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Prostaglandin-Induced Hair Growth

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Abstract. Latanoprost, used clinically in the treatment of glaucoma, induces growth of lashes and ancillary hairs around the eyelids. Manifestations include greater thickness and length of lashes, additional lash rows, conversion of vellus to terminal hairs in canthal areas as well as in regions adjacent to lash rows. In conjunction with increased growth, increased pigmentation occurs. Vellus hairs of the lower eyelids also undergo increased growth and pigmentation. Brief latanoprost therapy for 2–17 days (3–25.5 μg total dosage) induced findings comparable to chronic therapy in five patients. Latanoprost reversed alopecia of the eyelashes in one patient. Laboratory experiments with latanoprost have demonstrated stimulation of hair growth in mice and in the balding scalp of the stumptailed macaque, a primate that demonstrates androgenetic alopecia. The increased number of visible lashes is consistent with the ability of latanoprost to induce anagen (the growth phase) in telogen (resting) follicles while inducing hypertrophic changes in the involved follicles. The increased length of lashes is consistent with the ability of latanoprost to prolong the anagen phase of the hair cycle. Correlation with laboratory studies suggests that initiation and completion of latanoprost hair growth effects occur very early in anagen and the likely target is the dermal papilla. (**Surv Ophthalmol 47(Suppl 1)**:S185–S202, 2002. © 2002 by Elsevier Science Inc. All rights reserved.)

Key words. alopecia • anagen • eyelash • hair • hair follicle • hair growth • hypertrichosis • glaucoma • latanoprost • prostaglandin

Latanoprost, a prostaglandin analog, is an effective[15] and widely used medication in the treatment of open-angle glaucoma.[15] Recently, latanoprost has been recognized as a drug capable of regularly inducing hypertrichosis involving eyelashes, adjacent adnexal hair, and vellus hair of the skin.[46,121] The purpose of the present article is to reconcile latanoprost-induced hypertrichosis with what is known about hair characteristics and hair follicle behavior. Hair follicles are a complex structure that undergo recurring cycles of involution and growth. The factors regulating the transition between the three stages of the hair cycle are critical to understanding hair follicle behavior, but those factors are not well understood. Studying the response of hair follicles to latanoprost may offer some additional insights into mechanisms modulating follicle behavior.

For descriptive purposes, hair is typically characterized as having three different types: vellus, intermediate, and terminal. Vellus hair is soft, unmedullated, short, and unpigmented. Terminal hair is coarse, medullated, longer, and pigmented. The appearance of intermediate hair is between that of vellus and terminal, and presents a spectrum of appearances. Approximately five million hair follicles cover the human body at birth and no additional follicles are formed after birth.[92] However, the type of hair produced by a given follicle can change, as exemplified in changes in hair follicle behavior at puberty. Hairs of the eyelashes and those that form the eye-

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brows are the first terminal hairs to appear during development.[48] Eyelashes have the widest diameter of body hairs, are the most highly pigmented of the terminal hairs,[8] and generally do not become gray with age.[61]

Hair Cycle

EMBRYOGENESIS AND CYCLING

A unique feature of hair follicles is their cyclical behavior, which at each hair cycle recapitulates embryologic development. During embryogenesis, inducing signals from the dermal papilla,[125,128] originating from the mesoderm, cause epithelial elements in the ectoderm to proliferate, differentiate, and migrate downward into the dermis, culminating in development of a mature hair follicle. Hair follicles then begin to undergo cyclic behavior.

CATAGEN AND TELOGEN

Cyclic behavior leads to an involutional stage (*catagen*) during which epithelial elements undergo apoptosis[124] by a programmed dedifferentiation.[52] The epithelial elements migrate toward the surface, and by late catagen leave only secondary epithelial hair germ cells in an area called the bulge, which is located at the level of the arrector pili muscle (Fig. 1). A decrease to one-third of the hair follicle's former length occurs during the upward migration.[62] Associated with the upward migration and dedifferentiation, the residual epithelial stalk becomes surrounded by a greatly thickened and corrugated "glassy" basement membrane zone; the perifollicular connective tissue also becomes wrinkled and folded during late catagen, culminating in development of a club follicle surrounded by a club hair (Fig. 1). The club follicle thus finally matures to leave a club hair during the resting stage (*telogen*). Telogen then persists until the next anagen phase.

ANAGEN

In response to a stimulus of unknown origin from the dermal papilla, the secondary epithelial germ in the bulge[19] initiates a new growth phase of the hair follicle, namely, *anagen.* During mid anagen, the newly formed hair then dislodges the old club hair that still lies in the follicular canal. The germinative epithelial cells in the bulge are of a population unique from other follicular epidermis. When anagen is triggered, embryologic events are recapitulated and a new hair follicle is formed during early

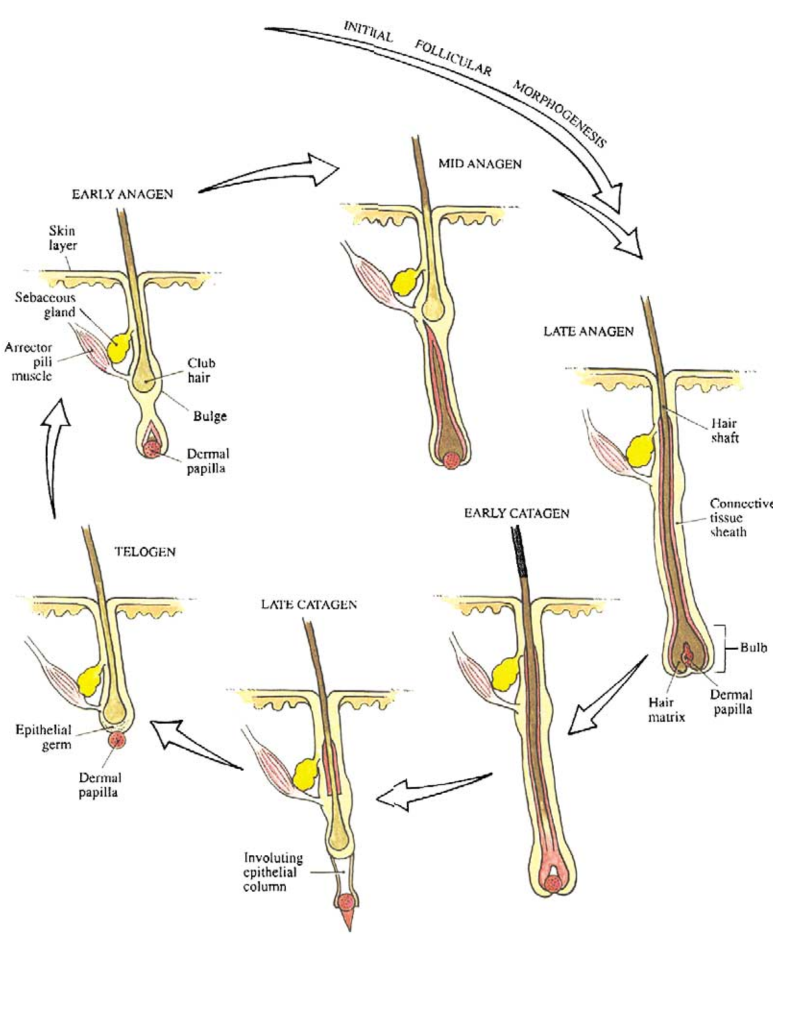

Fig. 1. Hair follicle cycle. After initial morphogenesis culminating in a mature follicle, the hair follicle undergoes an involutional phase (catagen) followed by a resting phase (telogen). A new growth phase (anagen) then ensues in response to signals from the dermal papilla, thus initiating a recurring cycle. Elucidation of the constellation of molecular signals that orchestrate the transition between the phases of the hair cycle is a central focus of hair research.

anagen. The dermal papilla is necessary to both induce and maintain the hair follicle.[6,53,125] The volume of the dermal papilla, which is determined by controlling the number of matrix cells in the hair bulb, determines the diameter of the induced hair shaft and may also determine the duration of anagen.[41,92]

SYNCHRONY AND DURATION

Although the hair cycle in many animals is synchronous, in humans it is asynchronous. The entire cycle varies in length depending on location in the body. On the scalp vertex, hair grows at a rate of 0.40 mm per day,[62] and scalp hair may grow for as long as 6 years.[92] Of the 100,000 hairs on the scalp,[76] approximately 84% are in anagen stage, 2% in catagen, 14% in telogen,[62] and about 70–100 are shed daily.[76] A much shorter anagen phase and relatively longer telogen phase characterize eyelashes and eyebrows compared to scalp hair, and they have the lowest ratio of anagen to telogen follicles. Eyelashes grow for approximately 30 days, undergo quiescence for 15 days, and remain dormant for about 100 days.[48] The total length of the cycle is reported to be 5 months.[61] The growth phase of the cycle in eyebrows is approximately 6 months with an equal period of rest.[76,116]

Hair Structure

To fully appreciate the myriad molecular signals that must be implicated in maintenance of the continuous cycling of the hair follicle, it is useful to review the numerous cellular and structural elements comprising the follicle. Anatomically, the hair follicle unit consists of a fibrous connective tissue sheath, an outer root sheath, an inner root sheath. and the hair shaft. A sebaceous gland and an arrector pili muscle complete the follicle unit (Figs. 1 and 2). The eyelashes are uniquely distinguished by the absence of an arrector pili muscle.[61] The entire follicle in the anagen phase may extend to a depth in the

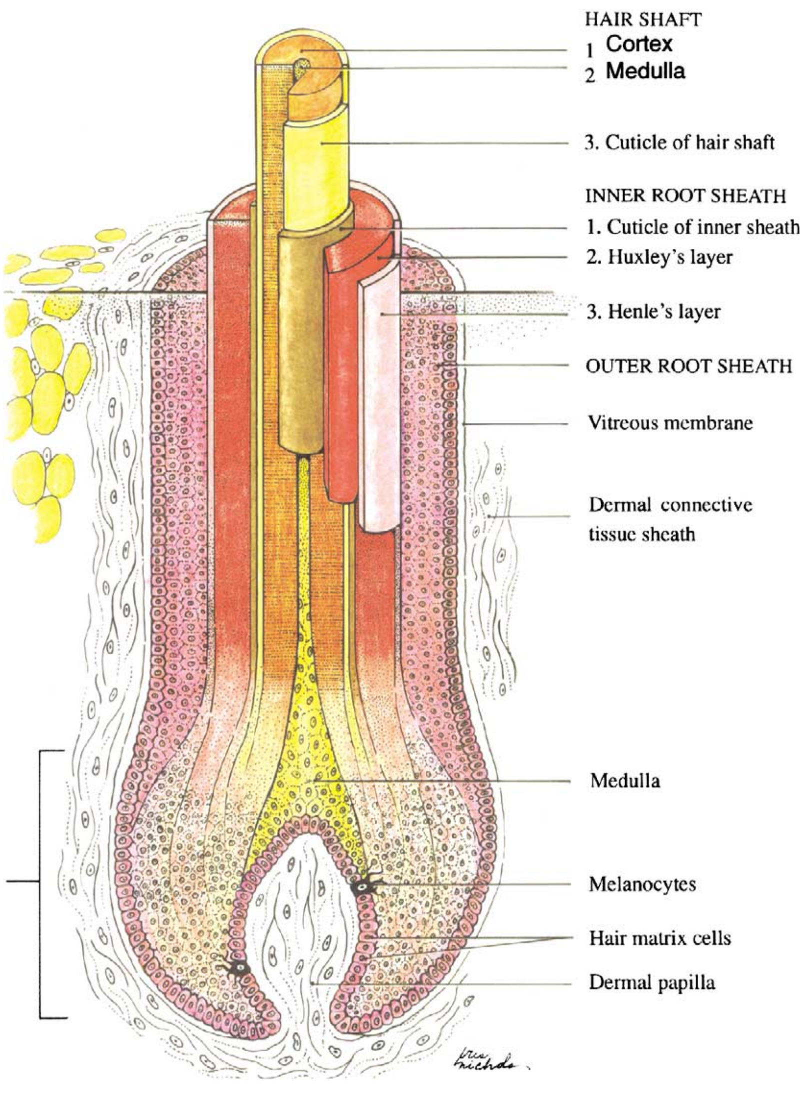

Fig. 2. Hair structure during the late anagen phase of the hair cycle. The illustration emphasizes the highly differentiated concentric layers of the follicle, each with their respective cell type and protein products. Components of the hair shaft undergo programmed involution and harden or cornify by a process of keratinization as they move upward within the inner root sheath. The inner root sheath and hair shaft move upward as a unit sliding past the outer root sheath.

dermis three times that of the distance from the surface to the arrector pili muscle. The section of the follicle below the arrector pili is transitory in the sense that it disappears during catagen and reforms during anagen.

FIBROUS SHEATH, BASEMENT MEMBRANE (VITREOUS MEMBRANE) AND OUTER ROOT SHEATH

The fibrous sheath surrounding the follicle is composed of thick collagen bundles. Beneath the fibrous sheath is a glassy or vitreous membrane similar to a subepidermal basement membrane but thicker. The outer root sheath of the hair follicle is continuous with cells lining the epidermis. In addition to epithelial cells, the outer root sheath contains amelanotic melanocytes,[109] Langerhan's cells,[29] and Merkel neurosecretory cells.[50]

INNER ROOT SHEATH

Moving inward, the next layer is the inner root sheath, which is composed of three separate cell types. The first is Henley's layer, containing a single layer of cells; the second is Huxley's layer, which is composed of two concentric rows of specialized cells containing trichohyalin granules; and the third is the cuticle of the inner root sheath, a single layer of flattened squamous cells with atrophic nuclei.

HAIR SHAFT

Moving further inward, the three layers of the hair shaft are encountered. They consist of the cuticle of the hair shaft, which surrounds the hair as it emerges from the surface of the skin. The hair shaft cuticle surrounds the cortex, which in turn surrounds the medulla. Cuticle cells of the hair become imbricated with their free ends directed upward, enabling them to interlock with the cells of the cuticle of the inner root sheath with their free ends directed downward. The inner root sheath and hair shaft move upward together gliding over the relatively more stationary outer root sheath.[76]

HAIR BULB AND MATRIX CELLS

The hair bulb is the thickest part of the follicle at the lower end. The bulb contains a proliferative zone composed of a germinative matrix of undifferentiated pluripotent polygonal cells capping the dermal papilla. These matrix cells of ectodermal origin give rise to the seven epithelial cell types that make up the layers of the follicle[125] (Fig. 2). The matrix cells of the bulb are involved in intense metabolic activity with a complete replication cycle in the human scalp of about 39 hours, which may be greater than that of any other tissue with the exception of bone marrow.[76]

Matrix cells that differentiate into medulla and cortical fibers of the hair shaft move upward where they are shaped and compressed into their final form by the rigid inner-root sheath, which keratinizes before the hair shaft.[62] The dimensions and curvature of the inner root sheath thus determine the thickness and curvature of the hair. Once the dimensions of the rigid inner root sheath are established, further changes in shape do not easily occur, suggesting that the size and shape of the follicle is determined early in anagen when cells of the inner root sheath begin to differentiate. The length of hair is directly proportional to the duration of anagen.[92] The dermal papilla contains specialized fibroblasts that control the number of matrix cells in the hair bulb and may by this means control the thickness of the resulting hair.[92]

MATRIX CELL DIFFERENTIATION AND KERATINIZATION DURING ANAGEN

Differentiation begins above the hair bulb, leading to formation of the concentric highly differentiated epithelial layers of the follicle. During anagen, programmed involution of the cortex and medulla cells begins above the hair bulb, ultimately leading to completion of keratinization and cornification (hardening) about half way up the shaft.[7] This region is defined as the keratogenous zone. The cells of the inner root sheath also undergo programmed involution during anagen as they reach the region of the arrector pili muscle and do not contribute to the emerging hair.[91]

MELANOCYTES AND MELANOGENESIS

Numerous large melanocytes, with well formed dendritic processes, are located over the apex of the papilla in the region of the superior hair bulb (Fig. 2) and divide infrequently.[52] The melanocytes are involved in intense melanin synthesis and their dendritic processes contain a dense accumulation of melanosomes. Melanin is actively transferred to the medullary and cortical cells of the hair follicle by phagocytosis of the melanosome-rich dendritic processes of the melanocytes.[8,104] Pigment production and transfer only occur during anagen. At the onset of catagen, melanocytes undergo involution, melanin synthesis ceases, the dendrites are resorbed, and the melanocytes undergo programmed dedifferentiation to take on the appearance of undifferentiated epithelial germ cells.[52]

Anagen-associated melanogenesis and the cyclic production of a pigmented hair shaft result from programmed and tightly coordinated epithelial, mesenchymal, and neuroectodermal interactions.[107] A phagocytic mechanism involving uptake of melanosomes from the dendritic processes of melanocytes also occurs in the cells of the epidermis that are constantly dividing but are not involved in cyclical growth and involution. Iris melanocytes in contrast are thought to be continent with no pigment transfer to the surrounding iris stromal cells.

Three types of melanosomes are present in hair. Eryrthromelanin granules, seen in red hair, are polymorphous and have an irregular internal structure. Homogenous eumalanin granules are seen in dark hair and lamellated pheomelanin granules predominate in light hair.[62,66] In gray and white hair melanosomes are reduced or absent.[66]

THE DERMAL PAPILLA

The dermal papilla is a connective tissue component inside the anagen hair bulb (Fig 2). The papilla contains specialized fibroblasts, histiocytes, melanophages, mast cells, Langerhans' granule-containing cells, ground substance, and collagen fibers. A profuse system of small blood vessels supplies the dermal papilla. A stalk connects the underlying connective tissue to the papilla and a basement membrane separates it from the matrix cells of the bulb.[7] During catagen the dermal papilla migrates upward with the hair bulb to lie beneath the residual secondary epithelial germ cells at the bulge.

BLOOD SUPPLY AND INNERVATION

There is a rich blood supply to the follicular unit with the greatest concentration of vessels in areas of greatest metabolic activity. The vascular supply undergoes active remodeling during the hair follicle cycle with a marked diminution of the blood supply of the lower portion of the telogen follicle.[18,59] It is hypothesized that the actively growing follicular unit is the primary stimulus determining the blood supply of the structure, with the blood supply largely a reflection of the growth needs of the follicle.[18] Hair follicles are the most richly innervated part of the skin and active remodeling of hair follicle innervation occurs throughout the normal hair-follicle cycle.[12] Furthermore, neurotrophins play an active role in modulating the phases of the hair cycle.[11]

INTEGRATION OF THE HAIR CYCLE WITH CELLULAR AND STRUCTURAL RELATIONSHIPS

Active features of the hair cycle thus include proliferation, differentiation into multiple epithelial cell types, migration, angiogenesis, and programmed dedifferentiation. Cellular elements involved in cyclical behavior include fibroblasts of the connective tissue sheath; epithelial cells, melanocytes, and Merkel cells (assumed to be touch receptors) of the outer root sheath; seven different derivatives of the germinal epithelial cells; melanocytes of the bulb; dermal papilla fibroblasts and melanocytes; vascular endothelial cells; and nerve fibers. Synchronization of a remarkable number of cellular processes and cell types is thus essential for proper maintenance of the hair cycle. Once a phase of the hair cycle is initiated, ensuing events in the follicular tissue are highly regulated and tightly coupled. By contrast, initiation of the various cycle phases is responsive to a variety of stimuli. A multiplicity of signals is known to be involved in controlling initiation of the phases during cycling, but their attributes and relative contributions remain to be clarified.[125]

Prostaglandin-Induced Hair Growth—Human Studies

ADVERSE EVENTS AND CASE REPORTS

In three phase III multicenter latanoprost clinical trials in Europe, Scandinavia, and Japan involving 829 patients,[4] one case of darker eyelashes[5] was reported with no cases of hypertrichosis seen.[5] A subsequent case report in a unilaterally treated eye reported hyperpigmentation of the lashes and also noted that the lashes appeared to be greater in density and thickness. Treatment later applied to the fellow eye caused a similar appearance.[121] Recently, in a case report latanoprost reversed alopecia of the eyelashes.[68]

PATIENT SERIES

The paucity of reports of hypertrichosis following latanoprost therapy suggested that this finding might be spurious or represent a rare or idiosyncratic event. However, hypertrichosis was independently identified by a prospective study initiated in a series of 43 patients who were unilaterally treated with latanoprost.[46] Careful comparison of latanoprost-treated and control eyes demonstrated that a number of different manifestations of hypertrichosis were regularly seen in the latanoprost-treated eye (LTE) of these patients. A mean increase in lash length of 19% (range 0–36%) was found in the LTE. Lashes were regularly thicker in the LTE; a finding illustrated in Figs. 3 and 4. The two patients who had no measurable lash length change exhibited increased numbers of lashes.

The types of manifestations also included increased numbers of lashes in preexisting lash rows as illustrated in Figs. 4, 5, and 6. In the areas of transition between the terminal lashes along the lash line and the vellus hair of the skin, hair in the control eye was a mixture of vellus and intermediate types, as illustrated in Figs 5b, 5d, and 5f. Hair in the same transition areas in the LTE had a more robust appearance, was longer, thicker, more heavily pigmented, and arose at a more acute angle from the skin than in the control eye as illustrated in Figs. 5a,

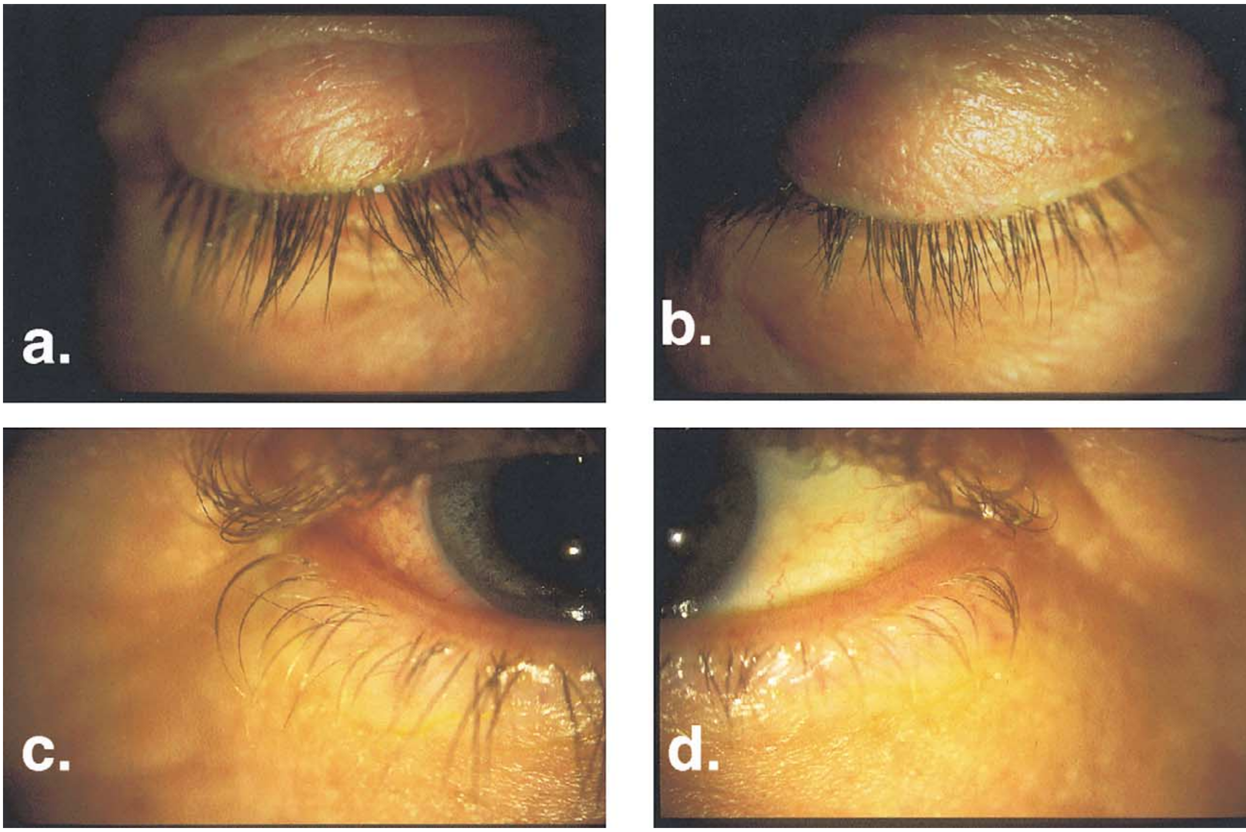

Fig. 3. *a:* Eyelashes of upper eyelid of latanoprost-treated eye (LTE), and *b:* control non-treated eye (NTE) of 71-year-old Caucasian man. *c:* Lashes of lower eyelids of LTE and *d:* NTE of 52-year-old Caucasian man. In the LTE in both patients eyelashes are longer and thicker (trichomegaly) as well as more numerous (polytrichia). In addition, lashes are more pigmented in the LTE. The pigmentation increase is more striking in the initially more darkly pigmented eyelashes of the patient in a and b.

5c, and 5e. The increased number of terminal versus vellus and intermediate hairs at times produced the appearance of partial new rows of terminal lashes (Figs. 5a, 5c, and 5e).

In the medial and lateral canthal area, where vellus and intermediate hairs were present in the control eye, a number of patients had a greater abundance of thicker, longer, and more pigmented terminal hairs in the same area of the LTE, a finding illustrated in Figs. 6a and 6b. Pigmentation of the eyelashes and associated intermediate hairs was regularly greater in the LTE than in the control eye. The increase in pigmentation was more notable in patients who initially had darker lashes (Fig. 3). Several patients had a striking curling of the lashes (Fig. 6c). Although usually not grossly visible, with slit-lamp examination the vellus hair of the skin of the lateral portion of the lower lid often appeared more abundant, longer, thicker, and darker in the LTE. The most obvious eyelid hypertrichosis observed clinically resolved following discontinuation of latanoprost (Fig. 7).

The findings pointed not only to a greater frequency of terminal lashes but also lash hypertrophy and hyperpigmention. In addition, altered differentiation occurred in intermediate hairs adjacent to the lash line and in regional adnexal and vellus hairs. The diffuse occurrence of manifestations (Table 1) of hypertrichosis observed in a study of 43 patients[46] provided evidence that hypertrichosis in response to latanoprost was a generalized phenomenon rather than a rare or idiosyncratic one.

More recently, in a prospective study, lash length was assessed in 14 eyes of 7 patients using a digital imaging technique after latanoprost treatment for a minimum of 5 months. Longer lashes (0.75 mm) were observed in two eyes of one patient (14% of total patients) following treatment. In the same patients, lash thickness was assessed subjectively. Ten of 14 eyes (71%) were judged to have thicker lashes.[82] In a subsequent report, 100% of treated eyes had increased eyelash lengths.[81] Follicle counts and sophisticated techniques for measurement of hair growth currently used on the scalp have not been applied to the eyelashes. Such techniques may in the future provide more sensitive tools for assessment of the hair growth-inducing effects of prostaglandins.

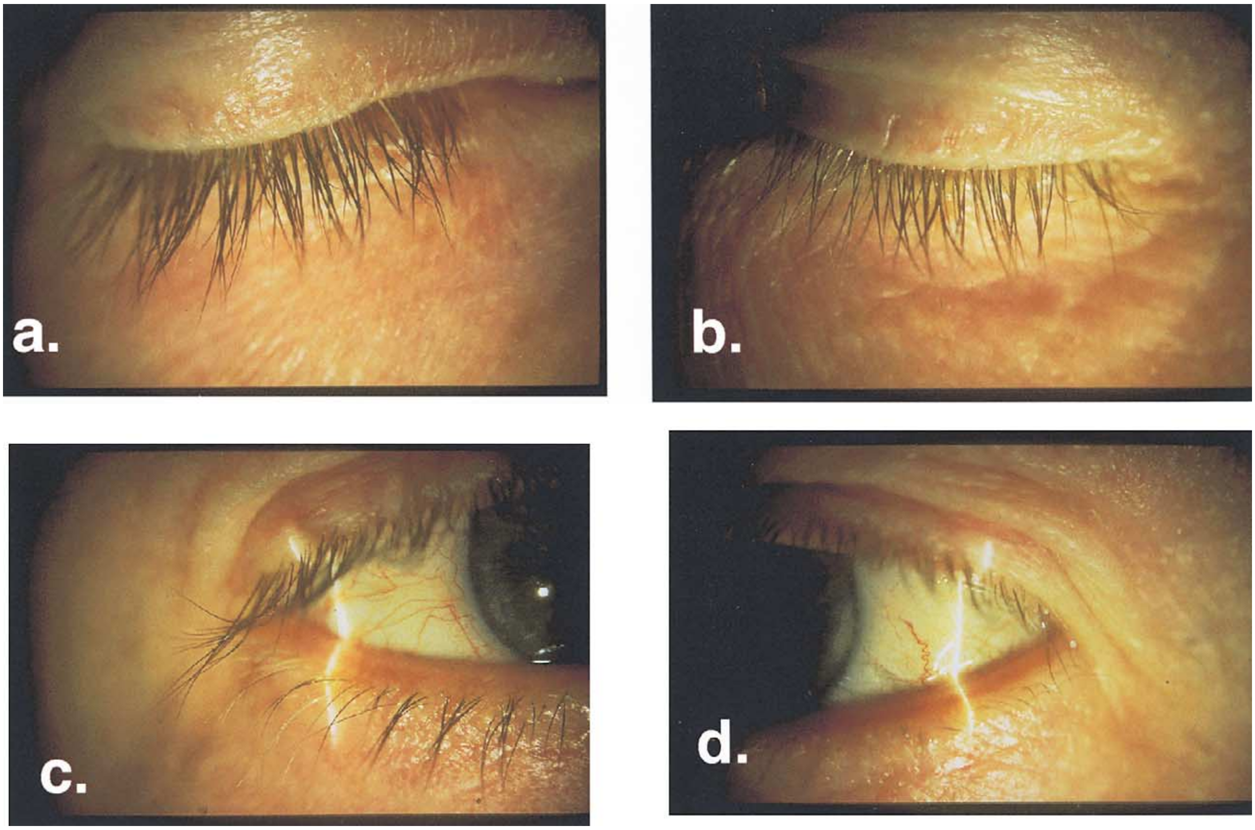

Fig. 4. 76-year-old Caucasian male. Eyelashes of upper eyelid of latanoprost-treated eye (LTE) (*a*) compared with control non-treated eye (NTE) (*b*). Eyelashes of lateral portion of lower lid of LTE (*c*) and NTE (*d*). Trichomegaly, polytrichia, and hyperpigmentation are apparent in the eyelashes of the LTE. Note the marked differences in the eyelash appearance in the lateral portion of the lower lids, a location where the latanoprost-associated eyelash differences were often most striking and easily appreciated.

Lash growth has been reported following installation of two topical prostaglandin eye drops recently introduced for pressure control in glaucoma. After taking travoprost 0.004% for 12 months, changes in eyelashes, including increased length, thickness, density, and color, were reported in 57% of patients.[79] In patients taking bimatoprost 0.03% for 3 months, eyelash growth was reported in 12%.[27]

EFFECTS OF BRIEF, LOW-DOSE LATANOPROST TREATMENT

A subsequent study[45] was initiated to determine the minimum interval of latanoprost exposure necessary to cause hypertrichosis of eyelashes and to examine the duration of the resulting effect. Records and photographs of 89 glaucoma patients with hypertrichosis following unilateral treatment with topical latanoprost were reviewed. Five patients had taken topical latanoprost for a brief interval (<21 days); male: female ratio, 2:3; all Caucasian; average age 72. Treatment duration was 2, 3, 5, 12, and 17 days. In each of these patients, latanoprost was stopped because of issues of intolerance or allergy. Follow-up listed in order determined by the previously described treatment duration was 13, 14, 5, 6, and 4 months. Brief treatment findings (≤21 days) were compared with sustained (>21 days) treatment findings.

In the 5 patients treated briefly,[45] increased number, length, thickness, and pigmentation of lashes occurred (Fig. 6c) and findings were similar in magnitude to those following unilateral sustained treatment. There was no obvious correlation between appearance and duration of treatment except in three patients who took latanoprost for ≤5 days. Each had marked curling of lashes (Fig. 6c) that was non-uniform in direction and degree, in contrast to the occasional more modest uniform curling seen with sustained treatment. Within a few months following cessation of latanoprost therapy, polytrichia was no longer obvious. In contrast to patients treated chronically (>21 days), in each patient treated briefly (<21 days), trichomegaly persisted to some degree throughout the duration of the follow-up interval.

IMPLICATIONS OF HAIR GROWTH INDUCED BY BRIEF TREATMENT

It is extremely unusual for a 2-day course of treatment to have manifestations up to 14 months later

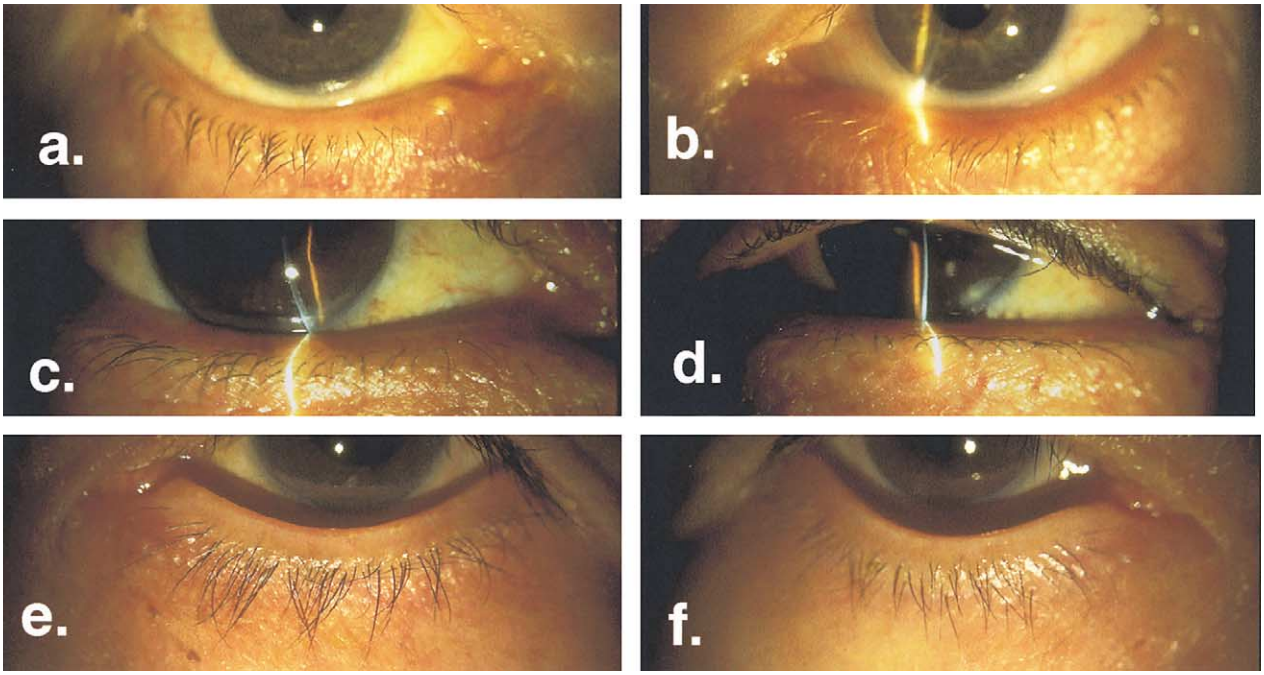

Fig. 5. Eyelashes of lower eyelid of 77-year-old Caucasian man: latanoprost-treated eye (LTE) (*a*), control non-treated eye (NTE) (*b*). Eyelashes of lower eyelid of 65-year-old African-American male LTE (*c*), NTE (*d*). Eyelashes of lower eyelid of 83-year-old Asian woman LTE (*e*), NTE (*f*). In all three racial groups, note apparent polytrichia, trichomegaly, and hyperpigmention. Note also development of partial additional row of eyelashes below the primary lash line in the LTE vs. the NTE in each patient.

and such observations deserve further consideration. Initiation of anagen following very low doses and brief exposure times to latanoprost is surprising but may have a rational explanation. Mutual inductive influences between the ectodermal and mesodermal elements initiate a programmed development of the follicle.[6,26] The type and duration of the inductive influences necessary to initiate and sustain the hair cycle are unknown.[26] However, very brief exposure to inductive stimuli during embryogenesis is capable of establishing a developmental path by means of tightly linked successive or sequential induction programs.[3] For example, some signaling ligand responses can begin abruptly as the concentration of ligand increases, providing a molecular basis for steep or even switch-like signals.[2] Once a cell has been directed into a particular path of differentiation, it may begin to secrete autocrine-signaling molecules that then reinforce a developmental decision.[3]

The very brief stimulus required to initiate increased growth and altered differentiation of hair follicles as observed in the study[45] suggests that a program is initiated to trigger the anagen phase of the hair cycle in the follicles of eyelashes and that this program is able to proceed in the absence of an ongoing stimulus. Whether a similar brief stimulus is required to initiate anagen in other hair types has not been studied.

Increased hair length as observed in the latanoprost-induced eyelash growth studies is associated with an increase in the duration of the anagen phase. The increased anagen duration has been hypothesized to be determined at the initiation of the anagen phase and is probably controlled by the dermal papilla.[92] The increased pigmentation in the eyelashes is different than that in the iris because the pigmentation in eyelashes is associated with melanocyte differentiation and the associated melanogenesis is tightly coupled to the process of differentiation.

A brief low total dosage, ($\leq$3 μg) administered over 2 days may cause the picture of polytrichia, trichomegaly, and hyperpigmentation.[45] Marked irregular lash curling was observed following 5 days of latanoprost treatment[45] and may result from a lack of uniform penetration into the hair follicle leading to slightly asymmetric development of the follicle and inner root sheath. Evidence of unilaterally greater lash thickness, length, curling, and pigmentation following brief treatment persisted for up to 14 months.[45] However, this retrospective study ended at 14 months. Whether the duration of trichomegaly may persist for a longer time has not been studied. Because the number of follicles remains constant throughout life, findings of polytrichia suggest that the ratio of anagen to telogen follicles (about 50:50 in eyelashes) is shifted to an increased percent of the

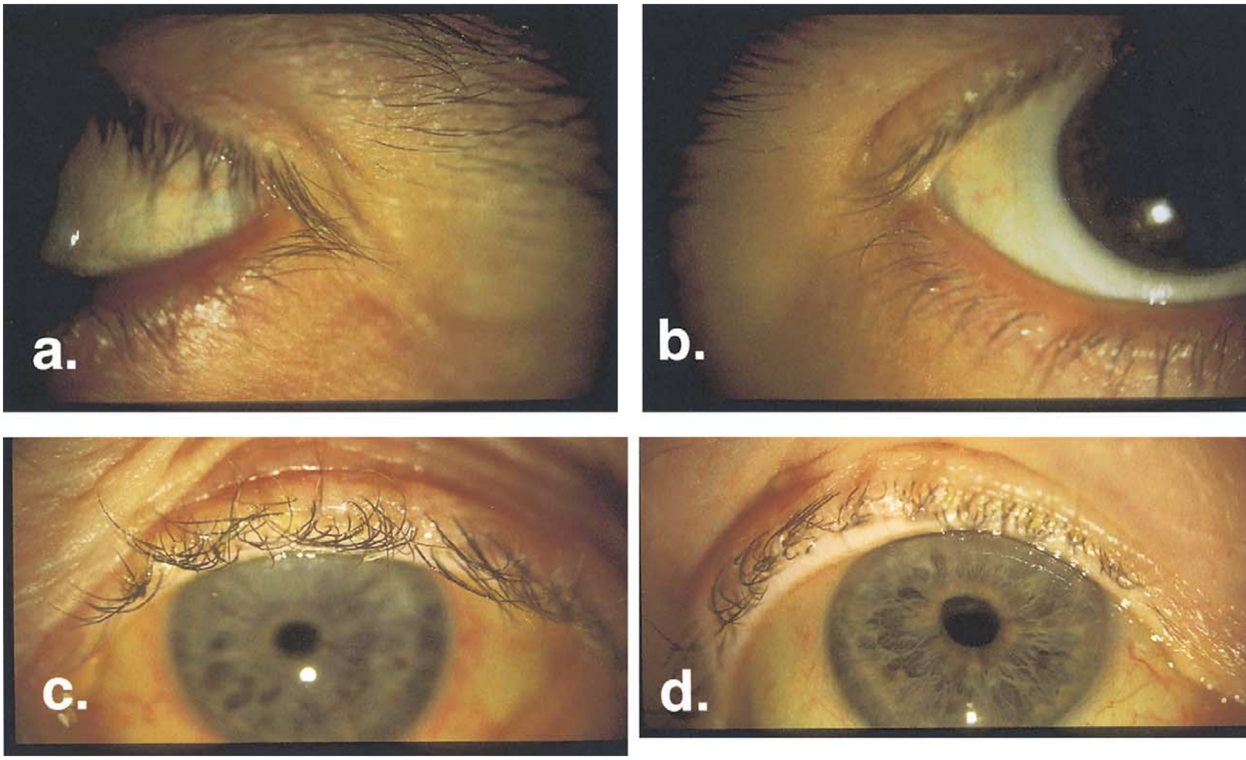

Fig. 6. In a 49-year-old Caucasian man, note the altered lash development in lateral canthal area in latanoprost-treated eye (LTE) (*a*) compared with control non-treated eye (NTE) (*b*). The altered development includes increased numbers of terminal lashes in the region as well as increased pigmentation. Photographs in 6c (LTE) and 6d (NTE) are of the eyelashes of a 79-year-old Caucasian woman taken 7 months following brief (2 days), low total dose (3 μg) latanoprost instillation. Lashes remain increased in number, are longer, thicker, more pigmented, and also more curled than in the fellow eye.

follicles entering the anagen phase. Without a persistent stimulus the ratio of anagen to telogen follicles eventually return to pretreatment levels.

The persistent trichomegaly following brief latanoprost therapy suggests either that some follicles have a prolongation of the anagen phase, that the data related to the normal length of the hair cycle in the follicles may be longer than the reported 6 months, or that there is an alteration in the developmental program carried by the germinative epithelium that then persists from one cycle to the next. Such changes in the developmental program can occur in adults as illustrated by androgenetic alopecia. For example, a gradual alteration in the developmental program is thought to occur in hair follicles during androgenetic alopecia. There is a progressive shortening of successive anagen cycles, miniaturization of the follicles, and an eventual change in the differentiation pattern to produce vellus rather than terminal hair. The observation that a trophic change in the developmental program may be carried by the germinative epithelium from one cycle to the next in response to a therapeutic agent is heartening and warrants further study.

A possible explanation for the difference in a pattern of persistence of trichomegaly in patients with chronic latanoprost therapy in contrast to those with brief therapy is that inhibitory effects or downregulation may occur in response to a greater cumulative dosage used in chronic therapy. A relevant example of such dose-dependent inhibitory behavior on cell proliferation in hair follicles is illustrated by minoxidil. Minoxidil increases DNA synthesis in both dermal papilla and follicular germ cells, but at higher concentrations suppressed DNA synthesis.[55] Furthermore, a similar increase in DNA synthesis has been found in skin cells treated with minoxidil, but cytotoxic effects occurred at higher concentrations, with a narrow margin between proliferation and cytotoxicity.[95]

Such observations with minoxidil, coupled with clinical observations following brief versus chronic latanoprost usage, are intriguing because they suggest that there may be a very narrow dose and duration-dependent therapeutic window for optimizing the effects of these hair growth agents. Scalp hair with an approximate 7-year growth cycle does not provide a convenient clinical model for studying the effects of hair growth-inducing agents. Because of their bilateral symmetry, their relatively short growth cycle, their normally well-defined length, and their normally high ratio of telogen to anagen follicles,

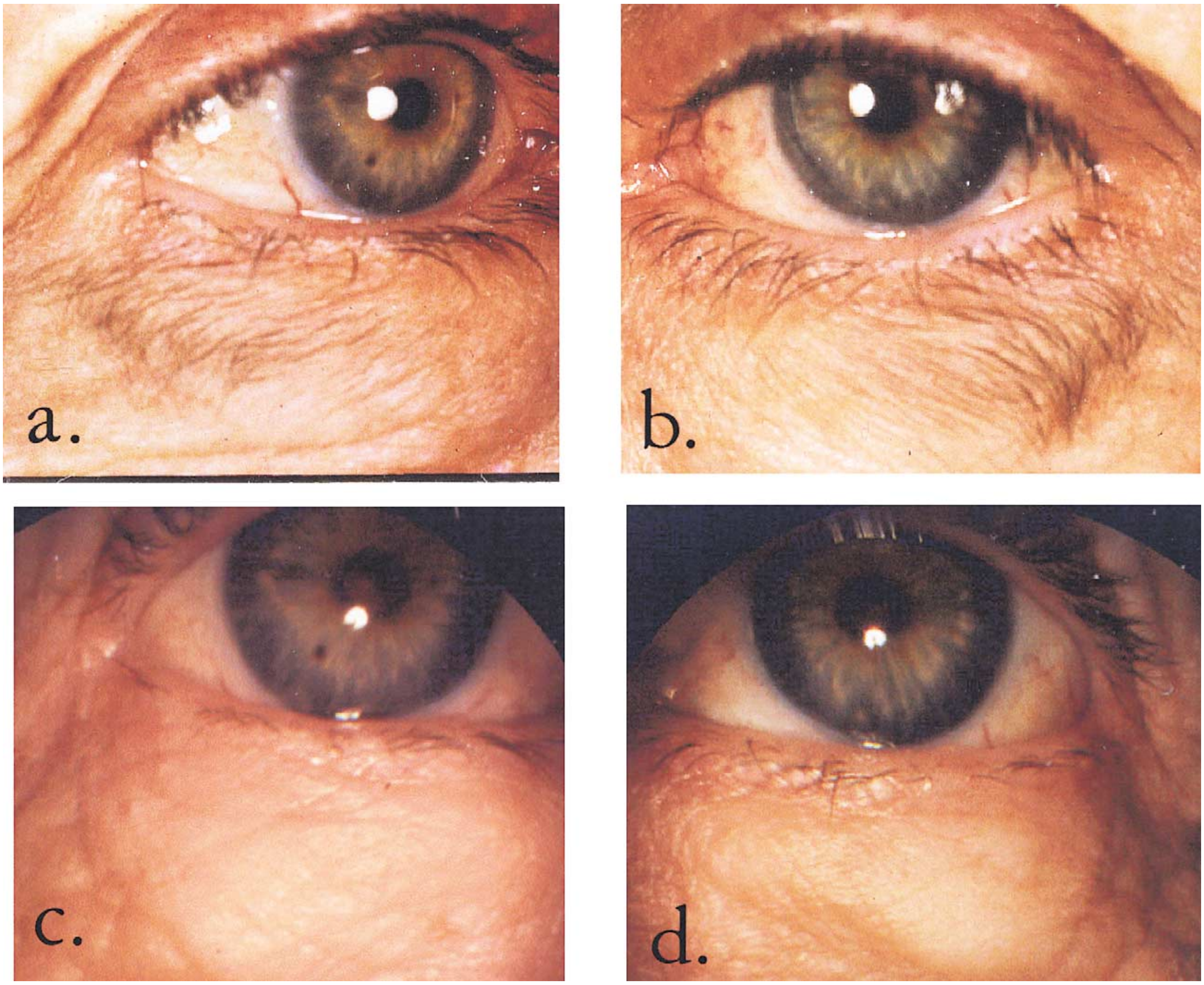

Fig. 7. Hypertrichosis of lower eyelids (*a* and *b*) following 4 months of latanoprost therapy in 80-year-old Caucasian female. Complete resolution of hypertrichosis occurred within several months following discontinuance of latanoprost. Photos *c* and *d* were taken 3 years following discontinuation of latanoprost therapy.

lash growth responses may represent a unique model for unlocking the mysteries of subtle but potentially extremely important dose-dependent responses of follicles exposed to hair growth agents.

PATIENT EXPECTATIONS AND EDUCATION

Clinical implications of the latanoprost-induced hair growth phenomenon relate primarily to cosmetic issues. One might advise patients as follows prior to starting the agent: An increase in apparent number, length, and thickness of lashes is likely following initiation of treatment. The increase in lash length and thickness is likely to be no more than about 20% and will reach its maximum in about 3 months. When administered bilaterally, the lash growth effects often go unnoticed by patients and their families. When lash growth is noticed, the growth generally is modest enough to not be of cosmetic concern and is often welcomed by women taking the agent. When administered unilaterally, the lash appearance is generally not a cosmetic concern, but occasionally may be moderately troublesome. The above explanation is probably adequate for most patients.

For patients wanting to know more detail the following may be useful: The apparent increase in lash numbers is a result of two things. Latanoprost stimulates resting lash follicles to grow, thus initially changing the ratio of growing follicles to those normally at rest. In addition, some lashes along the lid margin that are generally small may become enlarged. Over time the number of apparent increased numbers of lashes will likely diminish as the ratio of growing to resting lashes returns to equilibrium. The apparent increase in lash length and thickness is likely to persist while taking the agent. Following discontinuation of latanoprost, the increased length and thickness of lashes may persist for a period of

TABLE 1
Latanoprost-Induced Hair Growth Manifestations

Lashes
Increased lash numbers in lash row
Additional lash rows
Increased lash length
Increased lash thickness
Increased lash curling
Steeper lash angulation from follicle
Increased pigmentation
Medial and Lateral Canthal Hair
Increased number of visible hairs
Vellus and intermediate hair develops into terminal hair
Increased pigmentation
Skin of Lid
Vellus hair
Thicker
Longer
Increased pigmentation

months or longer. There may be some slight increase in growth of hair on the eyelids but it is extremely rare for the growth to be noticeable to patients or their families. Following the use of latanoprost in chronic therapy, latanoprost-induced growth of hair on the lids appears to be reversible (Fig. 7).

Latanoprost-Induced Hair Growth—Animal Studies

The underlying mechanism of latanoprost-associated hair growth is poorly understood at the present time. Preliminary experiments were carried out in the mouse and macaque to determine if these animals show a hair growth response to latanoprost and can serve as models for studying the mechanism of action.

MURINE MODEL

Using the C57 BL/6 mouse as a model of anagen induction on the normal hair-growth cycle, studies were designed to determine if latanoprost influences the timing or onset of anagen cycling in normal hair (Voss et al, in preparation). Previous studies have reported that hair growth in this mouse strain is induced by treatment with cyclosporin A.[69,94] Truncal skin pigmentation is also dependent on the melanocytes present in the hair follicles rather than epidermal pigmentation.[69] Mature melanocytes are not present in the telogen phase of the C57 BL/6 mouse hair cycle, causing the skin to be pink/white in color. The number of melanocytes in each follicle increases as anagen is initiated, causing skin pigmentation to turn gray/black in color. In addition to the gross observations of pigmentation changes, the mouse skin demonstrates thickening as the hair cycle progresses from telogen to anagen.

Paus et al reported that topical application of cyclosporin A, an immunosuppressant known for its hypertrichotic effects, induced anagen in 75% of treated mice within a 10-day period in the C57 BL/6 strain.[94] They also observed that this drug induced more complete hair growth when compared to controls.[94] Maurer et al have reported responses of 100% in experimental mice within a 15-day period using cyclosporin A and 90% in 17 days using FD 306, another immunosuppressant.[69] Preliminary studies with latanoprost applied topically to the C57 BL/6 model indicate that latanoprost promotes rapid induction of the hair growth cycle into anagen phase when compared to vehicle-treated mice. These changes can be observed grossly by skin pigmentation and microscopically by measuring skin thickness (Voss et al, in preparation).

PRIMATE MODEL

Using the primate model of androgenetic alopecia (male pattern baldness), the stumptailed macaque (*Macaca arctoides*), studies were done to determine whether latanoprost influenced hair type and thickness (Uno et al, in presss: Acta Dermato-Venereologica). These monkeys develop frontal alopecia and have been utilized for screening of several hair growth agents, including minoxidil and finasteride.[100,117,118] Analysis of the hair in the scalp of the stumptailed monkeys included grading of hair growth in sequential global photographs and phototrichographic analysis of vellus, intermediary, and terminal hairs as described in previous studies.[119,120] Preliminary experiments suggested that latanoprost increased hair density and converted vellus hair to intermediary hair type (Uno et al, in press: Acta Dermato-Venereologica.)

Hair Growth Changes Induced by Other Prostaglandins

PGE2- AND PGF2α-MURINE STUDIES

Prior to the introduction of latanoprost, hair growth modulation by prostaglandins had been investigated. Houssay examined the effect of PGE2 and PGF2α on the diffuse hair wave in mice. The prostaglandins were administered intraperitoneally twice a day.[37] After a 22-day period of treatment a marked inhibition of hair growth was noted in the prostaglandin-treated mice. PGE2 analogs have been investigated as agents against radiation- or doxorubicin-induced alopecia in a murine model of hair injury. The extent of hair loss and regrowth was evaluated. Both systemic and topical application of a PGE2 analog resulted in a significant degree of protection against radiation-induced[28,32,67] or doxorubicin-induced[67] alopecia.

Arachadonic acid metabolism in dermal papilla cells was stimulated by the calcium ion ionophore A23187 to produce large amounts of PG6ketoF1 alpha, PGE2 and leukotriene B_4. High concentrations of VEGF also induced production of the above metabolites. Low concentrations of minoxidil inhibited PG6KF1 alpha production but stimulated production of PGE2 and LTB_4, thus implicating VEGF and minoxidil in the modulation of eicosanoid production by dermal papilla cells.[57]

Growth effects were absent in skin keratinocytes after treatment with PGE1 or PGF2α[10] in one study. However, another study found that prostaglandin E receptor EP2 and EP3 subtypes have real effects on the rate of proliferation of keratinocytes.[54] Prostaglandin endoperoxide synthase-1 is present in the dermal papilla from human hair follicles, and minoxidil is an activator of the enzyme as evidenced by its ability to cause increased PGE2 production by murine 3T3 fibroblasts.[70] However, minoxidil had no effect on PGE2 or PGF2α production in keratinocytes.[56] In melanocytes of anagen hair bulbs, arachidonate may, through production of endogenous prostaglandins, stimulate dispersion of melanosomes into the dendritic processes. This was demonstrated by a series of cellular events characterized by peripheral orientation of microfilaments in the dendritic processes and by associated complexing of melanosomes.[103]

SELECTIVE PROSTANOID RECEPTOR AGONIST ACTIVITY-MURINE STUDIES

Regrowth of fur in adult CBA-J mice was assessed following treatment with DP, EP_1, EP_2, EP_3, FP, IP, and TP receptor agonists. Fur regrowth was significantly different from the control group only following application of the FP receptor agonist fluprostenol ($p < 0.01$).[113]

PGE2 ANALOG-HUMAN STUDIES

Viprostol, a PGE2 analog, is an effective antihypertensive agent in oral, intravenous, and even transdermal forms. It reduces blood pressure by direct relaxation of arteriole smooth muscle and has an established transdermal delivery system with marked follicular penetration and high perifollicular concentrations. In fact, mean percutaneous absorption of viprostol is approximately 40–60% with an elimination half-life of 4–6 days.[80] Because of evidence of reduced scalp blood flow in male pattern baldness, this drug was felt to be promising as a treatment for androgenetic alopecia. A randomized prospective controlled trial in 57 men was undertaken but demonstrated that hair counts declined in the treatment groups at the end of a 6-month study.[80] In another study viprostol administration led to human scalp hair growth providing an argument that the E series prostaglandins may have an effect on hair growth although to a lesser extent than the F series.[101]

Hair Growth Changes Induced by Non-Prostaglandin Drugs

Other drugs which have an impact in modulating hair growth are of interest because examination of their behavior may shed some light on the mechanism by which latanoprost induces changes in modulation of hair growth and cycling. Drug-induced hair loss generally affects the follicles in the anagen phase through two main modalities.

HAIR LOSS (ANAGEN EFFLUVIUM)

The first modality of drug-induced hair loss, anagen effluvium, involves abrupt cessation of mitotic activity in rapidly dividing hair matrix cells and the second (telogen effluvium) precipitates the follicles into premature rest. In response to anagen effluvium, hair loss usually occurs within days to weeks of drug administration.[22,23] Anagen effluvium is the typical adverse effect of antineoplastic drugs. Regions of the body with the highest percentage of anagen follicles, such as the scalp and beard, are most severely affected by these insults, while those with the lowest percentage of anagen follicles, such as eyebrows and eyelashes, are least affected.

HAIR LOSS (TELOGEN EFFLUVIUM)

The second modality, telogen effluvium, may be caused by a large number of agents, including anticoagulants, interferons, retinoids, and antihyperlipidemic drugs. Drugs, in fact, are the least frequent cause of telogen effluvium; post-natal, post-febrile, weight loss, and psychogenic states are other frequent causes. Some agents only occasionally cause hair abnormalities whereas others cause hair loss in most patients. In telogen effluvium, hair loss becomes apparent 2–4 months following treatment.[99] Hair loss is usually reversible after interruption of treatment.

HAIR GROWTH

Hirsutism and hypertrichosis may be associated with a number of drugs. Hirsutism is defined as the growth of terminal hair with masculine characteristics and pattern in women, whereas hypertrichosis describes the growth of terminal from vellus hair. Drugs that induce hair growth include cyclosporin (30–60% of patients following organ transplantation[9,16]), minoxidil (80% with systemic therapy[84]), diazoxide (almost 100% in children for hypoglycemia,[116] 1% in adults for hypertension[14]), erythropoietin (13% of patients[51]), calcium-channel blockers, benoxaprofen, and tretinoin.

Basic Mechanisms Involved in the Regulation of Hair Growth

MOLECULAR SIGNALS RELATED TO ONTOGENY

Review of the factors known to be involved in regulation of hair growth may provide insights into mechanisms through which latanoprost modulates hair growth. Molecular signals that control normal hair distribution and follicle formation originally were identified as the signals controlling ontogeny in drosophila and include the mammalian counterpart of genes such as hedgehog, patched, wnt, disheveled, armadillo, engrailed, and notch.[72,73,108] Protein products of homeobox genes also appear at the location where dermal appendages will form.[85] Because several of these gene products are present during the hair cycle in adults they appear to be important not only to embryogenesis but also to maintenance of the cyclical growth pattern.[30,73,93] Subsequent maturation of the hair follicle also involves morphogens such as sonic hedgehog and wnt.[73,108]

GROWTH FACTORS

Cytokine gene expression profiles identified during the anagen phase include insulin-like growth factor 1, transforming growth factor beta 1, tumor necrosis factor, and basic fibroblast growth factor.[65] Insulin-like growth factor 1 and fibroblast growth factor 7 are produced by the dermal papilla and corresponding receptors are found predominantly in the overlying matrix cells of the bulb.[20] Insulin-like growth factor 1 maintains and increases follicle growth in vivo.[20,110] Hepatocyte growth factor is a multifunctional polypeptide, which acts as mitogen, motogen, or morphogen and stimulates the growth of a variety of epithelial cells, and melanocytes.[106] Human dermal papilla cells express hepatocyte growth factor and stimulate DNA synthesis with elongation of the hair shaft.[44,106]

Cessation of anagen is controlled by fibroblast growth factor 5,[102] and absence of the factor results in persistence of anagen with an associated increase in length of hair.[36] Epithelial growth factor retards hair growth[74] and the receptor is involved in terminating the anagen stage.[31,78] Protein kinase C is a negative regulator of hair growth and may play a role in growth inhibitory signals.[34] A transcription factor encoded by the hairless gene is essential for the dermal papilla to ascend and interact with the stem cells of the bulge. If the dermal papilla does not properly ascend to reach the bulge, for example, when the hairless gene is defective, the follicle stops cycling and permanent alopecia results.[90]

Dermal papilla cells synthesize and release vascular endothelial growth factor.[59] Dermal papilla cells also bind vascular endothelial growth factor resulting in subsequent proliferation and migration.[60] Several studies suggest the growing hair follicle has the ability to stimulate its own blood supply.[111]

HORMONES

Hair growth-regulating hormones include growth hormone, thyroid hormones, glucocorticoids, estrogens, and androgens. Estrogen receptors are present in the dermal papilla and 17-beta estradiol arrests the follicles in telogen while an estrogen receptor antagonist causes exit from telogen.[87] Androgens act through androgenetic receptors in the dermal papilla and have the most striking effects. During adolescence, they cause vellus hair to differentiate into terminal hair in androgen-dependent areas. In older adults, this same androgen stimulation causes loss of hair in areas susceptible to androgenetic alopecia. Some dermal papillae secrete mitogens after androgenetic stimulation whereas others synthesize inhibitory factors, which could result from genetically determined differences in end organ responses of the different follicles.

Consideration of Basic Mechanisms Related to Latanoprost-induced Hair Growth

TRANSITION FROM TELOGEN TO ANAGEN FOLLICLES

Recently observed findings of hypertrichosis following latanoprost therapy suggest the induction of the anagen phase in telogen follicles. The findings following latanoprost treatment can be compared with what is known from the literature about signals that orchestrate the follicle transition from telogen to the anagen stage. Because the total number of lash follicles does not change, the ability of latanoprost to increase the number of lashes is consistent with the initiation of anagen in follicles normally in telogen. The proportion of follicles in telogen is normally higher in eyelashes (~50%) than in hair elsewhere (e.g., scalp ~14%). Many eyelash follicles are thus available to undergo transition from telogen to anagen. In addition, the bilateral presence of eyelashes provides a readily available control population. The large telogen population and bilaterality provide a uniquely sensitive and easily studied model to assess drug-induced hair growth.

FOLLICULAR HYPERTROPHY DETERMINATION EARLY IN ANAGEN

A stimulus from the dermal papilla determines the course of differentiation of the matrix cells[41,92] and the number of matrix cells that differentiate to form the bulb determines the follicle size.[92] After the rigid internal root sheath has formed, enlargement of the follicle is not feasible,[62] further supporting the concept that hair follicle size is determined very early in anagen. The follicular hypertrophy observed with latanoprost is thus likely to result from a stimulus very early in anagen and the dermal papilla may be considered as a target tissue. Altered differentiation of follicles from vellus and transitional to terminal hair must also occur very early in the anagen cycle for similar reasons.

DETERMINATION OF ANAGEN DURATION AND HAIR LENGTH

An increase in hair length results when there is a delay in cessation of anagen. Stimuli occurring during anagen may initiate its cessation, an extreme example of which occurs with telogen effluvium resulting from drug exposures. Delayed cessation of anagen may also result from a stimulus in early anagen that in part determines the duration of anagen for that hair follicle cycle.[41,92] One might postulate that increased length of hair follicles observed following chronic latanoprost therapy[46] was associated with a delay in onset of catagen and determined by chronic exposure to the agent. However, increased hair length that occurred following very brief latanoprost exposure[45] indicates that the continuous presence of the agent is not required to cause increased duration of anagen and increased hair length associated with latanoprost treatment.

VASCULAR ISSUES

The actual mechanism by which latanoprost exerts its action on hair follicles is unknown. PGF2α, the naturally occurring prostanoid from which latanoprost was derived, causes vasodilatation; therefore, a vascular stimulus could be postulated. However, studies with viprostol, an active vasodilator, caused reduced hair growth in one study. In addition, an exhaustive study demonstrated a striking lack of vasoactive behavior of latanoprost.[112] Finally, the follicle is thought to initiate a stimulus to recruit its blood supply rather than vice versa.[18] These combined observations make a vascular mechanism seem less likely.

MITOGENIC ISSUES

A mitogenic stimulus must be required to trigger cell division at the initiation of the anagen. Moreover, an ongoing mitogenic stimulus is also required to facilitate continued division of matrix cells of the anagen follicle.[76] Furthermore, minoxidil behaves as a mitogen in the hair follicle.[55,75,95] PGF2α, the parent compound of latanoprost, has been shown to be capable of inducing mitosis in aneuploid, immortal murine 3T3 cells,[25,43,122,123] endometrial cells,[88,89] and hepatocytes.[44,106] Although such a stimulus occurs in those unique cell systems, PGF2α has not been demonstrated to be mitogenic in hair follicles. In the eye, latanoprost and PGF2α did not enhance the mitotic index of human uveal or cutaneous melanoma lines, measured by thymidine uptake, although both drugs increased the mitotic index of one murine cutaneous line.[24]

CELL ADHESION MOLECULES

Rapid remodeling and downward migration is a salient behavior of the hair follicle. The development of hair results from reciprocal interactions between epidermal and mesenchymal tissues and is influenced by cell adhesion molecules and components of the extracellular matrix. In fact, one of the main roles of cell adhesion molecules is to mold the follicle by relaxing or reinforcing cell contacts in areas of increased morphogenetic activity.[33] Adhesion molecules involved in hair follicle development include tenascin, neural cell adhesion molecule (NCAM), E-cadherin, intercellular adhesion molecule 1 (ICAM-1)[47,77] and integrins.[17] Prostaglandins may be involved in regulation of integrin mRNA expression.[71] PGF2α has also been shown to upregulate ICAM-1 production.[83]

PROTEASES

Enlargement and downward migration of the hair follicle require rapid remodeling of the extracellular matrix surrounding and preceding the advancing follicle. In fact, extracellular matrix remodeling is a central feature of hair formation.[6,17,64,105,129] Hair follicle epithelial cells interact with dermal papilla cells to release matrix-remodeling proteases[105,129] that are crucial to controlled follicle development.[129] Latanoprost has been shown to induce nuclear transcription factors leading to increased synthesis of proteases[86] which alter the extracellular matrix environment.[63,86,114,115] These studies have demonstrated that proteases induced by latanoprost reduce the extracellular matrix material surrounding cells. Reduction of the extracellular matrix material may influence the behavior of the hair follicle by the following three mechanisms.[21,38–40] The first mechanism is by enhancement of the normal remodeling of the extracellular matrix by proteases at the leading edge of the expanding and downward migrating follicular unit. Extracellular matrix remodeling is essential to permit cell proliferation, hair bulb enlargement, and downward migration of the entire follicle unit that occurs during the initiation of anagen. Enhancement of the remodeling process by prostaglandins may lead to a larger more robust follicle. Second, extracellular matrix remodeling is known to initiate signals that alter differentiation decisions. Extracellular matrix induced alterations in differentiation decisions may explain the clinically observed prostaglandin-induced change of follicles from vellus to terminal hairs.

A third mechanism may take place at the cusp of the transition between anagen and catagen. Alterations in the extracellular matrix environment are capable of delaying apoptosis thus increasing the length of the cell cycle. Extracellular matrix alterations induced by prostaglandins may be similarly cytoprotective and prolong the cell cycle in the hair follicle leading to an increase in the duration of anagen and thus the length of the hair shaft.

TROPHIC STIMULAE

Latanoprost is selective for the FP receptor on the cell surface, which acts to cause release of Ca^{++} to the cytosol and stimulates protein kinase activity. Both of these actions result in trophic metabolic activity fundamental to cell growth and proliferation,[2] which may explain the observed behavior of latanoprost.

Therapeutic Agents Currently Used in Hair Growth

ANDROGENETIC ALOPECIA

Androgenetic alopecia occurs as a result of progressive shortening of successive anagen cycles with gradual miniaturization of hair follicles, during which large, pigmented terminal hairs are gradually replaced by fine, unpigmented vellus hairs.[49] This form of alopecia requires the presence of androgens. Hair follicles are still present and cycling so the process is theoretically reversible.[92] There is a physiologic process of programmed organ deletion in murine models; in which a few hair follicles are normally destroyed by inflammatory cell infiltrates.[1] However, in androgenetic alopecia, inflammation regularly surrounds the bulge area of the follicle and may result in irreparable damage to the follicle stem cells, leading to irreversible hair loss.[42]

MINOXIDIL (ROGAINE)

Minoxidil and finasteride are the two drugs approved by the FDA for treatment of hair loss. Minoxidil prolongs the anagen phase of hair growth; causes follicles in telogen to enter the anagen phase,[75] and enlarges the hair follicle.[92] The most probable site of action of minoxidil is the specialized mesenchymal cells of the dermal papilla.[35] The mechanism of action of minoxidil has been reported to be related to its effects on potassium channels.[13] Minoxidil is a potassium-channel opener that causes vasorelaxation[127] and stimulates cutaneous blood flow to the scalp.[126] Minoxidil sulfate, a metabolite of minoxidil, is a potent vasodilator. Uptake and conversion from minoxidil to minoxidil sulfate occurs within the hair follicle suggesting a direct action on the follicle.[117]

There is a mitogenic effect of minoxidil in murine 3T3 cells,[117] and minoxidil increased DNA synthesis in both dermal papilla and follicular germ cells,[55] but at higher concentrations suppressed DNA synthesis. A similar increase in DNA synthesis has been found in skin cells treated with minoxidil; however cytotoxic effects occured higher concentrations,[95] with a narrow margin between proliferation and cytotoxicity. A marked inhibition of collagen synthesis has been found in the presence of minoxidil,[58] suggesting modification of the extracellular matrix environment as another possible mode of action.

FINASTERIDE (PROPECIA)

Finasteride inhibits 5α-reductase type II, which converts testosterone to dihydrotestosterone, the active factor in determining hair follicle responses to androgens. The enzyme 5α-reductase type II has been shown to be essential to male-pattern hair growth and alopecia because these conditions do not develop in men who have an absence of the enzyme.[96] Finasteride, as a specific inhibitor of 5α reductase, slows or reverses the progression of androgenetic alopecia. The dermal papilla is the likely target of finasteride because it contains androgen receptors, which are increased in the papillae of the beard and androgenetic alopecia prone scalp areas.[98] Finasteride is not effective in treating androgenetic alopecia in women. Interestingly, androgens have no effect on eyelashes.[97]

LATANOPROST

Recently, latanoprost has been found to reverse alopecia of the eyelashes, suggesting the possibility of a therapeutic role.[68] Although latanoprost is capable of inducing increased growth of healthy lashes and adnexal hairs, a role in reversing androgenetic alopecia has not been systematically assessed. The scalp follicles are a different type than those in the lash region and the scalp follicles involved in androgenetic alopecia also have a poorly understood underlying pathology. It remains to be determined whether there could be a useful clinical effect from treatment with latanoprost or another prostaglandin analog.

Summary

Latanoprost has recently been reported to alter lash and adjacent adnexal hair growth. This drug also stimulates hair growth in mice and in the balding scalp of stumptailed macaques. Hair follicles represent a complex microorgan system characterized by constant cycling behavior involving growth, quiescence, and involution. Hair growth and cycling are under the influence of a number of gene products and growth factors. Latanoprost appears to be a stimulus altering growth and differentiation patterns as well as the transition between phases of the hair cycle. Mechanisms by which latanoprost might influence cells in the hair follicle include altering production of regulatory substances such as morphogens, growth factors, or gene products involved in the modulation of extracellular matrix components and cell membrane associated adhesion molecules. The mechanisms by which latanoprost triggers hair cycle changes are not clear and warrant further study.

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