CONTINUING MEDICAL EDUCATION

DISTURBED ANDROGEN METABOLISM AND SKIN
(Therapy with anti-androgens)

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Androgens possess the ability to induce and maintain the secondary sexual characters of the male. Of the structural and functional changes in the skin induced by androgens, those of the greatest clinical significance concern the activity of the sebaceous glands and the pattern of hair growth. In addition to their actions on the skin, androgens have many other physiological functions especially at puberty. These include development of the external genitalia, the adolescent growth spurt, hypertrophy of the larynx associated with a change of voice, and increased muscular development.

Clinical Manifestations of Androgen Lack

Absence of androgen dependent physiological changes in the body may be due to two causes : (a) defects in the testosterone biosynthesis, and (b) genetic defects in the intracellular metabolism of androgens and their transport to the nucleus.[1-3] The latter implies a target tissue resistance to the action of androgens, when both the gonadotrophin and the testosterone production are normal. This is a relatively new concept and various conditions have been described in which the target tissues are resistant to the action of androgens. Disorders included are complete testicular feminisation (partial absence of 5-alpha reductase),[1] type I pseudo-hermaphroditism (partial deficiency of androgen receptors),[2] and type II pseudo-hermaphroditism (deficiency of 5 alpha reductase).[3] The disorders which result in the clinical manifestations of androgen lack are shown in table I.

Table I. Disorders which result in clinical manifestations of androgen lack.

I. Decreased androgen production
A. Primary
1. Anorchia
2. Enzymatic defects in testosterone synthesis
3. Castration
4. Leydig cell failure
B. Secondary
1. Isolated gonadotropin deficiency
2. Panhypopituitarism
II. Decreased peripheral metabolism
1. 5 alpha reductase deficiency
2. Testicular feminisation syndrome
3. Incomplete testicular feminisation
4. Reifenstein syndrome
5. Partial androgen insensitivity

The skin changes which occur due to the lack of testosterone, depend on the age at which the defect occurs and also on the sex of the patient. Females, in general, do not have overt cutaneous manifestations of androgen deficiency. If males are deprived of testosterone before puberty, the fully developed picture of eunuchoidism results. The skin is thin, dry and fine. The sebaceous glands, the follicles of sexual hair and the apocrine glands remain dormant. Facial pores are small and acne is absent. The skin appears pale and ivory white due to decreased

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pigmentation and decreased blood flow. The genitalia remain infantile and the musculature does not develop to the normal extent. In the post-pubertal castrates, there are functional changes in the sebaceous glands. There is a decrease in the sebum excretion rate. The growth rate of sexual hair is decreased. The skin becomes thin and facial wrinkles appear.

Other changes of androgen deficiency are most readily seen in the pre-pubertal castrates. Manifestations include genital immaturity, juvenile body habitus and though the growth is slow, normal height is reached because the epiphysial closure is delayed. All these changes are reversed by giving testosterone.

Clinical manifestations of androgen excess

The clinical manifestations of androgen excess can result from either an increased availability of circulating androgens or an abnormal target tissue metabolism probably related to an enhanced 5-alpha reductase activity.[4] The causes which result in clinical features of androgen excess are summarised in table II.

Table II. Disorders which result in clinical manifestations of androgen excess.

I. Over-production of androgens
A. Ovarian source :
1. Polycystic ovarian syndrome
2. Ovarian tumours : Arrhenoblastoma
Hilus cell tumour
Microadenomas
(Testosterone secreting)
3. Pure gonadal dysgenesis
4. Chromosomal abnormalities
B. Adrenal source :
1. Congenital adrenal hyperplasia including adult onset variety
2. Cushing's syndrome and disease
3. Virilising adrenal tumours
4. Borderline adrenal dysfunction
C. Pituitary source :
1. Hyperprolactinemia galactorrhoea syndrome
2. Acromegaly
3. Stress
D. Iatrogenic :
1. Testosterone
2. Progestogens
3. Anabolic steroids
II. Abnormal target tissue metabolism : Idiopathic hirsutism

The cutaneous manifestations of androgen excess manifest either in childhood in both the sexes or in the adult female.[4] The skin is coarse, thick and oily. The skin pores are patulous. The patients develop severe nodulocystic acne. If the androgen excess occurs in childhood, the hair-line may conform to the adult configuration. In adult females, diffuse androgenic alopecia and hirsutism can develop. There is increased pigmentation of the perineum, external genitalia, axillae and nipples.

In certain patients, the cutaneous expressions of androgen excess are associated with the more severe manifestations of hyper-androgenemia such as alteration in the muscular habitus and laryngeal hypertrophy. Genital masculinisation with clitoral hypertrophy occurs in adult females. If the androgen excess occurs during fetal life, pseudo-hermaphroditism occurs; while if it occurs in childhood, precocious sexual development and eventual stunting of growth occurs. The clinical expression of androgen excess depends on the sex and the age of the individual and the severity of androgen excess.[4]

The pathological role of androgens in acne, androgenic alopecia and hirsutism will be discussed in detail.

Acne Vulgaris : Androgens are known to stimulate sebaceous gland activity. The most frequent disorder of sebaceous glands is acne vulgaris. The natural evolution of acne seems to be linked to the rising levels of androgens occurring at puberty. Androgens exert their acnegenic effect by stimulating the sebaceous gland secretion. However, the possibility that androgens may also influence sebaceous glands

in some other ways has received very little attention. Androgens might have adverse effects directly on the follicular epithelium, causing a retention hyperkeratosis[5] and formation of comedones. Kroepfli[6] has shown that the experimental comedo formation in the rabbit ear can be augmented by pretreatment with androgens.

In connection with the relationship between androgens and the development of acne, two factors need to be considered : namely, the possible over-production of the androgens centrally and/or an enhanced metabolic conversion to potent androgens peripherally in the pilosebaceous unit.

In the last 4-5 decades, a plethora of reports have appeared regarding the over-production of androgens centrally. A review of the studies measuring the urinary 17 ketosteroids (17 KS) excretion did not show an increase in most of the studies.[7] With advancement in technology for measurement of small quantities of individual hormones in blood, there has been a renewed interest in looking for the endogenous endocrine disturbance in acne. An unequivocal picture of a characteristic pattern of abnormal levels of circulating androgens has not yet emerged, despite intensive work. Logically, most of the interest has centred on the measurement of plasma testosterone leading to conflicting reports : results in the male patients have varied from normal levels[8] of circulating testosterone to increased levels.[9] In female patients also, testosterone levels have varied from normal[10] to slightly increased[10] to significantly increased levels.[8] Both dehydroepiandrosterone (DHEA)[11] and its sulphated precursor dehydroepiandrosterone sulphate (DHEA-S)[12] are frequently elevated in female subjects. Since both DHEA[13] and DHEA-S[14] have been demonstrated to stimulate sebum production in man when administered systemically, these hormones may be important in the androgen metabolism in the sebaceous gland. Delta-4 androstenedione levels have been found to be normal.[9,11] Studies on other 17 hydroxysteroids (17 HS) have also been done, but have not shown a clear picture.[9,11]

Lack of unanimity of findings is due to a variety of factors. It is important to appreciate that the level of total androgen in the blood is a measure of its production and metabolic clearance rates and not a measure of its activity. Most of the androgen in the blood is bound to the sex hormone binding globulin (SHBG). Only a small proportion of the testosterone is present free, and it is this free testosterone which is capable of entering the peripheral target cells and is presumed to be the active form of the hormone. If the levels of SHBG fall, then logically more free testosterone becomes available for action. In females, though earlier reports were controversial, there is now a general consensus that the mean SHBG levels are significantly below normal and the free testosterone levels rise above normal.[15,16] Levels of SHBG in males with acne have generally been normal.[17] However, for each endocrine assay study, there is some overlap between acne and normal ranges of SHBG.

About 50-75% of all female acne patients show some degree of systemic androgen imbalance. In the other 25-50% of the female acne patients and most of the male subjects, there is probably an enhanced peripheral target tissue (pilosebaceous apparatus) response. The observations of Sanson and Reisner[18] and Hay and Hodgkins,[19] that the skin of acne patients possesses greater 5-alpha reductase activity than normal skin, support this hypothesis. The increased levels of 5-alpha reductase result in higher tissue levels of dihydrotestosterone (DHT) and thereby greater stimulation of sebaceous glands.

Androgenic alopecia : Androgens are responsible for the progressive replacement

of terminal hairs in the scalp by vellus hair which occurs with age. This replacement is subject to a variety of variables like sex of the individual, age of the individual as well as the genetic predisposition. There is a shortening of the anagen phase of the follicular cycle as well as a decrease in the size of the follicle. This is followed by an increased shedding of the hair. A bitemporal recession of the frontal hair and sparsity of hair on the vertex becomes visible.[20] This change may even begin as early as in the second decade. By the age of 50, about 60% of caucasoid men show at least some degree of vertical alopecia and bitemporal recession.[21] In females this loss of hair tends to be diffuse.[22]

The genetic background of androgenic alopecia has not been fully elucidated but the inheritence is probably multifactorial.[23] According to Osbournes' hypothesis which incriminates a single pair of sex influenced factors, in the genotype Bb, baldness develops only with male levels of androgens; in the genotype BB with female levels and in the genotype bb it never occurs at all.[23] Genetic factors also influence the age of onset of the baldness and its pattern of extension.

The essential role of androgens in this type of baldness is established by the complete absence of androgenic alopecia in males castrated before puberty, by its development in some such individuals when testosterone is administered and by the higher incidence of this form of alopecia in females with increased androgen secretion.[24] The initial stage in the condemned follicle is probably the local accumulation of DHT, the tissue active androgen.[25] This accumulated DHT inhibits the metabolism of the hair follicle. What determines this accumulation is not quite clear.[26] The existence of testosterone receptors in scalp hair is implied by the fact that in the female, androgenic alopecia can be alleviated by oral antiandrogens which compete with testosterone for receptor sites.[27] The additional necessity for 5-alpha reductase is suggested by the evidence that male bald scalp has a greater capacity than non-bald scalp to convert testosterone to 5-alpha DHT.[28] Males deficient in 5-alpha reductase do not develop recession of frontal hairline.[29] However, the 17 KS may also be important, since in vitro studies have shown that the major metabolite produced by isolated hair roots is androstenedione.[30] Cipriani et al[30] have shown elevated levels of free testosterone in men and women with androgenic alopecia.

Hirsutism : Hirsutism implies growth in the female of coarse terminal hair in part or the whole of the adult male sexual pattern.

Causes : (Table II) Patients with hirsutism form a continuous spectrum. At one end are the few in whom even the most sophisticated investigations can detect no systemic androgen excess; the largest proportion are women with slight androgen excess and minimal clinical evidence of masculinisation; at the other extreme are those women in whom marked excess of androgen production is associated with obvious clinical manifestations of virilisation.[31]

The patterned transition from vellus to terminal hair is dependent on the level of androgenic stimulation, as well as the capacity of the follicle to respond. This capacity of the follicle to respond depends on genetic predisposition, the racial factors and age of the individual. It is perhaps also influenced by diencephalic or pituitary factors. Genetic factors determine not only idiopathic hirsutism but familial aggregation of hirsutism is also evident in the groups classified as adrenal dysfunction and ovarian dysfunction.[31]

Incidence : The incidence of hirsutism in any population is difficult to assess from hospital statistics, because the criterion of excessive growth of hair is largely social. The incidence

of hirsutism is highest in the people of the Mediterranean region and is rare in Japanese.[32] In one study,[32] 26% of females surveyed had some terminal hair on the face; in 4% it was considered disfiguring. Other sites in which terminal hair were present included breasts (17%), abdomen (35%), upper back (3%) and legs (84%).

Quantitative assessment of hirsutism : Ferriman and Gallway[33] and Hatch et al[34] proposed a semiquantitative grading for the degree of hirsutism. Each of the 9 hormone sensitive body areas are graded from 0-4, for example, hirsutism of the chest can be classified as follows : grade 1 : circumareolar hair; grade 2 : with midline in addition; grade 3 : fusion of these areas with three-quarters cover; grade 4 : complete cover. Appropriate grades have been proposed for other regions as well. The individual grades are totalled and final grading is made. Scores of less than 8 are considered non-hirsute; 8 to 16 mild hirsutism; 17 to 25 moderate hirsutism; more than 25 is graded as severe hirsutism.

Relationship to androgens : Most hirsute women have elevated androgen levels. If only urinary 17 KS are measured, only 15% of hirsute women will have elevated levels.[35] This indicates that 17 KS in the urine do not reflect the secretion of the more potent 17 HS. If the total plasma testosterone is measured, about 40% of hirsute women are found to have elevated levels.[36] If the plasma levels of several androgenic hormones and prehormones (testosterone, dihydrotestosterone, DHEA, DHEAS, androstenedione) are measured, approximately 80% of hirsute women have elevated values of one or more androgens.[37] Levels of SHBG are low in about 60% of hirsute females even though the total testosterone is normal.[38] A single plasma androgen level may not be representative of the average androgen levels because the androgen levels in the blood are pulsatile, seemingly reflecting episodic ovarian and adrenal secretion. A much better estimate of the daily plasma testosterone can be obtained by hourly sampling over a 3-hour period.

Investigations[39] : The investigation of hirsutism is amongst the most difficult and the least cost effective in clinical endocrinology. This situation can be remedied by the judicious separation of the patients with disorders of androgen metabolism capable of definitive treatment, from the remainder who, while having hirsutism have no serious underlying disorder.

The age of onset of hirsutism and acne is important : Sudden development and persistence into the third and fourth decades merit further investigation. The occurrence of acne and hirsutism in adolescence or of hirsutism at menopause may not be sinister. Increasing menstrual irregularity from menarche associated with obesity suggests polycystic ovary syndrome (PCOS). Amenorrhoea associated with galactorrhoea, loss of libido and superficial dyspareunia is suggestive of an underlying prolactin-secreting pituitary adenoma. The development of clitoromegaly and laryngeal hypertrophy suggests a serious disorder and merits a detailed investigation. Amenorrhoea associated with weight loss or stress is indicative of a depressive state and requires detailed psychiatric evaluation. A drug history including details of oral contraceptives, antiepileptic drugs, diazoxide, phenothiazines and various tonics is essential. A detailed family history of acne, hirsutism baldness, infertility and irregular menses should be sought.

The physical examination should involve a careful mapping of the distribution and severity of hirsutism, the appearance of the external genitalia, the presence or absence of laryngeal hypertrophy, abnormal distribution of body fat, pigmentation, the muscular development of the patient and a careful gynaecological evaluation.

The many uncertainties surrounding the significance of tests of endocrine function in hirsutism make elaborate diagnostic procedures unwarranted except in academic centres.[40] The goals of the diagnostic procedures are, (1) to determine whether a serious illness exists, (2) to establish an endocrine origin for the hirsutism, and (3) to recommend appropriate endocrine therapy, if warranted. The plan will vary depending upon whether there is unequivocal virilisation or only hirsutism.

If the 17 KS values are high, then a dexamethasone suppression is performed to distinguish between congenital adrenal hyperplasia and tumours of the adrenal wortex and ovary : in the former the 17 KS levels fall after dexamethasone suppression. The latter two are usually separated on the basis of physical examination, intravenous pyelography, steroid fractionation and measurement of steroid levels in effluent veins during venous catheterisation.

When 17 KS are normal and the plasma testosterone levels are high, the source is usually ovarian. Laparoscopy, differential venous catheterisation with testosterone measurements, or exploratory laparotomy will provide an answer.

When both the 17 KS and the plasma testosterone levels are normal then measurement of the other androgens and SHBG (if possible) is done. Since these measurements generally cannot be obtained, empiric therapy may be the best way to proceed.

Management :[40] In case of drug-induced hirsutism and hirsutism induced by neoplastic disease of the ovaries or adrenals, the treatment is straight forward : the drugs should be withdrawn or the tumour removed. Adrenal steroidogenic defects are treated with glucocorticoids to suppress the excess ACTH and hence inhibit adrenal androgen secretion. Removal of the cause in such cases is occasionally followed by partial and very rarely complete regression of hirsutism.

In most other instances (PCOS and idiopathic hirsutism), cosmetic treatment coupled with either the suppression of androgen production or antagonism of androgen action at the receptor level need to be employed. Cosmetic therapy is directed at the concealment (bleaching) or removal of the hair from the exposed skin areas. Where the coarse hairs are relatively few, electrolysis or diathermy in the hands of a trained person is useful. Both methods are effective but the shaft diameter of the hairs that may regrow is smaller after diathermy than after electrolysis. Regular courses of treatment at intervals of 6-9 months are usually necessary. Wherever many coarse hairs are present, depilation with waxes or with lotions containing barium sulphide may be helpful. Troublesome folliculitis is however a frequent complication. Some women find abrasion with sand-paper pads convenient and moderately effective. In general, if the hair is profuse then shaving may provide the best though admittedly an inadequate solution. It is a fallacy that shaving causes hair to grow faster and become coarser.

The role of anti-androgens in the treatment of hirsutism will be reviewed later in this article.

Anti-androgens in dermatology

An anti-androgen (AA) is a compound which will specifically inhibit the biological effects of androgens on their target cells. Most work on AA has centred on negating the actions of testosterone and DHT and inhibiting the activity of 5 alpha reductase. However, as recent studies have shown a correlation between DHEA and DHEAS and the sebaceous gland activity, drugs which block 3 beta HS dehydrogenase may also form a potent group of new AA.[41]

Classification : Theoretically, androgen stimulated activity can be inhibited at several points. At a systemic level, the androgen

production can be suppressed or the amount of androgen available to the target organ can be reduced by elevating the levels of SHBG thereby reducing the amount of free testosterone available to the tissues. Estrogens are a group of drugs which inhibit the production of endogenous androgens,[42] and reduce the availability of free androgens.[43]

The term AA is however generally restricted to drugs which act peripherally at the tissue level.[42] These drugs can be classified as, (a) receptor blockers, and (b) alpha reductase inhibitors. Receptor blockers block the androgen uptake by the receptor protein in the cytoplasm. These do not necessarily have to be steroidal in their configuration. The alpha reductase inhibitors act by competitive inhibition of the enzymic conversion of testosterone to DHT. At the prsesent state of our knowledge, six agents are defined as steroid AA compounds : cyproterone acetate (CA), spironolactone, RU-2956, BOMT, megestrol acetate and medrogestone; three agents are recognised as non-steroidal AA: stilboestrol, flutamide and cimetidine.[43A]

In this review the more commonly used drugs (estrogens, CA, spironolactone and cimetidine) will be discussed in details.

Estrogens : Estradiol reduces the size of sebaceous glands and markedly reduces the sebaceous secretion. It however does not inhibit cellular mitosis in the sebaceous glands.[44,45] Estrogens act predominantly by reducing the endogenous androgen production by their action on the gonadotropins.[42] Further, estrogens cause a marked increase in SHBG levels with a corresponding fall in free testosterone.[43] Although estrogens do not effect the uptake of testosterone in the skin, they have a direct inhibitory effect on the sebaceous glands; this peripheral effect of estrogens is additive to the effect of other AA like CA suggesting that estrogens and CA have different points of action in the skin.[42]

Systemic estrogens have been used, either alone or with other AA, for the treatment of acne and hirsutism. In women, estrogens are given cyclically; either in a two-week schedule or a three-week schedule. In the two-week schedule, estrogens are given daily for 2 weeks starting on the 14th day of the menstrual cycle. Response is seen in 50 to 70% of patients with acne.[46] In the three-week schedule, estrogens are given from the 5th day after the onset of menses for a period of 21 days. The non-androgenic progestins are given alongwith estrogens in this schedule for a short period to ensure withdrawal bleeding.[47] Side effects with estrogen therapy include nausea, weight gain, spotting, breast tenderness, amennorhoea and chloasma; these are usually not severe enough to necessitate discontinuation of therapy.[46,47] One side effect about which the patients should be fore-warned is that acne often flares up during the first 2 to 3 cycles of therapy. A minimal trial of 6 months should be given. The dosage of estrogens which is required for therapeutic effect in acne, absolutely contradicts their use in males with acne and their use even in females should be restricted to patients with recalcitrant acne and hirsutism.[46,47]

Topical application of ethinyl estradiol to one side of the forehead, produces an equal suppression of sebum secretion on the contralateral site as well, even at the minimal effective dose.[48] This clearly suggests that topical estrogens act perhaps, by suppression of endogenous androgen production and this is not a local phenomenon.

Cyproterone acetate : CA is a synthetic steroid derived from 17-hydroxy progesterone. The parent compound cyproterone has no central action and is a pure AA. Hence, in the experimental animals its AA effects are gradually overcome by increased testosterone production.[49] It has not been used clinically.

CA, on ths other hand, has been extensively used clinically. The drug is almost completely absorbed by the gut.[50] Since it is stored in the fatty tissue, withdrawal bleeding, after discontinuation of treatment, is often delayed in obese women.[50]

CA exerts its anti-androgenic effect, at least in part, by acting as a competitive inhibitor of the binding of testosterone and DHT to specific intracellular androgen receptors.[51] CA is a non-specific inducer of hepatic enzymes; this effect contributes to the increased rate of metabolic clearance of testosterone and the accelerated elimination of circulating androgens.[52] CA, by virtue of its potent progestational activities has antigonadotrophic actions and hence also reduces androgen production.[49] Both these effects result in a reduction in the level of circulating androgens. This reduction in the circulating androgens results in a reduction in the androgen dependent 5-alpha reductase activity.[49] So indirectly CA is an inhibitor of 5 alpha reductase.

CA reduces the sebaceous gland size, significantly suppresses sebaceous mitosis and decreases sebaceous gland secretion.[53] Though it has been found effective when used alone in a dose of 100 to 200 mg daily,[54] it is generally used along with ethinyl estradiol in a regimen which, by analogy with regimens for oral contraception, have been designated as reversed two phase therapy or reversed sequential therapy.[55,56] CA in the dose of 100-200 mg per day is given from the 5th to the 14th day of the menstrual cycle combined with 50 mg of ethinyl estradiol from the 5th to the 25th day. This regimen has been widely used for therapy of cystic acne, hirsutism and androgenic alopecia in women. More than 90% of patients having acne show a 90% improvement at 3 months. In hirsutism the response is less impressive and slower; 70% of patients usually get an improvement at 6 months. Only 50% of patients of androgenic alopecia show an improvement at the end of 1 year. Side effects resemble those produced by estrogens.[54] Pregnancy should be ruled out before starting therapy because CA produces serious abnormalities in the male foetus. The long-term effects of CA are not definitely known, especially with regard to the suppression of the pituitary adrenal axis. Recently, a comparison of high dosage CA (100 mg) and low dosage CA (2 mg) therapy has shown that although results with high dose therapy are achieved more quickly, the final rate of success after 12 months of treatment is similar for both regimens.[57] Except in exceptional cases, CA is not to be used in male patients, where the low dose CA regime may be used.[51] One redeeming feature of therapy with CA is the low rate of relapse when the treatment is stopped.[57]

Since CA acts substantially at the level of the target organ, logically it should prove efficacious when applied topically, without the unpleasant systemic effects. One percent CA has, however, been found ineffective for the treatment of acne.[59]

Spironolactone : This steroidal antihypertensive agent is a specific antagonist of aldosterone. It also has anti-androgenic actions. The anti-androgenic action of spironolactone is mainly as a result of competitive inhibition of DHT binding to the androgen receptors and the decreased nuclear uptake of the androgen.[60] It also markedly increases the apparent free estradiol concentration while decreasing the apparent free testosterone concentration.[61] Levels of plasma testosterone and androstenedione decline after spironolactone therapy and this effect is most marked in patients with PCOS.[62,63]

Spironolactone has been used successfully for the treatment of hirsutism,[62,63] androgenic alopecia in women[62] and acne.[64] A daily dosage of spironolactone in the range of 100-200 mg has been found effective. The drug should be

administered either cyclically or on a daily basis for 5-6 months. Side effects include metrorrhagia, mastodynia, gynaecomastia, gastric distress and decreased libido. Using spironolactone cyclically and the addition of an oral contraceptive pill reduces the incidence of unpleasant side effects.[65]

Topically applied spironolactone has been reported to be effective for the treatment of acne.[66] This is not surprising since spironolactone is a more potent inhibitor of DHT binding to the androgen receptors than CA.[67]

Cimetidine[68] : This is a H_2 receptor blocker. It also decreases the binding of DHT to androgen receptors but has no effect on the testosterone production. It has been found clinically useful in the management of hirsutism and acne in the daily dose of 1-1.5 gm. The side effects are generally mild : gynaecomastia, electrolyte imbalance and decreased libido.

Alpha reductase inhibitors : Until recently, it was not possible to test the hypothesis that 5 alpha reductase inhibitors may be clinically useful for treating androgen-dependent disease processes. This was because no compounds with pure alpha reductase inhibiting potential were available. However, lately a variety of compounds, primarily steroids, have been found to have predominantly alpha reductase inhibiting actions. A number of 4-azasteroids[69] have excellent activity, both in vitro and in vivo. It is expected that, in the near future, one or more of these highly active 5 alpha reductase inhibitors will soon be available for the treatment of hirsutism.

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