Aging Hair
“Aged? But he does not appear aged, just look, his hair has remained young!”

Marcel Proust, In Search of Lost Time (1913–27)

The appearance of hair plays an important role in peoples’ 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 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 such as minoxidil and finasteride also 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 the one hand, the esthetic 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, and molecular changes, in other words the “secret life” of the hair follicle in the depth of the skin.

Hair aging comprises hair shaft aging, and aging of the hair follicle. The former involves weathering and photoaging of the hair shaft, while the latter manifests as decrease of melanocyte function (graying) and decrease in hair production (alopecia). The scalp and hair are subject to intrinsic or physiologic aging, and extrinsic or premature aging due to external factors. Intrinsic factors are related to individual genetic and epigenetic mechanisms with interindividual variations. Prototypes are familial premature graying and androgenetic alopecia. Extrinsic factors include ultraviolet radiation, air pollution, smoking, and nutrition.

Finally, 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. Ultimately, a number of intrinsic and extrinsic modulating factors for hair growth and pigmentation have been identified and are being further tested. Current lines of research and future directions for therapeutic interventions are gene polymorphism diagnostics, the hair follicular route for targeted delivery of active compounds affecting the hair, stem cells of hair follicular origin, and tissue engineering of the hair follicle.

This monograph attempts to provide an up-to-date overview regarding all aspects of hair aging. It includes in-depth contributions from internationally recognized experts on the biologic basis as well as on current concepts for the diagnosis, treatment, and prevention of hair aging.

Zürich, Switzerland

Bradford, UK

Prof. Ralph M. Trüeb

Prof. Desmond J. Tobin
Aging from Where to There?

Hair is part of the appearance of oneself as it is perceived by oneself and by others. The most remote representation that could be traced dates back around 30,000 years and the story is still ongoing in our society (Fig. 1; [1, 2]).

Figure reprocessed with permission from [1, 2]

In the early days, differences of hair patterns between species and between individuals within the same species (patterns, colors, length...) as well as dynamic changes of patterning (seasonal variations of hair coat, the fluctuations of hairiness during maturation...) reflect another scale of time and are part of a biological process that has been called “aging.”

Human intervention has long been limited to representation, cutting, and sculpturing the mass of hair by physical removal of fibers. Some centuries ago, these aspects of hair care were exclusively privileged professional activities sometimes overlapping with medical/surgical practice. While styling and hair care modalities became – rather recently – part of personal care along with beauticians’ and hairdressers’ facilities, the biological and medical aspects became more and more part of the dermatological field of expertise, including all sciences associated with it (surgery, bioengineering, biology, biochemistry, physics, mathematics, etc.).
As hair and the hair follicle became a material for scientific observation, renewed interest is proposed in this book regarding the phenomenon of aging. Clearly, the arrow of time can be measured with various parameters. The exceptional regenerative properties of the hair follicle may lead to discoveries that are unsuspected by the scientific community as many keep a superficial understanding of the visible part of the iceberg: hair!

Let me give just one example taken from Bartholyn’s book on anatomy. In 1658, hair was thought to be an excretory process for elimination of “bad bloody humors.” One of the scientific arguments was that females after the arrest of menstruation grew beards. As those bloody humors had to find a way, the mechanistic interpretation was wrong, but it may still be considered as an appropriate clinical observation related to the field of endocrinology. Hence more recently better documented links were made between hormones (humors?) and the hair follicle productivity!

As usual, it took a long time between the accurate clinical observation and the proper understanding and scientific demonstration of a biological process underlying the expression of a clinical phenotype. It is to be hoped that this book will become a milestone to help anyone interested in hair and in aging leading to new avenues for a better understanding of the hair follicle biology during aging.

Top row of the figure shows four drawings were taken from wall engravings in a prehistorical cave. It took about 30,000 years in order to categorize patterned hair loss in males, shown in the bottom row. Most clinicians appreciate this as “progress” and use it daily in the hair clinic, but many agree that it is not sufficient when time-related changes are to be measured.

The arrow of time plays a major role in this chronic regressive process that affects the function and structure of the hair follicle. During the past 50 years and along with time, many steps involved in this process have been unravelled including but not limited to genetic predisposition, proper secretion of hormones, transport, metabolism, fixation on specific receptors, and translation in the cell nucleus of these hormones.

More research specifically devoted to aging will undoubtedly clear-up the hair-scene in the near future.

Prof. Dominique van Neste
Skinterface
Tournai, Belgium

References

Editors

Ralph M. Trüeb is Professor of Dermatology at the Department of Dermatology, University Hospital of Zurich, Switzerland, and currently President of the European Hair Research Society. His interests include hair and hair diseases, hair ageing, environmental factors and inflammatory phenomena in alopecia, patient expectation management and psychocutaneous disorders of hair and scalp. He is currently author of 145 peer-reviewed scientific publications and three textbooks on hair.

Desmond J. Tobin is Professor of Cell Biology and Director of the Centre for Skin Sciences (CSS) at the University of Bradford. He also severs in Faculty as Associate Dean for Research and Knowledge Transfer. He works on the basic and applied science of skin and hair follicle pigmentation, immunologic disorders of the hair follicle, hair growth and hair growth inhibition. He is a former board member of the European Hair Research Society and executive editor of the International Journal of Trichology. He has published widely with over 130 publications, edited including books.
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Contributors

Elisabeth Carpenter  Centre for Skin Sciences, School of Life Sciences, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK
e.carpenter1@bradford.ac.uk

Thomas L. Dawson  Beauty Technology Division, The Procter & Gamble Company, 11810 East Miami River Road, Cincinnati, OH 45252, USA
dawson.tl@pg.com

Zoe Diana Draelos  2444 North Main Street, High Point, NC 27262, USA
zdraelos@northstate.net

Justine A. Ellis  Department of Physiology, The University of Melbourne, Melbourne, VIC 3010, Australia
justine@unimelb.edu.au

Andreas M. Finner, MD  Trichomed Hair Medicine and Hair Transplantation, Bayreuther Str. 36, 10789 Berlin, Germany
info@trichomed.com

Brian K. Fisher  P&G Beauty, 11810 East Miami River Road, Cincinnati, OH 45252, USA
fisher.bk@pg.com

Desmond Gan  St. Vincent’s Hospital, PO Box 2900 Fitzroy, Melbourne, Victoria, Australia
drdesmondgan@gmail.com

Robert M. Hoffman  AntiCancer, Inc., 7917 Ostrow Street, San Diego, CA 92111, USA
all@anticancer.com

Jen-Chih Hsieh  Aderans Research Institute, Inc., 3401 Market Street, Philadelphia, PA 19104–3318, USA
jchsieh@aderansresearch.com

Pratima Karnik  Department of Dermatology, Case Western Reserve University, Biomedical Research Building – 2109 Adelbert Road, Cleveland, OH 44106, USA
Psk11@case.edu

Steven Kossard  Skin and Cancer Foundation Australia, 277 Bourke Street, Darlinghurst, NSW 2010, Australia
skossard@scfa.edu.au
Contributors

Won-Soo Lee  Department of Dermatology, Yonsei University Wonju College of Medicine, 162 Ilsan-Dong, Wonju, Kangwon-Do, 220-701, Republic of Korea
leewonsoo@yonsei.ac.kr

James Li  P&G Beauty, 11810 East Miami River Road, Cincinnati, OH 45252, USA
li.jx@pg.com

Fangyi Luo  P&G Beauty, 11810 East Miami River Road, Cincinnati, OH 45252, USA
luo.f@pg.com

Andrew G. Messenger  Department of Dermatology, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF, UK
a.g.messenger@sheffield.ac.uk

Paradi Mirmirani  Department of Dermatology, The Permanente Medical Group, 975 Sereno Drive, 2nd Floor, Hallway F, Vallejo, CA 94589, USA
University of California, San Francisco, CA, USA; Case Western Reserve University, Cleveland, OH, USA
paradi.mirmirani@kp.org

M. Javed Mohungoo  Department of Dermatology, Royal Hallamshire Hospital, Sheffield, S10 2JF, UK
javedmohungoo@hotmail.com

John Oblong  P&G Beauty, 11810 East Miami River Road, Cincinnati, OH 45252, USA
oblong.je@pg.com

Nina Otberg  Department of Dermatology and Skin Science, University of British Columbia, 835 West 10th Avenue, V5Z 4E8, Vancouver, Canada
Skin and Lasercenter Potsdam, Hair clinic, Bertinistr. 4, 14469 Potsdam, Germany
ninaotberg@gmx.com

Nikolaos Papageorgiou  Centre for Skin Sciences, School of Life Sciences, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK
spesaeterna@gmail.com

Eva M. J. Peters  Department of Internal Medicine, Biomedical Research Center, Charité, Campus Virchow Hospital, Augustenburger Platz 1, 13353 Berlin, Germany
frl.peters@yahoo.com

Gérald E. Piérard  Department of Dermatopathology, University Hospital of Liège, CHU Sart Tilman, 4000 Liège, Belgium
gerald.pierard@ulg.ac.be

Claudine Piérard-Franchimont  Department of Dermatopathology, CHU Sart Tilman, 4000 Liège, Belgium
claudine.franchimont@ulg.ac.be
Pascale Quatresooz  Department of Dermatopathology, CHU Sart Tilman, 4000 Liège, Belgium
pascale.quatresooz@chu.ulg.ac.be

Valerie A. Randall  Centre for Skin Sciences, School of Life Sciences, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK
v.a.randall@bradford.ac.uk

Isabel Restrepo  University CES, Department of Dermatology, Calle 10 A No. 22 - 04, Medellin, Colombia, South America
irestrepo@uces.edu.co
Department of Dermatology and Skin Science, University of British Columbia, 835 West 10th Avenue, V5Z 4E8, Vancouver, Canada

Jerry Shapiro  Department of Dermatology and Skin Science, University of British Columbia, 835 West 10th Avenue, V5Z 4E8, Vancouver, Canada
Department of Dermatology, New York University Medical School, New York, NY 10016, USA,
jerry.shapiro@vch.ca

Rodney Sinclair  University of Melbourne, St. Vincent’s Hospital, Skin and Cancer Foundation, PO Box 2900, Fitzroy 3065, Australia
sinclair@svhm.org.au

Kurt S. Stenn  Aderans Research Institute, Inc., 3401 Market Street, Suite 318, PA 19104, Philadelphia, USA
kstenn@aderansresearch.com

Desmond J. Tobin  Centre for Skin Sciences, School of Life Sciences, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK
d.tobin@bradford.ac.uk

Ralph M. Trüeb  Department of Dermatology, University Hospital of Zürich, Gloriastr. 31, 8091 Zürich, Switzerland
ralph.trueeb@usz.ch

David A. Whiting  Baylor Hair Research and Treatment Centre, 3600 Gaston Avenue, #1051, Dallas, TX 75246, USA
whiting@hairskinrtc.com

Andrew S. Wilson  Division of Archaeological Sciences, School of Life Sciences, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK
a.s.wilson2@bradford.ac.uk

Scott R. Youngquist  P&G Beauty, 11810 East Miami River Rd, Cincinnati, OH 45252, USA
youngquist.rs@pg.com

Ying Zheng  Aderans Research Institute, Inc., 3401 Market Street, Philadelphia, PA 19104, USA
yzheng@aderansresearch.com
1.1 Introduction

The function of scalp hair for humans is invested mostly in its value as a communication device or signal, and so together with epidermal pigmentation the hair fiber-producing mini-organ accounts for most of the phenotypic variation between different human subpopulations. Nature has made an enormous investment in the hair follicle, and as one of only two

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D. J. Tobin
Centre for Skin Sciences, School of Life Sciences, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK
e-mail: d.tobin@bradford.ac.uk

The word “gerontology” is familiar to most of us as a term that captures the study of the social, psychological, and biological aspects of aging. However, its derivative “gerontobiology” as applied to the hair follicle is more concerned with the latter aspect – the biology of aging in the hair follicle mini-organ. As with any complex multicellular tissue system, the hair follicle is prone to broadly similar underlying processes that determine the functional longevity of organs and tissues. No matter how complex the tissue system is, it will contain cells that eventually lose functionality, reproductive potential and will ultimately die.

The hair follicle is somewhat unusual among mammalian tissues in that it is a veritable histologic mélange of multiple cell types (e.g., epithelial, mesenchymal and neuro-ectodermal) that function contemporaneously in all stages of their life histories e.g., stem cells, transit-amplifying cells, and terminally differentiating cells. Some of these interactive cell systems appear to be nonessential for overall hair follicle survival (e.g., melanocytes). However, strikingly graying hair follicles may grow even more vigorously than their pigmented predecessors. Moreover, the hair follicle is unique in the adult mammal in that it follows a tightly regulated script of multiple lifelong cycles of cellular birth, proliferation, differentiation, and death. Powerful evolutionary selection ensures that the hair follicle is, in the main, hardwired against significant aging-related loss of function, even after 12 or more decades of life – although some would argue with this view, if only on purely cosmetic grounds.

Processes underlying aging in general, e.g., oxidative damage, telomere shortening, age-relating deficiencies related to nuclear/mitochondrial DNA damage and repair as well as age-related reductions in the cells’ energy supply, will all impact on whether some follicular cell subpopulations will enter cellular senescence. This chapter will focus on how gerontobiology of the hair follicle may impact on certain aspects of hair fiber phenotype.
uniquely mammalian traits (in addition to mammary glands) serves several important functions for most other mammals. These include thermal insulation, camouflage, social and sexual communication (involving visual stimuli, odorant dispersal etc.), sensory perception, and protection against trauma, noxious insults, insects, etc. Because of our relative nakedness most attention and study is focused on scalp hair that, uniquely amongst primates, can be very thick, very long, and very pigmented. Thus, it is not surprising that its absence especially from the human scalp can result in significant psychologic trauma [14], e.g., in cases of androgenetic alopecia, alopecia areata, and chemotherapy-induced alopecia. Our ancient psychologic preoccupation with hair is further heightened today as our increasing longevity inevitably fuels our desire to extend youthfulness, where hair fiber density, texture, length and color all drive the unrelenting growth of the hair-care market, already a multibillion euro enterprise worldwide (Euromonitor).

Human hair growth can be distinguished from that in most other mammals by its rather mosaic pattern of hair follicle activity; we have all but lost our ability to grow hair synchronously or as a wave. Instead, each hair follicle has significant autonomy for growth and pigmentation. The hair bulb exhibits the body's second highest rate of cellular proliferation (after hematopoietic and intestine tissue), and can still produce functional fibers right up until our last and oldest days of life – even if this extends beyond 12 decades.

1.2 Biologic vs. Chronologic Aging

Although humans have between 3 and 5 million individual hair follicles on their bodies, most attention be it academic or commercial is focused on the paltry 2% of these that are distributed on our scalps [37]. In fact, our “naked ape” moniker derives from the fact that the great majority of the other 4.9 million hair follicles produce only the finest of hair fibers. This diversity reflects, in part, the enormous differences in the time interval which hair follicles from different body sites spend in the growing phase of the hair growth cycle. The finest and shortest hairs spend only days to a few weeks in the anagen growth phase, while some scalp hairs can grow continuously for up to three decades to produce hair fibers of more than 4.6 m in length – all in a single although highly extended anagen phase! This biological variety of hair growth pattern complicates any discussion of hair follicle gerontology, as it draws immediate focus onto the hair follicle’s relative proliferative and regenerative potential invested largely in its complement of stem cells. In addition, the local environment of the hair follicle can influence its behavior, and here too the human body exhibits considerable variation. Take for example hair follicle density in different body regions. An approximation for an adult Caucasian is: adult cheek skin (880 ± 60 HF per cm²); forehead: 770 ± 60 HF per cm²); forearm: 100 ± 50 HF per cm²); upper arm: 40 ± 10 HF per cm²) [12]. Thus the cheek contains more than 20 times more hair follicles per unit area that the upper arm.

Against a backdrop of such hair growth diversity are the additional contributions made by race and ethnicity, sex, climate and season, hormonal status, nutrition etc. One needs to take these factors into consideration before deducing underlying abnormality or before conflating biologic and chronologic aging factors. For example, the observation that males castrated before puberty do not go bald (does this impact on hair senescence?) or grow beards (does this impact on hair follicle maturity?) and the subsequent confirmatory finding that these individuals did so upon treatment with testosterone, indicates a role of androgens in hair growth [15]. But do these changes really reflect aging in action, either accelerated or retarded?

1.3 Variation in Hair Types During the Life of a Hair Follicle

The hair follicle produces several different types of hair fiber during a normal lifetime; represented by fine unpigmented lanugo hair in the fetus/neonate, short (mostly unpigmented) vellus hair or fine pigmented intermediate hairs during childhood, and long thick terminal hair shafts in several body sites in the adult. It is worth emphasizing that such modulation of hair fiber form from the relatively long, downy and variably pigmented hairs (lanugo) before birth to almost imperceptible colorless fibers (vellus) after birth, to coarse terminal hairs of phenomenal length (up to 4 m) all appear to occur within the same single hair follicle. Indeed, terminal hairs can be as abrasive as copper wire at certain cut lengths. This is, in my view, even more impressive than the striking range of hair types
characteristic of other species, e.g., vibrissae, tylotrich, zigzag, achenes of mouse skin. In the latter mammal current data suggest murine hairs are each produced within their predetermined hair follicle subtypes [8]. Moreover, there is much clinical evidence of transformations between different forms of hair fiber produced by a single human follicle during the life of an individual in both health and disease.

1.3.1 Lanugo-to-Vellus Hair Follicle Transformation

Even before we are born our hair follicles have already produced two different types of hair fiber in utero. Lanugo hair is the first of these (produced during month 3–7) and is characterized by long pigmented unmedullated and silky hair. The exact function of lanugo hair during intrauterine life is unclear, though it is possible that this is related at least in part with the production of the vernix caseosa and additionally may be involved in the removal of toxic substances from the developing fetus – as this rapidly growing skin tissue produces millions of hair fibers that are usually shed en masse in a synchronized manner around month 7–8 of gestation. Thereafter these same follicles engage in the production of a much finer, shorter, variably medullated and less-pigmented hair fibers (so-called vellus hair), which are also shed en masse usually during the fourth month of extrauterine life. Before this second “molt” the entire surface of the neonate, with the exception of the scalp and eyebrows, is covered with short and very fine unpigmented vellus hairs. The third generation of hair to be produced by hair follicles in humans switches to a more mosaic pattern of hair cycling, where significant autonomy is invested in the individual hair follicle. It should be noted here however, that partial resynchronization of human hair follicles can be induced later by systemic extra-follicular stimulation including via endocrine factors etc. at different stages of life e.g., during pregnancy [23].

Hair fiber form can also to revert from vellus to lanugo in the adult. For example, acquired hypertrichosis with lanugo-like hair may be associated with an underlying neoplasm (mainly lung and colorectal cancer), so-called paraneoplastic hypertrichosis lanuginosa acquisita [4, 31]. Furthermore, reversion to lanugo-like body hair is one of several dermatologic signs in patients with eating disorders [34]. These cases highlight the extreme difficulty in applying general gerontobiologic scenarios to hair follicle aging, as the hair follicle appears to be able to “reinvent” itself regardless of the chronologic age of the individual. Congenital universal hypertrichosis (e.g., Ambras syndrome) represents a rather dramatic human phenotype where the sequence of hair type usually associated with normal development and growth is disrupted.

1.3.1.1 Congenital Universal Hypertrichosis

Recently interest in the life history of single hair follicles has focused on changes that occur in Ambras syndrome and other congenital hypertrichotic conditions. These have illuminated how the early hair follicle, formed during embryogenesis in the womb, may fail to correctly follow the usual transformational script from lanugo to vellus hair during the transition from intrauterine to extrauterine life. In this syndrome there appears to be a block on the normal shedding of lanugo hair from the hair follicle at around 7 months of gestational age [26]. Instead the child grows up with facial and body hair that can be very long and pigmented, although still mostly silky in texture. Affected individuals may have additional minor facial anomalies (dimorphism) or abnormalities of teeth, e.g., slower or even absent dentition. A further interesting feature of this disorder is the absence of any endocrine/hormone abnormality. The syndrome was first described in 1993 by Baumeister [2] and its multiple affected relatives suggest a genetic basis. Studies have recently implicated a chromosomal anomaly involving a breakpoint defect in the q22 region of chromosome 8. These data suggest that this region on chromosome 8 contains a gene that is disrupted in Ambras syndrome. Cases that have received cytogenetic analysis have shown at least a chromosomal inversion, though others additionally show an insertion and a deletion in addition to the inversion [11]. There remains some debate regarding the exact nature of genetic alteration required for a diagnosis of Ambras syndrome.

For most individuals however, the dramatic age-related change in hair form (excluding loss of hair color and loss of the hair itself) results from so-called hair follicle transformations after birth [17, 32, 36].
1.3.2 Vellus-to-Terminal Hair Follicle Transformation

Hormonal stimulation of vellus hair is known to drive vellus-to-terminal hair transformation in skin with secondary sexual characteristics (e.g., pubic, beard, axillary etc.) during puberty, and in hirsutism and hypertrichosis. The reverse transition from terminal-to-vellus is characteristic of androgenetic alopecia or male-pattern baldness [44]. These transformations can be remarkably rapid, classically evidenced by the puberty-associated changes in hair phenotype. However, other clinical evidence shows that sex steroids are not the only inducer of this change. For example, the reversal of the terminal-to-vellus transformations in finasteride- or minoxidil-stimulated hair follicles over a single hair cycle [44] does not appear to involve modulation of androgen action in any way, but indicates that the hair follicle itself remains susceptible to significant reprogramming in terms of fiber output.

Both routes to terminal hair transformation are likely to involve significant plasticity of the follicular papilla and dermal sheath [18], and alterations in follicular papilla cell number lie at the heart of any attempt to explain clinically important increases and decreases in hair fiber size. The hair follicle mesenchyme was long believed to consist of very stable fibroblastic cell populations. However, recent murine data indicate that follicular papilla cell number actually increases during early anagen and that this increase is driven primarily by cell proliferation in the proximal dermal sheath, followed by immigration of progeny cells into the follicular papilla [38]. Hypertrichosis (itself a form of vellus-to-terminal hair transformation) can also occur in certain body sites of both men and women of advancing age e.g., terminal hair growth on the upper lip and chin of postmenopausal women and on the ear pinae, nose, and nasal vestibules in aging men [43].

1.3.3 Terminal-to-Vellus Hair Follicle Transformation

It is not yet clear whether the terminal-to-vellus hair follicle transformation, most visibly manifested in androgenetic alopecia in males with age, is indeed simply a reversal of the earlier observed vellus-to-terminal hair follicle transition [10, 38, 39]. Several studies have helped to form a consensus that hair follicle miniaturization with age is most likely to occur via relatively abrupt reductions in follicular papilla and/or dermal sheath cell numbers both during and between individual hair cycles. This contrasts markedly with the previously dominant view that hair shaft miniaturization, in male-patterned alopecia at least, occurs via a slow and gradual cycle-by-cycle change. There is convincing clinical support for the “abrupt change” view however, not least via the rapid progression of male-patterned alopecia and the preponderance of fine hairs over intermediate hairs in balding scalp [44]. Similarly, the reversal of the vellus-to-terminal transformations in finasteride- or minoxidil-stimulated hair follicles over a single hair cycle in this type of alopecia [44] supports this view.

In addition to hair follicle transformations to vellus or invisible hairs (the usual clinical appearance of “hair loss”) there may also be a reduction in the absolute numbers of hair follicles, not only in the scalp but also throughout the body. The precise mechanism for this low-level hair follicle dropout is unclear, though it may mimic the programmed hair follicle organ deletion that can occur in mice with age [9]. Atrophic change and fibrosis can also be found in aging skin [25].

1.4 Age-Related Hair Growth Variation

In addition to the aforementioned significant variation in hair form during the extent of a normal human lifespan, hair growth rates also vary significantly during human aging and for different body sites. Indeed, when these are averaged for post-40-year old nonbalding males, hair actually grows most rapidly and with greater individual fiber thickness in certain body sites in individuals during their 50–70 years of age [25]. Increasing age can leave its mark on several phenotypic properties of the hair fiber.

While the most visually apparent of these include hair thinning, hair loss, reduction in the rate of growth, pigmentation loss [7, 19, 24, 40], aging can also affect change in the surface morphology of hair. This can be seen for both a reduction in the cuticular scale size, as well as loss of hair fiber lubrication/moisturization. Loss of hair shaft moisture and lubrication has been reported to occur as a function of increasing age in adults, especially in women. The hair exists within the context of the “pilo-sebaceous unit” – a term that
implicates the sebum-producing gland in several aspects of hair biology. The open and interactive nature of the pilo-sebaceous unit is facilitated by a duct that carries sebum from this holocrine tissue directly onto the hair fiber and from there to the skin surface. The activity of the sebaceous gland changes dramatically as a function of gender and age, from the relatively inactive prepubertal period, through to a very active adolescent and young adulthood, to markedly reduced activity after the fourth decade of age, especially in females [45]. In addition to crude overall changes in gland size and activity, more subtle changes involve modification of the composition of lipids being produced by this gland at different times during our lives. For example, sebum from children contains less squalene and cholesterol than sebum from adults [33].

Moreover, the concentrations of integral cholesterol sulphate and cholesterol have also been examined in human scalp hair shafts in 50 subjects, aged 18–87 years [3] to determine whether aging influences the integrity of the cell membrane complex which mediates cortical cell-to-cell cohesion in fully keratinized hair. A small but statistically significant increase with donor age was detected for hair cholesterol (but not for cholesterol sulphate), and was speculated to reflect changes in keratinization with age. The potential of this finding as a biomarker of aging was discussed by the authors of this study.

Aging is also associated with a reduction in the duration of active hair growth and in the diameter of hair shafts, which can be seen most readily in large caliber hair shafts. However, there can also be increased irregularity of the outline of the fiber, including increase angularity of the fiber’s cross-sectional profile. There is also lengthening of the duration of the kenogen interval of the hair growth cycle i.e., the period after exogen and before the emergence of new anagen hair [27]. These changes resemble those observed in the course of male-pattern balding, although their development is less marked [7]. The perception of changes in hair density and overall hair volume can be modified by contemporaneous changes in hair pigmentation. Thus, while miniaturization of terminal hair during androgenetic alopecia does not appear to be associated with either previous or simultaneous loss of pigmentation in the affected hair follicles, canities can at least for fair-skinned and dark-haired individuals mask some of the more dramatic visual effects of hair thinning.

Recently there have been attempts to characterize changes to the internal structure of hair fibers with age [22, 29]. In one study Raman spectroscopy was used to compare the scalp hair fibers of Japanese females in their twenties with those in their fifties. This study found that the cystine disulfide (–SS–) content of the hair cortex decreased somewhat with age [22]. More recently, researchers analyzed the hair of so-called “anagen-blocked” scalp hair follicles [29]. The advantage of examining this particular case (Mrs YD – a 42-year-old Chinese woman) was their avoidance of any chemical processing and their protection of the hair from external weathering elements. In this way an assessment of natural (intrinsic) aging has been possible and this was characterized by a progressive abrasion to the cuticle from root to tip over the hair fibers, which were growing continuously for over 26 years. This cuticular damage was further associated with a reduction in ceramides and 18-methyl eicosanoic acid and also in particular keratin-associated protein subfamilies (ultra-high sulfur proteins; high sulfur proteins; high glycine-tyrosine proteins). There was also a progressive decrease in mechanical resistance along these extremely long hair fibers.

1.5 Age-Related Hair Pigmentation Variations

Hair color in children tends to darken with advancing age [1] and it is not unusual for a blond child to be dark-haired even before the onset of puberty. Similarly, the phenomenon of heterochromia is much more apparent after puberty, with color differences between scalp and beard not uncommon. The fine scalp hair of the growing child and adolescent exhibits striking changes with increasing age to mature adulthood, not only in color (most typically a darkening of hair color e.g., blond to brown) but also by showing a coarsening of the hair fibers themselves. A reduction in the level of pigmentation of scalp hair in male-pattern baldness is associated with the reduction in the caliber of these hairs (see Chap. 9 elsewhere in this volume). This is thought to be largely the result of the reduced capacity of smaller, finer hairs to accommodate large numbers of melanocytes. There is also a tendency for these “miniaturizing” hairs to be less medullated than terminal scalp hair. By contrast, the loss of melanocytes from hair follicles producing hair fibers of normal
caliber (i.e., during hair graying or canities) may also result in a concomitant change in the structure of these hair fibers (see below). This is perhaps not surprising given the close interaction between melanin granule-transferring melanocytes and hair shaft-forming/melanin-accepting pre cortical keratinocytes.

It is likely that pigment-producing melanocytes in the hair bulb influence cortical keratinocyte behavior in several ways. For example, melanin transfer to cortical keratinocytes may hasten their terminal differentiation and cornification – a change may be mediated by increased levels of calcium, some of which may be transferred into the keratinocytes within melanin granules. For further discussion of the pigmentary changes associated with hair aging please refer to Chap. X–Z.

Briefly, there is evidence that gray and white hair fibers exhibit different mechanical properties compared to adjacent pigmented hairs. Hollfelder provided some evidence that pigmented-free hairs are not only coarser but also can be wavier than pigmented hairs [16]. Moreover, others have reported that the average diameter of newly white hair fibers is significantly greater than that of pigmented hairs [40, 41]. Development of a more prominent medulla in white, compared to pigmented, hair fibers has also been reported in this study [40, 41]. Interestingly, these researchers have also described an age-related reduction in hair growth rate and in hair fiber diameter, but that this was broadly limited to pigmented hairs in these individuals. Thus, the implication is that, counter-intuitively, the apparently more “aged” white hairs may be partially spared some aging changes. The tensile strength of hair also decreases with age, having increased from birth to the second decade [7, 24]. A study by Van Neste on scalp hair growth in young, mature and menopausal women reported that the growth rate of non-pigmented hair in menopausal women was higher than that of pigmented hair [42]. This difference remained statistically significant, when hair thickness (an important parameter of hair growth) was taken into account. Also, white hair was thicker on average, showed more medulla and grew faster than pigmented hair. However, the unpigmented hair of menopausal women grew at the same rate when compared with similar hair from younger women. Similar studies in scalp hair of younger and aging males are yet to be performed. The biology underlying these events requires further investigation, particularly in terms of observed regional variability as well as the potential influence of androgens or other hormonal factors involved [16, 29].

In a manner similar to the changes in lipid composition of sebum in individuals with advancing age, there is also an age-associated change in the chemical composition in the hair fiber. Metals that show this change in hair fibers include cadmium, copper, zinc and strontium [13]. Furthermore, reductions in glutathione reductase, glutathione-S-transferase, glucose-6-phosphate dehydrogenase and gamma-glutamyl transpeptidase have been reported [5, 6, 20, 35].

1.6 Hair Loss: An Aging Event?

Hair loss in men and women during aging is clearly a common event. However, the specificity of the finding in association with aging has been questioned. There have been anecdotal reports on so-called “senescent” alopecia [21], but the associated changes such as inflammatory infiltrates and fibrosis cannot be used to readily differentiate this type of alopecia from androgenetic alopecia [28, 30]. Independently of aging, hair color changes are suggestive but not specific for aging [21, 30]. The scalp is subject to both intrinsic (physiologic) aging and extrinsic aging caused by external factors. Intrinsic factors are related to individual genetic and epigenetic mechanisms and so show significant interindividual or interclan variation. Self-evident examples include familial premature graying and androgenetic alopecia. By contrast, extrinsic factors implicated in skin and hair aging include; ultraviolet radiation and smoking. Experimental evidence supports the hypothesis that oxidative stress plays a role in both skin and hair aging.

1.7 Conclusions

Aging of the hair follicle has traditionally been viewed in a rather simplistic and bipartite manner – namely alopecia and canities, and this has almost exclusively been limited to the scalp. This view may be too simplistic, as androgenetic alopecia can be already well-advanced in young scalps and premature graying does not appear to be linked to true chronologic aging of the general tissues systems of the affected individual. True hair follicle aging is instead likely to involve a much more subtle sequence of events, e.g., hair fiber cross-sectional
changes, which may be reversible (at least temporarily) as seen with re-stimulation of the melanocyte stem compartment after radiation of canities-affected scalp or the vellus-to-terminal hair follicle transformation upon successful finasteride or minoxidil treatment. Our increasing longevity has revealed that vigorous hair growth can continue for 120 years or more. Moreover, death of the individual (i.e., via other/multiple organ system failure) cuts short our view of the true life capacity of the hair follicle. In this context the hair follicle may be the best aging tissue of the body’s complex tissue systems. Still Werner syndrome may curb this enthusiasm somewhat, as this model of human aging exhibits both early graying of the hair, and alopecia. However, “normal” aging of the hair follicle is unlikely to be dependent, like Werner syndrome, on a single defective gene product. Thus, much of the mystery awaits investigation.

References


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2.1 Introduction

Androgenetic alopecia, the most common form of hair loss in men, involves the progressive loss of visible, pigmented terminal hair on the scalp, in response to circulating androgens. It may also occur in women. Other names include: male pattern baldness, common baldness, male pattern alopecia, androgen-dependent alopecia, androgenetic alopecia or simply “balding”. There are several other causes of hair loss such as the patchy baldness of the scalp and/or body of alopecia areata, generally believed to be an autoimmune disease [24]. These fall outside the scope of this book, but have been described elsewhere [10, 24, 94].

2.1.1 Patterns of Hair Loss

2.1.1.1 In Men

In men with androgenetic alopecia, the gradual replacement of long, pigmented, terminal hairs on the scalp...
by short, pale, *vellus* hairs normally occurs in a relatively precise pattern (Fig. 2.1). Hamilton graded this progression from type I, pre-pubertal scalp with terminal hair on the forehead and all over the scalp, through gradual regression of the frontal hairline and thinning on the vertex, to type VII where the bald areas became fully coalesced to leave hair only around the back and sides of the head [51]. Norwood modified Hamilton’s classification, including variations for the middle grades (see Fig. 2.1); this scale is used extensively during clinical trials [89].

**2.1.1.2 In Women**

Androgenetic alopecia is also reported in women, although androgen involvement is less established. Hamilton found post-pubertal recession to type II was common in Caucasian women with approximately 25% exhibiting the type IV pattern by age 50, although this did not develop further [51]. Although women can exhibit the “male” pattern, they usually show a different Ludwig pattern involving a progressive diffuse loss of hair from the crown while retaining the frontal hair line.

**Fig. 2.1** Patterns of hair loss in androgenetic alopecia in men (*upper diagram*) and women (*lower diagram*). Androgens cause a gradual inhibition of hair growth on the scalp in genetically pre-disposed individuals. This is much more common in men than in women, and the pattern of the hair loss in men differs from women. In men, the first signs are generally temporal regression, which spreads backwards and joins thinning regions on the vertex to give a bald crown. In women, the front hairline is normally retained, and a general thinning on the vertex gradually becomes more pronounced until the vertex becomes bald (after Hamilton [4] and Ludwig [67]).
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2.1.2 Incidence

Although there are no precise statistics, the incidence in Caucasians is often quoted as approaching 100% [24]; others suggest that about half of men and women above 40 exhibit androgenetic alopecia [93]. There is a marked variation in other races, which often show much less balding. Most Chinese retain the pre-pubertal hairline after puberty, and baldness is less common, less extensive and starts later [51]. Japanese men also show a lower incidence, beginning balding about 10 years later than Caucasians [130]. Four times as many African-Americans also retain a full head of hair than Caucasians [121]. The reason for this racial variation is unclear, but is probably genetic because differences appear to be retained regardless of location.

2.1.3 Significance of Androgenetic Alopecia

Androgenetic alopecia is also seen in other primates, including the orangutan, chimpanzee and stump-tailed macaque [135]. This suggests a natural progression of a secondary sexual characteristic rather than a disease. In the past, when many men died young, marked androgenetic alopecia would have distinguished the surviving older male as a leader, like the silver-backed older male gorilla and larger antlers on older deer. Others have speculated that the bald patch of an angry older dominant male would flush and look very aggressive [43] or help in fighting because there was less hair to pull [28]. Whatever the potential benefit, the reduced incidence of baldness in African men [121] suggests evolutionary pressure to retain scalp hair for protection from strong sunlight.

Although androgenetic alopecia is common and neither life-threatening nor painful, it is a distressing disorder; Egyptian men’s anxieties were recorded 4,000 years ago [40]! This reflects the important, although often underappreciated, roles of hair in human social and sexual communication, whatever the genetic background or culture. For example, the ritual head shaving of Christian and Buddhist monks and the short soldier haircuts are all designed to reduce individuality; these contrast with the religiously un-cut hair of Sikhs. In the youth-orientated culture of the industrialised nations, balding’s association with ageing has very negative connotations and androgenetic alopecia often causes marked psychological distress and reduction in the quality of life in men [12, 36, 42, 81, 131, 139] and women [13, 136]. Patients report poor self-image, feelings of being older and loss of self-confidence. Similarly, other people report men with visible hair loss as older, less attractive, weaker and duller. Importantly, the same results were obtained in those who had never sought treatment [42]. Whatever may be its original biological role, androgenetic alopecia reduces the quality of life in the current industrialised world.

2.2 Changes During Androgenetic Alopecia

2.2.1 Altering the Type of Hair Produced Via the Hair Follicle Growth Cycle

The progressive loss of visible hair during patterned balding results from the gradual transformation of terminal follicles, producing the long, thick, pigmented hairs of youth, to smaller vellus follicles forming short, colourless, virtually invisible vellus hairs. This is a major change in cell biological terms; follicles possess a unique mechanism, the hair follicle growth cycle, which allows these changes [27, 73]. Each follicle normally undergoes a continual series of active, growing phases called anagen, alternating with periods of rest or telogen; these are separated at the end of anagen by a brief regression or catagen phase [27, 73] (see Fig. 2.2). This involves the destruction of the original lower follicle, and its total regeneration to form another follicle that can produce a totally new hair. The original hair is lost via active shedding called exogen [128]. In this way, the post-natal hair follicle appears to retain the ability to recapitulate the later stages of follicular embryogenesis throughout life.
Many follicles will produce a new hair that is similar to the previous one, but the hair may differ in colour or size. It is unclear how much a hair can alter in size from the previous one, because many changes take place over several years e.g. developing a full beard [52]. The miniaturisation processes of androgenetic alopecia occur over many years with hair follicles reducing in size and depth in the skin and producing smaller and paler hairs (Fig. 2.2) [30, 119]. The type of hair produced by a follicle, particularly its length, depends greatly on the length of anagen. For example, long scalp hairs are produced by follicles with growing periods of more than 3 years [73, 119], whereas on the finger anagen may be only 1.5–3 months [119]. The cell biology and biochemistry of the local interactions involved in the control processes of the hair cycle are complex and not yet fully understood, but the size and length of the hair is controlled by the mesenchyme-derived dermal papilla situated at the base of the mainly epithelial hair follicle (see Fig. 2.2) [68, 92].

### 2.2.2 The Miniaturisation Processes

Scalp follicles pass through several cycles before the processes are complete (Fig. 2.2). Normally, scalp hair follicles are mainly in anagen; the average anagen of 2–3 years and telogen of approximately 100 days [73] gives an anagen-to-telogen ratio of about 9:1, although there is some seasonal variation in people living in temperate regions (see Sect. 2.3.1) [108]. While androgenetic alopecia develops, anagen shortens, increasing the proportion of telogen hairs [7, 97, 118, 140] which is detectable before any balding; it also results in shorter hairs. Follicle miniaturisation can be seen histologically [7, 74], indicating the hairs are also thinner [74, 118]. When scalp appears bald, most of the follicles are very short and small, with occasional resting terminal hairs.

Studies of androgenetic alopecia are complicated by senescent balding, the non-androgen-dependent hair thinning found in those more than 50 [28]. This also involves a progressive decrease in anagen follicles.
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and hair diameter [28], but does not normally lead to baldness. Kligman suggested that both forms may occur together, proposing a pronounced inflammatory component in androgenetic alopecia, not seen in senescent baldness [74]. Recent observations have confirmed peri-follicular inflammation [30]. The sclerotic remains of the fibrous sheath are seen below the shortened follicles as “streamers” [74]; damage to the dermal sheath by chronic inflammation may prevent the reformation of terminal hair follicles in long-term alopecia, although this is debated.

During the miniaturisation processes of androgenetic alopecia, the follicle’s associated arrector pili muscle reduces much more slowly than the follicle [82], while the androgen-dependent sebaceous gland becomes enlarged [74], often resulting in an oily, greasy scalp. Other changes include a reduced follicular blood supply [20, 111] and nerve networks twisting to form a type of encapsulated end organ below the follicle [41].

2.3 The Pathogenesis of Androgenetic Alopecia

Hair follicles are under hormonal regulation because of the importance of coordinating alterations in insulation properties and colour of an animal’s coat to the environment [29, 107], and changes in the social and sexual communication aspects to the appropriate stage in the life cycle. In mammals, seasonal changes are coordinated to day length and, somewhat less, to temperature in the same way as seasonal breeding. Changes are translated to the follicle via the pineal and hypothalamus-pituitary route, involving gonadal, thyroid and corticosteroid hormones [29, 107].

2.3.1 Seasonal Changes in Human Hair Growth

Regular circannual changes in human hair growth were only fully recognised comparatively recently [19, 108]. In white Englishmen with indoor occupations, androgen-dependent beard and thigh hair growth increase significantly in the summer [108] and are lowest in January and February. This may reflect changes in circulating androgen levels, because these rise in European men in the summer [115, 125]. Scalp hair shows a single annual cycle with more than 90% of hairs growing in the spring, falling to about 80% in the autumn, paralleled by increased numbers of hairs being shed per day, which more than doubled [108]. Which hormones regulate this is unclear. As most people’s scalp follicles will be in anagen for at least 2–3 years, such a marked seasonal effect is quite remarkable. Nevertheless, this effect has a major significance, as any new drug or treatment should be studied for at least a year to separate any effects from normal seasonal variations.

2.3.2 Paradoxical Effects of Androgens on Human Hair Growth

Androgens are the main regulator of human hair growth, although other hormones, including those of pregnancy, prolactin, melanocyte-stimulating hormone (MSH) and thyroid hormones, have effects in man and other species [105, 107]. One of the first signs of puberty is the gradual replacement of tiny vellus hairs with larger, more pigmented intermediate hairs in the pubis and later in the axillae [83, 84]; eventually, larger and darker terminal hairs are produced. These changes parallel the pubertal rise in plasma androgens that occurs earlier in girls than in boys [143, 144]. Similar changes occur in many areas in young men producing the beard, an extended pubic diamond, chest hair and greater hair on the limbs, which readily distinguish the mature adult man. These changes are gradual and often progress over many years. Beard growth increases rapidly during puberty, but continues to rise until the man is in his mid-30s [52], while terminal hair on the chest or ear canal may appear only years after puberty [50].

In marked contrast, androgens have no obvious effect on many follicles that produce terminal hairs in childhood, such as the eyelashes or many scalp follicles. Paradoxically, in individuals with a genetic pre-disposition, androgens promote the gradual transformation of large terminal scalp follicles to tiny vellus ones causing androgenetic alopecia [49, 51, 53]. Apart from the role of androgens, the precise mechanisms of these responses within the hair follicle are not well understood, although it is clear that the responses are intrinsic to the individual
follicle and dependent on body site. Not only do follicle responses range from stimulation to inhibition, but sensitivity to the androgens also varies within clearly defined patterns. Facial hair develops first above the mouth and centre of the chin in both young men and hirsute women, and regression in androgenetic alopecia occurs in a progressive manner, despite all follicles receiving the same circulating hormones [51]. Similarly, female circulating androgen levels are high enough to produce axillary and the female terminal pubic hair, but male patterns of body hair require normal male levels [4, 19, 49, 53, 58, 83, 84, 105, 115, 125, 143, 144]. Thus, androgens appear to promote and amplify an individual follicle’s genetic programming. This end-organ response is the basis for hair transplant surgery [98]; when “non-balding” regions of the scalp are transplanted to the balding vertex, they retain their innate lack of androgen response and maintain terminal follicles, while miniaturisation progresses in the vertex follicles behind them.

2.3.3 Essential Requirement for Androgens

Androgens are essential for the development of androgenetic alopecia. It does not occur in men who have never entered puberty; men castrated after puberty show no further progression of their baldness, although they do not regain the frontal hairline, and testosterone replacements stimulate progressive balding, which halts during temporary withdrawal of the anagen [49, 52, 53].

Androgens, like other steroid hormones, pass through the plasma membrane and bind to specific intracellular proteins, inactive androgen receptors. This activates the receptors causing shape changes, which enable them to bind to specific hormone-responsive elements (HREs) in the DNA, often in association with other co-activating proteins, to initiate the translation of specific androgen-regulated genes and synthesis of their proteins (see Fig. 2.3, upper diagram). The essential role of androgens is confirmed by the absence of any post-pubertal changes in body or scalp hair growth in men without functional androgen receptors (i.e. with androgen insensitivity syndrome) [85]. Individuals with the complete form exhibit no pubic, axillary, chest or beard terminal hair and do not develop androgenetic alopecia.

Although testosterone is the main circulating androgen in men, in many tissues, it is metabolised intracellularly to the more potent androgen, 5α-dihydrotestosterone, by the enzyme 5α-reductase [17]. Both testosterone and 5α-dihydrotestosterone can activate the androgen receptor to alter the expression of androgen-sensitive genes. There are also various weaker androgens in the circulation, particularly in women, which can be metabolised to more active androgens such as testosterone and 5α-dihydrotestosterone (see Fig. 2.3). Deficiencies in 5α-reductase also reduce androgen effects on some hair follicles. Although all hair follicles require intracellular androgen receptors to respond to androgens, the necessity for 5α-reductase activity to produce intracellular 5α-dihydrotestosterone for the androgen response varies [54]. Individuals with 5α-reductase type 2 deficiency do not develop male patterns of body hair growth, despite their circulating androgens; they produce only female patterns of pubic and axillary hair, although their body shape masculinis [142]. They appear not to exhibit male pattern baldness, but this is more difficult to interpret; however, the re-growth of hair in young balding men given the 5α-reductase type 2 inhibitor, finasteride, strongly supports the role of both androgens and 5α-reductase in androgenetic alopecia [69].

Despite the widely held belief that baldness is an indicator of increased male sexuality, there is little scientific evidence for this other than the clear link with normal androgen parameters. There was no relationship between androgenetic alopecia and other androgen-regulated parameters, including muscle, bone, sebum excretion rate or body hair growth in adult men [9]. Normal male testosterone levels have been reported in balding men [101, 103] with higher urinary dehydroepiandrosterone [101] or dehydroepiandrosterone sulphate [113]; other studies showed raised serum-free testosterone, i.e. that are not bound to sex hormone-binding globulin [16, 26]. Overall, normal male androgen levels appear to be sufficient to produce androgenetic alopecia; the response obtained appears related to the intrinsic follicular response. In women, raised circulating androgens, particularly free androgens, appear to be related to hair loss, although the means from studies are often within the normal ranges for pre-menopausal women [8, 14, 25, 39, 79, 88, 129]. Women who present with androgenetic alopecia also often exhibit polycystic ovarian disease and hirsutism [14, 38, 91], even if presenting with alopecia without menstrual abnormalities [14]. Therefore, androgenetic alopecia requires circulating androgens, androgen receptors and intracellular 5α-reductase type 2.
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Fig. 2.3 The mechanism of action of androgens. *Upper diagram* – simple schematic of the general mechanism of androgen action. Androgens diffuse from the blood through the plasma membrane. Inside the cell, like other steroid hormones, testosterone may bind to specific androgen receptors. This occurs in many tissues such as skeletal muscle and axillary and pubic hair follicles. However, in certain tissues, particularly the secondary sexual organs such as prostate or beard and balding hair follicles, testosterone is metabolised to the more potent androgen, 5α-dihydrotestosterone (see *lower diagram*). If both are available in similar quantities, the receptor will bind 5α-dihydrotestosterone. Once hormone has bound, the receptor complex undergoes a conformational change exposing DNA-binding sites and the hormone-receptor complex, in conjunction with other co-activating proteins, will bind to specific hormone response elements (HREs) in the DNA altering the expression of specific androgen-dependent genes. *Lower diagram* – androgen metabolism. Circulating androgens such as testosterone from the testis in men and weaker androgens such as dehydroepiandrosterone and androstenedione from the adrenals and ovaries in women can be metabolised in many skin tissues. Some metabolism causes an increase in potency, e.g. from testosterone to 5α-dihydrotestosterone (DHT) as the androgen receptor binds DHT more strongly even than testosterone, another potent androgen. Other metabolisms form weaker androgens normally involved in excretion pathways, e.g. the androstanediols or steroids which act via the other steroid receptors i.e. the oestrogens.