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Androgens and hair: a biological paradox

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6.1 Introduction

Hair growth plays significant roles in human social and sexual communication. People all over the world classify a person's state of health, sex, sexual maturity and age, often subconsciously, by assessing their scalp and body hair. The importance of hair is seen in many social customs in different cultures, such as shaving the head of Buddhist monks or no cutting of scalp hair by Sikhs. Body hair is also involved; for example, the widespread customs of daily shaving men's beards and women's axillary hair in Northern Europe and the USA. When this is considered, it is not

surprising that abnormalities of hair growth, either greater or less than "normal", even including common male pattern baldness, cause widespread psychological distress.

Androgens are the most obvious regulators of human hair growth. Although hair with a major protective role, such as the eyelashes, eyebrows and scalp hair, is produced by children in the absence of androgens, the formation of long pigmented hair on the axillae, pubis, face etc. needs androgens in both sexes. In contrast, androgens may also inhibit hair growth on the scalp, causing baldness. How one type of hormone can simultaneously cause these contradictory effects in the same tissue in different body sites within one person is an endocrinological paradox. The hair follicle has another exciting characteristic. It is the only tissue in the adult body which can regenerate, often producing a new hair with different features. This is how androgens can stimulate such major changes.

In the last 15 years, there has been a great deal of interest in the hair follicle promoted by the discovery that the antihypertensive drug, minoxidil, could sometimes stimulate hair growth. However, still relatively little is known about the precise functioning of this complex cell biological system at the biochemical level. Nevertheless, our increased comprehension of the mechanism of androgens in the follicle has enabled the treatment of hirsutism in women with antiandrogens, such as cyproterone acetate, and the 5α-reductase type 2 inhibitor, finasteride, developed to regulate prostate disorders, is now available in many countries for use in male pattern baldness. Greater understanding of hair follicle biology may also enable the development of further treatments in the future.

People have been intrigued by the changes in hair growth during a person's life for thousands of years. Various approaches have been used to establish the roles of androgens since Aristotle first recognised the connection between beard growth and the testes (reviewed Randall 2003). This chapter will cover our current knowledge of the structure and function of hair follicles, their responses to androgens, the mechanism of action of androgens in the follicle and current modes of control of androgen-potentiated disorders.

6.2 Structure and function of the hair follicle

6.2.1 The roles of human hair

Hairs cover almost all the body surface of human beings except for the soles of the feet, palms of the hands and the lips. They are fully keratinised tubes of dead epithelial cells where they project outside the skin. They taper to a point, but otherwise are extremely variable in length, thickness, colour and cross-sectional shape. These differences occur between individuals e.g. blonde, red or dark haired people and between specific body areas within one individual such as the long, thick scalp and adult male beard hairs and the short, fine ones on the back of the hand.

Changes also occur on the same parts of an individual at different stages of their life e.g. darker, thicker and longer beard hairs replace the fine, short, almost colourless hairs on a boy's face in adulthood.

The main functions of mammalian hair are insulation and camouflage. These are no longer necessary for the "naked ape," although vestiges of this remain in the seasonal patterns of our hair growth (Randall and Ebling 1991) and the erection of our body hairs when shivering with cold. Mammals often have specialised hairs as neuroreceptors e.g. whiskers and this remains slightly in human body hair with its good nerve supply. However, the main functions of human hair are protection and communication. Eyelashes and eyebrow hairs prevent substances entering the eyes and scalp hair may protect the scalp and back of the neck from sun damage during our upright posture. During puberty the development of axillary and pubic hair signals the beginning of sexual maturity in both sexes (Marshall and Tanner 1969; 1970; Winter and Faiman 1972; 1973) while the male beard, like the mane of the lion, readily distinguishes the sexes.

6.2.2 Structure of the hair follicle

Each hair is produced by a hair follicle. Hair follicles are cylindrical epithelial down-growths from the epidermis into the dermis and subcutaneous fat (Fig. 6.1). Each enlarges at its base into a hair bulb where it surrounds the tear-shaped, mesenchyme-derived dermal papilla. The dermal papilla, which contains specialised fibroblast-like cells embedded in an extracellular matrix and separated from the epithelial components by a basement membrane, regulates many aspects of hair growth (Jahoda and Reynolds 1996).

The hair is produced by epithelial cell division in the bulb; the keratinocytes move upwards, undergoing differentiation into the various layers of the follicle. The central portion forms the hair itself whose colour is produced by pigment donated by the follicular melanocytes. By the time it reaches the surface the cells are fully keratinised and dead. The hair is surrounded by two multi-layered epithelial sheaths: the inner root sheath, which helps it move through the skin and which disintegrates when level with the sebaceous gland, and the outer root sheath, which becomes continuous with the epidermis, completing the skin's protective barrier (Fig. 6.1).

6.2.3 The hair follicle growth cycle

Cell division continues until the hair reaches the appropriate length for its body site. The length of this period of hair growth, or *anagen*, can range from two years or more on the scalp (Kligman 1959) to only about two months on the finger (Saitoh and Sakamoto 1970). At the end of anagen, cell division stops and the lower follicle regresses, entering a transient stage known as *catagen* (Kligman 1959). The hair itself becomes fully keratinised with a swollen or "club" end and moves up in

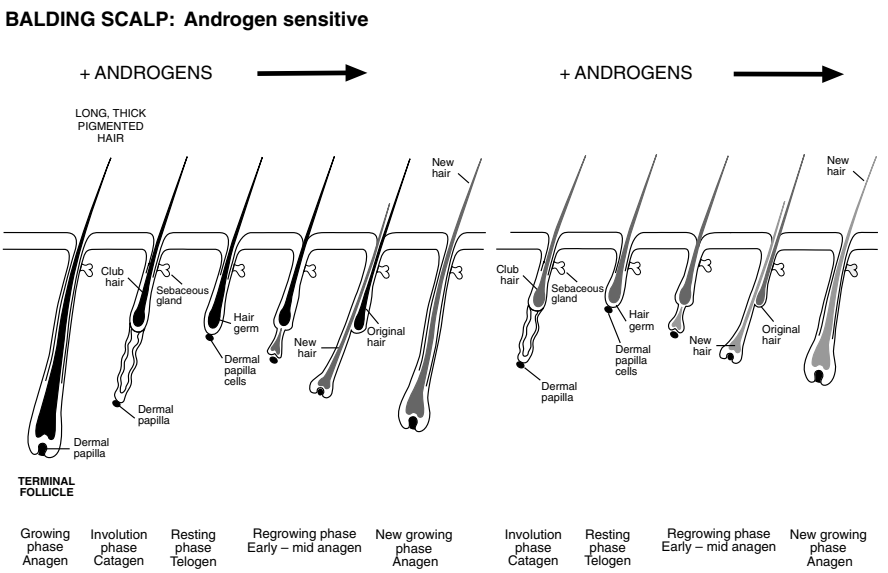

Fig. 6.1 Diagram of two hair follicle growth cycles where the new scalp follicle is smaller due to androgen inhibition

Hair follicles pass through regular cycles of growth (anagen), regression (catagen) and rest (telogen) during which the lower part of the follicle is regenerated. This enables the follicle to produce a different type of hair in response to hormonal stimuli to co-ordinate to changes in the body's development e.g. sexual maturity or seasonal climate changes. The regenerated follicle illustrated is smaller, protrudes less into the dermis and produces a smaller, less pigmented hair. Reproduced from Randall 2000b.

the skin, resting below the level of the sebaceous gland. The dermal papilla also regresses, losing the extracellular matrix and the cells become inactive. The dermal papilla cells rest below the *club hair* associated with epithelial cells (Fig. 6.1) and the follicle then enters a variable period of rest termed *telogen*. At the end of telogen the dermal papilla cells reactivate, epithelial cells recommence cell division and a lower follicle is regenerated growing back down into the dermis and producing a new hair (Fig. 6.1). The new hair grows up into the permanent part of the hair follicle alongside the old hair which is shed. The new hair may resemble the old one or may be larger, smaller and/or a different colour depending on the environment or stage of a mammal's maturity (Fig. 6.1). A further stage of *exogen* has recently been proposed involving an active, rather than passive, shedding of the old club hair (Stenn *et al.* 1998).

The origin of the epithelial cells which give rise to the new lower follicle is currently the subject of some debate. Epithelial stem cells were identified in the bulge region of the outer root sheath below the sebaceous gland (Cotsarelis *et al.* 1990), contrasting with the traditional view of stem cells in the epithelial germ, known as germinative

epithelial cells, supported by elegant cell co-culture experiments of the various follicular cell types (Jahoda and Reynolds 1996). The bulge contains stem cells with a wide potency which are able to replace cells of the epidermis and sebaceous glands as well as the hair follicle (Lavker *et al.* 2003; Taylor *et al.* 2000). It seems likely that both stem cell types are involved in the hair follicle, with the bulge cells as less specialised, higher order stem cells in line with the haemopoitiec system, possibly providing a source of cells ready to produce the germinative matrix cells for the anagen period of the next hair growth cycle (Pantelevev *et al.* 2001).

Although the hair follicle growth cycle has been well documented (Kligman 1959), the control mechanisms are complex and still not understood (Paus *et al.* 2000). It is clear that the early stages of anagen at least partially recapitulate the embryogenesis of the hair follicle to an unique extent in the adult. The processes of the hair growth cycle allow the follicle to replace the hair with a different type to correlate with changes in the environment or maturity of the individual. These changes are co-ordinated by the pineal-hypophysis-pituitary system (Ebling *et al.* 1991). Co-ordination to the environment is particularly important for some mammals, such as mountain hares, which need a longer, warmer and white coat in the snowy winter but a shorter, brown coat in the summer to increase their chances of survival (Flux 1970). Human beings in the temperate regions also exhibit seasonal changes in both scalp (Courtois *et al.* 1996; Orentreich 1969; Randall and Ebling 1991) and body hair (Randall and Ebling 1991). The main change in human hair growth is the production of adult patterns of body hair growth after puberty, like the male lion's mane, in response to androgens; some seasonal fluctuations in human body hair growth may also co-ordinate at least in part to those of androgens (discussed in Randall and Ebling 1991).

6.3 The paradoxical effects of androgens on human hair growth

6.3.1 Human hair growth before and after puberty

In utero the human body is covered with quite long, colourless *lanugo* hairs. These are shed before birth and at birth, or shortly after, babies normally exhibit pigmented, quite thick protective hairs on the eyebrows and eyelashes and variable amounts on the scalp; by the age of three or four the scalp hair is usually quite well developed, though it will not yet have reached its maximum length. These readily visible pigmented hairs are known as *terminal* hairs and are formed by large deep *terminal follicles* (Fig. 6.2). This emphasises that terminal hair growth on the scalp, eyelashes and eyebrows is not androgen-dependent. The rest of the body is often considered hairless but, except for the glabrous skin of the lips, palms and sole of the feet, is normally covered with fine, short almost colourless *vellus hairs* produced by small short *vellus follicles* (Fig. 6.2). The molecular mechanisms involved in the distribution and formation of the different types of follicles during embryogenesis are not

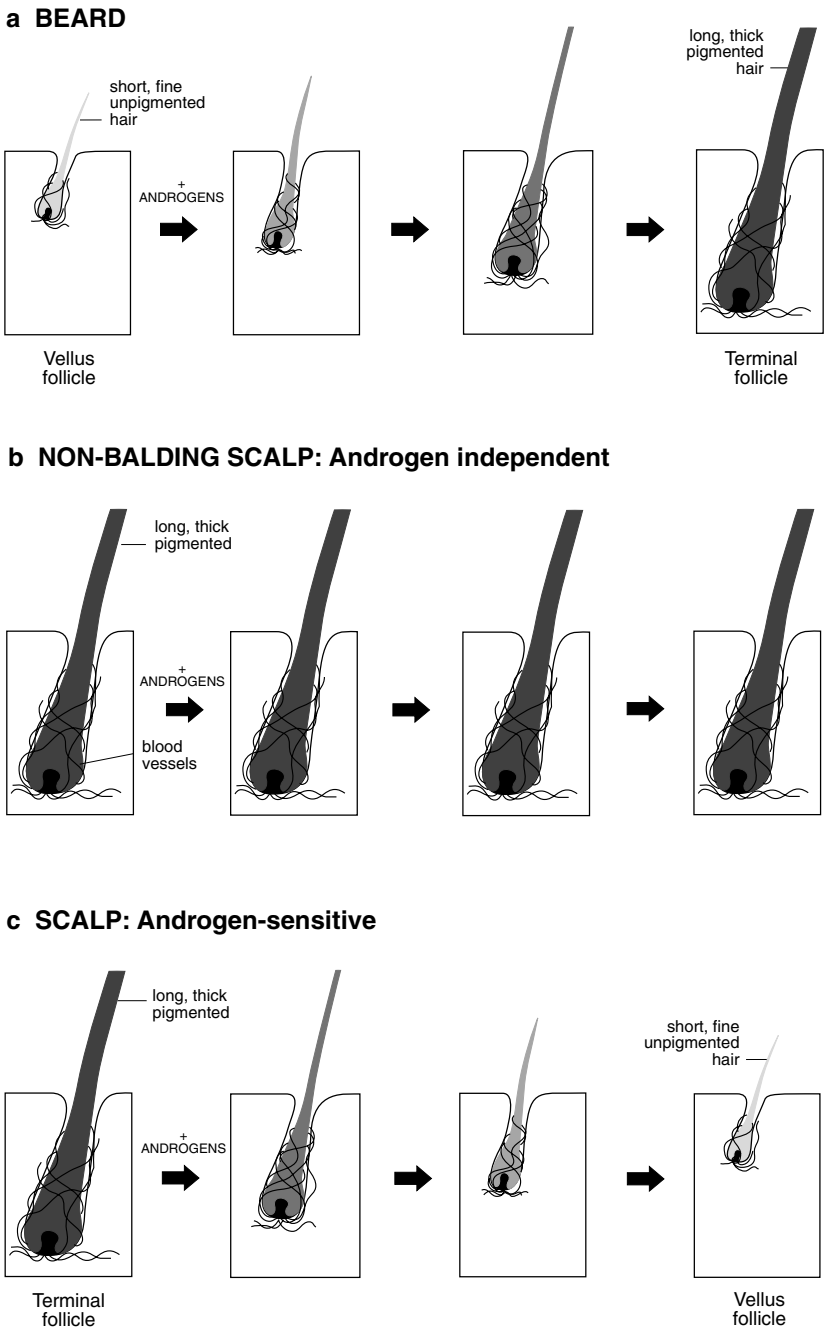

Fig. 6.2 Summary of various paradoxical effects of androgens on hair follicles
Androgens have no effects on some follicles (lower diagram), stimulate the gradual transformation of vellus follicles to terminal ones producing large pigmented hairs in many regions (upper diagram), while causing the reverse effect on the scalp in genetically-disposed individuals (middle diagram). The hair follicle undergoes several hair cycles (see Figure 6.1) between producing vellus and terminal hairs (modified from Randall 1996).

clear, but secreted signalling factors such as sonic hedgehog, Wnt and growth factors (e.g. the EGF and FGF families), nuclear factors including various homeobox genes and others such as *Hairless* and *Tabby* plus transmembrane molecules and extracellular matrix molecules have all been implicated (Wu-Kuo and Chuong 2000).

One of the first signs of puberty is the gradual appearance of a few larger and more pigmented *intermediate* hairs, firstly in the pubic region and later in the axillae. These are replaced by longer and darker hairs (Fig. 6.2) and the area spreads. In boys, similar changes occur gradually on the face starting above the mouth and on the central chin, eventually generally spreading over the lower part of the face and parts of the neck, readily distinguishing the adult male (Marshall and Tanner 1969; 1970). The adult man's pubic hair distribution also differs from the woman, extending in a diamond shape up to the navel in contrast to the woman's inverted triangle. Terminal hair on the chest and sometimes the back is also normally restricted to men, though both sexes may also develop intermediate terminal hairs on their arms and legs, with terminal hairs normally restricted to the lower limbs in women (Fig. 6.3). In all areas the responses are gradual, often taking many years. Beard weight increases dramatically during puberty but continues to rise until the mid-thirties (Hamilton 1958), while terminal hair growth on the chest and in the external ear canal may first be seen many years after puberty (Hamilton 1946).

The amount of body hair is very variable and differs both between families within one race and between races, with Caucasians generally exhibiting more than Asians (Hamilton 1958). This implies a genetically-determined response to circulating triggers. The responses of the follicles themselves also vary, with female hormone levels being sufficient to stimulate terminal hair growth in the pubis and axillae, but male hormones being required for other areas, such as the beard and chest. Beard hair growth also remains high, right into a man's seventies, while axillary growth is maximal in the mid-twenties and falls quite rapidly then in both sexes (Fig. 6.4) (Hamilton 1958). This is a paradoxically different response in the two areas to apparent stimulation by the same hormones.

During early puberty the frontal hair line is usually straight across the top of the forehead. With increasing age there is a progressive regression of the frontal hair line in a prescribed manner (described below 6.3.3.1) accompanied by progressive thinning of terminal hair on the vertex. This is characterised by a gradual inhibition of terminal follicles to smaller vellus follicles (Fig. 6.2) with the length of anagen decreasing and that of telogen increasing. This is another example of a much more dramatic biological paradox. How does one hormone stimulate hair growth in many areas such as the face, have no effect in others e.g. eyelashes, while inhibiting follicles on the scalp? These contrasts are presumably due to differential gene expression within follicles from the various body sites. The intrinsic response of individual follicles is retained when follicles are transplanted to other skin sites

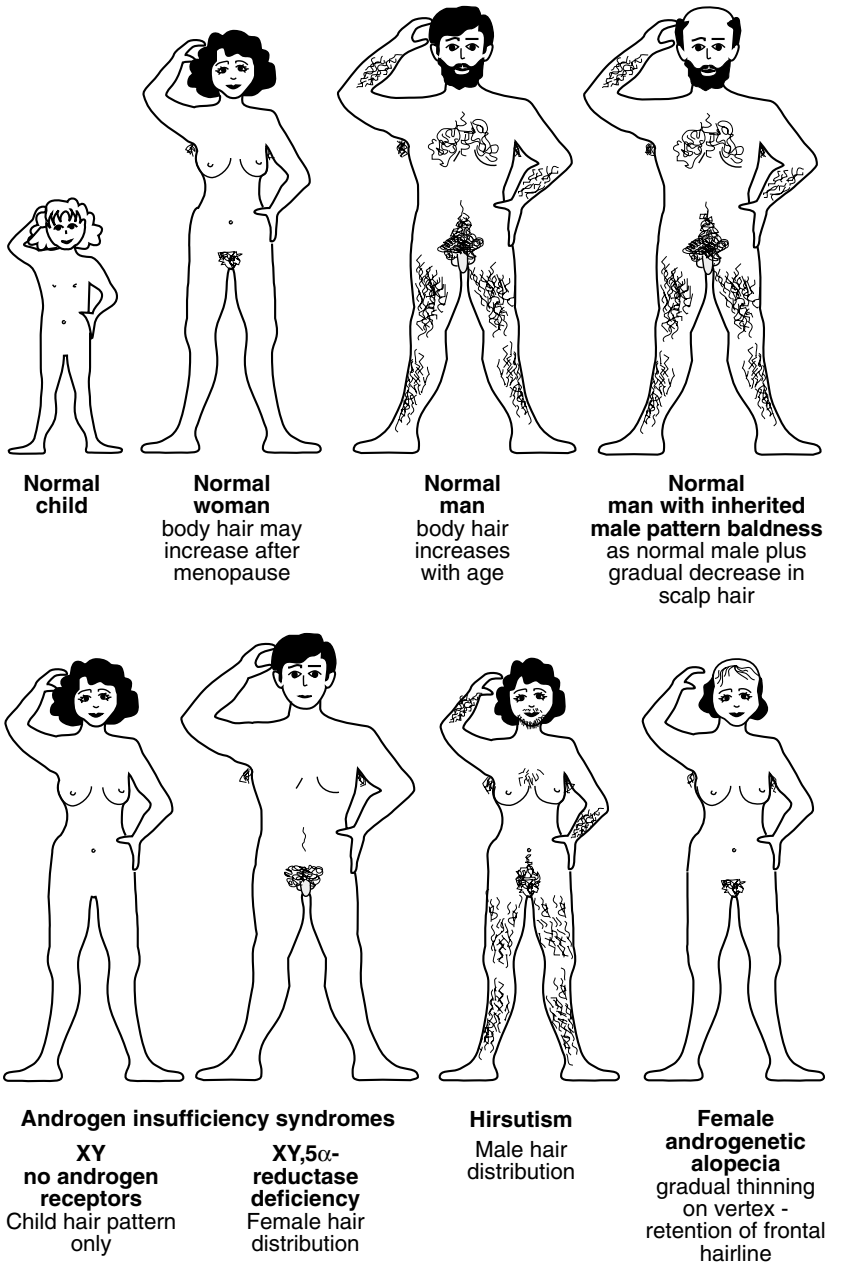

Fig. 6.3 Terminal hair distribution in people under differing endocrine conditions

Terminal hair with protective functions normally develops in children on the scalp, eyelashes and eyebrows. During, and after, puberty this is augmented by axillary and pubic hair in both sexes and beard, chest and greater body hair in men. In people with the appropriate genetic tendency, androgens may also stimulate hair loss from the scalp in a patterned manner causing androgenetic alopecia. None of this occurs without functional androgen receptors and only axillary and the lower pubic triangle hairs are formed in the absence of 5α-reductase type 2 (lower panel). Male pattern hair growth (hirsutism) may occur in women with circulating abnormalities of androgens or from idiopathic causes.

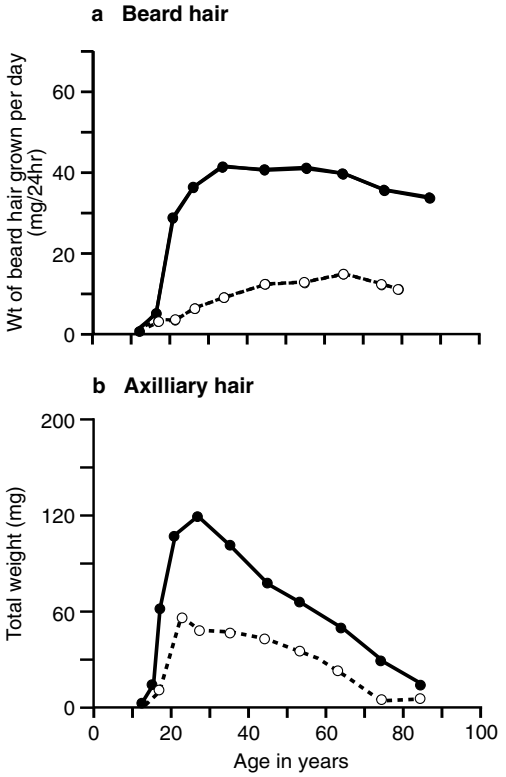

Fig. 6.4 Paradoxically different patterns of hair growth in two androgen-dependent areas: the beard and the axilla

Both beard and axillary hair growth is stimulated by androgens during puberty in Caucasian (solid lines) and Japanese (dotted lines) men. However, while beard growth is maintained at high levels into old age in both races, axillary hair growth is maximal at 30 and decreases regularly to prepubertal levels. Reproduced from Randall 2000b showing data redrawn from Hamilton 1958.

(Ebling and Johnson 1959); this is the basis of corrective hair follicle transplant surgery (Orentreich and Durr 1982).

6.3.2 Evidence for the role of androgens

Although androgens are the clearest regulators of human hair growth, unlike in most mammals (Ebling *et al.* 1991), various other circulating factors (reviewed in Randall 1994a) have an effect. These include adequate nutritional supplies, due to the follicles' high metabolic demands (Bradfield 1971), the hormones of pregnancy, which cause a prolonged anagen resulting in a synchronised shedding of a proportion of scalp hairs post-partum (Lynfield 1960), and lack of thyroid hormone which restricts hair growth (Jackson *et al.* 1972). Growth hormone is also necessary in combination with androgens for normal body hair development in

boys (Zachmann and Prader 1970). There is a range of evidence supporting the importance of androgens which fits in well with the concept of much terminal hair growth being a secondary sexual characteristic. Terminal hair appearance in puberty parallels the rise in circulating androgen levels and occurs later in boys than girls (Marshall and Tanner 1969; 1970; Winter and Faiman 1972; 1973). Testosterone also stimulates beard growth in eunuchs and elderly men (Chieffi 1949) and increased beard growth noted by an isolated endocrinologist is ascribed to his rising androgens on anticipating his girlfriend's arrival (Anonymous 1970)! An extensive study in the USA also showed that castration before puberty prevented beard and axillary hair growth and after puberty reduced them (Hamilton 1951a; 1958). Nevertheless, the strongest evidence for the essential nature of androgens is the lack of any body hair, even the female pubic and axillary pattern, or evidence of any male pattern baldness, in adult XY androgen insensitivity patients with absent or dysfunctional androgen receptors despite normal or raised circulating levels of androgens (see Chapter 3).

6.3.3 Androgen-dependent hair growth conditions

6.3.3.1 Androgenetic alopecia

A generalised loss of hair follicles from the scalp known as *senescent balding* has been reported in both sexes by the seventh or eighth decade (Courtois *et al.* 1995; Kligman 1988). This differs from the progressive baldness seen in *androgenetic alopecia*, also known as *male pattern baldness*, *male pattern alopecia, common baldness* or *androgen-dependent alopecia*. The connective tissue sheath left in the dermis when the follicle becomes miniaturised during androgenetic alopecia may become subject to chronic inflammation; this may prevent terminal hair regrowth in long-term baldness (Kligman 1988) although this is currently a matter of debate. Balding occurs in a precise pattern described by Hamilton (1951b), starting with regression of the frontal hairline in two wings and balding in the centre of the vertex. These areas gradually expand and coalesce, exposing large areas of scalp; generally the back and sides of the scalp retain terminal hair even in extreme cases (Fig. 6.3). Hamilton's scale was later modified by Norwood (1975) to include a wider range of patterns. The physiology and pathophysiology of androgenetic alopecia is reviewed more fully in Randall 2000a and 2001.

Male pattern baldness is androgen-dependent, since it does not occur in castrates, unless they are given testosterone (Hamilton 1942), nor in XY individuals with androgen insensitivity due to non-functional androgen receptors (Hiort this volume, Chapter 3). There is also a marked inherited tendency to develop it (Hamilton 1942), though the genetics are not yet established. Known dimorphic and polymorphic markers within the androgen receptor gene were recently investigated in Caucasian men (Ellis *et al.* 2001). The *Stu* I restriction fragment length polymorphism (RFLP) in exon 1 was present in 98% of 54 young balding men and 92% of 392 older balding men, but was also found in 77% of their older, non-balding

controls. When two triplet repeat polymorphisms were examined the distribution of neither short or long single triplet repeats of CAG or GAC differed significantly, but the incidence of short/short polymorphic CAG/GGC haplotypes were significantly higher (50% compared to 30%) in balding subjects and short/long were lower (7% rather than 22%) though no significance was stated in the paper. Interestingly, analysis of Spanish girls with precocious puberty i.e. appearance of pubic hair before 8 years of age showed the mean number of CAG repeats was shorter than controls (Ibanez *et al.* 2003). Shorter triplet repeat lengths have also been associated with another common androgen-dependent condition, prostate cancer (Stanford *et al.* 1997). Whether this has functional significance such as an increased androgen sensitivity or simply reflects linkage disequilibrium with a causative mutation is not clear. However, when the binding capacity for a range of steroids was compared between androgen receptors from balding and non-balding follicle dermal papilla cells no differences were detected (Hibberts *et al.* 1998).

The incidence of androgenetic alopecia in Caucasians is high with estimates varying widely but progression to stage type II being detected in 95% (Hamilton 1951b). Other races exhibit it to a lesser extent (Hamilton 1951b; Setty 1970) and it is also seen in other primates, being well studied in the stump-tailed macaque. This suggests a natural progression of a secondary sexual characteristic rather than the malfunction of a disease. Marked androgenetic alopecia would obviously highlight the surviving older man as a leader like the silver back of the chief male gorilla and the larger antlers of the mature deer stags. Others have speculated that the flushed bald skin would look aggressive to an opponent (Goodhart 1960) or mean there was less hair for the opposition to pull (Ebling 1985), giving the bald man important advantages. The lower incidence of androgenetic alopecia amongst men from African races (Setty 1970) suggests that any advantages did not outweigh the evolutionary survival advantages of the hairs' protection of the scalp from the hot tropical sun.

In the current youth-orientated culture of industrialised societies the association of increasing hair loss with age combined with the major role of hair in human communication means that androgenetic alopecia has strong negative connotations. It often causes psychological distress and reduction in the quality of life, even though it is not life-threatening or physically painful, in both men (Cash 1992; Franzoi *et al.* 1999; Girman *et al.* 1998; Maffei *et al.* 1990; Terry and Davis 1976; Wells *et al.* 1995) and women (Cash 1993; van der Dank *et al.* 1991). Other people perceive men with visible hair loss as older, less physically and socially attractive, weaker and duller. In parallel, people with androgenetic alopecia have a poor self-image, feel older and lacking in self-confidence, even those who seem accepting of their condition and have never sought treatment (Girman *et al.* 1998). Male pattern baldness primarily causes concern amongst those who develop marked loss before their forties and early balding has been linked to myocardial infarction (Lesko *et al.* 1993). Whether this indicates a dual end-organ sensitivity or reflects the psychological stress early

balding induces in the youth-orientated American culture is unknown. No relationship between the incidence of balding and prostatic carcinoma was detected in men between fifty and seventy (Demark-Wahnefried *et al.* 1997).

Androgenetic alopecia has also been described in women, but the pattern of expression is normally different. Women generally do not show the frontal recession, but retain the frontal hairline and exhibit thinning on the vertex which may lead to balding (Ludwig 1977) (Fig. 6.3). Post-menopausal women may exhibit the masculine pattern (Venning and Dawber 1988). The progression of balding in women is normally slow and a full endocrinological investigation is recommended if a rapid onset is seen (Dawber and Van Neste 1995). Although female pattern hair loss is seen frequently in association with hyperandrogenism, other women frequently have no other symptoms of androgen abnormality. Therefore, there is some debate about whether androgen is essential for this hair loss in women (Birch *et al.* 2002) though this is still generally assumed. If, as occurs in men, the changes develop due to the genetically influenced, specific follicular responses within the scalp follicles themselves, it is not surprising that circulating androgen abnormalities are often absent.

6.3.3.2 Hirsutism

Hirsutism is the development of male pattern body hair growth in women. This also causes marked psychological distress because the person erroneously feels that they are changing sex. The extent of body hair growth which causes a problem varies and depends on the amount of normal body hair amongst her race or sub-group. Normally hirsutism would include terminal hair on the face, chest or back. Ferriman and Gallwey (1961) introduced a scale for grading hirsutism which is widely used, especially to monitor hirsutism progression with, or without, treatment.

Hirsutism is often associated with an endocrine abnormality of the adrenal or ovary causing raised androgens and is frequently associated with polycystic ovarian (PCO) syndrome. Some women have no obvious underlying disorder and are termed "idiopathic". The proportion of these is larger in older papers as modern methods increase the range of abnormalities that can be detected e.g. low sex hormone binding globulin. The assumption that idiopathic hirsutism is due to a greater sensitivity of the follicles to normal androgens is given credence by hirsutism occurring asymmetrically on only one side of a woman (Jenkins and Ash 1973).

6.4 The mechanism of androgen action in the hair follicle

6.4.1 Hair growth in androgen insufficiency syndromes

As described in Chapters 1 and 2 of this book, androgens from the blood stream enter the cell and bind to specific, intracellular androgen receptors, usually in

the form of testosterone or its more potent metabolite, 5α-dihydrotestosterone. The hormone-receptor complex, generally in combination with transcriptional regulators then activates the appropriate gene transcription for that cell type.

Androgen insufficiency patients without functional androgen receptors demonstrate the essential requirement for androgen receptors within hair follicles for the development of the hair growth ascribed in 6.3.2 to androgens (Hiort, this volume Chapter 3). These individuals produce no body hair at puberty, even with high circulating androgen levels, nor do they go bald (Fig. 6.3).

Men with 5α-reductase deficiency also contribute to our understanding because they exhibit axillary and female pattern pubic hair, but very little beard growth; they are not reported to have male pattern baldness either (Griffin and Wilson 1989) (Fig. 6.3). A role for 5α-reductase in male pattern baldness is also supported by the ability of oral finasteride, a 5α-reductase type 2 inhibitor, to promote hair regrowth (Kaufman *et al.* 1998; Shapiro and Kaufman 2003). This suggests that the formation of terminal pubic and axillary hair can be mediated by testosterone itself, while that of the secondary sexual hair of men requires the presence of 5α-dihydrotestosterone. This demonstrates a third paradox in androgen effects on hair follicles. Why does the stimulation of increasing size in some follicles e.g. beard require 5α-dihydrotestosterone formation, while follicles in the axillary and pubic regions carry out the same changes in the absence of 5α-dihydrotestosterone? Since androgens are stimulating the same transformation, presumably via the same receptor, this is currently difficult to understand, although it is further evidence of the intrinsic differences within hair follicles. It suggests that some less well known aspects of androgen action are involved in hair follicles normally specific to men which requires 5α-dihydrotestosterone, such as interaction with a specific transcription factor. Interestingly, androgen-dependent sebum production by the sebaceous glands attached to hair follicles is also normal in 5α-reductase deficiency (Imperato-McGinley *et al.* 1993). The identification of two forms of 5α-reductase, type 1 and type 2, has made the situation more complex, but all individuals with 5α-reductase deficiency so far have been shown to be deficient in 5α-reductase type 2 (reviewed by Randall 1994b) which appears to be the important form for much androgen-dependent hair growth.

6.4.2 The current model for androgen action in the hair follicle

6.4.2.1 The role of the dermal papilla

The mesenchyme-derived dermal papilla plays a major role in determining the type of hair produced by a follicle as shown by an elegant series of experiments involving the rat whisker by Oliver, Jahoda, Reynolds and colleagues (reviewed by Jahoda and Reynolds 1996). Whisker dermal papillae transplanted into ear or glabrous skin stimulated the production of whisker follicles and hair growth could

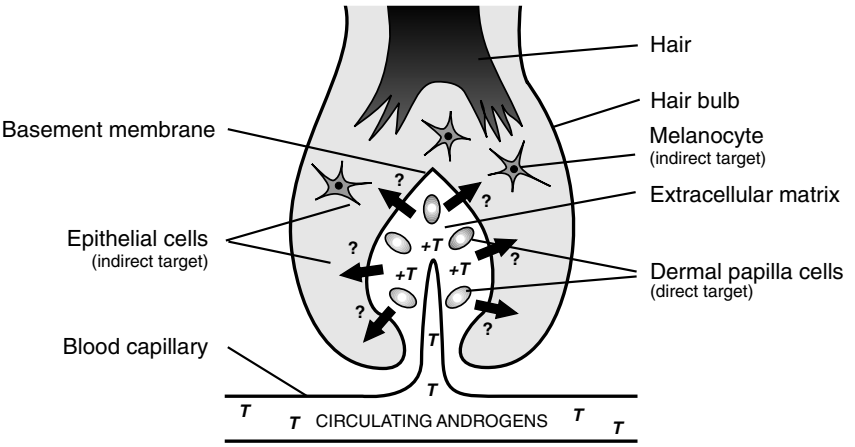

Fig. 6.5 **The current model of androgen action in the hair follicle**
Androgens from the blood enter the hair follicle via the dermal papilla's blood supply. They are bound by androgen receptors in the dermal papilla cells which then alter their production of regulatory paracrine factors; these then alter the activity of follicular keratinocytes and melanocytes. T = Testosterone; ? = unknown paracrine factors (modified from Randall 1994a).

also be stimulated by cultured dermal papilla cells reimplanted in vivo (Jahoda *et al.* 1984).

In many embryonic steroid-regulated tissues, including the prostate and the breast, steroids act via the mesenchyme (Cunha *et al.* 1987). Since hair follicles recapitulate the stages of embryogenesis during their growth cycles to reform a new lower hair follicle, they may behave like an embryonic tissue in the adult. Studies on testosterone metabolism in vitro by plucked hair follicles, which leave the dermal papilla behind in the skin, from different body sites did not reflect the requirements for 5α-reductase in vivo (reviewed in Randall *et al.* 1991; Randall 1994a), leading to the hypothesis that androgens would act on the other components of the hair follicle via the dermal papilla (Randall *et al.* 1991; Randall 1994a). In this hypothesis androgens would alter the ability of the dermal papilla cells to synthesise or release controlling factors which would affect follicular keratinocytes, melanocytes and connective tissue sheath cells and also probably the dermal endothelial cells to alter the follicles' blood supply in proportion to its change in size (Fig. 6.5). These factors could be growth factors and/or extracellular matrix proteins. This model would facilitate a mechanism for precise control of the follicle during the complex changes needed to increase or decrease the size of a follicle in response to androgens.

This hypothesis has now received a great deal of experimental support. Androgen receptors have been localised by immunohistochemistry in the dermal papilla and not the keratinocyte cells (Choudhry *et al.* 1992; Itami *et al.* 1995a). Cultured dermal papilla cells derived from androgen-sensitive follicles such as beard (Randall *et al.* 1992) and balding scalp (Hibberts *et al.* 1998) contain higher levels of specific, saturable androgen receptors than androgen-insensitive non-balding scalp in vitro; this has been confirmed by studies using RT-PCR (Ando *et al.* 1999). Most importantly, metabolism of testosterone by cultured dermal papilla cells also reflects hair growth in 5α-reductase deficiency patients with beard, but not pubic or non-balding scalp, cells forming 5α-dihydrotestosterone in vitro (Itami *et al.* 1990; Hamada *et al.* 1996; Thornton *et al.* 1993); similar results have been obtained examining gene expression of 5α-reductase type 2 by RT-PCR (Ando *et al.* 1999). All these results have led to wide acceptance of the hypothesis.

Recently the lower part of the connective tissue sheath, or dermal sheath, which surrounds the hair follicle and isolates it from the dermis has been shown to form a new dermal papilla and new human hair follicle development in another person of the opposite sex (Reynolds *et al.* 1999). Cultured dermal sheath cells from the beard hair follicles contain similar levels of androgen receptors to beard dermal papilla cells (Merrick *et al.* 2004) and balding scalp dermal sheath expresses the mRNA for 5α-reductase type 2 like the dermal papilla (Asada *et al.* 2001). Clearly the dermal sheath also plays an important role in the hair follicle. This may be as a reserve to replace the key inductive and controlling role of the dermal papilla cells if they are lost. Alternatively, or in addition, it seems highly probable that the dermal sheath cells may respond directly to androgens to facilitate the increase or decrease in size of the sheath or even the dermal papilla in the development of a new anagen follicle; this would enable the new hair follicle to be larger or smaller depending on the follicle's specific response to androgens. These results merit a modification of the model to include a direct action of androgens on the lower dermal sheath too.

6.4.2.2 Paracrine factors implicated in mesenchyme-epithelial interactions in the hair follicle

The production of growth factors by cultured dermal papilla cells derived from human and rat hair follicles has been investigated by several groups on the basis of the primary role of the dermal papilla, its potential probable role in androgen action and the retention of hair growth-promoting ability by cultured rat cells (discussed above). Cultured dermal papilla cells secrete both extracellular matrix factors (Messenger *et al.* 1991) and soluble, proteinaceous growth factors (Randall *et al.* 1991). Bioassays demonstrate that human dermal papilla cells secrete factors which stimulate the growth of other dermal papilla cells (Randall *et al.* 1991; Thornton *et al.* 1998), outer root sheath cells (Itami *et al.* 1995a), transformed epidermal keratinocytes (Hibberts and Randall 1996) and endothelial cells (Hibberts

et al. 1996c). Importantly, testosterone in vitro stimulated greater mitogenic capacity of beard cells to affect beard, but not scalp, dermal papilla cells (Thornton *et al.* 1998), outer root sheath cells (Itami *et al.* 1995a) and keratinocytes (Hibberts and Randall 1996). In contrast, testosterone decreased the mitogenic capacity of androgenetic alopecia dermal papilla cells from both men (Hibberts and Randall 1996) and stump-tailed macaques (Obana *et al.* 1997). As well as supporting the hypothesis for the mechanism of action, these results demonstrate that the paradoxical effects of androgen on hair follicles observed in vitro are reflected in vitro, strengthening the use of cultured dermal papilla cells as a model system for studying androgen action in vitro.

The main emphasis of research now lies in identifying specific factors whose production by dermal papilla cells is altered by androgens (reviewed Randall *et al.* 2001a). To date only insulin-like growth factor (IGF-1) has been identified as androgen-stimulated in vitro (Itami *et al.* 1995b), but stem cell factor (SCF), the ligand for the melanocyte receptor *c-kit*, is secreted in greater quantities by beard dermal papilla cells than non-balding scalp cells (Hibberts *et al.* 1996a) unlike vascular endothelial growth factor (Hibberts *et al.* 1996b). Other factors which have been implicated in the follicular dermal papilla include keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF), though many more have been located in the epidermis (reviewed by Philpott 2000). The expression of mRNA for the protease nexin-1 in dermal papilla cells is also altered by androgens (Sonada *et al.* 1999). This may play a role by altering the amount of extracellular matrix components produced (discussed Randall *et al.* 2001b) and therefore the size of the follicle and hair produced (Elliott *et al.* 1999). Recently, dermal papilla cell conditioned media from balding scalp follicles has been shown to inhibit the growth of both human and rodent whisker dermal papilla cells in vitro and delay mouse hair growth in vivo (Hamada and Randall 2003). This suggests the active secretion of an inhibitory factor or factors. A possible candidate is transforming growth factor-β1 (TGF-β1) which has been induced by androgens in balding dermal papilla cells with transfected androgen receptors (Inui *et al.* 2003). TGF-β also inhibits hair follicle growth in vitro (Philpott 2000) and a probable suppressor of TGF-β1 delayed catagen progression in mice in vivo (Tsuji *et al.* 2003). Further study of this area should increase our understanding of the complex hair follicle and lead to better treatments for hair follicle disorders.

6.5 The treatment of androgen-potentiated hair disorders

6.5.1 Androgenetic alopecia

Currently, the most effective treatment for male pattern baldness is the transplant of follicles from non-balding sites into the balding region, capitalising on the retention

of the different intrinsic responses to androgen discussed earlier. This has significant disadvantages; not only is it very invasive and heavily reliant on the skill of the operator for a good cosmetic result, but the alopecia continues to progress behind the transplanted area so that further transplants are often required.

Antiandrogen therapy is not a practical option for men due to the side-effects, but cyproterone acetate, in combination with estrogen to ensure contraception, has been used in women. It increased the percentage of hair follicles in anagen and may cause some regrowth, but is probably most effective in preventing further progression (Dawber and Van Neste 1995; Peereboom-Wynia *et al.* 1989). Since cyproterone acetate is unavailable in the USA, spirolactone and high-dose cimetidine have been used as alternative antiandrogens.

Minoxidil, a vasodilator used for hypertension, stimulated excessive hair growth as a side-effect. This provoked major interest in hair follicle biology because it demonstrated that vellus follicles could be stimulated to form terminal hairs. Topical application of minoxidil has been used in both male and female androgenetic alopecia. It stimulates regrowth in up to 30% with only about 10% obtaining complete regrowth, probably by acting as a potassium channel regulator; most success occurs with younger men and with the early stages of balding, i.e. Hamilton stage V or less (Dawber and Van Neste 1995). More recently, a stronger topical application of a 5% solution has been licensed for use in men (Olsen *et al.* 2002).

Finasteride, a 5α-reductase type 2 inhibitor, was developed to treat androgen-potentiated prostate disorders and is now available as an oral treatment for androgenetic alopecia in men in many countries at a lower dose of 1 mg per day. Clinical trials demonstrated significant effects on stimulating hair regrowth in men with mild to moderate hair loss (Kaufman *et al.* 1998; Shapiro and Kaufman 2003). Even if hair did not regrow, balding progression was frequently halted. Unfortunately, no effects of finasteride have been seen in post-menopausal women with androgenetic alopecia (Price *et al.* 2000); use in pre-menopausal women requires ensuring against contraception in case of potential feminisation of a male fetus.

Although a range of treatments are now available, they all need to be used continually because they are opposing a natural process which, if treatment is discontinued, retains all the components to continue to progress.

6.5.2 Hirsutism

Once a serious underlying pathology has been eliminated, a range of treatments is available for hirsutism (Azziz 2003). Cosmetic treatments such as bleaching, depilatory measures such as shaving, waxing, electrolysis or laser are common. Electrolysis with the aim of permanent removal by killing the dermal papilla and germinative epithelium/stem cells is the most established long-lasting treatment, but it is expensive, time consuming and may cause scarring; removal by laser

treatment is a more recently introduced alternative (Levy *et al.* 2001; Sanchez *et al.* 2002).

The most common endocrine treatment, outside the USA, is the antiandrogen, cyproterone acetate, given with estrogen if the woman is premenopausal; spirolactone or flutamide can be used as an alternative (Fruzzetti 1997; Lumachi and Rondinome 2003). Patients have to be well-motivated because hair growth on the face generally takes at least nine months before a noticeable effect occurs, although any acne will be cleared in a couple of months and effects on thigh hair growth will be seen in four to six months (Sawers *et al.* 1982). Facial responses are seen first on the sides of the face and last on the upper lip, in reverse order to the appearance of facial hair in men (personal observations). Finasteride has also been used for hirsutism with some success (Lacryc *et al.* 2003). This seems logical as 5α-reductase type 2 is necessary for male pattern body hair growth (see Section 6.4.1). Contraception is still required with all endocrine treatments due to the potential to affect the development of a male fetus. Metformin, insulin-sensitising therapy, aimed to alter the insulin resistance and hence the hyperandrogenism often associated with polycystic ovarian disease has been used clinically, but the evidence has yet to be rigorously tested (Harborne *et al.* 2003).

Overall, there have been major changes in the treatment of androgen-potentiated disorders over the last ten years. The ideal treatment of a uniformly effective, topical treatment which is inactivated on contact with the blood or is specific for hair follicles is not yet available. Further research on the biology of androgen action in the hair follicle may facilitate its development.

6.6 Key messages

- Androgens are the main regulator of human hair growth.
- Androgens have paradoxically different effects on hair follicles depending on their body site. They can stimulate the formation of large hairs e.g. beard, axilla, have no effect e.g. eyelashes or inhibit follicles on the scalp.
- All effects are gradual.
- Androgen-potentiated disorders of hair growth are common including hirsutism in women and androgenetic alopecia in both sexes.
- Androgen receptors are necessary for all androgen-dependent hair growth and 5α-reductase type 2 for most, but not for female patterns of axillary and pubic hair, even in men.
- The action of androgens on human hair follicles demonstrates several paradoxes: contrasting effects in different sites; major differences in the persistence of stimulatory effects depending on body region; a varying requirement for the formation of 5α-dihydrotestosterone even amongst follicles exhibiting increased growth. Since these are all site-related and retained on transplantation, these indicate intrinsic differences within follicles, presumably determined during embryonic development.

- The current model for androgen action in the hair follicle proposes that androgens act via the cells of the dermal papilla, altering their production of regulatory paracrine factors such as growth factors which then influence the activity of other follicular components, e.g. keratinocytes, melanocytes and endothelial cells. The dermal sheath may also play a role as a direct androgen target.
- Antiandrogens, generally cyproterone acetate, and a 5α-reductase type 2 inhibitor, finasteride, are being used to control androgenetic alopecia and hirsutism.
- Endocrine treatments may need several months to show their effects and will need to be used continually.
- Further understanding of the mechanism of androgens in the hair follicle is necessary to enable the development of better treatments, preferably working topically and specific to the hair follicle.

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