moderately obese, who had two larger than normal ovaries that were smooth and shiny *(48)*:

> But let us move on to the ovaries of the woman. On the day of February 3, a young married farmwoman who was infertile fell from a tree and died soon thereafter. I wanted to see the reason for this sterility, since the husband was also young and vigorous, and she was moderately plump, of good color, and well built.
>
> I found the two ovaries to be larger than ordinary: the left one was larger than a dove's egg, with a slightly dark color and more or less round, the right one was a little smaller, more white, and considerably crushed; and both of them were a tiny bit tuberculous, smooth, and shiny, almost as if from a paint that had been spread. Once the first tunica was removed, which was very fibrous and almost completely fleshy on the left, a blister was uncovered that was the size of a hazelnut with membranes that were very swollen and dense, covered and packed full of a material the color of soot, cloudy, nauseating, rather dense, but considerably liquid. On the left side, there were another two similar blisters that appeared to be only half as big which were also filled with the same material, as well as many others of various sizes although all of them were smaller, all dirty, stained, and likewise blackish. A healthy lymphatic blister does not appear this way, as it is usually pure and filled with transparent lymph.
>
> Between these, the usual fine membranes, fibers, and blood vessels could be distinguished, but they were nearly empty, and nothing else.

In 1844 Chereau *(49)* and Rokitansky *(50)* both described sclerocystic ovaries, which subsequent observers referred to as microcystic, cystic degeneration, polymicrocystic, cystic oophoritis, or hydrops folliculi, among other terms. Bulius and Kretschmar provided an early description of hyperthecosis *(51)*. Von Kahlden in 1902 *(52)* and Fogue and Massabuau in 1910 *(53–55)* published excellent in-depth reviews on the pathology and known clinical implications of these ovaries.

Multicystic ovaries were initially observed to be associated with menorrhagia, pelvic pain, and emotional disturbances. In 1872 Battey reported performing a bilateral oophorectomy in a 30-year-old patient who had intense pain during her menstrual periods, which had resulted in morphine addiction and epileptiform convulsions, among other complaints *(56)*. Although generally uninterested in the ovarian pathology of the hundreds of ovaries he subsequently removed as cure for similar ailments, Battey noted that while most ovaries were normal in appearance, some demonstrated cystic degeneration or sclerosis *(57)*. Encouraging this practice, Lawson Tait in 1879 affirmed the need for castration for the treatment of symptomatic cystic degeneration of the ovaries *(58)*. However, more conservative procedures, such as partial resection, were soon proposed *(59)*. Even then, critical voices

Fig. 4. (Left) Irving Freiler Stein (1887–1976); (right) Michael Leo Leventhal (1901–1971). (Reproduced with permission from: Harold Speert, Obstetric and Gynecologic Milestones. Parthenon Publishing Group, 1996.)

still abounded. John A. McGlinn, reading before the Obstetrical Society of Philadelphia on November 14, 1915, decried the use of ovarian resection in cases of microcystic disease of the ovary, and instead suggested simply puncturing "those cysts which are upon the surface" *(60)*.

Despite the proposed aggressive treatment of cystic degeneration of the ovaries, the etiology underlying this abnormality remained unclear. Fogue and Massabuau summarize the concepts of the time noting three potential mechanisms: inflammation, congestion, and dystrophy *(54)*. The inflammation theory proposed that the microcystic ovary was the result of an infection of either internal or external provenance. The congestion theory suggested that the lesion was the result of pressure, partial torsion, or other interruption in circulatory flow to the ovary. Finally, the dystrophy theory proposed that the abnormalities were caused by modifications or abnormalities in the nutrition of the ovary.

In 1935, in a seminal report, Stein and Leventhal brought together the disparate observations of menstrual dysfunction, microcystic or sclerocystic ovaries, and virilism or hirsutism *(61)*. Operating at Michael Reese Hospital in Chicago, these gynecologists (Fig. 4) reported on seven women in whom amenorrhea was associated with the presence of bilateral polycystic and enlarged ovaries; the heterogeneity of the syndrome was evident even at the initial description, with three of the women being obese and five hirsute. These investigators referred to the ovarian changes as "polycystic" rather than the terms used previously. Wedge resection was performed in all these patients, resulting in two pregnancies (both in the same patient, Case 1) and regular cycles in the remainder.

The etiology of the Stein–Leventhal syndrome remained unclear. Stein and Leventhal in their original report suggested that "the ovarian change in bilateral cystic ovaries is most probably a result of some hormonal stimulation" and that this stimulation was most likely the result of anterior pituitary secretions. They also proposed that "mechanical crowding of the [ovarian] cortex by cysts interferes with the progress of the normal Graafian follicles to the surface of the ovary." Although originally described as a distinct masculinization syndrome *(62)*, Culiner and Shippel suggested that theca luteinization (i.e., hyperthecosis) was an important ovarian mechanism in the Stein–Leventhal syndrome *(63)*.

A hypothalamic–pituitary–ovarian axis abnormality was initially hypothesized by Stein and Leventhal *(61)*, citing the works of investigators that had reported polycystic-looking ovaries after

the injection of anterior pituitary extracts to patients undergoing surgery for uterine fibroids *(64)*. A number of investigators observed excess interstitial cell-stimulating hormone (a.k.a. luteinizing hormone) activity in the urine of women with the Stein–Leventhal syndrome, determined using a bioassay (i.e., the ovarian response of immature female rats or the prostatic response of hypophysectomized male rats to urinary extracts) *(65–68)*. These findings were later confirmed by plasma levels determined by radioimmunoassay *(69)*.

Prior observations in patients suffering from adrenal hyperplasia or adrenal neoplasms had suggested that the adrenal cortex was the only source of androgens in women. However, grafting experiments in mice and rats demonstrated the ovaries were able to restore androgenicity in castrate animals *(70,71)*, and Plate went on to postulate that some androgenic substance secreted by the ovaries in patients with the Stein–Leventhal syndrome was responsible for the symptoms observed *(72)*. Nevertheless, an adrenal etiology for the androgens in Stein–Leventhal syndrome was still considered relevant by some investigators, who used cortisone therapy in an attempt to improve ovulatory function in these women *(73,74)*. The basis for this recommendation lay primarily in the supposition that women with postpubertal hirsutism, oligomenorrhea, and infertility, and in particular those with elevated levels of urinary 17-ketosteroids, suffered from a form of adrenal hyperplasia *(75)*. It is notable that regardless of source, significant confusion still reigned regarding the role of androgens in this hyperandrogenic syndrome, highlighted by the proposal by Netter and Lambert in 1953 to treat sclerocystic ovaries with exogenous testosterone *(76)*.

In an effort to more fully understand the pathophysiology of this elusive disorder, Goldzieher and collaborators produced a thorough and in-depth series of studies of the clinical, histological, and biochemical features of the disorder in patients whose pathology was confirmed by surgical resection *(77–81)*. Concerning an adrenal component for PCOS, biochemical studies were inconclusive, leading Goldzieher to note that "[o]n the basis of so much work and so little yield in the attempt to distinguish ovarian from adrenal factors, one might well begin to wonder if there is not indeed an adrenocortical components in some cases of polycystic ovarian disease" *(82)*. These investigators also built on the work of others to identify the complete series of steps from pregnenolone to estrogen in normal and polycystic ovary tissue, confirming the production of androgens by normal ovarian tissue and the excessive production of the same in patients with polycystic ovaries *(79)*. Abnormally high production of urinary 17-ketosteroids had been used as the primary sign of excess androgen production in affected women. However, following the description of a method for measuring testosterone in plasma in 1961 *(83)*, increased circulating levels of this androgen in patients with polycystic ovaries and/or hirsutism was demonstrated shortly thereafter *(84,85)*.

Recommended treatment of women with polycystic ovaries consisted primarily of bilateral ovarian wedge resection *(86)*, with Stein claiming high rates of success in the treatment of infertility *(87)*. The Stein–Leventhal syndrome was subsequently defined as patients with secondary amenorrhea, hirsutism, sterility, hypoplasia of the uterus, and bilaterally enlarged polycystic or sclerocystic ovaries *(88)*, a definition primarily used to identify women who would appear to benefit from ovarian wedge resection. The syndrome was deemed rare, however, with Stein himself collecting only 90 cases in almost 30 years of practice *(89)*. The advent of clomiphene citrate *(90)* and the observation that ovarian wedge resection was associated with significant periovarian and peritubal adhesion formation *(91)* began to relegate this procedure to women who were resistant to clomiphene ovulation induction. And with the introduction of ovulation induction with menopausal gonadotropins *(92–94)* and laparoscopic ovarian cautery *(95)* for the treatment of clomiphene-resistant patients in the early to mid-1960s, the use of bilateral ovarian wedge resection for the treatment of the Stein–Leventhal syndrome was extinguished.

The heritable nature of PCOS was recognized in the late 1960s *(96,97)*, leading to our current search for the responsible gene variants. More recently, Burghen and colleagues demonstrated that

patients with PCOS were more hyperinsulinemic than weight-matched controls, suggesting that these women were insulin resistant *(98)*, a finding rapidly confirmed by others *(99,100)*. It is noteworthy that Burghen and colleagues postulated finding hyperinsulinemia in patients with polycystic ovaries not because of the previous observations of the bearded diabetic woman or the observations made in women with acanthosis nigricans, but because of prior evidence suggesting that androgen administration altered carbohydrate metabolism. Shortly thereafter, the stimulatory effect of insulin in normal and polycystic ovary theca cells was demonstrated *(101–103)*, although it was not until the advent of insulin-sensitizing agents that reliable proof was obtained that insulin played an active role in the hyperandrogenism of patients with PCOS.

The utility of a polycystic ovarian morphology in the diagnosis of PCOS decreased considerably following the decline in the use of bilateral ovarian wedge resection for its treatment. However, the advent of ultrasonography once again revived the use of ovarian morphology as a sign of PCOS *(104,105)*. Additional details of the history of the discovery of PCOS have been published *(82,106,107)*.

3. CONCLUSIONS

Androgenization of women has captivated humankind for millennia, with early recognition of the relationship between menstrual dysfunction and the development of hirsutism and other virilizing features. Most early patients described appeared to suffer from ovarian or adrenal neoplasms, such that the hyperandrogenic symptoms were generally marked. Not until the early 20th century were lesser degrees of hyperandrogenism recognized as meriting medical evaluation, and only in the past century have significant strides been made in elucidating the etiology and pathophysiology underlying these disorders. Initially the adrenal cortex was recognized as a potential cause of androgen excess, with androgen-secreting neoplasms and frequently concomitant cushingoid features and later adrenal hyperplasia identified as a cause. Many of these women were also found to develop glucose intolerance or diabetes, a disorder known as “diabetes of the bearded woman” or the Achard–Thiers syndrome. NCAH was initially recognized in 1957, but it was not until three decades later that the molecular etiology could be established.

The presence of microcystic, sclerocystic, or cystic degeneration of the ovaries was recognized as early as the mid-19th century, although this pathology was primarily associated with pelvic pain, dysmenorrhea, and menorrhagia. Initially, treatment consisted of castration, although this was soon followed by the more conservative bilateral cuneiform or wedge resection. Recognition that this ovarian pathology could also be associated with amenorrhea, infertility, and hirsutism was not made until the report by Stein and Leventhal in 1935. The ovarian wedge procedure was used extensively to treat these women, although recognition that it could result in significant adhesion formation followed by the introduction of clomiphene citrate and then menotropins and laparoscopic electrocautery led to the demise of this surgical procedure for the treatment of polycystic ovary-associated amenorrhea and infertility. Our understanding of the steroidogenic, gonadotropic, heritable, and metabolic features of PCOS has increased in the past 50 years. It is hoped that progress in understanding the pathophysiology, and genetic and molecular basis, of this common and pervasive disorder will continue to increase exponentially.

KEY POINTS

- Multiple instances of hyperandrogenism, often significant and in association with amenorrhea, have been recorded, with the first cases attributed to Hippocrates in approx 500 BC.
- The first case of what appears to have been an adrenocortical carcinoma with cushingoid and virilizing features was reported by Sampson in 1697.
- Achard and Thiers first described the syndrome that eventually would bear their name in 1921; affected patients were generally postmenopausal and developed diabetes mellitus, hirsutism and/or virilization,

menstrual irregularity or amenorrhea, and suprarenal (adrenocortical) pathology.
- De Crecchio described the first patient with virilizing adrenal hyperplasia in 1865.
- Decourt and colleagues described the first patient with what would be later known as 21-hydroxylase-deficient NCAH in 1957.
- Large, smooth, and possibly polycystic-appearing ovaries were described initially by Vallisneri in 1752; the pathology of the sclerocystic or microcystic ovaries was then detailed separately in 1844 by Chereau and Rokitansky.
- In 1935, Stein and Leventhal described seven patients with bilateral polycystic ovaries and amenorrhea, reporting for the first time the disparate observations of menstrual dysfunction, microcystic or sclerocystic ovaries, and virilism or hirsutism.

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