Review Article

Aging of hair

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Summary

The appearance of hair plays an important role in people's overall physical appearance and self-perception. With today's increasing life expectation, the desire to look youthful plays a bigger role than ever. The hair care industry has become aware of this and also more capable to deliver active products that are directed toward 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 and aging of the hair follicle. The latter manifests as decrease of melanocyte function or graying, and decrease in hair production in androgenetic and senescent alopecia. The scalp is also subject to intrinsic or physiologic aging and extrinsic aging caused by external factors. Intrinsic factors are related to individual genetic and epigenetic mechanisms with interindividual variation. Prototypes are familial premature graying and androgenetic alopecia. Extrinsic factors include ultraviolet radiation and smoking. Experimental evidence supports the hypothesis that oxidative stress plays a role in skin and hair aging. Topical anti-aging compounds for hair include humefactants, hair conditioners, photoprotectors, and antioxidants. Current available treatment modalities with proven efficacy for treatment of androgenetic alopecia are topical minoxidil, oral finasteride, and autologous hair transplantation. In the absence of another way to reverse hair graying, hair colorants are the mainstays of recovering lost hair color. Topical liposome targeting for melanins, genes, and proteins selectively to hair follicles are under current investigation.

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

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

As early as can be traced in the history of civilization, the human race has shown interest to please by means of the natural ornament hair, given that its appearance is a feature of the body over which, unlike other hairy land mammals, we exert direct control. Hair length, color, and style play an important role in people's physical appearance and self-perception. We modify them according to how we wish to appear. The condition and style of hair play a role in how we discern the people we encounter, and how we are perceived by those we come upon. Our ancient preoccupation with hair is further heightened as our increasing life expectancy fuels our desire to preserve youthfulness. In today's world, physical appearance and the notion of looking young and energetic play a greater role than ever. 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. This attention reflects a hair care market that is a multibillion

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dollar enterprise worldwide. 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.

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.

Basic 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 also to the gerontologist for the study of age-related effects. Its complex multicell-type interaction system involving epithelium, mesenchyme, and neuroectoderm and its unique cyclical activity of growth, regression, rest, and regrowth provides the investigator with a range of stem, differentiating, mitotic and postmitotic terminally differentiated cells, including cells with variable susceptibility to apoptosis, for study. Finally, a number of intrinsic and extrinsic modulating factors for hair growth and pigmentation have been identified and are being further tested *in vitro*.[1]

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 also subject to intrinsic or physiologic aging and extrinsic or premature aging caused by external factors. Intrinsic factors are related to individual genetic and epigenetic mechanisms with interindividual variation. Prototypes are familial premature graying and androgenetic alopecia. 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.

It is the aim of this paper to review the manifestations and management of aging hair: hair weathering, graying, androgenetic and senescent alopecia, their prevention, and therapy.

Hair weathering

Weathering represents the wear and tear that mainly affects the free end of the growing hair fiber. 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. Because scalp hair has the longest hair growing phase, it is subject to more damage than hairs of other body sites. Given a hair growth rate of approximately 1 cm/month, the part of the hair fiber that is 12 cm from the scalp will reveal accumulated physical and chemical trauma of 1 year of growth! In normal hair the damage is most prominent only near the tip of scalp hair, which often appears lusterless and paler than the more proximal growth, with varying degrees of split ends (trichoptilosis). The hair fiber 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, excessive heat "blown" or from curling irons applied to the hair.

Chemical treatment of hair, i.e., bleaching, coloring, perming, and straightening, is a major cause of exaggerated hair weathering, as the cuticle becomes raised and softened in the course of these procedures, becoming more vulnerable to mechanical abrasion. Loss of cuticle leads to longitudinal fissures between exposed cortical cells, ultimately resulting in hair fractures (trichorrhexis nodosa, Figure 1) at these sites.[2]

Abnormal hairs with inherent weakness are susceptible to excessive weathering. An example is pili annulati, a disorder characterized by air-filled spaces at regular intervals within the hair shaft. Although pili annulati is generally classified as a congenital hair shaft disorder without increased fragility, scanning electron microscopic studies have demonstrated the ultrastructural sequence leading to fragility with trichorrhexis

Figure 1 Trichorrhexis nodosa of the centroparietal area. Patient has the impression that hair does not grow. In fact, hair loss is caused by breakage.

nodosa.[3] In as much as trichorrhexis nodosa is caused by external stress to the hair shaft secondary to physicochemical trauma, the exaggerated weathering pattern is a consequence of a lowered threshold level of susceptibility to trauma associated with some inherent weakness of the hair shaft. In pili annulati the affected hair shafts show surface abnormalities at regular intervals (nodes) associated with the underlying air-filled spaces of pili annulati. In severe cases there is marked damage to the cuticle at the nodes exposing the underlying cortex resulting in fractures of the hair shaft. In addition to the colocalization of trichorrhexis nodosa with the air-filled cavities, we previously found that in patients, pili annulati hair fragility may also develop in relationship with androgenetic alopecia.[4] In these cases, hair fragility manifests itself after onset of androgenetic alopecia, and trichorrhexis nodosa-like fracturing is exclusively limited to the androgenetic region. Thus, patients with androgenetic alopecia may be at a special risk for developing the more severe weathering pattern. Besides minimizing chemical and physical trauma to the hair and special hair care measures, specific and early treatment of androgenetic alopecia using appropriate systemic and / or topical therapy (see succeeding discussion) is of additional benefit for these patients.

Graying

Hair graying (canities) is a natural age-associated feature. The hair graying trait correlates closely with chronological aging and occurs in 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 (familial premature graying), it has also been associated with a similar cluster of autoimmune disorders such as occurs in vitiligo (e.g., pernicious anemia, autoimmune thyroid disease) and several rare syndromes with premature aging (e.g., Werner syndrome, Figure 2).

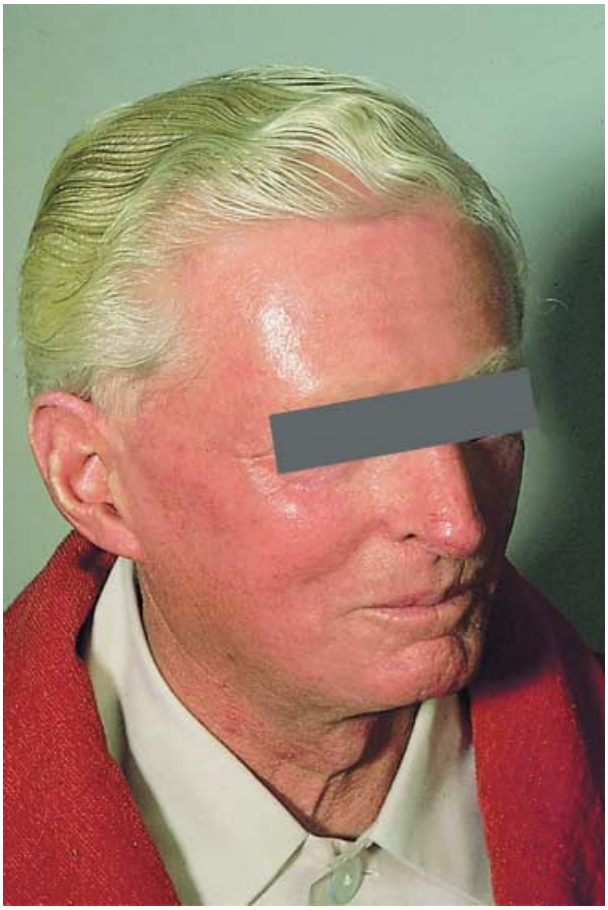

Figure 2 Werner's syndrome. Adult progeria with premature gray hair.

Although graying is understood as a loss of pigment in the shaft, its cellular and molecular origins are incompletely understood.[1] 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.[5] The net effect of this reduction is that fewer melanosomes are incorporated into cortical keratinocytes of the hair shaft. In addition, there appears 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 caused by either defective melanosomal

transfer to the cortical keratinocytes or melanin incontinence as a result of 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 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. Because 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 keratinoytes, 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.[6] 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.[7,8] 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 the sunlight-absorbing and thus heat-trapping properties of melanized dark hair.[1] 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 fiber 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.

Androgenetic alopecia

Androgenetic alopecia (AGA), also referred to as male-pattern hair loss or common baldness in men and 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 men in later life.[9] Estimates of its prevalence in women have varied widely, though recent studies claim that 6% of women aged under 50 years are affected, increasing to a proportion of 30–40% of women aged 70 years and over.[10] 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.[11] 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.[12] Androgen-dependent processes are predominantly caused by the binding of dihydrotestosterone (DHT) to the androgen receptor (AR). DHT-dependent cell functions depend on the availability of weak androgens, their conversion to more potent androgens via the action of 5-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. Because many extrinsic hair growth-modulatory factors, such as androgens,[13] 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,[14] and stem cell factor (SCF) has been found to be produced in higher amounts by androgen-dependent beard cells than in control nonbalding scalp cells, presumably also in response to androgens.[15] Because 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.[16–18] 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.[16] 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.[18] 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.[17] An important question is how the inflammatory reaction pattern is generated around the individual hair follicle. Inflammation is regarded as 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.[17] 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 UV irradiation, by producing radical oxygen species and nitric oxide, and by releasing intracellularly stored IL-1α. This pro-inflammatory cytokine by itself has been shown to inhibit the growth of isolated hair follicles in culture.[19] Moreover, adjacent keratinocytes, which express receptors for IL-1, start to engage the transcription of IL-1 responsive genes: mRNA coding for IL-1α, TNFα, and IL-1α, and for specific chemokine genes, such as IL-8, and monocyte chemoattractant protein-1 (MCP-1) and MCP-3, themselves mediators for the recruitment of neutrophils and macrophages, have been shown to be up-regulated in the epithelial compartment of the human hair follicle.[17] Besides, adjacent fibroblasts are also fully equipped to respond to such a pro-inflammatory signal. The up-regulation 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.[17] 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 to 77% in those patients without inflammation and fibrosis.[18]

Finally, the relationship of FPHL to (male pattern) AGA has been challenged. Arguments against FPHL representing the female counterpart of male AGA are probably a mother-to-daughter transmission of FPHL, a significantly lower incidence of FPHL in women than AGA in men,[10] occurrence of FPHL in the absence of circulating androgens,[20] lack of response to antiandrogen therapy in normoandrogenemic premenopausal women,[21] lack of response to 1 mg oral finasteride daily in postmenopausal women,[22] and occurrence of male pattern AGA in women with pathologically elevated androgen levels. Nevertheless, FPHL shares with AGA the miniaturization of the hair follicle with vellus hair transformation of terminal hairs. Venning and Dawber (1988) reported a frequency of male pattern hair loss in 13% premenopausal women with patterned hair loss, and a frequency of 37% in postmenopausal women (Figure 3).[23]

Senescent alopecia

Senile involutional or senescent alopecia (Figure 4) has been defined as nonandrogen-dependent hair thinning

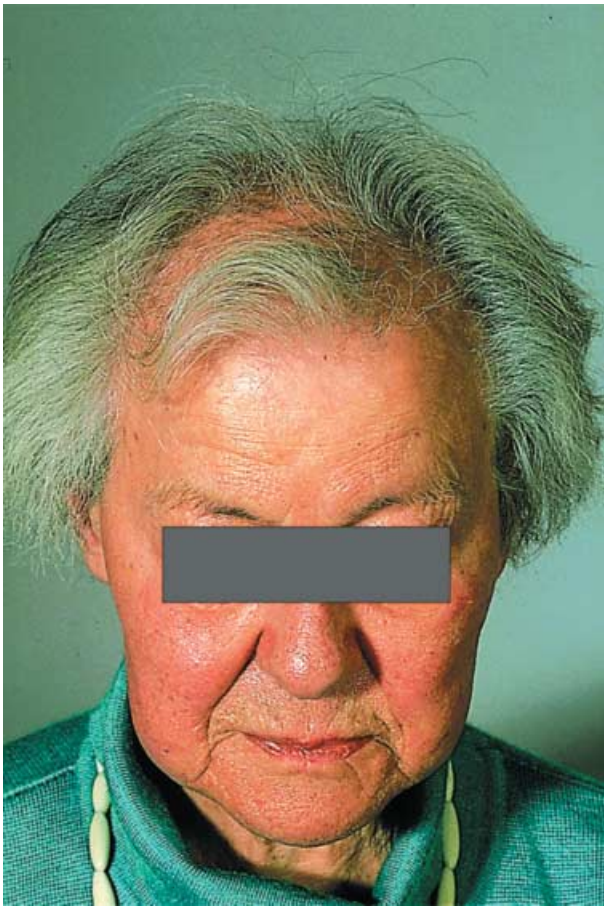

Figure 3 Male pattern hair loss in postmenopausal woman.

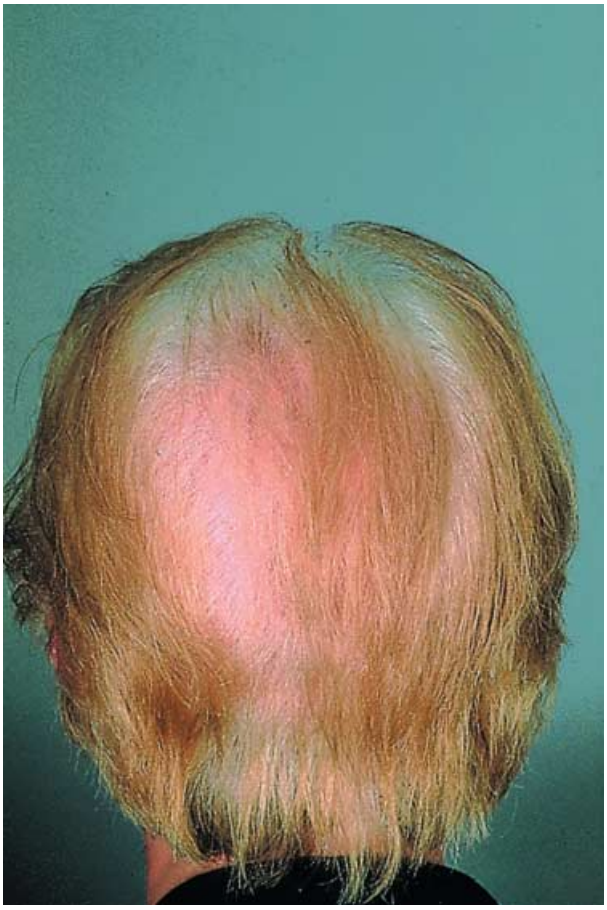

Figure 4 Senescent alopecia. This type of hair loss in the vertex area of aged women has also been termed "widow's cap"-alopecia.

found in those over 50 years of age.[24] 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.[25] On the other hand, in his original description, Kligman proposed a pronounced inflammatory component in AGA (see previous discussion) 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 to AGA.[26] 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[27] (Figure 5), and fibrosing alopecia in a pattern distribution.[28]

In their study on aging and hair cycles over an exceptionally long duration of 8–14 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).[29] These phenomena resemble those observed in the course of AGA, although their development is less marked, suggesting AGA 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

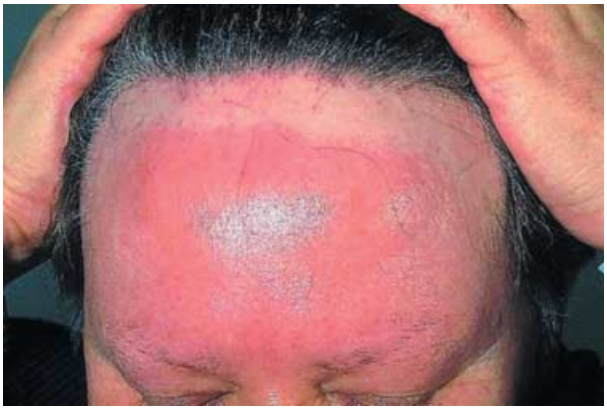

Figure 5 Postmenopausal frontal fibrosing alopecia.

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, reflecting perhaps the influence of individual factors such as the subject's general health, lifestyle, and risk factors for accelerated aging.

Role of smoking and UV radiation

Besides being the single most preventable cause of significant morbidity and an important cause of death in the general population, tobacco smoking has been associated with adverse effects on the skin. Smoke-induced premature skin aging has attracted the attention of the medical community, while only recently an observational study indicated a relationship between smoking and graying of hair and alopecia.[30] The mechanisms by which smoking causes hair loss are multifactorial, and probably related to effects of cigarette smoke on the microvasculature of the dermal hair papilla, smoke genotoxicants causing damage to DNA of the hair follicle, smoke-induced imbalance in the follicular protease/antiprotease systems controlling tissue remodelling during the hair growth cycle, pro-oxidant effects of smoking leading to the release of pro-inflammatory cytokines resulting in follicular microinflammation and perifollicular fibrosis, and finally increased hydroxylation of estradiol, creating a relative hypoestrogenic state.[31] The fact that cigarette smoke-associated hair loss is of the androgenetic type again indicates that genetic factors contribute. Of course, variances between individuals also may result from patterns of conduct, inasmuch as persons exposed to one risk factor (smoking) are often exposed to others as well, such as intake of androgens and their precursors (such as DHEA in anti-aging protocols), or of progestins with androgenic activity (in oral contraceptives or hormonal replacement therapy), excessive ultraviolet exposure (see succeeding discussion), and stress, all of which have been implicated in the one way or other in the pathogenesis of alopecia.

In view of the psychological effects of hair loss on affected men and women, increasing public awareness of the association between smoking and alopecia offers an opportunity for health education against smoking that may be more effective than the link between smoking and facial wrinkles or gray hair, as the latter can be effectively counteracted by current aesthetic dermatologic procedures, while treatment options for AGA have their limitations.

Progressive thinning of scalp hair in AGA results in a gradual decline in natural protection of the scalp from ultraviolet 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:[32] acute telogen effluvium from UVR has been described,[33] and the production of porphyrins by *Propionibacterium* sp. in the pilosebaceous duct, with photoactivation of porphyrins[34] 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:[35] the scalp dermis was significantly thicker in AGA than in unaffected control subjects. The difference was caused by more 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.

As a consequence of increased leisure time with a growing popularity of outdoor activities and holidays in the sun, awareness of sun protection has become imperative. 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. For cosmetic reasons their use on the hair-bearing scalp is problematic, unless complete baldness is present. Although hats provide the best protection of the scalp from UVR,

not all patients find it 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;[36] recent experimental work indicates 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;[37] and solid lipid nanoparticles have been developed as novel carriers of UV blockers for use on skin and hair, while offering photoprotection on their own by reflecting and scattering UVR.[38] Finally, systemic photoprotection has been the focus of more recent investigation, inasmuch as this would overcome some of the problems associated with the topical use of sunscreens; preclinical studies illustrate photoprotective properties of supplemented anti-oxidants, 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.[39] Nevertheless, these results suggest the probable utility of combining these compounds with known sunscreens to maximize photoprotection.

Possibilities for reversal of hair graying

In the absence of a natural way to reverse hair graying, hair colorants are the mainstays of recovering lost hair color. Whether a person decides to color his or her hair depends on many factors. The first is whether the person is really too young to feel comfortable with premature gray hair; a second factor is whether the gray hair affects an individual's career opportunity; a third is cosmetics: gray hair may be unbecoming to a person's complexion, especially if he or she is pallid or sallow. There are several choices open to a person with gray hair: if hair is less than 10% gray, to pluck out the grays; to apply blond streaks to some of the hair, a procedure called highlighting; to color only the gray, especially in the beginning when the gray in men affects only the temples, or the perimeter in women; to color about half the hair by wrapping it with a lighter shade, producing a natural look; finally, to color the entire head of hair, usually going two shades lighter than a person's natural color to prevent a harsh look.

The following major types of hair colors are currently used: 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. Its use dates back to ancient Egypt. Although the color can add red highlights to hair, occasionally on gray hair it may come out looking orange. 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 6 to 10 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. Such products are used with excellent safe results in millions of individuals worldwide. Studies have 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. Nevertheless, *Harvard Health Online* (www.health.harvard.edu/medline/Women/W801f.html) recommends that those who use dark hair coloring and want to "play it safe" should use it as infrequently as possible, wear gloves when applying the dye, leave it on the scalp only as long as necessary, and rinse the scalp thoroughly after using it. 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.

Finally, temporary hair darkening has been reported after ingestion of large doses of *p*-aminobenzoic acid.[41,50] Sieve (1941) gave 100 mg three times daily to 460 gray-haired individuals and noted a response in 82%.[40] 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.

Possibilities for reversal of hair loss during aging

Current available treatment modalities with proven efficacy for treatment of AGA are topical minoxidil, oral finasteride, and autologous hair transplantation.

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.[42] 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.[43–50] 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 a recent analysis of clinical trial data in 636 males and 630 females, a therapeutic benefit of topical 2% and 5% minoxidil solution were compared to age, duration of balding, and diameter of balding vertex area in males, and age and duration of hair loss in females.[51] 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 between 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 1 year compared to 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. Taking 1 mg oral finasteride daily has been shown to be effective in prevention and treatment of hair loss in men,[52–55] and has also shown some effect in aging males.[56,57] The efficacy of finasteride in women with FPHL has remained controversial. Because of teratogenicity for the male fetus, finasteride is contraindicated for use in premenopausal women.

Traditionally, pattern hair loss in women has successfully been treated with topical minoxidil and systemic anti-androgens, such as cyproterone acetate, although the efficacy of the latter has recently been challenged, at least in premenopausal women with normal androgen levels.[21] While oral finasteride has been shown to be effective in treatment of hair loss in men, its efficacy in women has remained controversial. In a double-blind, placebo-controlled, multicenter trial, oral finasteride, 1 mg/d, taken for 1 year did not slow progression of hair loss or promote hair growth,[22] and did not improve follicular counts in horizontal sections of scalp biopsies in postmenopausal women with FPHL.[58] The authors implied that the older age of the women enrolled in the clinical trial may have contributed to the lack of improvement with finasteride, as they assumed that men and women in the later decades of life develop senescent scalp thinning which is not 5α-reductase- or DHT-dependent. On the other hand, oral finasteride, 1 mg/d, is effective in men of older age.[56,57] It has been suggested that the different pattern of hair loss in the majority of women from that usually seen in men may be the result of differences in the relative levels of 5α-reductase, aromatase, and androgen receptors in scalp hair follicles in women compared with those in men.[59] More recently, Shum *et al.* (2002) reported four cases of hair loss with characteristics of both male and female pattern hair loss in women with hyperandrogenism, in which finasteride improved the alopecia.[60] Their patients differed from those in the trial reported by Price *et al.* in that the patients had increased androgen levels, and finasteride was used in a slightly higher dose (1.25 mg/d), and given for a longer period of time (24–30 months as opposed to 1 year). On the other hand, Carmina and Lobo (2003) did not find finasteride, 5 mg/d, to be effective in treatment of alopecia in hyperandrogenic women.[61] Finally, Thai and Sinclair (2002) were the first to report a single case of successful treatment of FPHL in a postmenopausal woman with androgen levels within normal values. Whether their success was the result of a different dosing schedule (5 mg finasteride weekly) or variation in individual patient response remains unclear. Because of inconsistent data with respect to efficacy of finasteride in the treatment of pattern hair loss in women, it has been suggested that not all types of female hair loss have the same pathophysiology, i.e., a distinction should be made between alopecia with early or late (postmenopausal) onset, and with or without hyperandrogenemia.[49] We recently published successful treatment of patterned hair loss with 2.5 or 5 mg/d oral finasteride in five postmenopausal women without clinical or laboratory signs of hyperandrogenemia[62] (Figure 6). Improvement with growth

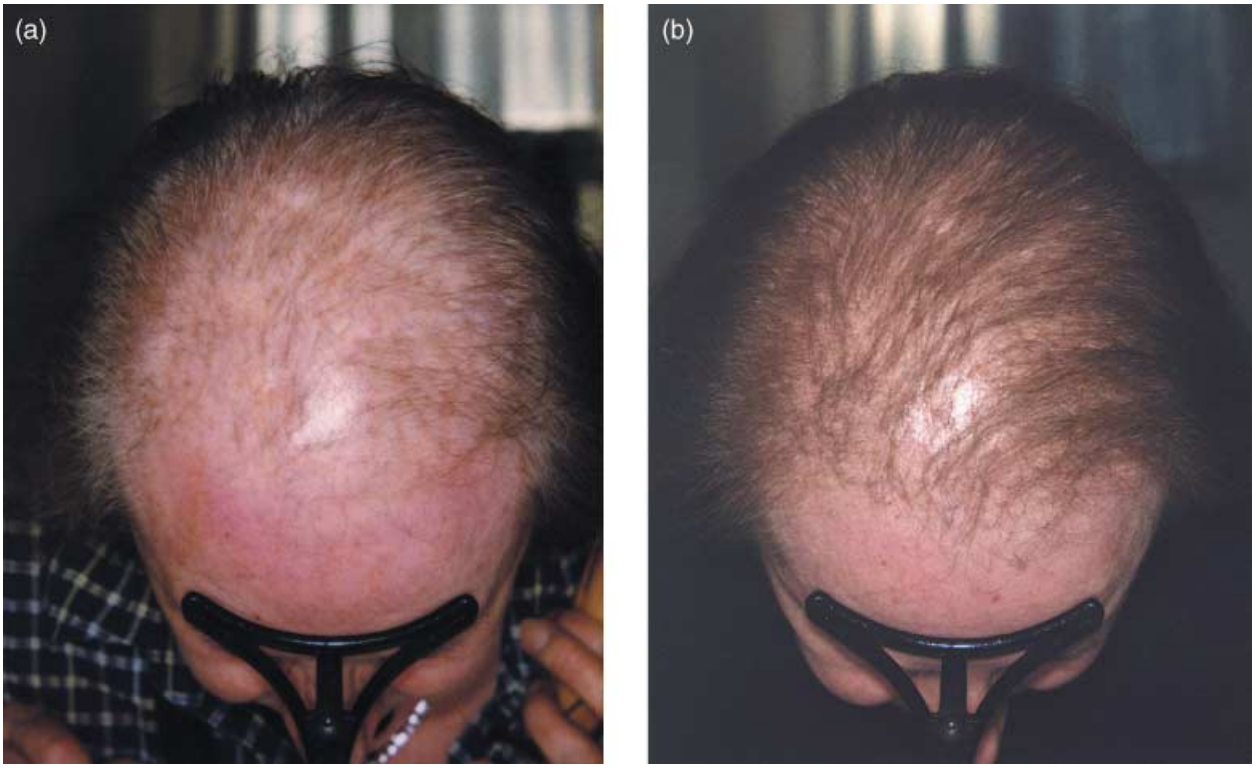

Figure 6 Postmenopausal female patient treated with oral finasteride 5 mg/day at baseline and at 12 months (from: *Dermatology* 2004; **209**: 202–7).

of hair was observed as early as 6 months of therapy, irrespective of the pattern of hair loss. Our patients differ in that significantly higher doses of finasteride were used.

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, darkening of hair in some cases 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.[63]

Autologous hair transplantation remains the only treatment option for advanced patterned baldness. With the advent of total micrografting and a sharp decline in scalp reduction procedures, hair restoration surgery has become more satisfying than in the recent past. Modern techniques use the visual qualities of hair and varying design patterns to create the optical illusion of more hair than is actually present. The main advances in hair restoration surgery have been the use of one to four hair grafts, which allows a natural, undetectable hairline, and the transplantation of large numbers of these small grafts during a single session (Figure 7). Careful patient selection and these newer techniques are geared toward naturalness and undetectability for the lifetime of the patient.[64]

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 capable of delivering active compounds toward meeting this consumer demand. The result is 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 recommendation is to shampoo frequently, especially when hair is greasy. This will leave

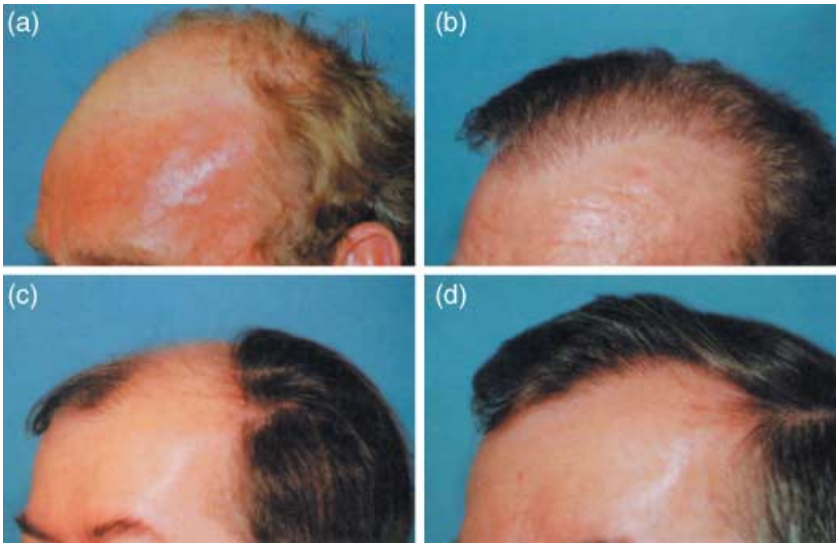

Figure 7 Result of autologous hair transplantation. a, b: result after two sessions with 1600 grafts. c, d: result after one session of 1000 grafts (patients of P. Nyberg, Zurich).

the hair fluffy and give the illusion of thicker hair. Men and women should avoid a part in their hair if possible, because it makes thin hair look more sparse. Individuals with thin hair should also avoid too-long hair-styles, because the weight of the hair will drag it down. Permanent waves can make hair feel thicker and impart more body. A larger soft wave will impart a more sophisticated look than "little orphan Annie" curls. Also, gray hair that has become thinner will feel thicker with hair color on it. Another technique is to get a haircut that is layered. This technique cuts the hair on the top of the head shorter than the hair on the bottom. In women, it can give the illusion of having long hair even though the top of the hair is quite short.

Dry hair is hair that 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.[65] To dry hair they impart softness, easier grooming, and luster. To damaged hair they give back smoothness, gloss, and manageability. 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 are examples.[66]

Recent advances in the care of aging hair and scalp are "anti-aging" compounds. Caused by water dilution and short contact time, both topical hair growth stimulants and anti-aging compounds do not have any effect in shampoos. Anti-oxidants in shampoos, such as vitamin C and E, protect fatty substances in the shampoo from oxidation, and not the scalp. The rationale for the development of topical hair growth stimulants in form of leave-on products are effect on androgen metabolism (e.g., inhibition of 5α-reductase), effect on sebum production and microbial flora,[67] effect on microinflammation and fibrosis, and effect on vascularization and VEGF (e.g., minoxidil). Topical anti-aging compounds of current interest are green tea polyphenols, selenium, copper, phytoestrogens, melatonin, as yet unidentified substances from traditional Chinese medicine (TCM), and ayurveda.

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.[68] For example, topical liposome selective delivery to

hair follicles has demonstrated the ability to color hair with melanin. 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.[69]

Figures 1–6 and 7 from: Trüeb RM. Haare Praxis der Trichologie. Steinkopff Darmstadt 2003 (with permission).

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