

Chapter 2

Hair loss; Causes, Clinical Manifestations, And Available Treatments

2A

Introduction

Androgenetic alopecia (AGA) is characterized by a receding hairline and/or hair loss within a given pattern on the scalp. This disorder, which can affect both men and women, is an inherited condition, caused by a genetically predetermined sensitivity in certain scalp hair follicles to the effects of the androgenic hormone dihydrotestosterone, or DHT. DHT is believed to shorten the growth, or anagen, phase of the hair cycle, causing miniaturization of the follicles, and producing progressively finer hairs. The production of DHT is regulated by an enzyme called 5-alpha reductase (5AR).

Testosterone (T) secreted by the testis is the principal androgen circulating in the plasma in men, whereas in women the adrenal and ovarian steroids 4-androstenedione and dehydroepiandrosterone sulfate are the most abundant circulating proandrogens. Human skin is an important site for the biotransformation and metabolism of androgens (1). It has the potential to enzymatically convert the primary adrenal androgen dehydroepiandrosterone sulfate to dehydroepiandrosterone and dehydroepiandrosterone to androstenedione to T and then to DHT (1) (figure 7-8).



Figure 7: Major pathways of steroid biosynthesis



2B

Cutaneous Androgen Metabolism

The primary ovarian proandrogen, Δ^4 -androstenedione, can also be converted to T in the skin. Published reports suggest that pretestosterone androgens contribute significantly to the total androgenization of women, especially in the second and third decades of life when dehydroepiandrosterone and its sulfate are at their highest levels (2).

The skin is also one of the major sites of peripheral conversion of T to DHT by 5 α -reductase (5AR), and 5AR activity is especially high in areas of high sebaceous gland density. 5AR activity has been demonstrated in plucked pubic hairs, and DHT formation is elevated in hirsutism in women.

In order to elucidate the relationship between androgens and hair growth, investigators assessed the metabolism of [3 H]T and [3 H]androstenedione using a micromethod. In this study, it was demonstrated that both anagen and telogen hair roots originating from 10 different body sites contain two major enzymatic systems, namely 5 α -reductase and 17 β -hydroxysteroid dehydrogenase. No significant relationship was found with either T or androstenedione as a substrate between the androgen-mediated

growth of hair and the capacity to form 5 α metabolites. Thus, the formation of DHT and androstenedione (the 5 α -reduced metabolite of androstenedione) in androgen-dependent sexual beard hairs proved to be approximately the same as in certain nonsexual hairs, for example, hairs of the nuchal site of the scalp of women. However, a significantly greater formation of 5 α -androstanes was found in the frontal area of balding men than in the same area in nonbalding men or women, regardless of whether the hairs were incubated with T or with androstenedione.

Since 5 α -reduction is irreversible and oxidation at carbon 17 is favored, androstenedione has been demonstrated to be the principal intracellular androgen in human hair roots (3). In telogen hairs of all body regions, less formation of 17-ketosteroids (androstenedione and androstenedione) was found when hairs were incubated with T. Furthermore, the formation of 5 α -metabolites in telogen hairs was always considerably less than in corresponding anagen hairs. Human hair roots were also shown to contain the complex enzymatic machinery required to aromatize androstenedione to estrone (3). This is an important finding that calls into question the simple theory that DHT is the only active androgen responsible for miniaturizing hair follicles.

Thus, in considering androgen mediated disorders of the skin, it is important to consider the activity of androgen metabolism of the skin and, specifically, its effect on hair follicles. For example, the scalp has an abundance of sebaceous glands, and these may be a major source of DHT to hair follicles because of their close proximity. Because 5AR activity is high in human scalp skin and because it may be highest in balding scalp sites, this factor alone may be enough to induce AGA in genetically susceptible individuals.

2C

Isozyme specificity

Cells in genetically programmed hair follicles express the genes encoding the steroid enzyme 5AR. 5AR is a membrane-bound enzyme that catalyzes the irreversible conversion of T to DHT with NADPH (nicotinamide adenine dinucleotide phosphate, reduced form) as a cofactor (4). Two isozymes exist: the type I enzyme with an alkaline pH optimum, encoded by the SRD5A1 gene, NCBI locus ID # 6715, localized to chromosomal position 5p15, and the type II isozyme with an acidic pH optimum, encoded by the SRD5A2 gene, NCBI locus ID # 6716, localized to chromosomal position 2p23 (5). Investigators have reported immunolocalization studies that showed that the type I enzyme is expressed primarily in newborn scalp, and in skin and liver.

The type II isozyme protein is expressed primarily in genital skin, liver and the prostate.

2D

Clinical Presentation of AGA

As previously noted, alopecia is a general term for hair loss and requires further definition. Androgenetic alopecia (AGA) is the most common cause of hair loss, presenting as loss of hair over the top (vertex) of the scalp in affected men and women. AGA is associated with normal levels of estrogens and androgens in both men and women. The term “androgenetic” alopecia denotes that both a genetic predisposition and the presence of “androgens” are necessary to cause disease expression. The specific mode of inheritance has not been determined, however, it is believed by geneticists to represent a polygenic (complex) trait. (6)

2E

Androgenetic Alopecia in Men

In men, AGA, also called male pattern hair loss, is characterized by hair loss in the frontal and vertex areas of the scalp. Several patterns are commonly recognized and classified according to the Hamilton and Norwood classifications (7). These classifications are based on the degree of hair

thinning and the affected areas of the scalp (figure 9). AGA in men can begin anytime after the onset of puberty.

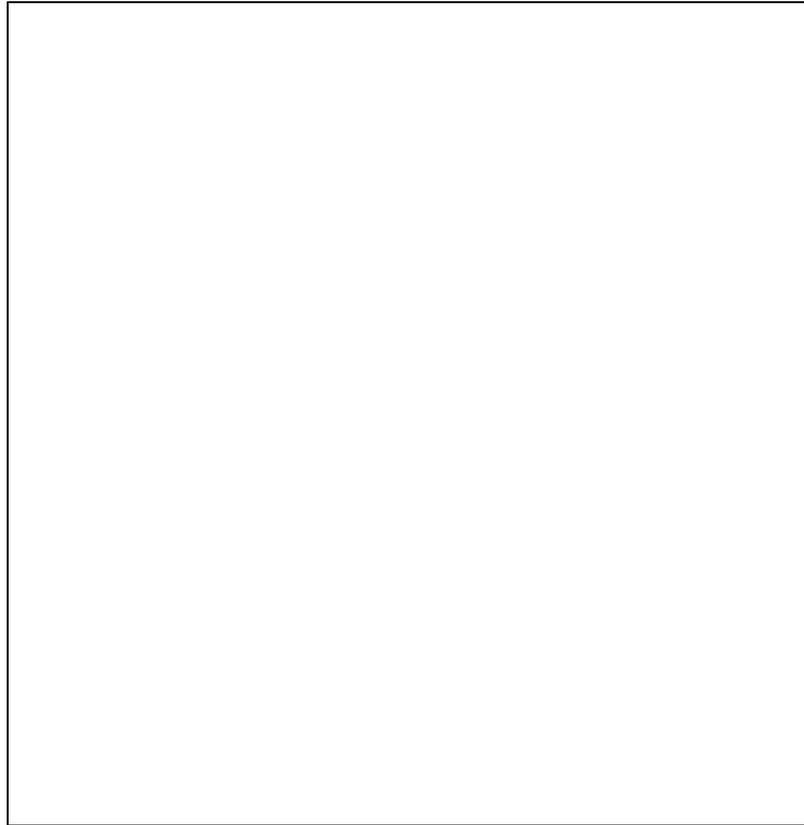


Figure 9: Norwood Scale for Men

2F

Androgenetic Alopecia in Women

In women, AGA, also called female diffuse thinning, presents with more diffuse thinning in a mosaic pattern over the vertex of the scalp. The frontal hairline is usually retained. Occasionally there is a prominent triangle of thinning behind the retained frontal fringe (8). The width of the part over the vertex is widened when compared to the back of the scalp, and onset is generally in the late 20s to 30s.

The hair loss in women is usually less dramatic than that seen in men. Originally, the degrees of thinning were divided into three categories by Ludwig (figure 10).

More recently, Savin (1994) devised a scale based on eight categories of density and part width over the vertex of the scalp. There has been no compelling evidence demonstrating that women effected with this disorder are virilized.

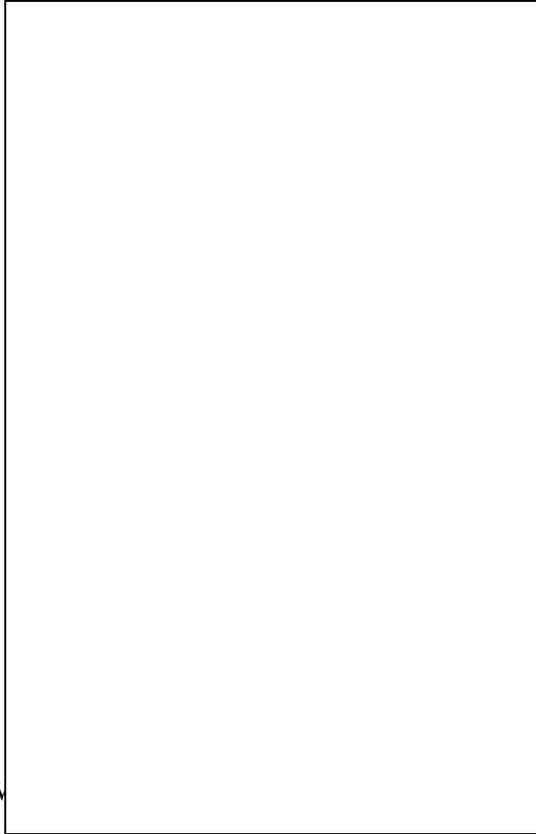


Figure 10: Ludwig Scale for W

Virilization may be defined as the process of developing masculine sex characteristics in a female. This phenomenon may include an increase in body hair, facial hair, deepening of the voice, male-pattern baldness, and clitoral enlargement. It may also result from excessive testosterone production in endocrine glands or use of anabolic steroids. Onset and exacerbation of hair loss often occurs at times of hormonal challenge, including the postpartum period, use of oral contraceptives, and the early post-menopausal period.

2G

Prevalence

Approximately 20% of Caucasian men are affected by the age of 20 with incidence increasing 10% per decade. Fifty percent of Caucasian women are affected by age 50 (8). Racial differences are noted with more Caucasians affected than Asian and African races.

2H

Psychosocial Aspects

Recent studies on the quality of life in men and women with AGA show that loss of scalp hair can have major psychologic effects. Men with AGA may feel less attractive and older than their peers leading to diminished self-esteem, stress, anxiety, depression, and social inadequacy. This is as true, if not more true, for women with AGA.

2I

Pathophysiology of Androgenetic Alopecia

Although the clinical presentation is different in men and women, the underlying cellular processes causing AGA are thought to be similar. AGA is

mediated by androgens in both men and women. Androgens are produced in men by the testes and adrenal glands. In women, androgens are produced by the ovaries and adrenal glands.

Androgens produced peripherally by endocrine-sensitive hair follicles and sebaceous glands also contribute significantly to circulating androgens in both men and women. For the most part, men and women with AGA have normal levels of circulating androgens (8).

The androgen dihydrotestosterone (DHT), a potent metabolite of the androgen testosterone (T), causes a gradual, progressive shrinkage in the length and caliber of genetically programmed hair follicles. This process is called “miniaturization”. Miniaturization results from shortening of the anagen phase and a decrease in the size of the dermal papilla and volume of matrix cells.

Consequently, each successive hair cycle results in the production of smaller, finer hairs which contribute less to the overall appearance and density of the hair (9). Increased shedding of miniaturized hairs and minor inflammation, as manifested by seborrheic dermatitis, may occur.

These biochemical events occur at the cellular level of the hair follicle. Because the dermal papilla is highly vascularized, it is continuously bathed in circulating androgens. It has been demonstrated that the dermal papilla is rich in androgen receptors and is the primary target of androgen action (10).

During AGA mediated follicle miniaturization, 5AR irreversibly converts T into the more potent DHT. DHT (or, less efficiently, T) is bound by an intracellular cytosolic receptor, the androgen receptor (AR). This complex is then translocated to the cell nucleus where it activates transcription of genes with androgen-responsive elements (ARE) in their promoters (11).

ARs in the cells of the dermal papilla bind with circulating DHT, forming DHT-AR complexes. These complexes are translocated and bind to specific target sites on the DNA to the nuclei of the dermal papilla (figure). Activated genes are transcribed which are believed to stimulate the overlying matrix cells to mediate the androgen effects of miniaturization on the hair follicle.

Aromatase, present in the outer root sheath of the hair follicle, is another enzyme that plays an important function in AGA. This enzyme converts T and DHT back into estrogens. Aromatase is approximately six times more abundant on the female frontal scalp as compared to males, and may be

responsible for the less severe expression of AGA in women (12). It may also explain retention of the anterior hairline in women.

2J

Differential Diagnosis of Clinically Relevant Alopecias

In general, the clinical appearance and history of AGA in men is straightforward and does not present a diagnostic challenge. Because the pattern is more ambiguous in women, several other types of hair loss may mimic AGA and should be kept in mind when evaluating patients.

2K

Telogen effluvium

Women are especially prone to increased shedding of telogen hairs from various physical insults, a condition called telogen effluvium. Acute and chronic illnesses, pregnancy, abrupt hormonal changes, iron and dietary protein deficiency, and many medications can all cause an increased shift of hairs into the telogen phase with a resultant increase in shedding. This

shedding is accentuated along the frontal hairline and vertex of the scalp and can easily mimic AGA. It has been shown that an episode of telogen effluvium may hasten the expression of AGA in genetically prone individuals.

2L

Alopecia areata

Alopecia areata (AA) is a putative autoimmune condition which usually presents as patchy hair loss, but occasionally presents initially as increased shedding and diffuse hair loss. The etiology of this disease, characterized by sudden hair loss, has remained obscure.

For example, it is not understood, how the characteristic inflammatory infiltrate that selectively attacks anagen hair follicles in AA is generated. Unlike cicatricial alopecia, AA is a nonscarring form of hair loss. Among the many factors under investigation in the pathogenesis of AA, the main areas of concentration have been genetic constitution as well as nonspecific immune and organ-specific autoimmune reactions. Treatment with intralesional corticosteroid injections for localized patchy AA and topical immunotherapy for extensive AA have proven successful in many patients, although all treatments are palliative and do not change the prognosis of the disease.

2M

Congenital atrichia

Congenital atrichia is a rare autosomal recessive disease of hair development, characterized by the complete loss of scalp and body hair shortly after birth. This disorder is noteworthy in that the loss of hair is often accompanied by a clinically evident presentation of cutaneous papules. Histologically, these papules denote artifactual indication of the total apoptotic destruction of the hair follicle, and are differentially diagnostic for this mutation. Evidence of linkage to chromosome 8p12 has been established, implicating the human version of the mouse hairless (*hr*) gene as a candidate ortholog.

The hairless gene appears to have a multitude of functions, and its relationship to thyroid hormone, transcriptional co-repression and apoptosis, among other cellular events, is currently under intense investigation. Hairless was the first gene identified to be implicated in hair cycle regulation, and it is anticipated that this discovery will lead to a better understanding of the genetic control of the hair cycle as the work unfolds.

More recently, Christiano et al mapped the first locus involved in autosomal recessive hypodontia (tooth malformations) to chromosome 16, and

the search for this gene is also underway. Taken together, this line of investigation should reveal a pathway(s) for the formation of epidermal appendages, which may bring investigators closer to answering long-standing mysteries in skin biology, such as the quest for elusive stem cells in the skin (13).

2N

Scarring or cicatricial alopecia

There are several types of hair loss which cause permanent destruction of the follicles. Hair loss is usually patchy with obvious signs of scalp inflammation. However, hair loss can be diffuse and the scalp may not appear clinically inflamed. Early recognition and treatment are important to prevent permanent hair loss (14).

The scalp shows loss of follicles and a biopsy is generally necessary in order to establish a definitive diagnosis. Cicatricial alopecia may be caused by lupus erythematosus, lichen planor pilaris, pseudopelade, morphea or folliculitis decalvans. Some infections and neoplasms also scar the scalp. Kenalog (triamcinalone malaete) may be indicated under some circumstances such as a diagnosis consistent with an autoimmune component (e.g. lupus

erythematosus), however, as in AA, these disorders have an uncertain prognosis at best.

20

Traction alopecia

Traction alopecia is caused by chronic traction (pulling) on the hair follicle and is observed most commonly in African-American females associated with tight braiding or cornrow hair styles. It is generally present along the hairline. Men who attach hairpieces to their existing hair can experience this type of permanent hairloss if the hairpiece is attached in the same location over a long period of time.

2P

Trichotillomania

Trichotillomania is a traction alopecia related to a compulsive disorder caused when patients pull on and pluck hairs, often creating bizarre patterns of

hairloss. In long term cases of trichotillomania, permanent hairloss can occur. The essential feature of trichotillomania is the recurrent pulling out of one's own hair that results in noticeable hair loss.

Sites of hair pulling may include any region of the body in which hair may grow (including axillary, pubic, and perirectal regions), with the most common sites being the scalp, eyebrows, and eyelashes. Hair pulling may occur in brief episodes scattered throughout the day or in less frequent but more sustained periods that can continue for hours.

Stressful circumstances frequently increase hair-pulling behavior, but increased hair pulling also occurs in states of relaxation and distraction (e.g., when reading a book or watching television). An increased sense of tension is present immediately before pulling out the hair. For some, tension does not necessarily precede the act but is associated with attempts to resist the urge. There is gratification, pleasure, or a sense of relief when pulling out the hair. Some individuals experience an itchlike sensation in the scalp that is eased by the act of pulling hair. The diagnosis is not given if the hair pulling is better accounted for by another mental disorder (e.g., in response to a delusion or a hallucination) or is due to a general medical condition (e.g., inflammation of the skin or other dermatological conditions). The disturbance must cause significant distress or impairment in social, occupational, or other important areas of functioning.

2Q

Clinical evaluation

Clinical evaluation of those experiencing hair loss should include documentation of increased hair loss by actual hair counts. An average daily loss of 50 to 100 hairs is normal. A careful medical history should be taken, including recent surgeries or illnesses, dietary habits, weight loss, medications, menstrual and pregnancy history.

Clinical examination of the patient includes evaluating hair density, pattern, length, and evidence of regrowth. The scalp should be checked for signs of scarring alopecia including inflammation, obliteration of follicular orifices, and atrophy. At a minimum, laboratory examinations, including thyroid and iron evaluation, should be obtained. Serum ferritin levels are the most helpful; desired values are 40-300 ng/ml. Women with AGA presenting with regular menses as well as normal fertility do not generally require endocrinologic evaluation.

2R

Treatments for AGA

A certain degree of scalp hair loss at some point in life is almost universal among all humans. Although this process is virtually the physiologic norm, hair has such a powerful role in a person's psychosexual self-image that anxiety about its loss will often prompt individuals to seek medical attention.

For the treating clinician, hair loss must be evaluated during the patient's relatively brief visit, without the benefit of lengthy observation. Careful attention should be given to history taking, and worried patients should be allowed to express anxiety about the expected outcome (ie, rapid hair loss leading to total baldness). A thorough history and physical examination usually helps focus on possible causes of hair loss, and the absence of clues to specific disease may differentially rule in a diagnosis of androgenetic alopecia. The treatment options for androgenetic alopecia are limited to surgical restoration, artificial prostheses (wigs and toupees), or medical treatment.

2S

Surgical Treatments

Surgical treatment of alopecia includes hair transplantation (macrografting and micrografting) and various forms of scalp reduction and rotational movement of hair-bearing scalp. These procedures are obviously better suited for pattern alopecia than for more diffuse forms. Consideration

should be given to the potential development of far more extensive alopecia than was first anticipated, resulting in esthetic problems such as obvious scars or rows of isolated grafts.

2T

Hair Restoration Surgery (HRS)

Choosing to have hair restoration surgery is a major decision for most people. HRS can often permanently change your appearance to a more youthful look. A balding person rarely conjures up the image of youth and vitality and, unfortunately, that is what most patients are striving for today. For individuals who have not lost their hair, this information will be of little value. But for those suffering from hair loss who wish their hair restored, HRS offers the potential of a renewed sense of self.

HRS currently offers the only permanent solution to AGA available. HRS will restore hair that will grow naturally. This hair will require styling and haircuts, just as in persons who do not suffer from AGA. The surgical treatment of hair loss can be broadly divided into three main areas: hair transplantation, scalp reduction and scalp flaps.

2U

Hair Transplantation

Hair transplantation is a surgical process, which takes hair from the back of the head and moves it to the area of hair insufficiency. The fringe (back and sides) of hair on a balding scalp is known as donor dominant hair which is the hair that will continue to grow throughout life. The transplantation of this hair to a bald area does not change its ability to grow due to the transplanted hair retaining its genetic identity and, concomitantly, its longevity. Donor dominance is the scientific basis for the success of hair transplantation.

Candidates for HRS are those individuals with hair loss that have sufficient donor hair from the fringe of the scalp to transplant to the balding area. In the past, many bald patients were not suitable candidates for HRS but modern techniques have advanced the art of HRS so that many more persons are candidates.

Hair transplantation surgery has improved tremendously over the past decade. The days of plugs and corn rows are gone for the most part, and the age of single hair-, micro-, and mini- grafting has arrived. Through the use of the these variable sized hair grafts along with new and improved

instrumentation, the accomplished hair transplantation surgeons can create a natural hair appearance that is appropriate for each individual patient. Single hair-grafts have the finest and softest appearance. Although they do not provide great density, they do provide the critical soft hairline that is the transition to thicker hair. Examining the hairline of a nonbalding person will show the presence of numerous single hairs in the very frontal hairline. Micrografts are small grafts containing 2-3 hairs that are placed behind the hairline to provide a gradually increasing hair density. Next, minigrafts contain 4 or more hairs are placed well behind the hairline so that the single hair and micrografts can blend naturally into the density provided by these larger grafts.

The side-effects of hair transplantation surgery are relatively minor consisting of mild pain and discomfort after the operation, swelling which may move down to the eyes, and the formation of scabs over the grafts which take approximately one week to resolve. Serious problems of bleeding, scarring, and infection are rare as the scalp is very well vascularized. Modern hair transplantation surgery is comfortable, predictable, and, in the proper hands, the results are generally pleasing to most patients.

Progressive hair loss or the desire for more density, requires serial transplant procedures. Modern techniques, however, generally allow HRS

specialists to transplant larger number of grafts, often reducing the number of procedures needed to complete a satisfactory result (15).

2V

Scalp Reduction

Scalp reduction surgery may be defined as the surgical removal of bald scalp. The concept of reducing the amount of bald scalp prior to hair transplantation surgery is logical. Since the amount of bald scalp is reduced, the number of grafts required to cover the residual bald area could be significantly reduced as well. In skilled hands, scalp reduction can be a very effective technique.

Reasonable candidates for this procedure are patients with excellent density hair on the sides and back of the scalp, and scalp laxity that can be stretched upward to cover the bald area that is to be excised . In order to prevent problems such as scarring, stretch back of the bald area, and the creation of an unnatural appearance called a slot deformity, careful planning and expert surgical skills are required to achieve appropriate results. The side effects of scalp reduction surgery are minor consisting of pain, swelling, and numbness. These typically resolve after surgery.

2W

Scalp Flaps

Scalp flap surgery entails moving entire segments of hair bearing scalp into a bald area. Typically, a dense hairline is immediately reconstructed after just one operation. The classic operation is known as the Juri flap that was first performed by Dr. Jose Juri of Argentina in the early 1970's (16). It involves taking a very long and narrow peninsula of hair bearing scalp which extends from the temple to the back of the head and rotating it approximately 90° from its original position to a new location at the hairline. This provides an instantaneous hairline reconstruction not available with other techniques. There are other variations of Dr. Juri's original procedure that achieve similar results.

Patients with frontal baldness exclusively may be good candidates for this approach since reconstruction of the hairline is the primary goal of this procedure. However, more extensively bald persons have also been known to benefit from this procedure with proper planning.

A different type of scalp flap, called a scalp lift, is very useful for treating hair loss in the crown of the scalp. This procedure involves moving the fringe

hair on the sides and on the back, upward towards the center of the bald area in a U-shaped pattern. Used in combination with hair transplantation, a patient with significant hair loss can achieve excellent hair restoration results.

The potential risks and complications associated with these techniques, are formidable however, and may include scarring, poor hair direction, loss of flap viability, greater bleeding, tissue necrosis, loss of donor, and greater discomfort. There are fewer practitioners of these techniques due primarily to the higher risk of complication.

In conclusion, surgical hair restoration, provides many potentially attractive benefits to the individual suffering from AGA. A critical element in the decision to pursue this surgery must include choosing the most qualified hair restoration expert. This should be a doctor who has performed the selected technique successfully on many patients. He/she should also be ready and willing to demonstrate his/her expertise with before and after photographs as well as patient referrals, as this field of medicine is as much an art as a science.

2X

Medical treatments

Medical therapy for androgenetic alopecia can be divided into the following categories: (a) nonspecific promoters of hair growth, (b) topical and systemic anti-androgens, (c) 5-reductase inhibitors.

2Y

Minoxidil

Minoxidil is the best known drug in the category of medical AGA treatment. Minoxidil is an oral medication used to treat refractory hypertension. It was noted to cause hypertrichosis (increased nonsexual hair growth). However, the mechanism by which it stimulates hair growth is unknown. Clinical trials have shown that a 2% solution applied topically to the scalp can stimulate hair growth in some men and women.

2Z

Pharmacology

When applied topically, minoxidil topical solution has been shown to stimulate hair growth in individuals with AGA. Although the exact mechanism of action of minoxidil in the treatment of AGA is not known, there may be more than one mechanism by which minoxidil stimulates hair growth, they include: vasodilation of the microcirculation around the hair follicles which may stimulate

hair growth; direct stimulation of the hair follicle cells to enter into a proliferative phase: resting phase (telogen) follicles being stimulated to pass into active phase (anagen) follicles; alteration of the effect of androgens on genetically predetermined hair follicles: minoxidil may affect the androgen metabolism in the scalp by inhibiting the capacity of androgens to affect the hair follicles.

Following topical application of minoxidil topical solution, minoxidil is poorly absorbed from normal intact skin, with an average of 1.4% (range 0.3 to 4.5%) of the total applied dose reaching the systemic circulation. The effects of concomitant dermal diseases or occlusion on absorption are unknown. Serum minoxidil levels resulting from topical administration are governed by the drug's percutaneous absorption rate; increases in surface area of application do not result in proportionate increases in the serum minoxidil level.

Steady state is achieved by the end of the third dosing interval (36 hours) when the drug is administered twice daily. Approximately 95% of the systemically absorbed minoxidil from topical dosing is eliminated within 4 days. The metabolic biotransformation of minoxidil absorbed following topical application has not been fully determined.

Known metabolites exert much less pharmacologic effect than minoxidil itself and all are excreted principally in the urine. Minoxidil does not bind to

plasma proteins; its renal clearance corresponds to glomerular filtration rate and it does not cross the blood brain barrier. Minoxidil and its metabolites are hemodialyzable, although this does not rapidly reverse its pharmacological effect.

Increased hair growth has not been associated with increased systemic absorption of topical minoxidil. The onset of hair growth stimulation requires twice daily applications of minoxidil topical solution for 4 or more months, and is variable among patients (17). Upon discontinuation of topically applied minoxidil, new hair growth has been anecdotally reported to stop and restoration of pretreatment appearance to occur within 3 to 4 months.

2AA

Competitive vs. noncompetitive vs. uncompetitive inhibition

Prior to discussing the anti-androgens utilized in the treatment of AGA, a short overview on the general properties of enzyme inhibition may be appropriate, as this reaction plays a critical role in the mechanism of action of a number of substances under discussion. There are three known classes of

inhibition with respect to enzyme kinetics as described in the literature (18). They are, competitive, noncompetitive, and uncompetitive inhibition, respectively.

2BB

Enzyme kinetics from a metabolic perspective

The kinetic properties of enzymes have been intensively studied for almost a century, starting soon after Buchner demonstrated that alcoholic fermentation was a chemical process, thereby disposing of the theory of vitalism that had dominated physiological thinking for much of the preceding century (19). Enzymes have long been studied both out of interest in understanding how they act as catalysts and as a way of delineating their role in the regulation of metabolism. However, regardless of whether the primary concern of the investigator is mechanistic or metabolic, kinetic experiments are designed as if the primary or sole objective were to shed light on mechanisms of action. It is well understood that most enzymes operate physiologically in complex mixtures with other enzymes and many metabolites as well as their substrates and products, yet often the first step in studying an enzyme, is to purify it and remove it from its physiological context. However desirable it may be to derive information about the mechanism of action of a given enzyme, this

practice presents profound drawbacks when one seeks to extrapolate such information onto its putative physiological role.

2CC

Kinetics at constant rate

The usual type of steady-state experiment involves measuring the rate that is produced by setting the concentrations of substrates, products, effectors, etc. at predetermined values. It is crucial to realize that this is not what happens in a living system. Virtually all substrates are products of other enzymes; virtually all products are substrates of other enzymes; their concentrations are all variables that respond to the activities of all the enzymes in this system, not just that of the enzyme towards which the experimenter's attention is directed. As Atkinson (20) pointed out over two decades ago, many enzymes operate in a regime far closer to fixed rates than to fixed concentrations, in other words most enzymes are required to turn over their substrates at the rates at which they arrive, and the concentrations of substrates and products have to adjust to whatever values are necessary to sustain these rates.

2DD

Competitive inhibition

Competitive inhibition is a term used to describe enzymatic activity in which two or more different substrates compete for the same enzyme (figure 11). One indication that competitive inhibition may be occurring is when the degradation of one substrate is repressed in the presence of another substrate. Clinically, one way in which drugs can block the action of a receptor is through binding to the receptor as would the substrate but without producing the same action. The drug competes with the endogenous ligand. This effect is therefore called competitive inhibition.

Because it literally is a competition between the drug and the normal ligand for binding to the receptor, the drug's inhibition can be overcome by adding sufficient ligand. The maximal effect of the receptor is unchanged—but, critically, the observed effect may be decreased based on the variability of a given concentration of ligand in the presence of the inhibitor.

If the inhibitor binds to the same site as the substrate or if the inhibitor directly block the binding of the substrate it is called a competitive inhibitor (i.e. both the inhibitor, I, and the substrate, S, cannot be bound to the enzyme, E,

simultaneously). Schematics of several models for competitive inhibition are shown below.



Figure 11: Competitive inhibition. Model 1 is the simplest model of competitive inhibition, where I and S occupy the same binding site. In models 2-4 binding of I blocks the binding of S because of overlap in the two binding sites. Model 5 shows a conformational change upon binding I that then excludes binding S.

2EE

Noncompetitive inhibition

If the inhibitor binds to a site different from the substrate it is called a noncompetitive inhibitor (i.e. both the inhibitor, I, and the substrate, S, can be bound to the enzyme, E, to form complexes EI and ESI simultaneously). Schematics of several models for noncompetitive inhibition are shown below (figure 12).

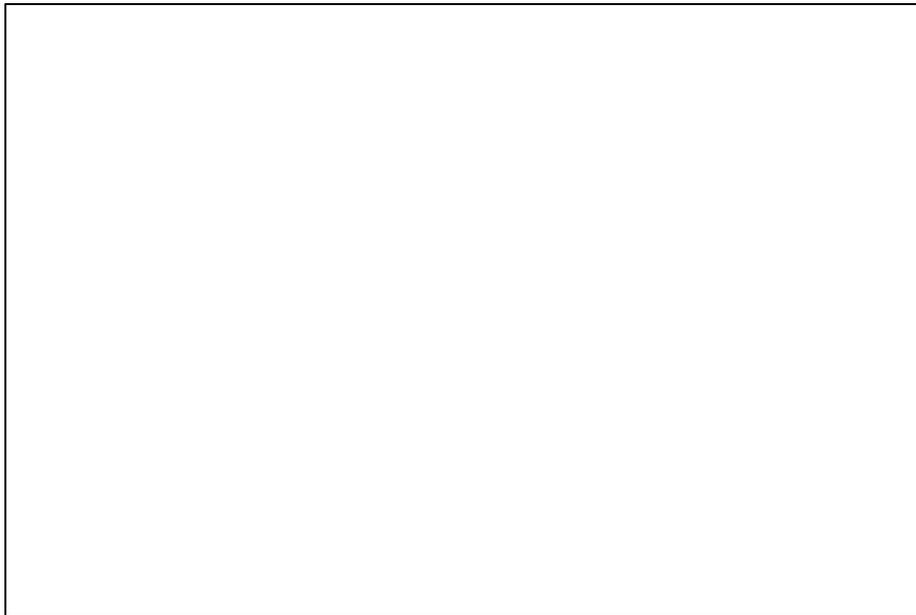


Figure 12: Noncompetitive inhibition. Both I and S can bind to the enzyme, however, upon binding I there is a conformational change to the active site (C=catalytic center) which does not allow the substrate to be converted to product.

2FF

Uncompetitive inhibition

Finally, one may consider the kinetics of uncompetitive inhibition, or more specifically the uncompetitive component in mixed (competitive and noncompetitive) inhibition. The distinction is important, as pure uncompetitive inhibition is rare enough in physiologic systems to be dismissed as having little metabolic importance, whereas mixed inhibition with an uncompetitive component is by no means rare and its metabolic consequences can be profound. If the inhibitor binds only to the ES complex and not to the enzyme alone it is called uncompetitive inhibitor. A schematic for a model of uncompetitive inhibition is shown below.



Figure 13: Uncompetitive inhibition. The inhibitor, I, cannot bind to the enzyme directly. The inhibitor, I, can bind only after the substrate, S, binds and a conformational change occurs at the I binding site. When both S and I are bound (the ESI complex) there is a conformational change to the active site (C) which does not allow the conversion of S to product.

2GG

Anti-Androgens

Cyproterone acetate

Cyproterone acetate (Androcur) is a progestin with potent antiandrogenic action. It competes with 5-alpha-dihydrotestosterone for binding to its receptor. It causes loss of libido, suppression of gonadotropin secretion, and gynecomastia in males. In females, it has been utilized in the therapy of hirsutism and virilization. In both sexes, it has been utilized in the treatment of acne and baldness. In males, it has been used to treat precocious puberty (males < 9 yr), to inhibit libido in sexual deviants, and in the therapy of prostate carcinoma.

2HH

Flutamide

Flutamide (Eulexin) is a potent competitive inhibitor of the binding of dihydrotestosterone to the androgen receptor. It is used in combination with GnRH agonists in the therapy of metastatic prostate cancer. This combination produces a potent blockade--termed maximum androgen blockade (MAB)--of the biological actions of circulating androgens, since GnRH agonists reduce the circulating levels of androgens by suppressing the release of LH from the anterior pituitary and flutamide inhibits DHT binding to its receptor (21).

2II

Bicalutamide

Bicalutamide (Casodex) is a newer anti-androgen related to flutamide with similar mechanism of action. The drug has fewer side effects than flutamide; in particular, it produces minimal diarrhea, night blindness, and alcohol intolerance, which are side effects of flutamide. The most common side effect is hot flashes. It is used in combination with GnRH agonists to produce MAB.

2JJ

Finasteride

Finasteride 1 mg (Propecia® , Merck) was approved by the US FDA December, 1997 for the treatment of male pattern hair loss (androgenetic alopecia, AGA) in men only. Safety and efficacy were demonstrated in men between 18 and 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area.

Efficacy in bi-temporal recession has not been established (22). Propecia® is not approved for use in women or children. Finasteride has been approved for this same indication in Australia, Argentina, Mexico and New Zealand and approval is being sought in more than 20 other countries.

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Efficacy of Finasteride

Efficacy has been demonstrated in three double-blind, randomized, placebo-controlled studies in 1,879 men between 18-41 years of age with mild

to moderate androgenetic alopecia. Two of the studies enrolled men with mild to moderate vertex loss, the third investigated mild to moderate loss in the anterior mid-scalp area with or without vertex balding. Primary end-points were hair count (assessed by photographic enlargements of a representative area of active hair loss) and patient self-assessment; secondary end-points were investigator assessment and ratings of global photography.

Clinical improvement was seen as early as three months in the patients treated with finasteride and led to a net increase in scalp hair count and hair regrowth. These effects have been maintained through two years in these studies and for up to three years in open-extension studies. Improvements have been seen across all racial groups.

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Side effects

Adverse effects are minimal. Results in men treated with finasteride for benign prostatic hyperplasia, where five times the dose has been studied in men for up to 6 years, have revealed no long-term problems or new effects over the longer period. In patients with AGA treated with 1 mg of finasteride daily for 12 months in controlled studies, 1.4% of finasteride treated patients versus 1.6% of placebo treated patients discontinued therapy because of

adverse drug experiences, and 1.2% of finasteride treated patients versus 0.9% of placebo treated patients discontinued because of drug-related sexual experiences.

Sexually related adverse effects reported as possibly, probably or definitely drug or placebo related were decreased libido, erectile dysfunction and ejaculation disorder. Analysis showed that 4% of 945 men treated with finasteride and 2% of 934 men treated with placebo reported one or more of these adverse effects ($p=0.04$). These problems resolved in all men who stopped therapy with finasteride because of these effects, and in 58% of those who continued therapy.

In older men with benign prostatic hyperplasia, PSA levels are decreased by 50% with finasteride therapy and consideration should be given to doubling the test level returned by men undergoing this test while taking finasteride (23).

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Contraindications

Finasteride is not indicated for use in women.

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Mechanism of action

It is thought that finasteride interrupts a key step in the pathogenesis of AGA, in those patients who are genetically predisposed. Finasteride is a preferential, competitive inhibitor of the intracellular, Type II, 5 alpha-reductase isoenzyme which converts testosterone into dihydrotestosterone (DHT), a more potent androgen.

In humans, the Type II 5 alpha-reductase isoenzyme is primarily found in the root sheath of the hair follicle, prostate, seminal vesicles, epididymis, fetal genital skin and in fibroblasts from normal adult genital skin, as well as liver, and is responsible for two-thirds of circulating DHT. In target organs, finasteride treatment is thought to result in selective androgen deprivation affecting DHT without lowering circulating levels of testosterone, thus preserving the desired androgen mediated effects on muscle strength, bone density and sexual function.

In AGA, the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with non balding scalp, and finasteride treatment produces inhibition of the isoenzyme, resulting in a rapid reduction in scalp and serum DHT concentrations.

Finasteride has no affinity for the androgen receptor, no androgenic, anti-androgenic, estrogenic, anti-estrogen or progestational effects, no effect on cortisol, thyroid-stimulating or thyroxine levels, and no effect on plasma lipid profile or bone mineral density. Circulating levels of testosterone and estradiol are increased by 15% but remain within the physiologic range.

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Summary

Androgenetic alopecia occurs frequently in both men and women. It is mediated by the action of DHT, a potent metabolite of testosterone, in endocrine-sensitive hair follicles. It can be the cause of significant social and emotional distress. By understanding the clinical presentation, differential diagnosis, pathophysiology, as well as current armamentarium of medical and surgical interventions for this condition, one may begin to appreciate the potential for the development of novel therapies.

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