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Idiopathic Hirsutism*

RICARDO AZZIZ, ENRICO CARMINA, AND MARTY E. SAWAYA

Departments of Obstetrics and Gynecology, and Medicine (R.A.), The University of Alabama at Birmingham, Birmingham, Alabama 35233; Department of Obstetrics and Gynecology, Columbia University, New York, New York 10032, and Department of Endocrinology, University of Palermo at Caltanissetta, 90139 Italy (E.C.); and Alopecia Research & Associated Technologies (ARATEC), and Department of Biochemistry and Molecular Biology, University of Miami School of Medicine (M.E.S.), Miami, Florida 34478

ABSTRACT

Hirsutism, the presence of terminal (coarse) hairs in females in a male-like pattern, affects between 5% and 10% of women. Of the sex steroids, androgens are the most important in determining the type and distribution of hairs over the human body. Under the influence of androgens hair follicles that are producing vellus-type hairs can be stimulated to begin producing terminal hairs (*i.e.*, terminalized). The activity of local 5α-reductase (5α-RA) determines to a great extent the production of dihydrotestosterone (DHT), and consequently the effect of androgens on hair follicles. While there are two distinct 5α-RA isoenzymes, type 1 and type 2, the activity of these in the facial or abdominal skin of hirsute women remains to be determined. Although the definition of idiopathic hirsutism (IH) has been an evolving process, the diagnosis of IH should be applied only to hirsute patients with normal ovulatory function and circulating androgen levels. A history of regular menses is not sufficient to exclude ovulatory dysfunction, since up to 40% of eumenorrheic hirsute women are anovulatory. The diagnosis of IH, when strictly defined, will include less than 20% of all hirsute women. The pathophysiology of IH is presumed to be a primary increase in skin 5α-RA activity, probably of both isoenzyme types, and possibly an alteration in androgen receptor function. Therapeutically, these patients respond to antiandrogen or 5α-RA inhibitor therapy. Pharmacological suppression of ovarian or adrenal androgen secretion may be of additional, albeit limited, benefit. New therapeutic strategies such as laser epilation or the use of new biological response modifiers may play an important role in offering a more effective means of treatment to remove unwanted hair. Further investigations into the genetic, molecular, and metabolic aspects of this disorder, including only well defined patients, are needed. (*Endocrine Reviews* **21:** 347–362, 2000)

I. Introduction

HIRSUTISM, the presence of terminal (coarse) hairs in females in a male-like pattern, affects between 5% and 10% of women surveyed (1–3). The presence of hirsutism is extremely distressing to patients, with a significant negative impact on their psychosocial development (4, 5). In the majority of patients hirsutism should be considered as a *sign* of other conditions [*e.g.*, the polycystic ovary syndrome (PCOS), androgen-secreting tumors, nonclassic adrenal hyperplasia (NCAH), or syndromes of severe insulin resistance], rather than an isolated disorder. The exception is possibly those patients with "idiopathic hirsutism" (IH), also called simple or peripheral hirsutism. While IH is often referred to as "familial hirsutism," this represents a misnomer. In fact, it is now well established that other forms of hyperandrogenism, *e.g.*, PCOS and NCAH, also demonstrate a strong familial predisposition (6, 7). In the following text, we discuss normal hair and peripheral androgen physiology; methods for determining hirsutism; and the definition, pathophysiology, prevalence, heritability, and therapy of IH.

II. Normal Regulation of Hair Growth and Differentiation

A. Development, types, and distribution of hair

There are approximately 50 million hair follicles covering the body, of which 100,000 to 150,000 are on the scalp; the

Address reprint requests to: Ricardo Azziz, M.D., M.P.H., Department of Obstetrics/Gynecology, University of Alabama at Birmingham, Birmingham, Alabama 35233-7333 USA. E-mail: razziz@uabmc.edu
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remaining follicles are on facial and other body sites. The only areas free of hair follicles are the soles of the feet, palms of the hands, and the lips. There are very few new hair follicles formed after birth, and the number of hair follicles begins to decrease after the age of 40 (8, 9).

The earliest stage of human embryonic life at which organization of the primitive epidermis leads to the formation of hair structure is between 9 to 12 weeks (10, 11). During development of hair structures the primitive mesoderm forms the hair germ, with an associated down growth bringing ectoderm cells to the newly forming hair peg. The hair germ from the mesoderm ultimately forms the fibrous sheath of the follicle and the dermal papilla, while the hair peg becomes a solid core of epithelial cells that encloses the dermal papilla. The ectodermal and mesodermal elements remain in intimate contact and reflect an association that continues throughout the life of the hair follicle. These embryonic hair follicles may be producing hair by the 16th to 20th weeks of development.

Hair is composed of keratin proteins, which form the hair shaft. The hair shaft grows within the outer hair root sheath, which forms part of the epidermis. Structurally, there are three types of hair. Lanugo is a soft hair densely covering the skin of the fetus, which is shed between the first and the fourth month postpartum. Vellus hairs are also soft fine hairs, but larger than lanugo hairs. Vellus hairs are usually nonpigmented, generally measuring less than 2 mm in length, and cover the apparently hairless areas of the body. Histologically, vellus hairs have diameters that do not exceed 0.03 mm, smaller in diameter than that of the investing root sheath (12). Terminal hairs are longer, pigmented, and course in texture. This hair makes up the eyebrows, eyelashes, scalp hair, and pubic and axillary hair in both sexes, and much of the body and facial hair of men (8, 9). Terminal hairs are often described as being "medullated." The "medulla" of the hair follicle is the innermost area of terminal hairs and is thought to consist of "collapsed protein," although the exact composition of this area remains controversial. The smaller lanugo and vellus hairs are thought be nonmedullated (*i.e.*, not having this inner pocket).

In skin, the hair follicles form groups, called follicular units (FU); each FU consists of approximately two to four hair follicles along with sebaceous glands and connective tissue sheaths (13–15). The concentration of FUs in skin, at least in the scalp, can vary between ethnic groups (13, 14). However, there is no gender difference in the number of FUs within each racial/ethnic group. Hence, the visible difference in body hair growth between men and women does not relate to the number of FUs, but to the type and quality of the hair within these follicles (8, 9).

B. Growth phases and regulation of hair growth

There are three phases to hair growth. An active growing phase (anagen); followed by an involutional stage (catagen), in which the hair stops growing and the hair bud shrinks; and finally, the telogen phase in which the hair is resting, and then shed, as new hairs displace it (8, 9). In humans, hair has the appearance of growing continuously, the result of disynchrony in the growth phases between the different hair follicles. In essence, while some hairs are in the active phase of growth (anagen), others are in the resting phase (telogen), and vice-versa, giving the impression of continuous growth. The length of time of the growth phase will vary depending on where the hair follicle is located. For example, on the scalp the anagen phase may last 2 to 6 yr, while the anagen phase of body hairs may only last 3 to 6 months. Alternatively, the duration of the catagen and telogen phases is similar in scalp and body hair, lasting 2 to 3 weeks and 3 to 4 months, respectively. The anagen-telogen ratio (the ratio of hairs in anagen to the number of hairs in telogen) is often used to estimate hair growth activity in specific areas of the skin, with a higher ratio indicating a more active hair growth.

Sex steroids and a number of local and systemic factors can act directly and indirectly on the dermal papilla to regulate hair growth. In addition, these factors may also act on other parts of the hair follicle, including the outer and inner root sheaths and the follicular stem cells of the "bulge" area (16), which may be as important as the dermal papilla in regulating hair growth (Fig. 1).

1. Local and systemic factors. Various growth factors and cytokines have been observed to affect hair growth (16–22). It has been suggested that these factors operate by increasing the synthesis of stromolysin, a matrix metalloproteinase that acts on the dermal papilla to accelerate growth (23).

Other hormones such as thyroid (24, 25) and GH (26) can also alter hair growth. In general, a deficiency of hormones such as thyroid hormone or GH, whether disease-associated or drug-induced, is associated with changes in the anagen-telogen ratio in scalp and body hair (24, 25, 27). Hypothyroid patients treated with thyroid hormone replacement generally begin to experience regrowth of scalp hair within approximately 8 weeks (24). Investigators have demonstrated the presence of thyroid hormone receptors in the outer sheath cells of hair follicles, and a positive effect of L-T_3 on cellular proliferation in cultured hair follicles (28). GH-deficient men treated with GH substitution demonstrate an increase in body hair that occurs without an observable increase in free androgen index (26), suggesting that GH can directly stimulate body hair growth independent of an increase in circulating androgens. Evidence of GH binding has been reported in all layers of the lower one-third of the hair follicle, the outer sheath of the upper two-thirds of the follicle, and in the dermal papilla (29). Notwithstanding, a direct effect of GH on *in vitro* hair follicle growth or morphology has not been observed (19). It is possible that the effect of GH may be mediated through increased production of insulin-like growth factor I (IGF-I). In human scrotal skin fibroblasts, IGF-I, but not IGF-II or insulin, increased the activity of 5α-reductase (5α-RA), an enzyme necessary for the peripheral potentiation of the androgen effect (30). In addition, in cultured hair follicles, IGF-I, more than IGF-II or insulin, stimulated hair follicle growth (19).

2. Sex steroids. Of the sex steroids, androgens are the most important in determining the type and distribution of hairs over the human body. Under the influence of androgens, hair follicles that are producing vellus-type hairs can be stimulated to begin producing terminal hairs. *In vivo* experiments

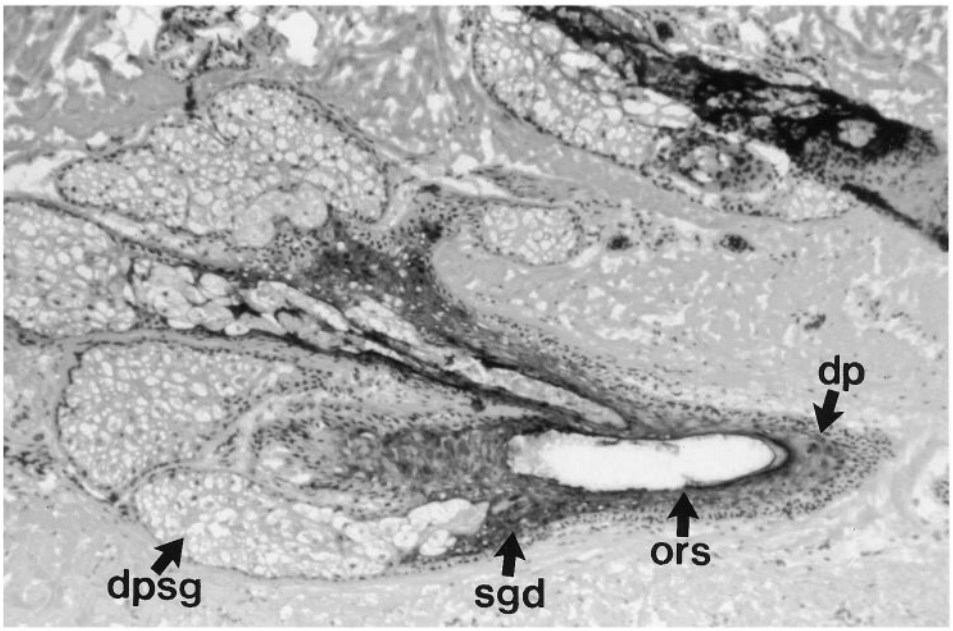

FIG. 1. Immunohistochemical localization of the type 2 5α-RA to the human hair follicle outer root sheath (ors) and sebaceous gland duct (sgd). Using polyclonal rabbit antibodies raised against synthetic peptides corresponding to amino acids 220–250 (39), less expression of this enzyme is noted in the dermal papilla (dp) of the hair follicle. These data indicate that the outer sheath may play a major role in androgen metabolism. Furthermore, the type 2 isoenzyme is not present in the distal portion of the sebaceous gland (dpsg).

clearly document the effect of exogenous androgens on the differentiation of hair follicles in androgen-sensitive areas of the body (*e.g.*, genitalia and facial beard area) in normal males (31), eunuchs (32), and female-to-male transsexuals (33). In addition to stimulating the production of terminal hairs in some skin areas, androgens prolong the anagen phase of body hairs, while shortening the anagen phase of scalp hairs (34, 35). Androgens also increase sebum secretion. Therefore, not only do androgens alter the type of hair present, but they may lengthen body hairs by increasing the length of the anagen phase, and will increase the oiliness of skin and hair.

Whether the ability of some hair follicles to produce terminal hairs (*i.e.*, "terminalize" vellus hairs) under the influence of androgens is due to differences in androgen sensitivity or to other (as yet undefined) primary differences in hair follicles remains unclear. There is considerable variability among body hairs (individually and between different skin areas) in their 5α-RA content and ability to metabolize androgens. It is very possible that the variability in the ability of androgens to stimulate the production and growth of terminal hairs may be regulated, to a large extent, by these differences. Finally, the concentration of the androgen receptor in determining the effect of androgens on terminal hair growth is critical, as is clearly demonstrated by the sparse terminal body hair of patients with incomplete and complete androgen insensitivity (36).

It should be noted that sex steroids may act on the hair follicle independently of their circulating levels. This local or intracrine effect is extremely important and may prove to play a significant role in the development of androgen excess disorders, particularly IH. The intracrinology of the hair follicle was recently demonstrated in androgenetic alopecia (*i.e.*, common male pattern hair loss), which affects both men and women. In this disorder androgens shorten the active anagen growth phase of the scalp hairs in genetically susceptible men and women, producing miniaturized hairs through subsequent hair cycles and a loss of grossly visible hairs. In men, androgenetic alopecia is associated with a progressive loss of frontal and occipital hair, followed by the loss of sagittal hairs (37). In contrast, in women this disorder presents as a diffuse thinning of hair growth in the frontal and sagittal scalp (38). It is possible that differences in local sex steroid metabolism accounts, at least in part, for the variations in clinical presentation between women and men with this disorder (39). To test this hypothesis we studied 12 men and 12 women with androgenetic alopecia and noted that the content of cytochrome P450 aromatase and 5α-RA in the frontal hair follicles of these women was 6-fold greater and 3-fold less, respectively, than in the frontal hair follicles of the affected men (39). Hence, it is possible that differences in local androgen metabolism could account for the different clinical presentations of androgenetic alopecia between genders. Nonetheless, it is still unclear whether these differences are due to increased local clearance of androgens (via conversion to estrogens) or from a direct estrogen effect. In fact, some investigators have suggested that estrogens can directly cause scalp hair loss by altering the anagen-telogen rate (40).

In contrast to scalp hair, a direct effect of estrogens on the regulation of body hair growth is still uncertain (41). In the rodent model, estrogens have been observed to inhibit the initiation of growth and prolong the entire growth cycle of the hair follicle (42, 43). Progesterone and estradiol, at least in high doses, also inhibit 5α-RA activity in human genital and pubic skin (44), possibly decreasing the local production of the potent androgen dihydrotestosterone (DHT). Little more is known regarding the direct effects of progesterones and estrogens on hair growth in the human.

3. Skin 5α-RA activity. Numerous experiments have documented the 5α-reduction of testosterone (T), androstenedione, and dehydroepiandrosterone to DHT *in vitro* by skin and individual hair follicles (34). In the intact organism, DHT

is primarily formed from the peripheral nonhepatic 5α-reduction of T in men and androstenedione in women (45, 46). In fact, the effect of androgens on the development of terminal hairs appears to require, to a significant degree, the action of 5α-RA. This concept is supported by the sparse beard development in patients with 5α-RA deficiency (36, 47, 48). However, even among patients with 5α-RA deficiency, the metabolism of T to DHT by dermal papilla cells *in vitro* correlates with terminal hair growth (49).

The important role of 5α-RA and DHT in determining male-type hair growth is further supported by the observations of Farthing and colleagues (50) in men with coeliac disease, individuals who experience a greater than normal divergence in their circulating concentrations of T and DHT (50). In these men the growth rate of facial hairs correlates directly with their plasma DHT levels, which are lower than normal. Alternatively, hair density correlates with T (but not DHT) levels, which in these patients are higher than normal. This dichotomous, yet synergistic, effect of T and DHT is consistent with the partial virilization observed in patients with 5α-RA deficiency at puberty (36, 47, 48). Overall, while circulating T in higher concentrations may have a direct effect on the FU, DHT is the primary androgen active at the target tissue (Fig. 2).

The activity of local 5α-RA determines, to a great extent, the production of DHT and, consequently, the effect of androgens on hair follicles. Progesterone and estradiol in high doses inhibit 5α-RA activity in human genital and pubic skin (44), while androgens were found to stimulate and increase peripheral 5α-RA activity (51). However, not all androgens may be equal in their ability to affect peripheral 5α-RA activity and hair growth. For example, pubic skin from patients with "adrenal hyperandrogenism" demonstrates levels of 5α-RA activity that are similar to those of controls and less than those of patients with ovarian hyperandrogenism (52). In addition to androgens, other factors may also control the distribution and activity of 5α-RA (Fig. 2). For example, preliminary data indicate that local (*e.g.*, transforming growth factor-β and epidermal growth factor) and circulating growth factors (*e.g.*, insulin-like factor-I, activin A, and inhibin A) alter the activity of this enzyme (30, 53, 54). Nonetheless, the specific role and mechanism of action of these regulatory factors remain to be better defined.

5α-RA activity is actually the product of the function of two distinct isoenzymes, type 1 and type 2 5α-RA (55) (Table 1). Each 5α-RA isoenzyme is encoded by separate genes located on chromosomes 5 and 2, respectively, and demonstrate different biochemical characteristics and tissue distributions (39). The type 1 isoenzyme has an optimum pH near 8.0, a Michaelis-Menten constant (K_M) of approximately 24 μM, and less cofactor specificity and is located primarily in the microsomal subcellular fraction. The type 2 isoenzyme has a more acidic pH range and a K_M of approximately 0.33 μM and is found in both the nuclear and microsomal subcellular fractions. Therefore, type 2 5α-RA can be considered to be more active in synthesis of DHT, based on their relative K_M values (Table 1).

The two 5α-RA isoenzymes are widely distributed throughout the body (Table 1), although recent studies have noted that the type 2 isoenzyme predominates in the testes, prostate, and the hair follicles of beard and genital hair (55). Controversy still exists regarding which isoenzyme is located in the hair follicles of the scalp. One investigator has reported that only type 2 5α-RA is present in scalp hair follicles, whereas both types 1 and 2 were demonstrated in human sebaceous glands (56). Other investigators (39, 57) have also found both isoenzymes in scalp sebaceous glands, but they also reported finding both types of 5α-RA isoenzymes in scalp hair follicles (Fig. 1). Interestingly, both types of 5α-RA can be localized to the outer root sheath of the hair follicle, with less expression in the dermal papilla (39) (Fig. 1). The type 1 isoenzyme is heavily expressed in the distal portions of the sebaceous gland, whereas type 2 5α-RA is found primarily in the proximal duct of sebaceous glands (39). This location of type 2 5α-RA may be clinically important, since the proximal duct of the sebaceous gland is where key pathological processes leading to acne vulgaris take place.

In addition to variances in gender and skin location, the two 5α-RA isoenzymes may also differ functionally. For example, preliminary data suggest that in skin the two isoenzymes may be regulated by androgens to a different degree, with the type 1 isoenzyme more susceptible to up-regulation by these steroids (58). Furthermore, type 2 5α-RA is present in skin beginning at birth, while the type 1 isoenzyme becomes evident in skin only at the end of childhood or around the time of puberty (55).

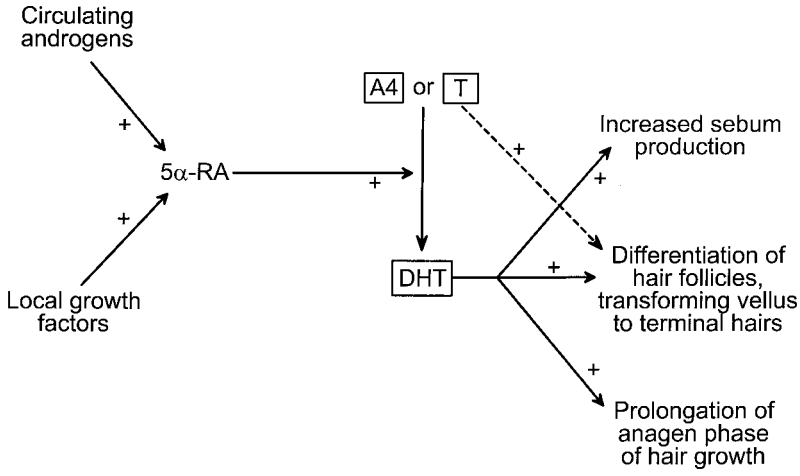

FIG. 2. Proposed regulation of the activity of 5α-RA and the production of DHT in body hair. Peripheral 5α-RA activity is increased by local growth factors and circulating androgens. This enzyme catalyzes the conversion of T or androstenedione (A4) to DHT. In body hair DHT stimulates 1) increased sebum production; 2) the differentiation of the hair follicle from vellus to terminal hairs; and 3) the prolongation of the anagen phase resulting in longer thicker hairs.

TABLE 1. Features of the 5α-reductase isoenzymes

	Type 1	Type 2
MW	29,000	29,000
# of a.a.	292	254
Optimum pH	Basic (8.0)	Acidic (6.0)
K_M (μM)	24	0.3
Chromosomic location of gene	5	2
Body sites	Skin,[a] liver, adrenal, kidney	Skin,[b] prostate, epididymis, seminal vesicles, testes, liver

Abbreviations: MW, molecular weight; # of a.a., number of amino acids; K_M, enzymatic Michaelis-Menton constant.
[a] Hair follicles and distal sebaceous gland lobes.
[b] Hair follicles and duct of sebaceous glands.

It should be noted that 5α-RA activity has been primarily measured biochemically in follicular cells of plucked and microdissected hairs and in skin minces and primary cell cultures. Most studies determining 5α-RA activity have been performed using genital or scalp skin without determining the specific isoenzyme forms present. Furthermore, the activity of these isoenzymes in the facial or abdominal skin of hirsute women remains to be determined. It should be noted that the recent availability of specific Northern blotting for identifying the individual isoenzyme mRNAs has improved our capacity to detect the presence of each of the 5α-RAs (39). The development of these techniques may lead to a better understanding of the differences in hair growth between genders and the underlying pathophysiology of hyperandrogenic disorders such as androgenetic alopecia, acne, and hirsutism.

III. Hirsutism: How Much Is Too Much?

A. Quantifying hirsutism

The clinical diagnosis of hirsutism is a relatively subjective process, based on visual assessment of hair type and growth. In evaluating patients suspected of hirsutism, clinicians must first determine whether the excess hair is of the terminal or vellus type and whether it follows a male-like pattern. Excess vellus hair growth alone is not a reflection of hyperandrogenism and may be due to familial/ethnic causes, abnormalities of corticosteroid, GH, or thyroid hormone production, or may be drug induced. Although vellus hairs can often be grossly differentiated from terminal hairs by their texture, thickness, and pigmentation, many androgenized patients will actually demonstrate excess growth of both hair types. The term hypertrichosis is strictly defined as the presence of excess hair growth. However, because it is used to describe hirsutism in general by some investigators and the excessive growth of vellus hairs by others, it will not be used further in this review.

Visual methods of determining the degree of hirsutism usually follow those originally described by Ferriman and Gallwey (1). In their study these investigators scored the density of terminal hairs at 11 different body sites (*i.e.*, upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, forearm, thigh, and lower leg) in 161 women ages 18 to 38 yr old attending a general medical outpatient clinic. In each of these areas a score of 0 (absence of terminal hairs) through 4 (extensive terminal hair growth) was assigned. In this study, hair growth over the forearm and lower leg was noted to be less sensitive or indifferent to androgens, and subsequent modifications of the Ferriman-Gallwey method have deleted scoring of these areas (59, 60). Scoring of hair growth in the sideburn area, lower jaw and upper neck, and buttocks have been included in more recent scoring systems (61).

B. Defining hirsutism

In their original report, Ferriman and Gallwey noted that if only the nine "hormonal" skin areas (*i.e.*, excluding the lower leg and forearms) were considered, 9.9% of their 161 women had a score above 5, 4.3% had a score above 7, and 1.2% had a score greater than 10 (1). From these data a score of 8 or more has been considered to represent hirsutism. It should be kept in mind that these studies were performed in a predominantly white population. Although racial/ethnic differences in the number, distribution, or androgen sensitivity of hair follicles in normal individuals remains to be better defined, information regarding the prevalence of hirsutism in different racial groups is scant.

We prospectively studied 369 consecutive reproductive-aged black (n = 195) and white (n = 174) women, examined at the time of their preemployment physical (62). A previously described modification of the Ferriman-Gallwey method (60), in which nine body areas are assessed, was used. Of these women, 7.6%, 4.6%, and 1.9% demonstrated a modified Ferriman-Gallwey score $\geq$ 6, 8, or 10, respectively. Obviously, the overall cutoff score used to define hirsutism will decrease as the number of areas assessed (or the maximum score assigned to each area) is reduced. For example, Lorenzo (59) studied 300 unselected female medical patients using a modification of the Ferriman-Gallwey score, in which only five areas of the body were scored (chin, upper lip, chest, abdomen, and thighs). Using this scoring method, this investigator did not observe a hirsutism score over 5 in any of these women. While the exact numerical cutoff score used to define hirsutism will vary according to the quantifying system used, a value of 7 or greater is evident in only 5% of the general population when a scoring system assessing nine body areas is used (62).

In the study prospectively evaluating the prevalence of hirsutism we did not note any significant racial differences: 8.0%, 2.8%, and 1.6% of white women and 7.1%, 6.1%, and 2.1% of black women had hirsutism scores $\geq$ 6, 8, or 10, respectively (62). Alternatively, various investigators have noted that, in comparison to white patients, hirsutism in Asian women is relatively uncommon even in the face of similar metabolic and endocrine abnormalities (63–65). Thus, in Asian women the absence of hirsutism cannot be used to exclude the presence of a hyperandrogenic disorder.

IV. The Evolving Definition of IH

A review of the literature clearly demonstrates that the definition of IH has been a dynamic process, evolving in

conjunction with our understanding of the role and etiology of the various androgen excess disorders (Table 2). The absence of a clear definition of IH has been one of the principal sources of continuing confusion and contradiction in the study of this disorder.

A. As the "hirsutism of unknown etiology"

Early reports defined IH as the "hirsutism of unknown cause" (Table 2). In essence, IH was presumed if the presence or source of androgen excess was not clear. Patients were included if they did not have polycystic ovaries, congenital adrenal hyperplasia, or androgen-secreting tumors, or if the limited battery of androgen assays then available yielded normal results (66–71). Importantly, at that time many investigators defined patients as having IH regardless of whether they had irregular menstruation/ovulation and/or elevated circulating androgen levels, which today would be more consistent with the diagnosis of PCOS (72). In addition, most of these studies did not exclude patients with NCAH, as the diagnostic criteria for this disorder had not yet been established.

B. As "hirsutism with a history of regular menstrual cycles"

Subsequently, IH was defined as affecting those patients with hirsutism and regular menses (73–75), regardless of circulating androgen levels (Table 2). However, a normal menstrual history in the hirsute patient does not exclude ovulatory dysfunction (76), elevated circulating androgen levels (77), or NCAH (78). For example, Mehta and colleagues noted that while 40% of their hirsute women had regular cycles, approximately one-half of these had elevated levels of one or more androgens (77). Furthermore, in a prospective study of 64 hirsute patients claiming to have regular monthly menses, approximately 40% actually had oligoovulation when examined more closely (76). The presence of oligoovulation in hirsute or hyperandrogenemic patients, after the exclusion of related disorders (*e.g.*, NCAH, thyroid dysfunction, or hyperprolactinemia) is consistent with the diagnosis of PCOS, as noted in the proceedings of a consensus conference sponsored by the NIH/NICHD in April of 1990 (72). Hence, a history of "regular menses" should not be used to exclude the presence of ovulatory dysfunction or hyperandrogenemia and cannot be used to determine IH.

C. As "hirsutism with normal ovulatory function and normal circulating androgen concentrations"

The presence of oligoovulation in a hirsute patient is generally considered to indicate the presence of androgen excess (as in PCOS or NCAH) and to exclude IH. Nonetheless, it is possible that a patient with IH (*i.e.*, with hirsutism not related to androgen excess) may incidentally be oligoovulatory due to other nonrelated causes. It is also difficult to consider hirsutism as being "idiopathic" if patients demonstrate clear-cut hyperandrogenemia. In essence, in the patient with hirsutism, normoovulation, and hyperandrogenemia, while the source of the elevated androgens may remain a mystery, the physical finding of hirsutism is explained by the increased circulating androgen levels. Consistent with this concept, investigators have defined IH as hirsutism in the presence of a normal total T, alone (67) or combined with normal levels of androstenedione, dehydroepiandrosterone sulfate (DHEAS), LH/FSH, and 17-hydroxyprogesterone levels, although the status of ovulatory function was not considered (79).

To exclude those patients with both ovulatory dysfunction and hyperandrogenemia, we (76, 80) and others (81–83) have defined IH more strictly as diagnosable only in women who have 1) hirsutism *and* 2) normal ovulatory function *and* 3) a normal androgen profile (Table 2). Since a history of "regular menses" does not accurately reflect ovulatory status in the hirsute patient (76), ovulatory function must be confirmed by using a daily basal body temperature (BBT) charting and/or a luteal phase (day 20–24 of the menstrual cycle) progesterone level. Hirsute patients demonstrating ovulatory dysfunction and no evidence of other related disorders (*e.g.*, NCAH, thyroid dysfunction) can be considered to have PCOS (72). Nonetheless, the presence of polycystic-appearing ovaries need not be used to exclude IH, as long as the patient has regular ovulation and normal androgen levels. Since the measurement of a total T serum level is insensitive (84–87), we prefer to exclude hyperandrogenemia by at least measuring DHEAS and total and free T levels. In addition, the follicular phase basal 17-hydroxyprogesterone level should be measured, or an ACTH stimulation test performed, to exclude 21-hydroxylase-deficient NCAH (88). Thyroid dysfunction should also be excluded, generally by the measurement of TSH. The ingestion of exogenous androgens should also be excluded.

In conclusion, the current diagnosis of IH should be one of exclusion, in which ovulatory dysfunction, hyperandro-

TABLE 2. The evolving diagnostic criteria for idiopathic hirsutism

Years in use	Definition	Criteria
1950s to 1970s	Hirsutism of unknown etiology	Hirsutism without pathologic evidence of polycystic or "enlarged" ovaries, elevated LH/FSH ratio, or increased 24 h urinary 17-ketosteroids.
1980s	Hirsutism with a history of regular menstrual cycles	Hirsutism with a history of regular menstrual cycles, frequently excluding patients with sonographic evidence of polycystic ovaries.
1990s to present	Hirsutism with normal ovulatory function and normal circulating androgen concentrations	Hirsutism without ovulatory dysfunction (verified by either BBT or P4 level in luteal phase) or elevated circulating androgens (measuring at least total and free T, and DHEAS); and excluding related disorders (*e.g.*, NCAH, thyroid disorders, and exogenous androgen ingestion).

Abbreviations: T, Testosterone, DHEAS, dehydroepiandrosterone sulfate; P4, progesterone; BBT, basal body temperature; NCAH, nonclassic adrenal hyperplasia.

genemia, and other defined androgen excess disorders are ruled out. This strict definition of IH excludes the hirsute patient with normal ovulatory function but with elevated circulating androgen levels. Although the underlying pathophysiology in these women remains unclear, a thorough discussion of these patients is beyond the scope of this review.

V. Prevalence of IH

Because the definition of IH has varied significantly over the past three decades, a precise estimate of its prevalence as a cause of hirsutism has been difficult to establish. Between 50% and 70% of all hirsute women demonstrate regular menses, suggestive of IH (75–77, 80). Nonetheless, of these women approximately 40% to 75% also have elevated circulating levels of either DHEAS, or total and/or free T (77), and/or frank ovulatory dysfunction (76, 80). Bernasconi and colleagues (89) defined IH as the presence of hirsutism in the absence of ovulatory dysfunction (determined by the measurement of a luteal progesterone level), and noted that 55% of 226 consecutive patients seemed to have IH. Unfortunately, these investigators did not consider the level of circulating androgens in the diagnosis of IH, and consequently the mean free T and androstenedione levels were higher among their IH patients, compared with controls.

We recently studied the prevalence of IH in Alabama, defining the disorder by the presence of significant hirsutism in the absence of both ovulatory dysfunction and hyperandrogenemia (76). Of 132 consecutive hirsute women studied, at initial evaluation 48% had cycles less than 35 days in length (*i.e.*, "regular"). Of these patients, 39% actually had oligo/anovulation as evidenced by their BBT chart and luteal phase progesterone level. Hence, among our hirsute patients, fully 71% had either overt or subtle ovulatory dysfunction and could be considered as having PCOS (Fig. 3). Of the remaining 39 patients with hirsutism and regular ovulatory function, 22 (17% of the total) with total T, free T, and DHEAS levels within normal were diagnosed as suffering from IH under the strict definition. A similar study in southern Italy confirmed these results. Of 598 consecutive Italian patients complaining of hirsutism, 298 (51%) reported "regular" cycles (80). Nonetheless, of these women only 36 patients (or 6% of all hirsute women seen) had normal circulating DHEAS and total and free T levels, consistent with the diagnosis of IH.

As these data demonstrate, when IH is defined strictly by the presence of hirsutism in conjunction with regular ovulation *and* normal androgen levels, only 5–15% of consecutive hirsute women carry this diagnosis. It must be emphasized that the prevalence of IH probably varies widely according to the ethnic or racial group studied, although this remains to be demonstrated. In addition, the quality of the laboratory measuring the androgen levels and the availability of normative data based on adequate numbers of well characterized healthy controls greatly influence the ability to detect hyperandrogenemia. Finally, it is clear that ovulatory function must be objectively assessed in hirsute patients who claim to have "regular" menstrual cycles, since 40% of these

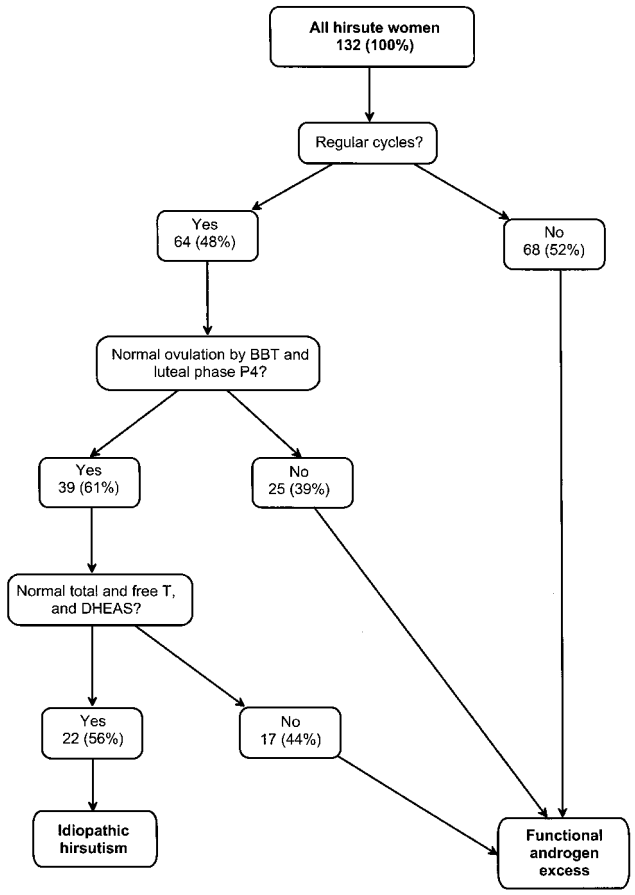

FIG. 3. Algorithm of 132 consecutive patients seen prospectively to determine the prevalence of IH. Patients with PCOS (oligo-ovulation and hirsutism and/or hyperandrogenemia) and women with hirsutism and hyperandrogenemia but apparently normal ovulatory function were considered as having functional androgen excess. If the diagnosis of IH is based solely on the presence of hirsutism *and* regular ovulation regardless of androgen levels, then 29% of our total untreated hirsute population could be considered affected. However, only 17% of all hirsute patients can be diagnosed as having the disorder if IH is defined as hirsutism *and* regular ovulation *and* normal androgen levels. BBT, Basal body temperature chart; P4, progesterone level. [Reprinted with permission from R. Azziz *et al*: *Fertil Steril* 70:274–278, 1998 (76) © American Society for Reproductive Medicine].

are actually oligo/anovulatory. Overall, our data suggest that IH, if strictly defined, is a relatively uncommon cause of hirsutism.

VI. Pathogenesis of IH

Little information is available regarding the pathogenesis of IH. This deficiency is due to a paucity of adequate molecular techniques to test the hypotheses proposed, compounded by the fact that most previous studies have included patients in whom the diagnosis of IH was not strictly established. In this section, we review some of the predominant hypotheses regarding the etiology of this disorder.

A. Exaggerated peripheral 5α-RA activity in IH

It could be postulated that women with IH have a primary increase in cutaneous 5α-RA activity. Jenkins and Ash (90) reported that in two of three women with "idiopathic hirsutism" the production of DHT from T by minces of suprapubic skin was 50–100% above the upper normal limit. Unfortunately, while these subjects with IH had normal androgen levels, no mention was made of their ovulatory function. Serafini and Lobo (91) studied 10 women with IH (defined by the presence of hirsutism, normal androgen levels, and regular menstrual cycles) and reported that these patients had higher levels of 5α-RA activity measured biochemically in genital skin, compared with controls. Although circulating androgens are known to increase peripheral 5α-RA activity (51, 92), the circulating androgen levels were normal in the IH women studied. Hence, the investigators tentatively concluded that in the patients studied increased skin 5α-RA activity could be a primary pathophysiological event (91).

It is possible that increased skin 5α-RA may not be a factor unique to IH and may simply reflect the development of hirsutism. For example, in the studies by Jenkins and Ash (90) and Serafini and Lobo (91), a similar increase in skin 5α-RA activity was observed among patients with PCOS. It was proposed that, in contrast to patients with IH, the increase in peripheral 5α-RA activity in women with PCOS occurs secondarily to their higher androgen levels (91). In fact, these investigators reported other data that suggest that peripheral events play a role in the development of hirsutism, even among patients with PCOS (93). Hence, it is possible that the increased peripheral 5α-RA activity observed in IH simply reflects the development of hirsutism, regardless of cause. Overall, from the available data it is not possible to conclusively establish that increased 5α-RA activity plays a primary role in the development of IH.

Likewise, it is still unclear which of the 5α-RA isoenzymes, if any, is predominant in the development of IH. Using molecular analysis of isoenzyme-specific mRNAs, the concentrations of the type 1 5α-RA isoenzyme in sebaceous glands was higher in patients with acne (94, 95), with no significant differences in the concentration of the type 2 isoenzyme. Consistent with this finding, the use of finasteride (a type 2 5α-RA inhibitor, see below) had no effect on sebum production in men being treated for prostate hyperplasia (96). Nonetheless, in contrast to acne, it is likely that the type 2 isoenzyme plays a significant role in hirsutism since finasteride is at least partially effective in its treatment (97, 98). Further studies using well defined patients are required to establish the precise role of each of these isoenzymes in the development of hirsutism, and specifically IH.

B. Androgen receptor polymorphisms

Although it has been postulated that a difference in the number of peripheral androgen receptors results in IH, no quantitative differences in androgen binding capacity (*i.e.*, androgen receptor content) between IH patients and controls have been found (81). However, it is possible that qualitative, rather than quantitative, differences in the androgen receptor may exist in women with IH. Such a functional difference may result from genetic alterations of the androgen receptor and may be sufficient to explain the development of hirsutism in the absence of changes in circulating androgen levels (99). In fact, genetic variations of the androgen receptor have been associated with the development of other androgen-sensitive disorders, such as prostate cancer (100). Furthermore, it is known that sequence variations occur more often in the androgen receptor gene than in other steroid receptor genes (101), and it is possible that these polymorphisms affect androgen sensitivity and phenotypic expression.

An example of a common genetic variation, possibly affecting the function of the androgen receptor, is the number of trinucleotide CAG repeats in exon 1 of the androgen receptor gene. These trinucleotide repeats have been found to vary widely (*i.e.*, be polymorphic) among humans (102). The CAG codons encode for a long stretch of glutamines within the amino terminus of the transactivation domain of the androgen receptor. Expansion of this region of the androgen receptor has recently been implicated in the development of androgen-related skin disorders in men and women alike, including androgenetic alopecia and hirsutism (99, 103). In one report the number of CAG repeats of the androgen receptor gene were studied in women with peripheral signs of hyperandrogenism (99). Healthy controls and women with acne were found to have a similar mean (±SD) number of trinucleotide repeats (21 ± 3 and 20 ± 3, respectively), which was higher than that of women with androgenetic alopecia or hirsutism (17 ± 3 and 16 ± 3, respectively). Similarly, another study of 110 Hispanic women with IH found an inverse correlation between the hirsutism score and the size of the CAG repeat in the androgen receptor gene (103). Overall, it is possible that shorter CAG-repeat lengths in the N-terminal domain of the androgen receptor may be associated with the development of androgenetic alopecia and hirsutism.

These studies suggest that the development of hirsutism, and possibly IH, may be influenced to some degree by the molecular characteristics of the androgen receptor. However, the androgen receptor gene is located on the X chromosome and, according to the Lyon hypothesis, only one allele will be generally expressed in target tissues depending on the random pattern of X chromosome inactivation. It is then uncertain which X-linked allele is expressed in the tissues of women with hirsutism, since many women are heterozygous for the size of the CAG repeat region of the androgen receptor gene. Overall, further studies are required to determine the role of these androgen receptor gene polymorphisms in the development of IH.

C. Altered androgen metabolism

Since androgens themselves stimulate peripheral 5α-RA activity (44, 51), the presence of increased 5α-RA activity is not sufficient proof of a primary exaggeration in the function of this enzyme. In fact, it remains unclear whether excessive exposure of the hair follicle to androgens from the circulation plays a role in the development of IH. In this regard, some investigators have reported that the production rate of various androgens was increased in patients with IH (66, 69).

However, in these studies IH was defined as the presence of "unexplained hirsutism," and a considerable fraction of patients also had irregular menstrual cycles and increased androgen levels.

Glickman and Rosenfield (104) studied androgen metabolism in the pubic hair follicles of four patients with IH. These investigators noted that only one of their patients had an abnormality in hair follicle metabolism. This patient had an exaggerated rate of inactivation of 17β-hydroxysteroids (*i.e.*, T and DHT) to 17-ketosteroids, which could not be considered to increase the effect of androgens on the hair follicle. Faredin and Toth (105) studied the lower abdominal skin of three patients with IH defined by the presence of regular menstrual cycles and normal androgen levels, although two of the women had increased circulating levels of androstenedione (105). These investigators reported a series of abnormalities in local androgen metabolism, although an exaggerated conversion of androstenedione to T appeared to be predominant, suggesting an exaggeration in 17β-hydroxysteroid activity. Overall, the role of systemic or local abnormalities in androgen metabolism in IH remains to be better defined.

Insulin resistance and hyperinsulinism are now recognized as important features of PCOS, stimulating ovarian androgen secretion and suppressing sex hormone-binding globulin (SHBG) production (106). Insulin has been demonstrated to stimulate hair follicle growth *in vitro* (19). Nonetheless, it is unclear whether patients with IH also have abnormalities of insulin action. Paoletti and colleagues (107) noted that patients with both IH and PCOS had significantly higher fasting and oral glucose-stimulated levels of glucose, insulin, and C-peptide, compared with controls. Furthermore, the administration of the antiandrogen flutamide significantly blunted the fasting and stimulated levels of insulin in IH, but not PCOS, patients. Nonetheless, the investigators did not confirm the presence of normal ovulatory function in their patients with presumed IH, although these women had regular menses, an LH/FSH level less than 1, and a normal ultrasound of the ovaries. Hence, the presence of abnormalities of insulin action and its role and importance in the pathology of women with IH remain to be demonstrated.

Overall, it is clear that only an improved understanding of the control and physiology of 5α-RA and the AR will allow us to further elucidate the pathophysiology of IH. Currently, with our limited understanding of the pathogenesis of IH, the term "idiopathic" for those patients who have regular ovulation, normal circulating androgens, and hirsutism remains appropriate. Nonetheless, as this disorder is under active investigation, the definition of the disorder is a dynamic one, subject to revision as our understanding of the pathogenesis of the disorder develops.

VII. Serum Markers of IH

A. DHT

If women with IH have a primary increase in peripheral 5α-RA activity, increased circulating levels of DHT could be expected. However, serum levels of this 5α-reduced androgen are frequently normal in hirsute women (93), probably because most DHT produced in skin is not secreted into the circulation but acts locally before its rapid metabolism.

B. 5α-Androstane-3α,17β-diol glucuronide

The DHT metabolites, 3α- and 3β-androstanediol, have also been studied as potential serum markers of IH. Similar to DHT, little or no unconjugated androstanediol is found in the circulation (108). However, the conjugated metabolites of these steroids have a much longer half-life and are present in significant amounts in serum, allowing their routine measurement. Unfortunately, although the circulating or urinary levels of the androgen metabolites, 3,17β-androstanediol sulfate or androsterone glucuronide, may be increased in patients with IH, they are also often normal. Overall, 3,17β-androstanediol sulfate or androsterone glucuronide are not useful as markers for the disorder (109).

A number of investigators have suggested that the levels of 3α-adiol-G may serve as a marker of peripheral 5α-RA activity (72, 108, 110, 111). However, the serum level of this conjugate is not only dependent on skin 5α-RA activity, but also on the circulating levels of androgen precursors (74, 112, 113). Consequently, higher levels of circulating 3α-diol-G have been reported in hirsute women with PCOS, and those with adrenal or ovarian androgen excess (93, 114–116). Since DHEAS and androstenedione are the major precursors of 3α-adiol-G, the level of this conjugate closely reflects adrenal androgen biosynthesis (109). Thus, elevated serum levels of this conjugate either simply reflect the presence of hirsutism, regardless of cause, or the excess production of DHEAS by the adrenal or androstenedione from any source. In fact, higher levels of circulating 3α-diol-G suggest the presence of IH *only* when all other circulating androgens are normal. However, up to 20% of women with IH may demonstrate normal serum levels of 3-adiol-G (111). The measurement of serum 3α-adiol-G does not appear to be of greater value than the physical observation of excess hair growth in the diagnostic evaluation of the hirsute female. In addition, the levels of this hormone do not predict therapeutic response (74, 117), and we do not recommend the routine measurement of 3α-adiol-G serum levels in the evaluation of IH or in other hirsute patients.

VIII. Therapy of IH

A. Androgen suppression

Oral contraceptive pills (OCPs) reduce circulating androgen levels through suppression of circulating LH and stimulation of SHBG levels and have been documented to reduce hirsutism in hyperandrogenic patients (118). Although many of these studies included patients with IH, investigators generally defined the disorder loosely and frequently did not distinguish between patients with IH and other hirsute women when analyzing results. Overall, studies documenting the effect of OCPs [not containing cyproterone acetate (CPA)] in patients with well defined IH are not available. Finally, it is possible that the administration of OCPs may further improve the results of antiandrogen therapy (see below).

In addition to OCPs, androgen suppression can be achieved using long-acting GnRH analogs. Defining IH as hirsutism in the face of regular menstrual cycles, treatment with GnRH analogs appeared to be generally effective in reducing hair growth in the small number of patients studied (119, 120). Falsetti and Pasinetti (121) studied 16 patients with IH, defined by normal androgen values, although 75% also had regular ovulatory cycles, and 16 patients had PCOS. All women were randomized to receive either leuprolide acetate or leuprolide plus an OCP containing 35 mg ethinyl estradiol (EE) and 2 mg CPA. Both regimens resulted in a 20–25% decrease in the hirsutism score and a reduction in hair diameter in either patient group. These data suggest that reducing androgen levels, even when originally within the normal range as in IH, can result in the amelioration of hirsutism. It is possible that the reduction in circulating androgens leads to a decrease in the availability of substrate for peripheral 5α-RA, as well as a reduction in the overall 5α-RA activity, which is generally stimulated by androgens (51).

B. Androgen receptor blockers

1. Spironolactone (SPA). The most common androgen blocker used for the treatment of hirsutism in the United States is SPA, an aldosterone antagonist structurally related to progestins. Overall, SPA is an effective therapy for hirsutism (122–124), including IH (98). In addition to antagonizing aldosterone, SPA competes with DHT for binding to the androgen receptor. However, SPA has only 1/20th the binding affinity of DHT for the androgen receptor, explaining why high doses of the drug may be required for adequate suppression of hair growth. In addition, SPA has an inhibitory effect on 5α-RA and competes with androgens for binding to SHBG (125–128). SPA, or its 17-hydroxylated metabolites, also inhibits the action of various enzymes involved in androgen biosynthesis, although this effect is generally observed only at doses greater than 200 mg/day (125–128). SPA also demonstrates variable progestational activity, which may decrease the circulating LH/FSH ratio by decreasing the response of LH to GnRH. In turn, this decrease may ameliorate the LH-stimulated secretion of ovarian androgens (127, 129).

Since SPA acts through mechanisms different from that of OCPs, it may be possible to improve the overall therapeutic effectiveness of this drug by combining these medications, even in patients with IH (130–132). As previously noted, the peripheral production of DHT is both the result of 5α-RA activity and of the circulating levels of precursors, primarily T and androstenedione. The use of OCPs in combination with SPA, while providing adequate contraception, also helps to minimize the dysfunctional uterine bleeding or worsening oligomenorrhea often observed in women using SPA alone.

SPA was initially approved and marketed as a diuretic, and primary side effects include polyuria, nocturia, and hypotension with associated headaches, fatigue, or even syncope. Nonetheless, patients rapidly develop a tolerance to this effect with chronic use, and few changes in serum electrolytes or blood pressure are seen with long-term therapy (122, 133). Because of its potassium-sparing nature, SPA should not be used in conjunction with other potassium-sparing diuretics, thiazides, in renal insufficiency, or with excess potassium intake, since patients may develop life-threatening hyperkalemia. Physicians may wish to evaluate serum electrolytes and blood pressure 2–4 weeks after treatment is started.

Other minor side effects commonly associated with SPA use include gastritis/dyspepsia and dry skin (122, 133). SPA should be taken with food, as this increases its absorption and reduces its potential for gastritis. In addition, the development of irregular ovulation and menstruation in women who previously had normal ovulatory function can occur (122, 133). The incidence of metrorrhagia or polymenorrhea in these patients may be decreased by administering SPA days 4 through 21 of the menstrual cycle (133) or by combining the medication with an OCP (see above) (130, 131). Minimization of other side effects may be also achieved by slowly increasing the dose by 25-mg increments, to a maximum of 100–300 mg/day. Before beginning therapy, patients should be educated regarding potential side effects and reassured that most will be temporary at best. While daily doses of 100 mg/day are generally effective for the treatment of hirsutism, higher doses (200 to 300 mg/day) may be preferable in very hirsute or markedly obese women.

Absolute contraindications to SPA use include renal insufficiency, anuria, chronic renal impairment, hyperkalemia, pregnancy, and abnormal uterine bleeding. The carcinogenic potential of SPA has been long debated. The package insert states that chronic toxicity studies in rats, using 25 to 250 times the usual human dose (on a body weight basis), resulted in benign adenomas of the thyroid and testes, malignant mammary tumors, and hepatic changes. Because of these findings in the rat, it has been recommended that SPA not be given to women with a genetic predisposition to breast cancer (134). SPA and its metabolites cross the placental barrier, and studies in rats indicate feminization of the male fetus. Therefore, SPA should be used in conjunction with an effective means of contraception.

2. Flutamide. Flutamide, a nonsteroidal antiandrogen, is available in the United States as adjunctive therapy for the treatment of prostate cancer. It is considered a pure androgen receptor blocker, although at high doses it may also reduce the synthesis of androgens or increase their metabolism (135). 2-Hydroxyflutamide is the principal metabolite of this drug which inhibits DHT binding to the androgen receptor. Flutamide has been found to be as effective or more effective than SPA for the treatment of hirsutism (82, 123, 124, 136, 137). In their study of patients with well defined IH, Couzinet and colleagues (82) noted a progressive decrease in the hirsutism score throughout 12 months of treatment with flutamide, 500 mg/day. None of the 10 patients experienced significant side effects. Nonetheless, there have been concerns regarding the possibility of serious adverse events, primarily hepatotoxicity (138, 139).

In the 5 yr after the marketing of flutamide, the U.S. Food and Drug Administration received reports of 20 deaths and 26 hospitalizations for flutamide-induced hepatotoxicity (139). While the vast majority of these were men, one of the hospitalized patients was a 45-yr-old female being given higher than standard doses of the drug (1,000 mg/day) for

the treatment of alopecia and oily skin (139). Hence, we recommend monitoring serum markers of hepatic function at regular intervals during therapy. Other lesser side effects of flutamide include dry skin and a greenish tint to the urine. While doses of 250 mg twice daily are generally used, a single dose of 250 mg/day may be effective in some patients (137). Finally, in animal models, flutamide has a feminizing effect in the male fetus (140, 141), and nonsterilized patients of reproductive age should be advised to use effective contraception.

3. Cyproterone acetate. Cyproterone acetate is a 17-hydroxyprogesterone acetate derivative with strong progestogenic properties, similar in potency to megesterol acetate (142, 143). The contraceptive properties of CPA occur in part due to gonadotropin suppression. CPA is also categorized as an antiandrogen, since it competes with DHT for binding to the androgen receptor. It produces a decrease in circulating T and androstenedione levels through a reduction in circulating LH and has been used as an effective treatment for hirsutism (144). In a dose ranging study, Barth and colleagues (145) noted that an OCP containing 35 mg EE and 2 mg CPA per day was as effective in reducing hirsutism as the same OCP with the addition of 20 mg/day or 100 mg/day of CPA for the first 10 days of the cycle. Cyproterone acetate in doses of 50–100 mg/day, combined with 30–35 mg EE, is as effective as the combination of SPA, 100 mg/day, and an OCP in the treatment of hirsutism (146, 147). In another study a triphasic OCP containing CPA, 12.5 mg/day for the first 10 days of the cycle (plus varying doses of EE), was found to be as effective as flutamide, 250 mg/day (148). In contrast, an OCP containing CPA, 2 mg/day, in combination with EE, 35 mg/day, seems less effective than 100 mg/day of SPA (149).

Few studies investigating the efficacy of CPA in patients with IH are available. Jasonni and colleagues (150) treated 11 subjects with IH, defined by normal T and DHS levels and ovulatory cycles, and 15 women with PCOS with CPA, 50 mg/day, from days 1–15 in combination with 0.1 mg/day transdermal 17β-estradiol. They reported that the hirsutism score fell by 50% over 6 months, although in reporting their results the investigators did not differentiate between women with IH and PCOS. Peereboom-Wynia and Boekhorst (151) treated another 11 well defined women with IH using CPA,100–200 mg, on days 5–15 and EE, 50 μg, on days 5–26 of the cycle, and reported a reduction in the hair density and diameter (151). Overall, it would appear that CPA is effective in treating patients with IH, although larger studies are still lacking.

This drug is currently not available in the U.S. but has been used for many years in other countries, sold as the OCP Diane-35 or Dianette (2 mg CPA and 35 μg EE/tablet, Schering AG, Germany) or Androcur (50 mg/tablet, Schering AG, Germany). Side effects may include loss of libido. Adrenal insufficiency is a rare complication of CPA therapy, seen primarily in children receiving high doses for the treatment of precocious puberty, and is unlikely to occur in adults (152). As with all antiandrogens, adequate contraception must be used to avoid the possibility of feminizing a male fetus, particularly when CPA is used at low doses in intermittent cycles (*e.g.*, 2 mg/day for the first 10 days of the cycle).

C. 5α-RA inhibitors

Since preliminary data suggest that IH is determined by increased peripheral activity of 5α-RA, ideal therapy should include agents able to inhibit the activity of this enzyme. One such agent, finasteride, is currently available in the United States for the treatment of men with androgenetic alopecia (Propecia, 1 mg finasteride, Merck & Co., Inc., West Point, PA) and benign prostate hyperplasia (Proscar, 5 μg finasteride, Merck & Co., Inc.), and has been found to be effective in the treatment of IH (97, 98). Finasteride primarily inhibits type 2 5α-RA activity (153).

In a 9-month prospective randomized trial, Erenus and colleagues (98) noted a greater decrease in hirsutism score in 20 patients with IH treated with SPA, 100 mg/day, compared with 20 patients treated with finasteride, 5 mg/day (a 42 $\pm$ 12% *vs.* 15 $\pm$ 15% decrease, respectively). Other investigators have also suggested that finasteride is somewhat less effective than the antiandrogens for the treatment of hirsutism. Venturoli and colleagues (148) compared the effects of finasteride (5 mg/day) on hirsutism to flutamide (250 mg/day), ketoconazole (300 mg/day), and CPA (12.5 mg for the first 10 days of each cycle, plus doses of EE ranging from 0.01 mg/day to 0.02 mg/day) in 66 hirsute women. Flutamide and the CPA-estrogen combination had efficacies similar to that of ketoconazole ($-$55%, $-$60%, and $-$53%, respectively), which was modestly, but significantly, better than that of finasteride ($-$44%). Although a significant number of side effects were observed with ketoconazole, few problems were noted with the remaining three treatments, in particular finasteride. Overall, finasteride may be a useful candidate for treating women with hirsutism at a dose of 5 mg/day. In fact, choosing between the various antiandrogens/5α-RA inhibitors available may depend more on side effects and patient tolerance than on specific drug efficacy.

A 5α-RA inhibitor still in clinical testing is dutasteride (GI198745, GlaxoWellcome Co., Research Triangle Park, NC), a "dual" type 1 and type 2 5α-RA inhibitor. It is thought that this compound, although similar in structure to finasteride, will be a more potent inhibitor. Overall, it appears to suppress the type 2 isoenzyme 2–3 times more strongly than finasteride, as well as inhibiting the type 1 form of 5α-RA (154). This compound effectively inhibits DHT production by 99% approximately 24 h after oral administration and may be potentially useful for the treatment of androgenetic alopecia, acne, and hirsutism. Finally, it must be remembered that all of these 5α-RA agents have the potential of feminizing a male fetus (141, 155). All women of reproductive age using these drugs must use effective contraception.

D. Biological modifiers of hair follicular growth

Eflornithine hydrochloride is a new agent (Vaniqa, DFMO/eflornithine 15% cream, Bristol Myers-Squibb Co., Buffalo, NY) that has completed clinical phase III testing as a topical cream for decreasing or arresting facial hair growth in women. Although this agent is thought to affect hair follicle growth by inhibiting keratin protein synthesis (156–158), the exact mechanism(s) of action and the degree of efficacy are still inconclusive.

E. Mechanical control of hirsutism

In general, mechanical means of controlling, removing, or destroying unwanted hairs should be considered complementary to medical management in the treatment of the hirsute. Various options are available including shaving, depilation, electrology, and laser epilation, as follows.

1. Shaving and depilation. Plucking, waxing, or shaving facial and body sites are common means of hair removal for many women. However, these cosmetic methods of hair removal can irritate the skin, possibly resulting in folliculitis, pseudofolliculitis, and ingrown hairs. Although the majority of reports studying the effect of hair removal methods on hair growth rates have used male subjects (for review see Ref. 159), Peereboom-Wynia (159) studied the impact of various shaving and depilating methods on thigh hair growth in 15 women with IH. Overall, neither shaving nor depilation performed either once or over a series of 12 treatments had any effect on hair growth. Unfortunately, in this study IH was defined as hirsutism without obvious cause, with 20% of subjects having irregular cycles and circulating androgen levels that were not assessed. Further studies of the impact of mechanical means of hair removal on the growth of facial and body hair in IH and other hirsute women are needed.

2. Electrology. The role of electrologists in the management of patients with hirsutism must not be overlooked. Electrolysis (*i.e.*, electroepilation) results in long-term, although gradual, hair destruction (160, 161). With repeated treatments, efficacy ranges from 15 to 50% permanent hair loss (162). Scarring can occur after electrolysis, especially if the procedure is inexpertly performed (163). It should be recognized that electrologists are often the first individuals to whom the hirsute patient turns for assistance. In one study of 779 consecutive new clients seeking electrology, 40% were noted to have potential risk factors for hyperandrogenism according to their response to a standardized questionnaire (164). Approximately 20% of women evaluated had a hirsutism score greater than 6, while PCOS was evident in more than 50%. Importantly, only 26% of clients referred for a free medical evaluation actually followed through, an indication of the high level of ignorance regarding the availability of medical treatment among hirsute women. Thus, it behooves all physicians caring for these women to establish and maintain communication with the electrology profession, referring patients for electroepilation to those who are properly trained. It should also be noted that certification and training requirements for electrology vary widely from state to state.

3. Laser epilation. Directed damage to hair follicles based on the theory of selective photothermolysis has been reported recently (165, 166). Various lasers have been evaluated for their effectiveness in treating body hair. High energy ruby light was shown to be effective as a tool for removal of unwanted hair growth in 1979 and was introduced for this clinical use in 1992, with the free running long pulse ruby laser introduced for routine use in 1995. The mode of action has been suggested to be selective hair thermolysis, which implies that light is selectively absorbed in certain structures of the FU. In recent years the 694-nm ruby lasers, the 1064-nm Q-switched Nd:YAG laser, the 755 nm long-pulsed alexandrite, and the 800-nm diode laser have been introduced for the removal of unwanted hair. For all instruments the principal mechanism underlying hair destruction has been photothermolysis of the darker pigmented hairs. Gray and fair-colored hair should not be expected to disappear. Laser-treated hair follicles go into temporary telogen (167), which may last for up 2 yr after treatment (165, 166). It is still unclear whether clinically significant permanent hair follicle destruction does occur with laser therapy.

Unfortunately, peer-reviewed reports of the long-term benefit of lasers for the treatment of hirsutism are scant. One investigator compared the results of a single treatment with the normal mode ruby laser (694 nm, 270 μsec, 6-mm beam diameter) in six skin areas on the thighs or backs of 13 volunteers, to shaving or wax epilation (165). Terminal hairs were counted before and after laser exposure. Results indicated that with a single treatment session 4 of the 13 (31%) subjects demonstrated permanent hair loss when evaluated 2 yr later, while 6 other volunteers (46%) experienced a partial hair loss. In three subjects hair regrowth was complete or nearly complete. Overall, this indicates that laser treatment may be effective in permanently removing hair in some patients, although most may require multiple treatments. Nonetheless, it is unclear whether hirsute women will experience this degree of therapeutic effectiveness, and further studies including these patients are required. Side effects of laser epilation include pigmentary changes of treated skin and burning and scarring of the treated area. Most current laser technologies have now minimized these side effects, with the use of more selective wavelengths and cooling devices attached to the probe.

IX. Conclusions

Although the definition of IH has been an evolving process, the diagnosis of IH should be applied only to hirsute patients with normal ovulatory function and circulating androgen levels. It should be remembered that a history of regular menses is not sufficient to exclude ovulatory dysfunction in the hirsute woman. Generally less than 20% of all hirsute women will be diagnosed as having IH, when the condition is strictly defined. The pathophysiology of IH is presumed to be a primary increase in skin 5α-RA activity, probably of both isoenzyme types; and possibly an alteration in androgen receptor function. Nonetheless, confirmation of these hypotheses awaits the study of well defined patients, using skin biopsy samples obtained from multiple body sites and molecular probes. While serum levels of 3α-adiol-G are frequently elevated in these patients, this measure is by no means an exclusive marker of the disorder and holds little clinical value. Therapeutically, these patients respond, at least partially, to antiandrogen or 5α-RA inhibitor therapy. Pharmacological stimulation of circulating SHBG levels, and/or suppression of ovarian or adrenal androgen secretion (*e.g.*, with an OCP), may be of additional, albeit limited, benefit. New therapeutic strategies such as laser epilation or the use of new biological response modifiers may play an important role in offering a more effective means of treat-

ment to remove unwanted hair. Further investigations into the genetic, molecular, and metabolic aspects of this disorder, including only well defined patients, are needed.

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