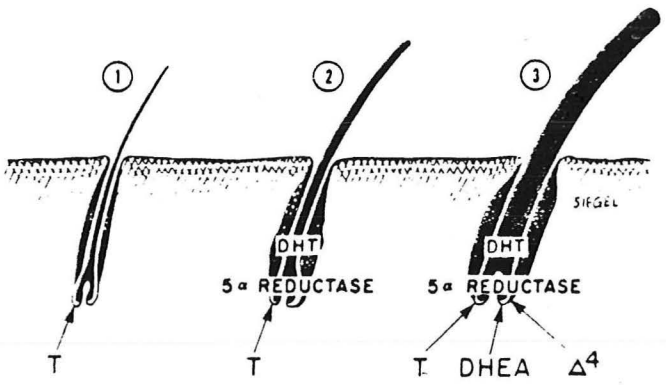
Endo

Hirsutism



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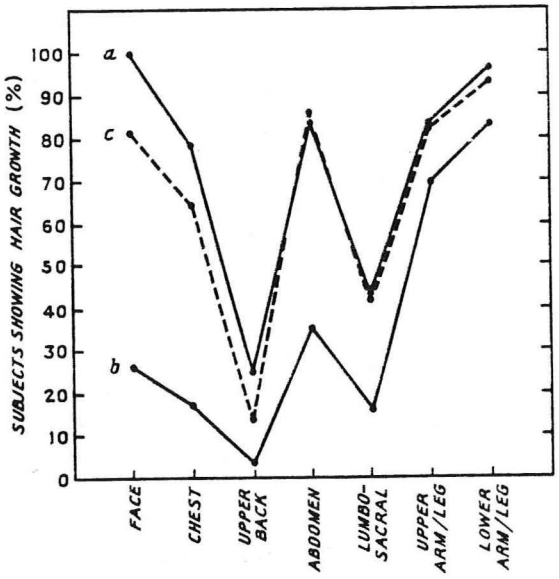
Hirsutism, the growth of excessive hair in women in a pattern characteristic of that seen in men, is a commonly encountered clinical problem. Several investigators have examined the prevalence of hirsutism in selected populations (1-3). In her study of 400 English and Welsh university women, McKnight identified 36 (9%) whom she considered to be particularly hirsute, and whose pattern of hair growth closely paralleled that seen in normal men (Fig. 1) (1). In a more semiquantitative analysis of hair growth comprising 161 women between the ages of 18 and 38, Ferriman and Gallwey found varying degrees of increased hair growth in approximately 10%, but in less than 5% was the hirsutism more advanced (2). However, it is clear from these various surveys that many other women not considered to be hirsute do have growth of terminal (coarse, pigmented) hair in what is generally perceived as a male distribution. For example, in the group of young women studied by McKnight, terminal hair was present on the face in 26%, on the chest or breast in 17%, on the abdomen in 35%, and in the lumbosacral area in 16% (Fig. 1). Similar prevalence data were obtained by Ferriman and Gallwey (2). In older women the pattern of hair growth is altered such that facial hair is more common, but growth of hair in other regions declines (2, 3). Thus there is a continuum of hair growth in women such that any separation between normal and hirsute must to some extent be arbitrary. The dividing line will vary depending on the age and genetic background of the individual as well as on prevailing cultural attitudes. From a clinical standpoint, it is important to be able to distinguish those women whose hirsutism heralds the onset of a serious underlying disorder from the majority in whom psychological distress is the predominant consequence of increased hair growth. Before discussing the evaluation and management of hirsutism, I will consider some of the factors that modulate normal hair growth and distribution, the features of androgen production in normal women, and characteristics of the hyperandrogenism found in hirsute women.

Figure 1



(Ref. 1)

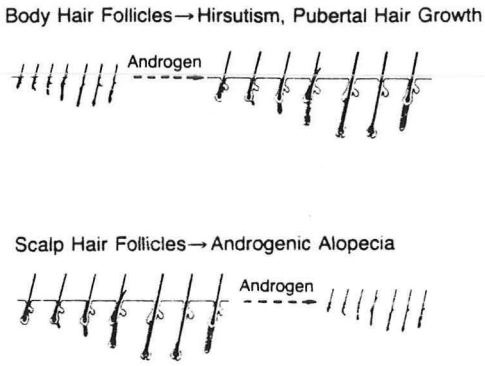
Regions of terminal hair growth in (a) 239 adult men, (b) 400 normal young women, and (c) 36 hirsute young women.

FACTORS MODULATING HAIR GROWTH AND DISTRIBUTION

Hair follicles first appear during the third month of gestation, increase in number over the next 3 months, and thereafter are fixed in number for the remainder of fetal and postnatal life (4). There are no differences in the number of hair follicles between men and women.

There are 3 basic types of hair. Lanugo hair, the fine, short, lightly pigmented hair that covers the fetus, usually completes its entire growth cycle before birth. Vellus hair begins to grow postnatally. This hair is thin in caliber and generally unpigmented, and is the type of hair that covers most of the body before puberty. In women, hair on the face and trunk usually remains vellus in character throughout life. Terminal hair is the thick, pigmented hair that before puberty is present only on the scalp, eyebrows, and eyelashes (5, 6). Any given hair follicle can produce either vellus or terminal hair. Follicles in certain regions of the body can be transformed from vellus to terminal on exposure to androgen (Fig. 2). On the other hand, terminal hair on the scalp in some individuals is transformed by androgen to vellus hair, producing so-called male-pattern baldness. During the gradual transition from vellus to terminal hair, an intermediate between the two types of hair is seen that has characteristics of both (5, 6).

Figure 2



(Ref. 5)

Effect of androgen on vellus follicles of the face, trunk, axillary, and pubic areas, and on terminal follicles in the scalp of bald trait men.

Androgen-dependent follicles are located on the pubis, axillae, back, face chest, abdomen, and extremities. Although postpubertal levels of androgen are necessary for the transformation of vellus to terminal follicles in these areas, other factors are integral determinants of the ultimate extent of the transformation (Table 1) (5). As in other androgen target tissues, expression of androgen action in the hair follicle is dependent on the presence of a high affinity intracellular hormone receptor. In addition, local conversion of

testosterone to its 5α-reduced product dihydrotestosterone is required for normal growth of androgen-dependent hair (7). The sensitivity of responsive follicles to androgen varies from site to site. For example, follicles in axillary and pubic areas grow in response to the low levels of circulating androgen present in normal women, whereas those on the face and trunk require much higher androgen levels for growth. There are also other poorly defined factors that either suppress or enhance androgen-mediated hair growth. Genetic factors act in a permissive manner with androgen. They account for much of the interindividual variability in the follicular response to a given level of androgen.

Table 1

Determinants of Androgen-Mediated Hair Growth

Postpubertal levels of circulating androgen
Intracellular androgen receptor
5α-Reductase
Genetic factors

Factors Influencing Androgen- and Non-Androgen-Dependent Hair Growth

Estrogen
Growth hormone
Thyroid hormone
Glucocorticoids
Aging
Seasonal variation
Nutritional status

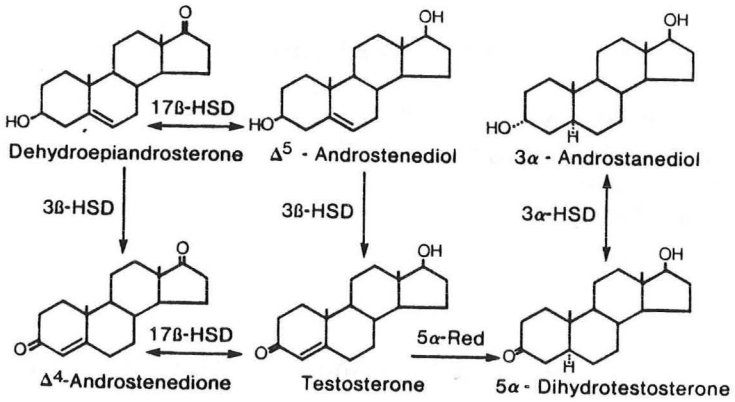
Estrogen also has an effect on hair growth. This is best demonstrated in untreated women with Turner's syndrome. These women usually have some pubic and axillary hair due to androgen secretion by the adrenals, but when given replacement estrogen, hair in these regions increases (8). Growth hormone, thyroid hormone, and glucocorticoids also modulate hair growth, but they do not effect transformation of vellus to terminal hair in androgen-responsive follicles. Other factors such as aging, seasonal variation, and nutritional status appear to affect hair growth by altering the length of the various phases of the normal hair growth cycle (5).

ANDROGEN PRODUCTION AND METABOLISM IN WOMEN

The 4 primary circulating androgenic steroids in women are dehydroepiandrosterone (DHEA) and its sulfo-conjugate (DHEA-S), androstenedione (A) and testosterone (T) (Fig. 3). Plasma levels and production rates of these steroids in normal women are summarized in Table 2 (9, 10). In addition to

these androgens, T may be converted by the enzyme 5α-reductase to 5α-dihydrotestosterone (DHT). Of these compounds only T and DHT, by virtue of binding to the intracellular androgen receptor, have intrinsic androgenic activity. In contrast, DHEA, DHEA-S, and A are androgen pre-hormones. These latter steroids do not bind to the androgen receptor and therefore possess no intrinsic androgenic activity. Their capacity to effect androgen action is solely a function of the extent to which they are metabolized to T or DHT in peripheral tissues.

Figure 3



Structures and pathways of interconversion of the major androgens in women. Reversible enzyme reactions are shown by double-headed arrows. 17β-HSD = 17β-hydroxysteroid dehydrogenase; 3α-HSD = 3α-hydroxysteroid dehydrogenase; 5α-RED = 5α-reductase.

Table 2

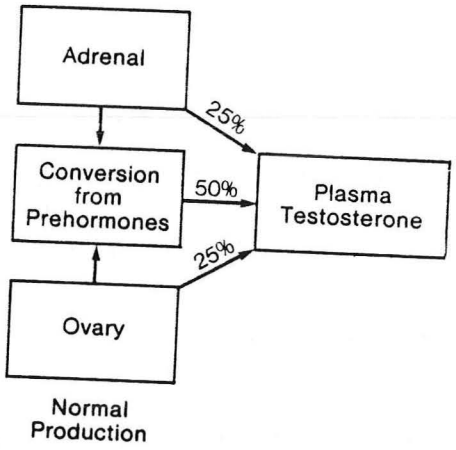
Plasma Androgen Levels and Production Rates in Women

	Plasma Concentration (ng/dl)		Production Rate (mg/day)
	Early follicular	Midcycle	
DHEA*	250-530		6.9
DHEA-S	160,000-260,000		8.1
Androstenedione*	100-150	210	3.3
Testosterone	20-30	50	0.23

*Diurnal variation occurs.

The origins of circulating T in normal women are depicted in Figure 4 (11). The majority of T production, 50 to 70%, is derived from the peripheral metabolism of A in skin and other, predominantly extrasplanchnic, tissues (10, 12). Metabolism of DHEA (and of another androgen precursor Δ^5-androstenediol) accounts for only 10 to 15% of plasma T (13, 14). The remaining 20 to 40% of circulating T is directly secreted by the ovaries and adrenal glands. Estimates of the direct ovarian contribution to T production range from 5 to 20% and of the adrenal contribution from 0 to 30% (11, 15).

Figure 4



Schematic diagram of the components of normal production that affect the plasma testosterone concentration in women. Prehormones, primarily androstenedione, are secreted by the adrenal and ovary and converted to testosterone in peripheral tissues.

Production of A, DHEA, and DHEA-S is primarily by direct glandular secretion. During the follicular phase of the cycle, approximately half of A production is from the ovaries and half is from the adrenals. At midcycle however the ovarian contribution increases to two-thirds of the total (16). Less than 10% of A production is by peripheral metabolism of precursors (DHEA and Δ^5-androstenediol) (13). Circulating DHEA and DHEA-S are almost exclusively of adrenal origin (80% and 90% respectively) (16).

By contrast, all of the DHT production in normal women (75 µg/d) arises from the peripheral conversion of A (66 µg/d) and T (9 µg/d) (17).

Production of T and other androgens in women is not regulated by a feedback mechanism between the adrenals and ovaries and the hypothalamus-pituitary. Although ACTH and LH do stimulate adrenal and ovarian androgen secretion, respectively, the secreted androgens do not feed back in an autoregulatory manner at the level of the pituitary (11). It is probably best to consider that T production in women is a byproduct of cortisol synthesis by the adrenals and estradiol synthesis by the ovaries.

In nonpregnant women approximately 75 to 80% of circulating T is bound to a specific β globulin termed testosterone-estradiol binding globulin (TeBG). The remainder circulates either free (1%) or loosely bound to albumin (20-25%) (18). It is only this non-TeBG bound fraction of total plasma T that is available for binding to the androgen receptor in androgen target tissues. TeBG does not bind A or DHEA (but does bind other circulating 17β-hydroxysteroids).

Plasma T levels in normal women fluctuate very little, either on a diurnal or day-to-day basis, or in relation to phase of the menstrual cycle (16, 19). A and DHEA levels on the other hand do demonstrate significant diurnal fluctuation, with plasma A concentration varying as much as 50% over a 24-hour period. In addition there is an increase in mean plasma A levels during midcycle.

In summary, T production in women arises principally through peripheral conversion of precursors (primarily A) secreted by the ovaries and adrenals. Some T however is secreted directly. Overall about half of the total daily T production is ovarian in origin and half is adrenal. Neither ovarian nor adrenal androgen secretion in women is directly regulated.

THE CLINICAL SPECTRUM OF HIRSUTISM

In women with hirsutism this pattern of androgen production is altered. Except in women who have been exposed to androgenic drugs, hirsutism is characterized by an increased production of T as well as T precursors. Depending on the amount of androgen overproduction, hirsutism may occur either alone or in association with other signs of defeminization and virilization (oligo/amenorrhea, clitoromegaly, and increased muscle mass). Specific disorders resulting in hirsutism due to increased androgen production are outlined in Table 3. In addition exogenous androgen administration can result in similar clinical effects.

Table 3

Causes of Hirsutism in Women

- Virilizing Tumors
  - Ovarian
    - Sex Cord
      - Sertoli-Leydig (Arrhenoblastoma)
      - Granulosa-Stromal
      - Lipoid Cell
    - Hilus Cell
    - Adrenal Rest
  - Adrenal
    - Virilizing adenoma
    - Carcinoma
- Adrenal Hyperplasia
  - Cushing's disease
  - Congenital adrenal hyperplasia
    - 21-hydroxylase deficiency
    - 11β-hydroxlase deficiency
    - 3β-hydroxysteroid dehydrogenase deficiency
- Ovarian and/or Adrenal Androgen Overproduction
  - Polycystic ovarian syndrome
  - Idiopathic hirsutism

Androgen-producing ovarian tumors. Most virilizing ovarian neoplasms fall into the category of sex cord-stromal tumors, and include Sertoli-Leydig, granulosa stromal, and lipoid cell tumors (20). Other virilizing tumors of the ovary include hilus cell and adrenal rest tumors. All typically secrete T either alone or in combination with A. Plasma DHEA and DHEA-S levels may be normal. Most (50 to 80%) of these tumors are palpable on pelvic examination (21) and are well differentiated and benign; malignant tumors frequently pursue an indolent course (20). They are an uncommon cause of hirsutism and virilization, but should be considered more strongly as a possibility in women with a plasma T greater than 200 ng/dl. Other ovarian tumors such as Brenner and Krukenberg tumors, teratomas, and mucinous cystadenomas do not directly secrete androgen, but stimulate secretion by adjacent ovarian stroma (22).

Virilizing adrenal tumors. These may be adenomas or carcinomas. Pure virilizing adrenal adenomas are very uncommon (23). They almost always secrete T, and less consistently A, DHEA, and DHEA-S. These tumors vary markedly in size but are usually large enough that they can be detected by computerized tomographic scanning and sonography. Adrenal carcinomas frequently result in virilization that is disproportionate to the degree of hypercortisolism (24). In some patients virilization occurs without any clinical evidence of cortisol excess. Because of inefficiency in steroidogenesis by adrenal carcinomas, these tumors are usually extremely large by the time they begin to produce signs of virilization. The characteristic finding is a marked elevation in plasma DHEA-S (resulting in very high levels of urinary 17-ketosteroids).

Cushing's disease. Hirsutism and oligo/amenorrhea are common sequelae of adrenocortical hyperplasia due to an ACTH-secreting pituitary adenoma. Excess ACTH secretion results in stimulation of adrenal androgen production in addition to hypercortisolism. (Cushing's syndrome due to an adrenal adenoma is not characteristically associated with hirsutism, since these tumors almost always overproduce cortisol alone. However, glucocorticoid excess may result in an increase in non-androgen dependent hair growth in these patients.)

Congenital adrenal hyperplasia (CAH). An attenuated or late-onset form of CAH due to 21-hydroxylase deficiency has recently been characterized (25-29). It is transmitted in an autosomal recessive pattern similar to that observed for the classical form of the disorder. Affected women are either homozygous for the "attenuated" allele of the 21-hydroxylase gene or are genetic compounds, carrying one classical and one attenuated allele (Table 4) (28). The prevalence of attenuated CAH among hirsute women is probably on the order of 1 to 2% (30). Manifestations typically do not begin until the peripubertal period. Hirsutism of varying severity, oligo/amenorrhea, and infertility are the principal presenting complaints, and may vary among affected individuals within the same family (28, 29). Moreover some women with biochemically documented 21-hydroxylase deficiency have no manifestations of androgen excess (designated asymptomatic or cryptic). Cortisol secretion remains normal. Heterozygotes for the disorder have no clinical evidence of androgen overproduction. The diagnosis of late-onset 21-hydroxylase deficiency is made by measurement of plasma 17-hydroxyprogesterone (see below). Late-onset forms of 11β-hydroxylase (31, 32) and 3β-hydroxysteroid dehydrogenase (33) deficiency presenting in a manner similar to attenuated 21-hydroxylase deficiency have also been described but are extremely rare.

Table 4

Glossary of terms for disorders of steroid 21-hydroxylase (21-OH) deficiency

Form of 21-OH deficiency	Clinical phenotype	Hormonal phenotype	21-OH deficiency genotype[a]
Classical	Virilized prenatally and symptomatic	Markedly elevated serum 17-OHP and Δ^4-A concentration	$\frac{\text{21-OH deficiency}^{\text{SEVERE}}}{\text{21-OH deficiency}^{\text{SEVERE}}}$
Nonclassical	Symptomatic: virilized postnatally and symptomatic Asymptomatic: not virilized prenatally or postnatally and asymptomatic	Modestly elevated serum 17-OHP and Δ^4-A concentration	$\frac{\text{21-OH deficiency}^{\text{SEVERE}}}{\text{21-OH deficiency}^{\text{MILD}}}$ or $\frac{\text{21-OH deficiency}^{\text{MILD}}}{\text{21-OH deficiency}^{\text{MILD}}}$

[a] The allelic variant which transmits severe 21-OH deficiency is in genetic linkage disequilibrium with HLA-Bw47. The allelic variant which transmits mild 21-OH deficiency is in genetic linkage disequilibrium with HLA-B14.

(Ref. 28)

Polycystic ovarian (PCO) syndrome. This is a common cause of hirsutism and oligo/amenorrhea. Manifestations typically begin during the pubertal period. The hallmark of the disorder is increased androgen production by ovaries that usually are palpably enlarged and contain multiple follicular cysts as well as atretic cysts lined by a hyperplastic theca (34). Evidence of increased adrenal

androgen production is also present. The pathogenesis of the disorder remains enigmatic. It has been speculated that the process leading to PCO syndrome is initiated at the time of adrenarche with an exaggeration of the increase in adrenal androgen secretion that normally occurs at this time (Fig. 5). The adrenal androgens are converted in peripheral tissues to estrogen (primarily estrone), which then feeds back at the hypothalamic-pituitary level to effect an increase in LH release. This increase in LH may then stimulate the ovarian stroma to increase its androgen production and thereby provide additional substrate for peripheral estrogen formation (35). Clinical manifestations of PCO syndrome include hirsutism and virilization, oligo/amenorrhea, infertility, enlarged cystic ovaries, and dysfunctional uterine bleeding. In addition approximately 40% of patients are obese. The clinical spectrum is wide, with the least affected demonstrating only chronic anovulation and no significant hirsutism or palpably enlarged ovaries. Endocrinologic features include elevated plasma levels of T, A, DHEA, estrone, and LH (with a normal or low FSH).

Figure 5

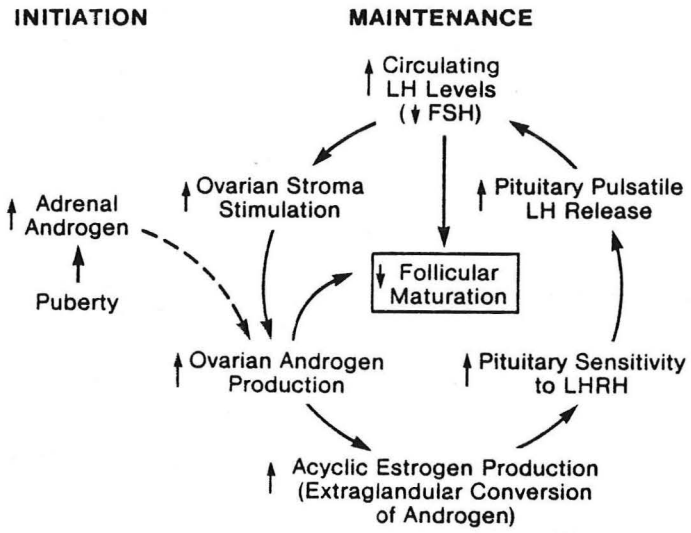


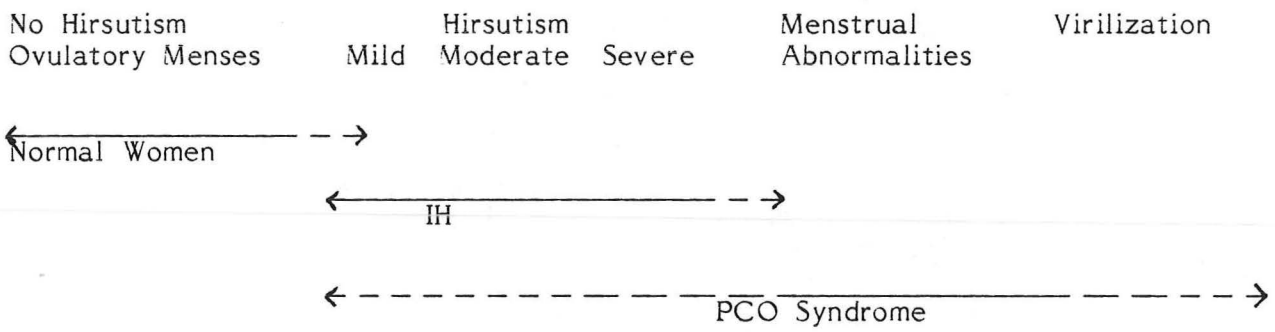
Diagram illustrating the proposed mechanisms for the initiation and maintenance of the chronic anovulation of polycystic ovarian syndrome. LH = luteinizing hormone; FSH = follicle-stimulating hormone; and LHRH = luteinizing hormone-releasing hormone.

Idiopathic hirsutism (IH). This category comprises the largest number of hirsute women. It encompasses all women who have hirsutism unassociated with any of the above described disorders, and is thus a diagnosis of exclusion. The term IH is to some extent a misnomer in that characteristic abnormalities in androgen production have been described in almost all women with the disorder. When strictly applied, IH defines those hirsute women who, in addition to having

none of the other recognized causes of hirsutism, maintain normal ovulatory menses. Often less stringent criteria are utilized (for example, inclusion of women with oligo/amenorrhea as long as there is not palpable ovarian enlargement) such that many studies of "IH" undoubtedly include women with PCO syndrome. However since the underlying pathogenesis of neither IH nor PCO syndrome has been elucidated, it is possible (indeed likely) that both syndromes encompass a heterogeneous group of disorders, and that there is overlap between the two. Thus a clinical spectrum may be envisioned as shown in Figure 6. In terms of what is currently understood about the end result of both disorders, i.e. androgen overproduction, similarities between IH and PCO syndromes abound. For this reason the description of androgen dynamics in women with hirsutism that follows applies to both IH and PCO syndrome.

Figure 6

The Clinical Spectrum of IH and PCO Syndrome



CHARACTERISTICS OF HYPERANDROGENISM IN HIRSUTE WOMEN

Plasma Androgens and Androgen Production in Hirsutism

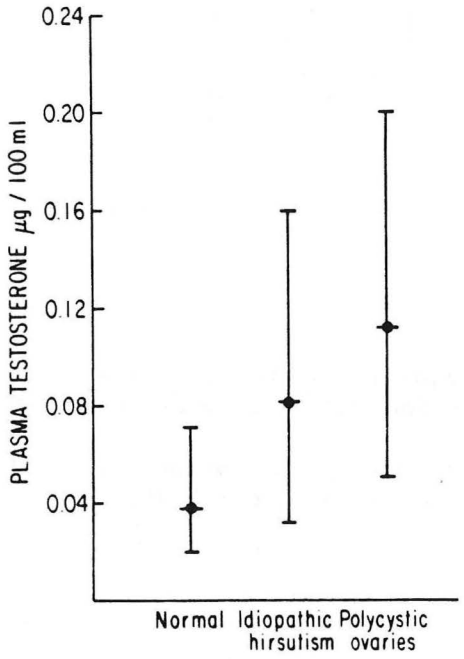
Mean plasma androgen levels are elevated in women with hirsutism (Table 5) (36-40). Figure 7 depicts the ranges and means of total plasma T concentrations in normal women and in women with hirsutism and with PCO syndrome (11). Note the considerable overlap in values among the 3 groups. In other series as well, between 25 and 60% of hirsute women have a normal total plasma T (36-39). In

Table 5

Frequency of Elevation of Plasma Androgens in Hirsute Women

	A(%)	T(%)	Free T(%)	DHEA-S(%)
Hirsute, regular menses (N=40)	42	19	63	58
Hirsute, oligomenorrhea (N=79)	77	40	88	59

Figure 7

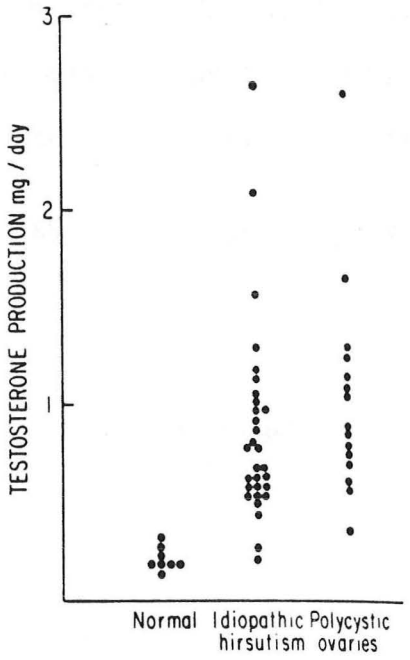


(Ref. 11)

Ranges of plasma testosterone in normal women and in 45 women with hirsutism.

cases of hirsutism associated with regular menses, a normal plasma T may be found in 80% (39). T production rates on the other hand are almost always elevated in hirsute women (Fig. 8) (10, 11, 41). Thus, a normal random plasma T

Figure 8



(Ref. 11)

Testosterone production rates in the same women depicted in Figure 7.

level in a hirsute woman frequently does not accurately reflect the T production rate. This discordance may be for one of at least 2 reasons:

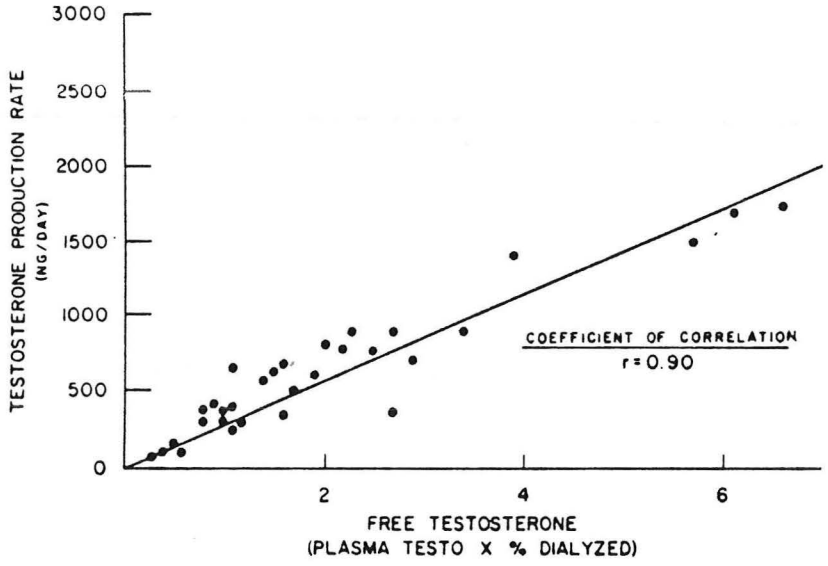
(1) The plasma T concentration in women is a function of its production rate (PR_T) and its metabolic clearance rate (MCR_T), as described by the formula

$$[T]_{plasma} = \frac{PR_T}{MCR_T} .$$

An increased T production rate therefore would result in an elevated plasma T level if the metabolic clearance rate remained constant. However, MCR_T does not remain constant in the setting of elevated T production. This is due to the fact that an increased PR_T results in a lowering of TeBG levels, which in turn is responsible for an increase in the MCR_T. The net result is that the $\frac{\text{total}}{PR_T}$ plasma T level can be maintained within the normal range as long as increases no more than 2- to 3-fold (11). It follows that unless an index of MCR_T (e.g., TeBG level) is known, total plasma T concentration may be a poor index of its production rate. However, because TeBG levels are lower in women with increased T production rates, the free fraction (or more accurately, the free plus albumin-bound fraction) of the plasma T is increased even when total T

levels are normal. Thus the free plasma T level is a more sensitive index of increased T production in women with hirsutism than is the total T level (Fig. 9) (39, 42, 43). Assessment of the free plasma T level can be made by equilibrium dialysis (42), by examining ratios of total plasma T to directly measured TeBG (44), and possibly by measurements of salivary T concentrations (45, 46). Also, non-TeBG-bound T can be assayed directly, and may be one of the most sensitive clinical markers of hyperandrogenism (47).

Figure 9

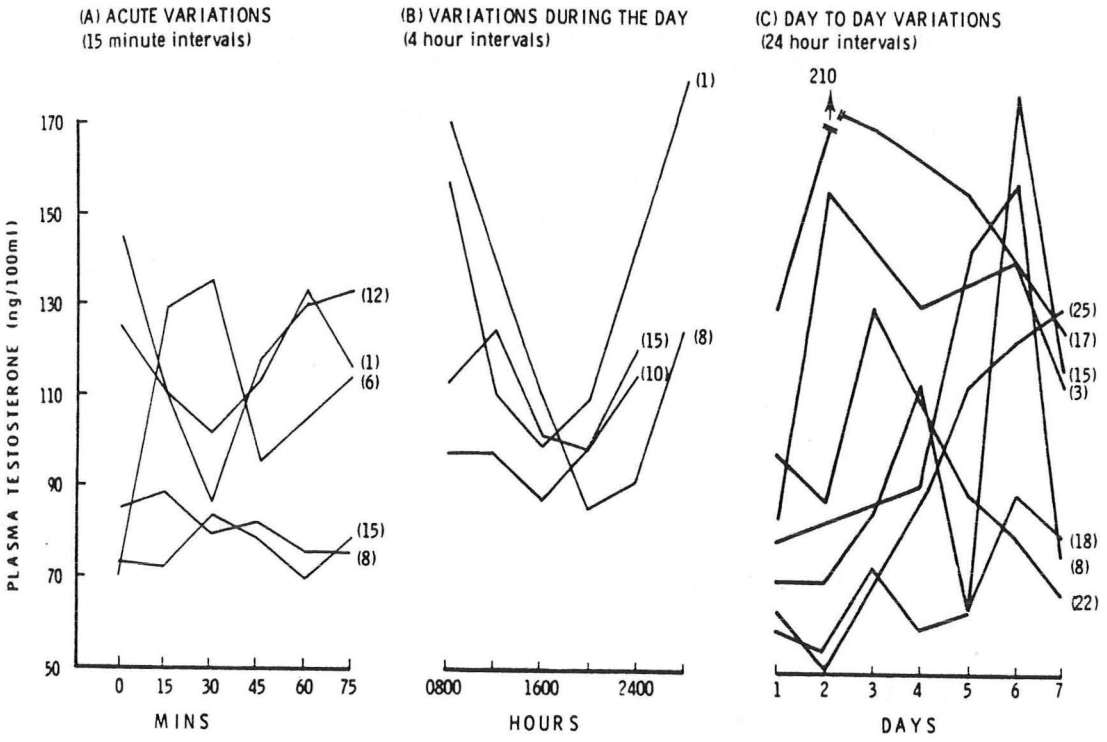


(Ref. 6)

Correlation of testosterone production rates with free testosterone measurements in women. The estimation of free testosterone serves as an excellent substitute for testosterone production rates, even in situations of altered androgen clearance.

(2) Unlike the characteristically nonfluctuating plasma T levels observed in normal women, plasma T (and free T) levels in hirsute women may fluctuate significantly (Fig. 10) (43, 48). A single plasma T determination may therefore not be representative of the mean T concentration over a 24-hour period.

Figure 10



(Ref. 48)

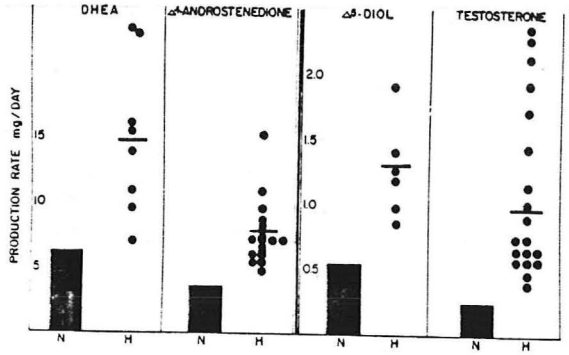
Variations in plasma testosterone levels measured in hirsute women at different intervals.

In summary, to invoke increased T production as the cause of hirsutism in a woman with a normal total plasma T concentration, it is necessary to obtain an index of the plasma free T level (e.g. by calculating a free T from equilibrium dialysis; by measuring TeBG and calculating the ratio of total T to TeBG; or by measuring non-TeBG-bound T). In some women plasma T measurements may need to be made on multiple occasions before the presence of an elevated mean T level can be documented. However, when all appropriate measurements have been made, there are still some hirsute women in whom elevated free T levels cannot be detected (43). Furthermore, even when elevated, the plasma free T level does not correlate well with the severity of hirsutism. These observations suggest that (1) some hirsute women have either no increase in T production or only a subtle increase that cannot be detected by measurement of free plasma T levels; and/or (2) factors other than or in addition to increases in T production are important in the pathogenesis of hirsutism. Examples of such other factors include secretion of unidentified potent androgens and increased metabolism of T to DHT in the skin and hair follicles of hirsute women. Evidence for the latter possibility will be presented later. It must also be kept in mind however that although increased T production and/or activity is necessary for the expression of hirsutism, it is not sufficient. Undefined genetic factors are integral in determining the ultimate response of the hair follicle to any given level of circulating androgen.

Sources of Increased Androgen Production in Hirsute Women

Increased androgen production in women with hirsutism is not limited to T. A, DHEA, and Δ^5-androstenediol production rates are also elevated (Fig. 11) (13). However the relative contribution of these T precursors to the total T production rate in hirsute women is significantly different from that found in normal women: only 25% of the T produced in hirsute women is derived by peripheral conversion of precursors (as compared to 60-80% in normal women) (Fig. 12) (10, 13). Thus 75% of plasma T in hirsute women arises by direct ovarian and/or adrenal secretion. This direct secretion most likely accounts for the greater temporal fluctuation in plasma T levels observed in hirsute women (as described above).

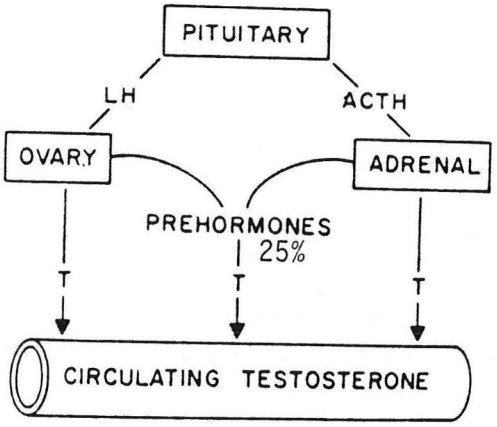
Figure 11



(Ref. 13)

Blood production rates of DHEA, Δ^4-androstenedione, Δ^5-androstenediol and testosterone in hirsute women vs. production rates in normal women. Bars represent mean values. Each androgen is 2- to 3-fold elevated.

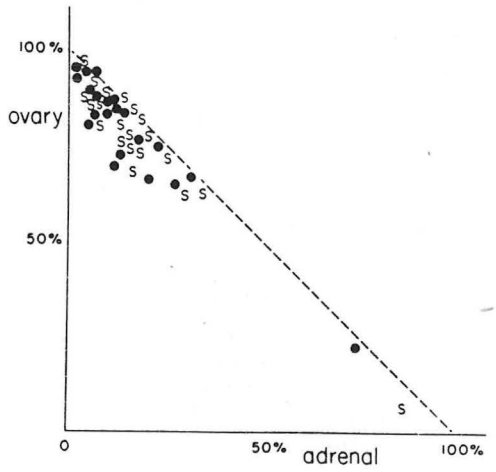
Figure 12



Schematic representation of the origin of testosterone in hirsute women.

The relative contribution by the ovaries and adrenals to this increase in T production in hirsute women has been the subject of numerous investigations. Kirschner et al. obtained selective adrenal and ovarian venous samples for measurement of A and T in 44 consecutive women referred for the evaluation of hirsutism (all of whom had elevated T production rates) (41). Mean ovarian to peripheral vein gradients were greater than gradients between adrenal and peripheral veins. Indirect calculation of T secretion by the ovaries and adrenals indicated the ovaries to be the predominant site of T secretion in 42 of the 44 women (Fig. 13). Furthermore, the ovaries appeared to be responsible for the excess T production even in those women whose peripheral plasma T levels were suppressed by administration of dexamethasone (thus casting doubt on the validity of dexamethasone suppression in being able to differentiate between adrenal and ovarian T secretion). However other studies utilizing selective ovarian and adrenal vein catheterization to obtain samples for androgen levels have shown apparent T secretion by the adrenals as well as by the ovaries (Table 6) (49-51). Discrepancies among studies such as these are not entirely unexpected. First, the design of the study with regard to patient selection may influence the results. For example, hyperandrogenism originating in the adrenals may have secondary effects on ovarian androgen secretion. Thus the predominant site of T secretion may change with progression of the disorder. Second, an inherent limitation of selective venous catheterization for measuring T gradients is the episodic nature of adrenal and ovarian androgen secretion. It is simply not feasible to obtain integrated measurements of ovarian and adrenal T secretion by the differential catheterization technique.

Figure 13



(Ref. 41)

Origin of testosterone and its prehormones in 44 women with unexplained hirsutism, as determined from adrenal and ovarian catheterization data. The hirsute women who exhibited at least 50 per cent suppression of testosterone and androstenedione after dexamethasone are indicated by an S, and the patients with no suppression after dexamethasone by a ●.

Table 6

Origin of Hyperandrogenism in Hirsute Women

Authors (Ref. no.)	Subjects (n)	Ovarian n (%)	Adrenal n (%)	Combined (%)	No Glandular-Peripheral Gradient (%)
Kirschner et al (41)	44	42 (95)	2 (5)	-	-
Northrop et al (49)	19	7 (37)	1 (5)	11 (58)	-
Farber et al (50)	13	4 (31)	3 (23)	6 (46)	-
Moltz et al (51)	60	16 (27)	7 (12)	25 (41)	12 (20)

Other more widely utilized approaches in attempting to dissect ovarian and adrenal contributions to hyperandrogenism involve analyses of androgen responses to stimulation and suppression maneuvers (52-56). As with selective venous sampling, there are discordant results among various studies. Differences can in part be attributed to variations in the amount and duration of stimulation (ACTH, hCG) or suppression (dexamethasone, estrogen-progestin). In addition, interpretation of data is clouded by the possibility that dexamethasone, particularly in larger doses, may directly interfere with ovarian steroidogenesis in women with androgen overproduction (41, 57). Likewise, estrogen-progestin administration suppresses adrenal steroidogenesis (58), to some extent by inhibiting ACTH secretion (59), and therefore cannot be considered to specifically inhibit the pituitary-ovarian axis. Another important difference among studies involves patient selection in that some more rigorously exclude potential ovarian hyperandrogenism by requiring the presence of normal menstrual function. It is therefore difficult to integrate the findings of these studies, but in general:

(1) Excess secretion of DHEA and DHEA-S in hirsute women is adrenal in origin (52, 53, 58).

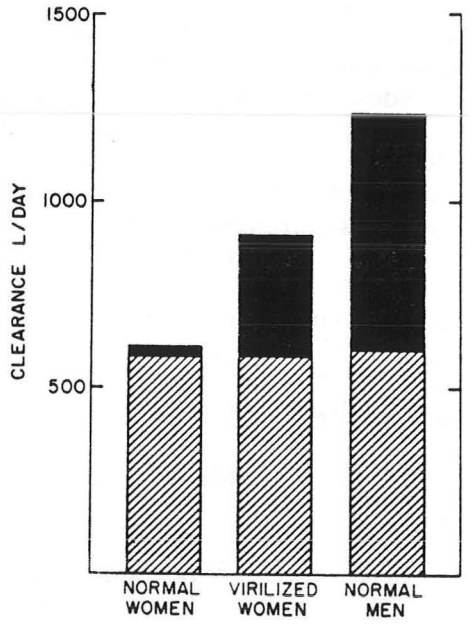
(2) Excessive production of A and T may be ovarian and/or adrenal in origin (49-54).

Many of those with evidence of primarily ovarian hyperandrogenism may represent a part of the spectrum of PCO syndrome. Primary adrenal hyperandrogenism in some hirsute women is the result of partial deficiencies of specific steroidogenic enzymes (56), whereas in others an undefined process leading to increased adrenal androgen secretion is suggested (55, 56). This latter process has been described as an exaggeration of the changes in adrenal steroidogenesis that occurs at the time of normal adrenarche (56), and may in some women represent the earliest evidence of the abnormality that leads eventually to development of PCO syndrome.

Androgen Clearance in Hirsutism

Not only is the pattern of T production altered in hirsute women, but there are also differences in T clearance between normal and hirsute individuals. In normal women virtually all of the T produced is cleared by the liver (i.e. hepatic clearance of T is essentially equivalent to MCR_T) (Fig. 14) (11). Thus there is very little T remaining for clearance in extrahepatic tissues, including androgen target tissues such as the hair follicle. However there is a limit to the hepatic clearance of T of approximately 600 L/day. In hirsute women therefore much of the excess T produced must be cleared in extrahepatic sites. This translates into a mean of approximately 30% (range of 20 - 50%) of plasma T that is available for metabolism outside the liver (comparable to the 50% metabolism of T in extrahepatic tissues observed in men) (Fig. 14). When presented to the hair follicle and other androgen target tissues, this T is available (either directly or after conversion to DHT) for binding to the androgen receptor and effecting androgen-dependent functions, including hair growth. A schematic representation of androgen metabolism in normal and hirsute women is depicted in Figure 15.

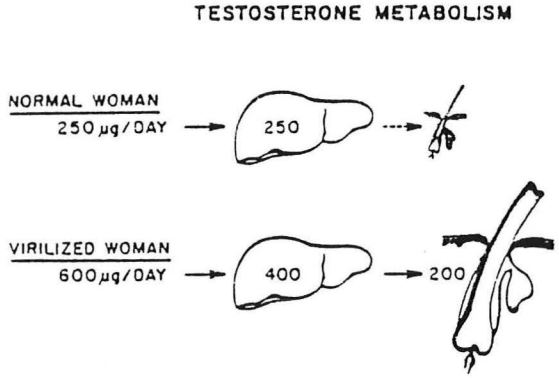
Figure 14



(Ref. 11)

Metabolic clearance rate of testosterone in normal and virilized women. Shaded area: hepatic clearance rate of testosterone. Solid areas: clearance of testosterone at extrahepatic sites.

Figure 15



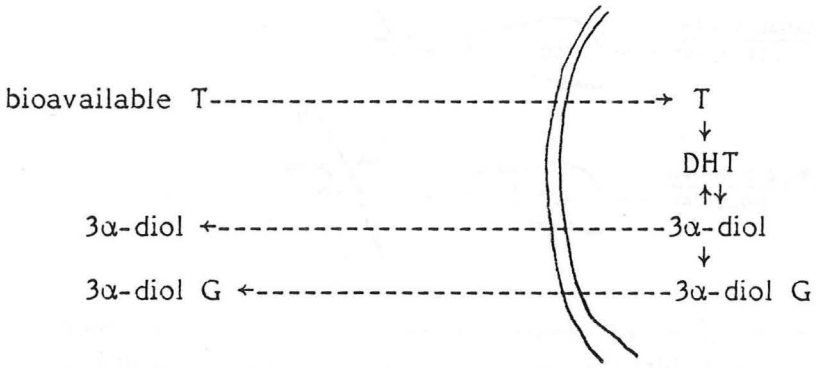
Schematic representation of testosterone metabolism and hair growth in normal and hirsute women. In the normal woman, hepatic clearance accounts for all of testosterone metabolism. In the hirsute woman, only 2/3 of testosterone is metabolized in the liver; 1/3 is metabolized at hair follicle sites leading to stimulation and terminal hair growth.

Direct evidence in hirsute women for increased availability or activity of T at the level of the hair follicle (and other androgen target tissues) has been sought. Such evidence is of particular importance in adducing hyperandrogenism as the cause of hirsutism in women who have normal or only slightly elevated plasma free T concentrations. (Measurement of T production rates should disclose hyperandrogenism in most such women, but this is strictly a limited research endeavor.)

Since conversion of T to DHT is necessary for the expression of androgen action in the hair follicle as well as in certain other androgen target tissues, plasma DHT levels have been measured in hirsute women. Plasma DHT in normal individuals is derived by conversion from circulating A and T (17). This conversion occurs almost exclusively in extrahepatic sites, and would therefore appear to be a potentially sensitive index of increased peripheral T availability in androgen target tissues. However DHT levels are normal in half or more of hirsute subjects (60, 61). Nonetheless, this observation does not exclude the possibility of increased peripheral T to DHT metabolism in hirsute women since DHT is itself rapidly metabolized at sites of formation. The major metabolites of DHT in androgen target tissues are 3α-androstanediol (3α-diol) and its glucuronide conjugate (3α-diol G) (60). 3α-Diol G is a unique metabolite in that more than 90% of the amount in plasma is derived from glucuronidation of locally formed 3α-diol (Fig. 16). Thus, plasma levels of

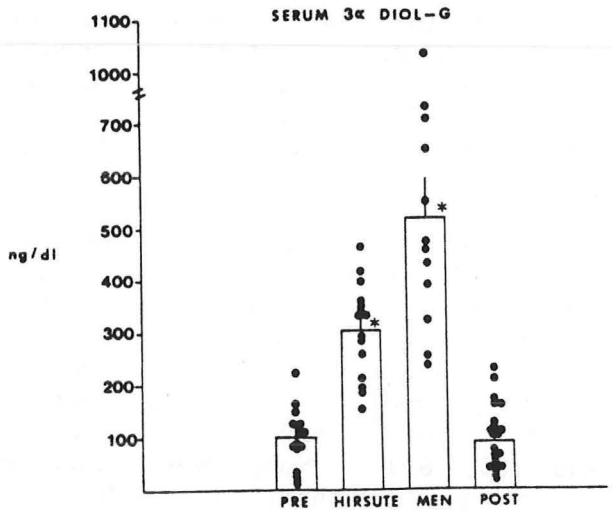
Figure 16

Formation of 3α-Androstanediol and
3α-Androstanediol Glucuronide



3α-diol and 3α-diol G reflect both the availability of T to the androgen target tissue as well as the amount of 5α-reductase activity in the tissue. Although no consistent correlation has been demonstrated between plasma 3α-diol concentration and hirsutism, approximately 80% of hirsute women have an elevation in plasma 3α-diol G, irrespective of their plasma T or free T levels (Fig. 17)(62). This finding suggests that the amount of tissue 5α-reductase

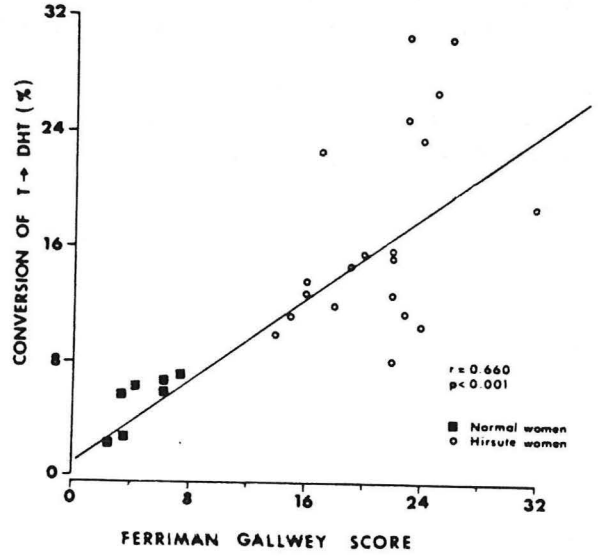
Figure 17



Mean ± SE and individual levels of serum 3 α-diol G in premenopausal (Pre) and hirsute women, in men, and postmenopausal women (Post).

activity is an important determinant in the expression of hirsutism. In fact, enzyme activity has been reported to be higher in pubic skin homogenates (63), in fibroblasts cultured from pubic skin (64), and in minces of genital skin (65) obtained from hirsute as compared to normal women. Because of inconsistent correlations between plasma free T (normal to varying degrees of increase) and genital skin 5α-reductase activity (consistently increased) in different groups of hirsute women, it has been postulated that increased 5α-reductase (and not increased T production) is the primary abnormality responsible for hirsutism in at least that subset of women with normal or near normal free T levels (61). This contention is further supported by the significant direct correlation between an index of the severity of hirsutism and the level of T to DHT conversion in genital skin minces (Fig. 18) (62). Others have cast doubt however as to the primary importance of local 5α-reductase activity in the pathogenesis of hirsutism because of the lack of any increase in enzyme activity in isolated hair follicles from hirsute women over that found in hair follicles from controls (66). Furthermore, in women who clearly do have increased T production, the observed increase in 5α-reductase activity in pubic and genital skin can be explained entirely on the basis of a secondary increase in the mass of androgen target tissue within the skin (e.g. hair follicles and sebaceous glands).

Figure 18



In vitro genital skin percentage of conversion of T to DHT (5α-RA) and the correlation with the clinical evaluation of hirsutism (Ferriman-Gallwey score).

EVALUATION OF THE HIRSUTE WOMAN

A formal evaluation of androgen excess should be undertaken in any woman presenting with (1) moderate to severe hirsutism or virilization or (2) mild hirsutism that is of recent onset or that is associated with oligo/amenorrhea,

infertility, or a pelvic mass. It should not be considered mandatory to evaluate every eumenorrheic, fertile women with long-standing mild hirsutism. Of paramount concern in evaluating a women with hirsutism is to identify the rare patient with a virilizing adrenal or ovarian tumor. In addition, it is important to recognize hirsutism secondary to Cushing's disease and late-onset CAH (21-hydroxylase deficiency). IH always and PCO syndrome frequently are diagnoses of exclusion. An appropriate evaluation begins with the history, physical examination, and selected hormonal measurements.

History. The age of onset of hirsutism should be established. Hirsutism associated with PCO syndrome, IH, and late-onset 21-hydroxylase deficiency characteristically begins during the peripubertal period, although in the latter disorder symptoms may begin a few years earlier at the time of adrenarche. A positive family history of hirsutism may be elicited in women with all 3 disorders. Associated menstrual abnormalities should be characterized.

The rate of progression of hirsutism is also important to note. Slowly progressive hair growth is typical of IH and most cases of PCO syndrome, as well as attenuated CAH. Rapid progression in association with other virilizing symptoms such as deepening of the voice and male-pattern baldness strongly suggests the possibility of an androgen-secreting tumor.

Inquiry regarding symptoms of hypercortisolism should be made.

Finally, a careful history of drug use should be taken. Most drugs that cause increased hair growth result in non-androgen dependent growth of vellus hair. Occasionally, growth of terminal hair is observed. The term hypertrichosis is generally used in describing this type of hair growth; it implies that androgen secretion and metabolism is normal. Conditions other than drug use may also lead to hypertrichosis (Table 7).

Table 7

Conditions Associated with Hypertrichosis

Drug use
- Minoxidil
- Phenytoin
- Corticosteroids
- Penicillamine
- Diazoxide
- Streptomycin (in children)
- Cyclosporine

Hypothyroidism in children
Porphyria
Malnutrition
Hurler's syndrome
Anorexia nervosa

Dermatomyositis
Epidermolysis bullosa
Nevoid hypertrichosis

Nerve injury
Local skin irritation

Trisomy 18
Congenital macrogingivae
Cornelia de Lange syndrome
Hypertrichosis lanuginosa

Physical Examination. Important features to note on physical examination include the amount and distribution of hair (Table 8). Growth of terminal hair on the upper back, shoulders, sternum, and upper abdomen suggests more severe hyperandrogenism. Although mild clitoromegaly may be observed in patients with IH, PCO syndrome, and attenuated CAH, more advanced clitoral enlargement with or without other virilizing signs is more likely to be associated with a serious underlying disorder.

Table 8

Hair gradings according to Ferriman and Gallway

Site	Grade	Definition
Upper lip	1	A few hairs at outer margin
	2	A small moustache at outer margin
	3	A moustache extending halfway from outer margin
	4	A moustache extending to mid-line
Chin	1	A few scattered hairs
	2	Scattered hairs with small concentrations
	3, 4	Complete cover, light and heavy
Chest	1	Circumareolar hairs
	2	With mid-line hair in addition
	3	Fusion of these areas, with three-quarter cover
	4	Complete cover
Upper back	1	A few scattered hairs
	2	Rather more still scattered
	3, 4	Complete cover, light and heavy
Lower back	1	A sacral tuft of hair
	2	With some lateral extension
	3	Three-quarter cover
	4	Complete cover
Upper abdomen	1	A few mid-line hairs
	2	Rather more, still mid-line
	3, 4	Half and full cover
Lower abdomen	1	A few mid-line hairs
	2	A mid-line streak of hair
	3	A mid-line band of hair
	4	An inverted V-shaped growth
Arm	1	Sparse growth affecting not more than a quarter of the limb surface
	2	More than this; cover still incomplete
	3, 4	Complete cover, light and heavy
Forearm	1–4	Complete cover of dorsal surface; 2 grades of light and 2 of heavy growth
Thigh	1–4	As for arm
Leg	1–4	As for forearm

A careful abdominal and pelvic examination is mandatory. A mass suggests the presence of a tumor. Approximately half of adrenal carcinomas are large enough by the time of presentation that they are palpable transabdominally, and at least half of ovarian tumors are palpable on pelvic examination.

Features of hypercortisolism (hypertension, striae, acne, facial plethora, fat distribution, and proximal muscle weakness) should be systematically evaluated.

Finally, hirsutism and virilization may be a component of a syndrome associated with insulin resistance and acanthosis nigricans (67), and a search for this latter characteristic lesion should be made.

Laboratory Evaluation of Hirsutism. The purpose of the screening endocrinologic evaluation is to identify those women who have a specifically

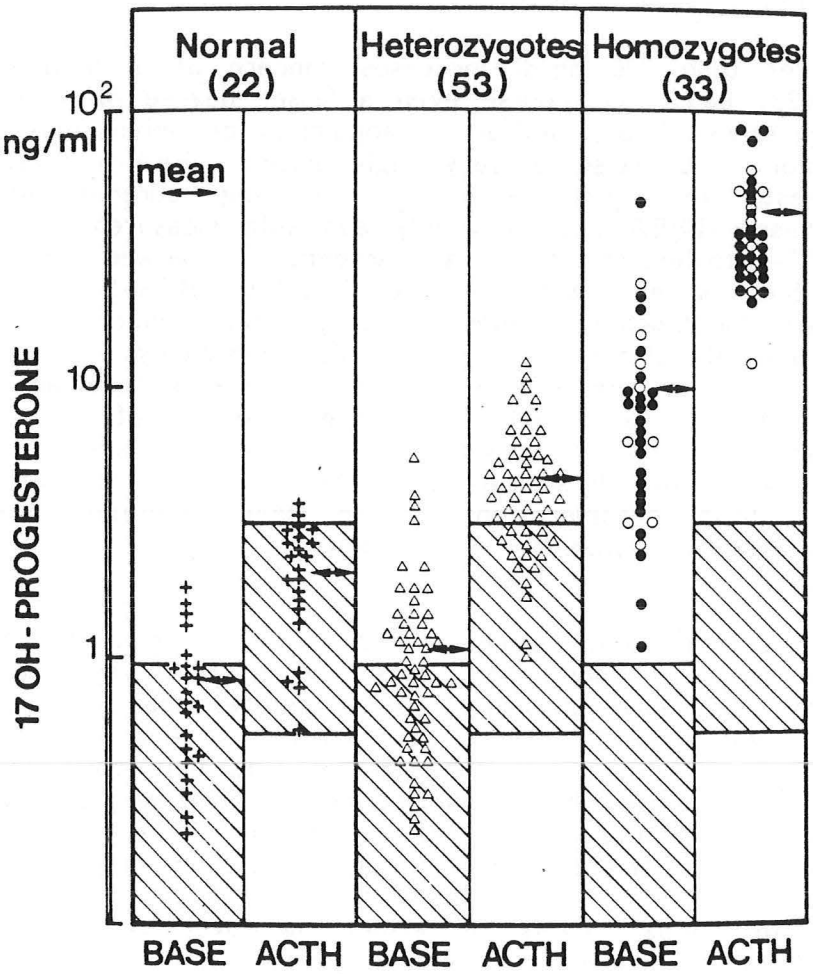
treatable condition responsible for their hirsutism. Recommended hormonal measurements include a (1) total plasma T, (2) plasma DHEA-S, (3) ACTH-stimulated 17-hydroxyprogesterone, and in the hirsute woman with irregular menses or amenorrhea (4) a serum prolactin.

A plasma T greater than 200 ng/dl increases concern of a virilizing ovarian or adrenal neoplasm (23, 68). Of course even a lesser degree of T elevation in a patient with a suggestive history and/or an abdominal or pelvic mass raises an equal concern of tumor. Likewise a very high plasma DHEA-S level (e.g. > 800-900 μg/dl) suggests the presence of a virilizing adrenal adenoma or carcinoma (21). (Plasma DHEA-S is a widely available measurement and should supplant urinary 17-ketosteroids as a screening marker for adrenal hyperandrogenism.) Thus, patients with elevated T and/or DHEA-S in these ranges should have noninvasive localization studies for a possible tumor, i.e. computed tomography of the adrenal glands and pelvic ultrasonography. The role of magnetic resonance imaging in the evaluation of adrenal and ovarian disease is currently under investigation (69, 70). In the absence of an identifiable lesion on CT or ultrasonography, hirsute women with very high levels of plasma T or DHEA-S, particularly if the hirsutism is of recent onset and other causes have been eliminated from consideration, should have selective ovarian and adrenal venous catheterization studies to attempt to localize the source of androgen overproduction.

It should be appreciated that some women with nonneoplastic causes of hirsutism and virilization, in particular those with PCO syndrome or IH associated with obesity, may have plasma T levels greater than 200 ng/dl (71). In this situation, if ovarian and adrenal visualization studies are negative or inconclusive, an attempt to inhibit any gonadotropin-dependent component of the hyperandrogenism may be made by administering a long-acting gonadotropin releasing hormone (GnRH) analogue for several weeks (72). Alternatively, combined gonadotropin- and ACTH-dependent androgen secretion may be assessed by observing the response of plasma T to an oral estrogen-progestin preparation. If suppression of T to normal levels by either maneuver is observed, it is unlikely that a small, nonvisualized androgen-secreting tumor is present.

The diagnosis of late-onset CAH due to 21-hydroxylase deficiency is easily made by measuring a plasma 17-hydroxyprogesterone 30 minutes following an intravenous injection of 250 μg of Cortrosyn. In homozygous individuals the stimulated plasma 17-hydroxyprogesterone exceeds 2000 ng/dl (Fig. 19) (27-29). Basal early morning levels are also usually elevated to greater than 1000 ng/dl. Routine evaluation for CAH due to late-onset 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase deficiencies cannot be justified because of their rarity.

Figure 19



(Ref. 29)

Basal and ACTH-stimulated levels of 17-hydroxyprogesterone in the patients and their families. All subjects were divided into three groups: Group 1, the 24 propositi (●) and 9 siblings (o) having the same two HLA haplotypes as the propositus (homozygotes); Group 2, 53 parents and siblings with only one HLA haplotype identical to that of the propositus (heterozygotes); and Group 3, 22 siblings having no HLA haplotype identical to that of the propositus (normal). Hatched areas indicate normal ranges.

Since hirsutism is observed in some women with prolactin-secreting pituitary adenomas, a serum prolactin should be measured if there is a history of oligo/amenorrhea and/or galactorrhea. A mild elevation in serum prolactin however is found in some women with PCO syndrome (34).

In the hirsute woman with clinical features of hypercortisolism an overnight dexamethasone suppression test should be performed. Further evaluation for

Cushing's syndrome is necessary if the plasma cortisol does not suppress to less than 5 μg/dl.

The majority of women evaluated in this manner will demonstrate only a modest elevation in plasma T and DHEA-S. Many have plasma androgen levels in the normal or upper normal range. In the latter situation, hyperandrogenism may be documented by multiple sampling for measurement of plasma T, by evaluating a free T index, or by measuring a plasma A-diol G. It should be recognized however that laboratory confirmation of mild hyperandrogenism in a hirsute woman is not necessary to make a diagnosis. Depending on associated clinical findings, a diagnosis of PCO syndrome or IH will be made regardless of plasma androgen levels. The primary role of plasma androgen measurements is to (1) ensure that T and DHEA-S levels are not in the tumor range and (2) to provide a baseline for monitoring the response to hormonal suppression in those hirsute women for whom such therapy is elected. In the case of IH, various protocols have been devised, most involving assessment of plasma androgen responses to dexamethasone suppression, in order to evaluate the relative contributions of the ovaries and adrenals to the hyperandrogenism (21, 41, 73). In this manner it has been suggested that a more rational approach to designing appropriate therapy may be made. However, as mentioned earlier, the specificity of these tests has been questioned. Even if it were possible to differentiate between ovarian-predominant and adrenal-predominant cases of androgen excess, it is not clear that this should play an important role in selecting a particular mode of therapy.

TREATMENT OF HIRSUTISM

In the proportionately few women who are found to have an identifiable cause of hyperandrogenism, treatment is relatively straightforward. Androgen-secreting tumors are surgically removed, CAH is treated with glucocorticoid replacement, and Cushing's disease is generally managed by removal of the ACTH-producing pituitary adenoma. Drugs that have been implicated as causes of hypertrichosis should be discontinued if possible.

For the majority of hirsute women however, in whom hirsutism is "idiopathic" or associated with PCO syndrome, there is no ideal specific therapy. Since hirsutism is basically a cosmetic problem, the decision as to the mode and vigor of treatment will largely depend on the woman's perception of the problem. There are 3 main categories of treatment modalities: (1) suppression of excess androgen secretion, (2) inhibition of androgen action at the level of the hair follicle, and (3) local cosmetic treatment.

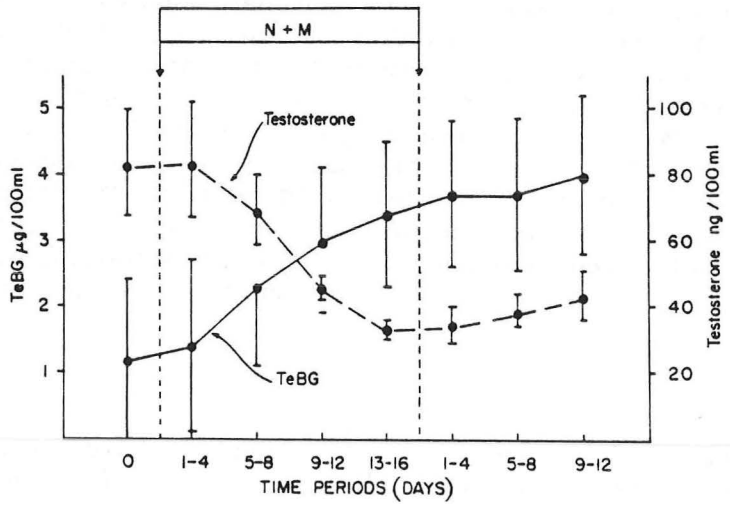
Suppression of Androgen Secretion

There are 2 classes of drugs that have been used extensively to suppress androgen secretion in women with hirsutism - estrogen-progestin combinations found in oral contraceptives and glucocorticoids. In addition, GnRH agonists have recently received attention as a possible means of suppressing androgen secretion in hirsute women.

Oral contraceptives. Combination estrogen-progestin preparations suppress ovarian androgen production by inhibiting pituitary LH secretion. Effective LH suppression is dependent on both the estrogen and progestin content (74). Oral

contraceptives have also been shown to have a suppressive effect on adrenal androgen secretion (75), most likely the result of ACTH suppression (59). In addition to their effect in suppressing androgen secretion, the estrogen component of oral contraceptives increases TeBG levels (independent of an effect in lowering T production), thereby further reducing the circulating free T concentration (Fig. 20) (76). In fact in some women given one of the lower dose estrogen-containing pills, the total T level may not change at all (because of the increase in TeBG) despite a lowering of the free T (77).

Figure 20



(Ref. 76)

Mean plasma TeBG-binding capacity and plasma T ± S.E. of all the women before, during, and after the administration of N + M. Pretreatment and treatment data are from seven women; posttreatment data are from 6 women.

Attention must be paid to the specific estrogen-progestin preparation prescribed in the treatment of hirsutism. In order to reduce the well-known complications associated with contraceptive use, formulations containing the lowest amount of estrogen effective in raising TeBG while suppressing total plasma T level are most desirable. Preparations containing 50 µg of mestranol or 30 to 50 µg of ethinyl estradiol are recommended (Table 9). Suitable progestins include norethindrone (0.5 - 1 mg) and ethynodiol diacetate (1 mg). Other progestins such as norgestrel possess sufficient androgenic activity that they may oppose the effect of estrogen in raising TeBG levels.

Table 9

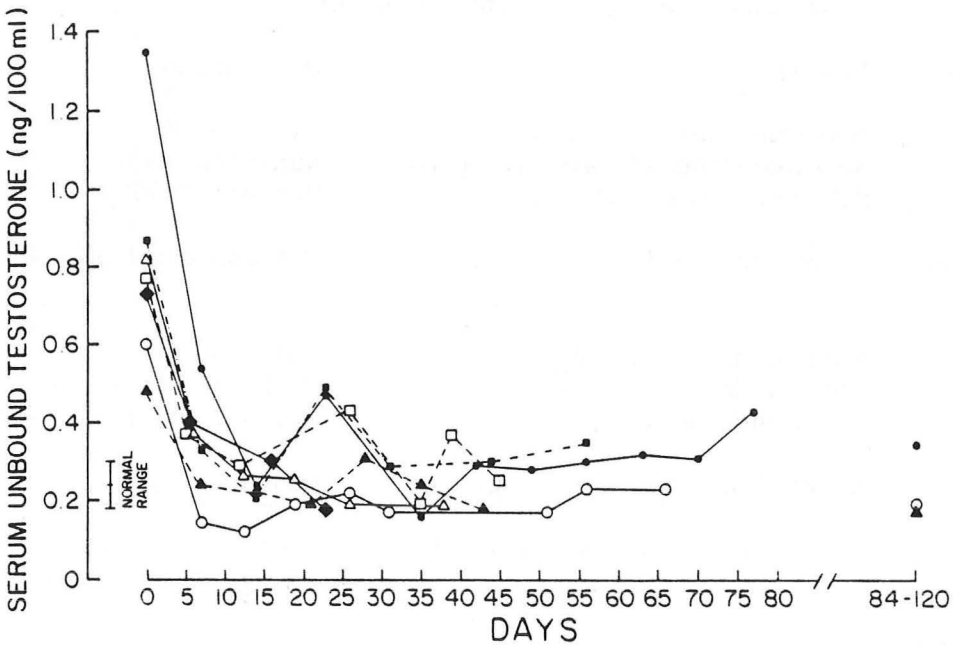
Lower Estrogen Containing Oral Contraceptives
Recommended For Treatment of Hirsutism

Estrogen	Progestin		Preparations
EE_2* 50 µg	Norethindrone Norethindrone acetate Ethynodiol diacetate	1 mg	Ovcon - 50 Norlestrin 1/50 Demulen 1/50
Mestranol 50 µg	Norethindrone 1 mg		Orthonovum 1/50, Norinyl 1+50
EE_2* 35µg	Norethindrone 0.4 mg Norethindrone 0.5 mg Norethindrone 1 mg		Ovcon - 35 Modicon, Brevicon Orthonovum 1/35, Norinyl 1+35
	Ethynodiol diacetate 1 mg		Demulen 1/35
EE_2* 30 µg	Norethindrone acetate 1.5 mg		Loestrin 1.5/30

*Ethinyl estradiol

Oral contraceptives have been effective in reducing hair growth in from 50 to 75% of women with IH and PCO syndrome (21, 77-80). Total plasma A and T are usually suppressed by 50% or more, frequently during the first cycle of use (Fig. 21). This is the maximum degree of suppression expected if ovarian androgen secretion were totally eliminated (as by oophorectomy). Because of the increase in TeBG, plasma free T falls within the normal range in most women. DHEA-S levels are also suppressed as pointed out previously. Total plasma T or an index of free T should be monitored at about 6-week intervals until a clear response of plasma androgen is seen.

Figure 21



(Ref. 79)

Rate of suppression of unbound testosterone levels in 7 women with polycystic ovary disease after the initiation of Loestrin treatment.

The clinical response lags considerably behind suppression of plasma androgen levels, and this delay needs to be discussed with the patient from the outset of treatment. The usual response to treatment consists of an initial reduction in new hair growth, followed by softening or thinning of existing terminal hair, and ultimately a less frequent need to use mechanical means of hair removal. If a reduction in hair growth is going to occur, it is usually apparent by 6 to 9 months of treatment (6, 74). Best results are obtained in women with a short history of hirsutism. In patients with more long-standing hirsutism, hair growth is never entirely obliterated despite a decline in the rate of growth. Only about one-third of women treated with oral contraceptives have sufficient reduction in hair growth that mechanical methods of hair removal can be abandoned. Long-term treatment of hirsutism is required in order to maintain effective androgen suppression.

Oral contraceptives are most suitable for treatment of hirsutism in young women who also desire contraception. They should not be used to treat hirsutism in any woman who is over 35 years of age, or who has a history of cerebrovascular or thromboembolic disease, hypertension, or an estrogen-dependent neoplasm. Cigarette smokers should also be excluded from regimens utilizing contraceptives.

Glucocorticoids. Exogenous glucocorticoids suppress ACTH secretion and thereby diminish adrenal androgen production. Large doses of glucocorticoid may

also suppress ovarian steroidogenesis as well, although this latter effect is controversial (21, 52, 73). Regimens utilizing bedtime administration of either dexamethasone (0.25 to 1 mg) or prednisone (5 to 7.5 mg) have been reported. Maximum T suppression does not occur for at least 2 months (40). Since the dosage required for adrenal androgen suppression varies widely among individuals (particularly with dexamethasone), careful titration is necessary for each patient. The maintenance dose utilized should be one that produces adequate adrenal suppression (DHEA-S level less than 400 ng/ml) without suppression of the hypothalamic-pituitary-adrenal axis. It has been suggested that this latter risk is minimized if a morning cortisol is maintained at a level of 2 μg/dl or greater (81). Differential suppression of adrenal glucocorticoid and androgen secretion is facilitated by the greater sensitivity of the latter to exogenous glucocorticoid (82).

Overall clinical response with a decrease in hair growth occurs in 25 to 50% of women (6, 21). Higher response rates of up to 70% are reported in women who have demonstrated plasma A and T suppression to normal levels during a 2-day (40) or 2-week (73) dexamethasone suppression test. As with oral contraceptives, glucocorticoids are less effective in reducing hair growth in women whose hirsutism is long-standing than in those with hirsutism of shorter duration. It is claimed that in many women who do respond to dexamethasone, it is possible to discontinue therapy after 1 year without seeing a recurrence of hair growth for as long as 6 to 12 months (73). The potential of overtreating with glucocorticoids (resulting in Cushing's syndrome and possible hypothalamic-pituitary suppression with adrenal insufficiency during periods of increased stress or on discontinuation of treatment) creates risks that must temper their routine use in the treatment of hirsutism. I restrict their use as a primary therapeutic modality to women with hirsutism secondary to CAH. If however alternative therapeutic modalities are limited by side effects or by response failure, a trial of glucocorticoid may be offered to a woman with moderate to severe hirsutism. Even if there is a clinical response, therapy should be discontinued after 1 year and the patient followed for recurrence of new hair growth.

GnRH Agonists. When administered continuously, GnRH agonists suppress gonadotropin secretion. In a recent study, the GnRH agonist nafarelin acetate was administered as a nasal spray (500 μg twice daily) to 6 hirsute women (83). Total and free plasma T levels declined significantly within 1 to 3 months. Four of the 6 women responded with a decrease in hair growth. Side effects due to concomitant estrogen deficiency were observed in most, but were mild and did not necessitate discontinuation of the drug. More extensive studies are needed however before GnRH therapy can be considered as a means of treating hirsutism. In particular, the possibility that long-term administration may result in decreased bone mass due to prolonged estrogen deficiency needs to be addressed. It is possible that GnRH analogue therapy in combination with physiologic estrogen replacement will prove to be a practical therapeutic approach in women who are not able to take oral contraceptives.

Inhibition of Androgen Action

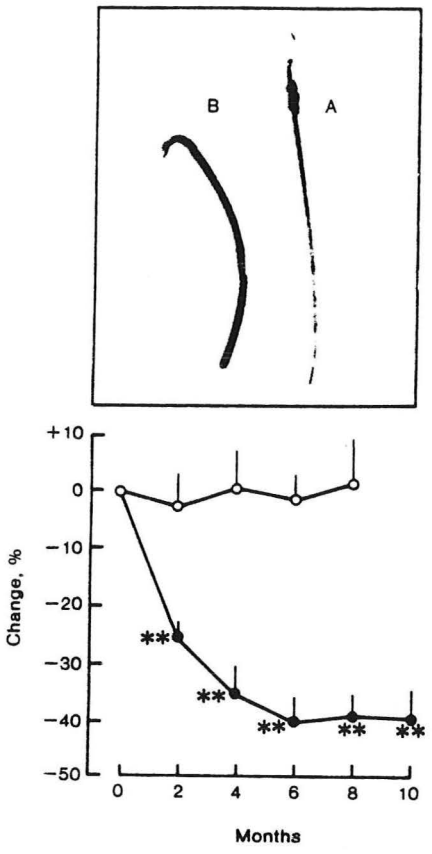
Agents that interfere with androgen activity may act either by (1) competitively inhibiting the binding of T and DHT to the androgen receptor or (2) inhibiting conversion of T to DHT in target tissues (such as the hair

follicle) that require DHT. Spironolactone is the only antiandrogen that is currently available in the United States. Cyproterone acetate is an antiandrogen that has been used extensively in Europe to treat hirsutism.

Spironolactone. Spironolactone is an aldosterone antagonist that was developed as a potassium-sparing diuretic for treating hypertension as well as conditions associated with aldosterone excess. Its effect as an antagonist to aldosterone action is mediated via competitive inhibition of aldosterone binding to the mineralocorticoid receptor. In addition spironolactone was noted early on to have side effects that suggested it may interfere with the action of other steroid hormones. For example, gynecomastia, impotence, and decreased libido in men and oligo/amenorrhea in women were observed when moderately high doses were administered (84, 85). It is now known that spironolactone inhibits androgen activity by blocking T and DHT binding to the androgen receptor (86) as well as inhibition of T biosynthesis. The latter is most likely due to inhibition of the 17α-hydroxylase/17,20-desmolase enzyme required for androgen synthesis (87). In addition there is some evidence that spironolactone inhibits the 5α-reductase enzyme, with consequent diminished conversion of T to DHT (88). The primary antiandrogen action of spironolactone is probably at the level of blocking T and DHT binding to the androgen receptor.

A number of clinical trials have reported a beneficial effect of spironolactone in reducing hair growth in hirsute women (89-92). A clinical response, as judged by a reduction in hair shaft diameter, decreased rate of hair growth, and decreased hair density, is observed in most women beginning within 2 to 6 months of initiation of therapy (Fig. 22) (90). Improvement continues or is sustained for the duration of treatment. The response of spironolactone occurs in women with PCO syndrome as well as with IH. A reduction in total plasma T occurs in most women whether or not pretreatment levels are elevated (89-92). Reductions in plasma free T with spironolactone therapy are less consistent. Usual regimens employ 50 to 200 mg of spironolactone per day in two divided doses. Higher doses (100 to 200 mg/day) appear to be more effective (92). The drug has been given either continuously or cyclically for 20 to 25 days each month (89, 90). Combinations of spironolactone with an oral contraceptive or dexamethasone may produce a clinical response beyond that seen with either drug alone (93, 94).

Figure 22



(Ref. 90)

Per cent (mean ± SE) change in hairshaft diameter in 11 patients receiving spironolactone compared with seven untreated hirsute controls (double asterisk indicates $P < .01$) (bottom), and representative hair samples, including hair root collected before (B) and after (A) six months' treatment with spironolactone (top). Vertical lines at each coordinate denote SEs.

Side effects of spironolactone such as headache, nausea, and lassitude are transient and resolve within 1 to 2 months. Hyperkalemia is another potential complication, particularly in patients with renal insufficiency or hypoaldosteronism. A transient polyuria has also been described. Although there are few studies in humans, it has been claimed that long-term administration of spironolactone may be associated with an increased incidence of breast cancer in both men and women (95). The most commonly observed side effect is disturbance of the menstrual cycle, including oligo/amenorrhea as well as menometrorrhagia, in women with previously normal menses. Cyclic administration or reduction in the dosage of spironolactone appears to minimize

this side effect. In contrast, many women with anovulation experience resumption of normal ovulatory menses with spironolactone. For this reason, adequate contraception is necessary for every woman of childbearing age who is given spironolactone. It should not be administered during pregnancy --not only has its safety not been evaluated, but it has the potential of interfering with the normal virilization of a male fetus.

To alleviate potential side effects associated with the use of spironolactone, a cream containing canrenone, the principal metabolite of spironolactone, has been evaluated. Although canrenone has less than 2% of the androgen receptor binding inhibitory activity of spironolactone (96), twice daily direct facial application of a cream containing 3% canrenone (delivering 30 to 50 mg of the drug per day locally) reduced growth of facial hair over a 4-month period in more than 50% of women with moderate hirsutism. No side effects were observed (97). Canrenone cream is not available in the United States.

Other Antiandrogens. Cyproterone acetate has been studied extensively and used widely in Europe for the treatment of hirsutism, but is not available for clinical use in the United States. Like spironolactone, cyproterone acetate inhibits binding of T and DHT to the androgen receptor, but in an in vitro assay exhibits only 20% of the inhibitory activity of spironolactone (96). In addition, because of its progestational properties, cyproterone inhibits gonadotropin-dependent androgen secretion. Improvement in hirsutism and reduction of plasma T levels is seen in from 50 to 90% of patients (95, 98-101). It is administered in a cyclic regimen with estrogen in order to prevent disturbances in menstrual bleeding.

Cimetidine, an H_2 receptor antagonist, also competes with T and DHT for binding to the androgen receptor. This accounts for the occurrence of gynecomastia in men receiving cimetidine for treatment of peptic ulcer disease. Cimetidine however, unlike spironolactone and cyproterone, is a very weak competitor of androgen receptor binding. Limited studies of the efficacy of cimetidine in the treatment of hirsutism have been performed, but the numbers of women treated are too small for meaningful analysis (102, 103).

Cosmetic Treatment (6, 74)

For mild hirsutism, bleaching and mechanical hair removal are usually adequate to produce the desired cosmetic result. In women with more severe hirsutism for whom drug therapy is elected, some form of local cosmetic treatment is also usually required in addition to the drug. Although most hirsute women have already explored the various approaches available to remove unwanted hair by the time they seek medical advice, it is still important to review these methods with the patient so that appropriate guidance can be offered and misconceptions allayed.

Bleaching. Dark hair may be made less visible by bleaching. Commercial bleaching creams containing a 6% hydrogen peroxide solution, ammonia, and some soap chips to form a paste are available, but homemade preparations are easily constituted. The bleach is applied by dabbing with a swab and must remain in contact with the hairs for 15 to 30 minutes. Skin irritation may occur, in which case the exposure time should be decreased or a lower concentration of

ammonia tried. The procedure can be repeated daily provided that extensive skin irritation does not develop. Preparations containing potassium persulfate should be avoided because of reports of anaphylactoid reactions.

Shaving. This is the safest method of mechanical hair removal, but many women are reluctant to shave because of the misconception that it coarsens the hair and increases its rate of growth. Reassurance is often necessary to allay this fear. Although shaving is psychologically and cosmetically acceptable for removing hair from the extremities and axillae, shaving the face is considered by many women to be unfeminine, and frequently does not give an acceptable cosmetic result (particularly if the natural hair color is dark).

Chemical depilatories. Many women prefer depilatory creams to shaving. The most common depilatories contain calcium thioglycollate, which acts by reducing the disulfide bonds between the polypeptide chains of keratin. Osmotic pressure then increases within the fiber, resulting in swelling and eventual deterioration of the hair shaft to a jelly-like consistency, after which it can be wiped from the skin. Regrowth of hair occurs within 24 to 48 hours, but unlike the bristly feel of the hair following shaving, the regrowing hair tips following use of a depilatory are soft. Good cosmetic results can usually be achieved on the face. The most common causes of failure are using an insufficient quantity of cream and an inadequate application time. The main drawbacks to depilatories are that they are expensive and time consuming. Before using a depilatory cream, it is important to test a sample on a small area of the skin over a 24-hour period to assess for any skin irritation. Depilatories should not be used in the presence of acne or eczema, on areas with nevi, or around the nostrils or eyes.

Waxing. This is an alternative to shaving or use of chemical depilatories that is acceptable to some women. Wax preparations are usually made of glucose, beeswax, a resin, and an emulsifier. They are usually solid at body temperature but have a low melting point. After the wax is melted and applied to the area of skin to be treated, it solidifies rapidly to form a pliable material that can then be pulled off. This must be done quickly, as when ripping off an adhesive bandage, and must be completed before the wax hardens. This method permits many hairs to be removed at once and is suitable for circumscribed areas such as the chin and upper lip. One limitation is that the hairs must grow to a certain length before they can be gripped and removed by the wax. However the skin is left smooth, and regrowing hair is soft as opposed to the "stubble" left following shaving. The procedure is not painless, but is nonetheless usually well tolerated. The major drawback to waxing is that it may cause a folliculitis which can become chronic and lead to scarring. Also, some hairs may break off below the surface and cause inflammation as they grow. This is not a common problem however.

Tweezing. This is a commonly used and cosmetically acceptable method of hair removal for sparsely affected areas. Infrequent tweezing is generally without risk, but it is painful, tedious, and may result in a folliculitis if adequate precaution is not taken in cleaning the area beforehand. If done too frequently tweezing may cause scarring, and women with a tendency to keloid formation should not use this method. Hairs should not be plucked from circumareolar regions or from nevi.

Electrolysis. Destruction of the hair follicle by needle electrolysis can be an effective procedure for permanent hair removal. A thin needle is inserted along the hair shaft to a point below the skin and an electric current of predetermined voltage is introduced. With shortwave radio frequency thermolysis units that are most frequently used, local temperatures of 170-200°F are generated that produce electrocoagulation of the hair root. Immediately after electrolysis there is a temporary blanching of the hair follicle that is usually followed by a mild erythema lasting 15 to 20 minutes. The treated hair is easily removed with no resistance. An interval of 2 to 3 weeks between treatments is recommended to minimize scarring and to assess the results of therapy. Multiple treatments to any given follicle may be necessary before permanent destruction ensues, and treatment courses can become expensive. Electrolysis is a practical therapeutic alternative only for very mild hirsutism, but can be a useful adjunct to medical therapy in more severe cases. Any acne should be under reasonable control before beginning a course of electrolysis. Although the procedure is safe in skilled hands, it is not painless and may cause scarring and postinflammatory pigmentation. A home version of electrolysis utilizing an electrified tweezer has been recently marketed but is ineffective.

In summary, although a reduction in hair growth can be achieved in most hirsute women, it is distinctly unusual to obtain a lasting reversal even in the majority of women who have near-normal circulating levels of androgen. Once an abnormal terminal hair growth pattern has been established, usually during menarche, very minimal amounts of circulating androgen are required for its maintenance. Mild hirsutism can frequently be managed with local cosmetic measures, but medical therapy is frequently elected in more severe cases. It must be understood by the patient before committing herself to any long-range treatment that no drug or combination of drugs completely suppresses terminal hair growth. Once a specific treatment has been initiated, it should not be abandoned as unsuccessful before concluding an 8- to 10-month trial, unless a serious side effect develops. Even when a reduction in hair growth is achieved, physical removal of excess hair remains an important therapeutic adjunct.

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