Review of the 6th World Congress for Hair Research

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Dr. Bruno Bernard of L'Oreal.

The 6th World Congress for Hair Research was recently held in Cairns, Australia, under the chairmanship of Prof. Rodney Sinclair. It attracted 300 delegates from around the world, and was judged a great success. Highlights of the meeting were new elucidations of the myriad hormonal influences and transcription factors involved in the incredibly complex organ known as the hair follicle and new treatment directions. This Congress is held once every 3 years uniting the various regional hair research societies including the Australasian, Japanese, Korean, North American, and European. The following is a small selection of topics presented and excludes the countless fascinating posters on show.

Dr. Bruno Bernard introduced a new Equilibrium Theory regarding the hair cycle that involves a new phase (neogen) between telogen and anagen. He described a bi-stable system with phases of high activity (neogen and catagen) alternating with phases of low activity (telogen and anagen). He reminded delegates that there was much individual variation in the length of anagen phases in a single follicle.

Dr. Ralf Paus postulated that "Clock Genes" (originating in the hypothalamus) modulate cyclic organ regeneration in the hair follicle via TRH. These clock genes show a circadian rhythm and decreased clock genes create a prolonged anagen and increased melanin production. TRH prolongs anagen, modulates the clock genes, and decreases period 1 genes (again to prolong anagen). Any possible influence of TRH in male pattern balding and female pattern hair loss is still unclear. Astoundingly, recent evidence shows that the hair follicle is capable of producing every known human hormone!

Dr. Paus also stipulated that prolactin stimulates female fronto-temporal hairs but induces catagen in male occipital hairs. Both TRH and estradiol regulate intra-cutaneous prolactin, but it is unclear if it affects stem cell populations in the hair follicle. TRH does modulate epithelial stem cells.

The hair follicle, via a peripheral hypothalamic-pituitary-adrenal (HPA) axis, secretes cortisol for a negative feedback effect that also protects hair follicle immune privilege. The possible role of stress in up-regulating cortisol production was suggested as influencing the development of alopecia areata (AA) whereby AA might be seen to involve defective stress up-regulation by CRH. The role of stress in inducing telogen was also explained as involving nerve growth factor (NGF) and substance P in the dorsal root ganglia, which induces mast cell neurogenic inflammation and thereby inhibiting hair growth. Thyrotropin (TSH) proteins in the scalp are differentially regulated by TRH (increased) and T3 and T4 (decreased), but this does not change hair growth or pigmentation in the follicle. Dr. Paus also emphasized that vitamin D3 affects hormone regulation and maintains cycling in the hair follicle. He postulated that vitamin D might increase conversion of T4 to T3.

It was pointed out that the stimulatory effect of estradiol treatment was dose dependent and that finasteride increases estradiol by 10% via increased aromatase conversion. In addition, aromatase has a different expression in occipital versus frontal scalp hair follicles. Beta estrogen receptors occur in the hair follicle and, interestingly, there are decreased beta estrogen receptors in the occipital scalp of both men and women. Angiotensin 1 and 2 receptors occur in the skin and this raises the possible effectiveness of angiotensin receptor 2 blockade via spironolactone in preventing follicular fibrosis and hair loss.

Dr. George Cotsarelis stated that bald scalp lacks progenitor cells (CD 34+), but that stem cells are intact. This suggests that balding might involve a defect in stem cell activation. Various factors such as TGFβ1 and interleukin-8 are stimulated by androgens in balding dermal papilla (DP) cells, but interleukin-6 is over-expressed in balding DPCs and is induced by dihydrotestosterone (DHT), thereby inhibiting hair shaft elongation and inducing catagen.

First session chairs, Drs. Nilofer Farjo and Kurt Stenn.

Dr. Rodney Sinclair showed computer-generated 3-D reconstructions of the arrector pili muscle demonstrating that, contrary to classical drawings, a single arrector pili (AP) muscle may serve 2-5 follicles within a follicular unit. He pointed out that no histological evidence existed of arrector pili musculature in severely miniaturized hairs. He suggested that miniaturized hairs drift away from the AP and that separation from the AP is the point of no return for hair re-growth potential, while in alopecia areata for instance, the muscle maintains its proximity to the hairs possibly explaining its reversibility. He also suggested there were primary and secondary follicles in the follicular unit with the primary hair follicle the last to drift. Dr. Sinclair also speculated that the AP might be a reservoir for DP cells as well as cytokines and hormones, and may thereby have a role in hair follicle homeostasis. He also raised the possibility that nerve endings in the AP muscle might be involved in the "pain" sometimes associated with hair loss. Alternatively, this pain could be explained by the inflammation Whiting found to be present in 10% of cases of androgenetic alopecia.

Dr. Pratima Karnik and others from a Vera Price group noted through gene expression profiling that there are similarities between lymphocytic and neutrophilic cicatricial alopecias. There is a shared decrease in cholesterol biosynthesis raising the idea for new treatments. There is also upregulation of TGFβ.

Dr. Elise Olsen addressed the subject of central centrifuging cicatricial alopecia (CCCA), a condition almost exclusive to Blacks and in particular women. A 9-centre pilot study identi-

An update on the pathophysiology of female pattern hair loss

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Introduction

There is an ontological and hormonal sensitivity hierarchy within a follicular unit that is observed in certain mammals. In general terms, ontology is the hierarchical organisation of knowledge about beings and things by subcategorising them according to their essential qualities.

The concept of the follicular unit in humans was first described by Headington in 1984 with the observation that in-utero central primary follicles are surrounded by smaller secondary follicles. The follicular unit, rather than single-hair transplantation, has become the dominant hair transplant method due to higher survival rates of grafted hairs with such a technique. Hair transplant surgeons have long observed that women commonly lack adequate donor tissue and indeed miniaturization is also observed in occipital scalp of females affected with androgenetic alopecia. Recently it has been suggested that the Ludwig pattern of androgenetic alopecia is due to a hierarchy of androgen sensitivity within follicular units that leads to selective miniaturization and a reduction in the terminal hairs per follicular unit. The concept of primary and secondary follicles and hierarchy within a follicular unit observed in the animal kingdom deserves further attention in humans. It appears to be relevant both from a pathophysiological and a therapeutic point of view.

Discussion

Androgenetic alopecia is the most prevalent form of hair loss affecting men and women. The presentation of this condition differs in males and females with diffuse hair thinning over the crown, widening of the central part and preservation of the frontal hairline in the latter. Lack of involvement of occipital scalp is considered to be one of the clinical signs that characterises this condition. The role of androgens in the pathogenesis is clearly established in male androgenetic alopecia but not fully understood in female pattern hair loss (FPHL). Factors other than androgens may also play a role in its pathogenesis.[1,2]

Ontological Hierarchy in Mammals

Ontological hierarchy of follicles and hormonal influences other than androgens on seasonal growth patterns of fibre follicles in animal species have been extensively studied.[3,4] Investigations on small seasonal species such as ferrets[3] and mink[4] have revealed that seasonal variation in pelage density is attributed to development and regression of compound follicles. A compound follicle is the single original follicle that develops first from which smaller, derived follicles are formed by branching morphogenesis. Variations in pelage density are due to variations in the numbers of these derived follicles that grow finer, shorter fibres.[3]

Development of wool follicles is similar in sheep.[5] First to develop are the primary follicles, followed by the secondary follicles and the secondary derived follicles that form by branching off from the secondary follicles. The primary follicle has a typical trio pattern with a central primary follicle and two lateral primaries. The identifiable features of the trio include attachment of arrector pili muscle to the outer root sheath and presence of characteristically large sebaceous glands. A distinguishable cluster forms with development of secondary follicles in close association with the primary follicle. Ovine follicle population density is determined by the secondary derived follicles, which are essentially branches of the secondary follicle and form the bulk of the fleece.

Role of Melatonin and Prolactin on Pelage Growth Cycles

Cyclical activities of the hair follicle are the way by which mammals modify their coat of hair to meet seasonal and environmental changes. Seasonal variations in the pelage growth cycles of small mammals have been studied in a number of different species. It is believed that the timing of the fibre growth cycles is sensitive to the length of the photoperiod, thought to be mediated by melatonin secreted from the pineal gland. It is the detection of decreasing day length via the retina rather than temperature changes that controls the pelage growth. In ferrets, interference with photoperiodic and hormonal control mechanisms have been shown to affect the pelage growth cycles, inducing earlier winter fibre growth in response to exogenously administered melatonin.[3] Similar findings have also been described in the winter fur growth in mink.[4]

Another important hormone regulating pelage growth cycles in mammals is prolactin.[6] Animal models, especially studies performed on seasonal breeds of sheep, have demonstrated that increased levels of prolactin in the spring is associated with induction of telogen follicles and a declining level of prolactin in autumn induces regrowth of winter pelage. Prolactin surges may also be linked to entry of follicles into catagen, as seen in Wiltshire sheep breeds in late spring. This means that prolactin has multiple effects on follicle growth, which could be explained by the observation that prolactin receptors are present in the dermal papilla, matrix, and outer root sheath, and that these cycle-dependent prolactin actions could be controlled by the different follicular cell populations where the prolactin receptors are located.

This concept of seasonal variation in hair growth and shedding has also been observed in humans.[7] Kunz et al. suggested through their large retrospective case study of over 800 healthy women with hair loss (with or without FPHL) that annual periodicity in the human hair growth and shedding does exist, with maximal proportion of telogen hairs in summer and lowest proportion in winter. The role of hormones in the seasonal variations in human hair growth is unclear at this stage. These findings indicate a potential to complicate the assessment of pharmacological effects.

Selective Miniaturization of Follicles in FPHL

In humans, hair follicle organisation resembles the ontological hierarchy of follicles seen in sheep and other small mammals. Human hair follicles exist within follicular units (Figure 1). A follicular unit typically consists of a larger, central primary follicle surrounded by smaller secondary follicles.[8] A single arrector pili muscle is predominantly attached to the primary follicle with variable attachment to secondary follicles (Figure 2). Yazdabadi et al. provide an additional explanation for the diffuse

hair loss pattern seen in females with the Ludwig pattern of androgenetic alopecia, which is not observed in male pattern baldness.[8] They suspect an increased susceptibility of secondary follicles to androgen-sensitive miniaturization to vellus hairs and demonstrate that in these patients the diffuse hair thinning is due to reduction in the number of terminal hairs per follicular unit rather than miniaturization of entire follicular units. Also, it is thought that not all hair follicles within a follicular unit have the same susceptibility to androgen-induced hair follicle miniaturization, with secondary follicles changed into vellus hair follicles first.[8] Indeed, it is the experience of the authors that females may present much earlier to a dermatologist complaining of reduction of the volume of the ponytail with no other clear signs of androgenetic alopecia. With further progression, the primary follicle may be miniaturized and this would lead to the development of bald patches as in male androgenetic alopecia.

Figure 1. Trichoscope photograph showing follicular units.

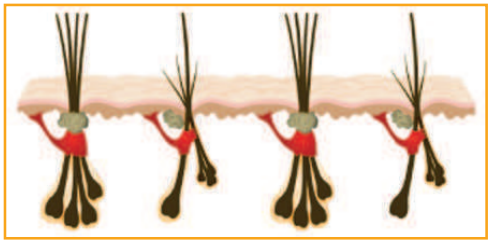

Figure 2. Illustration of follicular units and the variable attachment of arrector pili muscle to secondary follicles.

The traditional concept of sparing of the occipital region in FPHL can also be challenged. Contrast-enhanced phototrichogram techniques have demonstrated that physiologically there is reduced hair density at occipital sites compared to the top of the head.[9] Although FPHL is thought to be confined to the top of the scalp, histopathology[10] and phototrichogram[11] findings suggest that occipital scalp may also be affected. Because of poor donor hair density over the occipital scalp, many women are not suitable for hair transplantation.[2,12]

Summary

The concept of primary and secondary follicles and hierarchy within a follicular unit observed in the animal kingdom appears relevant to clinicians from the pathophysiological point of view. It may explain differences in clinical patterns in females versus males with androgenetic alopecia, and it provides additional explanation for the earlier presentation to a dermatologist of female patients. It may also explain why contrary to the previous notion there is also involvement of the occipital scalp and why women are less suitable candidates for hair transplantation due to poor donor areas. The mechanism for this selective miniaturization deserves further attention. In androgenetic alopecia, there is progressive shortening of the duration of anagen phase leading to progressive shortening of terminal hairs and decrease in the total size of the follicle; together both processes combine to replace the long terminal hairs with short, fine vellus hairs. The vellus hairs lack an associated arrector pili muscle. Further understanding of the relationship between primary follicle and the arrector pili muscle may provide clues to this selective and potentially irreversible miniaturization.

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Editors' note: Several years ago at an ISHRS meeting, Dr. O'Tar Norwood first controversially raised the debate on female pattern hair loss as a different entity to male pattern hair loss. In the intervening years it has become more or less accepted that this is in fact the case. The article above proposes a new theory behind female genetic hair loss that may help to explain the difference in patterns that we see in women, and perhaps this understanding will help us in our strategy of treating these patients. The article also demonstrates some of the potential benefits that can be derived from hair follicle research in different animal species. The Hair and Wool Research Society is particularly prominent in Australia and New Zealand, and here we see how this has benefited our understanding of some of the mechanisms involved in hair follicle behaviour. In July 2010, Dr. Sinclair presented this research in his keynote address at the International Hair Research Society meeting in Cairns, Australia.◆

Letters to the Editors

Francisco Jimenez, MD *Las Palmas, Spain*
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Enrique Poblet, MD *Albacete, Spain*

Re: Pathophysiology of female pattern hair loss

We have read with great interest the article by Patel, Perez, and Sinclair on the pathophysiology of female pattern hair loss.[1] The hypothesis of a hierarchical organisation of human follicles into primary and secondary follicles is daring and intriguing, but difficult to reconcile with our current knowledge of the anatomy of the follicular unit.

We would like to add the following comments:

1. In one part of their article the authors state that a *"follicular unit typically consists of a larger, central primary follicle surrounded by smaller secondary follicles."* We, as hair transplant surgeons, are used to dissecting thousands of hair follicles and have not noticed such an arrangement. Is it possible that this hierarchical arrangement would be noticeable only at an optical microscopic level? If that is the case, it is important that the authors clarify the histomorphological criteria that they are using to classify a follicle as primary or secondary. Is there any morphometric data (measurements) data available?
2. In the second paragraph of their article, it is stated that *"the concept of the follicular unit in humans was first described by Headington in 1984 with the observation that in utero central primary follicles are surrounded by smaller secondary follicles."* Unless the authors are referring to a different paper, in his seminal article published in the *Archives of Dermatology,* Headington described the follicular unit after analyzing transverse (horizontal) sections of human adult scalp biopsies.[2] As far as we know, Headington did not observe the existence of a primary and secondary follicles, but rather defined the follicular unit as a *"well-circumscribed structure composed of two to four terminal follicles, and one or, rarely, two vellus follicles, the associated sebaceous lobules, and the insertions of the arrector pili muscles."* Needless to say, primary and secondary follicles should not be confused with terminal or vellus follicles.
3. We share with the authors a special interest in the anatomy of the arrector pili muscle and its relationship with the hair follicles. In 2002, we published an anatomical drawing of the arrector pili muscle as a single muscular unit that divides into branches that are finally inserted into each of the follicles contained in the follicular unit.[3] Before that paper, the arrector pili muscle had always been drawn and represented as a single muscle attached to a single follicle, and not as a single unit associated with a single follicular unit. Our anatomical model was basically confirmed by the works of Song, et al., using a three-dimensional reconstruction.[4] Patel, et al. note that *"as terminal hairs miniaturize into vellus hairs, they lose their arrector pili muscles."* As we did not look into the anatomy of arrector pili muscles in vellus follicles, this is a question that interests us greatly. We would like to know if the authors could show photomicroscopic evidence of this fact (disappearance of the arrector pili muscle as the terminal hair miniaturizes into vellus hair) or whether perhaps there is a paper on this subject pending publication.

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Re: Response to Jimenez/Poblet

We thank Drs. Francisco Jimenez and Enrique Poblet for their comments relating to our article on the pathophysiology of female pattern hair loss.[1]

We would like to respond to their comments:

1. The hierarchical arrangement of hair follicles in humans is inferred from that seen in other mammalian species (Figure 1). Histomorphological criteria or markers to classify human follicles into primary and secondary hair follicles have not been identified.

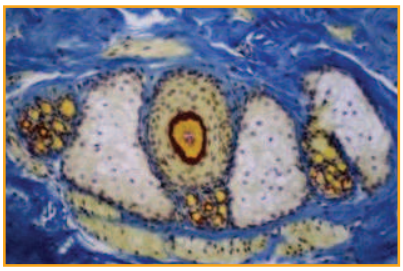

Figure 1. Photograph showing a compound follicular unit in a goat with a single large primary follicle and multiple smaller secondary follicles.

2. We stand corrected. The observation that, in utero, hair follicles grow in groups of three or more, with a central primary follicle surrounded by smaller secondary and tertiary follicles, was made by Montagna, et al. in their illustration (Figure2) and not Headington as we suggested. Indeed, Headington defined the follicular unit as a "well circumscribed structure composed of two to four terminal

Figure 2. Illustration showing developing groups of hair follicles with each group consisting of a primary follicle (P) surrounded by secondary follicles (arrows)

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Expanded Newcomers Program set for 2011 ISHRS annual meeting

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I am very excited to chair the Expanded Newcomers Program, a unique offering in Anchorage this year. This event exemplifies one of the founding tenants of our Society, which is to welcome colleagues from all specialties to participate in the world's premier educational conference in the field of hair restoration surgery. Since its inception in 1993, the ISHRS offers its members an opportunity to create and grow friendships that can last throughout one's lifetime.

And…it all begins at the Newcomers Reception!

How It Works

This program is designed to help our newest ISHRS meeting attendees become acquainted with the Society, its members, and the field. "Newcomers" will be paired with volunteer member "hosts" prior to the meeting. We encourage longstanding members to sign up as hosts. All physician and surgical assistant registration types may participate in the program. We expect that non-members who wish to participate for the longer term program apply for membership.

New, Expanded Program

In its third year, the Newcomers Program is expanding its role into an informal mentorship relationship intended for a term of 2 years. This longer period of time will allow the new person to ask questions and become more closely acquainted with the Society, its members, and the field. In addition, the Host may allow the Newcomer to visit his or her practice.

Active Members

If you plan to attend the Anchorage meeting, please consider signing up! Active members will be paired with 2-3 Newcomers. The plan is that your Newcomers will also meet and talk with each other, sit together, and hang out at the meeting.

Guidelines

1. Host contact the Newcomer prior to the meeting and answer questions.
2. Host and Newcomer must attend the Newcomers Orientation & Reception on Wednesday/September 14, 2011, 5:30PM–6:30PM, Quarter Deck, Hotel Captain Cook, Anchorage, Alaska. Meet and greet!
3. Host and Newcomer check in with one another; sit together during opening session.
4. Host and Newcomer communicate with each other throughout a 2-year term via email, phone, or face-to-face. Newcomers are encouraged to email and call their host with questions or for advice regarding hair restoration surgery matters.
5. Neither the Host nor the Newcomer may claim that they "trained" as a result of this Host-Newcomer relationship. Neither may advertise this relationship in their promotional materials, on their website, or in their curriculum vitae.

During the registration process, please select the option (Newcomer or Host) if you would like to sign up for this program.

If you have any questions, please contact Liz Rice-Conboy at ISHRS Headquarters, info@ishrs.org, or me at hairdr@pol.net. We shall be in contact with you once you sign up for the program.

See you in Alaska!◆

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follicles, and one or, rarely, two vellus follicles, the associated sebaceous lobules, and the insertions of the arrector pili muscles."[2]

3. We do have a paper in press on the anatomy of the arrector pili muscle and its relationship with the hair follicle that shows loss of contact of AP muscle with miniaturised hair follicle within a follicular unit (Yazdabadi, A., et al. Miniaturized hairs maintain contact with the arrector pili muscle in alopecia areata but not in androgenetic alopecia: A model for reversible miniaturization and potential for hair regrowth).

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