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Androgens and hair growth

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ABSTRACT: Hair's importance in human communication means that abnormalities like excess hair in hirsutism or hair loss in alopecia cause psychological distress. Androgens are the main regulator of human hair follicles, changing small *vellus* follicles producing tiny, virtually invisible hairs into larger *intermediate* and *terminal* follicles making bigger, pigmented hairs. The response to androgens varies with the body site as it is specific to the hair follicle itself. Normally around puberty, androgens stimulate axillary and pubic hair in both sexes, plus the beard, etc. in men, while later they may also inhibit scalp hair growth causing androgenetic alopecia. Androgens act within the follicle to alter the mesenchyme–epithelial cell interactions, changing the length of time the hair is growing, the dermal papilla size and dermal papilla cell, keratinocyte and melanocyte activity. Greater understanding of the mechanisms of androgen action in follicles should improve therapies for poorly controlled hair disorders like hirsutism and alopecia.

KEYWORDS: alopecia, balding, hirsutism, hormones, review

Introduction

Functions of human hair

Human hair growth is very important to our health and well-being. This is despite its growth being so reduced compared to most other mammals that we are termed the "naked ape." Although often seen as rather irrelevant medically because human hair loss is not life-threatening, hair is highly significant for people in many different cultures around the world (1,2). Many Western men spend a great deal of time and effort shaving daily, while "having a bad hair day" is a common expression for days when everything goes wrong! This reflects the important roles hair plays in human communication in both social and sexual contexts.

Human hair's main functions are protection and communication; it has virtually lost the insulation and camouflage roles important in mammals (1), although seasonal variations in growth (3–5) and our remaining ability to erect our hair when cold or nervous (goosebumps) indicate the evolutionary history. The visible hairs produced in childhood are mainly protective; eyebrows and eyelashes stop things from entering the eyes, while scalp hair probably protects the head and neck from sunlight, cold, and physical damage (6). Head hair is also important for social communication. Good scalp hair signals health, contrasting with the sparse, brittle hair seen during disease or starvation (7). Many cultures across history exhibit customs involving head hair. Hair removal generally has strong depersonalizing roles, for example, shaving prisoners and Christian or Buddhist monks, or covering female hair, while long uncut hair has positive connotations like Samson's strength in the Bible or among Sikhs.

Human hair is also involved in sexual communication. The development of visible pubic and axillary hair signals puberty in both sexes (8–10), while men exhibit sexual maturity with visible beard, chest, and upper pubic diamond hair (FIG. 1) (10). The beard's strong signal of masculinity and its potential involvement in threatening display behavior like the lion's mane (2,6,11) may explain its common removal. These important communication roles explain why hair disorders have serious psychological consequences and negative impact on the quality of life even among

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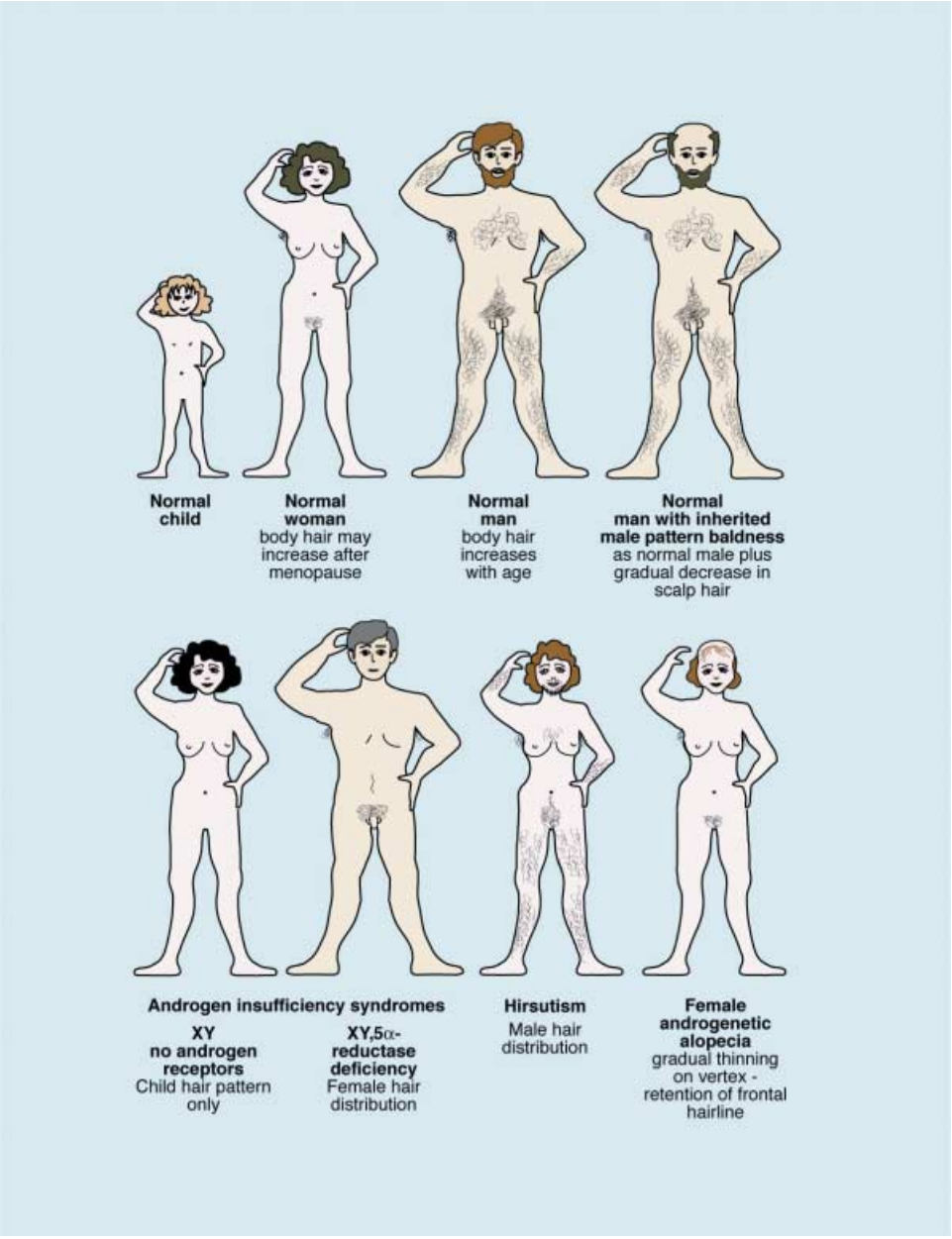

FIG. 1. Human hair patterns under differing endocrine conditions.
Visible (i.e. terminal) hair with protective functions normally develops in children on the scalp, eyelashes, and eyebrows. Once puberty occurs, more terminal hair develops on the axilla and pubis in both sexes and on the face, chest, limbs, and often on the back in men. Androgens also stimulate hair loss from the scalp in men with the appropriate genes in a patterned manner causing androgenetic alopecia. People with various androgen insufficiency syndromes (lower panel) demonstrate that none of these occurs without functional androgen receptors and that only axillary and female pattern of lower pubic triangle hairs are formed in the absence of 5α-reductase type 2. Male pattern hair growth (hirsutism) occurs in women with abnormalities of plasma androgens or from idiopathic causes and women may also develop a different form of hair loss, female androgenetic alopecia. Reproduced from Randall 2000 (132).

people who have never sought medical help (12). These include both excessive hair growth, such as hirsutism, or drug-induced abnormal hair growth, and hair loss, such as alopecia areata, an autoimmune disease affecting both sexes (13) or even androgenetic alopecia (common male-pattern hair loss) (14). Whether the high incidence of androgenetic alopecia indicates a natural phenomenon, that is, a secondary sexual characteristic, rather than a disorder can be debated (1), but in the current youth-oriented culture, looking older is not beneficial.

Hormonal control

Hair is produced by the hair follicle, a highly dynamic organ only found in mammals and crucial for their evolutionary success. It has an almost unique ability in mammals to regenerate itself during regular hair cycles which each produce a new hair, the previous hair being shed (15,16). Hormones coordinate hair growth with an individual mammal's age and stage of development or alterations to their environment, like day-length or temperature (1,17). Follicles undergo appropriate changes in response to hormonal instructions so that during the next hair cycle, the new hair produced may differ in color and/or size like the white winter, but brown summer coat of the Scottish hare (18). The main hormones regulating changes in human hair follicles are the androgens.

Androgens stimulate tiny *vellus* follicles producing fine, virtually colorless, almost invisible hairs in many parts of the body to transform into larger, deeper follicles forming longer, thicker, more pigmented hairs (FIG. 2). Although androgens stimulate hair growth in the axilla and pubis of both sexes (8–10) and greater hair on the face, upper pubic diamond, chest, etc. in men (19), they can also have the opposite effect on specific scalp areas, often in the same individual, causing balding (20). This involves the reverse transformation of large, deep follicles producing long, often heavily pigmented *terminal* scalp hairs to miniaturized vellus follicles forming tiny, almost invisible hairs (FIG. 2). In this way, human follicles pose a unique endocrine paradox as the same hormones, the androgens, cause enlargement of an organ, the hair follicle, in many areas while simultaneously inhibiting the same organ on the scalp causing balding (1,21,22).

This paper focuses on the effects of androgens on human hair follicles. It also outlines important background information about how a follicle alters the type of hair it produces, how hormones affect other mammals' hair growth, seasonal variation in human scalp and androgen-stimulated hair growth, and the effects of other hormones on human hair growth.

Changing the hair produced by a follicle via the hair growth cycle

Human hair follicles

Human skin produces hair everywhere except for the glabrous skin of the lips, palms, and soles, but until puberty most hair produced is so tiny and virtually colorless (vellus hair) that this is not well recognized; many people think that children's hair is only found on the head, eyebrows, or eyelashes as they only notice the protective larger, and more pigmented, terminal hairs (FIG. 1). Outside the skin hairs are flexible tubes of dead, fully keratinized epithelial cells that vary in thickness, length, cross-sectional shape, and color. They are produced by individual living hair follicles, cylindrical epithelial downgrowths into the dermis, and subcutaneous fat that enlarge at the base into the hair bulb surrounding the regulatory mesenchyme-derived dermal papilla (FIG. 2) (23).

Unlike other organs, the hair produced by a hair follicle frequently needs to be changed because of its important roles in camouflage, temperature regulation, such as developing a thicker coat for cold winters, or social and sexual signaling, like the lion's mane or a man's beard. Hair follicles possess a unique ability in a mammalian tissue of being able to partially regenerate via the hair follicle growth cycle (15,16,24), replacing a hair with a new one that may differ from the previous one in size or color (18) or be the same like human eyelashes (FIG. 3). Exactly how differently sized a hair can be to its immediate predecessor is currently unclear because many changes take several years like producing a full beard (19). Hair follicles pass through many cycles during an individual's life each consisting of a growth phase, anagen, during which the hair is produced, a short regressive stage, catagen, and a resting phase, telogen (FIG. 3). The upper parts of the hair follicle, the infundibulum and the isthmus, are permanent, whereas the lower follicle, the suprabulbar area and the hair bulb, regenerates in the anagen phase of each hair follicle cycle.

The hair follicle growth cycle

In anagen, the hair bulb contains extensively dividing keratinocytes and pigment-producing melanocytes of the hair matrix surrounding a pear-shaped dermal papilla. The dermal papilla consists of specialized fibroblast-type cells embedded in an extracellular matrix and separated from the keratinocytes by a basement membrane (25). Under dermal papilla cell regulation (26,27), the hair matrix keratinocytes divide and move upwards differentiating into the various layers of the hair and its surrounding inner root sheath; matrix melanocytes transfer pigment into the developing hair keratinocytes to give the hair color. Surrounding the inner root sheath, the epithelial outer root sheath

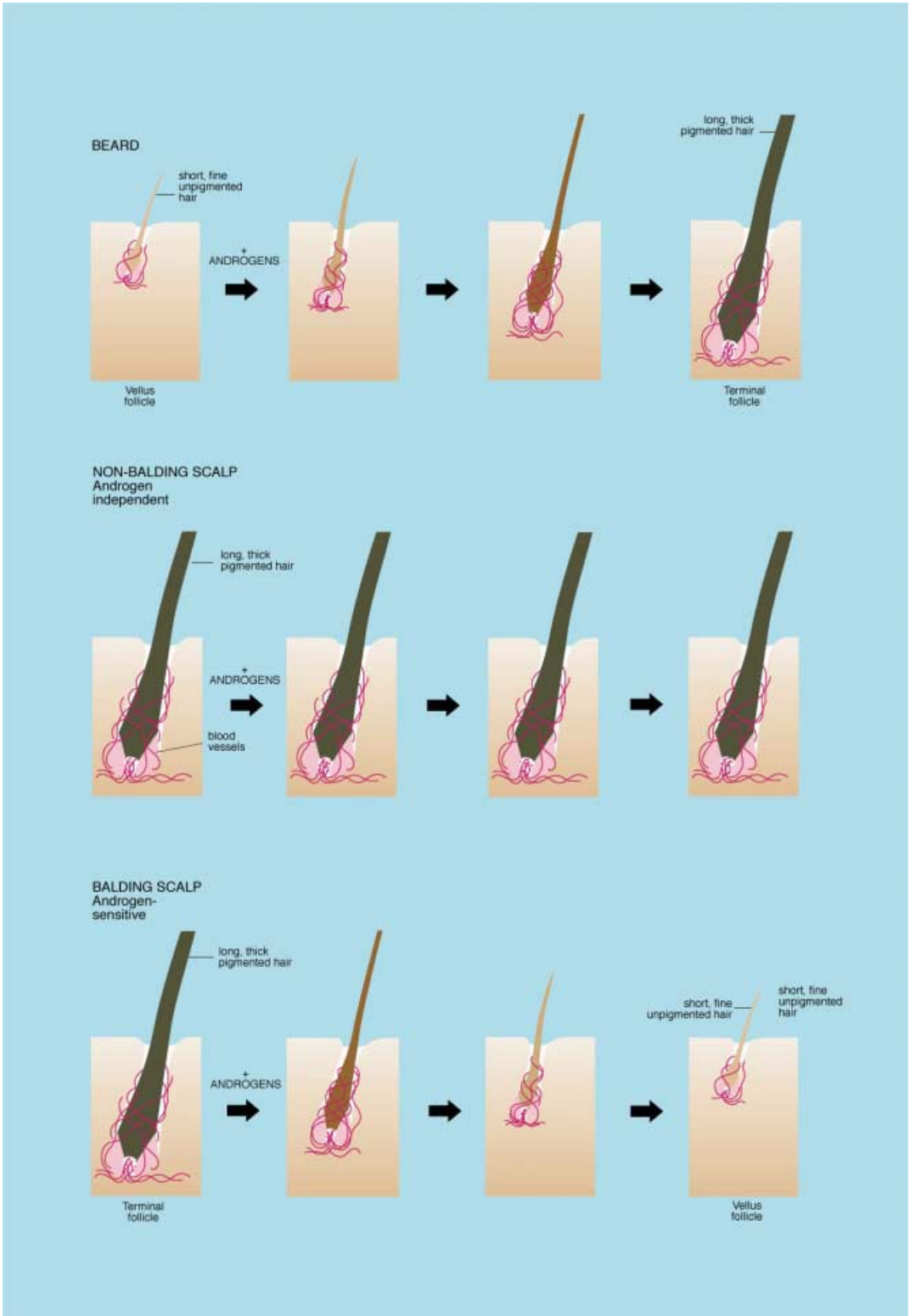

FIG. 2. Androgens have paradoxically different effects on human hair follicles depending on their body site.
During, and after, puberty androgens stimulate the gradual transformation of small follicles producing tiny, virtually colorless, *vellus* hairs to terminal follicles producing longer, thicker and more pigmented hairs (upper panel) (19). These changes involve passing through the hair cycle (see FIG. 3). At the same time many follicles on the scalp and eyelashes continue to produce the same type of hairs, apparently unaffected by androgens (middle panel). In complete contrast, androgens may inhibit follicles on specific areas of the scalp in genetically susceptible individuals causing the reverse transformation of terminal follicles to *vellus* ones and androgenetic alopecia (20). Diagram reproduced from Randall 2000 (132).

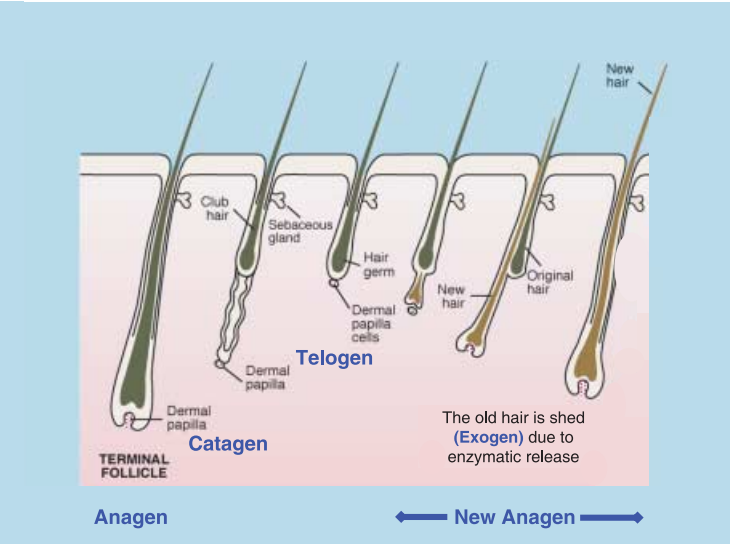

FIG. 3. The hair follicle growth cycle.
Hair follicles go through well-established repeated cycles of development and growth (anagen), regression (catagen), and rest (telogen) (1,2) to enable the replacement of hairs, often by another of differing color or size. An additional phase, exogen, has been reported where the resting club hair is released (42–44).

contains both the epithelial (28,29) and melanocyte stem cells (30) in its permanent mid-region and becomes continuous with the epidermis at the skin surface. The connective tissue, or dermal, sheath encloses the follicle, separating it from the dermis. The dermal papilla produces paracrine factors determining the size and color of the hair produced (26,27,31); it is also believed to interpret circulating signals such as hormones for the follicle (1,21) (discussed in 5). Although the cell biology and biochemistry of hair growth are not fully clarified, factors implicated in anagen so far include insulin-like growth factor-I (IGF-I) (32), keratinocyte growth factor (KGF) (33), hepatocyte growth factor (HGF) (34), noggin, and bone morphogenic protein (BMP)/Wnt5a (35) (reviewed in (36–38)). In addition, stem cell factor (SCF) from the dermal papilla (39,40) is essential for the proliferation, differentiation, and melanin production by follicular melanocytes expressing its receptor c-kit (40,41).

Once a hair reaches its full length, a short involution phase, catagen, occurs. During this phase where cell division and pigmentation stops, extensive apoptosis occurs, and the dermal papilla shrinks; the hair becomes fully keratinized with a swollen "club" end and moves up in the skin with the regressed dermal papilla, stopping near the arrector pili muscle insertion. After a period of rest, telogen, the dermal papilla cells and associated keratinocyte stem cells reactivate and the cycle begins again; another anagen phase develops a new lower follicle which grows back down into the dermis, inside the guidelines of the dermal sheath which surrounded the previous follicle. The new hair then grows up into the original upper follicle (FIG. 3). The existing hair is generally lost; although previously thought due to the new hair's upward movement (24), a further active shedding stage, exogen, involving the activation of proteolytic processes has now been identified (42–44).

Significance of the hair cycle for hair length

The length of the hair cycle stages varies dramatically in different parts of the human body (45). Scalp follicles have the longest anagen phases, which can last up to several years; waist length hair will have grown for about 7 years. They have a much shorter catagen phase (1–2 weeks) and a telogen phase lasting several months. This means that the majority of normal scalp follicles are in anagen (80–85%), with the rest either in catagen (2%) or in telogen (10–15%), though this varies with the time of the year for people living in temperate zones (see Seasonal changes in human hair growth). The anagen phase in other body regions is substantially shorter; on the arms, legs, and thighs it is about 3 to 4 months (45). Anagen length generally determines hair length; long scalp hairs are produced by follicles with anagen periods of over 2 years, while short finger hairs only grow for around 2 months (45). The rate of hair growth varies much less over the body

usually being close to 0.3–0.4 mm per day (45,46). This means that to change the amount of hair produced for clinical reasons the main target is to alter the length of anagen either by decreasing it for hirsutism or by increasing it for alopecia.

Hormonal factors affecting mammalian hair growth

Mammalian hair follicles, including human follicles, are under hormonal regulation due to the importance of coordinating alterations in insulative and color properties of a mammal's coat to the environment or its visibility to changes in sexual development. This is of life-threatening importance to many mammals as too thin or incorrectly colored hair could mean death from cold or predation.

Hormonal coordination of seasonal changes in animals

Seasonal changes usually occur twice a year in many mammals living in temperate or polar regions with coordinated waves of growth and moulting to produce thick, warm winter coats and shorter summer pelage. These are linked to day-length and, to a lesser extent, temperature, such as seasonal breeding activity (17,47). Nutrient availability can also affect hair type because of the high metabolic requirements of hair production (48). Studies in many species show that long daylight hours initiate short periods of daily melatonin secretion by the pineal and summer coat development, while short day-length increases melatonin secretion and stimulates a longer, warmer pelage (47,49 reviewed in 1,17). The pineal gland acts as a neuroendocrine transducer converting nerve impulses stimulated by daylight to reduced secretion of melatonin, normally secreted during the dark. Melatonin signals are generally translated to the follicle via the hypothalamus–pituitary route; prolactin particularly, but also growth hormone and IGF-1 are implicated at the follicle level (reviewed in 1).

Other hormones implicated in regulating mammalian hair growth cycles include the sex steroids, estradiol and testosterone, and the adrenal steroids (1,17); these delay anagen in rats (17,50). Topical application of 17β-oestradiol to mice skin inhibits hair growth and accelerates catagen, while antiestrogens promote early anagen (51–54). Testosterone also delays seasonal hair growth in badgers (55), while urinary cortisol levels are negatively correlated with hair loss in rhesus macaque monkeys (56). In contrast, thyroid hormones in rodents advance anagen while thyroidectomy or propylthiouracil delays it (17,50). How these circulating hormones interact is still unclear, but the main drivers in seasonal coat changes are light, melatonin, and prolactin.

Seasonal changes in human hair growth

Seasonal alterations are much less obvious in human beings, where follicle cycles are not usually synchronized after the first year, other than in groups of three follicles called Demeijère trios (45). Regular annual cycles in human scalp (3–5) and beard and other body hair growth (3) were only recognized relatively recently. Scalp hair showed a single annual cycle with over 90% of follicles in anagen in the spring, falling to around 80% in autumn in 14 healthy Caucasian men aged 18–39 in Sheffield, UK (latitude 53.4°N); the number of hairs shed in the autumn also more than doubled (3). Similar increased autumnal hair shedding has been reported in New York women (4) and French men (5). Since scalp hair usually grows for at least 2–3 years and often longer (45), detection of an annual cycle indicates a strong response to seasonal hormonal changes by any follicles able to react, presumably those in later stages of the hair anagen phase.

Androgen-dependent body hair also showed annual changes in men (3). Winter beard and thigh hair growth rate were low, but increased significantly in the summer (see (1)). French men showed similar summer peaks in semen volume, sperm count and mobility (57) suggesting androgen-related effects, while higher summer testosterone levels with lower winter values were also reported in European men (58,59) and pubertal boys (60). Although testosterone changes probably alter beard and thigh hair growth, they seem less likely to regulate scalp follicles as women also show seasonal changes. Annual fluctuations of thyroid hormones, with peaks of thyroxine (T3) in September and free triiodothyronine (T4) in October (61), could also influence scalp growth, but hypothyroidism is normally associated with hair loss (62).

Thigh follicles also showed biannual changes in the numbers of hairs actually growing, reaching 80% in May and November, but falling to around 60% in March and August (3). This pattern is similar to the spring and autumn moults of many temperate mammals and our seasonal study population definitely exhibited seasonal behavior despite indoor occupations (3); these cycles are

presumably controlled like those discussed earlier in "Hormonal coordination of seasonal changes in animals." Human beings can respond to altered day-length by changing melatonin, prolactin, and cortisol secretion, but artificially manipulated urban lighting suppresses these responses (63). Nevertheless, people in Antarctica (64) and those with seasonal affective disorder (65) maintain melatonin rhythms.

Significance of annual seasonal human hair changes for patients and therapies. These annual changes are important for any investigations of androgen-dependent or scalp hair growth, particularly in individuals living in temperate zones. Hair loss may be exacerbated during the increased autumnal shedding in both male and female patients. They also have important implications for any assessments of new therapies or treatments to stimulate, inhibit, or remove hair; to be accurate, measurements need to be carried out over a year to avoid natural seasonal variations.

Androgen regulation of human hair growth

Endocrine control of human hair growth

Androgens are the clearest regulators of human hair growth, as long as individuals have good nutrition (7,66) and normal thyroid function (62,67); hypothyroidism is associated with hair loss (62). Pregnancy hormones also alter hair growth, keeping follicles in anagen, but many enter catagen and telogen postpartum, causing diffuse hair loss due to a synchronized partial shedding or moult (68). Hair loss can be obvious in the autumn due to seasonal shedding (see Seasonal changes in human hair growth): which hormones control this shedding is unclear, but estrogen and prolactin are possible. Human follicles have prolactin (69) and 17β-estradiol (70) receptors, but 17β-estradiol inhibits cultured human follicles (71) and rodent hair growth, stimulating catagen (52–54), the opposite to pregnancy. Prolactin reduces human follicular growth in vitro (69) supporting a role in postpartum shedding. Estrogens are used as treatment for androgen-dependent disorders, but their effects are probably due to interfering with androgen action, for example, by reducing androgen availability by increasing blood sex hormone binding levels, rather than direct effects on hair follicles. The role of estrogens in hair growth is currently under investigation (71,72).

Androgens have paradoxically different effects on human hair follicles

The importance of androgens is shown when pubertal pubic and axillary hair develops (8–10) in girls before boys (73,74), paralleling increasing circulating androgens. Testosterone also stimulates beard growth in eunuchs and elderly men (75), while castration inhibits beard (19) and balding (76). The roles of androgens and androgen receptors in adult hair are emphasized in XY individuals with complete androgen insufficiency, i.e., unable to respond to androgens due to dysfunctional androgen receptors (77); they develop a female-type phenotype, but lack pubic and axillary hair or androgenetic alopecia (FIG. 1). Sexual hair development is inhibited in growth hormone deficiency (78), suggesting that growth hormone is also essential.

When androgens stimulate the tiny vellus follicles to produce longer, thicker, more pigmented hairs (FIG. 2), the follicles must pass through the hair cycle, regenerating the lower follicle to carry out such changes (see "The hair follicle growth cycle"). Although androgens stimulate hair growth in many areas, causing greater hair on the face, upper pubic diamond, chest, etc. in men (19), they can also have the opposite effect on specific scalp areas, often in the same individual, causing balding (20). This involves a reverse transformation via hair follicle cycles, changing large, terminal follicles producing long, often heavily pigmented scalp hairs to miniaturized vellus follicles forming tiny, almost invisible hairs (FIG. 2). This balding usually occurs in men in a precise pattern starting with regression on the forehead and thinning in the center of the vertex and may continue exposing large areas of scalp (20,79); the lower sides and back normally retain terminal hair. A different pattern of androgen-dependent alopecia may present in women; the frontal hairline usually remains unaffected while generalized thinning occurs on the central scalp and vertex (80) (FIG. 1). Androgenetic alopecia is reviewed elsewhere (14). At the same time, androgens have no apparent effect in other areas such as the eyelashes (FIG. 2). How does this paradoxical effect occur of one hormone frequently stimulating hair follicles, but also having no effect or inhibiting the same organ in the same person?

There are also significant differences between androgen-stimulated follicles. Female androgen levels affect axillary and lower pubic follicles, while other follicles require male levels (72,73). Follicle sensitivity also varies; facial follicles enlarge first above the mouth (moustache) and on

the chin in boys and hirsute women, spreading gradually over the face and neck (10). Similar gradual progression occurs elsewhere taking many years to show the full response like on a man's chest (19) or balding (20,79); terminal hairs may only appear on the ear canal in the fifties (49). Interestingly, these slow changes resemble the late androgen-dependent responses in the prostate-causing prostatic benign hypertrophy and carcinoma (81). Beard and axillary hair growth show another paradox; after their pubertal growth spurt, beard growth remains high, while axillary hair growth decreases rapidly in both sexes (19).

Why do follicles respond so differently?

These contrasts must be due to intrinsic differences in gene expression within follicles at different sites, since all receive the same circulating hormones and use the same receptors. A follicle's retention of its original androgen response when transplanted, the basis of cosmetic hair transplants, confirms this (82). Presumably, this genetic programming occurs during embryonic patterning processes. The molecular mechanisms involved in the development of different follicle types are not clear, but secreted signaling factors (such as Eda, sonic hedgehog, Wnt) and various growth factor families (like the BMPs), nuclear factors (including various homeobox genes), and others such as Hairless and Tabby, plus transmembrane and extracellular matrix molecules are all implicated (83,84).

Human follicles require androgens to initiate these marked changes. However, if adult men are castrated, although beard growth falls (19) and balding halts (85), neither returns to prepubertal levels, indicating that androgens have altered some gene expression permanently or that the lower androgen levels provided by the adrenals can maintain a partial effect. Increased summer beard growth (3), probably due to raised androgens (Seasonal changes in human hair growth), and inhibition of hirsutism (86) or regrowth stimulation in androgenetic alopecia (87,88) by drugs interfering with androgen action confirms that androgens are also needed to maintain follicular responses.

Genetics also appears important (reviewed in 1). Heavy beard growth (19) and balding (75) run in families and Caucasians generally exhibit more hair than Japanese (19) and more baldness than Africans (89). Several genes have been investigated for association with androgen-sensitive hair disorders with some links with those involved with androgen metabolism or receptors (reviewed (1)). Interestingly, women with polycystic ovaries and their brothers with early balding show links to the steroid metabolism gene, CYP17 (90). A recent study of androgenetic alopecia families suggests a new susceptibility gene on chromosome locus 3q26 (91).

How do androgens carry out these changes?

General mechanism of action of androgens

Steroid hormones diffuse through cell membranes to act on target cells by binding to specific intracellular receptors. These hormone-receptor complexes undergo conformational changes, exposing DNA binding sites, and bind to specific DNA hormone response elements (HRE) often in combination with accessory (coactivating) proteins, promoting expression of specific, hormone-regulated genes. Androgen action is more complex than other steroids (92). The main male androgen, testosterone, binds receptors in some tissues, for example, skeletal muscle; in others, including secondary sexual tissues like prostate, testosterone is metabolized intracellularly by 5α-reductase to more potent 5α-dihydrotestosterone (DHT), which binds more strongly to the androgen receptor (see FIGS 4 and 5) (93).

The mechanism of androgen action in hair follicles

Androgen-dependent follicles all require androgen receptors to respond ("Endocrine control of human hair growth"), but the need for 5α-reductase varies with body region. Men with 5α-reductase type 2 deficiency only produce female patterns of pubic and axillary hair growth (94) (FIG. 1), indicating that DHT is necessary for male-specific follicles like beard, while testosterone can stimulate the axilla and pubic triangle in both sexes. Why some follicles need DHT and others testosterone to stimulate the same cell biological changes is unclear; presumably, the cells use different intracellular coactivating proteins to act with the receptor. Since 5α-reductase type 2 deficient men do not show alopecia and the 5α-reductase type 2 inhibitor, finasteride, can restore hair growth (87), 5α-reductase type 2 also seems important for androgen-dependent balding. Skin contains many enzymes that can metabolize weak androgens, like dehydroepiandrosterone, to more powerful

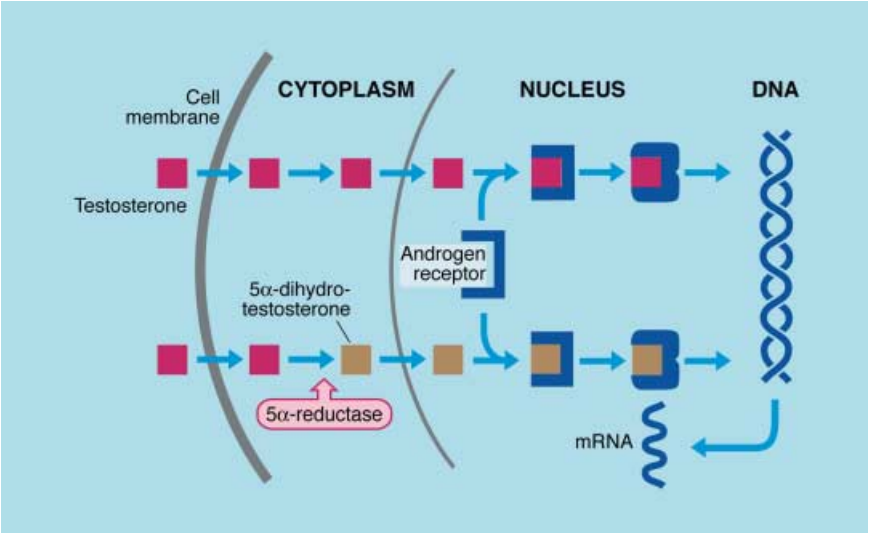

FIG. 4. Simple schematic of the general mechanism of androgen action.
Androgens diffuse from the blood through the plasma membrane. Inside the cell, like other steroid hormones, testosterone may bind to specific androgen receptors (upper scheme). This occurs in many tissues such as skeletal muscle and 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 metabolized to the more potent androgen, 5α-dihydrotestosterone (lower scheme). 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 coactivating proteins, will bind to specific hormone response elements (HREs) in the DNA altering the expression of specific androgen-dependent genes.

ones, or testosterone and androstenedione to estrogens, 17β-estradiol or estrone (see FIG. 5). However, hairs' absence when androgen receptors are dysfunctional ("Endocrine control of human hair growth") indicates that androgens binding to the receptor, i.e., testosterone and DHT, are the most important.

Specific effects of androgens on hair follicle cells

Androgens must alter many aspects of follicular activity to change the hair produced. They must modify the ability of epithelial matrix cells to divide, determine whether they should differentiate into the central medulla (found in some large hairs), and regulate the pigment (color) produced and/or transferred by follicular melanocytes. They must also change dermal papilla size, as this is proportional to the hair and follicle size (95,96), and ensure that the surrounding dermal sheath adjusts to fit the new sized follicles. Androgens definitely alter these aspects as interfering with androgen action reduces hair diameter, growth rate, length, pigmentation, and medullation in hirsute women (97) and increases them in alopecia (87).

Current model for androgen action in hair follicles

Hair follicle growth is complex but rarely abnormal indicating a highly controlled system. This suggests that androgen action is coordinated through one part of the follicle. The current hypothesis, proposed in 1990 by Randall et al. (98), focuses on the dermal papilla with androgens acting directly on dermal papilla cells where they bind to androgen receptors and then initiate altered gene expression of regulatory factors which influence other target cells (FIG. 6). These factors could be soluble paracrine factors and/or extracellular matrix factors; extracellular matrix forms much of the papilla volume and dermal papilla size corresponds to hair and follicle size (95,96). In this model, the dermal papilla is the primary direct target, while other cells such as keratinocytes and melanocytes are indirect targets.

This hypothesis evolved from several concepts (reviewed in 21,98) including: dermal papilla determination of the hair type produced (27); adult follicle cycles partially recapitulating their embryogenesis; strong parallels in androgen-dependency and age-related changes between

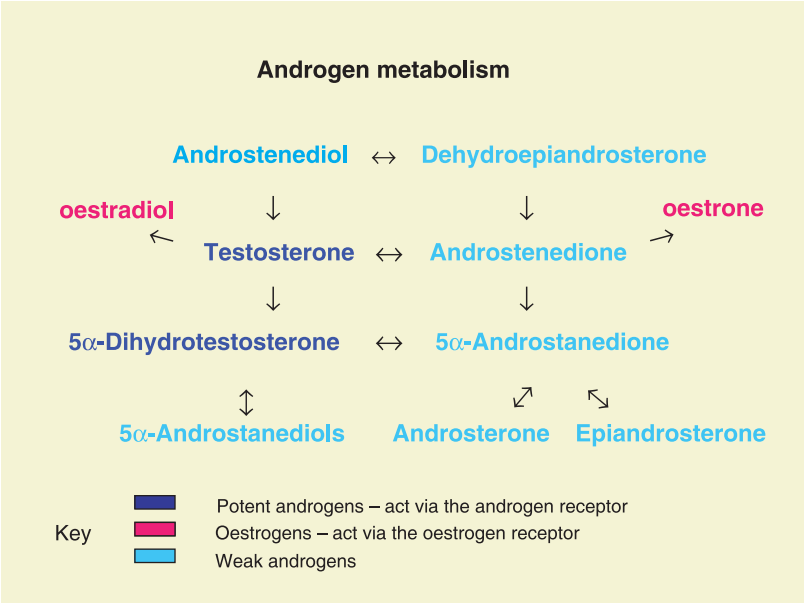

FIG. 5. Androgen metabolism.
Circulating androgens such as testosterone from the testis in men and weaker androgens such as dehydroepiandrosterone and androstenedione from the adrenals and ovaries in women can be metabolized in many skin tissues. Some metabolism causes an increase in potency, e.g., from 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 estrogens.

follicles and prostate; and androgens acting on embryonic prostate epithelium via the mesenchyme (81). This model now has strong experimental support. Androgen receptors are found in the dermal papilla and cultured dermal papilla cells derived from androgen-sensitive follicles including beard, balding scalp, and deer manes (99–103). Cells from androgen-sensitive sites contain higher levels of specific, saturable androgen receptors than androgen-insensitive ones (99,101,102). Importantly, beard, but not pubic or nonbalding scalp, dermal papilla cells metabolize testosterone to DHT in vitro (104–106), reflecting hair growth in 5α-reductase deficiency; 5α-reductase type 2 gene expression also supports this (103).

However, some recent observations suggest minor modifications. It is now clear that the dermal sheath has other roles as well as isolating the follicle; it can form a new dermal papilla and stimulate follicle development (107). Cultured dermal sheath cells from beard follicles contain similar levels of androgen receptors to dermal papilla cells (personal observations) and balding dermal sheath express 5α-reductase type 2 mRNA (108), indicating that the dermal sheath can respond to androgens without the dermal papilla acting as an intermediary. The sheath may be a reserve to replace a lost dermal papilla's key roles because of hair's necessity for mammalian survival and/or sheath cells may respond directly to androgens to facilitate alterations in sheath, or dermal papilla, size to form a differently sized follicle.

Investigations into keratins in the hair medulla (only seen in the middle of large human hairs) found a specialized keratin, hHa7, in beard, pubic, and axillary hair (109). Beard medulla cells showed coexpression of keratin hHa7 and the androgen receptor. Since the hHa7 gene promoter also contained sequences with high homology to the androgen response element (ARE), keratin hHa7 expression may be androgen-regulated. However, no stimulation occurred when the promoter was transfected into prostate cells and keratin hHa7 with the same promoter is also expressed in androgen-insensitive body hairs of chimpanzees making the significance unclear. Nevertheless, the current model needs modification to include possible specific, direct action of androgens on lower dermal sheath and medulla cells.

The alteration of signaling molecules in the hair follicle by androgens

The last aspect of androgen action involves the alteration of paracrine signaling factors produced by dermal papilla cells. Although paracrine signaling

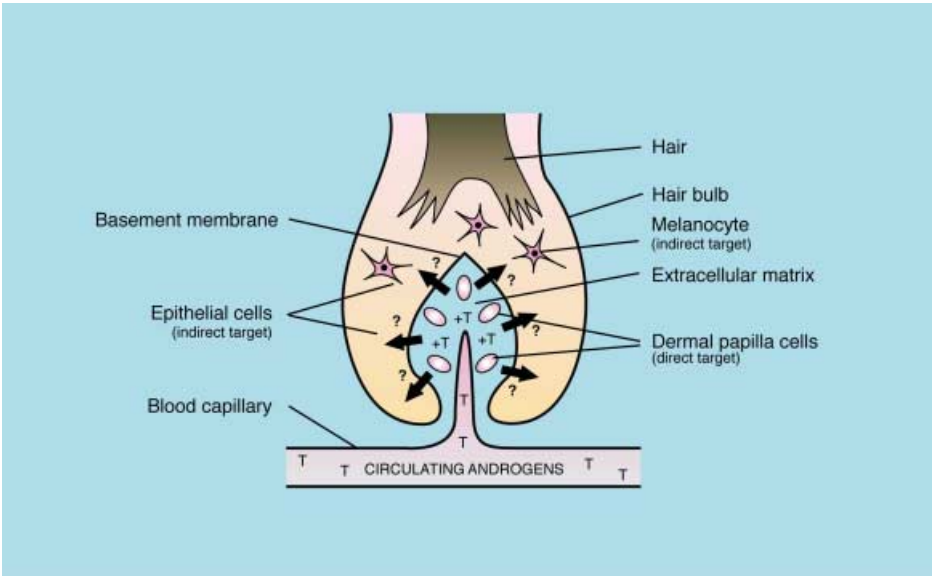

FIG. 6. Model of androgen action in the hair follicle.
In the current hypothesis androgens from the blood enter the hair follicle via the dermal papilla's blood supply. If appropriate they are metabolized to 5α-dihydrotestosterone (DHT) (see FIG. 4). They bind to androgen receptors in the dermal papilla cells causing changes in their production of regulatory paracrine factors; these then alter the activity of dermal papilla cells, follicular keratinocytes, and melanocytes. T = testosterone; ? = unknown paracrine factors. Reproduced from Randall 2000 (132).

in developing and cycling follicles is currently a major research focus, there are few practical animal models for studying androgens (110) because of their special effects on human follicles. Cultured dermal papilla cells from follicles with different sensitivities to androgens offer a useful, though difficult to work with model in which to study androgen effects (reviewed in 1). They secrete both extracellular matrix (111) and soluble proteinaceous factors that stimulate growth in other dermal papilla cells and various epithelial cells (98,112–114). Soluble factors from human cells can cross species affecting rodent cell growth in vitro and in vivo (115), paralleling the ability of human dermal papillae to induce hair growth in vivo in athymic mice (116).

Importantly, testosterone in vitro increases the ability of beard cells to promote increased growth of other beard dermal papilla cells and keratinocytes (112–114) but decreased that of androgenetic alopecia dermal papilla cells from both men (114) and stump-tailed macaques (117). This implies that an autocrine mechanism is involved; androgen-mediated changes do involve alterations in dermal papilla cell numbers as well as the amount of extracellular matrix (96). A need to modify the autocrine production of growth factors could contribute to the slow androgenic response that often takes many years to reach full effect (19). This all supports the model (FIG. 6) and shows that the paradoxical androgen effects in vivo are reflected in vitro, strengthening the use of cultured dermal papilla cells as an in vitro model system.

Identifying the factors androgens alter could lead to novel treatments for hair disorders. So far, only insulin-like growth factor (IGF-1), a potent mitogen, is identified as secreted by beard cells under androgens in vitro (100). Beard cells also secrete more SCF than nonbalding scalp cells (118), while balding cells produce less (119). Since SCF plays important roles in hair pigmentation (reviewed in 119), the dermal papilla probably provides local SCF for follicular melanocytes. Androgens in vivo appear to alter *scf* expression by facial dermal papilla cells to change melanocyte activity thus altering hair color (119). Recently, DNA microarray methods also revealed that three genes, *sfrp-2*, *mn1*, and *atp1β1*, were expressed at significantly higher levels in beard than normal scalp cells, but no changes were detected due to androgen in vitro (120). Despite difficulties in culturing androgenetic alopecia dermal papilla cells (121), androgens inhibit their expression of protease nexin-1, a potent inhibitor of serine proteases, which regulate cellular growth and differentiation in many tissues (122). Androgens also stimulate their production of transforming growth factor-β (TGF-β) and TGF-β2 (123,124) and dickkopf 1(DKK1) (125). TGF-β is a

strong candidate for an inhibitor of keratinocyte activity in alopecia (reviewed in 1), although TGF-β2 and TNF-α were actually slightly reduced in balding cells in a limited DNA macroarray analysis (126). Thus, studying dermal papilla cells implicates several factors already: IGF-1 in enlargement; SCF in altered pigmentation; and nexin-1, TGF-β, and DKK1 in miniaturization. Alterations in several factors are probably necessary to precisely control the major cell biological rearrangements required when follicles change size.

Summary and conclusions

In summary, changes in hair growth promoted by androgens often have strong negative effects on an individual's quality of life because human hair plays such important roles in human communication. This is particularly true in hirsutism, that is, excessive hair growth in women in the characteristic male pattern, the subject of this issue. Although many methods are available to remove excess hair as described in this issue (Physical Means of Treating Hirsutism) or drugs that help to modify the excess growth (127,128 (in this issue, Medical Treatment of Hirsutism)), most treatments must be applied continually to counteract the constant supply of hormones. New therapeutic development is hampered because we do not fully understand how androgens cause their different effects on hair follicles depending on the body site. However, our current knowledge has already led to the use of antiandrogens, such as cyproterone acetate and spironolactone, and 5α-reductase inhibitors, like finasteride, for hirsutism.

Our increased awareness that androgen signals are received by the hair follicle dermal papilla and translated to the hair follicle by paracrine signals, like growth factors, opens future avenues for novel therapeutic approaches. Recently, successful clinical response to the 5α-reductase inhibitor, finasteride, was related to increased dermal papilla expression of IGF-1 (129), confirming the importance of dermal papilla-produced paracrine factors. Basic research has also recently identified potassium channels in hair follicles which can be opened by minoxidil or other potassium channel openers, enabling a mechanism for minoxidil's previously unexplained action in stimulating hair growth despite its use for balding for over 20 years (130,131). Inhibiting/closing these channels could also potentially treat hirsutism as potassium channel blockers, e.g., tolbutamide, inhibit cultured hair follicles in vitro (130,131). Greater understanding of hair follicle biology, particularly androgen action, should lead to new ways to treat hair disorders.

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