Review Articles

Mechanisms of Disease

FRANKLIN H. EPSTEIN, M.D., *Editor*

THE BIOLOGY OF HAIR FOLLICLES

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HAIR has many useful biologic functions, including protection from the elements and dispersion of sweat-gland products (e.g., pheromones). It also has psychosocial importance in our society, and patients with hair loss (alopecia) (Table 1) or excessive hair growth often suffer tremendously. Not surprisingly, the demand for drugs that alter hair growth and appearance has led to a multibillion-dollar industry, yet few drugs that are effective for these purposes are available. However, recent progress in our understanding of the biology and pathology of hair follicles should lead to more effective therapies for disorders of hair growth.

STRUCTURE AND FUNCTION OF HAIR FOLLICLES

Hair follicles vary considerably in size and shape, depending on their location, but they all have the same basic structure (Fig. 1 and 2). Rapidly proliferating matrix cells in the hair bulb (Fig. 1A) produce the hair shaft, whose bulk — the cortex — is composed of hair-specific intermediate filaments and associated proteins. Pigment in the hair shaft is produced by melanocytes interspersed among the matrix cells. As the matrix cells differentiate and move upward, they are compressed and funneled into their final shape by the rigid inner-root sheath, whose dimensions and curvature largely determine the shape of the hair. The dermal papilla, which is composed of specialized fibroblasts located at the base of the follicle (Fig. 1 and 2), is thought to control the number of matrix cells and thus the size of hair.

TABLE 1. GLOSSARY OF TERMS FOR HAIR AND DISORDERS OF HAIR GROWTH.

TERM	MEANING
Alopecia	Abnormal hair loss
Androgenetic alopecia	Baldness caused by miniaturization of genetically predisposed follicles in the male pattern (frontal recession and thinning at the vertex) or the female pattern (loss of hair primarily over the crown, with sparing of frontal hair)
Alopecia areata	Hair loss in patches, thought to be caused by an autoimmune response to hair follicles in the anagen stage; extensive forms of the disorder are called alopecia areata totalis (hair loss over the entire scalp) and alopecia areata universalis (hair loss over the entire body)
Permanent alopecia	Caused by destruction of hair follicles as a result of inflammation, trauma, fibrosis, or unknown causes; examples include lichen planopilaris and discoid lupus erythematosus
Anagen	Growth stage of the hair-follicle cycle
Anagen effluvium	Abrupt shedding of hair caused by interruption of active hair-follicle growth (e.g., in patients undergoing chemotherapy)
Bulb	Lowermost portion of the hair follicle, containing rapidly proliferating matrix cells that produce the hair
Bulge	Portion of the outer-root sheath of the hair follicle, located at the region of the insertion of the arrector pili muscle; thought to contain epithelial stem cells responsible for regenerating follicles in the anagen stage
Catagen	Stage of the hair cycle characterized by regression and involution of the follicle
Club hair	Fully keratinized, dead hair — the final product of a follicle in the telogen stage; 50 to 150 club hairs are shed daily from a normal scalp
Hirsutism	Excessive hair growth in androgen-dependent areas in women
Hypertrichosis	Excessive hair growth (usually diffuse) beyond that considered normal according to age, race, sex, and skin region
Lanugo hair	Fine hair on the body of the fetus, usually shed in utero or within weeks after birth
Miniaturization	Primary pathological process in androgenetic alopecia, resulting in conversion of large (terminal) hairs into small (vellus) hairs
Telogen	Resting stage of the hair cycle; club hair is the final product and is eventually shed
Telogen effluvium	Excessive shedding of hair caused by an increased proportion of follicles entering the telogen stage; common causes include drugs and fever
Terminal hair	Large, usually pigmented hairs on scalp and body
Vellus hair	Very short, nonpigmented hairs (e.g., those found diffusely over nonbeard area of face and bald scalp as a result of miniaturization of terminal hairs)

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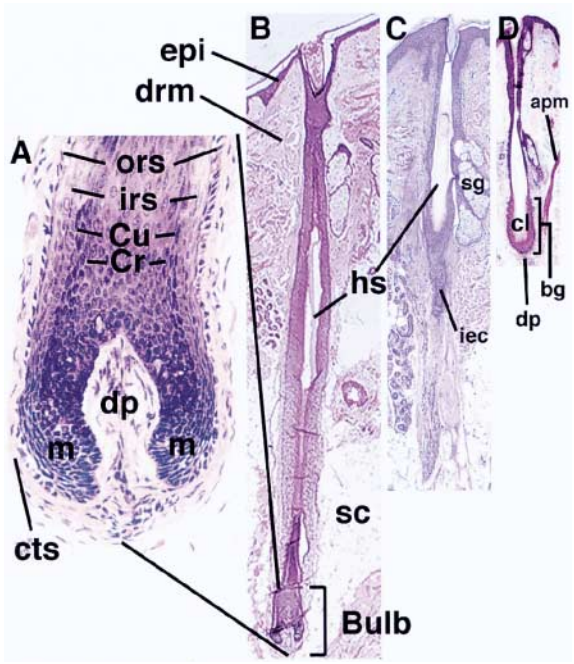

Figure 1. Structure of Hair Follicles during the Anagen, Catagen, and Telogen Stages of Cycling (Hematoxylin and Eosin). Panel A (a high-magnification view of the bracketed portion of Panel B) shows a hair bulb during the anagen (growth) stage (×100), Panel B shows a scalp-hair follicle during the anagen stage (×25), Panel C shows a scalp-hair follicle during the catagen (involutional) stage (×40), and Panel D shows a scalp-hair follicle during the telogen (resting) stage (×25). In these panels, apm denotes arrector pili muscle, bg bulge, cl club hair, Cr cortex, cts connective-tissue sheath, Cu cuticle, dp dermal papilla, drm dermis, epi epidermis, hs hair shaft, iec involuting epithelial column, irs inner-root sheath, m matrix cells, ors outer-root sheath, sc subcutaneous fat, and sg sebaceous gland.

Normal development and cycling of hair follicles depend on the interaction of the follicular epithelium with the adjacent mesenchymal dermal papilla (Fig. 2).[1,2] The dermal papilla induces hair-follicle formation from the overlying epithelium during fetal development,[2] and at the onset of each new follicular cycle in adults the dermal papilla interacts with secondary germ cells in the hair-follicle bulge to regenerate the lower follicle.[3,4] The bulge consists of a cluster of biochemically distinct cells in the outer-root sheath (Fig. 1D), which are located near the insertion of the arrector pili muscle. These cells have the characteristic properties of epithelial stem cells: they are the slowest-cycling and longest-lived epithelial cells within the hair follicle.[3,4]

Epithelial stem cells in the bulge portion of the outer-root sheath may also serve as a reservoir for epidermal and sebaceous-gland cells.[3,5] Cells in the outer-root sheath normally express an array of keratins, adhesion molecules, cytokines, and growth factor receptors that are distinct from those expressed by epidermal cells.[1,4,6] They migrate out of the follicle and regenerate the epidermis after injury or loss. In hyperproliferative states such as psoriasis and during wound healing, epidermal cells produce keratins 6, 16, and 17, which are normally found only in the outer-root sheath of hair follicles[7] — further evidence of the close relation between the epidermis and the hair follicle.

The outer-root sheath of the hair follicle also contains melanocytes,[8] Langerhans' cells (dendritic antigen-presenting cells),[9] and Merkel cells (specialized neurosecretory cells).[10] All these cells repopulate the epidermis after injury, and they also play a part in certain functions of the hair follicle. For example, the hair follicle acts as a sensory organ and immunologic sentinel for the skin. Hairs detect mechanical stimuli above the surface of the skin, and the slightest bend in a hair activates neuroreceptors in the follicle, relaying important sensory information to the nervous system. The Langerhans' cells at the opening of the follicle detect surface pathogens and activate the immune system. The hair follicle has a complex immunologic profile, with immunologically "privileged" matrix cells (lacking major-histocompatibility-complex class I expression) at its base, and a complement of perifollicular macrophages, mast cells, and other immunocytes that act as the effector arm of the immune system.[11,12]

MORPHOGENESIS OF HAIR FOLLICLES

In utero, the epithelium and underlying mesenchyma interact to form hair follicles.[1,2,13,14] During this time, the precise distribution of hair follicles over the surface of the body is established and the future phenotype of each hair (e.g., long scalp hair and short eyebrow hair) is determined. Many of the molecular signals that control these events were first discovered in drosophila (fruit flies). For example, the mammalian counterparts of the *hedgehog, patched, wnt, dishevelled, armadillo, engrailed, notch,* and other genes — all necessary for the normal development of drosophila — are critical for the normal formation of hair follicles as well.[1,15,16]

Roughly 5 million hair follicles cover the human body at birth. No additional follicles are formed after birth, although the size of the follicles and hairs can change with time, primarily under the influence of androgens (see below). The precise spacing and distribution of the follicles are established by genes that are expressed very early in the morphogenesis of the follicles.[1,15,17-19] For example, lymphoid-enhancer factor 1, bone morphogenetic protein 4, and the type II receptor for transforming growth factor β are all expressed before there is any morphologic evidence of hair-follicle formation.[17-19] Slightly later in development, cells containing the protein products of homeobox genes, including *Msx* genes, appear in

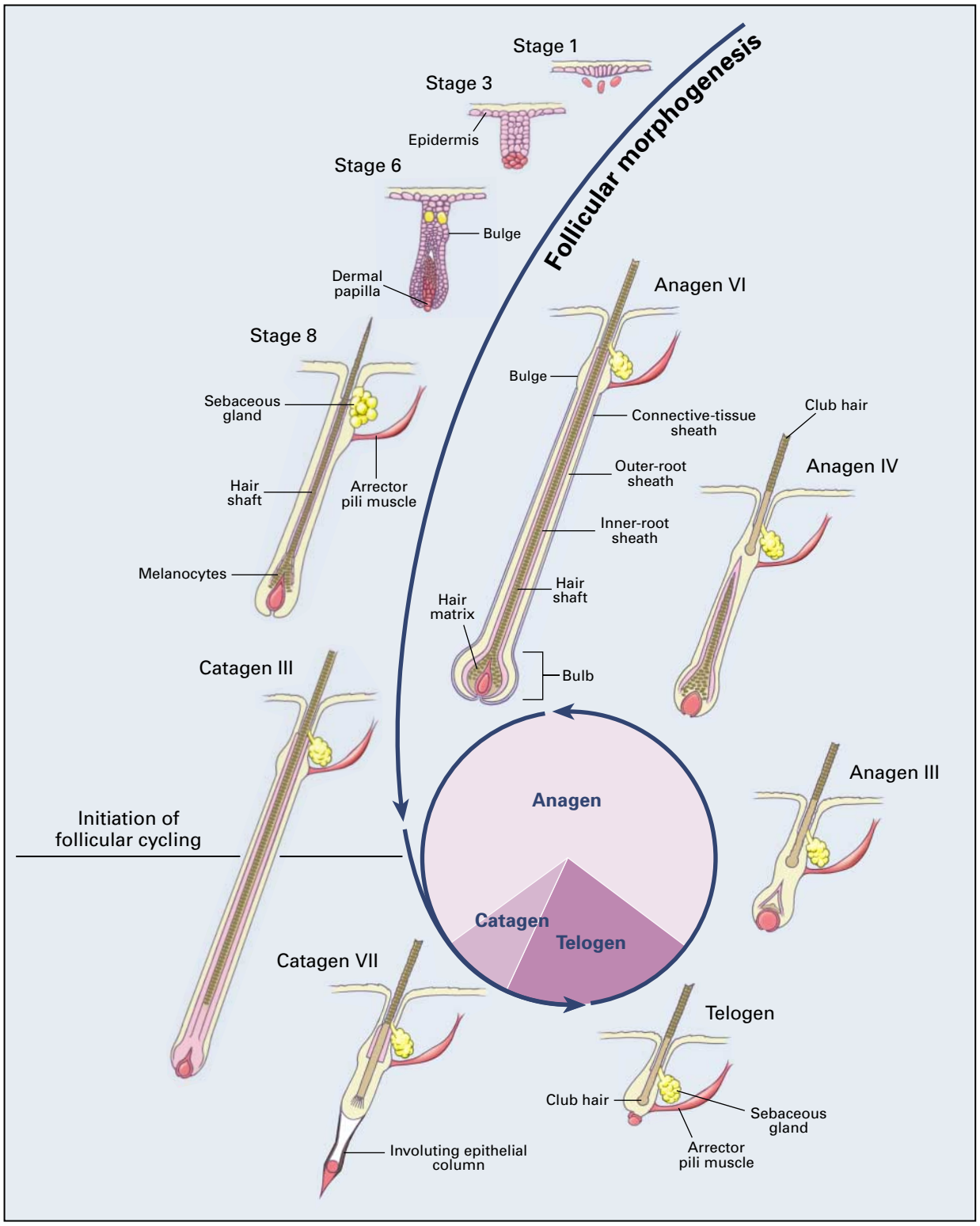

Figure 2. Development and Cycling of Hair Follicles.

Selected stages of the morphogenesis of hair follicles and the three stages of follicular cycling (anagen, catagen, and telogen) are shown. The roman numerals indicate morphologic substages of anagen and catagen. The pie chart shows the proportion of time the hair follicle spends in each stage.

the precise locations where the hair follicles will form. The protein products of several of these genes are also present at different times during the hair cycle in adults, suggesting that they are important not only for the normal distribution and development of follicles but also for their continued growth.[1,18,20]

Once the distribution of the follicles has been established, subsequent molecular events in the developing follicle determine the future phenotype of each hair.[1,2,13] Morphogens such as sonic hedgehog and wnt, together with intracellular signaling molecules such as β-catenin and lymphoid-enhancer factor 1, influence the maturation of the new hair follicles.[15,16,21]

HAIR-FOLLICLE CYCLING

Each hair follicle perpetually goes through three stages: growth (anagen), involution (catagen), and rest (telogen) (Table 1 and Fig. 1 and 2). Determining the molecular signals that orchestrate the follicle's transit between these stages is one of the key challenges of hair research. Although most of our current knowledge of the substances that modulate hair growth in humans is derived from clinical observations (Table 2), studies in mice have identified some of the molecular events associated with hair-follicle cycling.[6,15,16,21,25,26] Numerous growth factors and growth factor receptors are critical for normal hair-follicle development and cycling, but no single growth factor appears to exert ultimate control over these processes.

Anagen Stage

The onset of the anagen stage recapitulates hair-follicle development, since the formation of the new lower hair follicle begins with the proliferation of secondary germ cells in the bulge (Fig. 1A and 2).[3,4] Whether the same proteins and signaling pathways are responsible for both folliculogenesis in utero and the onset of anagen in adults is not known. However, interactions between the dermal papilla and the overlying follicular epithelium are critical for both processes.[1,2]

Two secreted molecules that have important roles in hair-follicle development and cycling are insulin-like growth factor 1 and fibroblast growth factor 7. Both are produced by the dermal papilla, and their receptors are found predominantly in the overlying matrix cells.[6] Mice that lack insulin-like growth factor 1 or its receptor have poorly developed hair follicles. Insulin-like growth factor 1 maintains and increases follicle growth in vitro.[6,26] Mice that lack fibroblast growth factor 7 have relatively normal hair follicles,[28] but disruption of the receptor for fibroblast growth factor 7, which is also the receptor for fibroblast growth factor 2, causes markedly reduced and aberrant hair-follicle formation.[29]

Hair follicles in different areas of the body produce hairs of different lengths, with the length proportional to the duration of the anagen cycle. For example, scalp hair follicles stay in the anagen stage for two to eight years and produce long hairs, whereas eyebrow hair follicles do so for only two to three months and produce short hairs. The cessation of the anagen stage is controlled by fibroblast growth factor 5, which is first expressed in the follicle just before the end of this stage.[30] Mice that lack fibroblast growth factor 5 have an extended anagen stage, resulting in the "angora" phenotype, with hair that is 50 percent longer than normal.[31] Even in these mice, the follicle still eventually enters the catagen stage, suggesting that other signaling pathways are also important for the induction of this stage. Indeed, the system of epidermal growth factor receptors also controls this transition, because in mice without epidermal growth factor receptors or with nonfunctional receptors, the anagen stage is prolonged,[32,33] and exogenous epidermal growth factor terminates the anagen stage in sheep and delays its initiation in mice.[6,25]

TABLE 2. MODULATORS OF HAIR-FOLLICLE CYCLING IN HUMANS.*

MODULATOR	ACTION
Endogenous	
Androgens	Promote miniaturization of follicles and shorten duration of the anagen stage in androgen-sensitive areas of scalp; enlarge follicles in androgen-dependent areas (e.g., male beard) during adolescence
Estrogens	Prolong the anagen stage; postpartum reduction in estrogen secretion causes telogen effluvium
Growth hormone	Acts synergistically with androgen during virilization in adolescence
Prolactin	Can induce hirsutism
Thyroxine	Low levels cause telogen effluvium; high levels may have a similar effect
Exogenous	
Anabolic steroids	Same actions as those of androgens; accelerate androgenetic alopecia and aggravate hirsutism
β-Adrenergic antagonists	Can cause telogen effluvium
Cyclosporine	Causes hypertrichosis
Estrogens	Prolong duration of the anagen stage, counteracting telogen effluvium and androgenic alopecia
Finasteride	Blocks 5α-reductase type II, inhibits miniaturization, and prolongs the anagen stage in androgen-dependent scalp follicles; converts vellus follicles to terminal follicles
Minoxidil	Induces and prolongs the anagen stage and converts vellus follicles to terminal follicles
Oral contraceptives	Cessation may cause telogen effluvium
Phenytoin	Causes hypertrichosis
Retinoids	Can cause premature onset of the catagen stage or premature loss of club hair, manifested as telogen effluvium

*Information is from Orfanos and Hertel,[22] Headington,[23] Olsen,[24] Paus,[25] Stenn et al.,[26] and Dawber.[27]

Catagen Stage

During the catagen stage, hair follicles go through a highly controlled process of involution (Fig. 1C and 2) that largely reflects a burst of programmed cell death (apoptosis) in the majority of follicular keratinocytes.[34] Follicular melanogenesis also ceases during this stage,[35] and some follicular melanocytes undergo apoptosis as well. Toward the end of the catagen stage, the dermal papilla condenses and moves upward, coming to rest underneath the hair-follicle bulge (Fig. 1 and 2). If the dermal papilla fails to reach the bulge during the catagen stage, the follicle stops cycling and the hair is lost, as observed in both humans and mice with mutations of the *hairless* gene.[36,37] This gene encodes for a transcription factor whose disruption prevents the dermal papilla from ascending and interacting with the stem cells of the bulge, resulting in permanent alopecia.[3,36,37] During the catagen stage in mice, a few hair follicles are also destroyed by an inflammatory-cell infiltrate, in an apparently physiologic process of "programmed organ deletion."[38] Aberrant programmed organ deletion may account for certain permanent forms of alopecia.[39]

Telogen Stage

During the telogen stage, the hair shaft matures into a club hair, which is eventually shed from the follicle, usually during combing or washing. It is unclear whether shedding is an active, regulated process[1] or a passive event that occurs at the onset of the anagen stage, as the new hair grows in. Most people lose 50 to 150 scalp hairs per day. The telogen stage typically lasts for two to three months before the scalp follicles reenter the anagen stage and the cycle is repeated.

The percentage of follicles in the telogen stage varies substantially according to the region of the body (e.g., 5 to 15 percent of scalp follicles are in the telogen stage at any one time, as compared with 40 to 50 percent of follicles on the trunk).[27] An increase in the percentage of scalp follicles in the telogen stage leads to excessive shedding. Therefore, drugs that maintained or reduced the percentage of follicles in this stage would be valuable in treating hair loss.[25]

HORMONAL AND NEURAL FACTORS CONTROLLING HAIR GROWTH

Estrogens, thyroid hormones, glucocorticoids, retinoids, prolactin, and growth hormone all modulate hair growth (Table 2). The hormones with the most dramatic effects are androgens. Testosterone and its active metabolite, dihydrotestosterone, act through androgen receptors in the dermal papilla.[40,41] These hormones increase the size of hair follicles in androgen-dependent areas such as the beard area during adolescence, yet later in life they can cause miniaturization of follicles in the scalp (resulting in androgenetic alopecia).

Hair follicles in balding skin differ from those in nonbalding skin with respect to the metabolism of androgen,[27,42] the numbers of androgen receptors in the dermal papilla,[43] and the secretory responses of the cells in the dermal papilla.[44] Some dermal papillae secrete mitogens after androgenic stimulation, thus increasing hair growth, whereas others synthesize inhibitory factors, thus reducing hair growth.[45] These paradoxical effects of androgens on hair growth may be explained by genetically determined differences in the end-organ response of individual hair follicles.

Skin cells contain both isoenzymes of 5α-reductase (types I and II), the enzyme that catalyzes the conversion of testosterone to the more potent dihydrotestosterone.[40,41] The type I enzyme is found predominantly in sebaceous glands, and the type II enzyme is found in hair follicles (and the prostate gland). Androgenetic alopecia does not develop in men with a congenital absence of 5α-reductase type II, and finasteride, which inhibits 5α-reductase type II, slows or reverses the progression of androgenetic alopecia.[40,46]

The hair follicles are the most richly innervated parts of the skin, and constant remodeling of this innervation occurs throughout the normal hair-follicle cycle[47] and in alopecia.[48] The bulge region of the hair follicle is especially rich in nerve endings[47] and Merkel cells,[10] the neurosecretory cells that produce nerve growth factor or other neuropeptides that may control the proliferation of follicles. Several neurotrophins that inhibit hair growth and their receptors are found in hair follicles during the catagen stage.[49] Other peptides, such as substance P and corticotropin, which can be produced in the skin, and neuropeptide-depleting agents, such as capsaicin, induce the onset of the anagen stage in mice.[12,25]

PATHOBIOLOGY OF DISORDERS OF HAIR GROWTH

Except for rare congenital hair defects, caused by mutations in keratins or other structural proteins, and "scarring" alopecias, hair loss and unwanted hair growth reflect aberrations of hair-follicle cycling. Thus, in principle, they are reversible phenomena.[25] For example, the transient shedding of hair — telogen effluvium — that is associated with drugs, fever, endocrine abnormalities, parturition, anemia, and malnutrition occurs when an increased number of hair follicles prematurely enter the telogen stage and then shed their hair shafts. Transient shedding typically begins two to four months after the inciting event and lasts for several months.[23,27] Regrowth routinely follows, barring any metabolic or nutritional deficiency.

Androgenetic alopecia is due to the progressive shortening of successive anagen cycles and is commonly manifested as telogen effluvium. Along with

the shortening of the anagen stage, genetically predisposed follicles are gradually miniaturized in the presence of androgens, and large, pigmented hairs (terminal hairs) are replaced by barely visible, depigmented hairs (vellus hairs) (Table 1).[40] Nonetheless, hair follicles are still present and cycling, even in bald scalps; therefore, androgenetic alopecia is often classified as reversible.[24,27] However, simply removing androgens does not usually result in the conversion of miniaturized follicles to terminal ones; thus, current treatments for advanced androgenetic alopecia, including minoxidil and finasteride, are usually ineffective. Since the volume of the dermal papilla determines the diameter of the hair shaft and may determine the duration of the anagen stage,[27,50] abnormalities of the dermal papilla may underlie androgenetic alopecia.

In contrast to androgenetic alopecia, hirsutism and hypertrichosis result from an extended anagen stage with an abnormal enlargement of hair follicles. Small vellus hairs are transformed into large, terminal hairs. Depilatory creams and waxes, the usual treatments, alleviate the problem only temporarily, because irritation or plucking rapidly induces the anagen stage and hair-follicle growth.[25,27] Electrolysis and selective photothermolysis with the use of lasers destroy the hair shaft, outer root sheath, bulge, and dermal papilla of the hair follicles.[51] The extent of the destruction determines whether the follicle regenerates.

Antineoplastic drugs disrupt the rapidly proliferating bulb matrix cells. As a result, hair production ceases, and the hair shaft becomes narrower, with subsequent breakage and loss of the hair. Because the hairs that are lost are those in the anagen stage, this phenomenon is called anagen effluvium.[34] The stem cells of the hair follicles are spared,[52] presumably because of their slow cycling,[4] and they subsequently generate a new hair bulb. Radiation therapy can also result in reversible anagen effluvium.[27] However, high doses of radiation (50 to 60 Gy) typically cause permanent alopecia,[27] probably because of the destruction of the epithelial stem cells or the dermal papilla.[39]

Some types of inflammatory alopecias (such as those caused by lichen planopilaris and discoid lupus erythematosus) are scarring and permanent, whereas others (such as alopecia areata) are nonscarring and reversible.[24,27,39] In scarring alopecias, the inflammation usually involves the superficial portion of the follicle, including the bulge area, suggesting that the stem cells necessary for the regeneration of the follicle are irreversibly damaged. In contrast, the acute follicular inflammation in alopecia areata attacks the hair bulb in the subcutaneous fat.[24,27] This inflammation terminates the anagen stage, forcing the follicles into the catagen stage. However, because the bulge area is spared, a new hair bulb and hair shaft grow at the start of the anagen stage, once the inflammation has subsided or has been blunted with glucocorticoids.

In graft-versus-host disease[27,53] and androgenetic alopecia,[54] inflammation surrounds the bulge area of the outer-root sheath. Over time, the inflammation may irreparably damage the follicle stem cells, accounting for the decrease in hair-follicle density that often occurs in androgenetic alopecia. (Rare cases of scarring alopecia have been noted in women with severe androgenetic alopecia.[27])

THERAPEUTIC CHALLENGES

Two drugs have been approved by the Food and Drug Administration for the treatment of hair loss due to androgenetic alopecia: topical minoxidil solution and oral finasteride. Minoxidil prolongs the anagen stage, causes follicles at rest to grow, and enlarges the follicles (although the drug's exact mechanism of action at the cellular level is not known). Thus, treatment with minoxidil lengthens and enlarges the small vellus hairs and decreases shedding. Unfortunately, these effects are variable and occur in only a minority of patients, making it difficult to predict the efficacy of treatment on an individual basis.

Finasteride blocks 5α-reductase type II and decreases both serum and cutaneous dihydrotestosterone concentrations; it thus inhibits androgen-dependent miniaturization of hair follicles.[40,46] In well-designed clinical trials involving men between the ages of 18 and 41 years, finasteride prevented hair loss or increased hair growth in the majority of the men.[46] However, at least 17 percent of the men continued to lose hair while taking finasteride,[46] suggesting that pathways of androgen metabolism other than that involving 5α-reductase type II probably also contribute to miniaturization.[41] Finasteride is also beneficial in women with hirsutism, but the drug should be used very cautiously in women because of its potential feminizing effects on male fetuses.

Additional therapies for hair loss will almost certainly become available in the future (e.g., topically effective androgen-receptor antagonists). A better understanding of the pathophysiology of alopecias should lead to more successful treatments involving the use of drugs that specifically alter hair-follicle cycling or that protect hair follicles from immune attack.[25] The development of drugs that shield rapidly proliferating bulb cells from chemotherapeutic damage or that protect stem cells from irreversible damage by autoimmune inflammatory-cell infiltrates or ionizing radiation would also be valuable. Once the genes that confer a predisposition to alopecia have been identified, gene therapy may be a useful alternative approach. Given the accessibility of the follicle and the availability of liposome preparations that target the follicle, the topical introduction of genes seems feasible.[55]

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