Pharmacologic interventions in aging hair

Ralph M Trüeb

Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland

Abstract: The appearance of hair plays an important role in people's overall physical appearance and self-perception. With today's increasing life-expectations, the desire to look youthful plays a bigger role than ever. The hair care industry has become aware of this and is delivering active products directed towards meeting this consumer demand. The discovery of pharmacological targets and the development of safe and effective drugs also indicate strategies of the drug industry for maintenance of healthy and beautiful hair. Hair aging comprises weathering of the hair shaft, decrease of melanocyte function, and decrease in hair production. The scalp is subject to intrinsic and extrinsic aging. Intrinsic factors are related to individual genetic and epigenetic mechanisms with interindividual variation: prototypes are familial premature graying, and androgenetic alopecia. Currently available pharmacologic treatment modalities with proven efficacy for treatment of androgenetic alopecia are topical minoxidil and oral finasteride. Extrinsic factors include ultraviolet radiation and air pollution. Experimental evidence supports the hypothesis that oxidative stress also plays a role in hair aging. Topical anti-aging compounds include photoprotectors and antioxidants. In the absence of another way to reverse hair graying, hair colorants remain the mainstay of recovering lost hair color. Topical liposome targeting for melanins, genes, and proteins selectively to hair follicles are currently under investigation.

Keywords: hair weathering, graying, androgenetic alopecia, senescent alopecia, hair anti-aging

"Aged? But he does not appear aged,
just look, his hair has remained young!"
– Marcel Proust, *Remembrance of Things Past*

In today's world, physical appearance and the notion of looking young and energetic play a greater role than ever. Hair length, color, and style are important for people's physical appearance and self-perception. The condition and style of hair determine how we discern the people we encounter, and how we are perceived by those we come upon. Hair is not only intended to invoke male recognition of feminine appeal and desirability, but it has even become a predicate upon which social success and career opportunities are based. Our preoccupation with hair is further heightened as our increasing life-expectancy fuels our desire to preserve youthfulness.

The study of hair aging focuses on two main streams of interest: on one hand, the aesthetic problem of aging hair and its management, in other words everything that happens outside the skin; on the other hand, the biological problem of aging hair, in terms of microscopic, biochemical (hormonal, enzymatic), and molecular changes, in other words, the "secret life" of the hair follicle in the depth of the skin. Scientists interested in the biology of hair growth and pigmentation have exposed the hair follicle as a highly accessible and unique model that offers unequaled opportunities to the gerontologist for the study of age-related effects.

Correspondence: Ralph M Trüeb
Department of Dermatology, University Hospital of Zurich, Gloriastr. 31, 8091 Zurich, Switzerland
Tel +41 44 255 30 79
Fax +41 44 255 44 31
Email ralph.trueeb@usz.ch

Finally, the discovery of pharmacological targets and the development of safe and effective drugs for the treatment of alopecia indicate strategies of the drug industry for maintenance of healthy and beautiful hair in the young and old.

It is the aim of this paper to review the manifestations of aging hair and the basis for pharmacologic interventions in aging hair.

Aging of hair

Hair aging comprises weathering of the hair shaft, and aging of the hair follicle. The former involves progressive degeneration of the hair fiber from the root to the tip, while the latter manifests as decrease of melanocyte function or graying, and decrease in hair production in androgenetic and senescent alopecia. The scalp is subject to intrinsic or physiologic aging, and extrinsic or premature aging due to external factors. Intrinsic factors are related to individual genetic and epigenetic mechanisms with interindividual variation. Prototypes are familial premature graying, and androgenetic alopecia (AGA). Extrinsic factors include ultraviolet radiation, air pollution, smoking, nutrition, and lifestyle. Experimental evidence supports the hypothesis that oxidative stress plays a major role in premature skin and hair aging.

Hair weathering

Weathering represents the wear and tear that mainly affects the free end of the growing hair fibre. Once the hair shaft leaves the skin and grows longer, it undergoes some degree of degeneration depending on the extent of environmental and cosmetic damage. Since scalp hair has the longest hair growing phase, it is subject to more damage than hairs at other body sites. In normal hair, the damage is most prominent only near the tip of scalp hair, which often appears lusterless and paler than more proximal growth, with varying degrees of split ends (trichoptilosis). The hair fibre with its normal surface structure of overlapping cuticular cells is potentially susceptible to friction damage from excessive combing and brushing, particularly when wet. Associated procedures may cause additional damage, in particular from excessive heat "blown" or from curling irons applied to the hair. Chemical treatment of hair, ie, bleaching, coloring, perming, and straightening, is a major cause of exaggerated hair weathering, since the cuticle becomes raised and softened in the course of these procedures, and becoming more vulnerable to mechanical abrasion. Loss of cuticle leads to longitudinal fissures between exposed cortical cells, ultimately resulting in hair fractures (trichorrhexis nodosa) at these sites (Dawber 1996).

Graying

Hair graying (canities) is a natural age-associated feature. The hair graying trait correlates closely with chronological aging and occurs to varying degrees in all individuals. While the normal incidence of hair graying is 34 ± 9.6 years in Caucasians and 43.9 ± 10.3 years in Africans, it has been described that, by 50 years of age, 50% of people have 50% gray hair. This graying incidence appears irrespective of sex and hair color. In men, graying usually begins at the temples and in the sideburns. Women will usually start around the perimeter of the hairline. Gradually, the gray works its way back through the top, sides, and back of the hair. The rate at which an individual turns gray depends on genetics. It is not uncommon to observe kinships with marked early graying throughout. Hair is said to gray prematurely if it occurs before the age of 20 in Caucasians and before 30 in Africans. While premature canities more commonly appear without underlying pathology, presumably inherited in an autosomal dominant manner, it has also been associated with a similar cluster of autoimmune disorders as occurring in vitiligo (eg, pernicious anemia, autoimmune thyroid disease) and several rare syndromes with premature aging (eg, Werner's syndrome).

Although graying is understood as a loss of pigment in the shaft, its cellular and molecular origins are incompletely understood (overview in: Tobin and Paus 2001). The color of hair mainly relies on the presence or absence of melanin pigment. Skin and hair melanins are formed in cytoplasmic organelles called melanosomes, produced by the melanocytes, and are the product of a complex biochemical pathway (melanogenesis) with tyrosinase being the rate-limiting enzyme. It has been shown that gray hair has undergone a marked reduction in melanogenically-active melanocytes in the hair follicle (Commo et al 2004). The net effect of this reduction is that fewer melanosomes are incorporated into cortical keratinocytes of the hair shaft. In addition, there appears also to be a defect of melanosome transfer, as keratinocytes may not contain melanin despite their proximity to melanocytes with remaining melanosomes. This defect is further corroborated by the observation of melanin debris in and sometimes around the graying hair bulb. This anomaly is due to either defective melanosomal transfer to the cortical keratinocytes or melanin

incontinence due to melanocyte degeneration. Eventually, no melanogenic melanocytes remain in the hair bulb. This decrease of melanin synthesis is associated with a decrease in tyrosinase activity, as indicated by a reduced 3,4-dihydroxyphenylalanine (DOPA) reaction. Ultrastructural studies have shown that remaining melanocytes not only contain fewer melanosomes, but the residual melanosomes may be packaged within autophagolysosomes. This removal of melanosomes into autophagolyosomes suggests that they are defective, possibly with reactive melanin metabolites. This interpretation is supported by the observation that melanocytes in graying hair bulbs are frequently highly vacuolated, a common cellular response to increased oxidative stress. The extraordinary melanogenic activity of pigmented bulbar melanocytes, continuing for up to 10 years in some hair follicles, is likely to generate large amounts of reactive oxygen species via the hydroxylation of tyrosine and the oxidation of DOPA to melanin. If not adequately removed by an efficient antioxidant system, an accumulation of these reactive oxidative species will generate significant oxidative stress. It is possible that the antioxidant system becomes impaired with age leading to damage to the melanocyte itself from its own melanogenesis-related oxidative stress. Since mutations occur at a higher rate in tissue exposed to high levels of oxidative stress, and these accumulate with age, the induction of replicative senescence with apoptosis is likely to be an important protective mechanism against cell transformation.

Anecdotal evidence indicates that gray hair is coarser and less manageable than pigmented hair. Moreover, gray hair often fails to hold a temporary or permanent set, and is more resistant to incorporating artificial color, both of which suggest significant changes to the underlying substructure of the hair fiber. Given the very close interaction of melanin transferring-melanocytes with hair shaft-forming precortical keratinocytes, it is conceivable that other functions of these cell types are affected by this activity. One possibility is that melanin transfer decreases keratinocyte turnover and increases keratinocyte terminal differentiation. Indeed, white beard hair has been shown to grow up to four times the rate of adjacent pigmented hair (Nagl 1995). In this way, aging hair follicles may reprogram their matrix keratinocytes to increase production of medullary, rather than cortical, keratinocytes. In fact the medulla is often enlarged and collapsed, forming a central cavity in gray and white hairs (van Neste 2004; van Neste and Tobin 2004). An evolutionary basis for this increased medullation in senile white hair may reflect the enhanced insulation provided by these hairs which would confer an important benefit for temperature regulation. In this way, it may compensate for the loss of the sunlight-absorbing and thus heat-trapping properties of melanized dark hair (Paus and Tobin 2001). Besides being thicker and displaying a more developed medulla, white hair was also found to have increased sensitivity to weathering, increased cysteic acid residues and decreased cystine, and increased fibre reactivity to reducing and oxidizing agents. Whether these differences, seemingly related to the lack of melanin and to the enlarged medulla, are also directly responsible for the coarseness of white hair and their relative resistance to hair setting and coloring, is not clearly established.

Hair loss

Androgenetic alopecia, also referred to as male-pattern hair loss or common baldness in men, and as female-pattern hair loss (FPHL) in women, affects at least 50% of men by the age of 50 years, and up to 70% of all males in later life (Norwood 1975). Estimates of its prevalence in women have varied widely, though recent studies claim that 16% of women aged under 50 years are affected, increasing to a proportion of 30%–40% of women aged 70 years and over (Norwood 2001). The hair loss is heritable, androgen-dependent, and occurs in a defined pattern. It is assumed that the genetically predisposed hair follicles are the target for androgen-stimulated hair follicle miniaturization, leading to gradual replacement of large, pigmented hairs (terminal hairs) by barely visible, depigmented hairs (vellus hairs) in affected areas (overview in: Trüeb 2002). The result is a progressive decline in visible scalp hair density. While male pattern AGA is characterized by its typical bitemporal recession of hair and balding vertex, FPHL is set apart by its diffuse thinning of the crown and intact frontal hairline.

While the genetic involvement is pronounced, but poorly understood, major advances have been achieved in understanding principal elements of the androgen metabolism involved in the pathogenesis of AGA (overview in: Kaufman 1996): Androgen-dependent processes are predominantly due to the binding of dihydrotestosterone (DHT) to the androgen receptor (AR). Dihydrotestosterone-dependent cell functions depend on the availability of weak androgens, their conversion to more potent androgens via the action of 5α-reductase, low enzymatic activity of androgen inactivating enzymes, and functionally active AR present in high numbers. The predisposed scalp exhibits high

levels of DHT, and increased expression of the AR. Conversion of testosterone to DHT within the dermal papilla plays a central role, while androgen-regulated factors deriving from dermal papilla cells are believed to influence growth of other components of the hair follicle. Since many extrinsic hair growth-modulatory factors, such as androgens (Randall et al 1992), apparently operate at least in part via the dermal papilla, research is currently also focused on identifying androgen-regulated factors deriving from dermal papilla cells. Of the several factors that have been suggested to play a role in hair growth, so far only insulin-like growth factor (IGF-1) has been reported as altered in vitro by androgens (Itami et al 1995), and stem cell factor (SCF) has been found to be produced in higher amounts by androgen-dependent beard cells than in control non-balding scalp cells, presumably also in response to androgens (Hibberts et al 1996). Since SCF is the ligand for the cell surface receptor c-kit on melanocytes, this may also play a role for hair pigmentation.

The limited success rate of treatment of AGA with hair growth promoters or modulators of androgen metabolism means that further pathogenic pathways may be taken into account. The implication of microscopic follicular inflammation in the pathogenesis of AGA has recently emerged from several independent studies (Jaworsky et al 1992; Whiting 1993; Mahé et al 2000). An early study referred to an inflammatory infiltrate of activated T cells and macrophages in the upper third of the hair follicles, associated with an enlargement of the follicular dermal sheath composed of collagen bundles (perifollicular fibrosis), in regions of actively progressing alopecia (Jaworsky et al 1992). Horizontal section studies of scalp biopsies indicated that the perifollicular fibrosis is generally mild, consisting of loose, concentric layers of collagen that must be distinguished from cicatricial alopecia (Whiting 1993). The term "microinflammation" has been proposed because the process involves a slow, subtle, and indolent course, in contrast to the inflammatory and destructive process in the classical inflammatory scarring alopecias (Mahé et al 2000). An important question is how the inflammatory reaction pattern is generated around the individual hair follicle. Inflammation is regarded a multistep process that may start from a primary event. The observation of a perifollicular infiltrate in the upper follicle near the infundibulum suggests that the primary causal event for the triggering of inflammation might occur near the infundibulum (Mahé et al 2000). On the basis of this localization and the microbial colonization of the follicular infundibulum with *Propionibacterium* sp., *Staphylococcus* sp., *Malassezia* sp., or other members of the transient flora, one could speculate that microbial toxins or antigens could be involved in the generation of the inflammatory response. Alternatively, keratinocytes themselves may respond to chemical stress from irritants, pollutants, and ultraviolet (UV) irradiation, by producing radical oxygen species and nitric oxide, and by releasing intracellularly stored interleukin (IL)-1α. This pro-inflammatory cytokine by itself has been shown to inhibit the growth of isolated hair follicles in culture (Philpott et al 1996). Moreover, adjacent keratinocytes, which express receptors for IL-1, start to engage the transcription of IL-1 responsive genes: mRNA coding for IL-1β, tumor necrosis factor-α (TNFα), and IL-1α, and for specific chemokine genes, such as IL-8, and monocyte chemoattractant protein (MCP)-1 and MCP-3, themselves mediators for the recruitment of neutrophils and macrophages, have been shown to be upregulated in the epithelial compartment of the human hair follicle (Mahé et al 2000). Besides, adjacent fibroblasts are also fully equipped to respond to such a pro-inflammatory signal. The upregulation of adhesion molecules for blood-borne cells in the capillary endothelia, together with the chemokine gradient, drive the transendothelial migration of inflammatory cells, which include neutrophils through the action of IL-8, T cells and Langerhans cells at least in part through the action of MCP-1. After processing of localized antigen, Langerhans cells, or alternatively keratinocytes, which may also have antigen presenting capabilities, could then present antigen to newly infiltrating T lymphocytes and induce T-cell proliferation. The antigens are selectively destroyed by infiltrating macrophages, or natural killer cells. On the occasion that the causal agents persist, sustained inflammation is the result, together with connective tissue remodeling, where collagenases, such as matrix metalloproteinase (also transcriptionally driven by pro-inflammatory cytokines) play an active role (Mahé et al 2000). Collagenases are suspected to contribute to the tissue changes in perifollicular fibrosis. The significance of these findings has remained controversial. However, morphometric studies in patients with male pattern AGA treated with minoxidil showed that 55% of those with microinflammation had regrowth in response to treatment, in comparison with 77% in those patients without inflammation and fibrosis (Whiting 1993).

Finally, the relationship of FPHL to (male pattern) AGA has been challenged. Arguments against FPHL representing the female counterpart of male AGA are a probably mother-

to-daughter transmission of FPHL, a significantly lower incidence of FPHL in women than AGA in men (Norwood, 2001), occurrence of FPHL in the absence of circulating androgens (Orme et al 1999), lack of response to antiandrogen therapy in normoandrogenemic premenopausal women (Vexiau et al 2002), lack of response to 1 mg oral finasteride daily in postmenopausal women (Price et al 2000), and occurrence of male pattern AGA in women with pathologically elevated androgen levels. It has been suggested that the different pattern of hair loss in the majority of women from that usually seen in men may be due to differences in the relative levels of 5α-reductase, aromatase, and androgen receptors in scalp hair follicles in women compared with those in men (Sawaya and Price 1997).

In contrast to AGA, senile involutional or senescent alopecia has been defined as nonandrogen-dependent hair thinning found in those over 50 years of age (Kligman 1988). Much like AGA, it involves a progressive decrease in the number of anagen follicles and hair diameter. It frequently occurs together with AGA, further complicating its delineation from the latter. Some authors proposed that senescent alopecia may result from cumulative physiological degeneration of selected hair follicles. In healthy murine skin they described clusters of perifollicular macrophages as perhaps indicating the existence of a physiological program of immunologically controlled hair follicle degeneration by which malfunctioning follicles are removed by programmed organ deletion (Eichmuller et al 1998). On the other hand, in his original description, Kligman (1988) proposed a pronounced inflammatory component in AGA, but not in senescent alopecia. Moreover, Price et al (2001), did not identify any "drop-out" of follicles in senescent alopecia upon staining biopsies for elastin, whereas there was less 5α-reductase enzyme activity in comparison with AGA. Nevertheless, some forms of primary fibrosing alopecia may represent pathological exaggeration of immune-mediated, programmed organ deletion, resulting in a follicular lichenoid reaction pattern, specifically postmenopausal frontal fibrosing alopecia (Kossard 1994), and fibrosing alopecia in a pattern distribution (Zinkernagel and Trüeb 2000).

In their study on aging and hair cycles over an exceptionally long duration of 8 to 14 years, Courtois et al (1995) found a reduction in the duration of hair growth and in the diameter of hair shafts, and a prolongation of the interval separating the loss of a hair in telogen and the emergence of a replacement hair in anagen (latency phase). These phenomena resemble those observed in the course of AGA, although their development is less marked, suggesting AGA is a premature aging phenomenon. This aging process was evidenced by a reduction in the number of hairs per unit area and deterioration in the quality of scalp hair. The reduction in density was manifested to different degrees in different individuals. It amounted to less than 10% in 10 years in the individuals with the least alopecia, and was much more pronounced in the balding subjects. The maximal length of hair diminished as the subjects aged, in parallel the hairs became finer. However, among nonbalding subjects, there was a tendency for the proportion of thicker hairs to increase. Finally, aging did not appear to follow a perfectly regular course over time. Periods of stability, or even partial remission, alternated with periods of more marked evolution, perhaps reflected the influence of individual factors such as the subject's general health, life-style, and risk factors for accelerated aging.

Role of UV radiation

Progressive thinning of scalp hair in AGA results in a gradual decline in natural protection of the scalp from UV radiation (UVR). While the consequences of sustained UVR on the unprotected scalp are obvious and well appreciated, specifically photocarcinogenesis and solar elastosis, the effects of UVR on hair loss have widely been ignored. However, clinical observations and theoretical considerations suggest that UVR may have negative effects (overview in: Trüeb 2003): acute telogen effluvium from UVR has been described (Camacho et al 1996), and the production of porphyrins by *Propionibacterium* sp. in the pilosebaceous duct, with photoactivation of porphyrins (Johnsson et al 1987) leading to oxidative tissue injury, may contribute to follicular microinflammation operative at the level of the follicular stem cells. Histopathologically elastosis is regularly found in scalp biopsies, especially in alopecic conditions. A recent study demonstrated a relationship between the degree of scalp elastosis and severity of AGA (Piérard-Franchimont et al 2002): the scalp dermis was significantly thicker in AGA than in unaffected control subjects. The difference was due to severe elastosis in baldness. The earliest signs of solar elastosis preceded hair thinning. When elastosis was thicker than 0.2 mm, a negative exponential correlation was found between hair diameter and severity of solar elastosis.

Care of aging hair

While shampoos have been the most common form of cosmetic hair treatment, primarily aimed at cleansing the

hair and scalp, today's consumer expects more options. With the cosmetic market being consumer driven, the industry has become aware of this, and at the same time became capable of delivering active compounds towards meeting this consumer demand. The result are dermocosmetic agents that achieve cosmetic benefits by some degree of physiologic action. Current hair care products are tailored to the variations associated with age, gender, hair quality, hair care habit, and specific problems related to the superficial condition of the scalp. Problems frequently associated with aging hair are hair thinning, dryness, and damaged hair.

The mechanics of taking care of thin hair can be rewarding. The first thing to be recommended is to shampoo frequently, especially when hair is greasy. This will leave the hair fluffy and give the illusion of thicker hair. Permanent waves can make hair feel thicker and impart more body. Also, gray hair that has become thinner will feel thicker with hair color on it.

Dry hair is hair which does not have enough moisture. It is difficult to style and has lost its shine. This is usually because the cuticle has become heavily weathered and porous, in damaged hair usually as a consequence of repeated cosmetic procedures. The hair cortex is exposed and cannot retain humidity. Treatment of dry and damaged hair consists of intensive conditioning. Conditioners protect the edges of the cuticle scales, although they cannot cure broken hairs where the cortex fibers have burst out (trichorrhexis and split ends). Hair care products (conditioning shampoos, hair conditioners) designed for dry or damaged hair contain large molecules that collect on the edges of the damaged scales of the cuticle, helping to smooth over and fill in the fractures and fissures (overview in: Bouillon 1996). They impart softness, easier grooming, and luster to dry hair. They give back smoothness, gloss, and manageability to damaged hair. Cationic polymers, hydrolyzed proteins, and silicones, such as dimethicone, are useful in this process. In addition, panthenol is absorbed into the shaft and acts as a humefactant by providing moisture. Constant research to find new formulas is at the base of the progress achieved in the development of effective hair care products. The recent identification of different amino acid profiles in normal and weathered hair, and the development of a system of amino acids lost from the hair shaft in the course of weathering and capable of being delivered from cosmetic formulations, is an example (Gummer and Shiel 2004).

Abnormal hairs with inherent weakness are susceptible to excessive weathering. Besides minimizing chemical and physical trauma to the hair and special hair care measures, specific and early treatment of AGA with progressive weakening of the hair shaft using appropriate systemic and/or topical pharmacologic therapy (see Possibilities for prevention or reversal of hair loss) is thus of additional benefit for those affected.

Pharmacologic and other interventions in aging hair

Possibilities for reversal of hair graying

Temporary hair darkening has been reported after ingestion of large doses of *p*-aminobenzoic acid (Sieve 1941; Zarafonetis1950). Sieve (1941) gave 100 mg three times daily to 460 gray-haired individuals and noted a response in 82%. Darkening was obvious within 2–4 months of starting treatment. The hairs turned gray again 2–4 weeks after stopping therapy. The mechanism of action has remained unclear. Side effects were frequent, primarily gastrointestinal upset.

In the absence of a natural way to reverse hair graying, hair colorants are the mainstay of recovering lost hair color. The major types of hair colors currently used are: temporary (textile dyes), natural coloring (henna), semipermanent (low molecular weight direct dyes), and permanent (aromatic amines).

Temporary hair colorants consist of large complex organic structures that do not penetrate the cuticle. The colors are not intense but are capable of covering gray hair in a subtle way. This may be a good way for an individual to experiment with the coloring idea. The colorant washes out with the next shampoo

Henna, obtained form the plant *Lawsonia alba*, is a naturally occurring hair colorant. Although the color can add red highlights to hair, occasionally it may come out looking orange on gray hair.

Semipermanent colorants consist of small molecules that penetrate the cuticle. These compounds color gray hair very nicely, are easily applied in a lotion or foam at home, and last for six to ten shampoos.

The most frequently used hair colorant is permanent hair dye. In permanent hair coloring the formation of colored molecules from their precursors occurs inside the hair fibers as a result of oxidation by hydrogen peroxide. The advantage of permanent color is that the color withstands normal hair washing. Because new growth comes out, the roots need to be touched up. There have been studies that raised the possibility that long-term usage of permanent hair dyes (particularly black dyes) may be associated with an increased

risk of developing certain cancers. However, taken together the evidence is insufficient to state with certainty whether there is a link between using hair dye and cancer. A small number of users may develop irritative and allergic contact reactions (commonly due to *p*-phenylenediamine) that may result in dermatitis and even hair loss.

Possibilities for prevention or reversal of hair loss during aging

It has been known for over 30 years that minoxidil stimulates hair growth, yet its mechanism of action on the hair follicle is still poorly understood (overview in: Messenger and Rundegren 2004). A number of in vitro effects of minoxidil have been described in monocultures of various hair follicle cell types including stimulation of cell proliferation, inhibition of collagen synthesis, and stimulation of vascular endothelial growth factor (VEGF) and prostaglandin synthesis. In animal studies, topical minoxidil shortens the resting phase (telogen) of the hair cycle, causing premature entry of resting hair follicles into the growing phase (anagen), and it probably has a similar action in humans. Minoxidil may also cause prolongation of anagen and increases hair follicle size. Clinical trials of topical 2% and 5% minoxidil in male and female hair loss have all shown remarkably rapid increase in hair growth, measured by hair counts or hair weight (Olsen et al 1985, 1987, 1990; Price and Menefee 1990; De Villez et al 1994; Olsen, Dunlap, et al 2002; Lucky et al 2004). The increase is evident within 6–8 weeks of treatment and has generally peaked by 12–16 weeks. However, topical minoxidil has not been studied in the specific perspective of aging and senescent alopecia. In an recent analysis of clinical trial data in 636 males and 630 females, a therapeutic benefit of topical 2 and 5% minoxidil solution was compared with age, duration of balding, and diameter of balding vertex area in males, and age and duration of hair loss in females (Rundegren 2004). Age was found to be the denominator for predicting treatment success for both males and females. The younger subjects experienced better efficacy than the older subjects although clear treatment effects were noted also in the older age group. Males showed an inverse relationship between effect and duration of balding. Males with duration of balding <5 years showed a significantly better effect than those with duration of balding >21 years. Females, in contrast, showed no correlation with duration of balding. The diameter of vertex balding in men showed an inverse relationship with efficacy of minoxidil. Males with <5 cm diameter vertex balding area showed a better effect of treatment than subjects with diameters >15 cm. Finally, duration of hair loss less than one year compared with more than 10 years at onset of treatment resulted in a significantly more effective treatment with respect to stabilization of alopecia and new hair growth.

Finasteride, an inhibitor of type 2 5α-reductase, inhibits conversion of testosterone to DHT, resulting in decrease in serum and scalp DHT levels believed to be pathogenic in AGA. 1 mg oral finasteride daily has been shown to be effective in prevention and treatment of hair loss in men (Kaufman 1996; Kaufman et al 1998; Leyden et al 1999; FMPHL 2003), and has also shown some effect in aging males (Brenner and Matz 1999; Whiting et al 2003).

Traditionally, pattern hair loss in women has successfully been treated with topical minoxidil, and with systemic antiandrogens, such as cyproterone acetate or spironolactone (Sinclair et al 2005), though the efficacy of the latter has also been challenged, at least in premenopausal women with normal androgen levels (Vexiau et al 2002). While oral finasteride has unanimously been shown to be effective in treatment of hair loss in men, its efficacy in women has remained controversial (Whiting et al 1999; Price et al 2000; Shum et al 2002; Thai and Sinclair 2002; Carmina and Lobo 2003; Trüeb and STSG 2004). Due to inconsistent data with respect to efficacy of finasteride in women, it has been suggested that not all types of female hair loss have the same pathophysiology, ie, a distinction should be made between alopecia with early or late (postmenopausal) onset, and with or without hyperandrogenemia (Olsen, Hordinsky, et al 2002). Due to teratogenicity for the male fetus, finasteride is contraindicated for use in premenopausal women.

Photoprotection of hair and scalp

Awareness of sun protection has become imperative as a consequence of increased leisure time with a growing popularity of outdoor activities and holidays in the sun. Topically applied chemicals that act as sun protectors are widely utilized and offer the most convenient means of protecting the glabrous skin against acute (sunburn) and chronic pathologic effects of UVR. Their use on the hair-bearing scalp is problematic for cosmetic reasons, unless complete baldness is present. Although hats provide the best protection of the scalp from UVR, not all patients find them convenient or acceptable for this purpose. While protection of the hair against photodamage has been extensively studied, there are no data on photoprotection of the hair-bearing scalp. It has been found that hair dyes may protect hair against photodamage (Pande et al 2001); recent

experimental work indicate that cinnamidpropyltrimonium chloride, a quaternized UV absorber, delivered from a shampoo system, is suitable for photoprotection of hair, while simultaneously providing an additional conditional benefit on hair (Gao and Bedell 2001); and solid lipid nanoparticles have been developed as novel carriers of UV blockers for the use on skin and hair, while offering photoprotection on their own by reflecting and scattering UVR (Wissing and Muller 2001). Finally, systemic photoprotection has been the focus of more recent investigation, in as much as this would overcome some of the problems associated with the topical use of sunscreens: Preclinical studies illustrate photoprotective properties of supplemented antioxidants, particularly beta-carotene (pro-vitamin A), α-tocopherol (vitamin E), and L-ascorbate (vitamin C). However, clinical evidence that these prevent, retard, or slow down solar skin damage is impending. The same applies to topical melatonin, which has been found to suppress UV-induced erythema, and UV-induced reactive oxygen species in a dose-dependent manner (Bangha et al 1996). Nevertheless, these results suggest the probable utility of combining these compounds with known sunscreens to maximize photoprotection.

Anti-aging compounds

Recent advances in the care of aging hair and scalp are "anti-aging" compounds. Due to water dilution and short contact time, anti-aging compounds do not have any effect in shampoos. Antioxidants in shampoos, such as vitamin C and E, protect fatty substances in the shampoo from oxidation, and not the scalp. Topical anti-aging compounds of current interest are green tea polyphenols, selenium, copper, phytoestrogens, melatonin, and as yet unidentified substances from traditional Chinese medicine (TCM), and Ayurvedic medicine.

In the course of hormonal anti-aging protocols containing recombinant human growth hormone at the Palm Springs Life Extension Institute, Chein (1998) reports improvement of hair thickness and structure in 38% of patients, in some cases darkening of hair, and in few increased hair growth. It is noteworthy that in primary growth hormone insensitivity (Laron syndrome), hair growth, and hair structure (but not hair color) have been shown to be impaired (Lurie et al 2004).

Future directions

There is an increasing interest in the hair follicular route for delivery of active compounds affecting the hair. Current research activities focus on topical liposome targeting for melanins, genes, and proteins selectively to hair follicles for therapeutic and cosmetic modification of hair (Hoffman 1998). For example, topical liposome selective delivery to hair follicles has demonstrated the ability to color hair with melanin. Finally, yet another line of research in the quest of new treatments for hair loss is tissue engineering with cells of hair follicular origin with inductive properties (Reynolds et al 1999).

References

Bangha E, Elsner P, Kistler GS. 1996. Suppression of UV-induced erythema by topical treatment with melatonin (N-acetyl-5-methoxytryptamine). *Arch Dermatol Res*, 288:522–6.

Bouillon C. 1996. Shampoos. *Clin Dermatol*, 14:113–21.

Brenner S, Matz H. 1999. Improvement in androgenetic alopecia in 53–76-year-old men using oral finasteride. *Int J Dermatol*, 38:92–3.

Camacho F, Moreno JC, Garcia-Hern·ndez MJ. 1996. Telogen alopecia from UV rays. *Arch Dermatol*, 132:1398–9.

Carmina E, Lobo RA. 2003. Treatment of hyperandrogenic alopecia in women. *Fertil Steril*, 79:91-95.

Chein E. 1998. Age reversal, from hormones to telomeres. *WorldLink Med Pub.*

Commo S, Gaillard O, Bernard BA. 2004. Human hair greying is linked to a specific depletion of hair follicle melanocytes affecting both the bulb and the outer root sheath. *Br J Dermatol*, 150:435–43.

Courtois M, Loussouarn G, Hourseau C, et al. 1995. Aging and hair cycles. *Br J Dermatol*, 132:86–93.

Dawber R. 1996. Hair: its structure and response to cosmetic preparations. *Clin Dermatol*, 14:105–12.

De Villez RL, Jacobs JP, Szpunar CA, et al. 1994. Androgenetic alopecia in the female. Treatment with 2% topical minoxidil solution. *Arch Dermatol*, 3:303–7.

Eichmüller S, van der Veen C, Mill I, et al. 1998. Clusters of perifollicular macrophages in normal murine skin: physiological degeneration of selected hair follicles by programmed organ deletion. *J Histochem Cytochem*, 46:361–70.

Gao T, Bedell A. 2001. Ultraviolet damage on natural gray hair and ist photoprotection. *J Cosmet Sci*, 52:103–18.

Gummer Ch, Schiel S. 2004. Amino acids – a potential solution for cosmetic hair problems [poster]. 4th Intercontinental Hair Research Societies Meeting, Berlin, June 17–19, 2004.

Hibberts NA, Messenger AG, Randall VA. 1996. Dermal papilla cells derived from beard hair follicles secrete more stem cell factor (SCF) in culture than scalp cells or dermal fibroblasts. *Biochem Biophys Res Commun*, 222:401–5.

Hoffman RM. 1998. Topical liposome targeting of dyes, melanins, genes, and proteins electively to hair follicles. *J Drug Target*, 5:67–74.

Itami S, Kurata S, Takayasu S. 1995. Androgen induction of follicular epithelial cell growth mediated via insulin-like growth factor I from dermal papilla cells. *Biochem Biophys Res Commun*, 221:988–94.

Jaworsky C, Kligman AM, Murphy GF. 1992. Characterization of inflammatory infiltrates in male pattern alopecia: implications for pathogenesis. *Br J Dermatol*, 127:239–46.

Johnsson A, Kjeldstad B, Melo TB. 1987. Fluorescence from pilosebaceous follicles. *Arch Dermatol Res*, 279:190–3.

Kaufman KD. 1996. Androgen metabolism as it affects hair growth in androgenetic alopecia. *Dermatol Clin*, 14:697–711.

Kaufman KD. 1996. Clinical studies on the effects of oral finasteride, a type II 5α-reductase inhibitor, on scalp hair in men with male pattern baldness. In: van Neste D, Randall VA (eds) Hair research for the next millenium. Elsevier, Amsterdam. p 363–5.

Kaufman KD, Olsen EA, Whiting DA, et al. 1998. Finasteride in the treatment of androgenetic alopecia. *J Am Acad Dermatol*, 39:578–89.

Kligman AM. 1988. The comparative histopathology of male-pattern baldness and senescent baldness. *Clin Dermatol*, 6:108–18.

Kossard S. 1994. Postmenopausal frontal fibrosing alopecia. *Arch Dermatol*, 130:770–4.

Leyden J, Dunlap F, Miller B, et al. 1999. Finasteride in the treatment of men with frontal male pattern hair loss. *J Am Acad Dermatol*, 40:930–7.

Lucky AW, Piacquadio DJ, Ditre CM, et al. 2004. A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. *J Am Acad Dermatol*, 50:541–53.

Lurie R, Ben-Amitai D, Laron Z. 2004. Laron syndrome (primary growth hormone insensitivty): a unique model to explore the effect of insulin-like growth factor 1 deficiency on human hair. *Dermatology*, 208:314–18.

Mahé YF, Michelet JF, Billoni N et al. 2000. Androgenetic alopecia and microinflammation. *Int J Dermatol*, 39:576–84.

Messenger AG, Rundegren J. 2004. Minoxidil: mechanisms of action on hair growth. *Br J Dermatol*, 150:186–94.

Nagl W. 1995. Different growth rates of pigmented and white hair in the beard: differentiation vs. proliferation? *Br J Dermatol*, 132:94–7.

Norwood OT. 1975. Male pattern baldness: classification and incidence. *South Med J*, 68:1359–65.

Norwood OT. 2001. Incidence of female androgenetic alopecia (female pattern alopecia). *Dermatol Surg*, 27:53–4.

Olsen EA, DeLong ER, Weiner MS. 1987. Long-term follow-up of men with male pattern baldness treated with topical minoxidil. *J Am Acad Dermatol*, 16:688–95.

Olsen EA, Dunlap FE, Funicella T, et al. 2002. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol*, 47:377–85.

Olsen EA, Hordinsky M, Roberts JL, et al. 2002. Female pattern hair loss. *J Am Acad Dermatol*, 47:795.

Olsen EA, Weiner MS, Delong ER, et al. 1985. Topical minoxidil in early male pattern baldness. *J Am Acad Dermatol*, 13:185–92.

Olsen EA, Weiner MS, Amara IA, et al. 1990. Five-year follow-up of men with androgenetic alopecia treated with topical minoxidil. *J Am Acad Dermatol*, 22:643–6.

Orme S, Cullen DR, Messenger AG. 1999. Diffuse female hair loss: are androgens necessary? *Br J Dermatol*, 141:521–3.

Pande CM, Albrecht L, Yang B. 2001. Hair photoprotection by dyes. *J Cosmet Sci*, 52:377–89.

Philpott MP, Sander DA, Bowen J, et al. 1996. Effects of interleukins, colony stimulating factor and tumour necrosis factor on human hair follicle growth in vitro: a possible role for interleukin-1 and tumour necrosis factor-α in alopecia areata. *Br J Dermatol*, 135:942–8.

Piérard-Franchimont C, Uhoda I, Saint-Léger D, et al. 2002. Androgenetic alopecia and stress-induced premature senescence by cumulative ultraviolet light exposure. *Exog Dermatol*, 1:203–6.

Price VH, Menefee E. 1990. Quantitative estimation of hair growth I. Androgenetic alopecia in women: effect of minoxidil. *J Invest Dermatol*, 95:683–7.

Price VH, Sawaya M, Headington J, Kibarian M. 2001. Histology and hormonal activity in senescent thinning in males [abstract]. *J Invest Dermatol*, 117:434.

Price VH, Roberts JL, Hordinsky M et al. 2000. Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. *J Am Acad Dermatol*, 43:768–76.

Randall VA, Thornton MH, Messenger AG. 1992. Cultured dermal papilla cells from androgen-dependent human hair follicles (eg, beard) contain more androgen receptors than those from non-balding ares of the scalp. *J Endocrinol*, 133:141–7.

Reynolds AJ, Lawrence C, Cserhalmi-Friedman PB, et al. 1999. Trans-gender induction of hair follicles. Human follicle cells can be induced to grow in an incompatible host of the other sex. *Nature*, 402:33–4.

Rundegren J. 2004. Pattern alopecia: what clinical features determine the response to topical minoxidil treatment? 4th Intercontinental Hair Research Societies Meeting, Berlin, June 17–19. *Journal der Deutschen Dermatologischen Gesellschaft*, 2:500 (abstract B2.4).

Sawaya ME, Price VH. 1997. Different levels of 5α-reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. *J Invest Dermatol*, 109:296–300.

Shum KW, Cullen DR, Messenger AG. 2002. Hair loss in women with hyperandrogenism: four cases responding to finasteride. *J Am Acad Dermatol*, 47:733–9.

Sieve B. 1941. Darkening of gray hair following para-aminobenzoic acid. *Science*, 94:257–8.

Sinclair R, Wewerinke M, Jolley D. 2005. Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol*, 152:466–73

Thai KE, Sinclair RD. 2002. Finasteride for female androgenetic alopecia. *Br J Dermatol*, 147:812–3.

[FMPHL] The Finasteride Male Pattern Hair Loss Study Group. 2003. Long-term (5-year) multination experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. *Eur J Dermatol*, 12:38–49.

Tobin DJ, Paus R. 2001. Graying: gerontobiology of the hair follicle pigmentary unit. *Exp Gerontol*, 36:29–54.

Trüeb RM. 2002. Molecular mechanisms in androgenetic alopecia. *Exp Gerontol*, 37:981–90.

Trüeb RM. 2003. Is androgenetic alopecia a photoaggravated dermatosis? *Dermatology*, 207:343–8.

Trüeb RM; Swiss Trichology Study Group. 2004. Finasteride treatment of patterned hair loss in normoandrogenic postmenopausal women. *Dermatology*, 209:202–7.

van Neste D. 2004. Thickness, medullation and growth rate of female scalp hair are subject to significant variation according to pigmentation of scalp location during aging. *Eur J Dermatol*, 14:28–32.

van Neste D, Tobin DJ. 2004. Hair cycle and hair pigmentation: dynamic interactions and changes associated with aging. *Micron*, 35:193–200.

Vexiau P, Chaspoux C, Boudou P, et al. 2002. Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol*, 146:992–9.

Whiting DA. 1993. Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia. *J Am Acad Dermatol*, 28:755–63.

Whiting DA, Waldstreicher J, Sanchez M, et al. 1999. Measuring reversal of hair miniaturization in androgenetic alopecia by follicular counts in horizontal sections of serial scalp biopsies: results of finasteride 1 mg treatment of men and postmenopausal women. *J Invest Dermatol Symp Proc*, 4:282–4.

Whiting DA, Olsen EA, Savin R et al. 2003. Efficacy and tolerability of finasteride 1 mg in men aged 41 to 60 years with male pattern hair loss. *Eur J Dermatol*, 13:150–60.

Wissing SA, Muller RH. 2001. Solid lipid nanoparticles (SLN) – a novel carrier for UV blockers. *Pharmazie*, 56:783–6.

Zarafonetis C. 1950. Darkening of gray hair during para-aminobenzoic acid therapy. *J Invest Dermatol*, 15:399–491.

Zinkernagel MS, Trüeb RM. 2000. Fibrosing alopecia in a pattern distribution. Patterned lichen planopilaris or androgenetic alopecia with a lichenoid tissue reaction pattern? *Arch Dermatol*, 136:205–11.