The problem of excessive hair growth in women has challenged clinicians for a long time. In a 1963 monograph on hirsutism, Robert B. Greenblatt, acknowledged by many physicians as one of the founding fathers of contemporary reproductive endocrinology, wrote, “The hairy female, a subject of much anguish and concern to herself and her family, has been the object of great curiosity to men and women of all generations, a bewildering puzzlement and decided challenge to physicians from time immemorial.”

Indeed, excessive hair growth in women has long been the subject of curiosity and fascination. One of the most famous illustrations of excessive hair growth dates back to 1631. In his painting “La Barbuda,” the Spanish painter Ribera depicts a woman holding her newborn baby while displaying a thick beard rivaling that of her husband. The painting is said to have been commissioned by the king of Spain, highlighting the deep fascination with such a condition.

Today, the terms hirsutism and virilization are used to describe the clinical spectrum of disorders of excess hair growth in women. Much progress has been accomplished in the past decades in understanding the cause and management of these conditions. This article reviews the current approach to these conditions when they present in the adolescent woman.
DEFINITION

It is helpful to clarify some of the terms used to refer to disorders of excessive hair growth in women. Hirsutism refers to the “appearance of excessive coarse (terminal) hair in a pattern not normal in the female.” This definition highlights the abnormal distribution of excess hair growth, such as facial, chest, or upper abdominal hair. In contrast, hypertrichosis refers to growth of hair in excess of the normal while limited to a normal pattern of distribution. The latter condition is beyond the scope of this discussion but is frequently associated with the use of medications such as antiepileptics.

Virilization refers to the concurrent presentation of hirsutism with a broad range of signs suggestive of androgen excess, such as acne, frontotemporal balding, deepening of the voice, a decrease in breast size, clitoral hypertrophy, increased muscle mass, and amenorrhea or oligomenorrhea. Virilization is seen much less frequently than hirsutism and may reflect a severe underlying pathologic condition, such as a malignancy.

Although these definitions may seem semantic in nature, they are of great clinical relevance. Hypertrichosis is a totally separate entity. Hirsutism and virilization are more closely linked, and hirsutism may actually be the first manifestation of a condition that ultimately will lead to virilization if left untreated. In this context, one must consider the range of causes that may account for either isolated hirsutism or virilization.

BASIC FACTS ABOUT HAIR

Several facts regarding hair and hair growth are relevant to the workup of these disorders. Hair grows from individual hair follicles that are part of a pilosebaceous gland unit. The number of hair follicles is set from birth. The number of hair follicles is also comparable between men and women. The main difference between sexes is the degree of differentiation of the hair.

The growth of hair can follow one of several patterns. Humans display continuous hair growth in contrast to many animal species that have a cyclical or seasonal pattern. In addition, hair grows in a so-called “mosaic pattern,” that is, in any given area, hairs are in a different stage of development. The end result is a stable and static number of hairs in a given area despite a constant but stable turnover. This growth pattern is important clinically. Some conditions may cause a high level of synchrony between the growth cycles of hair, leading to the appearance of either massive hair loss (alopecia) or excess hair for a limited period of time.

The number of hairs in any given area of the body is highly variable, with the scalp generally being the best endowed with more than 100,000.
Scalp hair generally has a growth cycle of about 2 to 6 years and displays a growth rate of about 12 cm/year. By contrast, hair in other areas of the body tends to have a much shorter life cycle, ranging from 1 to 6 months. This shorter life cycle accounts for the shorter length of hair in other parts of the body. It also means that 3 to 6 months will pass before the effect of any therapy modifying hair growth can be assessed, corresponding to the turnover of hair in a given area.

The growth cycle of hair comprises three discrete phases (remembered by the mnemonic, ACT). Anagen refers to the growth phase and comprises 85% to 90% of the life cycle of hair. Catagen is the rapid involution phase, and the telogen phase is the quiescent part of the cycle. The second and third phases constitute 10% to 15% of the entire life cycle. The growth phase, or anagen, is primarily influenced by disorders that stimulate hair growth as well as therapeutic modalities.

Three types of hair can present. Lanugo hair refers to the body hair seen in the fetus and newborn. This term should be reserved to this stage of life. The fine adult hair covering the body is referred to as vellus hair. The thick pigmented hair seen in areas such as the scalp and pubic areas represents terminal hair.

There is a marked range in the appearance of terminal hair, which can sometimes be misleading in a clinical setting. The thickness of terminal hair varies greatly from one individual to another, depending primarily on genetic and, possibly, nutritional factors. In addition, the color of the pigment may influence the way the hair is perceived. Black, red, or blond pigmented hair will be more or less apparent depending on the individual’s complexion and skin color.

Only certain areas of the body depend on androgen input for hair growth. These areas include the face, neck, chest, abdomen, axillary, upper arms, inner thighs, and pubic regions. Part of the scalp is also androgen-sensitive. The androgen metabolism within the pilosebaceous unit is complex and involves the interaction of testosterone with the androgen receptor as well as intracellular conversion of testosterone to the more potent dihydrotestosterone by the enzyme 5α-reductase. The androgenic stimulation of the pilosebaceous unit in these areas leads to the conversion of vellus to terminal hair (Fig. 1). In contrast, hairs on the forearms, hands, and lower legs are less influenced by androgenic mechanisms.

**PRESENTATIONS OF HIRSUTISM**

Most cases of virilization seen clinically are acute and striking in nature. They seldom remain unrecognized and usually prompt immediate medical intervention. In contrast, hirsutism presents in a variety of ways and depends on several factors. Numerous studies have attempted to assess the prevalence of hirsutism or underlying disorders.
The author has found it helpful in the clinical setting to consider cases of hirsutism as manifesting in one of several ways:

- Hirsutism alone
- Hirsutism and associated pilosebaceous unit overactivity (e.g., acne)
- Hirsutism and ovulation disorder
- Hirsutism and signs of virilization

Hirsutism that presents alone is the greatest challenge because it is the manifestation of a variety of disorders that are associated with hirsutism. These patients usually present to a generalist or dermatologist for work-up. The concurrent presence of hirsutism and associated skin conditions, such as acne, is seen most frequently during the teenage years. The occurrence of hirsutism in a woman with chronic anovulation or other ovulatory disorders is the most frequent presentation seen by the gynecologist. Hirsutism with signs of virilization requires an immediate workup for virilization. These signs may not be evident to the patient.

It is difficult to assess the prevalence of hirsutism in the general population. The biggest challenge arises from the subjective nature of defining what constitutes excessive hair growth. The perception of hirsu-
tism by the patient may be influenced by several factors, including the degree of hair growth in relatives and racial and ethnic factors.

Few studies have focused on the prevalence of hirsutism. Such studies have incorporated some form of an objective assessment scale to determine hair excess. In a study conducted in Wales and reported in 1964, approximately 10% of women presented with some degree of hirsutism, and nearly 4% had true disfigurement. A more recent study conducted in the southeast United States evaluated a randomly selected population of 369 women for the prevalence of hirsutism. Depending on the clinical threshold selected, 2% to 8% of the women were found to have hirsutism, with no racial difference between black and white women. These estimates of prevalence are remarkably concordant considering the variance in time and geographic location.

The frequency with which one sees the various presentations of hirsutism varies greatly. Azziz et al studied a population of hirsute women in Alabama. Of the 132 women, more than 70% presented with concurrent ovulation disorder. Similar findings were reported in the study of a group of women of primarily Arabic origin. In contrast, in a study of more than 600 women undergoing cosmetic electrolysis, more than 70% of women self-reporting hirsutism had normal menstrual cycles.

Approximately 2% to 10% of the population manifests some evidence of hirsutism. The underlying cause and accompanying presentations vary greatly from one population to another. The clinician must remain alert when formulating an appropriate differential diagnosis for these patients.

CAUSE OF HIRSUTISM

The clinical approach to the patient with hirsutism rests on a solid understanding of the potential causes of excess hair growth. Several classification systems have been proposed for these causes. The following system offers a simple and logical approach:

- Excess androgen production
- Relative circulating androgen excess and low binding globulins
- Excess end-organ response
- Patient perception

Disorders of Excess Androgen Production and Circulating Levels

Excess androgen production is the most common triggering factor for hirsutism. The source of androgens can be exogenous but is most commonly endogenous. There are two primary endogenous sources of androgens: the adrenal glands and the ovaries.
steroid synthesis enzyme deficiency, to a malignant adrenal neoplastic process, or to other conditions such as Cushing's syndrome. Three recognized steroidogenic adrenal enzyme deficiencies have been linked with hirsutism: (1) 21α-hydroxylase deficiency, (2) 11β-hydroxylase deficiency, and (3) 3β-ol-dehydrogenase deficiency. These disorders may be evident from the prenatal or neonatal period with ambiguous genitalia in the female, usually referred to as the classic form of the disorder. The nonclassic forms of these enzymatic defects are linked with hirsutism. The genetic basis of this class of disorders recently has been elucidated.

21α-Hydroxylase deficiency is the most common of these disorders. Estimates of the prevalence of this condition among hirsute women range from <1% to >10%. There is a wide range in the prevalence of the nonclassic form of the disorder depending on the specific ethnic group studied. Estimates range from 1 in 300 in an Italian population to 1 in 50 in Slavs to 1 in 40 in Hispanics in the United States to 1 in 27 in Ashkenazi Jews. The likelihood of identifying this disorder depends greatly on the origin of the population.

Although hirsutism is associated with the nonclassic form of 21α-hydroxylase deficiency, heterozygous carriers for 21α-hydroxylase deficiency do not seem at increased risk for hirsutism. 11β-Hydroxylase deficiency among hirsute women has been demonstrated with a prevalence of approximately 5%. The link between hirsutism and 3β-ol-hydroxysteroid dehydrogenase deficiency has been viewed with some degree of skepticism. Recent studies using molecular diagnostic techniques support this enzyme deficiency as an etiologic factor, albeit, a potentially rare one.

Cushing's syndrome and disease can be seen in adolescents; however, the presentation may differ from that in adults, with weight gain and growth retardation as the primary manifestation. Hirsutism as well as acne and other cutaneous manifestations are associated with this condition in this patient population. Although it is rare, Cushing's syndrome should be considered in the differential diagnosis.

The most common cause of androgen excess of ovarian origin is polycystic ovary syndrome (PCOS) and its many linked disorders. PCOS is discussed in more detail elsewhere in this issue. On occasion, a neoplastic ovarian process may be involved.

Disorders of Relative Androgen Excess and Sex Hormone-Binding Globulin

Usually, less than 3% of testosterone circulates freely in serum. Most androgens circulate in a bound form, primarily to sex hormone-binding globulin (SHBG). Any condition that impacts on the levels of SHBG or other binding proteins can lead to a relative excess of circulating androgens. Several conditions that decrease SHBG levels have been identified. In patients with hirsutism, the major conditions linked with abnormal
SHBG levels include PCOS (chronic anovulation) and obesity. Several other factors are known to affect the levels of SHBG or its binding potential, including medications.

Disorders of Excess Responsivity to Androgen

Once androgens reach target cells, they must interact with the androgen receptor, which is encoded by a gene on the X chromosome. Testosterone is converted within the cell to dihydrotestosterone, a more potent androgen, under the action of 5α-reductase. Excess activity of 5α-reductase is recognized as a cause of hirsutism. Mutations in the androgen receptor have also been linked to hirsutism.

Two genes encoding different types of 5α-reductase, type 1 and type 2, have been identified. Recent studies suggest that the type 1 enzyme is involved in hirsutism. Recent studies have identified mutations within the androgen receptor that account for excess responsiveness to circulating androgens, including mutations in the highly polymorphic region of the androgen receptor. Another proposed mechanism of excess responsivity is preferential inactivation of the X chromosome with greater androgen sensitivity.

Disorders of Perception and Self-Image

Hirsutism is a condition that is subjective in nature by definition. Although a certain threshold level may be proposed on semiobjective scoring scales, the patient’s perception of the condition is most important. Semiobjective scales compile a score from a number of different sites, such as the face, the chest, and the perineum, whereas patients potentially perceive these areas and the presence of hair in these regions as very different. The presence of a few coarse facial hairs may be considered a medical emergency by some patients, whereas other patients with coarse hirsutism remain unconcerned.

In teenagers, the concurrent appearance of acne and hirsutism can compound the sense of distress. The clinician must consider both elements when formulating a management plan. The clinician should be reassuring and show appropriate concern but should also establish reasonable medical expectations.

One dangerous path to avoid is heeding to the concerns of a teenager who desires therapy for excessive hair growth limited to non-androgen-dependent areas, such as the forearms or the lower legs. Hair growth in these areas is genetically determined and independent of the endogenous androgenic environment. It is inappropriate to perform a workup for this presentation, and any therapeutic attempt will be futile.
Other Conditions

Several medical conditions have been associated with hirsutism:

**Disorders of excess androgen production**
- **Ovarian disorders**
  - PCOS (includes HAIRAN: hyperandrogenism, insulin resistance, acanthosis nigricans)
  - Severe insulin resistance
  - Hyperthecosis
  - Tumors
  - Enzyme deficiency (17-ketosteroid reductase)
- **Adrenal disorders**
  - Congenital adrenal hyperplasia (21α-hydroxylase/11β-hydroxylase/3β-hydroxysteroid dehydrogenase)
  - Cushing’s syndrome
  - Tumors
- **Disorders of sexual differentiation (mixed gonadal dysgenesis)**

**Relative circulating androgen excess/low binding globulins**
- Drugs
- Pregnancy
- Anorexia nervosa, malnutrition

**Excess end-organ response**
- Genetic or idiopathic
- Racial or familial

**Other**
- Hypothyroidism
- Hyperprolactinemia
- Acromegaly
- Central nervous system lesions
  - Multiple sclerosis
  - Encephalitis
- Porphyria
- Stress
- Syndromes
  - Hurler’s
  - Trisomy E
  - de Lange
  - Achard-Thiers

The mechanism underlying the hirsutism is often unclear. In some cases, the hirsutism may be related to drug effects. An example is the hirsutism described in patients receiving medications for seizure disorders.70

**BASIC APPROACH TO THE DIAGNOSIS OF HIRSUTISM AND VIRILIZATION**

Diagnosis in the patient presenting with hirsutism or virilization is simple if one follows a methodical approach. Several algorithms have
been proposed, but there is considerable overlap. This section outlines the author’s approach to diagnosis in the teenage patient.

The first step consists of identifying the true nature of the presentation. In some cases, the patient presents because of an ovulatory disorder, and, although clinically apparent, hirsutism is not reported or noticed by the patient. In other cases, the patient may present with the primary complaint of hirsutism, although a fully normal complement of hair is present. In rare instances, signs of virilization are manifest. Defining the problem accurately is essential to further investigations and the ultimate treatment of the patient.

When hirsutism is evident to the clinician but is not reported by the patient, the clinician must bring up the issue using tact. He or she should not give the teenager a message that she is grossly abnormal and create a new problem for her. The hirsutism may be idiopathic and a reflection of the genetic and familial background of the patient. Raising the issue of hirsutism may make the teenager highly self-conscious and may create a self-image problem when it did not exist before.

A careful history must be taken. Specifically, the timing and the chronologic progression of the excess hair growth must be established. In the teenage woman, one must document the age of onset of pubertal development and the progression. Any evidence of precocious puberty associated with a history suggestive of androgen hyperactivity is particularly relevant in determining the need for further steps in the workup and is highly suggestive of an adrenal enzyme defect. The presence of any associated medical condition must be noted. The family history is important and should focus not only on problems that may suggest androgen excess disorders but also the familial pattern of hair growth. The evaluation of this group of patients frequently requires completion of the physical examination and a return to history taking to elucidate the diagnosis.

The physical examination should focus on establishing the presence of hirsutism and quantifying it, if present. Several different scales have been proposed to assess the level of hirsutism. In addition, the clinician should identify the presence of acne and virilization and rule out the presence of hypertrichosis versus hirsutism. The presence of skin hyperpigmentation, acanthosis nigricans, is suggestive of insulin resistance and is often associated with PCOS. Other relevant elements during the physical examination include the measurement of height, weight, and blood pressure. These parameters may suggest conditions of androgen excess related to adrenal enzyme deficiencies. Clinical evidence of any of the associated medical conditions, such as galactorrhea, should be noted. Tanner staging is appropriate in the early adolescent patient to relate the presentation to the stage of pubertal development. The presence of hirsutism before Tanner stage 3 to 4 is alarming and suggests a serious underlying pathology. Visual examination of the external genitalia is critical in identifying early signs of virilization. For many teenagers, this examination may represent the first gynecologic evaluation, and appropriate consideration should be given to this aspect. Visualization of the external genitalia will suffice versus a full pelvic examination.
An adequate evaluation of hirsutism requires an objective method for assessing the amount of hair growth. Some clinicians obtain detailed photographs so that they can follow the progression or regression of hair over time. Although this practice may be appropriate in some settings, in the author's experience, most teenagers dislike this approach. In addition, high-quality photography is required for the method to be valid. The use of a semiobjective scoring system is preferred, such as the Ferriman and Gallwey system (Fig. 2). No absolute cutoff level defines hirsutism on the Ferriman and Gallwey scale, but most investigators and clinicians choose a score between 6 and 12 as the lower end for hirsutism.

The author solicits the full cooperation of the patient when using the Ferriman and Gallwey scale. The physician and patient assess the score together, and the completed scoring sheet is placed in the patient's chart. At a follow-up visit, the patient can repeat the scoring and evaluate for herself the progress over time.

When the patient presents with virilization, a full investigation is warranted. Virilization is the clinical manifestation of gross androgen excess. The workup focuses on the identification of the source of androgen excess:

- Rule out exogenous androgen
  - Testosterone or other androgenic preparation
- Evidence of endogenous androgen excess
  - Serum total testosterone
  - Serum dehydroepiandrosterone sulfate (DHEAS)
• Imaging studies
  Pelvic ultrasonography (ovaries)
  Adrenal imaging
    Ultrasonographic
    CT or MR imaging
• Specialized studies
  Selective venous catheterization (adrenal or ovaries)
  Radioisotopic studies

These cases are rare, and one should consult liberally. A full workup must be completed to avoid jumping to conclusions too early. The author and many of his colleagues are aware of several cases in which an invasive and irreversible operation was performed before reaching an appropriate diagnosis of a condition that could have been treated medically.

Controversy remains regarding what investigations are appropriate in the patient presenting with hirsutism. The real issue is to define the ultimate goal of laboratory investigations. One must distinguish between clinically relevant investigations and laboratory tests that belong to the realm of structured clinical scientific investigation protocols.

For some clinicians, the clinical finding that the patient has an ovulatory disorder and hirsutism is sufficient evidence to initiate a treatment plan. Although this approach may be highly cost-effective, it is unacceptable in the adolescent patient. At a minimum, the patient should undergo an investigation to determine the cause of the ovulatory disorder. An accurate diagnosis is essential in this age group before undertaking a management plan that will span several decades of life.

At the other extreme, some clinicians propose an elaborate workup that includes sophisticated assays and provocative testing. This approach is appropriate in the context of structured clinical investigations performed to determine the prevalence of certain conditions. For most clinicians, such tests are not available. Possibly worse, the tests that are available are based on a different assay system that does not truly reflect the findings outlined in reported studies.

The best clinical approach seems to be a "middle-of-the-road" position. The goal of the investigations should be to rule out serious potentially life-threatening conditions and to gain information that may help guide the treatment approach.54 Recommended investigations are as follows:

Evaluation of androgen production
  Testosterone (total or free)
  DHEAS
  In selected cases
    17-Hydroxyprogesterone (fasting morning sample)
    3α-Androstaneadiol glucuronide
Evaluation of accompanying medical disorder
  Ovulation disorder (follicle-stimulating hormone [FSH] and luteinizing hormone [LH])
Thyroid dysfunction
Hyperprolactinemia (prolactin)
Other investigations (in selected cases)
Androgen production
Androstenedione
3α-Androstanediol glucuronide
Provocative testing
Corticotropin stimulation test
Insulin resistance determination

Evaluation of androgen production is appropriate. Either total or free testosterone can be measured. Evaluation of total testosterone will help to rule out a gross excess of androgen, as will measurement of DHEAS. Measurement of free testosterone will provide evidence of subtler androgen excess in a patient. The challenge clinically is the wide range of assays for free testosterone and the lack of uniformity in determining normal and abnormal ranges. Obtaining a free testosterone level may add little information for clinical management. An alternative to the measurement of free testosterone is the evaluation of SHBG; however, there are also wide variations in the measurement of serum levels and a wide range of normal levels.

The need to screen for a form of adrenal enzyme deficiency is generally accepted; however, the ethnic origin of the patient may be a better guide in the selection of patients for testing. The simplest way to test is to obtain a fasting morning plasma 17-hydroxyprogesterone level. Several investigators advocate the routine use of provocative testing to screen for these disorders.

To rule out accompanying medical disorders, the workup should include tests to detect an ovulation disorder, thyroid dysfunction, or prolactin excess if there is any suggestion from the history or clinical examination that one or more of these conditions may be present. A detailed discussion of the investigations for these medical conditions is beyond the scope of this article.

Several other investigations may be appropriate depending on the clinical presentation. Measurement of androstenedione has been advocated for a long time, but its clinical relevance is unclear. Similarly, many studies have advocated the evaluation of 3α-androstanediol glucuronide as a measure of peripheral androgen metabolism. Although this assay is appropriate in the research setting, it has limited value in the clinical setting, primarily because of wide variations in the clinical assays used to measure this metabolite and related compounds. An evaluation of thyroid function, prolactin, FSH, and LH, may be appropriate in some patients, but the author does not believe these tests should be included routinely in the workup of the adolescent with hirsutism unless there is suggestive evidence for one of these disorders.

Numerous protocols exist for provocative adrenal testing in search of an adrenal enzyme deficiency. These protocols are appropriate to make a specific diagnosis. Some clinicians advocate the routine testing
of all patients for these disorders. Their ultimate impact on the management of hirsutism is often moot, and the author prefers to reserve testing for specific conditions. Patients with a family history suggestive of an adrenal enzyme deficiency or who belong to an ethnic or racial group in which the disorder is highly prevalent may be more appropriate for testing. Recent reports have proposed the use of ovarian suppressive testing in the evaluation of these patients. This investigation should be considered experimental at present. It is most appropriate to conduct provocative testing in a setting in which it is performed regularly and in which appropriate laboratory standards have been established and are maintained. The same recommendations apply to testing for insulin resistance.

A battery of additional tests can be useful in clinching a final diagnosis. These tests include ultrasonography of the ovaries and adrenal glands and CT or MR imaging of the adrenals. These modalities should be reserved for patients in whom a final diagnosis cannot be made without this information.

There is great variation in the laboratory investigations that are recommended in the evaluation of hirsutism. The clinician must clearly outline the goals of the investigations and be intimately familiar with the methods used. Appropriate sensitivity should be given to the number of tests and procedures to which the patient will be submitted before formulating a diagnosis and treatment plan.

**THERAPEUTIC OPTIONS**

The goal of therapy in the patient presenting with virilization is clear. It consists of identifying the underlying cause and correcting it. Most often, the virilization is related to a malignant process and requires a surgical approach.

In contrast, the management of hirsutism is generally multifaceted. It involves two separate but linked goals: (1) the prevention of further stimulation of hair growth and (2) cosmetic correction of the problem. The management plan should be structured and clear to the patient from the onset. The basic steps in the management of hirsutism are as follows:

- Define the problem
- Quantify the degree of hirsutism
- Identify pathophysiology
- Correct the problem, whether acute or chronic
- Define success with the patient
- Follow-up

When selecting the appropriate therapeutic modality to correct the hirsutism, the clinician should consider both a short- and long-term perspective. A key element of any therapeutic plan is to define what will ultimately be viewed as successful therapy by the patient. Regular
follow-up is indicated at appropriate intervals, usually, every 3 to 6 months.

**General Measures**

Treatment is targeted at the underlying cause. Several measures are indicated in most cases:

- Eliminate causative factors
- Optimize weight
- Manage hair
  - Bleaching
  - Cutting or shaving
  - Electrolysis
  - Laser epilation

Any exogenous source of androgens should be avoided. Achieving a normal body weight is highly desirable; obesity is linked to chronic anovulation, insulin resistance, and lowered circulating levels of SHBG.

Ultimately, medical therapies can slow or halt the further growth of hair but will not reverse an already established hair pattern. The approach to managing existing hair growth varies among clinicians. Some physicians advocate an initial attempt at reducing the visible nature of the hair with bleaching. Ultimately, the author prefers some form of hair removal. Hair must be removed to its base within the hair follicle so that the follicle is eradicated or the next hair emerging from that follicle is exposed to the improved hormonal environment induced by the concurrent medical therapy. Medical electrolysis is an effective way of achieving hair removal. Recently, laser-assisted hair removal has been performed. Little evidence suggests that this newer modality offers much advantage over traditional electrolysis.

**Management of Excess Ovarian Androgen Production**

The most common cause of hirsutism is PCOS. The standard therapy in these patients includes the use of a combined estrogen-progesterin preparation, most commonly administered as a combined oral contraceptive preparation. This approach is extremely sound on scientific grounds because it reduces the ovarian production of androgens, increases serum levels of SHBG, and induces competition at the cellular level for binding to the androgen receptor. Offering this form of therapy to the adolescent patient may be met with great resistance by the parents, who become concerned that the use of a contraceptive preparation will encourage their daughter to become sexually active. An open discussion with the parents and the patient usually is adequate to clear up any misunderstanding.

Much controversy remains regarding the choice of an oral contra-
ceptive preparation for the management of hirsutism. Based on primarily preclinical data, some investigators believe that certain progestins are preferable to others. Other researchers maintain that all preparations are comparable in efficacy.

Comparative studies have been reported, and others are underway. Some studies have failed to demonstrate any clinical difference among different preparations. In the United States, the only oral contraceptive preparation for which data have been presented to the Food and Drug Administration to obtain an on-label indication for acne is the combination of ethinyl estradiol and norgestimate (Ortho Tri-Cyclen package insert [Ortho-McNeil Pharmaceutical, Raritan, NJ]). No preparation in the United States has received on-label approval for the management of hirsutism. In many other countries, cyproterone acetate is available and is used as the progestin component of oral contraceptives.

Another therapeutic approach for excess androgen production from the ovaries is to achieve ovarian suppression with a long-acting gonadotropin-releasing hormone analogue (GnRHa). The effectiveness of this therapy has been demonstrated in the context of functional ovarian androgen overproduction as well as malignant ovarian conditions. This approach is effective as a single-agent treatment modality, with long-acting GnRHa preparations including leuprolide, buserelin, triptorelin, and goserelin. Because of the hypoestrogenic consequence of this form of therapy, a more rational long-term management strategy is to combine long-acting GnRHa therapy with estrogen or estrogen-progestin therapy. It is unclear whether this combined form of therapy offers any advantage over more traditional approaches.

Over the past decade, there has been increasing interest in the relationship between PCOS and insulin resistance. Two cutaneous manifestations of insulin resistance are hirsutism and acanthosis nigricans. Several studies have looked at the effects of insulin-sensitizing agents on PCOS and hirsutism. The agents studied to date include metformin and troglitazone.

Management of Excess Adrenal Androgen Production

Most patients who present with adrenal androgen overproduction as the source of hirsutism have a steroid synthesis enzymatic defect. For these patients, the primary therapeutic modality is metabolic correction of the disorder, usually with exogenous corticosteroids.

Agents to suppress adrenal androgen production, such as dexamethasone, have been advocated as essential components in the medical management of hirsutism. The author believes there is a limited role for corticosteroid therapy in the management of hirsutism in the adolescent patient unless it is absolutely mandated and a definite adrenal enzyme deficiency has been identified.
Management Directed to the Target Organ and Cells

Several therapies target the androgen receptor as they compete with testosterone during binding. These therapies include antiandrogens such as spironolactone, flutamide, and ketoconazole. Although not currently available in the United States, cyproterone acetate is widely used in other countries in the management of hirsutism.\textsuperscript{42, 63, 73, 74}

Spironolactone is by far the best studied antiandrogenic agent for hirsutism and is the gold standard with which other preparations are compared.\textsuperscript{26, 57, 62, 65} Mechanisms of action of spironolactone in the management of hirsutism include androgen receptor blockade, the suppression of adrenal androgen biosynthesis, and increased metabolic clearance of testosterone with increased conversion of androgens to estrogens.\textsuperscript{58} The usual dosage ranges from 50 to 200 mg/d in two divided doses. Spironolactone is used concurrently with oral contraceptives in a well-established combination regimen.

Flutamide acts by blocking the androgen receptor and decreasing adrenal androgen production.\textsuperscript{21} It has been shown to be effective in the management of hirsutism.\textsuperscript{48, 50, 51} One report suggests that flutamide may have a role as a primary therapeutic modality in patients with PCOS.\textsuperscript{20} Several studies have investigated the combination of flutamide with an oral contraceptive. Although this combination is effective, few data suggest a marked increase in efficacy in comparison with the oral contraceptive regimen alone.\textsuperscript{22}

Ketoconazole has been shown to be equally effective as other treatment modalities.\textsuperscript{35, 40} Its use has been associated with hepatic failure, and the author cannot justify its use over other equally effective options.\textsuperscript{16}

Finasteride inhibits 5α-reductase and reduces androgen input within the cell. Recent studies suggest a potential role for finasteride in the management of hirsutism.\textsuperscript{15, 17, 28, 29, 63, 79} It is unclear whether it offers much advantage over other therapies. In addition, the agent is teratogenic, and undermasculinization of a male fetus would most likely result with exposure to finasteride during pregnancy. More research is needed before this therapy can be used in a clinical setting.

Several clinical trials have compared the various agents targeting the androgen receptor or cellular mechanism. Some of these studies, such as trials of cimetidine, have demonstrated little clinical efficacy. Overall, there seems to be little difference between the effectiveness of these agents.\textsuperscript{27, 30, 33}

Selecting the Best Medical Therapy

Current data suggest that most therapies for hirsutism are comparable in efficacy. The dominant consideration in the selection of treatment is the safety and tolerability of the approach. The choice should be made in close consultation with the patient.

Correction of an underlying medical disorder is the primary thera-
DISORDERS OF EXCESSIVE HAIR GROWTH IN THE ADOLESCENT

peutic target. This treatment includes correction of a thyroid disorder or hyperprolactinemia or long-term therapy for an adrenal enzyme deficiency. Because many patients who present with hirsutism manifest signs of PCOS, oral contraceptives are a frequent treatment modality.

The best therapy encompasses an approach that is familiar to the clinician and that instills confidence. For most patients, this regimen includes an oral contraceptive preparation and an antiandrogen, usually, spironolactone. The first step in management of the refractory patient should be to assess adherence to the therapy and the selection of the specific contraceptive preparation. Although most oral contraceptives are effective, in some patients, the response differs markedly from one preparation to another, and the least androgenic preparations should be tried before moving on to other forms of therapy. In patients receiving low-dose spironolactone, the dosage should be increased to 200 mg/d before switching to another antiandrogen.

Approximately 75% to 80% of patients can be expected to show a response. An interval of 3 to 6 months is needed before an effect of treatment is seen. Once a positive response is achieved, the treatment should be continued for at least another 6 months and, in most cases, should be continued for a number of years. Although little information is available on the appropriate duration of therapy, some improvement in the underlying condition can be expected over time.

For patients who are truly refractory to an approach combining oral contraceptives and spironolactone, other therapeutic modalities can be considered. Many of these therapies are still experimental, and patients should be monitored closely.

FUTURE PERSPECTIVES

Knowledge of the hair growth cycle is increasing. These scientific insights may ultimately yield new therapeutic approaches focused on the specific phase of hair cell growth relevant to hirsutism. New therapeutic compounds under development may provide improved efficacy and safety when compared with current progestational or antiandrogenic agents.

SUMMARY

Virilization is most often the reflection of a serious underlying condition. Diagnosis and management should be prompt, thorough, and comprehensive. Hirsutism is the manifestation of a variety of disorders. It may be associated with serious acute medical conditions, chronic disorders, or idiopathic. The diagnosis should be methodical and adjusted to the nature of the clinical presentation. Several therapeutic modalities are effective and produce satisfactory results for most patients.
References

alone and combined with an oral contraceptive for the treatment of idiopathic hirsutism. Clin Endocrinol (Oxf) 43:575-582, 1995


69. Sundaraman PG, Amminini AC, Khurana ML, et al: Late onset adrenal hyperplasia


Address reprint requests to
Leo Plouffe, Jr, MD, CM
Lilly Research Laboratories
United States Medical Endocrine Division
Drop Code 4121
Eli Lilly and Company
Indianapolis, IN 46285

e-mail: lplouffe@lilly.com