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Sebum

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SEBACEOUS GLANDS

Anatomy

Sebaceous glands are multilobular holocrine glands generally associated with hair follicles (1). The basal sebocytes sit on a basal membrane at the outer limits of the lobes, and as cells move from the basal layer toward the lumen of the gland they synthesize lipids, which accumulate as intracellular lipid droplets. As they synthesize lipid, the cells become larger, and the nucleus and other internal organelles are degraded. Ultimately, the entire mass of the cell is converted into a viscous liquid-phase lipid mixture. In most pilosebaceous units, sebum passes from the sebaceous gland into the hair follicle via the short sebaceous duct and outward onto the skin surface through the follicle. Generally, the hair follicle is large compared to the associated sebaceous gland; however, large sebaceous glands are associated with vellous hairs. These units are called sebaceous follicles and predominate on the forehead and cheeks.

Distribution

Pilosebaceous units are found over the entire surface of the skin except for the palmar and plantar regions (2). The density of follicles is greatest on the head,

neck, and shoulders. In adults, the density of follicles on the scalp and face is in the range of 310 to 900 per square centimeter (1,3,4). On the torso and limbs the density of follicles is generally less than 100 per square centimeter (3). Large sebaceous glands are present in the submucosal connective tissue of the lip and buccal mucosa (5,6). Sebaceous glands in the oral mucosa often appear as slightly raised yellow spots, called Fordyce spots. Specialized sebaceous glands are also present on the edge of the eyelid (7) and the areolae of the nipples (3).

Sebum Secretion

Methods for Measurement

Early attempts to measure sebum secretion rates involved removal of lipid from the skin surface, followed by protection of a defined area of skin for a standard time (8,9). At the end of the timed interval, lipids were collected by extraction and analyzed either gravimetrically or chromatographically. These extraction-based methods tended to remove sebum from the follicles as well as some of the epidermal lipid from the stratum corneum. Therefore, methods based on direct extraction invariably overestimated the amount of lipid on the skin surface.

More recent investigations of sebum secretion have been based on adsorption of sebum as it is secreted. The adsorbents used for this purpose have included cigarette paper (10,11), bentonite gel (12), and Sebutape (Cuderm Corporation, Dallas, TX) (13,14). With all three methods, the most frequent site of measurement has been the forehead, and the skin surface is depleted of sebum at the outset of measurement.

With the cigarette paper method, the paper is delipidized by extraction with ethyl ether. After thorough drying, the paper is held in contact with the skin surface by means of a gauze strip. After a defined, standardized collection time, the paper is removed, and adsorbed lipids are extracted into ethyl ether and analyzed. Total lipid can be determined by evaporating the solution onto a tared aluminum planchet or by thin-layer chromatography in conjunction with photodensitometry (15). The latter analytical method gives composition in addition to total amount. Although the cigarette paper method has been useful, it may overestimate sebum secretion because the paper tends to deplete sebum from the follicular reservoir in addition to that which would have been secreted in the absence of an adsorbent.

The complications introduced by the follicular reservoir were most effectively addressed by the bentonite method (12), where bentonite gel is applied to the forehead 14 h before the start of the measurement period; the bentonite coating is replaced after 6 h. This pretreatment completely depletes the follicular reservoir of excess sebum. At the beginning of the measurement period, two

small dacron disks are imbedded in freshly applied bentonite near the center of the depleted region. After 3 h, the disks are removed, and the lipids are extracted into ethyl ether and analyzed by quantitative thin-layer chromatography. This method yields the sustainable sebum secretion rate, which should reflect the rate at which sebum is synthesized. Although this method has been used in several studies of great importance (cited later in this chapter), it has not been widely used. This is at least in part because the suitability of bentonite for this application varies from one batch to another.

Currently the most widely used method for studying sebum secretion is based on a porous polymeric tape called Sebutape, which is coated with a weak adhesive sufficient to hold it in contact with the skin. As sebum is secreted from the orifice of a follicle, it is adsorbed into the pores in the polymer and the appearance of the tape changes from opaque to transparent. Densitometric and computer-assisted image analysis methodology can yield information on the sebum secretion rate per unit area of skin or per follicle, as well as follicle density.

A more extensive review of the above methods—as well as several variant methods based on the decrease in light scattering of a rough surface when it becomes coated with lipid—has recently been published (16).

Hormonal Control

Sebaceous glands are stimulated by androgenic hormones produced by the testes, ovaries, and adrenal glands (3,17,18). Testosterone and androstenediol are produced by the testes. The ovaries also produce some testosterone, androstenediol, and dehydroepiandrosterone; however, the significance of these steroidal hormones in regulation of female sebaceous gland activity is uncertain. Dehydroepiandrosterone and dehydroepiandrosterone sulfate produced by the adrenal glands are the major circulating androgens in women and are also significant in men. In the sebocytes, the androgenic hormone binds to a cytosolic receptor, which then translocates to the nucleus and modulates gene expression (19–21).

Variation with Age and Gender

Sebaceous gland activity is high in utero, and this is responsible for production of the vernix caseosa, a coating of sebaceous lipid and exfoliated stratum corneum material that coats the newborn (22). By 1 year after birth, the sebum secretion rate is extremely low and remains so until the onset of puberty (23). At that time, the increased concentrations of androgenic hormones cause a rapid increase in sebum secretion rates. Although there is great individual variation in sebum secretion rates, on average sebum secretion rates begin to decline in the late teen years (24). This decline continues for the remainder of life. Although there is

considerable overlap, the average sebum secretion rate at any given age is greater for men than for women (24).

SEBUM COMPOSITION

Human

Lipid Class Composition

Human sebum from isolated sebaceous glands consists mainly of squalene, wax esters, and triglycerides with small proportions of cholesterol and cholesterol esters (25). As this viscous liquid flows outward through the follicle, lipases of both microbial and epithelial origin hydrolyze some of the triglycerides (26). Thus, sebum collected from the skin surface has a reduced proportion of triglycerides compared to sebum from the lumen of the gland, and free fatty acids are now present. The extent of triglyceride hydrolysis varies widely. Representative compositions of sebum expressed from isolated glands and from the skin surface are summarized in Figure 1. The large error bars associated with the triglyceride and fatty acid fractions from the skin surface lipid reflect the variability in triglyc-

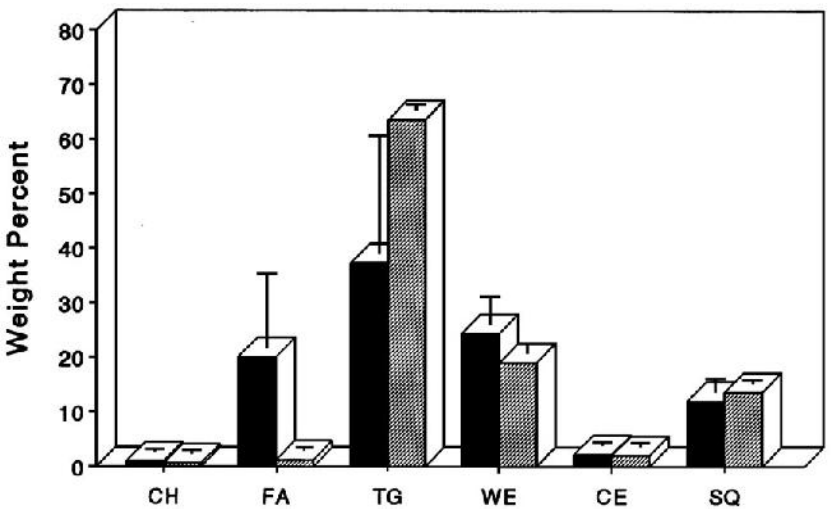

Figure 1 Composition of neutral, nonpolar lipids from the skin surface (solid bars) and isolated sebaceous glands (shaded bars). Error bars indicate 1 standard deviation. CH, cholesterol; FA, fatty acid; TG, triglyceride; WE, wax ester; CE, cholesterol ester; SQ, squalene. (Based on results from Refs. 59 and 60.)

eride hydrolysis. Representative structures of the major sebaceous lipids are illustrated in Figure 2. Squalene is normally an intermediate in the synthesis of cholesterol (27); however, in differentiating sebocytes, the enzymes beyond this point in the biosynthetic pathway are not expressed. The small proportions of cholesterol and cholesterol esters present in sebum are derived from the original basal sebocyte membranes. It is also noteworthy that the wax ester fraction consists of fatty acids ester-linked to primary fatty alcohols.

Fatty Chains

Unsaturated Species The proportions of saturated and unsaturated fatty acids vary markedly among the several ester lipid classes in human sebum (22,25). The wax ester fraction contains about 60% monounsaturated and 40% saturated fatty acids (22), whereas in the cholesterol ester fraction 65% of the fatty acids are saturated and 30% are monounsaturated (22). Small proportions of dienoic acids are present in sebum (22,28). Both linoleic acid (C18:2 Δ9, 12) and the Δ5, 8 isomer of linoleic acid have been identified (28). The Δ9, 12 isomer is derived from the diet (29); whereas, the Δ5, 8 isomer is synthesized in the gland. Interestingly, the proportion of the Δ5, 8 isomer relative to Δ9, 12 is increased in acne patients (28). In the triglyceride fraction, the saturated and mo-

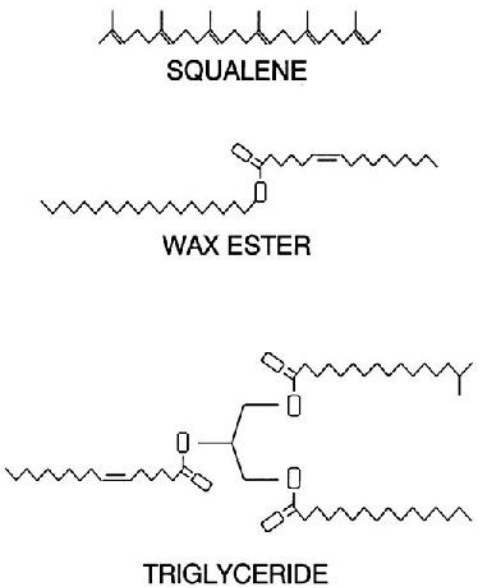

Figure 2 Representative structures of the major lipid classes of human sebum.

nounsaturated fatty acids comprise 70 and 30%, respectively (30). Most of the monounsaturated fatty acids are derived from C16:1 Δ6, or to a much lesser extent 18:1 Δ9, by extension or removal of 2-carbon units, and a small percentage of the monounsaturated fatty chains have iso or anteiso methyl branches (22,25). The chain lengths of the monounsaturates are almost entirely within the range of 14 through 18 carbons with C16:1 Δ6 (called sapienic acid) being the most abundant. Sapienic acid is shown in Figure 3.

Saturated Species The saturated fatty acids are almost entirely in the range of 12 through 18 carbons in length with palmitic acid (C16:0) being the most abundant (22,25). Generally, the straight-chain species predominate, but the proportions of methyl branched species can be highly variable (31). The methyl branched species include iso and anteiso branches (Fig. 3). There are also a wide variety of other mono and multi methyl branched saturated chains (32), but for a given individual the pattern of methyl branching appears to be constant (31).

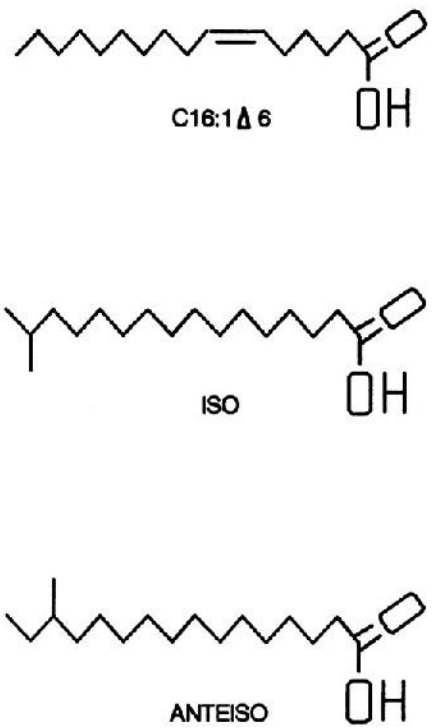

Figure 3 Fatty acids found in human sebum.

Also, identical twins appear to have identical sebaceous fatty acid compositions, including the pattern of methyl branching, while nonidentical twins, although generally having similar branching patterns, sometimes differ as much as nontwin groups (33). All of this supports the contention that sebum composition is largely under genetic control.

Other Species

All terrestrial mammals produce sebum, and in all cases the lipid mixture is a viscous liquid consisting of several types of nonpolar lipids (34,35). The lipid class composition is species-specific. Among the most widely distributed sebaceous lipids are sterols and sterol esters. In addition to the wax monoesters found in humans, the sebum from many species contains type I wax diesters in which a normal fatty acid is ester-linked to the hydroxyl group of an α-hydroxyacid, which in turn is ester-linked to a fatty alcohol or type II wax diester in which two fatty acids are esterified to 1,2-diols. Sebum from the cow also contains triesters that contain 1,2-diols with an α-hydroxyacid esterified to one of the hydroxyls and a normal fatty acid ester-linked to the other (36). A second normal fatty acid is ester-linked to the α-hydroxyl group.

Members of closely related species tend to have similar sebum compositions. For example, sebum specimens from the members of the genus *Equus* all contain cholesterol, cholesterol esters, type II wax diesters, and giant ring ω-lactones (37,38). The lactones constitute from about 50 to 70% of the total sebum mass and are formed by cyclization of 30- through 36-carbon ω-hydroxyacids. In general, the degree of unsaturation and methyl branching of the giant ring lactones from the different species of the equidae are in accord with the taxonomic relationships among these species (38). *Equus caballus*, the domestic horse, produces lactones that predominantly contain one double bond and a methyl branch on the penultimate carbon. The lactones of the donkey, *Equus asinus*, are made from 30-, 32-, and 34-carbon straight-chained ω-hydroxyacids. The lactones of the mule, *Equus caballus/Equus asinus*, are monounsaturated and 50% of the chains have the methyl branch while the other 50% are straight (38). Again, this observation indicates genetic control of sebum composition.

SEBUM IN HEALTH

In hairy mammals, sebum serves two clear functions. First, it is a water repellent on the fur, which is clearly advantageous for aquatic mammals and for mammals living in moist environments. Second, 7-dehydrocholesterol secreted from the sebaceous glands onto the skin surface is photochemically converted to previtamin D, which is then converted to vitamin D in a temperature-dependent, nonen-

zymatic reaction (39). When the animal licks its fur during grooming, the vitamin D is recovered by means of a salivary vitamin D binding protein (40). In humans, a function for sebum is less well established, and it is possible that sebum production is a functionless vestige of our ancestors. One clue in this regard comes from the species known to produce squalene as a component of their sebum. In addition to human sebum, squalene is found in the sebum of the otter, beaver, kinkajou, and mole, *Scalopus aquaticus* (41,42). The otter and beaver are aquatic; the kinkajoo lives in the canopies of tropical rain forests; and *Scalopus aquaticus* lives in moist–wet soil. Could it be that our ancestors spent a great deal of their time in water along coasts or rivers and benefited from the waterproofing afforded by a coating of squalene?

Sebum no doubt contributes a degree of lubrication to the skin surface, and it has sometimes been suggested that dry skin results from insufficient sebum production. However, two lines of evidence argue against this. First, as has been pointed out, prepubertal children produce almost no sebum but most do not suffer dry skin or other skin problems (43). Second, in one study in which the sebum secretion rate was measured and subjects were surveyed about the condition of their skin, no correlation could be found between the occurrence of xerosis and sebum production (44).

Sebum definitely does not contribute to the permeability barrier function of the skin. In fact, if human sebum is applied to neonatal rodent skin, barrier function is decreased (45).

One possible function of sebum is a contribution to the antimicrobial defense of the skin. It has long been known that fatty acids produced by sebaceous triglyceride hydrolysis have antibacterial properties (46), and it has more recently been demonstrated that sebaceous lipids can interfere with the adherence of yeast to the stratum corneum (47). In addition to a decline in function of the immune system, the decline in sebum secretion with age could contribute to the increased incidence of bacterial and fungal infections of the skin in the elderly (48). The fact that prepubertal children do not have a high incidence of skin infections may be attributed to their healthy immune systems. So sebum is clearly not essential for the avoidance of skin infections, but it may be helpful in this regard in some individuals.

SEBUM IN DISEASE: ACNE

There is a clear, positive correlation between the occurrence and severity of acne and the sebum secretion rate (49). In one study comparing age- and gender-matched subjects with moderate, mild, or no acne, the subjects with moderate acne had the highest sebum secretion rates, while those with mild acne had sebum secretion rates intermediate between those measured for subjects without acne

and those with moderate acne (49). The average sebum secretion rate for all subjects with acne was three times that for the subjects without acne, and in no case did a subject with acne have a sebum secretion rate that was not greater than the sebum secretion rate of the matched control.

The development of an inflammatory acne lesion is a multistep process (3). The initiating event is the formation of a keratinous plug, or comedo, that blocks the pore of the follicle. Bacteria within the follicle then grow and it becomes distended. The follicular epithelium becomes thin, and an inflammatory response is induced as bacterial products diffuse into the surrounding tissue.

It has been suggested that the development of acne may result from essential fatty acid deficiency localized to the follicular epithelium (50). In experimental systemic essential fatty acid deficiency, the skin becomes scaly and more permeable (29,51). If sebaceous fatty acids were to penetrate into the follicular epithelial cells and compete with linoleic acid from the circulation for incorporation into lipids, a localized essential fatty acid deficiency could be produced. The resulting scaling could lead to comedo formation, and the defective barrier function would facilitate exchange of materials between the follicle and surrounding tissue. This would include an influx of water and nutrients into the follicle to support bacterial growth as well as the eflux of inflammatory mediators.

Reduction of the sebum secretion rate is therapeutic for acne. This can be achieved by oral administration of retinoids (52,53), estrogen (54,55), or antiandrogens (55,56). Estrogen is thought to act by reducing production of testosterone, and antiandrogens act by blocking the androgenic receptors on sebocytes, thereby preventing binding of androgens.

Orally administered 13-cis-retinoic acid is an effective treatment for moderate-to-severe acne vulgaris (52,53). Although the retinoids probably act through specific receptors (57), details of their mechanisms of action remain uncertain (58). Chapter 9 deals with retinoids, so further discussion will not be included here.

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6
Hair Growth Enhancers

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INTRODUCTION

Hair has played a significant role in the lives of people throughout history, not only impacting their outward appearance but also on their inner self. Both men and women regard an abundance of hair as ideal, providing them with positive self-image attributes such as beauty, strength, virility, youthfulness, and confidence. Conversely, the lack of hair is associated with negative attributes and historically people have gone to great extremes to conceal their baldness. In early times, Egyptians used ''artificial braids'' to hide their baldness and outlandish hair-growth concoctions (e.g., snake oil) were prolific. In more recent history, minoxidil topical solution (Rogaine® 2%, Pharmacia & Upjohn) became the first clinically proved, safe, and effective hair-growth stimulant after it was discovered that its active ingredient (minoxidil) caused hypertrichosis when taken orally for hypertension. The 2% concentration of minoxidil topical solution became available in 1986 for men and in 1991 for women; a higher, more effective concentration (5%) is now available as either a prescription or nonprescription product in over 20 countries including the United States. The favorable findings with minoxidil topical solution have led to a flurry of activity to find new pharmacological agents to treat androgenetic alopecia. One such agent, finasteride (Propecia® tablets, 1 mg, Merck), was recently introduced into several countries including the United States as a prescription product for males only. Other agents are as-

suredly yet to come, as research endeavors remain intense. Since 1995 nearly 70 patent applications have been submitted for androgenetic alopecia, immunomodulatory related hair diseases, and antichemotherapeutic alopecia agents (1).

HAIR GROWTH BIOLOGY

Hair grows from primary follicles. Actively growing hair follicles penetrate the entire epidermis and dermis. There are approximately 5 million total body hair follicles, of which 100,000 to 150,000 are scalp follicles. In adults, 90% of the hair follicles are in the growing (anagen) stage and the remainder are in the resting (telogen) stage. Follicular density decreases with age (1135/cm^2 at birth to 485/cm^2 at ~30 years to 435/cm^2 at 80 years). Scalp hair grows at a rate of 0.37 to 0.44 mm/day and normal scalp hair loss or shedding in adults ranges from 50 to 100 hairs per day (2).

The growth of hair in humans is controlled by complicated mechanisms that can differ among various body locations. Morphologically, there are three types of hair: vellus, terminal, and intermediate. Vellus hairs are short, fine (<0.3 mm in diameter), soft, usually nonpigmented, and unmedullated. Terminal hairs are large (>0.3 mm in diameter), darkly pigmented, and medullated. Ninety percent of the hairs on the chest, trunk, shoulders, legs, and arms of men are terminal hairs, whereas only 45% of hairs in the same regions on women are terminal (3). Intermediate hairs occur on the scalp, and they demonstrate a morphology between those of terminal and vellus hairs. Intermediate hairs are medullated and contain a moderate amount of pigment (i.e., less than that found in terminal hairs) (4).

There are four types of hair follicles: terminal, vellus, miniaturized, and senescent. Terminal follicles bear terminal hairs at some time during the life of an individual, whereas vellus follicles do not bear terminal hairs at any time during an individual's life. Miniaturized follicles are those terminal follicles that have lost their ability to produce terminal hairs and instead produce vellus hairs. Senescent follicles are any of the three types of follicles that no longer produce hairs and have lost histological evidence of the ability to produce hairs.

The character of human hair is constantly changing from the prenatal period to old age; and under given physiological conditions, the same hair follicle can successively form different types of hair. Despite differences among individuals, follicle development for all types of hair is virtually the same.

Hair undergoes repeated cycles of active growth and rest. The relative duration of each cycle varies with the age of the individual and the region of the body where the hair grows. The length of the cycle is often modified by a variety of physiological and pathological factors. The cyclic phase of the hair follicle is

identified by an active growth period known as *anagen*, an intermediate period known as *catagen*, and a resting stage known as *telogen*.

In the anagen phase, which lasts from 2 to 8 years (2), the follicle reaches its maximum length, and there is a proliferation of the matrix cells. Anagen hair generally has a thick shaft, and in given segments its medulla is clearly visible. The proximal-most part of the bulb in anagen hair is deeply pigmented. The bulb gradually tapers and becomes lighter in color at and beyond the keratogenous zone of the follicle. Catagen hair, in its involutional form, differs from telogen (clubbed) hair in two ways: (1) its keratinized (proximal) part is darker than that of clubbed hair; and (2) its inner and outer root sheaths are better preserved (5). Unlike the anagen phase, the catagen phase is short, lasting from 2 to 4 weeks (2). Telogen hair, or clubbed hair, is easily recognized because it generally contains a thin shaft, which is transparent near the root and devoid of a medulla and keratogenous zone. The telogen phase also is much shorter than the anagen phase, lasting from 2 to 4 months (2). The normal anagen/telogen ratio is 9:1.

ANDROGENETIC ALOPECIA

Androgenetic alopecia is the most common type of hair loss in humans. Its prevalence in any population has not been accurately studied, but it occurs much more often in Caucasians than in other races (6). Androgenetic alopecia affects approximately 50% of men over 40 years of age and may also affect just as many women (7). It occurs in both men and women as a result of genetic and hormonal factors.

Morphology and Control

Androgenetic alopecia appears to be autosomal dominant with gene expression apparently determined by hair follicle location (7). Expression of androgenetic alopecia can vary considerably from one person to another. In androgenetic alopecia, genetically predisposed hair follicles become progressively miniaturized over time. In men, the thick, pigmented terminal hairs in the affected area of the scalp eventually are replaced by the fine, unpigmented vellus hairs. Eventually, the affected scalp may become completely devoid of any hair. Women, however, rarely become completely bald but usually experience thinning characterized by an intermixing of the normal terminal hairs with finer vellus hairs (7). In both men and women, the hair growth cycle is altered, with fewer hairs in the anagen stage and more hairs in the telogen stage for longer periods of time (7).

Although scalp hair growth is not androgen-dependent, androgens are necessary for the full expression of androgenetic alopecia whereby they diminish

the size of the hair follicle and diameter of the hair fiber, as well as shift hairs from the growing to resting state (6). The main androgen circulating in the plasma of men is testosterone, whereas the most important androgen in women is androstenedione. These androgens are metabolized by the enzyme 5α-reductase, reducing testosterone to dihydrotestosterone (DHT) and androstenedione to testosterone (and some DHT). In balding scalps, DHT production and the level of 5α-reductase activity are increased relative to nonbalding scalps (7). Another important enzyme, aromatase, has recently gained some attention (8,9). Aromatase is specifically located in the outer root sheath of hair follicles. It converts androgens (e.g., testosterone) to estrogens (e.g., estradiol), and there may be a two- to fivefold increase in the amount of aromatase in the scalp of women relative to men (8,9). This finding may explain the different clinical presentation of androgenetic alopecia in men and women.

Clinical Presentation

The clinical presentation of androgenetic alopecia is different for men and women. It may occur as early as 17 years of age in normal males and by 25 to 30 years of age in endocrinologically normal females (6). There is no evidence, however, to suggest that there is an age at which the onset of the balding process is no longer initiated or a threshold age at which the progression of baldness ceases to continue (7,10). Invariably, both men and women see increased shedding of hair, which prompts them to seek out medical advice.

In men, androgenetic alopecia is usually progressive, typically receding from the normal hairline in an M-shaped pattern with an enlarging balding vertex (6). Several classification systems have been used to characterize the balding state of men, the most popular being the Hamilton scale as modified by Norwood (Fig. 1) (11) and the Savin scale (Fig. 2). Women often do not present with a distinct pattern, but rather have diffuse hair loss or thinning of the temporal and parietal areas with retention of the frontal hairline in most cases. Ludwig (12) has described this pattern commonly seen in women (Fig. 3) and this classification is widely used and accepted. Women may present with the typical male patterning of hair loss, with this occurring more frequently in postmenopausal women than premenopausal women (13). In both sexes, concomitant loss of hair in the temple–sideburn areas and nape of neck can be observed as well as occasional increases in body hair.

Psychological Factors of Hair Loss

Hair loss can profoundly affect people and the clinical significance of androgenetic alopecia should not be trivialized as just a cosmetic nuisance. The World Health Organization (14) in fact classified androgenetic alopecia as a disease

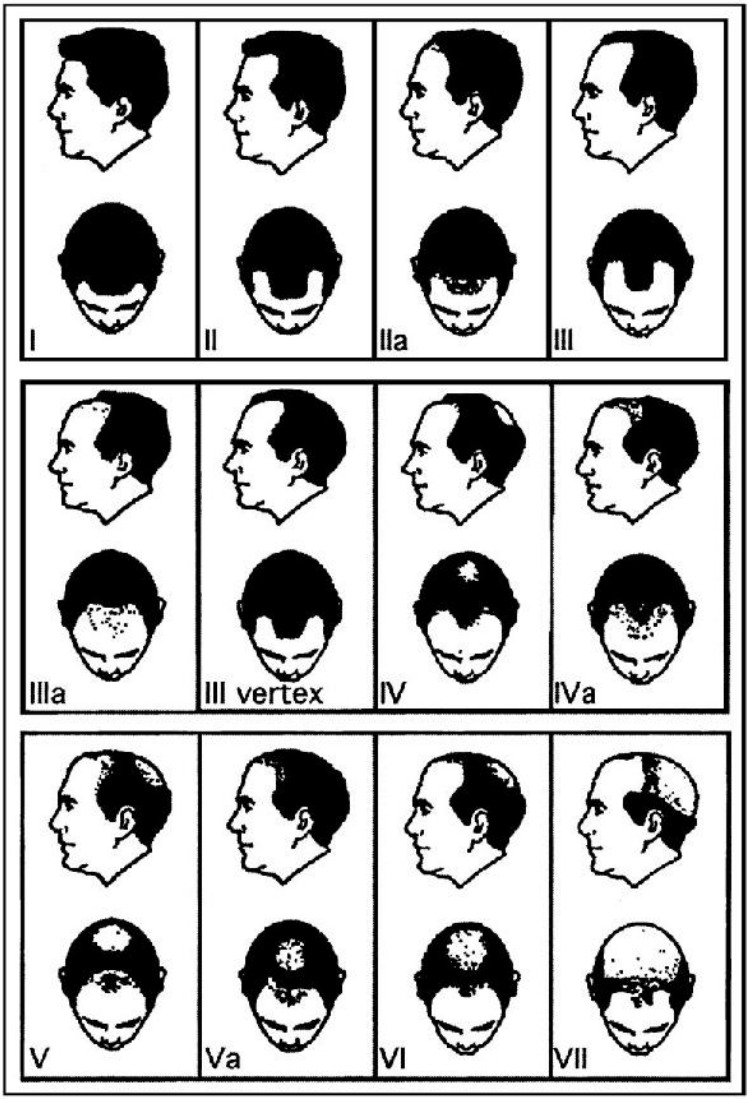

Figure 1 Hamilton baldness scale as modified by Norwood.

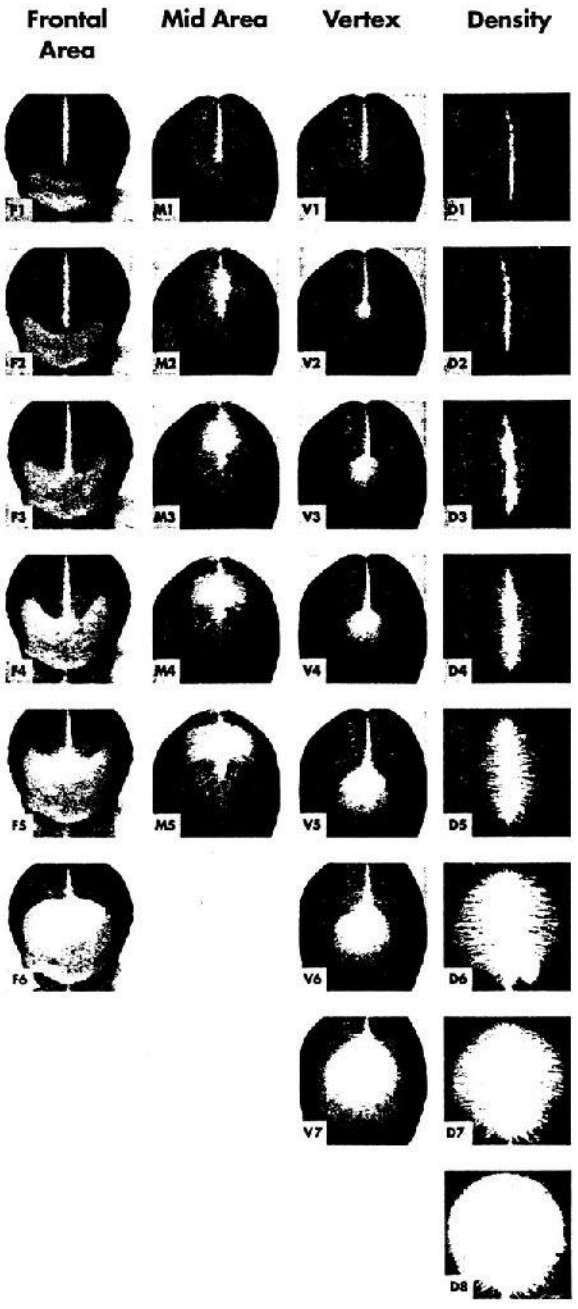

Figure 2 Savin baldness scale.

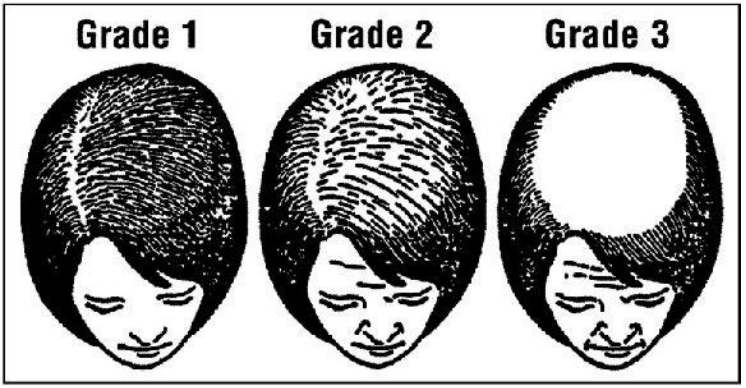

Figure 3 Ludwig baldness scale. (Reproduced with permission from Ref. 12.)

(L64). Although androgenetic alopecia is seen as a normal variant of aging by most individuals, it can have both psychological and pathological consequences and these effects are taken seriously by both the patient and physician (15,16). Despite the age of onset and the ongoing progression of the baldness per se, the main area of concern in individuals is a psychological one. The majority of men and women (90% or more) want to reverse or halt their hair loss, feel frustrated or helpless about the condition, and are self-conscious about their looks.

Psychopathological symptoms in patients with androgenetic alopecia have been well documented. Maffei et al. (17) showed that the prevalence of personality disorders in subjects with androgenetic alopecia proved to be significantly higher than the prevalence of such diagnoses in the general population. Cash (18) reported that, in men with androgenetic alopecia, the effects of balding resulted in considerable preoccupation, moderate stress or distress, and copious coping efforts. In another study by Cash et al. (19), women were nearly twice as likely as men to be ''very upset'' or ''extremely upset'' about their hair loss condition. Relative to a control group, women with androgenetic alopecia had a more negative body image as well as more social anxiety, poorer self-esteem, less of a sense of control over their lives, and less life satisfaction.

Treatment of Androgenetic Alopecia

Nonspecific Biological Response Modulators

Minoxidil Topical Solution How minoxidil topical solution affects hair growth has not been fully characterized, but it can be categorized as a nonspecific biological response modulator, with a direct effect on the hair follicle. This results

in increased size of the hair follicle with treatment, increased proliferation of dermal papilla cells, and opening of potassium channels (20).

As mentioned previously, minoxidil topical solution was first available as a 2% product for use in both men and women with androgenetic alopecia, but now a higher, more effective concentration (5%), is available in over 20 countries. The 5% product is approved for use in both men and women in most of these countries, although in Australia, Denmark, and the United States it is indicated for men only. Further research is warranted to fully delineate this apparent gender-specific situation.

Efficacy and safety of the 5% product have been clearly established in men. The results of a controlled clinical trial involving 393 men with androgenetic alopecia showed statistically significant differences favoring the 5% product over the 2% product with regard to change in nonvellus hair counts; the placebo response was generally minimal (21). The nonvellus hair count data also support that the response to treatment occurred faster with the 5% product, with effects being realized as early as 2 months. The use of minoxidil topical solution (be it at the 2% or 5% concentration) is established as a safe treatment for androgenetic alopecia with systemic medical events rarely reported in over 10 years of consumer use. Local dermatological symptoms (e.g., drying, itching, erythema) are known to occur and these tend to be more frequent with the 5% product.

Topical minoxidil solution also has the ability to stabilize hair loss, that is retardation of the existing hair loss process or, simply, maintenance of an existing head of hair. Numerous anecdotal reports by patients and clinicians as well as clinical trial data support this clinical phenomenon. Price and Menefee (22) report the results of a placebo-controlled clinical trial in 32 men with androgenetic alopecia where both 2% and 5% minoxidil topical solution were found to promote hair regrowth and retard the hair loss process over a 96-week period. Comparatively, the 5% product provided a greater benefit than the 2% product, and both were better than placebo.

Minoxidil topical solution has also been used in combination with topical retinoids. The results of a pharmacokinetic study showed that absorption of 2% minoxidil topical solution was increased when used concomitantly with 0.05% tretinoin cream (23). In a small ($n = 36$), pilot study of 0.025% tretinoin and 0.5% minoxidil topical solution, over 50% of the patients had moderate-to-good hair regrowth (24). However, in a larger ($n = 136$), controlled trial that evaluated concomitant use of 0.05% retinoic acid with 2% and 5% minoxidil topical solution, results were equivocal (unpublished data, Pharmacia & Upjohn). Nevertheless, as reported by Comacho (25), clinicians use minoxidil topical solution (2% or 3%) in combination with tretinoin (0.01%) with acceptable results.

Other Biological Responses Modulators Several other biological response modifiers (i.e., diazoxide, viprostol, tretinoin, cyclosporin A) have been tested as treatments for androgenetic alopecia (25). None of these products has

proved more effective than minoxidil topical solution, and in some cases the risks of the treatment outweighed any possible benefits. Thus, none of these products have been commercialized.

5α-Reductase Inhibitors

Finasteride Finasteride is a specific inhibitor of steroid type II 5α-reductase, an intracellular enzyme that converts testosterone to DHT. By inhibiting type II 5α-reductase, this conversion is blocked, resulting in significant decreases in serum and tissue DHT concentrations. Merck & Co. developed finasteride as an oral treatment for androgenetic alopecia after men taking finasteride (5 mg/day) for prostate enlargement noticed regrowth of their hair. Three controlled clinical trials were performed in men (18 to 41 years), with mild-to-moderate degrees of androgenetic alopecia. In these studies, 1879 men ingested either a 1-mg finasteride tablet or placebo tablet once daily for 12 months; after 12 months, finasteride-treated patients were switched to placebo and placebo-treated patients were switched to finasteride and they were followed for an additional 12 months (26,27). Clinical improvement was seen as early as 3 months in finasteride-treated patients and hair regrowth continued throughout the trial. Finasteride also had a stabilizing effect on hair loss, which was maintained through the second year of treatment. Hair counts in placebo-treated patients decreased during the study. Finasteride was generally well tolerated in these studies. Some men, however, experienced decreased libido, difficulty in achieving an erection, and decreased semen volume ($<$2% of patients in each case). These side effects resolved in 58% of the men who continued treatment and completely abated upon discontinuation of the drug (28).

Finasteride is indicated for use in men only. Women of childbearing age cannot take finasteride because it may cause hypospadia (a developmental abnormality of the penis) in the male offspring if taken during pregnancy.

Other 5α-Reductase Inhibitors Several other 5α-reductase inhibitors are currently being developed as treatments for hair loss (1), but no further information regarding their effectiveness is available at this time.

Androgen Receptor Inhibitors

RU58841 RU58841 (Roussel Uclaf) is a nonsteroidal topical antiandrogen without significant systemic effects apparently due to its metabolism in the skin. This appears to be a promising new hair growth agent that promotes hair growth on the scalp as well as retards hair growth of both beard and body hair follicles (29–32). RU58841 has produced highly efficacious results in stumptailed macaques (31,32).

The synergistic effects of RU58841 and minoxidil topical solution (2% and 5%) have also been reported in stumptailed macaques. The effect of combined

treatment was most remarkable early on, but by 1 year no significant benefit of combined treatment was apparent relative to either treatment alone (33).

Other Androgen Receptor Inhibitors Other androgen receptor inhibitors are receiving a lot of attention as evidenced by development of several agents of this type (1). No further information regarding their effectiveness in treating hair loss is available at this time.

Unproved Treatments

With the increased interest in hair growth promotion, numerous products and remedies are marketed to consumers purporting their beneficial effects. The efficacy (and safety) of these products has not been established in large, controlled clinical trials as was done for minoxidil topical solution and finasteride.

ALOPECIA AREATA

Etiology and Clinical Presentation

Alopecia areata is a nonscarring, reversible hair disorder that can cause hair loss anywhere on the body. The occurrence of alopecia areata is reported as $<0.1\%$ of the Caucasian population and between 0.9% and 4% of dermatological patients (34). It appears to affect males and females equally. Although alopecia areata can occur at any age, its onset is before the age of 20 years in about one-half of the cases (35). The course of alopecia areata is extremely variable, with hair loss occurring rapidly, slowly, or intermittently. In some cases, spontaneous hair regrowth occurs immediately, whereas in other cases, it may take days or even years for normal regrowth to occur. Recurrence and severity of the disease are unpredictable, and it can have a life-long presence for many patients.

The etiology of alopecia areata is unknown but many theories have been postulated: (1) a chronic inflammatory disease with an autoimmune basis; (2) genetic predisposition; (3) a result of psychological factors (e.g., stress, anxiety) or exposure to chemicals or infectious agents; and (4) directly related to destruction of follicular or epidermal keratinocytes and melanocytes (35,36). It very well may be that one or more of these plays a role in the disease process.

The clinical appearance of alopecia areata varies from small patches of hair loss to total loss of scalp hair (alopecia totalis) to loss of all body hair (alopecia universalis). It is not usually associated with any symptoms, although some individuals may experience pruritus or paresthesias before or coincident with the loss of hair. A variety of other diseases may also occur in association with alopecia areata, including allergic rhinitis, asthma, atopic dermatitis, diseases of the thyroid gland, vitiligo, systemic lupus erythematosus, discoid lupus erythematosus, rheumatoid arthritis, pernicious anemia, scleroderma, ulcerative colitis, myasthe-

nia gravis, and lichen planus. Alopecia areata also may occur in association with Down's syndrome and Turner's syndrome, as well as in diabetics and patients with human immunodeficiency virus (35). The diagnosis of alopecia areata can be challenging given the multitude of concomitant diseases and conditions; however, it can be absolutely confirmed by biopsy of hair follicles in the area of hair loss.

Treatment

In some cases of alopecia areata, no therapeutic intervention is necessary because of the patient's spontaneous regrowth of hair. In many cases, however, long-term therapeutic intervention is necessary in order for patients to see cosmetically acceptable hair regrowth. There are many treatment options available for alopecia areata but no one treatment stands foremost because of the variable nature of the disease and its unpredictable course (Table 1). The benefits and risks of each treatment must be carefully evaluated on a case-by-case basis.

DIFFUSE ALOPECIA

Etiology and Clinical Presentation

Patients afflicted with diffuse alopecia typically complain of hair loss all over the scalp not just in the areas usually seen in androgenetic alopecia. However, the differential diagnosis of diffuse alopecia versus androgenetic alopecia, particularly in females, can be difficult because of the similar presentation, and biopsy and histological assessment may be required to confirm the diagnosis. The course of the diffuse alopecia can be continuous or episodic. Diffuse alopecia may present as telogen or anagen effluvium and can be caused by drug and chemical exposure, thyroid disorders, nutritional influences, and psychological stress.

Telogen effluvium is characterized by abrupt, diffuse hair loss. Common causes are childbirth, febrile illnesses, surgery, psychological stress, crash diets, and drug therapy (38). The excessive shedding usually begins 3 to 4 months after the inciting event (39). Anagen effluvium is characterized by widespread or circumscribed loss of anagen hairs from growing follicles. Alopecia due to anagen effluvium is quite obvious because 90% of the hair follicles are in anagen (growing) phase. In contrast with telogen effluvium, loss of anagen hair begins within days to a few weeks after the inciting event. Common causes of anagen effluvium are radiation, toxic drugs, environmental and occupational exposure to hazardous chemicals, and loose anagen syndrome (39). Drug- and chemical-induced hair loss is usually confined to the scalp and is most often diffuse, but it can be patterned or localized. It can also manifest itself as a telogen or anagen effluvium. Hypothyroidism is directly correlated with diffuse alopecia, whereas

Table 1 Treatment Options for Alopecia Areata

Immunomodulating agents	Topical sensitizers
Intralesional steroids (triamcinolone acetonide, triamcinolone hexacetonide)	Dinitrochlorobenzene
Topical steroids (fluocinolone acetonide cream, halcinonide cream, betamethasone dipropionate cream)	Squaric acid dibutyl ester
Intramuscular steroids (triamcinolone acetonide	Diphencyprone
Systemic steroids (cortisone acetate, prednisone, prednisolone)	Combined therapies
Cyclosporine (oral or topical)	Topical, intralesional, and/or systemic steroids
Thymopentin (intravenous or intradermal)	Minoxidil topical solution with betamethasone dipropionate cream, anthralin cream, diphencyprone, or oral prednisone
Nitrogen mustard (topical)	Topical diphencyprone and oral inosiplex
Azathioprine (oral)	Oral prednisone with topical fluocinolone acetonide cream and/or intralesional triamcinolone acetonide
Phototherapy with ultraviolet B light	Oral prednisolone with oral cyclosporine
Psoralen (topical or oral) plus ultraviolet A light	Other agents
Biological response modifier	Oral zinc
Minoxidil (topical or oral)	Cosmetic management
Irritants	Liquid nitrogen
Anthralin (topical)	Turbans
	Scarves
	Hairpieces
	Custom prostheses

Source: Refs. 35 and 37.

alopecia due to hyperthyroidism is less clearly established (40). Examples of nutritional influences that can cause diffuse alopecia include caloric deprivation (crash diets), protein-calorie malnutrition, and deficiency in zinc, iron, essential fatty acid, and biotin levels (40). Finally, with regard to psychological stress, it is often difficult to determine its role in hair loss because hair loss itself can be very stressful, thus making it nearly impossible to ascertain which is the precipitating event, stress or hair loss (40).

Treatment

Diffuse alopecia is usually temporary and resolves without scarring. Once the cause is identified and eliminated, the prognosis for hair regrowth is usually good (40). In some cases (e.g., exposure to multiple chemotherapeutic regimens or ionizing radiation), hair regrowth may be incomplete and may be different in terms of color, shape, or texture (39).

In one of the most common causes of diffuse alopecia, chemotherapy, minoxidil topical solution may have utility in reducing the duration of the induced hair loss. In two studies, one controlled (41) and one uncontrolled (42), minoxidil topical solution was not effective in preventing hair loss associated with chemotherapy. In a placebo-controlled clinical trial by Duvic et al. (43) in which 22 women had undergone surgery and adjuvant chemotherapy for breast cancer, 2% minoxidil topical solution did not prevent hair loss, but it did decrease the duration of chemotherapy-induced hair loss relative to the placebo group.

FUTURE

The future for hair growth research and potential forms of treatment is very bright. The cross-disciplinary efforts of academia, the pharmaceutical industry, and clinicians have led to new understanding of hair growth regulation, both biochemically and genetically. Sawaya and Price (8) have recently shown that there are differences in the amounts of steroid-metabolizing enzymes in the hair follicles of males and females with androgenetic alopecia. The isolation of two forms (type I and type II) of the enzyme 5α-reductase requires further study to elucidate their specific roles in regulation of hair follicle growth/regression. The recent finding that the enzyme aromatase is specifically located in the outer root sheath of hair follicles refocuses our efforts to study the entire hair follicle, not just the dermal papilla cells (8). Based on the numerous patent applications since 1995 (1), it is clear that industry is highly involved in developing hair growth enhancers. And finally, Ahmad and colleagues' (44) discovery of the gene for hair loss in alopecia universalis provides momentous progress at the molecular level. These exciting findings highlight the great strides that have been made in hair

growth research and provide impetus to researchers in their quest for new and/or refined therapies for hair loss (45,46).

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