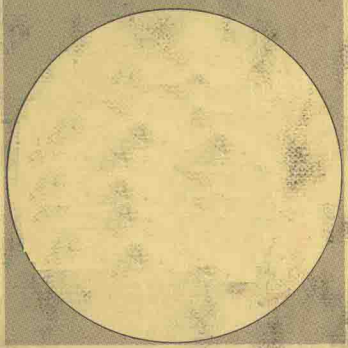
HIRSUTISM AND VIRILISM

PATHOGENESIS DIAGNOSIS AND MANAGEMENT



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FOREWORD

THE APPEARANCE OF SIGNS AND SYMPTOMS OF ANDROGEN excess in persons with a female gender assignment is alarming to both the affected persons and their families. Depending upon the magnitude and duration of exposure to androgen, severity of these manifestations may range from excessive growth of facial and other body hair to increased oiliness of the skin with or without acne, masculinization of the external genitalia, changes in the timbre of the voice, distressing changes in libido, and aggressive behavioral traits more characteristic of males.

As usual, in clinical medicine, other disorders may mimic these syndromes of androgen excess, and distinguishing among these alternatives is the task of physicians called upon to provide relief to these patients. When the signs and symptoms reflect excessive androgenic activity, the sources may be secretion of the hormones by ovaries or adrenals or conversion of relatively inactive precursors to more highly active analogs in peripheral tissues.

Over the last two decades many advances have been made in clinically applicable methods used to determine the etiology and to provide rational therapy for these distressing signs and symptoms. These include: 1) measurement of sex steroid hormone levels in blood and urine in the basal state and following perturbations inhibiting or stimulating production of these substances in normal persons; 2) studies on the chromosomal composition of tissues; and 3) invasive and noninvasive methods for imaging the ovaries and adrenals and for sampling the venous effluents of these organs. Many of these test procedures are time-consuming, expensive, and not entirely risk-free. Moreover, not all of them are required to evaluate the problem in every patient. Thus discriminant use of these sophisticated procedures is the responsibility of the physician providing care for these patients.

Although the information instructing the physician about how to apply these procedures effectively is available in the literature, it is dispersed,

often diluted with a plethora of other information, and sometimes treated cursorily. Furthermore, in medical school curricula, the volume of material which must be encompassed "crowds out" detailed consideration of these problems. To facilitate ready access to the information by students at all levels of career development, Greenblatt and Mahesh have not only drawn upon their wide experience but have motivated colleagues with recognized expertise in relevant areas to contribute to this volume. Here, the information is uniquely focused on the problems of hirsutism and virilism in women and children, covering the spectrum from the most common to the rarest syndromes associated with these signs and symptoms.

The efforts expended in writing and editing this work will make a substantive contribution to the libraries of all serious students of human biology and medicine and to the care of patients who consult them.

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CONTENTS

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HIRSUTISM – ANCESTRAL CURSE OR ENDOCRINOPATHY?

ROBERT B. GREENBLATT

HOMO SAPIENS, IN HIS PHYLOGENETIC DEVELOPMENT, EMERGED erect but void of the thick pelage which covers the bodies of all other primates. Neanderthal man, who lived in Europe some 70,000 to 40,000 years ago, lost some of the hairy tegument that covered the bodies of his earlier ancestors. The thick coarse hair of man's anthropoid heritage remains only in a few areas, but the vestiges of this hair-covering persist as follicles producing fine, lightly pigmented lanugo (vellus) hair over most of the body's surface. The human remains potentially a naked ape and retains the capacity to grow coarse, thick (terminal) hair on face, chest, abdomen, back, extremities, along with pubic and axillary hair. Thus, human hair is of two types: vellus and terminal. Both types are found on all skin areas except the palms of the hands and soles of the feet which have no hair follicles.[1]

The growth of hair is cyclic. There are three phases: "anagen" is the growing phase; "catagen," the transitional period of rapid involution; "telagen," the quiescent phase.[2] The duration and variation in anagen and telagen cycles in the human depend on many factors, and unlike the hair follicles of animals which molt periodically, human hair follicles are not synchronized. Each follicle is supplied by one or more sebaceous glands which produce oil or sebum to lubricate the hair. In humans, excessive hairiness is usually accompanied by increased oiliness. To each hair follicle a special muscle is attached, the arrector pili. Downy vellus hair lacks this muscle. Human hair, as in some animals, can become erect in moments of great stress

because of this special muscle. Shakespeare made this point quite explicit when the ghost of Hamlet's father said:

> I could a tale unfold whose lightest word
> would harrow up thy soul; . . .
> And each particular hair to stand on end.

Hair is second only to skin as a physical sign of racial difference. Almost all Mongolians (Chinese, Japanese, Koreans, American Indians, Eskimos) have dark straight coarse hair on their heads; it is crinkly or wooly in the Negro, and curly or straight in the Caucasian. As for body and facial hair, the Mongolian, Negroid, and American Indian races are noticeably less hirsute than Caucasians, and among the Caucasians there are ethnic differences: hair growth is heavier in those of Mediterranean than in those of Nordic ancestry.

Man's interest and fascination with hair—absence or excess—have been known since recorded time. The Bible relates that Esau's body and arms were covered by an abundance of hair; Aristotle wondered why eunuchs failed to grow beards but maintained their full head of hair; St. Paul wrote that a woman's (head) hair is "her crowning glory." In all generations, however, the bearded woman has been the object of great curiosity and the subject of much derision. The storied legends of the past have designated the bearded woman as an unnatural individual. Shakespeare seized upon this motif when he wrote about the three weird sisters in *Macbeth*:

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

The statue of a bearded lady stands in Westminster Abbey. She is Saint Wilgefort, a Portuguese princess who was betrothed against her will to a suitor she did not love. According to legend, she prayed that she might become so unattractive that he would no longer wish to marry her. Her prayers were answered—she grew a coarse beard which repelled her suitor. Saint Wilgefort then devoted the rest of her life to religion and died a virgin.[3] Does such a case purport to underline a possible influence of the psyche as a factor in abnormal sexual hair growth? Indeed, hirsutism is said to be far more prevalent in women confined to institutions for the insane. Bush and Mahesh reported a temporary increase in facial hairiness in a woman following an ill-fated love affair. The abnormal hairiness regressed soon after a favorable resolution of the situation. They were able to demonstrate an increased production of adrenal androgens during the period of emotional stress.[4]

Quite a different message issues from the celebrated painting "La Barbuda" by Jusepe de Ribera which hangs in the Tavera Hospital Museum in Toledo, Spain. In 1631, Ribera portrayed a 52-year-old woman from Naples with a luxuriant beard nursing her infant, and her somewhat meek husband standing beside her (Figure 1-1). At age 37, after she had expe-

FIGURE 1-1 The celebrated "La Barbuda" by Ribera, a 52-year-old bearded woman nursing her child, hangs in the Museum of the Tavera Hospital at Toledo, Spain. She became markedly hirsute at age 37 after having had three spontaneous abortions. The picture, commissioned by the Duke of Alcala, serves to place on record that hirsute women have become and do become mothers.

rienced three spontaneous abortions, the growth of facial hair began. The reproductive history of this woman suggests some hormonal disturbance for the unusual course of events. Ribera, much against his esthetic sense, was commissioned by the Duke of Alcala to record for posterity this unique phenomenon.[5]

The masculine distribution of hair in a girl or woman is not only a cosmetic catastrophy but is also a source of considerable anguish and emotional trauma. Excessive growth of hair on the face of a woman, known as hirsutism, may or may not be accompanied by menstrual disorders or unwanted hair on the chest and abdomen. Although hirsutism is often regarded as presumptive evidence of a lack of femininity, it need not be a deterrent to essential womanhood or functional fertility.[6] However, when clitoral hypertrophy, varying degrees of regression of the cephalic hair line or even male pattern baldness, deepening of the voice, increased muscle mass, and amenorrhea (in almost all instances) are accompaniments of hirsutism, then the symptom complex is called virilism. On the other hand, hypertrichosis is a term frequently employed to denote overgrowth of hair on arms,

thighs, and legs, and sometimes of the back, which may or may not be associated with facial hirsutism or virilism.

FACTORS INFLUENCING THE GROWTH OF HAIR

Some knowledge of the biology of hair growth and its relationship to the endocrine system is essential for an understanding of aberrations in hair distribution. Hair is a derivative of the epidermis, and the hair follicle is a component of the pilosebaceous apparatus. The full complement of these units is present three months before birth. It is unlikely that hair follicles can develop de novo in the human adult. There are no differences between the male and female in the distribution of hair follicles. The difference in sexual hair patterns between males and females is due mainly to the titer of circulating androgens. Thus, the tendency to abnormal hairiness in the female remains quiescent but may burgeon forth at any time because of a variety of intrinsic and extrinsic factors (Table 1-1).

In the human, facial hair follicles, like those for pubic and axillary hair, lie more or less dormant until puberty, becoming fully active only under the chemical impulses of androgenic hormones. As has been mentioned already, aside from hormonal influences, there are genetic or hereditary factors. The plasma concentration of testosterone in Japanese males and females is the same as in Caucasians.[7] There is a systemic difference in the sensitivity of the epidermal appendages to androgens; hirsutism is extremely rare in Japanese women, as is acne. Furthermore, Japanese women tolerate exogenous androgens in doses which result in hirsutism or even masculinization in Caucasian females.

In rats, estrogens retard the initiation and rate of hair growth and produce a finer hair; androgen induces a coarse pelage. Hormones, such as androgens and growth hormone, increase the rate of hair growth, while estrogens decrease the diameter of hair. Estrogens not only decrease the rate of anagen activity but also lessen sebum activity. All body processes are temperature sensitive, and the skin is much more subject to changes in environmental temperature than any other organ. Hair growth in the human, as well as in a variety of mammals, is more rapid in the summer. Increased blood flow and the resultant increase in dermal temperature are probably responsible for increased local hair growth in areas chewed or sucked by psychotic patients, in areas overlying bone fractures, or unilaterally on the side of sympathectomy.[8]

ACTION OF ANDROGENS

Male and female epidermal teguments are quite similar, as is steroidogenesis for the adrenals, the ovaries, and testes. Androgens derive from the adrenals, testes, and ovaries. The ovary converts nonandrogenic C_{21} steroids (pregnenolone and progesterone) into androgens such as dehydroepiandrosterone (DHA), Δ^4-androstenedione, and testosterone which then convert to estrogens. Androgens, whether of adrenal or gonadal origin, are

Table 1-1
Factors Influencing Abnormal Hairiness in the Female

A.	An inborn androgen sensitivity of the pilosebaceous apparatus
B.	Undue metabolic clearance rates of certain endogenous androgens
C.	A decrease in testosterone's protein-binding capacity
D.	An inherent facility for androgen conversion to testosterone and/or dihydrotestosterone
E.	Psychogenic stresses that either increase adrenal androgen output or modify pilary responsiveness
F.	Endocrinopathies which produce increased amounts of androgens—seen in certain ovarian and adrenal disorders
G.	Iatrogenic: androgen administration; certain drugs

the obligatory estrogen precursors. Estrogens are more efficiently produced in the female, and these hormones are believed to limit testosterone's physiologic action by increasing its protein-binding capacity. However, derangements in the pathways for estrogen synthesis resulting in increased androgen turnover may readily occur. All these factors—and many more—are at play to create hirsutism and hypertrichosis.[9-14]

We can think of the skin as an enormous endocrine gland. It extracts androgens from the circulation, binds them, and converts them to both more active and inactive products. Certain skin—the prepuce, for example—can convert androgens to dihydrotestosterone more readily than other tissues. It is dihydrotestosterone, derived from testosterone and perhaps in even greater amounts from Δ^4- androstenedione, which acts at the receptor-protein level in the hair-follicle cell. In instances where there is an inherent defect in the receptor sites—the feminizing insensitive androgen syndrome—neither testosterone nor dihydrotestosterone will induce hair growth, acne, clitoral enlargement, or voice changes (Figure 1-2). On the other hand, certain endocrine states play a permissive role for hairiness. The hypertrichosis of juvenile hypothyroidism and the hirsutism observed following large chronic doses of cortisone are not due to excessive androgens.

The clinician is apt to view every hairy female as an endocrine problem. In the larger sense, such a conclusion is essentially correct. When examined from the point of view that the hair follicle is an end organ influenced and stimulated by certain hormones, then it would be fair to assume that "all excessive hairiness" is indeed an endocrine problem, provided the roles of heredity, genetic factors, and sensitivity of the target gland receptors are considered.

Many hirsute females do not manifest any obvious or latent disorder in endocrine balance. Secondary sexual characteristics such as bodily contour, breast development, and fat deposits may be completely normal. The menstrual cycles may be regular and ovulatory, and the ability to conceive and bear children may not be impaired in any way. Aptitudes and attitudes may remain astonishingly feminine; pelvimetry usually reveals the perfect gynecoid pelvis, and hormonal surveys may reveal quantitatively average outputs of urinary 17-ketosteroids and normal serum androgen levels. Why

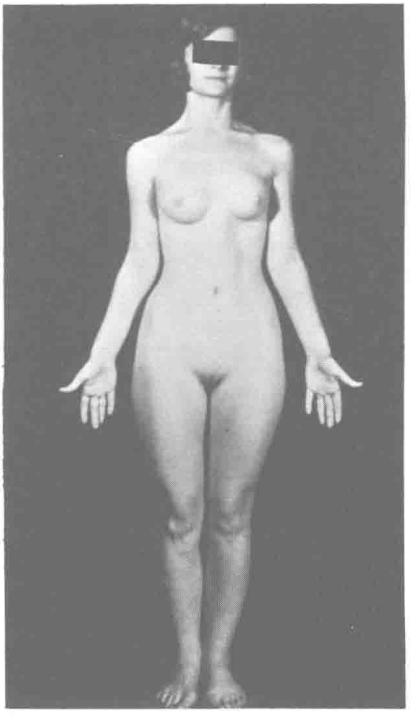

FIGURE 1-2 A 21-year-old woman with syndrome of feminizing abdominal testes. Note absence of all sexual hair. (Reproduced with permission from Greenblatt RB: *Recent Prog Hor Res* 1958;14:335.)

then the hirsutism? Excessive hair growth may be caused by an increased sensitivity of the androgen receptor in the pilosebaceous unit, particularly the hair follicle, to endogenous androgens. This may be either a dominant or a recessive hereditary trait. On the other hand, in the greater number of hirsute women with so-called idiopathic hirsutism, there may be minor to major enzymatic defects in the biosynthesis of certain steroids by the ovary or adrenal, or there may be disturbances in intrinsic liver or kidney metabolism which may alter the nature and rate of excretion of certain steroids. According to Ishmail et al[15] and Vermeulen,[16] anomalies of androgen metabolism, however mild, can be demonstrated in a majority of women with so-called idiopathic hirsutism if sophisticated endocrine studies are performed. The question may then be asked, "Is hirsutism an ancestral curse or an endocrinopathy?"

All hair growth, wherever it is on the body, may be said to be hormone-dependent. However, it is the facial (beard) hair, axillary hair, chest hair, and the abdominopubic hair that is considered "sexual hair." Such hair growth is directly dependent on the glands of internal secretion and appears only after androgens, which were produced by the adrenals and gonads, have made their presence felt over a sufficient length of time. Although head