Aging Hair (Intrinsic and Extrinsic Factors)

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"Aged? But he does not appear aged, just look, his hair has remained young"

G. Boldini's Count de Montesquiou (Proust's role model for the Baron de Charlus)

Marcel Proust (1871-1922)  
In Search of Lost Time
The **appearance of hair** plays an important role in people’s overall physical appearance and self-perception.

With today’s increase life-expectation, the **desire to look youthful** plays a bigger role than ever.

**Aging of hair** is particularly visible.

The **hair care industry** has become aware of this and capable to deliver active products 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 in the young and old.

Finally, basic scientists interested in the biology of hair growth and pigmentation have exposed the **hair follicle as a highly accessible and unique model for the study of age-related effects**.
Science of Hair Care

**Esthetic problem** of aging hair and its management in terms of

- hair quality
- hair quantity
- hair colour

associated with the aging process

**Biological problem** of aging hair in terms of

- microscopic
- biochemical
- molecular changes

underlying the aging process
The Hair Aging Phenotype

Hair Weathering and Hair Photoaging

Aging of the Hair Follicle and Hair Pigmentary Unit

- Failure to pigment the hair shaft (graying)
- Loss of follicle rigor, consistent with slowing of other body activities with age
- Decrease in rapidity of hair growth
- Reduction in the diameter of the hair shaft

Aging of Scalp and Age-Related Disorders of Scalp

Age-Related General Problems Affecting the Condition of Hair: nutritional, endocrine, psychological, drug-related, multimorbiditiy

Hair Graying

Hair graying is a natural age-associated feature correlating closely with chronological aging and occurring to varying degrees in all individuals.

Caucasians: at 34.2 ± 9.6 years

Africans: at 43.9 ± 10.3 years

Premature hair graying: before 20 y. in Caucasians
before 30 y. in Africans

Familial premature graying (AD)

Immunologic:
- pernicious anemia
- autoimmune thyroid disease
- diffuse alopecia areata
- Vogt-Koyanagi-Harada syndrome
- HIV infection

Syndromatic (rare):
- progeria (Hutchinson-Gilford, Werner)
- Rothmund-Thompson syndrome
- myotonic muscular dystrophy Curshmann-Steinert
Physical Properties of Graying Hair

- White beard hair **grows faster** than adjacent pigmented hair
- Gray hair is **coarser, wirier, and more unmanageable** than its pigmented equivalent; often unable to hold a set, and more resistant to incorporating artificial color

Hair follicle keratinocyte proliferation in anagen

Terminal differentiation of follicle keratinocytes

- Gray hair follicles re-program their matrix keratinocytes to **increase the production of medullary, rather than precortical keratinocytes**
- The increase of air inclusions within the medulla may compensate for the loss of insulation associated with pigment dilution

_Tobin and Paus. Exp Gerontol 2001;36:29-54_
Biology of Hair Graying

Reduction of active melanocytes, tyrosinase activity, and melanosome transfer to hair follicle keratinocytes

Defective melanosomes with reactive melanin metabolites, degeneration of melanocytes with vacuolisation as marker for oxidative stress, increase in melanin debris, melanin incontinence, and autophagolysosomes

The loss of functional melanocytes is a consequence of replicative senescence and apoptosis, accelerated by the oxidative metabolism of hair follicle melanogenesis

Wood et al recently been demonstrated that white scalp hair shafts accumulate H$_2$O$_2$, and almost absent methionine sulfoxide reductase protein expression in association with functional loss of methionine sulfoxide repair. Accordingly, methionine sulfoxide formation of methionine residues in the active site of tyrosinase, the key enzyme in melanogenesis, limits enzyme functionality.


Nishimura et al have recently demonstrated that hair graying may be caused by defective self-maintenance of melanocyte stem cells, and not of differentiated melanocytes.

Rare premature aging syndromes with alopecia (Hutchinson-Gilford, Curshmann-Steinert, Rothmund-Thomson, Laron syndrome)

Androgenetic alopecia (AGA)

Female pattern hair loss (FPHL)

Senescent alopecia
<table>
<thead>
<tr>
<th></th>
<th>Androgenetic alopecia</th>
<th>Senescent alopecia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Early (teens, twens)</td>
<td>Late (60 years +)</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Patterned</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Increased activity of 5-α reductase (DHT)</td>
<td>Senescence (decreased activity of 5-α reductase)</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>Polygenic</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Association or risk factor for other diseases</strong></td>
<td>Cardiovascular diseases</td>
<td>Age-related disorders?</td>
</tr>
<tr>
<td></td>
<td>Benign prostatic hyperplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostate cancer</td>
<td></td>
</tr>
<tr>
<td><strong>Gene expression profiles</strong></td>
<td>Decreased expression of genes required for anagen onset and maintenance / increased expression of catagen and telogen inducers</td>
<td>Increases expression of markers for mitochondrial dysfunction and oxidative stress</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Finasteride</td>
<td>Minoxidil</td>
</tr>
<tr>
<td></td>
<td>Minoxidil</td>
<td>Antioxidants?</td>
</tr>
<tr>
<td></td>
<td>Estrogens (anecdotal)</td>
<td>hGH (anecdotal)</td>
</tr>
</tbody>
</table>

Andro(chrono)genetic Alopecia

Genetically determined, androgen induced, age-dependent progressive hair loss with sex-dependent differences in incidence, pattern and severity

<table>
<thead>
<tr>
<th>Men:</th>
<th>18 - 29: 12%</th>
<th>Women:</th>
<th>20 - 29: 3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 39:</td>
<td>38%</td>
<td>30 - 39:</td>
<td>17%</td>
</tr>
<tr>
<td>40 - 49:</td>
<td>45%</td>
<td>40 - 49:</td>
<td>16%</td>
</tr>
<tr>
<td>50 - 59:</td>
<td>52%</td>
<td>50 - 59:</td>
<td>23%</td>
</tr>
<tr>
<td>60 - 69:</td>
<td>65%</td>
<td>60 - 69:</td>
<td>25%</td>
</tr>
<tr>
<td>70 - 79:</td>
<td>64%</td>
<td>70 - 79:</td>
<td>28%</td>
</tr>
<tr>
<td>&gt; 80:</td>
<td>70%</td>
<td>80 - 89:</td>
<td>32%</td>
</tr>
</tbody>
</table>

Hamilton-Norwood I-VII


Androgens

Androgen metabolism

Genetics

Progressive shortening of anagen phase +
Reduction of volume of dermal papilla

Follicular microinflammation

Hair follicle miniaturization/hair growth arrest

Increased shedding of hair:
Telogen effluvium

Perifollicular fibrosis

growth arrest

Decreased hair growth:
Terminal-to-vellus hair transformation

Empty hair follicle
**Current Treatment for Androgenetic Alopecia**

- **FINASTERIDE**
  - Long-term treatment with finasteride 1 mg decreases the likelihood of developing further visible hair loss in men with androgenetic alopecia (male pattern hair loss). Eur J Dermatol 2008;18:400-6

- **MINOXIDIL**
  - Price et al. Changes in hair weight and hair count in men with androgenetic alopecia, after application of 5% and 2% topical minoxidil, placebo, or no treatment. J Am Acad Dermatol 1999;41:717-21

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Kaufman et al. Long-term treatment with finasteride 1 mg decreases the likelihood of developing further visible hair loss in men with androgenetic alopecia (male pattern hair loss). Eur J Dermatol 2008;18:400-6
Finasteride in Men Age 40+

24-month, double-blind, randomized, placebo-controlled, multicenter study

424 men 41-60 years with mild-to-moderate, predominantly vertex male pattern hair loss:
- 1mg finasteride: N = 286
- placebo: N = 138

Global photographs of vertex scalp taken at baseline and at months 6, 12, 18, and 24

Patient self-assessments and investigator clinical assessments

Results:

**Placebo:**
- 4% improvement
- 23% worsening

**Finasteride:**
- 39% improvement
- 6% worsening

## Tolerability of Finasteride in Men Age 40+

### Study Details


### Age Groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Finasteride</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>18-40 Y. (24 M.)</td>
<td>1.6%</td>
<td>1.7%</td>
</tr>
<tr>
<td>41-50 Y.</td>
<td>8.1%</td>
<td>2.6%</td>
</tr>
<tr>
<td>51-60 Y.</td>
<td>9.4%</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

### Sexual AE’s

<table>
<thead>
<tr>
<th>AE Type</th>
<th>Finasteride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Libido</td>
<td>1.3%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Erection</td>
<td>0.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Libido

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<td>51-60 Y.</td>
<td>3.6%</td>
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### Erection

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<td>51-60 Y.</td>
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Finasteride in Postmenopausal Women

Randomized, double-blind, placebo-controlled study with 1 mg oral finasteride during 12 months in 137 postmenopausal age 41-60 Y.

Study endpoints:
• Hair count
• Global photographic assessment
• Biopsy (morphometric)

Results: For all endpoints no difference in comparison to placebo


5 normoandrogenic postmenopausal women treated with 2.5 – 5 mg oral finasteride for up to 18 months showed improvement on global photographic assessments.

Trüeb et al. Dermatology 2004;209:202-207
Iorizzo et al. Arch Dermatol 2006;142:298-302
Prognostic factors for response to topical minoxidil in men:

- Younger age
- Duration of hair loss: < 1 year versus > 10 years
- Duration of balding: < 5 years versus > 21 years
- Diameter of vertex balding: < 5 cm versus > 15 cm

Rundegren J. (IHRS 2004 abstract B2.4) JDDG 2004;2:500

- Histological presence of significant perifollicular inflammation and fibrosis: Without fibrosis morphometric response to therapy in 77%, with fibrosis in 55%

Whiting. JAAD 1993;28:755-763
Minoxidil is Effective in Treatment of Alopecia in Women of 60+

Personal observation
Dermoscopy of Scalp (Trichoscopy)

Tosti A. *Dermoscopy of Hair and Scalp Disorders* with clinical and pathological correlations. Informa healthcare UK 2007


Zinkernagel MS, Trüeb RM. *Fibrosing alopecia in a pattern distribution*: patterned lichen planopilaris or androgenetic alopecia with a lichenoid tissue reaction pattern? Arch Dermatol 2000;136:205-11
Follicular microinflammation and fibrosis:
Whiting D. Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia.
JAAD 1993;28:755-763

Kossard S. Postmenopausal frontal fibrosing alopecia.
Scarring alopecia in a pattern distribution.
Arch Dermatol. 1994;130:770-4


Zinkernagel MS, Trüeb RM. Fibrosing alopecia in a pattern distribution: patterned lichen planopilaris or androgenetic alopecia with a lichenoid tissue reaction pattern?
Arch Dermatol 2000;136:205-11
Genetic factors
- Polygenic transmission
- Polymorphisms of androgen receptor?
- Others?

Precipitating factors
- Androgens
- Steroidogenic enzyme activity
- Others: Microbes, irritants, pollutants, UVR?

Follicular microinflammation
- Radical oxygen species, Nitric oxide
- Androgen receptor

Dermal papilla fibroblasts
- IGF-1, SCF
- Others?

Follicular epithelium
- Follicular stem cells
- Hair matrix keratinocytes
- Apoptosis
- Catagen induction

Perifollicular fibrosis?

Stem cell apoptosis?

Hair follicle miniaturization

Therapeutic strategies:
1. Gene therapy? (currently not available)
2. Modifiers of androgen metabolism: finasteride (available for men)
3. Antimicrobial shampoos?
4. Antiandrogens: cyproterone acetate (available for women)
5. Hair growth promoters: minoxidil (available for men and for women)
6. Antiinflammatory agents?
7. Apoptosis modulating agents? (currently not available)
8. Hair transplantation (available), implantation of dermal papilla cells or cells of follicle dermal-sheath (impending)

Environmental Factors: Smoking

There are significant positive associations between premature hair loss and smoking


- effect on microcirculation
- direct (geno-) toxic effect
- imbalance in the follicular protease/antiprotease systems involved in tissue remodelling and the hair follicle cycle
- oxidative stress
- inhibition of aromatase, hydroxylation of E2, relative hypoestrogenic state

Trüeb RM. Association between smoking and hair loss: another opportunity for health education against smoking? Dermatology 2003;206:189-191

Environmental Factors: Smoking

Premature senescence of balding DPC in vitro in association with expression of p16(INK4a)/pRB suggests that balding DPC are sensitive to environmental stress and identifies alternative pathways that could lead to novel therapeutic strategies for treatment of AGA.


Combination Treatment with Finasteride, L-Cystine and Vit. B₆ in a 60+ Year Old Cigarette Smoker

Personal observation

3 months
Combination Treatment with Finasteride, L-Cystine and Vit. B₆ in a 60+ Year Old Cigarette Smoker

Personal observation

3 months
Environmental Factors: UV-R

Photodamage is a common cause of poor hair condition in an aging population

Effects of UV-R on hair:

- Sunlight damages both **hair color** and **hair structure** (hair photogaging)
- **Gray hair is more susceptible** to UV-induced damage than pigmented hair
  

- acute telogen effluvium
  

- production of porphyrins by *Propionibacterium sp.* in the pilosebaceous duct, with photoactivation leading to **oxidative tissue injury and follicular microinflammation**
  

- direct physicochemical stress from UV-R to keratinocytes with production of radical oxygen species and nitric oxide and release of proinflammatory cytokines, eventually leading to **injury of the putative site of follicular stem cells in the superficial portion of the hair follicle**
  
Effect of UV-R on Scalp

Scalp is altered by both UVA and UVB

A mottled interfollicular melanoderma is related to cumulative sun exposures

There is evidence that AGA is adversely influenced by UV exposures

Actinic field carcinogenesis of the scalp is responsible for actinic keratoses and SCC of the scalp

Some specific disorders such as the red scalp syndrome are restricted to the light-exposed scalp

Trüeb RM. Is androgenetic alopecia a photaggravated dermatosis? Dermatology 2003;207:343-348
Summary: Aging of Hair (Intrinsic and Extrinsic Factors)

**Intrinsic Factors:**
- **Genetic:** AGA, familial premature graying (AD), progerias (rare)
- **Hormones und hormone metabolism:** AGA
- **Replicative senescence:** Graying, senescent alopecia?
- **Oxidative metabolism** (melanogenesis): Graying

**Extrinsic Factors:**
- Oxidative stress from UV-R
- Oxidative stress from tobacco smoking
- Others?

Hair Anti-Aging

Procedures for delaying, lessening or reversing the effects of aging on the hair

Cosmetic Hair Treatment:
- Cleansing hair
- Conditioning hair
- Styling hair
- Changing hair colour/colouring hair
- Perming hair

Medicinal Treatment of Specific Problems Relating to Condition of Hair and Scalp

“Cosmeceuticals”
- Promoting hair growth?
- Preventing hair aging?

- Hair loss
- Specific dermatologic conditions of the scalp

**Hair Anti-Aging**

- **Primary prevention:** Hair photoprotection, prevention of tobacco smoking

- **Secondary prevention:** Pharmacologic treatment of androgenetic alopecia with **minoxidil** and **finasteride**

- **Hair care:** Special **shampoo** and **conditioner** selection for aging hair

- **Care of more general, age-related health problems affecting the condition of hair:** nutritional deficiency, endocrine disorders, psychological disorders, drug-related, multimorbidity

- **Role for nutritional supplementation**? Amino acids (L-cystine, methionine), vitamins, micronutrients, antioxidants, others?

- **Role for anti-aging hormonal treatments**? Estrogens, hGH, thyroid replacement therapy, melatonin, others?
Future Directions

Gene polymorphisms diagnostics:
- Prediction of risk
- Prevention
- Diagnosis
- Targeted treatment development
- Personalized medicine (pharmacogenomics)


Stem cell technologies:
- Tissue regeneration (hair follicle, follicular melanocytes)


Bioengineering of the hair follicle:
- For reconstructing hair follicles (Phase III studies)

Interested in hearing or reading more?

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EHRs 2011

July 6-9, 2011
www.ehrs.org/conference/2011jerusalem

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Desmond J. Tobin
Editors

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