



## *The Mystery of Alopecia*

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Alopecia is a condition of hair loss resulting from changes to the hair follicle or hair cycle or a combination of both.<sup>1</sup> This loss of hair may occur on the scalp, eyebrows, extremities or on the entire body. There are many conditions that may cause alopecia including emotional stress, genetics, hormones, aging and local or systemic disease. Treatment of alopecia may consist of removal of the causative agent, drug therapy, cosmetic or surgical intervention, psychological counseling, patient education or a combination of these.

### **Etiology and Pathophysiology**

Gestation is the beginning of hair follicle formation. The total number of hair follicles that the body will have are formed during the fourth and fifth months of the fetal growth period.<sup>2,3</sup> The last stage of the first hair growth cycle begins during the 26th and 28th weeks of gestation.<sup>2</sup> During infancy the hair follicles on the scalp increase in size, forming the largest hair follicles in the body.<sup>4</sup>

Hair growth is a continuous cycle that occurs in three phases with each hair follicle acting independently of one another.<sup>2,4</sup> The *anagen* phase is the growth stage, lasting two to five years, and the length of this phase determines how long the hair grows. This phase is followed by the *catagen* phase, which is the degenerative stage and lasts only a few days. The last phase is the *telogen* or resting phase lasting about three months. During this phase the hair does not grow at all and eventually falls out.<sup>2,5</sup> At any given point in time, most of the hair follicles can be found in the anagen phase with only a small percentage in the telogen phase and just a few in the catagen phase. The palms of the hands, soles of the feet and the glabrous skin of the genitalia are the only areas on the body that do not have hair follicles.<sup>2</sup> The normal scalp has approximately 100,000 hair follicles (1,300 follicles per inch) and normal daily hair loss is between 50 and 100 hairs.<sup>2,3,5</sup>

Scalp hairs may be divided into three groups. *Vellus* hairs are nonpigmented hairs resembling "peach fuzz" and are less than 1 cm in length. *Indeterminate* hairs have

characteristics of both vellus and terminal hairs. They are approximately 1 cm in length, and are typically identified for research purposes.<sup>2,3</sup> Pigmented *terminal* hairs cover the majority of the scalp and are longer than 1 cm. The shape of the terminal hair, whether straight, curly or in between, is determined by the shape of the follicle.<sup>3</sup>

Hair growth is influenced by such factors as genetics, thyroid hormones, corticosteroids and sex hormones.<sup>2</sup> The mechanism of action of hormones in the regulation of hair growth is not fully understood.<sup>2,3</sup> Pubic, axillary and facial (beard) hair are up-regulated by androgens, while the hair of the scalp that is genetically predisposed to androgenetic (male pattern baldness) alopecia is down-regulated by androgens.<sup>2,5</sup>

The loss of hair production may be temporary or permanent.<sup>1,4</sup> There are two primary classifications of hair loss: nonscarring (noncicatricial) and scarring (cicatricial). The forms of nonscarring alopecia include androgenetic alopecia, alopecia areata, hereditary syndromes, systemic disease or process, and traumatic alopecia.<sup>3,5</sup> Scarring alopecias may be caused by developmental defects and hereditary disorders, infections, neoplasms, physical and chemical agents and dermatoses.<sup>3,5</sup>

## **Non-Scarring Alopecia**

**Androgenetic Alopecia (Male Pattern Baldness):** This is by far the most frequent cause of hair loss in men and is frequently referred to as "male pattern baldness."<sup>3</sup> *Androgenetic alopecia* usually begins during the twenties<sup>4</sup> when many hair follicles switch from producing pigmented terminal hairs to vellus hairs and may eventually produce no hairs at all.<sup>3</sup> Both men and women are affected by androgenetic alopecia. Men are affected in the parietal and temporal areas and older women are affected over the crown of the scalp. For androgenetic alopecia to occur, there must be two factors present: 1) a genetic predisposition to this condition, and 2) the presence of dihydrotestosterone. In these areas of the scalp, there appears to be excessive conversion of testosterone to dihydrotestosterone and a miniaturization of the terminal hair follicles.<sup>3,5,6</sup> The majority of the hair on the body is not dependent on testosterone for growth and, therefore, does not present with androgenetic alopecia.<sup>6</sup> In the genetically predisposed individual, the follicles of the scalp have high levels of 5-alpha-reductase, the enzyme responsible for converting testosterone to dihydrotestosterone. The follicles of the scalp are the only follicles affected by this down-regulation.<sup>6</sup> It has also been suggested that receptors on the hair follicles may have a deficiency of a factor needed to aggregate androgen receptor subunits in the hair follicle.<sup>2</sup> In women, somewhat paradoxically, androgenetic alopecia may also be associated with hirsutism (abnormal hair growth caused by hypersecretion of androgens), perimenopausal depletion of estrogens, polycystic ovarian disease and underlying endocrine abnormalities.<sup>5</sup>

**Systemic Disease and Processes:** Telogen effluvium (effluvium is Latin for "a flowing out") is hair loss precipitated by a physiologic event such as childbirth, menstrually related changes, fever, infection, crash diets, surgery, discontinuation of birth control pills after long and high-dose use of corticosteroids, among other drugs (see **TABLE 1**).

In this condition, the follicles which are actively growing (anagen phase) rapidly enter the resting stage (telogen phase). The follicles then begin the active growing phase again and the telogen hairs fall out as they are displaced by the anagen hairs.<sup>5</sup> Usually there is less than a 50% loss of hair, and regrowth is seen in about two to four months. Treatment consists of identifying and eliminating the cause of hair loss, if possible.<sup>1,5</sup>

**Table 1.**

Drugs Causing Telogen Effluvium
<ul style="list-style-type: none"> <li>• Warfarin, heparin</li> <li>• Propranolol, metoprolol</li> <li>• Imipramine, desipramine, fluoxetine</li> <li>• Propylthiouracil, methimazole</li> <li>• Levodopa, naproxen</li> </ul>

Anagen effluvium is caused by drugs, radiation therapy and antineoplastic agents that affect cell mitosis (see **TABLE 2**). About 90% of the hair follicles on the scalp are in the anagen phase at any given time and the follicular damage precipitated by these drugs causes the anagen hairs to fall out, producing almost complete baldness. The only telogen hairs remaining on the scalp are those not affected by the therapy.<sup>5</sup> This type of alopecia can cause emotional and psychological trauma.<sup>7</sup> Some attempt has been made to decrease this type of hair loss during chemotherapy by decreasing the blood flow to the scalp. In disease involving nonhematologic malignancies or scalp metastases, ice caps (which cause hypothermia) and pneumatic scalp tourniquets have been used in hopes of decreasing the flow of medications to the scalp hair follicles, but their use is no longer approved by the FDA because of a lack of evidence of safety and efficacy.<sup>7,8</sup>

**Table 2.**

Drugs Causing Anagen Effluvium
<ul style="list-style-type: none"> <li>• Cimetidine, allopurinol, colchicine</li> <li>• Haloperidol, trimethadione</li> <li>• Carbamazepine, methotrexate</li> <li>• Bromocriptine, cyclophosphamide</li> <li>• Doxorubicin, dactinomycin, bleomycin</li> <li>• Daunorubicin, vindesine, mechlorethamine</li> <li>• Ifosfamide, fluorouracil, paclitaxel</li> <li>• Thiotepa, etoposide, hydroxyurea, vincristine</li> </ul>

Endocrine disease such as hypopituitarism, hyperpituitarism and hyperthyroidism cause diffuse and sometimes patchy hair loss from the scalp. Lateral hair loss on portions of the eyebrows may be seen in hypothyroidism. In endocrine disease, if the atrophy of the

follicles is not severe, the condition is usually reversible with medications designed to return the patient to the normal hormone state.

Nutritional and metabolic conditions such as protein, calorie, iron, zinc and fatty acid deficiencies seen in patients with prolonged inadequate parenteral hyperalimentation may produce abnormal hair loss.<sup>1</sup>

Syphilis produces a "moth eaten" appearance on the scalp with loss of hair in other areas of the body. It is not usually scarring unless it has progressed to tertiary syphilis.

AIDS causes hair to become more diffuse and to decrease in density. Longer, lighter, soft and silky hair and occasional hair color changes have been noted in various races of patients with this condition.<sup>1</sup>

**Hereditary Syndromes:** Congenital defects in which alopecia is the only abnormality or alopecia along with other birth defects is sometimes seen.<sup>1</sup>

**Traumatic Alopecia:** *Trichotillomania* is a condition in which the patient pulls his or her own hair out. Hair loss is usually seen on the scalp, but the loss of eyebrows or eyelashes is not uncommon. Usually appearing in children, the condition may go undiagnosed for a long time. This problem may be seen in the mentally retarded, and although sometimes seen in healthy children, it may be a sign of underlying psychological problems when present in adults. Treatment for this condition consists of psychiatric counseling, patient education and drug therapy for obsessive-compulsive disorder, such as clomipramine (Anafranil) or fluvoxamine (Luvox).<sup>1,5</sup>

Traction alopecia is caused by tightly braided hair, corn rows, ponytails, hair weaving and hair tightly wound around curlers. A pattern of alopecia in these areas may develop.

Hot comb alopecia is caused by applying oil to the hair and straightening it using a hot comb. The shafts of the hair are damaged and the scalp becomes inflamed with permanent scarring if treatment is not discontinued.<sup>1,5</sup>

**Alopecia Areata:** *Alopecia areata* and its variants may occur at any age, and both sexes are equally affected. This disease manifests itself with a sudden onset. Though its cause is unclear, it is thought to be caused by emotional stress or autoimmune disease and may be seen with thyroid conditions, vitiligo, pernicious anemia, Down's syndrome and Addison's disease.<sup>1,5</sup> (See photo on page 49.)

This condition may occur as patchy hair loss (*alopecia areata*) on various areas of the body, total hair loss on the scalp (*alopecia totalis*) or total hair loss on the entire body (*alopecia universalis*).<sup>1,5</sup> Other physical findings may include pitting and ridging of the fingernails; cataracts may also be seen with *alopecia totalis*. Hair regrowth often occurs within six months with nonprogressive disease. When severe forms are present, there may be chronic and progressive hair loss.<sup>1,9</sup>

*Alopecia areata* is often a chronic condition and difficult to treat. Injections to the scalp of triamcinolone acetonide (Kenalog) or hexacetonide (Aristospan) have been shown to help in some cases. This therapy is less effective in cases of *alopecia totalis* and those lasting longer than two years. The pain of the injections is often a limiting factor in these treatments.<sup>1,9</sup> Studies of other treatments for *alopecia areata* have included the use of topical 5% minoxidil<sup>10</sup> and oral prednisone (tapered dose over six weeks starting with 40 mg and ending with 5 mg) combined with scalp application of 2% topical minoxidil. Corticosteroids have been shown to induce hair growth but after drug therapy is discontinued, hair loss often resumes. Studies have shown that minoxidil may limit the hair loss after steroids have been discontinued.<sup>1,11</sup> Other drug therapies include the combined use of topical anthralin (Dritho-Scalp, Drithrocreme) and topical minoxidil. Local and total body photochemotherapy (PUVA) have shown some effectiveness for this condition.<sup>1,5</sup>

## Scarring Alopecia

**Developmental Defects and Hereditary Disorders:** Varying degrees of alopecia are seen in conditions such as Conradi's syndrome (a rare disorder that presents with bone abnormalities and skin lesions), Albright's syndrome (a childhood condition of the long bones that presents with fibrous dysplasia and skin osteomas) and many other disorders.

**Infections:** Infections caused by acid fast bacilli (e.g., leprosy), spirochetes (e.g., syphilis), gram positive and gram negative bacteria, fungi (e.g., *tinea capitis*), protozoa and herpes virus may cause tenderness, pruritus and eventual follicular damage and hair loss on the body.<sup>3,4</sup> Treatment consists of elimination of the causative organism. The use of griseofulvin (Fulvicin, etc.), ketoconazole (Nizoral) or itraconazole (Sporanox) is effective in the treatment of fungal infections.

**Neoplasms:** Basal cell carcinoma, squamous cell carcinoma, lymphoma and metastatic cancers may produce this condition.

**Burns:** Burns, high-dose radiation, chemical agents such as acids and alkalis,<sup>3</sup> and chemical agents used in hair care products such as dyes, bleach and permanents can cause scarring.

**Dermatoses:** Systemic and discoid lupus erythematosus lesions can develop into telangiectatic scars with hair loss. Treatment using oral hydroxychloroquine (Plaquenil), or chloroquine (Aralen)<sup>5</sup> has shown some success. Treatments with topical and intralesional injections of corticosteroids (Kenalog) have been beneficial to some; permanent scarring is present in most cases.<sup>1,5</sup> Systemic scleroderma, lichen planus, sarcoidal granulomas and many other syndromes that cause the loss of hair follicles are resistant to any drug therapy.<sup>1,5</sup>

## Psychological Effects

Approximately 50% of people with alopecia suffer psychological effects from this condition.<sup>7,12</sup> Some individuals perceive hair loss as signifying a loss of masculinity or femininity and self-identity. Significant loss of hair as in *alopecia areata* and cancer chemotherapy may evoke feelings of nakedness and vulnerability as well as a loss of self-esteem.<sup>9</sup> These feelings of loss may evoke a grief reaction<sup>9</sup> of successive denial, anger, depression and, finally, acceptance.

## Treatment Options

For thousands of years men have been trying to treat hair loss. Hippocrates made a mixture of pigeon droppings, opium, horseradish, beet root and spices as a treatment for his own hair loss. Men have used devices to try "to suck hairs to the surface of the scalp" and electrical stimulators to increase hair growth. Scalps have been shampooed with "Packer's Tar Soap," cow urine and goose dung.<sup>4</sup>

In today's society, men have been lured to try modern "lotions and potions" advertised in magazines, newspapers and via radio and television commercials. These ineffective treatments are just a few examples of the many desperate attempts men have made in trying to deal with hair loss.

In an effort to halt the promotion of ineffective and unsafe treatments for hair loss, the FDA has banned the use of products such as lanolin, wheat germ, B vitamins, amino acids, nucleic acids, jojoba oil, estradiol and benzoic acid for hair loss and hair loss prevention, stating that they are ineffective and/or unsafe.<sup>3</sup>

Alopecia is a difficult condition to treat. There are numerous cosmetic options available to the public. Wigs, toupees, hair styling, hair weaving and tinted sprays are often used to hide the scalp when hair loss is present. More modern approaches include surgical procedures such as hair transplants, hair grafting, scalp reduction and hair implants.<sup>3,13</sup> Hair transplants require a surgical procedure that involves removing a small area of hair called a punch graft from the back of the head. This punch graft is then transplanted to the balding area of the scalp. Hair grafting is done by relocating a section of the scalp that is covered with hair to a section that has hair loss. Scalp reduction requires the removal of a loose area of the scalp in the balding area of the head. The remaining scalp is sewn together, reducing the size of the balding area.<sup>4,13</sup> Implants are sutures that are sewn into the scalp to act as anchors for the attachment of a hairpiece.<sup>4</sup>

**Androgenetic Alopecia:** Androgenetic alopecia has been treated with drug therapy. Spironolactone (Aldactone) has been used to treat this condition but its use has been limited due to its effects on blood pressure and the adrenal system.<sup>14</sup> In Europe, cyproterone (an anti-androgen used to decrease testosterone levels) is used alone or combined with ethinyl estradiol in women with this condition.<sup>15</sup> Other treatments may include minoxidil co-administered with tretinoin cream, which increases absorption of the

minoxidil.<sup>16</sup> Final trials are presently being conducted by Merck in anticipated release of the first oral, once-daily dose, medication for androgenetic alopecia. The proposed trade name of this agent is Propecia, which is finasteride. This medication, a 5-alpha-reductase enzyme inhibitor that results in decreases in dihydrotestosterone in the plasma, has been shown to increase hair growth by 48%, compared with a 7% increase from the use of a placebo. It is also anticipated that a 5% solution of minoxidil will soon be approved by the FDA.

### **Topical Minoxidil Therapy**

Topical minoxidil 2% solution (Rogaine) is the only FDA-approved treatment for alopecia and was approved for over-the-counter distribution in 1996. It has also recently become available as a generic product. Minoxidil is a direct-acting peripheral vasodilator that was originally studied and marketed for the treatment of hypertension. It is available as an oral tablet form (Loniten) for this condition. During clinical trials of oral minoxidil, the study groups reported increased hair growth on the scalp and this resulted in studies of its use in alopecia.

**Mechanism of Action:** The proposed mechanism of action of minoxidil appears to be related to a sulfonated active metabolite. In animal studies using minoxidil, DNA synthesis appears to increase in the follicle.<sup>10</sup> Follicles appear to grow longer, hair epithelial cells proliferate in the follicle and there appears to be a decrease in the loss of terminal hairs. These effects were lost when the drug was discontinued. The effects of minoxidil on the blood flow in the scalp and on the androgenetic stimulation of hair loss are not clear.<sup>10</sup>

**Efficacy:** Minoxidil may prove beneficial in preventing extensive balding in those who begin treatment as soon as hair loss begins.<sup>10</sup> Some patients do not respond to minoxidil (Rogaine) therapy. Patience and strict compliance on the part of the patient are required to obtain successful results, and expectations must be realistic. This product is not a cure but it does stimulate new hair growth and appears to stabilize the loss of hair.

Men with Hamilton categories I, II and III, and younger-aged men who have had hair loss from this condition for less than 10 years, appear to respond best to topical therapy. Women with Ludwig grade I and II hair loss also show increased hair growth.<sup>10,13</sup> (The newer Savin Scale is now used to assist physicians in gauging progressive hair loss patterns, as well as changes in hair loss density.)

In 1983, the manufacturer of topical minoxidil sponsored a double-blind, placebo-controlled study. An evaluation was made of approximately 2,300 males aged 18–49 years old and in good health. Hair growth was evaluated in a one-inch circle on the vertex of the scalp. A group of 714 patients used 2% minoxidil, 721 patients used 3% minoxidil, and 717 patients were in the placebo group. Each group was evaluated after a four-month period of twice-daily applications of 1 mL of minoxidil or placebo solution. Subjective evaluations were made by the patient and the investigator, and manual hair

counts and periodic photographs were compared to the baseline evaluations. Investigators reported that the 2% minoxidil group showed an average increase of 71 non-vellus hairs in the one-inch circle, while the placebo group had an average increase of 39 non-vellus hairs and the 3% minoxidil group had an average increase of 76 non-vellus hairs. Evaluations were then made as to the increase in density of the hair growth. Of the 714 patients in the 2% minoxidil group, approximately five (0.7%) patients showed dense regrowth (hairs in thinning area growing as closely together as hairs on the rest of the scalp); 57 (8%) patients showed moderate regrowth (hairs growing more closely together, but not as close together as hairs on the rest of the scalp); and minimal regrowth (hairs in thinning area do not grow as closely together as hairs on the rest of the scalp) was seen in 179 (25%) patients. The placebo group had an increased dense hair growth in one (0.1%) patient, moderate regrowth in 27 (4%) patients, and minimal regrowth in 114 (16%) patients. The last eight months of the study were uncontrolled. At the end of the 12-month study, the 2% minoxidil group had an average increase from a baseline of 121 hairs in the one-inch circle to 304 hairs in the one-inch circle. After this 12-month period, patients were given minoxidil for continued use but followup was sporadic and uncontrolled.<sup>10</sup>

A study of 256 women, aged 17–45 years and in good health, with Ludwig grade I and II diffuse frontoparietal hair loss were treated with a 2% minoxidil solution, 1 mL applied twice daily for 32 weeks.<sup>10</sup> Hair growth was measured in enlarged photographs used to assess number of hairs, fixed location of hair loss to be measured, and subjective evaluation. At the end of the study, there was an increase in 23 (16%) non-vellus hairs in the minoxidil group and an increase of nine non-vellus (6%) hairs in the placebo group in the fixed location of hair loss. Although hair increase was minimal, there appeared to be an increase in the diameter of the hair shaft and an increase in the "body" of the women's hair and a stabilization of hair loss.<sup>10</sup>

As noted, hair growth appears to occur in both groups, but does minoxidil increase hair growth enough to warrant its use? Effectiveness of minoxidil may lie "in the eyes of the beholder." However, an important question for the pharmacist may be: "Is it safe for our patients, especially those with hypertension?"

**Side Effects:** Although absorbed to some extent, in a placebo-controlled study, topical minoxidil did not affect the cardiovascular system in adults who were free of cardiac disease, hypertension, and kidney disease. The safe use of minoxidil in patients with coronary artery disease has not been established. The most common side effects are due to dermatologic sensitivities producing itching and dryness. Reports of hair growing on other parts of the body not treated with topical minoxidil are few, and it is unclear if this is from systemic absorption or unintentional application of the drug in these areas.<sup>10</sup>

## Conclusion

Hair loss must be seen as a condition affecting the physical and psychological aspects of a person's life, whether young or old, male or female. Fortunately for some, hair loss



can be stopped by the use of medications that restore proper balance to the body's hormonal system and for others, minoxidil offers some hope of hair regrowth. Drug therapy for others may be painful and produce temporary hair growth (e.g., corticosteroid injection). Those who have permanent hair loss must simply accept the fact that there is no effective drug therapy available for them.

Understanding on the part of the pharmacist of the underlying causes and effects of hair loss is essential for compassionate care to be given to these individuals. The counseling role of the pharmacist lies in: 1) educating the patients in the use of drugs such as minoxidil and realistic expectations from minoxidil therapy; 2) informing patients of the side effects of the medications that cause hair loss; 3) preparing those who face cancer chemotherapy for the possible loss of their hair; and 4) possible referral of the patient to a dermatologist for a proper diagnosis of the underlying cause of hair loss.



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