Hair and Scalp Disorders

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Few dermatologic problems carry as much emotional overtones as disorders of the hair and scalp.

The best way to alleviate the emotional distress related to the respective complaints is to effectively treat the condition.

Once the diagnosis is certain, treatment appropriate for that diagnosis is likely to control the problem.

Prerequisite for delivering appropriate patient care is an understanding
• of the pathologic dynamics of hair loss and scalp disease
• of the multitude of cause relationships.
New Insights into the Management and Care of Hair and Scalp

New insights focus on the role of internal and external factors such as:

- Nutrition
- Hormones
- Aging
- Seasonality of hair growth and shedding
- Cigarette smoking
- UV radiation
- Hair care.

It must be borne in mind that hair loss often does not result from a single cause effect, but from a combination of factors. Therefore the concept of combined treatments and multitargeted approach to hair loss is emerging.

Ultimately, the problems of co-morbidities and of multimorbidity in the elderly population have to be taken into account.
Spotlights and Pearls on New Insights into the Understanding, Management, and Care of Hair and Scalp Disorders

Hair Aging
Effect of Cigarette Smoke on Hair Growth
Seasonality of Hair Growth and Shedding
New Insights into Diffuse Red Scalp Disease
Role of Follicular Inflammation and Fibrosis in AGA
Advances in Alopecia Areata
Role of Evidence in Successful Trichologic Practice
Patient Compliance Issues
Hair Aging

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

Androgenetic alopecia (AGA)
Female pattern hair loss (FPHL)
Senescent alopecia

Peculiarities of androgen metabolism
Polygenetic trait
External factors

Advancing Age
<table>
<thead>
<tr>
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<th>Androgenetic alopecia</th>
<th>Senescent alopecia</th>
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<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) in men</td>
<td>Senescence (decreased activity of 5-α reductase )</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>Polygenic</td>
<td>Unknown</td>
</tr>
</tbody>
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| **Association or risk factor for other diseases** | Cardiovascular diseases  
Benign prostatic hyperplasia  
Prostate cancer | Age-related disorders? |
| **Gene expression profiles** | Decreased expression of genes required for anagen onset and maintenance / increased expression of catagen and telogen inducers | Increased expression of markers for mitochondrial dysfunction and oxidative stress |
| **Treatment**          | Minoxidil  
Finasteride  
Estrogens (anecdotal) | Minoxidil  
Antioxidants/nutritional supplements?  
hGH (anecdotal) |

Biology of Hair Aging

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

Extrinsic (Accelerated) Aging:
- Oxidative stress from UV-R
- Oxidative stress from cigarette smoking
- Others?

Trüeb RM. Is androgenetic alopecia a photogravitated dermatosis? Dermatology 2003;207:343-348

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


After 3 months **whole-body cigarette smoke exposure**, C57BL/6 mice developed areas of alopecia and grey hair. **Cell apoptosis** occurred massively in the hair bulbs at the edge of alopecia areas.

D'Agostini et al. Induction of alopecia in mice exposed to cigarette smoke.. Toxicol Lett. 2000 Apr 3;114(1-3):117-23

- 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
In a population study of Asian men smoking status, current amount of cigarette smoking, and smoking intensity were statistically significant factors responsible for AGA after controlling for age and family history. Patients with early-onset AGA should receive advice early to prevent more advanced progression.

Su LS, Chen THH. Association of androgenetic alopecia with smoking and ist prevalence among Asian men. Arch Dermatol 2007;143:1401-1406

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.


High-dose environmental cigarette smoke induces apoptosis-related alopecia in mice, and oral administration of L-cystine/vitamin B6 is an effective preventive treatment.

Seasonality of Hair Growth and Shedding

Reports 3 women in New York who experienced maximum hair loss in November


Demonstrate in 14 men over a period of 18 months that the proportion of telogen hair and of hair shedding were maximal in September


Demonstrate in 10 men with or without alopecia during a period of 8-14 years a maximal proportion of telogen hairs at the end of summer

Fluctuations in frontal telogen rates (n = 823) in relation to the day of the year:

Telogen rates showed an overall annual periodicity, manifested by a maximal proportion of telogen hair in July.

A second telogen peak seems to exist, although less pronounced, in April.

Seasonal fluctuations in telogen rates may be significant enough to be clinically apparent in women with female androgenetic alopecia!

Seasonality of Hair Growth and Shedding in Women

Subsequent images taken in January 2007, August 2007, and February 2008

The existence of seasonal fluctuations in hair growth and shedding complicates the assessment of pharmacological effects.

Awareness of these fluctuations is prerequisite to providing the correct cause and prognosis to the patient, ensuring patient compliance with therapy.

Awareness of these fluctuations has potentially serious implications for investigations with new hair-growth-promoting agents:

- Depending on the stage of periodicity in growth and shedding of hair for a particular subject, the heterogeneity of included subjects may be enough to distort the clinical efficacy results and the perceived benefit of an investigational agent.

- In the active stage of seasonal telogen effluvium, the involved hair follicles would probably fail to respond to the therapeutic agent, which may cause a false-negative result.

- In the recovery stage, the increased amounts of spontaneously regrowing hair might be interpreted falsely as a positive result.

Double Blind Placebo Controlled Study with CYP-Complex in Women 60+ Complaining of Hair Loss

Placebo (n=21)  Active (n=15)
74  73  77  76  77  79

Inaugural Dissertation, Barbara Hotzenköcherle Trüeb, University of Zurich 2012
Effect of Seasonality on Hair Growth and Shedding; Inclusion

Placebo: 26% T
(n = 21)

Active: 27% T
(n = 15)

Inaugural Dissertation, Barbara Hotzenköcherle Trüeb, University of Zurich 2012
Effect of Seasonality on Hair Growth and Shedding: 3 Months

Placebo: 23% T  
(n = 21)

Active: 24% T  
(n = 15)

Inaugural Dissertation, Barbara Hotzenköcherle Trüeb, University of Zurich 2012
Effect of Seasonality on Hair Growth and Shedding: 6 Months

Inaugural Dissertation, Barbara Hotzenköcherle Trüeb, University of Zurich 2012
Diffuse Red Scalp Disease

First described by **Thstrup-Pedersen and Hjorth** in 1987

Thstrup-Pedersen K, Hjorth N. Rod skalp. En ikke tidligere beskrevet harbundssygdom? (A previously undescribed disease of the scalp?) Ugeskr Laegerm 1987;149:2141-2

Subsequently commented on by **Moschella** in 1994 as „diffuse red scalp disease which can also be itchy and burning. It is unresponsive to any therapy including potent topical steroids or anti-seborrheic terapy“


Further analyzed by **Grimalt et al.**, who presented their findings on 18 patients at the EHRS Annual Meeting 2000:
- middle-aged females consulting for hair loss
- associated with androgenetic alopecia in 13/18 patients
- 3/10 biopsies showed evidence of scarring alopecia NOS
- some patients reported discomfort of the scalp

Red Scalp/Red Scalp Syndrome/Diffuse Red Scalp Disease: Definition

Terminology used synonymously for a condition, characterized by:

- persistent redness of the scalp
- not explained by a specific dermatologic disease of the scalp
- with or without sensation of itching or burning
- refractory to topical corticosteroids and antiseborrhoeic agents
- aggravation in the sun
- dermoscopic finding of teleangiectasia of the scalp
Red Scalp: Rosacea-like Dermatosis of the Scalp?

Oberholzer et al (2009): 57-year old male and 57-year old female with complaint of itching and burning of scalp that was refractory to topical corticosteroid and antiseborrheic treatment.

Dermoscopic finding of telangiectatic erythema with follicular papules and pustules.

Lesional biopsies taken from both patients showed telangiectasia, perifollicular mixed-cellular inflammation with granuloma formation in the mid dermis consistent with rosacea and moderate elastosis. No fungal spores were found.

DIF: No immune deposits.

Red Scalp: Rosacea-like Dermatosis of the Scalp?

Successful treatment with **oral tetracycline, omittance of topical corticosteroids, protection of scalp from UVR-exposure and neutral shampoo.**

Role of Follicular Microinflammation and Fibrosis in Androgenetic Alopecia

Genetically determined, androgen induced, age-dependent progressive loss of hair with sex-dependent differences in pattern of alopecia

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Men (%)</th>
<th>Women (%)</th>
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<tbody>
<tr>
<td>18 - 29</td>
<td>12%</td>
<td>3%</td>
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<tr>
<td>30 - 39</td>
<td>38%</td>
<td>17%</td>
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<tr>
<td>40 - 49</td>
<td>45%</td>
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<tr>
<td>50 - 59</td>
<td>52%</td>
<td>23%</td>
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<tr>
<td>60 - 69</td>
<td>65%</td>
<td>25%</td>
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<tr>
<td>70 - 79</td>
<td>64%</td>
<td>28%</td>
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<tr>
<td>&gt; 80</td>
<td>70%</td>
<td>32%</td>
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Hamilton-Norwood I-VII

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Men (%)</th>
<th>Women (%)</th>
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<tbody>
<tr>
<td>20 - 29</td>
<td>3%</td>
<td></td>
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<tr>
<td>30 - 39</td>
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<td>17%</td>
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<td>70 - 79</td>
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<td>28%</td>
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<tr>
<td>80 - 89</td>
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<td>32%</td>
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Current Concept of Pathobiology and Treatment of Androgenetic Alopecia

Androgens + Androgen metabolism

Polygenic Trait

Progressive shortening of anagen phase

Hair follicle miniaturization

Increased shedding of hair:
Telogen effluvium

Decreased hair growth:
Terminal-to-vellus hair transformation

Role of follicular microinflammation and perifollicular fibrosis?

Increased shedding of hair: Telogen effluvium

Decreased hair growth: Terminal-to-vellus hair transformation
Hair Follicle Microinflammation and Fibrosis

1992 Jaworsky et al refer to an inflammatory infiltrate of activated T cells and macrophages in the upper third of the hair follicle associated with an enlargement of the follicular dermal sheath composed of collagen bundles.

1993 Whiting demonstrates in morphometric studies on patients with male pattern androgenetic alopecia (AGA) a frequency of 40% significant perifollicular inflammation and fibrosis, and finds with 55% of patients with follicular inflammation and fibrosis vs. 77% in those without, lesser regrowth in response to treatment with minoxidil.

2000 Mahé et al propose in a review on AGA and inflammation the term „microinflammation“ in contrast to the inflammatory and destructive process in the classical inflammatory scarring alopecias.

2004 Deloche et al demonstrate in a study of the scalp in a large cohort of volunteers with AGA using macrophotographs presence of peripilar signs (PPS) around the hair ostia, and find a significant relationship between PPS and superficial perifollicular infiltrates in early AGA.
Peripilar Signs (Peripilar Cupular Atrophy)

Androgenetic alopecia without peripilar signs

Androgenetic alopecia with peripilar signs

Degeneration of Selected Follicles by Programmed Organ Deletion?

In back skin sections from C57BL/6 mice, perifollicular inflammatory cell clusters (PICC) were found located around the distal non-cycling portion of 2% of hair follicles.

PICC consisted of macrophages (MAC) and CD4+ cells.

During anagen and catagen 10% of PICC+ hair follicles showed degenerative phenomena reminiscent of scarring alopecia.

This may indicate existence of a physiological program of MAC-dependent controlled follicle degeneration by which damaged or malfunctioning follicles are removed.

Scarring alopecia may represent an exaggerated form of this physiological program.

Concept of Cicatricial Pattern Hair Loss

Original report in 1994 by Kossard as a distinct entity in postmenopausal women

Kossard S. Arch Dermatol 1994;130:770-4

In 1997 revised by Kossard et al to be a frontal variant of lichen planopilaris

Kossard et al. JAAD 1997;36:59-66

Progressive scarring alopecia in a pattern distribution with histologic findings of:

• androgenetic alopecia with increased numbers of miniaturized hair follicles with underlying fibrous streamers
• a pattern of follicular interface dermatitis targeting the upper follicle in early lesions
• perifollicular lamellar fibrosis and presence of selectively fibrosed follicular tracts in late lesions

Zinkernagel MS, Trüeb RM. Arch Dermatol 2000;136:205-11
In **2005 Olsen** acknowledges existence of clinically significant inflammatory phenomena and fibrosis in androgenetic alopecia and proposes the term „*cicatricial pattern hair loss*“


**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
Fibrosing Alopecia in a Pattern Distribution

Androgenetic alopecia with inflammatory phenomena and fibrosis

Androgenetic alopecia with peripilar signs (early)

Fibrosing alopecia in a pattern distribution (late)
Pathobiology of Perifollicular Inflammation and Fibrosis

Inflammation is a **multistep process** with the question arising with regard to the **primary event**:

- Localization of the inflammation near the infundibulum
- **Role of microbial colonization?**
- Specifically, bacterial toxins, antigenic stimulus, and porphyrins?
- **Role of environmental stress from irritants and pollutants?**
- **Role of UVR?**
- Follicular keratinocytes themselves can respond to stressors by producing radical oxygen species, nitric oxid, and **releasing IL-1α**
- Transcription of IL-1 responsive genes: IL-1β, TNFa, IL-8, MCP-1,-3
- **Antigen presentation to T lymphocyte and induction of T-cell proliferation**
- **Sustained inflammation** results in **connective tissue remodeling (fibrosis)**, where collagenases (MMP's) play a role,
- ultimately preventing the follicle to reform a terminal hair follicle in the course of the hair cycle

Revised Concept of Pathobiology and Treatment of Androgenetic Alopecia

Therapeutic strategies:
1. Gene therapy?
2. Modifiers of androgen metabolism: finasteride, dutasteride
3. Antimicrobial treatments?
4. Antiandrogens: CPA, spironolactone
5. Hair growth promoters: minoxidil
6. Antiinflammatory agents?
7. Apoptosis modulating agents?
8. Hair transplantation/implantation of dermal papilla cells or cells of follicle dermal-sheath

Combined Topical Minoxidil And Anti-Inflammatory Treatment

Fibrosing alopecia in a pattern distribution, F, 69 years old, after 6, 12, and 15 months treatment with oral hydroxychloroquine, and topical 5% minoxidil, 0.2% triamcinolone acetonide lotion

(Personal observation)
Advances in Alopecia Areata

"17 trials ... with a total of 540 participants. Each trial included 6-85 participants and assessed a range of interventions that included: topical and oral corticosteroids, topical ciclosporin, photodynamic therapy, topical minoxidil. None showed significant treatment benefit in terms of hair growth when compared with placebo."

"Few treatments have been well evaluated in randomised trials. We found no RCTs on the use of DCP, DNCB, intralesional corticosteroids or dithranol, although commonly used. Although topical steroids and minoxidil are widely prescribed and appear to be safe, there is no convincing evidence that they are beneficial in the long-term. Most trials have been reported poorly and are so small that any important clinical benefits are inconclusive.

"Considering the possibility of spontaneous remission especially for those in the early stages of the disease, the options of not being treated therapeutically or, depending on individual preference wearing a wig may be alternative ways of dealing with this condition."

Complexity in pathogenesis may be an opportunity in terms of targeting the disease therapeutically.

Evolving therapies:
- CTLA4-Ig fusion protein (Abatacept) blocks co-stimulation of T-cells
- anti-IL15Rβ mab blocks activation of CD8+ T-cells
- (Janus Kinase) JAK3-inhibitor (Tofacitinib) blocks signal transduction (IL-15 receptor)
- JAK1/2-inhibitor (Ruxolitinib) blocks signal transduction (IL-15 receptor)

Hordinsky MK. Treatment of alopecia areata: "What is new on the horizon?". Dermatol Ther 2011;24(3):364-8

F, 66-years old, diffuse alopecia areata, methylprednisolone pulse therapy, 3 x 500 mg i.v. on 3 consecutive days, 3 times on monthly basis

M, 38-years old, 6 month clobetasol propionate under occlusion overnight 6 days/week

F, 12-years old, subtotal alopecia areata (ophiasis), 12 months DCP therapy (1.0%)

F, 43-years old, total alopecia (areata), 18 months, initialy methotrexate 30 mg weekly and prednisone 20 mg daily, tapered to methotrexate 15 mg weekly and prednisone 5 mg daily

F, 47-years old, autosuggestion therapy/visualization exercises, 12 months

Evidence-based medicine (EBM) is a relatively young discipline that aims to apply the best available evidence gained from the scientific method to clinical decision making.

Using techniques from science, engineering and statistics, such as
• the systematic review of medical literature
• meta-analysis
• risk-benefit analysis
• and randomized controlled trials (RCTs),

EBM aims for the ideal that healthcare professionals should make
• conscientious
• explicit
• judicious use of
• current best evidence in their everyday practice.
Ex cathedra statements by the medical expert are considered to be the least valid form of evidence. Nevertheless, knowledge gained from clinical research does not directly answer the primary clinical question of what is best for the patient at hand and suggests that EBM should not discount the value of clinical experience.

The influence of the prescribing physician should be kept in mind, since inspiring confidence versus scepticism and fear clearly impacts the outcome of treatment.

Treatment success relies on patient compliance that, on its part, relies on comprehension of treatment benefit, confidence, and motivation.

Trüeb RM. Role of EBM in Successful Trichological Practice. Hair India. 2nd International Congress of Trichology. Chennai, India, September 7-9, 2012
Prerequisites for Successful Treatment of Hair Loss

Psychological Level  Technical Level

Trüeb RM. Role of EBM in Successful Trichological Practice.
Hair India. 2nd International Congress of Trichology.
Chennai, India, September 7-9, 2012
For a successful encounter at an office visit, be sure that the patient's key concerns have been directly and specifically solicited and addressed!

• Acknowledge the patient’s perspective on her hair loss problem

• Recognize the psychological impact of hair loss, especially adjustment disorders with depressed mood, anxiety, and/or disturbance of conduct, somatic and/or sexual dysfunction, and feelings of guilt and/or obsession

• Explore patient’s expectations from treatment

• Educate patients into the basics of the hair cycle, and why patience is required for effective cosmetic recovery

Trüeb RM. Role of EBM in Successful Trichological Practice. Hair India. 2nd International Congress of Trichology. Chennai, India, September 7-9, 2012
Diagnosis:
- A diagnosis is prerequisite to treatment!
- Remain open-minded for the possibility of a multitude of cause-relationships underlying hair loss

Pathophysiological Understanding:
- Causal treatment wherever possible!
- Remain open-minded for the possibility of combined treatments and multitargeted approaches to hair loss
- Ultimately, in the elderly the problems of co-morbidities und multimorbidity must be taken into account

Evidence Based Medicine (EBM):
- Apply best available evidence gained from the scientific method to clinical decision making!
- Remember, GMP means integrating individual clinical expertise with best available external evidence from EBM

Regular Follow-Up:
- Standardized global photographic assessments
- Epiluminiscence microscopic photography

Trüeb RM. Role of EBM in Successful Trichological Practice. Hair India. 2nd International Congress of Trichology. Chennai, India, September 7-9, 2012
Ensuring Patient Compliance

**Treatment success** relies on patient compliance that, on its part, **relies on comprehension of treatment benefit, confidence, and motivation.**

A **positive physician-patient relationship** and **regular follow-up visits** are the most important factor in determining the degree of patient compliance.

Only recommend **treatments that are effective in circumstances they are required.**

The overall goal is to **gain short-term compliance as a prerequisite to long-term adherence to treatment.**

**Short term compliance issues** addressed by the physician **within the first three months of therapy** are: winning the patient’s confidence in the diagnosis and treatment plan, and detecting problems relating to the prescribed treatment regimen, or drug tolerance.

**Long term compliance issues** addressed **at 6, 12 months of follow up and thereafter** are: treatment efficacy and sustainability, long term toxicities, and treatment costs.
Ensuring Patient Compliance

Prescribing the minimum number of different medications, i.e., combining active ingredients into a single compound, e.g. 5% minoxidil 0.2% triamcinolone acetonide)

Simplifying dosage regimen by selecting different treatment or using a preparation that needs fewer doses during the day, e.g.


Selecting treatments with lower levels of side effects or fewer concerns for long-term risks

Discussing possible side effects, and whether it is important to continue medication regardless of those effects

Advice on minimising or coping with side effects

Regular follow-up for reassurance on drug safety and treatment benefits

Finally, patients should be aware of seasonal fluctuations in hair growth and shedding, at times complicating the assessment of pharmacological effects. Awareness of these fluctuations is prerequisite to providing the correct cause and prognosis to the patient, ensuring patient adherence to therapy.
Thank you for your attention!