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Controls of Hair Follicle Cycling

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Stenn, K. S., and R. Paus. Controls of Hair Follicle Cycling. *Physiol Rev* 81: 449–494, 2001.—Nearly 50 years ago, Chase published a review of hair cycling in which he detailed hair growth in the mouse and integrated hair biology with the biology of his day. In this review we have used Chase as our model and tried to put the adult hair follicle growth cycle in perspective. We have tried to sketch the adult hair follicle cycle, as we know it today and what needs to be known. Above all, we hope that this work will serve as an introduction to basic biologists who are looking for a defined biological system that illustrates many of the challenges of modern biology: cell differentiation, epithelial-mesenchymal interactions, stem cell biology, pattern formation, apoptosis, cell and organ growth cycles, and

pigmentation. The most important theme in studying the cycling hair follicle is that the follicle is a regenerating system. By traversing the phases of the cycle (growth, regression, resting, shedding, then growth again), the follicle demonstrates the unusual ability to completely regenerate itself. The basis for this regeneration rests in the unique follicular epithelial and mesenchymal components and their interactions. Recently, some of the molecular signals making up these interactions have been defined. They involve gene families also found in other regenerating systems such as fibroblast growth factor, transforming growth factor-β, Wnt pathway, Sonic hedgehog, neurotrophins, and homeobox. For the immediate future, our challenge is to define the molecular basis for hair follicle growth control, to regenerate a mature hair follicle in vitro from defined populations, and to offer real solutions to our patients' problems.

I. INTRODUCTION

A. Scope and Goals of This Review: Chase in Retrospect

In these pages nearly a half-century ago Chase (63) published a review on the growth of hair that has become a classic in the field. In his discussion of the state of current hair biology, ". . . . which only recently [has] come under serious investigation," Chase carefully defined the development, structure, and cycling of the follicle. His emphasis throughout was the central place and the dynamics of hair growth in relation to the biology of skin itself. Implicit in his discussion were the basic themes in the biology of his day (63, 64).

In this review we revisit the controls of mature hair follicle cycling. At the outset it is obvious to the reader that a lot has changed since Chase; above all, more scientists are considering the hair follicle as an attractive system for studying major biological phenomena (75, 167, 410, 534). Moreover, today we enjoy powerful analytical tools, which he did not have, and we study hair with the confidence that therapeutic intervention can indeed influence hair growth (e.g., Refs. 248, 616).

Our focus in this review is on the mature hair cycle and its controls. We attempt here to integrate the morphology, which was pretty well known by Chase, with the physiology, molecular biology, and genetics, about which we have learned much since then. Except for a broad outline, we do not cover hair morphogenesis (384, 422, 438) or pigmentation (522, 563) because these are major subjects deserving complete attention in and of themselves. Moreover, because of space restrictions, we do not cover the formation of the shaft (455), the hair follicle immune system (223, 406), and the fine details of hair follicle neurobiology (41, 155, 423). Our goal is to put into perspective our understanding of the cyclic growth of this deceptively simple structure, to signal hiatuses in our understanding, and to project where we think we need to go in the future. Although we try for a balanced presentation, our essay is neither meant to be encyclopedic nor a tabulation of relevant factors (see Refs. 92, 250, 300, 405, 410, 530). We have tried to refer to the literature liberally so that the interested student will have a confident starting point.

B. Foundations of Hair Biology

Before considering the elements of the hair cycle in detail, we present in this section a broad overview of the biology of hair follicle growth and cycling because it is relevant to everything that comes hereafter.

The most obvious function of the hair follicle is to produce a hair shaft, or fiber. The latter serves many more functions than are usually appreciated (Table 1). Although this is also true for other mammals, for humans the most important function of the shaft is as a physical medium of social communication; in fact, scalp, facial, and body hairs are essentially the only body parts an individual can shape to influence social intercourse. This point underscores the importance of hair and the psychosocial consequences of its pathology. To effect its function, follicles differ from site to site producing shafts differing in size, shape, curl, and color. Coarse body hair is referred to as terminal hair, and fine, short, nonpigmented hair as vellus hair (see sect. XI).

The hair follicle develops from the embryonic epidermis as an epithelial finger (Figs. 1 and 2). This peg differentiates into three enclosed epithelial cylinders. The central most cylinder forms the shaft (fiber). The outermost

TABLE 1. *Functions of the hair shaft and follicle*

Functions of the hair shaft
Decoration; social communication and camouflage
Protection against trauma and insect penetration
Protect against electromagnetic radiation
Provide a sensory "antennae" to feel the environment
Insulation against heat loss and heat gain
Mechanism of cleansing skin surface of squames, dirt, and parasites
Mechanism of outward transport of environmental signals: sebum, pheromones
Functions of pilosebaceous follicle
Produce and moor the shaft
Provide epithelial and dermal reservoir for normal renewal and reparative response
Provide sensory apparatus for detecting shaft movement
Provide melanocyte reservoir for shaft pigmentation and epidermal repigmentation
Produce and release sebum for shaft processing and epidermal surface protection
Provide reservoir of Langerhans cells

cylinder forms the outer root sheath (ORS) that separates the whole structure from the dermis. The middle cylinder, the inner root sheath (IRS), molds and guides the shaft in its passage outward. The shaft and the IRS move outward together. All mature follicles undergo a growth cycle consisting of phases of growth (anagen), regression (catagen), rest (telogen), and shedding (exogen). The anagen follicle consists of a so-called "permanent" portion above the muscle insertion and a cycling portion below. Because the hair shaft may not shed before the next anagen starts, it is important to appreciate that the hair cycle with respect to the shaft is different from the hair cycle with respect to the follicle; in other words, the fully formed telogen shaft ("club hair"), adherent to the pilary canal wall, may rest completely independently of the cycle expressed in the underlying follicle (we will return to this concept in sect. VII).

As manifest by its cycle, the hair follicle is a regenerating system (512); the inferior hair follicle dramatically reforms itself over the cycle but the upper, permanent, follicle undergoes substantial remodeling (297). Hair follicle cycling is a developmental process, which occurs over the total lifetime of a mammal, well beyond the organogenesis of other systems and the cycling lifetime of the ovary or endometrium. This cyclic regeneration is thought to require many of the cellular signals integral to other morphogenetic (e.g., salivary glands, kidney, breast, and tooth) and regenerating systems (e.g., the amphibian limb). In all these systems, there is an intercommunicating epithelium and mesenchyme. For example, the regenerating amphibian limb needs a very special mesenchyme, the blastema, as well as an intact overlying epithelium to orchestrate the regenerative process (566). It is not surprising then to recognize that to grow and cycle, the normal follicle also requires intimate epithelial-mesenchymal interactions, receptive follicular epithelium, and follicular connective tissues. The regeneration theme is also upheld on a molecular level in that growth factor families found active in the regenerating amphibian limb are also expressed in the cycling hair follicle (384, 438).

C. Hair Follicle Morphogenesis

As we will use the terms in this discussion, follicular regeneration is considered to be an integral part of the follicle growth cycle. On the other hand, follicular morphogenesis and the follicle cycle are, at least in part, considered to be different phenomena (Fig. 1). Although these two processes share many features, they differ from one another in at least one fundamental way: in the one a whole structure generates from a primitive epidermis (morphogenesis), and in the other, a partial structure generates from adult tissues (regeneration) (for recent reviews, see Refs. 82, 336, 384, 438).

For most mammals during the prenatal period, body follicles (pelage follicles) form in certain regions and then extend as a wave over the skin surface (63, 167). Follicles form from the primitive epidermis as a result of signals arising in both the primitive epithelium and the underlying mesoderm. The elements necessary for follicle formation are inherent to embryonic epithelium and mesenchyme (e.g., they do not need intact hormonal or neural circuits) since follicles can form de novo from organ-culture fragments of embryonic skin (164, 166). Early in development, specific foci of the primitive epidermis become competent to produce hair. Whether that signal is primary to epidermis or secondary to an inductive stimulus from the dermis is debated (38, 167, 266, 384, 438, 618). The epithelium grows down into the dermis as a plug that joins at its proximal end a mesenchymal condensation, referred to as the follicular, or dermal, papilla.[1] As the isolated papilla has inductive properties in the adult, it is thought to play a significant role in the morphogenesis of the follicle (214, 379, 380).

Follicle formation occurs but once in the lifetime of an individual, so a mammal is born with a fixed number of follicles, which does not normally increase thereafter. However, postnatal folliculoneogenesis is probably allowable in biology under certain unique circumstances. For example, new follicles are formed in the skin growing over newly formed (regenerating) antlers in mature deer (146, 534), and it has been proposed that follicle neogenesis can be associated with wound healing in rabbit skin (25). Relative to this phenomenon is that experimentally when β-catenin is constitutively overexpressed in the skin of a transgenic mouse, new follicular structures form (K14 promoter, Ref. 132).

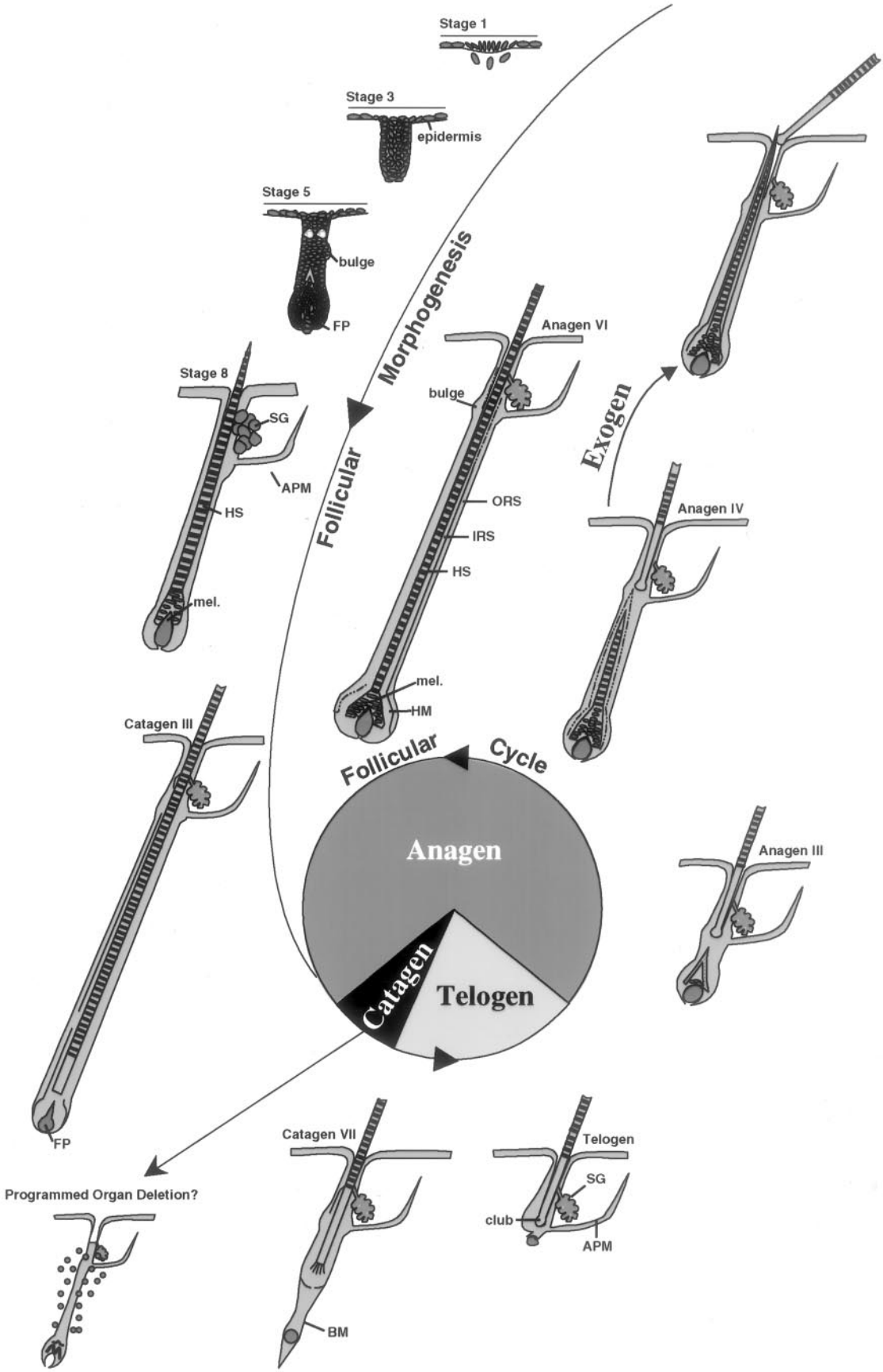
At the end of its morphogenetic phase, the follicle has a cycling inferior (proximal) region and a so-called permanent superficial (distal) region. Once fully formed, the follicle enters its first genuine cycle.[2]

II. ASSAYS USED TO ASSESS HAIR GROWTH

To measure hair growth, relevant, easy, and inexpensive experimental models are essential. To be effective,

[1] The anatomical designation of "proximal" and "distal" follicle is embedded in the old hair research literature (e.g., Ref. 96). The concept is most readily appreciated if the observer pictures the orientation of the shed shaft where the tip is considered to be distal and the club base proximal. This same directionality is retained in the follicle.

[2] The literature does not clearly distinguish the end of follicular morphogenesis from the beginning of the first follicle growth cycle. The first fully formed follicle (morphogenesis stage 8, Refs. 167, 422) appears morphologically identical to the full anagen of later cycles. Some workers contend that the first true cycle begins after morphogenesis with the first catagen (407, 422), the first full anagen, or telogen (63, 538). Others suggest that the cycle may begin with morphogenesis itself and that the separation is artificial (538).


Stage 1
Stage 3
epidermis
Stage 5
bulge
FP
Morphogenesis
Follicular
Exogen
Stage 8
SG
APM
HS
mel.
Anagen VI
bulge
ORS
IRS
HS
mel.
HM
Anagen IV
Catagen III
FP
Follicular Cycle
Anagen
Catagen
Telogen
Anagen III
Programmed Organ Deletion?
Catagen VII
BM
Telogen
SG
club
APM

these models, in vivo or in vitro, have to reflect the major regulatory processes. The phenomena which the assays must describe include *1*) hair follicle morphogenesis; *2*) hair follicle cell differentiation leading to shaft and sheath formation; *3*) hair follicle cycling including anagen, catagen, telogen, and exogen; *4*) hair follicle heterogeneity; *5*) hair follicle switch from the vellus to the terminal state; and *6*) hair shaft pigmentation. In this section we discuss laboratory models currently used for assessing hair growth. It is important to recognize at the outset that the assays we describe are limited vis-à-vis the foregoing list.

In constructing assays for hair growth, the challenge has been to ensure that the system used actually measures hair growth and not a nonspecific or irrelevant biochemical/physiological pathway. Because we have not yet defined the cellular and molecular pathways, which uniquely control the cycle, the use of pure molecules or cells for measuring the cycle is limited. For all hair follicle assays, the parameters of donor animal type, donor animal age, and site of follicle origin are all very important to any experimental interpretation.

Although relevant as an assay, hair follicle organ cultures are limited by their difficulty of preparation, variability (the cycle phase during which a follicle is harvested for study may influence its experimental response in culture, Ref. 457), and viability (it has not yet been convincingly shown if dissected follicles can traverse the full cycle in vitro).

A. Whole Animal Systems

Whole animal systems are the most relevant but also the most difficult to control, quantify, and analyze. Animals commonly used include mice (63, 177), rats (231), sheep (203), and monkeys (569), but studies have been conducted on other mammals including the cat (181), horse (595), rabbit (553), opossum (305), guinea pig (55), prairie vole (527), and hamster (333). In this regard it is notable that there is no evidence that the most basic controls of hair follicle cycling among mammalian species are different. In assessing hair growth for human disorders, the most relevant model is still the human, but the second best is considered to be the macaque (569). Although most difficult to use routinely because of its rarity, housing, handling, expense, and ethical implications (of primate research), the macaque has, nonetheless, been effectively used as a quantifiable model (569). In this system both female and male adults show patterned scalp alopecia.

The laboratory mouse has been a favorite subject for hair studies, and the pigmented C57BL/6 (63, 426) and C3H (177) mice are the most commonly used strains. The rationale for choosing these mice is that their truncal pigmentation is entirely dependent on their follicular melanocytes; their truncal epidermis lacks melanin-producting melanocytes. Because pigment production is active only during the follicle growth (anagen) phase, the only time skin is dark is when the hair is growing. Therefore, by assessing the skin color one can also assess follicle growth phase. Another feature of the mouse system is that the growth phase of its follicles can be synchronized, allowing the investigator to isolate and analyze follicles of certain phases after hair growth induction by plucking (63, 513). Growth can also be stimulated by chemicals (464), including depilatory creams. Because active hair growth can be induced by minoxidil (54) or cyclosporin A (426) in these mice (as in humans), it is argued that the mouse model has some use in a drug discovery environment. Finally, the mouse system is particularly attractive because of the existing genetic databases, the availability of specific mutants (544), and the possibility of generating desired hair mutations by transgenic manipulation. It is also notable that gene delivery to mouse hair follicles has been successfully achieved (6, 95a, 121, 136, 188, 615). Because the C57BL/6 strain has been most extensively studied, we recommend to the researcher new to the field to start with this strain. We are indebted to Chase for this model.

B. Ex Vivo Systems

Ex vivo systems combine in vitro and in vivo approaches. Workers have dissected out follicular structures, grew follicular cells and tissues in culture, and then transplanted these tissues back to the skin of immunoincompetent animals (292, 477, 585) or under the kidney capsule of a syngeneic living animal (e.g., Ref. 257).

In the very incisive Lichti system (292, 477), newborn follicular epithelium and mixed or cloned (457) follicular papilla cells are first grown in culture and then transplanted to immunodeficient mice. This system can be used to study not only folliculoneogenesis and skin organ

FIG. 1. Follicular morphogenesis and cycling. The hair cycle is envisioned here as a number 6, where the limb of the number represents the morphogenetic phases and the circular base represents the repeating cycle after the morphogenesis. Although the morphogenetic limb occurs just once in the lifetime of a follicle, the cycle repeats many times. Although morphogenesis and cycling are distinct phenomena, they share morphologic and molecular features (see text). DP, follicular papilla; SG, sebaceous gland; APM, arrector pili muscle; HS, hair shaft; mel, melanin; BM, basement membrane; POD, programmed organ deletion; HF, hair follicle; ORS, outer root sheath; IRS, internal root sheath. [Adapted from Paus et al. (414) and Slominski et al. (521).]

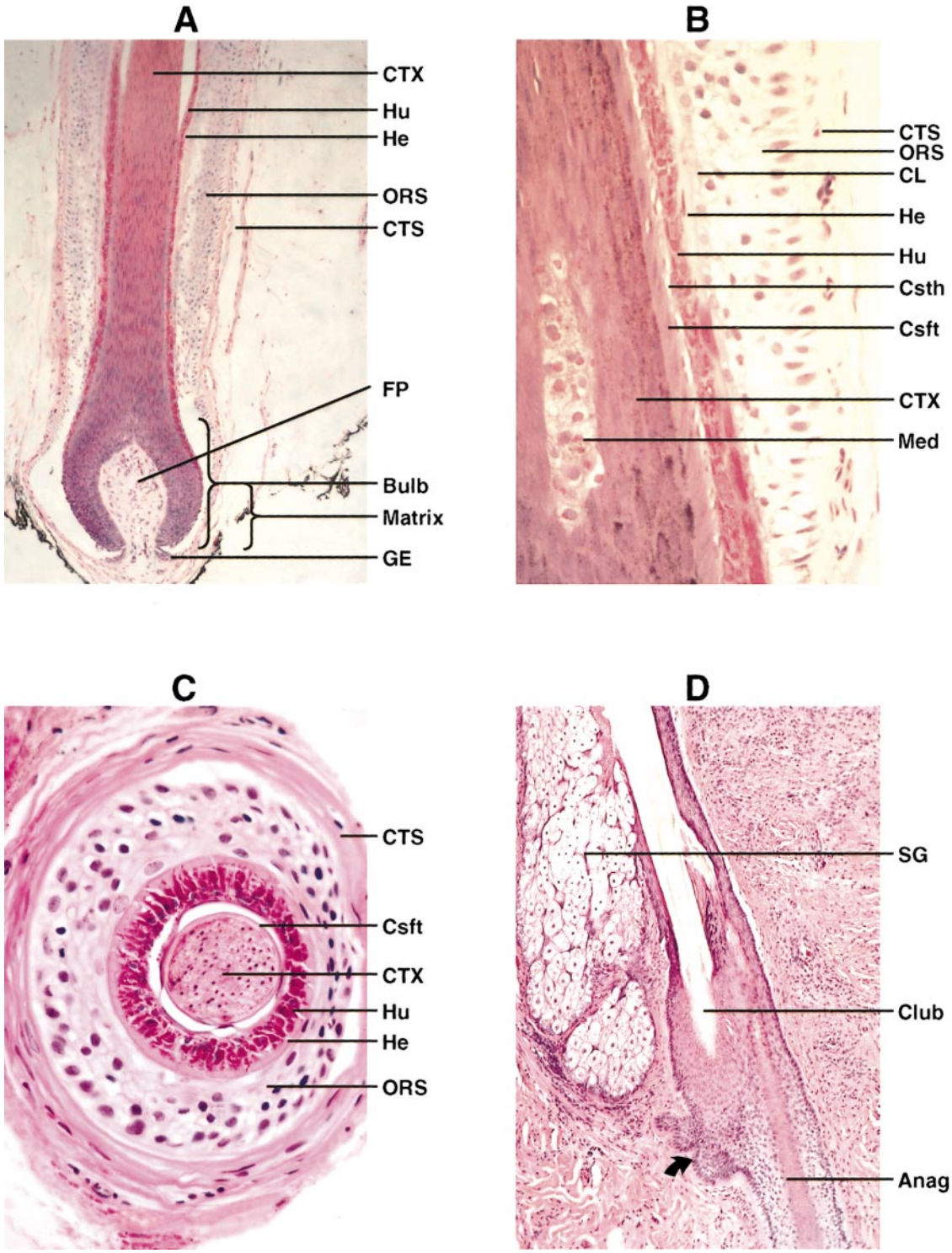


FIG. 2. Follicular histomorphology: human skin. The 8 cellular lineages of the mature follicle are illustrated by these histological preparations. The defined lineages are the outer root sheath (ORS), the companion layer (CL), the internal root sheath Henle's layer (He), internal root sheath Huxley's layer (Hu), the cuticle of the internal root sheath (Csth), the cuticle of the hair shaft (Csft), the cortex of the shaft (CTX), and the medulla of the shaft (Med). It is notable that the shaft and the IRS move up the follicle as a unit, with the IRS falling from the shaft just below the sebaceous gland duct. The slippage plane for the outward-moving shaft sheath is in the companion layer. *A*: vertical section of proximal anagen follicle, low power. *B*: vertical section of proximal anagen follicle, high power. *C*: cross section of proximal anagen follicle. *D*: telogen shaft with anagen follicle below. Note the secondary hair germ epithelium at the base of the telogen follicle (arrow). CTS, connective tissue sheath; SG, sebaceous gland; Club, telogen shaft base; Anag, proximal anagen follicle; FP, follicular papilla; GE, germinative epithelium. (Histology provided by Dr Leonard Sperling.)

regeneration but also follicular cell lineages (241) and the effect of specific cellular and genetic manipulations on follicle growth (253).

Reminiscent of the rotation-mediated method of Moscona (355), Takeda et al. (552) aggregated cells in a rotating in vitro culture system and then transplanted the aggregates to a receptive animal. Similar results have been found by growing follicular fragments beneath the kidney capsule of syngeneic animals (257). These cultures, like the Lichti system, also readily regenerate complete, cycling, mature hair follicles.

C. In Vitro Systems

Whole skin explants have been used to study hair growth. Early attempts to grow embryonic skin in vitro demonstrated that such explants retain the ability to form hair (independent of vicinal influences such as intact blood vessels or nerves) (164, 194). More recently, mature whole skin from mice and humans has been used to study the hair cycle (286, 287, 416, 417). Whole skin on a gelatin sponge at the air/liquid interface can be sustained for up to 40 days in culture (286). Variations of this whole skin explant technique on collagen sponges ("histoculture") allows one to follow and pharmacologically manipulate hair follicle morphogenesis (36, 49, 124, 538a), anagen I-VI development, anagen-catagen transformation in vitro (36, 49, 124), and hair follicle pigmentation (287).

It has been demonstrated that dissected mature human anagen follicles can be successfully grown in culture (435). In this approach, human scalp/facial growing skin follicles are truncated below the dermis, dissected free of dermal/subcutis tissue, and placed free-floating in serum-free culture medium. With the use of this method, successful hair follicle organ cultures from multiple other species have been demonstrated (e.g., rat, Ref. 436; sheep, Refs. 34, 594; horse, Ref. 595). Although these follicles continue to grow for ~9 days in culture and are thus useful for studying the anagen phase and the onset of catagen, they do not traverse the full hair cycle and do not generate new follicles. It is important to note that this system, unlike a whole skin organ culture, lacks potentially important influences from the more distal pilosebaceous apparatus, namely, the epithelial stem cell region, the sebaceous gland, the perifollicular connective tissue sheath, and the epidermis (427, 595). A method for preserving whole follicles in a skin equivalent has recently been described (334).

Although growing dissociated cells, both mesenchymal (216, 217, 328, 578, 594) and epithelial (295), from mature hair follicles has been successfully achieved, generating follicles in vitro from these cells has been less successful. Jahoda and Reynolds (220) found that dissociated follicle matrix epithelial cells and follicular papilla fibroblasts placed within the connective tissue sheath of a vibrissae follicle would, in turn, generate a follicle. Limat et al. (294) found that growing ORS cells in an extracellular matrix in vitro supported the reorganization of hair follicle-like structures. Although in these studies aggregates suggestive of sebaceous gland and infundibulum were seen, clear-cut hair follicle formations were not.

A major current challenge for the laboratory assessment of hair follicle growth is to have inexpensive, biologically relevant systems for assessing hair follicle cycling. No such system is now available. In fact, we currently have no good in vitro system for assessing the vellus to terminal switch, for measuring anagen (growth phase) induction, or exogen (shedding) induction. For this reason, we are unfortunately dependent on the living, nonhuman animal assays for our initial assessment.

III. NATURE AND THEORIES OF FOLLICLE CYCLING: A CYCLE ON CYCLES

A. How and Why Cycling

Whatever the evolutionary pressure, we recognize that the most unique feature of hair growth is its cycle. So, why does a hair follicle cycle? The answer is not obvious, but biologists have suggested several notions recognizing that skin molting (and the shedding of its appendageal products) is inherent to the integument of all organisms. It is suggested that hair follicle cycling may have arisen because it offers a mechanism whereby animals could *1*) expand and grow (488); *2*) control the length of body hair uniquely from site to site; *3*) shed fur periodically to cleanse the body surface; *4*) adapt and change its body cover in response to changing environmental (e.g., winter to summer), and perhaps social, conditions; *5*) protect from the improper formation of the follicle; or *6*) protect against malignant degeneration that might occur in this rapidly dividing tissue.

The hair growth cycle describes the changing morphology of the shaft, grossly, and the follicle, histologically, over time (96) (see Figs. 1 and 2). Starting with anagen, the follicle and its shaft pass through catagen, telogen, and finally exogen. All body hairs manifest this cycle, although the duration of that cycle, the duration of the individual phases, and the length of the individual shafts vary dramatically from site to site (490, 565). In the human and guinea pig, each follicle has its own inherent rhythm, and thus the cycles are asynchronous (63). In most rodents, however, large collections of follicles cycle together; in this situation, synchronous follicle growth

occurs in waves that sweep posteriorly and dorsally.[3] As the mouse ages, the waves become less frequent so that in the mature and senile mouse synchronous hair growth occurs only in relatively small patches. How the cycle spreads in waves is not clear, but experimental studies suggest that growth waves are controlled by factors intrinsic to the hair follicle groups in a manner that has been pictured as a "reaction-diffusion" system (103, 105, 365). This inherent rhythm, however, is influenced by neighboring follicles (229) and/or systemic (e.g., endocrine) stimuli, since in parabiotic rats the waves of hair growth tend to become synchronized with time (107). So, although the cycle is intrinsic and essentially autonomous, it is influenced by environmental systemic and local factors (entrained).

Although circannual rhythms are obvious in animal fur follicles, seen as shedding, and as a change of coat character (e.g., seasonal molting), their expression is subtler in humans (90, 382, 461). In the end, though, the long hair follicle cycles observed in human scalp hair, sheep wool, and horse mane represent very special cycles in biology: these follicle cycles are independent of the sun, moon, or constellations over a period of 2–6 years, a biological clock not yet characterized. The scalp follicle clock, then, being supra-circannual and independent of seasons (light) and temperature, demands its own paradigm in the field of chronobiology (102, 149).

Where the rhythm center rests in the follicle is unknown, and no experimental data indicate whether this site resides in the epithelium (e.g., bulb or bulge), mesenchyme (papilla), or a resonance between factors in the environment of the follicle (420, 535). Recent work suggests that many cell types have the ability to generate unique rhythms, independent of other tissue rhythms (18). It is important to recognize and distinguish the fact that the hair growth cycle is imposed on the cycle of growing cells that make up the follicle and its fiber; these cells undergo many cell divisions during the follicle growth cycle. The follicle cycle, then, is a cycle imposed on many cellular cycles.

B. Initiation

From where is hair growth cycling initiated? What is the initiating stimulus? How does it get to its target? How does it affect hair growth? These are the most fundamental unanswered questions in contemporary hair biology (discussed in a recent forum, Ref. 535). The first signal for hair follicle formation (i.e., morphogenesis) is generally held to come from the mesenchyme (38, 167, 422). However, what initiates anagen from telogen in the mature follicle and from where that stimulus comes is debated. The signal could arise in the resting papilla, the resting epithelial germ, the adjacent epidermis, or, in theory, even the supportive vessels, nerves, lymphatics, and resident dermal hematopoietic cells of the region. Tissue culture and in vivo studies suggest that the signal arises independent of central organized neural elements and vascular or endocrine signals (166, 323).

The cells initiating anagen growth must have certain features: they must have stem cell-like characteristics (see below), they must have the machinery to maintain a unique rhythm (see below), and they must be able to send its signal to the surrounding epithelium and/or mesenchyme. That many soluble growth factors have been associated with the anagen follicle (530) suggests that a paracrine mechanism is plausible (365). How the signal spreads is unanswered. If the signal is spread from site to site by means of the epithelium, then it might, besides classical paracrine and juxtacrine signaling forms, also be transduced by means of an electrical pulse or ion flow through gap junctions. The epidermis and the hair follicle are richly endowed with such junctions (474). That these gap junctions might serve as the conduit for message transmission has been tested. Although communication by means of these junctions is seen in the developing follicle and in the germinative matrix, such interactions between the epithelial cells, between the mesenchymal and epithelial cells of the differentiated follicle (71, 240), or between epithelial cells of neighboring hair follicle via the interfollicular epidermis have not yet been found.

C. Theories of Hair Follicle Cycling

Theories proposing a mechanism for hair follicle cycling must include the characteristics of the cycle (its periodicity, persistence, and autonomy), epithelial-mesenchymal interactions, the variation from site to site, and the exquisite sensitivity to numerous extrafollicular growth-modulating signals, such as hormones, growth factors, and dietary changes. Six theories on the regulation of hair cycling have been recently presented and discussed (535) (see Table 2). In the past, arguments in favor of both a stimulatory and inhibitory control of spontaneous hair growth induction have been presented (231, 421). Chase (63) and others (12, 471) held that anagen initiation was due to the loss of an inhibitor, namely, an inhibitor release mechanism (the inhibition-disinhibition theory). Concrete evidence for the theory is scant, although telogen epidermis has been reported to contain an inhibitor to hair growth induction while anagen epidermis does not (427). If a parallel can be drawn, the recent demonstration that follicle formation is at least in part controlled by an inhibitor release mechanism (bone morphogenic protein-4/noggin complex, Ref. 38) encourages

[3] Human follicles also grow synchronously before and around birth (431, 515).

TABLE 2. *Theories of hair follicle cycling*

Title	Concept	Reference No.
Epithelial theory	In the bulge cell area of the follicle, the slow cycling cells harbor a second cycle that orchestrates the follicle cycle.	535
Papilla morphogen theory	The papilla cells express a cycle of released growth morphogens that orchestrate the cycle. Anagen switches on when the papilla morphogen concentration exceeds a critical threshold. The cell cycle-dependent fluctuation in papilla morphogens is inversely correlated with fluctuations in endogenous mitotic inhibitors. The follicle cycle is set up by the cell cycle of the papilla cells that secrete morphogens only during the G_0/G_1 phase.	535
Bulge activation theory	Factors in the papilla act on the stem cells of the bulge region to orchestrate the cycle. The transit amplifying cells generated from the stem cells can undergo only a limited number of mitoses, thus establishing the length of anagen and the onset of catagen.	84
Resonance theory	The "clock" controlling the cycle does not reside in a single cell compartment but is rather a resonating control set up by the tissues, i.e., diffusing and reacting morphogens interact within a defined tissue space.	535
Oscillating signal theory	Like a quartz clock, telogen cells house an oscillation (e.g., transcription factor levels within the cells), which eventually trip the alarm moving the follicle into anagen.	535
Inherent embryonic cycle theory	The hair cycle is due to an inherent cycle clock, which is first established during embryogenesis and continues throughout life.	535
Inhibition-disinhibition theory	An endogenous mitotic inhibitor accumulates during each anagen phase in the epithelial hair bulb. At a certain threshold level, follicular cell growth would cease. In telogen the activity would decrease to a level of disinhibition and anagen would start again.	63, 421

one to reassess Chase's inhibitor-release hypothesis for mature cycle initiation.

IV. ANAGEN

A. Anagen Initiation

Anagen initiation is studied in the laboratory either as it arises, spontaneously, from telogen or, artificially, by experimental induction. As discussed above, we still do not know what spontaneous initiation means in terms of cells or molecules, except that its occurrence is, generally, quite predictable. In the laboratory, anagen can be induced under controlled conditions by taking advantage of the fact that hair growth is initiated by trauma/wounding (10, 11, 63, 135, 289). Trauma/wounding may mean hair plucking, vigorous shaving, or chemical exposure (e.g., caustic materials, depilatory agents). In this respect, we do not know what "trauma/wounding" actually means, although we do know that clipping the hair shaft without injury to the skin surface and follicle epithelium does not initiate growth (306). That trauma may have effects (cell necrosis, inflammation) besides the induction of growth has been documented (513). We assume trauma/wounding causes the release of proinflammatory cytokines that directly initiate anagen. Although we doubt that this form of initiation accurately reflects the spontaneous event, we assume that at least some aspects of the pathway(s) activated are common to the two situations.

It has been found that the traumatic stimulus has a certain threshold below which synchronized growth will not occur. Chase and Eaton (65) found that at least 1,000 hair shafts have to be plucked to initiate hair growth; plucking a single hair in the mouse does not initiate anagen activity in that follicle (65). This observation suggests that the pathway requires a quantifiably minimal threshold stimulus. It is also notable that the traumatic signal does not appear to spread beyond the area of wounding (63).

Although they are believed to have a specific mechanistic effect, selected pharmaceuticals, such as minoxidil (54), cyclosporin A (322, 420, 425), FK506 (213, 322, 425), norepinephrine-depleting agent (433), estrogen receptor antagonist (mouse, Ref. 376), tretinoin (596), tumor promoter agent (TPA) (375, 596), and various growth factors and neural mediators, such as keratinocyte growth factor (KGF) (92), hepatocyte growth factor (HGF) (228), sonic hedgehog (492), substance P (419), capsaisin (419), the antagonist parathyroid hormone (PTH)-(7—34) (195, 500), ACTH, and mast cell degranulation (409) can all induce anagen. The participation of any of these components, or the pathway they implicate, in the spontaneous signal for anagen induction is not yet clear.

It has long been known that anagen is suppressed by glucocorticoids (375). What was not appreciated is that the anagen stimulus, for spontaneously and traumatically induced signals, is actually only suspended, not abrogated, by glucocorticoids (534). The overriding aspect of the glucocorticoid block is that the trauma-induced signal is preserved as long as the steroid is applied. It is as if, paradoxically, the activated follicles were frozen in morphological telogen. Once the steroid applications cease, anagen begins. The implication is that the steroid block occurs downstream of a common pathway, but which mediator pathway it affects is unclear. The fact that the cyclosporin A signal for anagen induction is completely

suppressed by betamethasone (Paus et al., unpublished data) while the morphogenetic signal cannot be blocked by corticosteroids (596) suggests that the latter two signal pathways differ somewhat from the spontaneous and trauma-induced signals. The implicated role of KGF and HGF in hair growth (see below) and the fact that the production of KGF and HGF are blocked by glucocorticoids may suggest a role for KGF and HGF in the glucocorticoid effect (68, 297). In any case, the steroid block would appear to be an ideal tool for dissecting the signals of anagen initiation before any morphological features of anagen are apparent. In the mouse, anagen induction is also blocked by 17β-estradiol (207, 375, 376) and, reportedly, by androgens (375), but the relationship of the sex hormone steroid block to the glucocorticoid block has not been determined.

B. Anagen Development

Anagen is that phase of hair follicle growth extending from the termination of the quiescent phase, telogen, to the beginning of the regressing phase, catagen. Although morphologically it is comparatively simple to define when anagen and catagen begin and end (64), the molecular sign posts are less clear. Anagen involves the complete regrowth or regeneration of the lower, cycling portion of the follicle, i.e., the hair shaft factory. To that end, the cells regenerating the lower follicle (i.e., the cells of the secondary hair germ; Fig. 2*D*) must receive a signal to proliferate, grow down into the dermis, form the epithelial lineages making up the essential cylindrical layers, and differentiate to produce that shaft which is characteristic of the skin region. Because there is a limit to the time a follicle stays in anagen, there is also a limit to the length of its product, the hair shaft. The anagen phase has been divided into six subphases (64, 359). Except for the last subphase, anagen VI (the duration of which dictates the shaft length), the length of the anagen subphases I–V does not differ substantially between follicles from different regions (490, 565).

Transcriptional activation, the earliest observed changes of anagen, occurs in the cells of the papilla and the secondary hair germ (a cluster of epithelial cells at the base of the telogen follicle) (511, 513). Before that time, the lower follicle is widely thought to be fundamentally "quiescent," mitotically and transcriptionally (however, see sect. VI).

In early anagen, the epithelial cells of the secondary hair germ grow down into the dermis as an epidermal finger. Once they reach their destined depth, the cells in the central cylinder reverse their growth direction and now progress distally (outward), forming the IRS and the hair shaft. Most of the cell divisions occurring in the bulb appear below a horizontal line drawn across the widest portion of the papilla (Auber's critical level, Ref. 6). This relative restriction of substantial cell division to the lowest region of the anagen follicle appears to reflect the profound structural changes the central portion of the follicle must undergo in its differentiation toward a highly rigid structure. The cell kinetics of the matrix during the cycle have been reviewed (313, 573). Such studies indicate that the matrix cell cycle time is 12–13 h in mice and 23 h in humans. In anagen, the cells of the bulb show a mitotic index of 2.4% in mice (4.3% in humans) with a labeling index of 32% and a growth fraction for the proliferative compartment of ~60%.

Although their function is not yet clear, a group of molecular markers of the anagen follicle bulb/matrix has been described (93, 250, 299, 300, 427, 531, 535). For example, actively dividing cells of the lowest portion of the bulb express telomerase, but as anagen approaches catagen, this expression ceases (374, 460). The same pattern is found for the zinc finger protein basonuclein, which is expressed in the basal layer of the ORS as far distal as the bulge and in the peripapilla cells of the bulb (586). Proliferating hair matrix cells are distinguished from other epithelial cells of the skin by their high level of LEF1 expression (60, 132, 618).

In contrast to the epithelial compartment of the follicle and the endothelial cells in the papilla (444), the fibroblastic cells of the papilla, in the normally cycling follicle, have been reported to show no division, thymidine uptake, or mitotic figures (589). However, in organ culture of human hair follicles, fibroblasts of the papilla incorporate thymidine apparently exclusively during anagen (20). In addition, it has been found that ferret follicles show a burst of proliferative activity in their papillary fibroblasts in very early anagen (535), as do murine hair papilla fibroblasts (M. Magerl, D. Tobin, and R. Paus, unpublished data). The significance of this proliferative activity to the hair cycle, as an effect of or a regulatory element of hair cycle control, remains to be established.

C. Stem Cells of the Follicle

Any cellular structure that periodically renews itself depends on stem cells, cells that retain the ability to divide over the lifetime of the animal and regenerate that structure. Characteristics of stem cells include their paucity; their infrequency of division (slow cycling cells); their ability to generate transient amplifying (TA) cells in response to stimuli; their location in protected, well-vascularized, well-defined areas; their undifferentiated properties; and their colony-forming ability (82). However, what exactly defines a stem cell and what markers reliably delineate stem cell properties are debated (see Ref. 82); moreover, to make the concept even more complex, there may be some plasticity, or interconversion, between TA cells and stem cells (82).

Because the hair follicle is, above all, a regenerating system, workers have puzzled over the location and property of the cells that support this regenerative property. Because the bulb of the follicle shows significant cell division, it was implicit in the older literature that the site for important cell division and new anagen formation was in the bulb (e.g., Refs. 6, 573). Although that rationale is less obvious today, it appears stem cells were thought to reside among the cells that have the largest capacity to divide. Chase (63) was not so sure. In his review he states that "there is an equipotentiality of the epithelium . . . of the upper, 'permanent' external sheath" that can "refurnish lost epidermis in wound healing, . . . give rise to a new sebaceous gland . . . [and]. . . serve as the 'germ' in the presence of the dermal papilla."

In fact, when slow-cycling label-retaining cells were initially looked for, they were not found in the bulb but were found in the area of the follicle at the level of the muscle insertion site, the bulge/isthmus region (83, 353). These bulge cells are slow cycling (over 14 months in the mouse, Ref. 354), relatively undifferentiated, located in a well-protected well-nourished environment, and, finally, are indispensable to follicle cycling. The label-retaining cells have convoluted nuclei reflecting their proliferative inactivity (83). In addition, in the region of the bulge, and somewhat below it, there are colony-forming epithelial cells that have the greatest ability, compared with cells of other follicular levels, to form colonies in culture (holoclone or meroclone) (258, 476, 611). Although in young mice these special cells are found in the subsebaceous/muscle insertion site, the bulge area, in adult mice the bulge itself is not very apparent (83, 353). In humans, these cells are found deep to the muscle insertion site (258, 476).

There is reason to believe that the nature and location of stem cells may differ between follicle types. The vibrissal follicle in this respect differs in many ways from the pelage follicle. Specifically, "germinative" epithelial cells of vibrissae have been identified at the extreme base of the follicle bulb and display many of the characteristics of stem cells; they have unspecialized, primitive features and are located in a well-vascularized and sheltered region. This distinct group of epithelial cells remains behind when the rest of the matrix regresses; they appear to remain attached to the telogen papilla (468, 470) (Fig. 2*D*).

Biochemical studies also support the notion that cells in the bulge segment and its surrounding mesenchyme are special. For example, *1*) the bulge cells are rich in keratin 15 (304), keratin 19 (K19) (273), epidermal growth factor (EGF) receptor, $\alpha_2\beta_1$- and $\alpha_3\beta_1$-integrins (236), high levels of α_6-integrin and low levels of the proliferation marker 10G7 (283), and platelet-derived growth factor (PDGF)-A/PDGF-B ligand chains. *2*) In contrast to the surrounding bulge cells, the label-retaining cells are CD24 negative (310). *3*) Recently, it has been found that among the K19-positive cells in the bulge is a subset that lacks a specific differentiation marker, a gap junction protein, connexin (Cx) 43; it was proposed that these cells may represent the actual stem cells (317). *4*) That certain papillomavirus expression is limited to the epithelial cells of the hair bulge region suggests a unique follicular stem cell surface receptor that the papillomavirus exploits (499, 503). Potentially, this marker might have use in follicle stem cell studies. *5*) Finally, the surrounding connective tissue of this region is also unique. The follicular connective tissue sheath cells in this area stain for both PDGF-α and PDGF-β receptors and versican (5, 101). Despite considerable effort, no definitive follicular stem cell marker has yet been found, although a combination of the above parameters provides a reasonable cellular signature for the stem cell region of the hair follicle.

It has been observed that as cells age the telomeric ends of their chromosomes shorten. This phenomenon is inversely related to the activity of telomerase, a ribonucleoprotein complex, which is able to reconstitute chromosome ends. Telomerase activity is high in proliferating cells and low in differentiating cells (169). Recent work suggests that telomerase is an important component of cells undergoing growth. Although quiescent stem cells normally would not be expected to express this enzyme (23), the transient amplifying cells, which they generate, would. A working definition of a stem cell, in this regard, would be a cell in which telomerase is inducible (while in differentiated cells telomerase would not be expressed, in transient amplifying and cancer cells it would be constitutively expressed) (C. Harley, personal communication). In the hair follicle, telomerase is only weakly expressed in the area of the bulge and strongly expressed in the lower bulb cells (460). It is found that telomerase expression ceases with the onset of catagen, a change that may reflect no more than the dramatic decline in cell proliferation associated with this phase of the cycle.

Although most workers in cutaneous biology have focused on epithelial stem cells, in other fields there is a concept of mesenchymal stem cells as well (58). It is possible that cells with stem cell-like properties also reside in the dermis. In fact, slow-cycling cells are found in the dermis (354). That the dermal sheath cells may regenerate a papilla suggests that it houses cells with stem cell-like properties (216, 377–379, 472). Papilla cells have the property of orchestrating the regeneration of the whole skin organ from dissociated epithelial-mesenchymal cells (292, 457, 473). In one set of experiments, complete hair follicle and dermal regeneration was demonstrated starting with newborn mouse epidermal cells and cloned papilla cells (457, 458). These experiments show that hair follicles house mesenchymal (papilla) cells with stem cell-like properties.

Evidence suggesting that there are precursor cells for

other resident cells in the follicle, such as melanocytes (563) and Langerhans cells (140), has been presented.

D. Epithelial-Mesenchymal Interactions

Central to hair follicle growth are powerful epithelial-mesenchymal (E-M) interactions. Because we are focusing in this review on the mature cycling follicle, we will not discuss in detail those E-M interactions important to folliculomorphogenesis, which has been reviewed elsewhere (84, 85–87, 217, 330, 337, 384, 442).

Mature hair follicle mesenchyme is placed in two communicating compartments: the surrounding connective tissue sheath (CTS) and the follicular papilla (FP). The CTS embeds the follicle in the dermis and subcutis. The FP, a nubbin of connective tissue and cells, is separated from the proximal follicle in telogen but is embraced by the lower follicle matrix or bulb portion of the follicle during anagen.

The character of both mesenchymal regions changes dramatically over the growth cycle (212). In early anagen, the CTS consists of a thin basal lamina surrounded by collagen and stromal cells. With the development of anagen, the connective tissue (outside of the basal lamina) thickens into three separate layers. The innermost layer lacks cells and consists of collagen fibers running parallel to the long axis of the follicle. The middle layer consists of spindle-shaped fibroblasts and collagen fibers running transversely to the long axis of the follicle. The outermost layer contains cells and collagen fibers that run in various directions parallel to the outer surface of the follicle. In late anagen/catagen, the basal lamina of the connective tissue sheath thickens. Later, it and the other connective tissue layers become, by light microscopy, hyalinized and corrugated. Fibroblasts within and surrounding the CTS actively produce the collagen fibers of the sheath, which appear to fill the spaces left by the retracting catagen follicle (212). In telogen, the CTS at the level of the bulge stains intensely for versican, but as the follicle enters anagen, versican expression in this region disappears and reappears within the papilla (101, 253).

In anagen, the papilla is composed of a group of fibroblasts, embedded in a loose connective tissue stroma. It is encapped by the epithelial cells of the bulb but separated from the epithelium by a well-defined trilaminar basement membrane (167, 372, 398). During morphogenesis, in culture and after retinoid treatment, the papilla-matrix BMZ becomes fenestrated, allowing processes from papilla cells to contact epithelial hair matrix cells, an important relationship that appears to play a role in E-M signal transmission (143, 167). In the earliest phases of catagen, the papillary stroma decreases, and the bulb epithelium withdraws to release the papilla. In telogen, the papilla rests at the proximal base of the follicle as a tight cluster of cells containing virtually no ultrastructurally recognizable extracellular matrix (ECM) (398).

The morphological changes of the papilla over the cycle reflect primarily changes in its ECM. As anagen progresses, the extracellular matrix of the papilla enriches in mucins (347). In catagen, total glycosaminoglycan content of the papilla decreases; in telogen, it is scant (85, 220).

This unique ECM is characterized by its similarity to the basement membrane zone ECM (86). It contains typical basement membrane components such as type IV collagen, laminin, fibronectin, chondroitin sulfate, heparan sulfate, and versican (85–87, 101, 591).

Embedded in the papilla are very unique fibroblastic cells. These cells not only produce but also require their unique stoma to facilitate E-M communication (298, 404, 413). An excellent marker of mouse papilla cells is alkaline phosphatase, which, in contrast to earlier studies (67, 165), has been found to be expressed in the FP throughout the cycle (161). With respect to the regeneration concept and the cycling hair follicle mentioned above, it is of interest that the blastema of regenerating newt limb is also rich in alkaline phosphatase (566), a property thus shared by these two inductive mesenchymal tissues. Typical of papilla cells in vivo and in vitro (214, 329) is that they have a tendency to aggregate. In that regard, it is of interest that throughout the cycle papilla cells express neural cell adhesion molecule (NCAM) (80, 360), a molecule mediating cell-to-cell and cell-to-matrix adhesion. The presence of this molecule suggests that it plays a role in the integrity of the papilla over the cycle. The role of NCAM in follicle cycling is also demonstrated in the hairless (*hr/hr*) mouse where the papilla disintegrates shortly after hair follicle morphogenesis is complete (393–395). It is of interest that the papilla of hairless mice (*hr/hr*) express an abnormally low amount of NCAM. So, the notion is that the *hr/hr* gene plays a role in the control of NCAM expression, and NCAM plays a role in holding the papilla cells together.

During anagen, and not telogen, papilla cells express a potent protease inhibitor of the serpin family, nexin-1 (614), which has been implicated in normal organogenesis (315). Because the expression of nexin-1 correlates directly with the inductive ability of papilla cell lines (like versican, Ref. 253), it is believed this molecule is linked to a very important pathway in papilla-mediated follicle growth induction (614). In various cell strains, the expression of nexin-1 was shown to be influenced by molecules to which hair follicles are exposed; for example, it is upregulated by interleukin (IL)-1β (fibroblasts, Ref. 153), up- or downregulated by androgens (seminal vesicle, Ref. 574; papilla cells, Ref. 528), and downregulated by dexamethasone (fibroblasts, Ref. 153). The mechanism by which this protease inhibitor influences the cycle is yet to be shown, but it could be related to follicle extension into

the dermis or to the activation of hair growth modulating factors, such as HGF/scatter factor (SF) (297).

Except for the substantial changes in its extracellular matrix, the FP stays remarkably constant over the hair cycle as a cluster of cells. Although the cells of the papilla continue to show RNA synthesis over the cycle, it is generally held that papilla cells themselves do not undergo cell division or take up tritiated thymidine (342, 589). The notion is that the number of cells for any specific papilla remains constant over the cycle, and thus over the lifetime of the mammal. As mentioned in section IV*B*, this dogma may be shaken as we analyze the papilla more carefully. In the ferret (496), sheep (537), and mouse (308), for example, papilla cells show new DNA synthesis in the early stages of hair growth initiation. Preliminary evidence from mouse pelage hair follicles suggests that the number of papilla fibroblasts changes significantly throughout the hair cycle (308). In the vellus-to-terminal follicle switch during adolescence (where the papilla increases in size) and, conversely, in the terminal-to-vellus switch in the pathogenesis of male pattern balding (where the papilla decreases in size), there is a change in the number of cells making up the papilla (115).

The papilla is an inductive structure that sends and receives signals. Its effect depends on continuous and intimate interaction with the hair matrix epithelium via native extracellular matrix (298). Epithelial stimulatory signals produced by human scalp papilla cells in culture have been demonstrated in tissue culture where ORS cells grow in the direction of dissected, contiguously placed papillae (8). Early workers demonstrated the hair-inductive properties of the papilla and its passaged cells (77, 199, 216, 379, 380, 451). Anagen papillae dissected free of the epithelial follicle and inserted into nonhair bearing skin can be shown to induce hair follicle formation from the resident epithelium (470). The inductive properties can also be demonstrated in skin equivalents (580). For effective follicular induction, continuous and close papilla contact with the receptive epithelium appears to be needed; in fact, if the papilla is separated from a growing follicle experimentally (298) or developmentally (*hr/hr* mouse) (393), follicle growth ceases. The importance of the papilla-epithelium interactions in the mature cycle is illustrated by the hairless (*hr/hr*) mouse and its human counterpart where disintegration of the papilla due to a transcription factor defect irreversibly abrogates the follicle's capacity to cycle, and ultimately leads to hair follicle destruction and alopecia (mouse, Refs. 56, 57, 392, 393, 395; human Ref. 2). Within the theme of E-M interactions, it is of interest that keratinocytes may act in turn on the mesenchyme; for example, keratinocytes produce a specific factor, which stimulates the growth of human scalp papilla cells in vitro (579).

As hair follicles differ from site to site, so do their papillae (e.g., Refs. 209, 463). Moreover, it is the papilla that appears to establish the character and size of the follicle and its shaft (204, 215, 572, 573). So, changes in the size of the hair follicle (important to folliculogenesis and to the vellus-terminal switch, see sect. XI) involves parallel changes in the volumes of both the epithelial and dermal parts of the lower follicle, namely, the FP dictates the size of the bulb (541, 572).

Many E-M interacting systems, such as the developing or regenerating limb bud, tooth, and feather (75, 79, 390, 557), express a set of patterning gene families (517). Because of the developmental/regenerative properties of the follicle, we are not surprised to find that many, if not all, of these same morphogenetic molecules are also used by the cycling follicle. Six major morphogenetic molecular family systems are now recognized to be important in this context: fibroblast growth factor (FGF), transforming growth factor (TGF)-β, sonic hedgehog (shh), Wingless or wnt pathway, neurotrophins, and homeobox (hox) gene families (82, 384, 438).

In Table 3, we list these and other gene family molecules that appear to impact the control of the normal hair cycle. The published descriptions of the actions of these factors are in the main phenomenological, although new laboratory techniques, such as transgenic (gene addition and knockout) models, are offering new mechanistic insights. At the outset, it is important to appreciate that there are four themes regarding what we know about these molecular systems. First, the key signaling molecule families provide the metaphorical letters for the cross-talk occurring between the populations of the hair follicle mesenchymal and epithelial cells. Second, these gene families consist of cognate members at several levels: at the level of the ligand, the cell surface receptor, cytoplasmic transmitter, and nuclear transcription factor (e.g., Ref. 267). Third, these gene families have been found to interact extensively with one another and with other gene families (517). Although we have little direct data, we have every reason to believe that since these gene families are present, they are also interacting with many signaling pathways of the cycling follicle. Fourth, nature has endowed the hair follicle with substantial redundant pathways with which to function. The role of FGF5 is one example where, in its absence, catagen is only temporarily, but not permanently, delayed (179); this observation suggests, for example, that there are other catagen-inducing factors in the follicle. A second example deals with follicle morphogenesis where it has been found that no gene is absolutely crucial to hair follicle morphogenesis (providing that the animal develops to the stage where follicles first appear). The themes described are not dissimilar from those seen in other developmental systems (138). Undoubtedly, the organizing themes that will surface as we sort out the apparent welter of factors influencing hair growth and cycling will offer insights and new

TABLE 3. *Molecular mediators of hair follicle growth*

Factor Family	Location in Follicle	Function	Reference No.
	Growth, patterning, and transcription factors		
Fibroblast growth factor (FGF)			
FGFR1	Papilla		385, 482
FGFR2	Matrix		482
FGFR3	Precuticle cells of bulb		
FGFR4	IRS, ORS bulb periphery		482
FGF1	Follicular epithelial cell		35, 100
FGF2	Follicular epithelial cell	Blocks follicle morphogenesis	35, 99
FGF5 (short form)	ORS	Terminates anagen	179, 434, 548, 549
FGF5 (long form)	Macrophage-like round cells in dermis	Blocks short form	
FGF7 (KGF)	Papilla	Induces anagen; cytoprotective to chemotherapy	93, 152, 445
Sonic hedgehog (SHH)			
SHH	Anagen bulb, IRS	Initiates anagen	14, 28, 128, 233, 336, 383, 538a, 492
PATCH	Bulb and surrounding mesenchyme	Mutation leads to basal cell carcinoma	
Transforming growth factor-β (TGF-β)			
TGF-β-RI	ORS: late anagen/catagen	Signal transducing receptor for TGF-β isoforms; plays a role in catagen development	123, 124, 411, 506, 588
TGF-βRII	ORS: late anagen/catagen		
TGF-β1 TGF-β2 TGF-β3	All expressed in developing follicle; in mature follicle in IRS, ORS, and CTS	TGF-β1 plays a role in catagen induction and blocks anagen induction in vivo and anagen growth in vitro; TGF-β1 and TGF-β2 stimulates ORS cell proliferation and opposes TGF-2 stimulus	123, 352, 436, 501, 584, 603
BMP2	Anagen bulb prekeratogenous zone	Suppresses proliferative activity and supports differentiation	30
BMP4	Lower follicle mesenchyne	Suppresses hair growth	28, 234, 538a
BMP6	Epithelium	Supports hair follicle development and growth	31
Noggin	Follicular mesenchyne	Suppresses activity of BMP4 allowing for hair growth	38
WNT			
WNT-3	Prekeratogenous zone	Hair shaft structure	336, 338, 571
β-Catenin	Keratogenous zone ORS	Follicular morphogenesis	132, 618
Lef-1	Peripapillary matrix Epithelium and papilla cells		266
Dishevelled-2	ORS; precursor cells and hair shift cortex and cuticle		336
Insulin-like growth factor (IGF)			
IGF-I	Upper bulb ORS Anagen FP (but not catagen or telogen) CTS	Essential for follicle growth in vitro	210, 242, 300, 439, 486, 539
IGF-I receptors	Basal cell of the ORS, sebaceous gland, upper hair matrix keratinocytes		187
IGFBP-3	FP	Thought to play regulatory role on IGF expression	21, 180
IGFBP-5	FP, CTS		
IGFBP-4	Papilla epithelial matrix margin, CTS		180
Epidermal growth factors (EGF)			
EGF TGF-α		Follicle morphogenesis stimulates cell growth in the ORS but inhibits it in the matrix	162, 302, 314, 335, 349, 350, 363, 437
EGF-R	In anagen ORS and matrix; in catagen on all undifferentiated cells of epithelial strand and secondary hair germ		98, 150
Hepatocyte growth factor (HGF)			
HGF	Papilla	Mediates E-M interactions, stimulates follicle growth in vitro	227, 228, 297, 509
HGF receptor, c-*met*	Follicular bulb epithelium	Upregulation shows accelerated hair follicle morphogenesis and retarded entry to catagen	228, 297

TABLE 3—*Continued*

Factor Family	Location in Follicle	Function	Reference No.
BRCA-1	Whisker placode and peg		274
Homeobox cluster genes			
HOX c8	Expression in matrix and papilla depending on gene	Apparently imparting patterning character to the follicle and shaft	24, 243
HOX d9			
HOX d11			
HOX d12			
HOX d13	Hair matrix	In KO mouse defective shaft	142
Agouti gene	FP		337
Stem cell factor	FP		183
MSX1	Epithelial placode; matrix of mature follicle		371, 465
MSX2			
A1x4	papilla		201
p53	Hair germ epithelium		501
Amphiregulin	Bulbous hair peg, canal, bulge, FP, IRS		443
Platelet-derived growth factor (PDGF)			
PDGF-A	Matrix, hair germ epithelium		247, 386
PDGF-B	Matrix		5
PDGF receptor	FP		247
Winged helix nude			
Whn (nude)	Follicular epithelium in differentiating cells of the hair follicle precortex, innermost cell layer of the ORS and a subclass of cells in the matrix	Whn is a transcription factor that suppresses expression of differentiation genes; upregulating Whn prolongs anagen	53, 126, 280, 327, 369, 459
	Cytokines		
Interferon		Overexpression of IFN-α leads to hair loss	59
TNF-α	ORS of developing follicle, CTS of late bulbous	K14 driven overexpression leads to short, distorted hair follicles	69
Interleukins (IL)			
IL-1α, IL-1β	Epidermis, IRS, ORS, CTS, sebaceous glands, dermal vasculature, and arrrector pili muscle	Upregulation leads to diminished and atrophic hair follicles; IL-1α and IL-1β inhibit hair growth in vitro	2, 33, 151, 170, 189, 190, 311, 440
	Other factors		
Alkaline phosphatase	In the papilla over the whole cycle, proximal ORS late anagen and early catagen	Expressed in the mesenchyme of other regenerating systems	63, 161
PKA		Inhibitors block hair follicle growth	171
PKC		PKC is a negative regulator of hair growth; PKC inhibitors induce hair growth	111, 171–173, 550, 551
PKC-α	Follicle fibroblasts and papilla cells but low in follicle epithelium; high in full anagen and low in telogen		191, 290
PKC-ζ	High in follicle keratinocytes and low in papilla cells		191
PKC-δ	Low in anagen and high in telogen		191, 290
Cyclin-dependent kinase inhibitors p21cip1/waf1	Differentiating cells of the epithelial follicles: shaft and IRS precursor cell but not in the ORS or bulb matrix		131, 453
Metallothionein	Matrix cells, ORS but not papilla		246
Vitamin D receptor	Expressed in ORS and papilla in late anagen (catagen)	Mutated receptor results in alopecia in mice despite normal calcium levels; topical calcitriol in mice has a catagen-promoting effect	467, 623
Calcyclin	Medulla and IRS of anagen hair follicles		605
Calcineurin			
Cyclosporin A		Inhibits calcineurin and induces anagen, blocks onset of catagen, and gives some protection to chemotherapy-induced hair follicle damage	322, 409, 413, 426, 555, 610
FK506			

TABLE 3—*Continued*

Factor Family	Location in Follicle	Function	Reference No.
		Hormones	
PTHrp	Viable epithelial portion of hair follicle	Follicle morphogenesis antagonist PTH-(7—34)-amide increases hair growth, induces anagen, and provides some protection from chemotherapy-induced follicle damage	15, 195, 500, 608
PTHrp receptor	Dermal fibroblasts		159
17β-Estradiol		Blocks hair growth	374, 376
Estrogen receptor	FP cell nuclei of telogen follicle	Estrogen receptor antagonist induces anagen	376
Prolactin	Receptor found in FP, matrix, ORS	Stimulates anagen and catagen onset	72, 430
Neurotrophin 3, neurotrophin 4, BDNF	Complex hair cycle-dependent expression profile	Promotes follicular morphogenesis, induces catagen in mature follicles	36, 37, 40, 43, 46
Substance P binding sites	FP		446
Retinoic acid receptors (RAR) RARα RARβ RARγ	Papilla and epithelium of developing follicle		576
Androgen receptor	FP cells		70, 210
Aromatase cytochrome	ORS		494
5α-Reductase type 1	Sebaceous gland, ORS, FP, and CTS		22, 109, 495
5α-Reductase type 2	Follicular epithelium, interfollicular dermal cells, IRS, cuticles		22, 109, 495

KGF, keratinocyte growth factor; IGFBP, insulin-like growth factor binding protein; TGF, transforming growth factor; PKA, protein kinase A; PKC, protein kinase C; PTHrp, parathyroid hormone-related peptide; BDNF, brain-derived neurotrophic factor; ORS, outer root sheath; IRS, inner root sheath; FP, follicular papilla; BMP, bone morphogenic protein; CTS, connective tissue sheath of the follicle; BRCA, breast carcinoma gene.

paradigms to the biologist, the pharmacologist, and the clinician.

E. Movement Into the Dermis and Subcutis

For complete hair growth, the proliferative epithelium of the resting follicle must grow down into the deep dermis and, for large follicles, the subcutis. The downgrowths occur along a dermal trail, the fibrous stele (or streamer), which is established in the dermis by the first mature follicle (255). In contrast to the pelage follicle, cycling of the vibrissae follicle is fundamentally different in that the lower follicle does not regress upward; nevertheless, there is a cyclical change in the diameter of the vibrissae follicle with apparent movement of cells upward from the deep follicle bulb (613).

Although the downward growth of the early anagen follicle occurs by growth pressure (i.e., primarily by epithelial cell proliferation rather than migration, Refs. 308, 422), in order for this finger of cells to penetrate the dermis, the fibers of the fibrous stele must loosen. That the early anagen follicle is associated with proteolytic enzyme production (416, 584) suggests that the stroma is conditioned by enzymes produced by the down-growing follicular epithelium. Gene expression (4) and immunolocalization studies of matrix metalloproteinases (MMPs) show that while the papilla is negative for these enzymes, the epithelial cells of the down-growing bulb and ORS are positive. Follicles placed in vitro have been shown to have the ability to lyse collagen gels (584) and to synthesize and secrete various MMPs including interstitial collagenase, stromelysin-1, gelatinases, collagenase, and matrilysin (MMP-7) (145, 246, 324, 416, 584). EGF and TGF-α which impact follicle growth also stimulate follicles to release various MMPs and lyse collagen gels (an action synergized by TGF-β1 and TGF-β2; Ref. 584).

Controlled degradation of ECM in the cycle requires a fine balance between the MMPs and their inhibitors. There is cyclic expression of the tissue inhibitor of metalloproteinases (TIMP) in the adult human follicle with localization, unexpectedly, to Henle's layer (249). TIMP is also found in the sebaceous gland and the proximal papilla (249). It is relevant that TIMP-3 is expressed by the anagen hair follicle, infiltrating basal cell carcinoma cells, and the stromal cells of squamous cell carcinoma (4). The similarity of the early anagen finger invading into the dermis to invasive basal or squamous carcinomas suggests a common mechanism between the down-growing follicle and invasive skin tumors (239). In contrast to its disruption in carcinomas, the BMZ of the follicle is never disrupted during anagen, but rather undergoes a highly coordinated process of constant remodeling so as to fully and continuously ensheath the growing follicle epithelium (398, 399).

At the end of anagen, terminal pelage hair follicles come to reside in the subcutis. Because the additional

downward movement of the anagen follicle into the subcutis occurs at the expense of much energy and nutrient consumption, it would appear that follicular placement in the subcutis must be important; however, why the follicle base comes to be surrounded by adipocyes is unknown. Because the actual length of a hair follicle does not appear to dictate the length of its shaft (rather the duration of anagen determines hair shaft length), it is tempting to speculate that the subcutis offers optimal growth conditions (e.g., nutrients, temperature, hormones, neural stimulus) for the hair shaft factory and protects it from environmental insults by "buffering" it in fat cells as far removed from the skin surface as possible.

F. Patterning

Excepting bilateral symmetry, it is probably true that no two follicles on the body are the same (e.g., Refs. 490, 504, 565). This point cannot be overemphasized because in experimental and clinical situations follicles from different regions are quite dissimilar. Follicles, and their shafts, differ grossly in length, thickness, curl, color, cross-section pattern, hormone sensitivity, innervation, vascularity, and the average time periods they spend in each of the phases of the cycle (203, 463, 490). The character of a follicle and its shaft is established by its papilla (214, 358, 438). Direct evidence for this conclusion is found experimentally where follicles induced by transplanted papillae are found to reflect the follicle from which the papilla originated (214).

Because the follicle regenerates itself in the course of each cycle, those factors affecting the character and placement of the follicle and its shaft must be active throughout the cycle. It is believed that follicle patterning occurs during follicle morphogenesis and that, in general, the character of the follicle is retained for the lifetime of the individual. Support for the unique and conserved character of a given follicle is most powerfully demonstrated by transplantation (381, 382, 568). A transplanted follicle retains the characteristics of its skin of origin. Thus eyebrow hair growing on the scalp would not be of value and scalp hair in the eyebrow region could be downright dangerous. Although one assumes that the patterning of a follicle is inherent to that follicle, in fact, with aging and in some disease states (e.g., acquired immunodeficiency syndrome, trichopathy, hair regrowth after chemotherapy, Ref. 94), the pattern of hair growth can change. The basis for the latter newly programmed structural changes is not yet clear, although its elucidation will be of great practical value.

The molecular basis for follicle pattern formation is only now being addressed. The regulatory gene families mentioned above, which impact hair morphogenesis, such as FGF, Wnt, TGF-β, and hedgehog, undoubtedly play a critical role in the patterning of numerous developmental systems (138, 604). Because homeobox gene transcription factors play a pivotal role in body and limb development (138, 604) and are expressed in the follicle (24, 243), it is reasonable to assume that they also impact hair character. When one looks for the expression of these genes in the follicle, they are present. *Hoxc8* gene, for example, is expressed in the papilla of follicles in a caudal to cephalic gradient; expression is most prominent in the papillae of the dorsal posterior pelage hairs (24, 243). *Hoxd9* and *Hoxd11* are expressed in the differentiating matrix of the anagen follicle. *Hoxd11* is also strongly expressed in the basal cells of the ORS. *Hoxd13* is restricted to the matrix cells of the follicular bulb, and its expression ceases in catagen (243). *Msx1* and *Msx2* are both restricted to the lower epithelial layers of the anagen follicle (465), and *Alx-4* to the papilla (201). Because many patterning genes are expressed in the follicle, the situation is complex. It may be that the variable expression of patterning genes gives each follicle a unique address and thus a unique morphology. Arguing by analogy to the *Drosophila* (138, 604) perhaps it is the gradients of these gene products that color the actual heterogeneity of hair morphology. We assume these genes influence those aspects of the follicle and shaft that vary from site to site, and they act by orchestrating the expression of many downstream genes.

The first example of a defective homeobox gene with a corresponding hair phenotype was found with the *Hoxc13* transgenic null mouse. It was found that *Hoxc13* is essential to normal hair shaft development. In the absence of functional *Hoxc13*, hair shafts form but are friable (142). Paradoxically, this patterning gene plays a structural function in the mature follicle in addition to its patterning role in early development (97).

Without any idea as to its molecular basis, the embryologic origin of the dermis is also postulated to influence the pattern of scalp hair follicles. Chicken (88) and mouse (389) embryologic studies have shown that the mesenchyme of the scalp crown, face, and anterior neck are derived from the neural crest while the temporal and occipital scalp regions are derived from cephalic or somitic mesoderm (138). It is notable that in clinical hair disorders such as male pattern baldness and alopecia areata (ophiasis type) the respective regions are dramatically circumscribed and differ substantially in their clinical course and prognosis (94); in the former, the bald area corresponds to the neural crest mesoderm, whereas in the latter, the bald area corresponds to the somitic-derived mesoderm. The basis for hair follicle heterogeneity, then, may result from signals arising very early in development, which are expressed by a complex of patterning genes.

It is increasingly appreciated that the controls of patterning during anagen development are likely to in-

volve the participation of direct cell-cell communication via adhesion molecules such as cadherins, cell adhesion molecules (CAMs), and integrins (358, 359). These serve as key elements in translating the one-dimensional genetic code into a three-dimensional tissue architecture (74, 75, 108, 138). A body of information is slowly emerging on the expression patterns and functional significance of adhesion molecules such as E- and P-cadherins, specific integrin pairs, NCAM, and intercellular adhesion molecule (ICAM)-1, during hair follicle morphogenesis (80, 127, 185, 244, 356–358, 360). The expression patterns of NCAM, ICAM-1, and E- and P-cadherin during murine anagen development have recently been characterized (80, 127, 185, 244, 356, 358, 359, 361). Although we now know their expression pattern, we know very little about how any of these adhesion molecules act in anagen initiation, development, or hair cycle control.

G. Differentiation of the Anagen Follicle: The Cell Lineages

Generating from stem cell-like precursors in the "resting" telogen bulb epithelium (secondary hair germ, Fig. 2*D*), the earliest phase of anagen downgrowth (anagen I) shows no cylindrical layer differentiation. By very early anagen III (357), the IRS/ORS are identifiable. At the point that the finger of epithelium reaches its deepest level and perhaps somewhat before (anagen III), the layers of the follicle begin to form. Morphologically, there are at least eight cell lineages in the anagen follicle: ORS, companion layer, Henle's layer, Huxley's layer, cuticle of the IRS, cuticle of the shaft, shaft cortex, and shaft medulla (Fig. 2). In this section we focus on the cell lineages making up the cycling portion of the follicle. We would like to know from where each of the follicular layers arises and what controls their differentiation. Although the answers we have are still unsatisfactory, some basic principles are clear.

As mentioned above, the cycling portion of the anagen follicle is a solid epithelial cylinder made of embedded, concentric, unique cylindrical layers. The outermost cylinder, the ORS, separates the whole hair shaft factory from the dermis and subcutis. The ORS appears to be established during the early stages of anagen by the downward migration of the regenerating epithelium and then maintains itself (in contrast to the IRS and shaft), independent of the bulbar matrix, by basal cell growth (469). The thickness and cellularity of the ORS vary with the level of the follicle: it is single-layered just about the bulb, higher up it is composed of multilayered cuboidal cells which accumulate glycogen, and at the level of, and distal to, the sebaceous gland it becomes multilayered and is structurally similar to the epidermis (397). Although its role is thought to serve predominately as a support for the outward-growing shaft and IRS, the ORS is not quiescent; in fact, the ORS may well play an active role in hair cycle control. During anagen, the basal cells of the ORS below the sebaceous duct divide and replenish this layer (540); in addition, the innermost cells, but not the outermost cells, migrate distally and, ultimately, slough into the pilary canal (61, 62). That the ORS produces catagen-producing growth factors, like FGF5 and neurotrophins (40, 46), supports the idea that the ORS plays an important role in regulating the cycle (179, 432).

The middle cylinders of the follicle make up the IRS (541). The IRS molds and holds the shaft on its way to the surface. The IRS consists of three layers: the cuticle of the IRS, Huxley's layer, and Henle's layer. The cuticle layer of the IRS is made of scales that point distally and interlock with similar but opposing scales making up the cuticle of the hair shaft surface. The hair shaft scales point proximally. The combined, interlocked, cuticle structure allows the hair shaft and IRS to move together during the period of growth. Henle's layer, the first layer of the anagen follicle to keratinize (63, 357), encloses the shaft-sheath structure and interfaces the stationary ORS. As a supporting structure, Henle's layer appears to be inherently strong and tightly attached to the ORS. Its durability is appreciated by the rare separation that occurs within this plane after hair shaft pull (e.g., during preparation of a trichogram, Ref. 94) or histological preparation (540); in contrast, there is often disruption of Huxley's layer in such preparations. The IRS may move distally somewhat ahead of the shaft (human, Ref. 119; sheep, Ref. 62).

Huxley's layer is the major component of the IRS. It varies eccentrically in its thickness and thus molds the shaft to have round, oval, or flat cross-sectional morphology. The hair shaft and its IRS are complementary in shape so that together they form a solid core of hardened tissue with a nearly circular cross-section (456, 541). When the IRS is distorted, the shaft formed by that follicle is also distorted. This was observed in a mouse transgenic model in which ORS cell division was enhanced leading to malformed IRS and abnormal hair shafts (339). In addition, mice that have no TGF-α, or EGF receptor (EGFR) expression (normally found in the ORS, Ref. 150), form irregular and curled hair shafts (302, 314); such findings suggest a role for the EGFR pathway in normal hair curl (shaft crimp is briefly discussed elsewhere, Ref. 455).

The molecular structure of the IRS is discussed in detail elsewhere (455). It is interesting and puzzling that many molecules of apparently disparate function are found within the IRS, such as FGF-1, FGFR4, TGF-α, sonic hedgehog, dishevelled, β-catenin (337), TIMP (249), and clusterin (506). Although we have no reason to doubt the latter observations, we recognize that the IRS takes up marker antibodies nonspecifically in many instances.

In addition to the shaft and its cuticle, at least five products normally pass from the pilary canal to the sur-

face: sebum, sloughed IRS, sloughed ORS, apocrine secretions (in certain regional follicles), and organisms that inhabit the pilary canal (422). The egress of these materials is assisted by the cuticle of the outwardly moving hair shaft, which functions not unlike a "conveyor belt" made up of cuticular shovels that transport these materials to the skin surface. Thus the growth phase of the shaft, anagen VI, not only serves as the main production period for the fiber but also as a system for transporting skin secretions, debris, and parasites/microorganisms from the pilary canal to the skin surface.

In a study testing the origin of the hair follicle cell lineages, Kamimura et al. (241) labeled follicular epithelial cells in culture and recombined them with papilla cells using the nude mouse model of Lichti et al. (292) (see sect. II). They found that, instead of finding labeled cells at random throughout the newly formed follicles, the majority of the follicles appeared to derive from a minimum of two or three progenitor cells: one for the shaft, one for the IRS, and one for the ORS. The results suggest that only three precursor cells are needed to generate the eight epithelial cell lineages seen in the mature anagen follicle.

One conceivable molecular pathway for the control of the epithelial cell lineages of the hair follicle was suggested by studies of the Notch gene family. The Notch genes encode transmembrane proteins which, by facilitating local cellular interactions, serve to signal various cell fate decisions during development (13, 604). The Notch signaling system is one of the major pathways involved in cell fate specification and is characterized by the interaction between two types of transmembrane proteins: the Notch receptors and the Delta/Jagged families of ligands (13, 251, 604).

During neonatal hair follicle morphogenesis in mice, Notch-1 is expressed in the bulb, but not in the cells directly adjacent to the papilla or in the proximal ORS (262, 454). Jagged-1 is found in the bulb cells destined to form the shaft cortex and cuticle; Jagged-2 is restricted to bulb cells adjacent to the papilla. Because Notch-positive cells do not appear to contact the papilla, Notch probably does not participate in E-M signaling directly. In contrast to basonuclin, a molecule characteristic of proliferating epithelial cells (586), Notch is not present in actively dividing cells. Because the Notch receptor is abundantly expressed on differentiating cells, it is thought to play a role in establishing or maintaining a differentiated state, but how it effects this event is not yet clear (262). The controls for Notch expression during the cycle are not yet apparent.

The central column of epithelial cells in the follicle generates the shaft. The hair shaft is essentially a product of proliferating and terminally differentiating keratinocytes that differ substantially from epidermal keratinocytes in their biochemical and keratin gene expression (455). It is important to appreciate that there is an ecology, or a spatial/temporal variation, in the keratins expressed at specific levels of a given shaft (455) and that hair keratin expression varies over the cycle (52, 275). In fact, not only do the types of keratins expressed vary over the cycle, but the character of the shaft itself also varies (202, 275). For example, the shaft of vibrissae follicles in early anagen is thin and in late anagen thick (475); moreover, the major cross-sectional axis of human scalp shafts varies over the growth cycle while the minor axis remains constant (202). Recognizing this variation is important to the biology of shaft formation but also experimentally if the shaft diameter, for example, is used as an end-point determinant.

Although it is chiefly epithelial, the hair follicle has embedded within it cells of other lineages, e.g., melanocytic, Merkel, Langerhans, and lymphocytic cells. These cells may all influence hair growth but to what extent and how we do not know. For example, it has been proposed that the numerous Merkel cells found in the bulge region may modulate follicle stem cells and thus hair growth (344, 366) and that melanocytes in the precortical hair matrix may affect follicular keratinocyte differentiation (522, 526).

H. The Slippage Plane

Once the IRS-packaged shaft is formed, it must move distally to the skin surface. The slippage plane at which this occurs is at the level of the companion layer (innermost layer of the ORS) (211, 387). Although not clear how this layer permits outward sliding of the shaft, it is clear that this layer is very unique. The companion layer consists of a band of longitudinally oriented flat cells that move outward together with the differentiated cells of the IRS. The companion layer cells are tightly bound to Henle's layer by desmosomes, whereas those contacts are not found on the ORS side of the companion layer (211, 387). This finding supports the idea that the actual slippage interface is on the ORS side. At the level of the midfollicle, the cells of the companion layer shed into the pilary canal. The ORS cells underlying them undergo trichilemmal keratinization (450). As the companion layer cells stain for Ki67, it appears these cells are actively cycling (341), and that they contain keratin 17 (394) and a unique keratin, K6hf (484, 601), suggests that the cells making up this layer have a very special cytoskeletal structure. Moreover, that there is significant expression of TIMP, a protease inhibitor, in Henle's layer (249) and plasminogen activator inhibitor-2 (PAI-2) in the companion layer (278) implicates a proteolytic process in the slippage phenomenon.

It is notable that when liposome preparations are applied topically to hairy skin, they are found to extend into the deep follicle (188, 284, 285, 293). Along what path

the liposomes take is less clear at this time, but an important candidate pathway is the slippage plane (G Krueger, personal communication). Because therapeutic approaches could exploit this slippage plane for the targeted delivery of agents into the deep proximal hair follicle, careful fluorescent dye labeling and ultrastructural studies are needed to characterize this potential route.

I. Shaft-Sheath Dissociation

At the level of, or a little lower than, the sebaceous gland duct, the packaged shaft and sheath separate as the sheath "dissolves." Straile (540) refers to this region as the "zone of sloughing"; here the IRS breaks down and cells of the ORS slough into the pilary canal. Regarding shaft-sheath relationships, earlier workers thought that there was something very important about this region (540, 541). It was suggested that the IRS breaks up at this level because of enzymes secreted by the ORS, by components of the sebaceous gland, or a combination of both (16, 134, 540).

The notion that either the sebaceous gland and/or the pilary canal walls in this region have the property to dissolve the sheath was tested by in vitro studies. When whole follicles (sheep, horse, human) are cultured in the presence of their own sebaceous gland/mid-follicle region, the shaft grows out free of sheath. When the same preparation is grown in the absence of the sebaceous gland/mid-follicle region, the shaft grows out with the sheath (441, 594). Apparently acting by decreasing sebaceous activity, retinoids also alter the sheath-shaft relationship (19, 595). The mouse mutant *asebia*, which has hypoplastic sebaceous glands and retained IRS on the outgrowing shaft, also illustrates the importance of the sebaceous gland in sheath/shaft dissociation (545). Although Orwin (388) reported there is no evidence for the degradation of the IRS by a lysosomal system, there is a chymotryptic enzyme in the pilary canal at this level (human, Ref. 114; mouse, Refs. 17, 326) that may play a role in this process. What in the sebaceous gland/sebum is responsible for sheath dissociation is under current study.

J. Anagen in Perspective

Anagen, then, is the period in the cycle when the lower follicle regenerates itself, reconstructs its hair shaft factory, and actively generates a pigmented hair shaft. In understanding anagen we will have to acquire greater insight into the controls of tissue regeneration, the signals initiating anagen growth and stem cell arousal, the character of the molecular system controlling follicle/shaft character, the mechanism of shaft outward movement, and shaft sheath dissociation. Some fundamental questions include: is the initiating signal(s) positive or negative? How does a growth wave spread? What are the molecular inputs necessary to achieve specific shaft character? How much and what element of distal movement is produced by growth pressure? What in the sebaceous gland/ORS supports shaft-sheath dissociation? How similar or dissimilar are the molecular controls of anagen induction and development and those of hair follicle morphogenesis?

V. CATAGEN

A. Mechanism

After a predictable period of time anagen ends (dependent on host and site factors), follicle growth stops, and catagen begins. Why does the cycle end when it does? Is this due to the fact that a limited number of mitoses of the transit amplifying cell population becomes exhausted (84)? Or, is it due to a change in the paracrine factor milieu, such as to the accumulation of growth inhibition and proapoptotic agents, or to changes in activities of perifollicular mast cells and macrophages, or to a combination of all of the above (405, 420, 535)? The unknown signal, either inherent in or delivered to the follicle, causes the cycling, deep, portion of the follicle to involute at a surprisingly rapid rate. This phase, catagen, is a highly controlled process of coordinated cell differentiation and apoptosis, involving the cessation of cell growth and pigmentation, release of the papilla from the bulb, loss of the layered differentiation of the lower follicle, substantial extracellular matrix remodeling, and vectorial shrinkage (distally) of the inferior follicle by the process of apoptosis.

Although we do not know the spontaneous inductive signals, we do know that severe stress characteristically precipitates catagen (255, 410, 412, 425). We know that environmental factors, such as chemicals, dexamethasone (412), and trauma (229), can induce catagen as can experimentally administered endogenous hormones, like ACTH (419) and 17β-estradiol (567).

The catagen stage of the hair cycle has been divided into eight subphases beginning with late anagen and ending in early telogen (357, 542). The first ultrastructural sign of regression in the catagen follicle is the withdrawal of papilla cell fibroblast projections from the basement membrane (95). The papilla shrinks, probably through the loss of extracellular matrix substance. The cessation of bulbar epithelial cell division coincides with massive epithelial cell apoptosis in well-defined regions of the regressing hair follicle (see below and Ref. 296). In addition, there is a dramatic change in the cytoskeletal proteins of follicle epithelial cells in that trichohyalin, transglutaminase I, and desmoglein production cease (81). Concomitantly and progressively, the lower follicle shrinks and

withdraws as an epithelial strand. Thickening and wrinkling of the vitreous membrane and lower CTS follows as the volume of the anagen hair bulb decreases (255). The condensed papilla moves distally, apparently, attached to the BMZ of the regressing epithelial column above and to the vascular stalk below.

Mouse experiments have shown that total skin FGF5 expression increases in late anagen (179, 434, 482) and that, in its absence, catagen induction is delayed (anagen is prolonged), resulting in the *angora* phenotype (unusually long hair) (179). Recent work has found that two splice variants of FGF5 are in fact expressed in different regions of the skin: the full transcript in the perifollicular macrophages and the FGF5S variant in the ORS (548, 549). Direct studies show that the variant blocks the catagen-inducing properties of the complete FGF5 transcript. That FGF5S is expressed in high concentrations during mid anagen and in low concentration during late anagen VI, catagen, and telogen could explain the mechanism of this important pathway, i.e., the decreased FGF5S blocking signal in late anagen would allow increased functional activity of the anagen-blocking effect of FGF5. The macrophage source of the full transcript further supports a functional role for these cells in cycle regulation (549) (see sect. x). Other molecules that could serve as anagen-supporting signals include insulin-like growth factor I receptor (IGF-IR) (300, 487), KGF (482), and HGF (297), which are downregulated, and BDNF, NT-4, NT-3, and TGF-β1 (36, 37, 40, 43, 48, 49, 123, 588), which are upregulated upon catagen initiation. Like FGF5S, tretinoin and phorbol ester block catagen induction (596).

During anagen-catagen transformation, there is an increase in the number of deeply situated perifollicular mast cells (319, 321). In early catagen in the rat (but not the mouse, Ref. 428), there is also a light mononuclear inflammatory cell infiltrate surrounding the lower follicle (590). The role of these cells in catagen development is not clear. Are these perifollicular macrophages assisting catagen progression, i.e., by phagocytosizing excess basement membrane of the shrinking bulb (399) and/or of apoptotic cells of the regressing lower follicle (312), or are they actively regulating catagen development by, for example, the FGF5S pathway (see sect. x)?

B. Apoptosis

In developing biological systems, organs and tissue structures are sculpted by adding and taking away constituent cells by the processes of cell division and controlled cell death (programmed cell death, apoptosis) (138, 592). Because the inferior hair follicle is a prototypical developmental system, forming and regressing over each growth cycle, it too uses these cellular modeling processes. Cell division in the dividing follicle occurs predominately in the follicle bulb during the phase of anagen. Controlled epithelial cell apoptosis occurs predominately in the lower follicle during catagen (583, 296), but it also occurs during hair follicle morphogenesis in human and mouse (308, 452). Because apoptosis is a central element of hair cycling, a brief relevant review is presented here.

Apoptosis refers to a highly controlled form of cell death where the affected cell implodes; this process exhibits characteristic morphological changes including cell shrinkage, loss of cell-cell contacts, condensation of chromatin, cytoskeleton collapse, nuclear contraction and fragmentation, cytoplasmic eosinophilia, cell fragmentation, and phagocytosis by reactive histiocytic or adjacent cells in the tissue in which apoptosis occurs (301). Apoptosis may be activated by loss of growth factors, loss of cell-cell or cell-substrate interactions, changing cytokine interactions, hormone exposure, immune action, viral infection, sublethal damage (chemotherapy, radiation), or purely genetic initiation factors such as in tissue modeling (programmed cell death). Programmed cell death (PCD) refers to a situation in which cells are scheduled to die at a fixed time; it usually refers to cell death in embryonic tissues, such as the cells that form the web between the digits of an animal. This form of cell death is programmed in that a genetic clock selects a given time for the death of certain cells. Although we recognize the precise time PCD will occur in developmental systems, we do not know what initiates it (120, 301, 581, 592). In this sense the cell death occurring in catagen is PCD, since the time of apoptosis initiation is predictable. However, what constitutes the initiating signal is unknown.

Although the dynamic ultrastructural morphology of apoptosis is characteristic, dramatic, and definitive (130), it occurs late in the process. In practice DNA fragmentation is generally accepted as the sine qua non for nuclear apoptosis (606). The corresponding assay that detects DNA fragmentation is based on the observation that in the final stages of apoptosis irreversible cleavage of nuclear DNA occurs at the sites of nucleosomes. Such cleavage gives rise to a harmonic pattern of DNA fragments that by gel electrophoresis is visualized as a DNA ladder. These changes are detected and quantified by staining the DNA fragment ends (terminal deoxy-nucleotidyl transferase-mediated dUTP nick end labeling, TUNEL stain, Ref. 133). Not surprisingly, therefore, DNA extraction from mouse skin with hair follicles in the anagen-catagen transformation phase show this DNA laddering pattern; moreover, distinct foci of apoptosis within the catagen hair follicle become identifiable by the TUNEL technique (296, 360). Although TUNEL staining has been correlated with apoptosis and the characteristic DNA ladder (296, 318), accepting TUNEL positivity as the single definitive proof of apoptosis may be misleading since this method can be

both falsely negative and positive; for this reason, structural evidence of apoptosis should also be sought (130, 308, 424).

The signals that initiate apoptosis can be roughly divided into two groups: one group of signals activates the cellular apoptosis machinery by delivering a positive signal (e.g., stimulation of "death receptor"); the second group opposes apoptosis by stimulating the release of a preexisting molecular "brake" on apoptosis (e.g., by the withdrawal of apoptosis-suppressive factors). Although it is believed that apoptosis operates intracellularly by a common final pathway (mainly involving caspase and endonuclease activations, Ref. 301), we recognize that further studies may reveal yet more complex pathways (91, 316, 360, 362, 554, 581). In this discussion we shall adhere to the simpler scheme, since we have no information otherwise regarding the follicle.

The apoptotic signal may start by means of a surface membrane perturbation, or by means of a receptor signal/specific ligand interaction [e.g., APO1/Fas receptor or tumor necrosis factor receptor (TNFR) and their ligands, FasL and TNF, respectively, as well as specific *trk* tyrosine kinase receptors by neurotrophins, such as nerve growth factor (NGF), and p75 receptor (125, 581) and act through a mitochondrial signal (e.g., cytochrome *c*)]. Those signals initiating the apoptotic process are then transmitted into the cell by means of a cascade of enzymes. These enzymes, termed caspases, belong to a family of enzymes, each having a cysteine in its active site and each cleaving its substrate COOH terminal to an aspartic group. There are two classes of caspases, "instigator" or "upstream" enzymes, and "terminator," "downstream," or effector enzymes. The instigator caspases activate the terminator caspases, and the terminator caspases ultimately activate *1*) specific deoxyribonucleases that irreversibly denature host DNA leading to the DNA ladder, and *2*) other enzymes that cleave cytoskeletal proteins, such as gelsolin and lamins, leading to clumping of the cell's cytoplasm (118, 120, 301, 581).

To balance the proactivator enzyme system there is a group of proteins that attenuate or block the apoptotic signal (76, 268). Best known of these are independent acting members of the Bcl-2 family of proteins (263, 269). This family contains apoptotic antagonists, Bcl-2 and Bcl-X_L (1, 263), as well as apoptotic agonists, e.g., Bax and Bcl-x_S. Bcl-2 acts by stabilizing mitochondrial membranes and complexing with caspases or cofactors that potentiate the activation of caspases (1, 91).

Another family of antiapoptotic mediators are the inhibitor of apoptosis (IAP) family of factors. These factors were first identified within viruses as factors that nullify the apoptotic response of the host cell by an infecting virus. Cellular homologs of this family have been found to modulate the TNF apoptotic pathway. Mutations of members of the IAP family have been shown to lead to human disease (76).

TUNEL positivity over the hair growth cycle has been studied in mice (296, 318), guinea pigs (254), and humans (186, 528). It is notable that unlike other tissues where cells undergoing apoptosis are usually not clustered, but are individual, in the catagen hair follicle apoptotic keratinocytes are found in distinct clusters (296). Weedon et al. (582) first recognized that apoptosis is found in the epithelial strand of catagen (154, 360, 424, 452, 583). In the proximal follicle keratinocytes around the papilla are the first to show TUNEL positivity. After that they appear in the deep (proximal) central epithelial column and then, with time, in a distal direction in the regressing epithelial strand (296, 360). The vectorial placement of apoptotic cells has suggested to some workers that apoptosis could serve a role in supporting the epithelial regression itself (see sect. v*C*). In mid catagen, apoptotic cells are most numerous in the bulb region, the ORS, the central IRS, but also in the isthmus, bulge, and even sebaceous gland areas (296, 366). As a consequence of the latter, the concept of a strictly permanent portion of the follicle is not tenable, and the entire hair follicle is best viewed as a dynamic, constantly remodeling structure (296).

Anagen follicles also contain apoptotic (TUNEL positive) cells, albeit in smaller number. Such cells are found in the medulla, IRS (cell nuclei of Henle's, Huxley's and cuticle layers), companion layer, the bulb, the distal portion of the isthmus encircling the pilary canal, just below the entry of the sebaceous duct within cells undergoing trichilemmal keratinization, and the central sebaceous gland (186, 254, 296, 528). However, separating terminal keratinocyte differentiation from genuine apoptosis in these sites must be determined (cf. Refs. 130, 308). In contrast to the follicular epithelium, fibroblasts of the papilla have not been demonstrated to show apoptotic changes or to stain with the TUNEL technique in situ even where intrafollicular apoptosis is extensive after application of the chemotherapeutic drug cyclophosphamide (296, 562).

Where they have been looked for, molecular members of the apoptotic cascade have been found in the follicle. For example, interleukin-1β converting enzyme (caspase) is expressed within the cells of the proximal follicle (296). From in situ hybridization studies, Soma et al. (528) found that four members of the caspase family are expressed in apoptotic follicle cells. In the developing hair follicle, Bcl-2 is expressed in the epithelium of the earliest stages of morphogenesis as well as in the surrounding mesenchyme. It is found in the matrix epithelium adjacent to the papilla and in the bulge region in mouse and human follicles (279, 296, 308, 452, 532). In the adult hair follicle Bcl-2 is expressed in the follicular papilla throughout the cycle (296, 532). In anagen it is found in the bulb, the proximal IRS, the ORS, and the bulge. The

Bcl-2 positivity of the bulge is reminiscent of other stem cell areas of the body (279).

With the development of catagen, there is a progressive decline of Bcl-2 expression in the follicular epithelium (296). Although it is logical to believe that Bcl-2 expression protects cells from PCD and, therefore, would be important to normal hair growth, it is notable that hair growth is largely normal in the Bcl-2 knockout mouse (575) and that overexpression of Bcl-2 or Bcl-xL in the ORS actually accelerates apoptosis and promotes catagen development (360, 432). This puzzling finding illustrates the complexity of apoptosis controls in the hair follicle, since undoubtedly other apoptotic regulators also play a role in hair growth in addition to Bcl-2. The continuous expression of Bcl-2 in the papilla is of interest regarding the apparent longevity of this structure and its role as a critical support and signal center (221, 532, 589). Bax expression (an apoptosis promoter) is present in the proximal IRS, ORS, and matrix in later anagen and is increased in catagen (296).

In a detailed analysis of the mouse hair cycle, Lindner et al. (296) found that while the apoptosis-associated receptors, Fas/Apo, p55TNFR, or p75NTR were not expressed in the FP, they were expressed in the proximal follicle epithelium during catagen. The noncycling distal follicle expresses Fas/APO-1, p55, and p75 diffusely throughout the cycle, whereas distinct regions of the regressing follicle show differential upregulation of these receptors. In early catagen only p55 is seen in the hair matrix while Fas/Apo-1 and p75 are restricted to the ORS. In late catagen, all three receptors are found in the regressing central ORS, the epithelial strand, and the secondary hair germ. The central IRS expresses only Fas/Apo-1 (296, 507). TGF-β1 transcripts are found within the follicular epithelium immediately before catagen and throughout the anagen-catagen transformation period (123). TGF-β1 administration to mice stimulates catagen development, whereas TGF-β1 reduction, as seen in the knock-out mouse, retards catagen (123). Transcripts for TNF-β are expressed during catagen (507). In addition, several transcription factors associated with the induction of apoptosis in other systems (559, 560), namely, c-*myc*, c-*myb*, and c-*jun*, change immediately before or during catagen (507). Of interest is that p53 remains unchanged over the cycle (507) and thus would appear to be nonessential to catagen control. The expression of heat shock proteins (HSP27, HSP60, and HSP72) in late anagen and catagen, along with their absence in telogen and early anagen, suggests a role for these proteins in the regression process (176). Mast cells and macrophages have also been implicated in the control of catagen (see sect. x).

What initiates the apoptotic processes in catagen? By referring to the apoptosis that occurs in catagen as "programmed cell death" only begs the question. At present we do not know what this signal might be (release or withdrawal of paracrine cytokines, calcium waves, neural signals, changes in molecule expression) or even from where the signal arises (epithelium, mesenchyme, immune cell). It is recognized in other systems that changes in cytokine or hormonal concentration will induce apoptosis (301, 556, 592). EGF infusion induces apoptosis in sheep (196) and mouse skins (349). A major signal for entry into catagen (apoptosis) appears to be the turning off of the IGF-I receptor (250) and of HGF expression (297). Furthermore, the neurotrophins, NT-3, NT-4, and BDNF (36, 37, 46), as well as TGF-β1 all have recently surfaced as key catagen-promoting agents (123).

C. Distal Movement of the Shaft in Catagen

The challenge of catagen is to keep the machinery of the follicle together during the shrinking process and to ensure that no follicular residue remains behind. The upper follicle, then, must efficiently drag up and package the inferior regressing follicle and its papilla. The papilla remains attached to the epithelial column above and the vascular stalk below (449). How the inferior follicle moves upward in catagen is debated in the literature (63). Two possible forces are envisioned, a push or a pull (449). It is notable that direct evidence for either the push or pull theories has not been offered. For the "push theory" the lower follicle is envisioned to be driven upward by mitotic pressure of the epithelial strand (63, 505) or by contraction of the surrounding follicular CTS (63, 602). Regarding the push theory, we now know that once catagen is in full swing neither mitotic pressure nor substantial cell migration in the bulb could account for this egress (540). With regard to the contraction mechanism, the thickened corrugated glassy membrane of the catagen follicle is postulated to squeeze the follicle upward (63, 255, 449). Implicated in the CTS contraction theory are the contractile properties of actin-rich fibroblasts in the CTS (e.g., myofibroblasts, Refs. 255, 332, 468). These cells are envisioned to have the ability to squeeze the catagen follicle in a toothpaste-tube like fashion. Ito and Sato (212) hypothesize that as the lower follicle atrophies, the epithelial cells secrete enzymes that cause the degeneration and folding of the glassy membrane followed by shrinkage of the membrane. Concomitantly, the surrounding fibroblasts produce collagen, which could support the upward push of the retracting follicle.

For the pull theory, the epithelial cells of the strand are envisioned to effect the shrinkage. One concept involves the upward movement of cells in the lower ORS of the mouse hair follicle during late anagen and catagen that would pull the lower follicle upward ("immigration theory," Ref. 540). Another hypothetical concept in support of the epithelial strand pull theory is that of an apoptotic force ("apoptotic force theory," Ref. 534 and

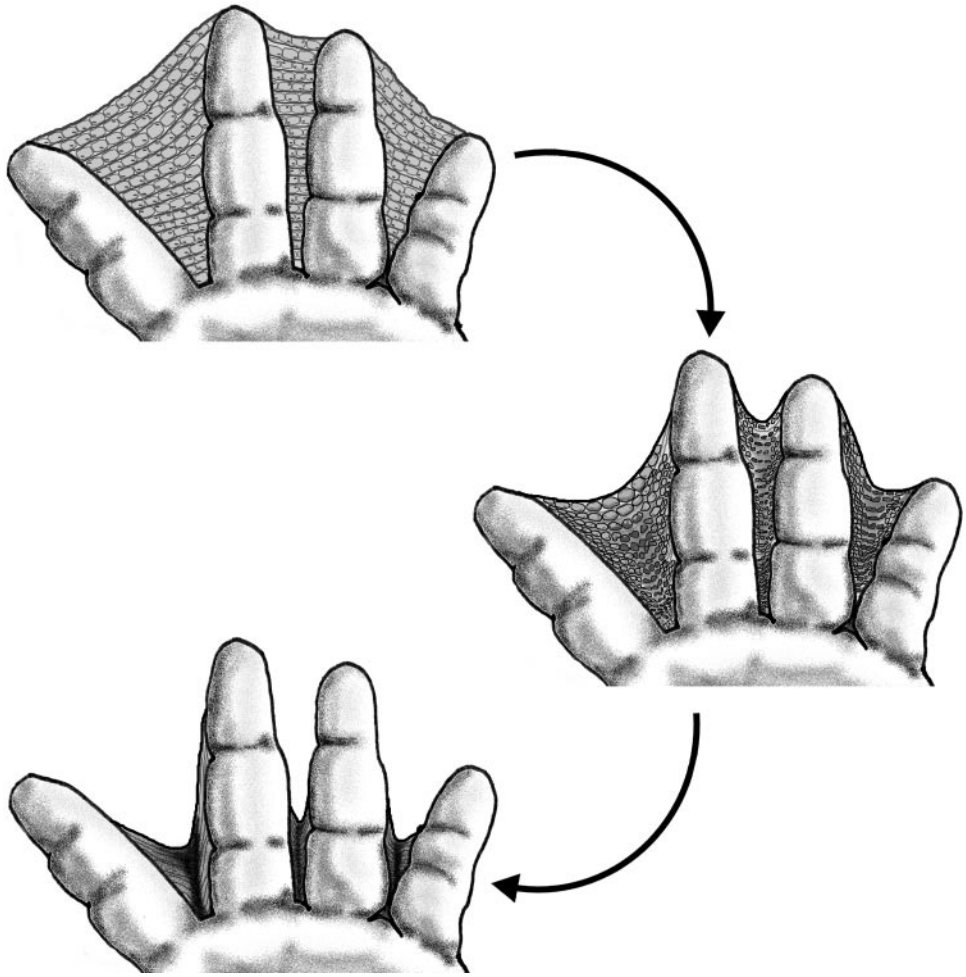


FIG. 3. Apoptotic force hypothesis. The concept of an apoptotic force depends on a population of cells that are tightly bound to one another, that are not dividing rapidly, and that have contractile cytoplasmic machinery. In a sheet of such cells, here illustrated as the epithelial web between 2 digits (in the follicle it is the epithelial finger of the lower anagen/catagen follicle), the sheet is pulled by the surrounding epithelial cells when individual cells undergo apoptosis. As a single cell undergoes apoptosis it contracts and is absorbed by the adjacent cells. The adjacent cells are envisioned to pull against each other to fill in the missing space and thus shift the whole structure.

Fig. 3). This force is envisioned to occur when the epithelial cells surrounding an apoptotic cell fill the space left by that first shrunken and then phagocytosed cell (534). In developmental systems, this force would play a role in the retraction of the interdigital webs of the developing embryonic hand (138, 604). If apoptosis occurs in a gradient, the resultant force would be envisioned to be directional. Even though intrafollicular apoptosis occurs in clusters, there appears to be an apoptotic gradient in the regressing follicle where the lower follicle epithelium exhibits substantially more apoptosis than the central or distal ORS (296, 360). Parenthetically, that an apparent apoptotic process also occurs in the lower follicle during anagen (in the area of the keratogenous zone, Ref. 528) might also implicate this same force in the movement of the shaft outward. In that case, however, shaft egression would be the result of both mitotic and apoptotic forces. Unfortunately, concrete experimental evidence for such an "apoptotic" force has not been presented, and this explanation for the upward movement of the lower follicle remains hypothetical.

Whatever the actual mechanism, the distal movement of the proximal follicle in catagen is very efficient. The epithelial strand itself, shrinking by the process of apoptosis, is cleaned up by adjacent epithelial cells and perifollicular macrophages. At the end of catagen, no deeplying follicular fragments remain (95, 399). Like anagen, catagen is a highly regulated event, in its initiation, development, and termination. In fact, catagen occurs so rapidly and in such a highly reproducible manner that one marvels at the accuracy and efficiency of the underlying controls. The purpose of catagen is to delete the old hair shaft factory and to bring the inductive machinery of the cell to a point where a new follicle can form, utilizing, once again, the stem cells of the bulge and the inductive powers of the papilla. As catagen regression occurs by means of apoptosis, it is clear that understanding the controls of apoptosis will be central to understanding catagen control.

VI. TELOGEN

By the end of catagen, the follicle extends no deeper than the upper dermis. The telogen follicle sits in the dermis as a small finger of "quiescent" epithelial cells above a tight cluster of papilla fibroblasts. The telogen

papilla, compared with the anagen papilla, is extracellular matrix poor, and its fibroblasts have scant cytoplasm (543). As mentioned above, it is believed that the papilla cells of the telogen follicle are largely the same as those of the anagen follicle (589); nevertheless, the actual proliferation dynamics of papilla fibroblasts as well as the exchange that may occur between fibroblast populations of the follicular papilla and the proximal CTS remain to be clarified (473, D. Tobin, unpublished data). The epithelial cells of the lower telogen follicle show little or no DNA or RNA synthesis (511), and although they no longer synthesize proteins characteristic of the anagen follicle, such as trichohyalin and the hair cortical keratins, K14 synthesis continues in the epithelial sac to which the telogen hair fiber anchors (52).

Embedded in the epithelial sac is the club hair (or telogen) shaft. This shaft has a brushlike base attached to the two-layered epidermal ORS sac (450). The region of the epidermal sac at the very base of the club hair is composed of tightly packed, small cells known as the hair germ. Where it interfaces the papilla, the hair germ is flattened. When the telogen follicle transits to the next anagen phase, the cells of the germ swell and grow down to enclose the papilla (63, 357). No unique molecular markers of the telogen follicle have been identified as yet, although estrogen receptor expression is reported to be restricted to fibroblasts of the telogen papilla (376), and the germ cells of telogen follicles express basonuclin (586) and FGF5 (179, 482).

It is surprising to realize how little attention, biochemical or morphological, has been given to telogen. However, a few studies do indicate the importance of specific molecules. For example, the deletion of selected adhesion molecules (desmoglein-3) or proteases (cathepsin L) in transgenic mice induces abnormalities in telogen club hair formation and shaft anchorage (260, 483). Although it is widely believed to be a quiescent period, in fact, telogen as a "resting" phase may be a misnomer. If Chase (63) was correct that telogen is an anagen brake, a hypothesis we find very appealing, then there must be a lot more going on during this phase than we are able to describe at this time, even if it is only to synthesize and release a hair cycle inhibitor.

VII. EXOGEN

Little interest or attention has been given to the mechanism of hair shedding, although it would appear that shedding is probably the most important aspect of hair growth from a patient's perspective (178, 256, 515). For animals it is most common for new hairs to grow before old ones fall out. This is a protective mechanism, which minimizes the possibility of shedding the protective fur before new fur is available. Rats and mice, for example, have two and often three hair shafts in a follicle at the same time while only one is growing. The remainder persists from earlier growth cycles (65, 488). Rook and Dawber (480) noted that it is not unusual for human telogen hairs to be retained for more than one follicular cycle; this suggests that the anagen phase and the exogen phase are independent events. It is almost certain that the release involves more than a mere mechanical stimulus (489). Because the shedding phase occurs independent of telogen and anagen, it probably utilizes a separate set of controls; for this reason, the shedding phase has been given a distinct name, exogen (534), in line with the anagen, catagen, and telogen phase names coined by Dry (96).

Knowing factors that affect seasonable molt may give some insight into the controls of exogen (230). A correlation between a sexual cycle and the molt was first described by Bissonnette (27). Parameters influencing the molt in sheep have been defined to be light (primarily), temperature, nutrition, and genetic factors (518, 519). Although influenced by environment (light, temperature, and nutrition) and systemic (endocrinological factors) parameters, it is generally believed that there is considerable innate local control of hair shedding; each fiber grows to a specific length, for a specific period of time, before being shed (420, 518, 519, 535).

In addition to simple morphology, we know neither how the resting hair shaft comes to lie in the base of the telogen follicle nor how it is attached to the follicle wall. As catagen ends, the hair follicle moves upward, and the IRS gets shorter until it forms only a collar around the telogen shaft base (449). In the area where the ORS and hair cuticle touch, trichilemmal keratinization starts and adds an adherent base to the periphery of the lower keratinizing shaft. The lower end of the catagen hair shaft is embedded in keratinized cells that bind it to the trichilemmal sac (ORS = trichilemma) (448, 449, 570).

Thus the telogen shaft base tucks into the trichilemmal soil of the inner aspect of the upper ORS just below the duct of the sebaceous gland. Here the now pilary canal-exposed ORS undergoes a unique trichilemmal keratinization. The lining cells enlarge vertically, lose their nuclei, and form dense K17-containing keratin without forming a granular layer (394, 450). It is this capsular trichilemmal keratinous mass that embeds and anchors the shaft. Histochemical studies of the shaft have revealed an abundance of free thiol groups in the germinal cells of the trichilemmal sac surrounding the club hair (489, 570), with restriction of disulfide cross-links to the club itself. In the mouse, thiol-disulfide conversion occurs simultaneously with the development of the succeeding hair generation and comes to a maximum when the club hair is about to fall out (96, 256, 570). Moreover, that the hair club appears to have a greater content of disulfide than the hair cortex (570) suggests that the hair club stroma differs from cortical hair keratin.

Surrounding the attachment site of the hair club are cells rich in desmosomes (desmoglein) and keratin K14 (81). Transgenic mouse studies have demonstrated that the desmoglein 3 (DG3) null mouse inadequately moors its club hairs (260). A mooring defect, along with the formation of a malformed abnormally large club hair and a defect in IRS structure, is also seen in mice that lack a lysosomal protease, cathepsin L (483; Tobin, unpublished data). Although the loss of DG3 may not describe the mechanism of exogen, it does indicate that tight junctions of the surrounding epithelial cells are important to telogen hair shaft mooring. Recent work suggests that a chymotryptic enzyme is expressed in the sebaceous gland and pilary canal (114) and that a plasminogen activator inhibitor localizes to the cells in the area of the club hair attachment site (277). Taken together, these observations implicate proteolytic pathways in the process of club hair formation and shedding. It is of interest that human immunodeficiencey virus patients under treatment with proteases inhibitors suffer from hair loss (184), a condition due perhaps to the modulation of the protease-antiprotease systems on exogen. If proteolytic systems (and their inhibitory controls) do play a role, we may conclude that the critical bonds holding the club shaft in place are proteinaceous. However, lipid bonding may also play a role because lipids have been found to be fundamental to the adhesion of cuticle cells (235).

The exogen phase may be altered in recognized disease states. For example, in trichostasis spinulosa, the infundibulum of a hair follicle becomes dilated with retained hair shafts from previous cycles, implicating an abnormally delayed exogen process (94). In androgenetic alopecia (AGA), it has been noted that the hair shaft sheds well before anagen starts, giving rise to a latency period when no shaft fills the pilary canal (89, 90). So, in AGA, either the exogen phase occurs earlier or the telogen phase is prolonged (anagen is delayed) well beyond the normal time of exogen onset.

What is the relevance of exogen to the hair cycle? Exogen is an integral part of the hair growth cycle, but it describes what the shaft base is doing and not what the follicle is doing. It appears that a shaft undergoing exogen may be quite divorced from the cycling activity of the underlying follicle. Although we believe the processes of anagen induction and exogen (or exogen induction and late anagen) are dissociated, they must influence one another (Milner and Stenn, unpublished data), but through what coupling mechanisms and to what extent are unanswered questions.

VIII. PROGRAMMED ORGAN DELETION: IRREVERSIBLE EXIT FROM CYCLING

Although it is true that the hair follicle appears destined to cycle throughout the entire life span of the mammalian organism, once the follicle has completed its morphogenesis (see Fig. 1), there may be one, albeit irreversible and possibly physiological, escape route from perpetual cycling (420). This permanent exit from cycling has been called "programmed organ deletion" (POD) and describes the physiological phenomenon of the complete elimination of selected, individual hair follicles as the result of an inflammatory cell attack on the follicle's epithelial stem cell region in the distal ORS (112).

First indications of the existence of this phenomenon arose in the course of analysis of the murine hair follicle immune system (HIS) and its hair cycle-associated remodeling (406, 428). Regularly distributed about isolated telogen or anagen hair follicles in normal C57BL/6 and Balb/c mice are dense perifollicular inflammatory infiltrates of mononuclear cells encircling the isthmus and bulge region (112). The cells extend onto and into the distal ORS of the affected individual hair follicles. Further analysis showed that these perifollicular inflammatory cell clusters represent largely major histocompatibility complex (MHC) class II+ cells consisting of activated macrophages with a few interspersed CD4+ T cells (112). The regions of the distal ORS infiltrated by these cells, which normally show strong ICAM-1 expression during catagen only (356), now express ICAM-1 and begin to show focal apoptosis. Eventually, the entire ORS in these follicles is destroyed, leaving only the nude hair shaft stranded in the dermis, without any signs of "scarring." Signs of actual hair follicle degeneration are restricted to anagen VI and catagen hair follicles and are present in ~10% of all hair follicles that displayed such a macrophage infiltrate.

Given that this occurs in completely healthy-appearing, uninfected, normal mouse skin, it was postulated that this phenomenon represents an essential physiological program of controlled follicle deconstruction, designed to get rid of malfunctioning or otherwise undesired hair follicles in an act of "immuno-microsurgery" (112).

This phenomenon may be clinically relevant. It has long been noted that AGA, alopecia psoriatica, and alopecia areata, three forms of hair loss that are usually not associated with a permanent loss of hair follicles, do, rarely, show signs of permanent hair follicle destruction associated with a perifollicular inflammatory cell infiltrate at the level of the distal ORS (94, 182, 568). No convincing explanation has yet been proposed for this decline in hair follicle density. Could it be that a pathologically exaggerated POD of hair follicles underlies all these cases? Could exaggerated POD be therapeutically induced and exploited for the management of hirsutism?

IX. NEURAL MECHANISM IN CYCLE CONTROL

Transplantation studies of skin in rats show that the hair follicles of functionally denervated homografts continue along their original cyclic rhythm for at least one full

cycle, before finally falling into step with the hair cycle pattern of the surrounding recipient skin (106). Similar observations can be made with human hair follicle micrografts from occipital skin that are severed from their original neural and vascular supply and are transplanted to other scalp locations (94, 381, 516, 568). Furthermore, functionally denervated hair follicles can traverse at least part of their cycle in organ culture (46, 287, 435, 441, 442). Finally, it has been demonstrated that an intact sensory and autonomous skin innervation is not essential for anagen induction and development in mice (323). Such studies show that hair follicle cycling is dictated by an autonomous, intrafollicular "oscillator" system, whose proper functioning is not critically dependent on neural influences (410, 420, 535). However, this does not exclude important direct or indirect modulating effects of skin nerves on hair follicle cycling, which could be clinically relevant to the course and management of hair growth disorders. A number of observations support this notion.

Previous studies suggested that the innervation of mature hair follicles remains essentially constant throughout the hair cycle, and only collapses in catagen/telogen to be reextended again during each new anagen phase (137, 597, 598). However, more recent work indicates that hair follicle innervation does indeed change with the cycle, most notably at the level of the isthmus and bulge region (41, 45). Unanswered is if the plasticity of the follicular and interfollicular neural networks over the cycle (41, 42, 45) is a result of, or a determination of, the cycle.

Actually, it is not clear why the follicle is so richly innervated (423). Is it because the tactile properties of the shaft are dependent on the dense and complex corona of neuropeptide-positive sensory and autonomic nerve fibers in the direct vicinity of the isthmus and bulge region (37, 41, 45)? Or is it to facilitate the exchange of secreted signals between perifollicular or intraepithelial nerve fibers and these stem cells (420)?

A similar question has been raised regarding the purpose of the high density of Merkel cells located directly above the bulge region of the distal human hair follicle epithelium (366). Although the distal ORS of human hair follicles houses numerous Merkel cells, the same region in murine pelage hair follicles is devoid of them (344). Although direct evidence for any communication between Merkel cells, ORS cells, or follicle stem cells is wanting, because of their presence, number, and proximity it is likely Merkel cells play an important role in the control of epithelial stem cell activities.

The possibility that there are direct neuroepithelial contacts between nonmyelinated, intraepithelial nerve fibers and ORS keratinocytes, which are mediated by neurotransmitters and neuropeptides (7, 41, 137, 155, 175, 597), is supported by a number of observations. *1*) Keratinocytes express several neurotransmitter and neuropeptide receptors, whose stimulation can alter keratinocyte proliferation and/or differentiation (7, 148, 391, 497). *2*) Experimentally administered substance P can induce both anagen and catagen development in mice (319, 415). *3*) There is prominent expression of β_2-adrenoreceptors in the epithelial stem cell region of hair follicles, and this expression is restricted to early anagen (45). This adrenoreceptor appears to be functionally relevant, since the β_2-adrenoreceptor agonist isoproterenol promotes hair cycle progression from anagen III to IV in murine skin organ culture (45), whereas norepinephrine depletion in vivo induces premature anagen onset in murine back skin (198). Such findings support the notion that neuropeptides and neurotransmitters play a role in hair cycle control.

In addition to direct neuroepithelial interactions, indirect neural influences might also alter hair follicle cycling (423). By controlling vasomotor tonus and endothelial cell functions, for example, cutaneous nerve fibers could regulate hair follicle blood supply and thus their supply of oxygen and nutrients in the hair follicle environment. This may explain some of the clinical observations that have long suggested the existence of neural mechanisms of hair growth control.

Traumatic, inflammatory, toxic, or degenerative damage to peripheral nerves and/or their connecting central pathways could lead to the dysfunction or loss of skin appendages (514, 577). In rat skin, for example, hair growth retardation, along with alopecia and a decrease in hair shaft thickness, follows as a consequence of capsaicin-induced sensory denervation (309), not unlike the hair growth retardation seen in dogs after sectioning of peripheral nerves and dorsal roots of the spinal cord (259). Conversely, peripheral nerve damage may promote hair growth as seen, e.g., in the form of "hemitrichosis" after major thoracic surgery (259), possibly as a consequence of posttraumatic sympathetic hyperinnervation, and in the precocious hair follicle development observed in partially neuralectomized opossum pups (237).

Although its occurrence is probably much rarer than commonly thought, severe psychoemotional stress can sometimes be linked to acute hair loss (e.g., in the rare, diffuse, fulminant form of alopecia areata that seems to underlie the phenomenon of "overnight graying," and in some forms of telogen effluvium, Refs. 94, 238, 391, 516, 593). In that regard it is of interest that a number of abnormalities of follicle innervation have been described in patients with alopecia areata (e.g., Refs. 197, 599). Even though these changes could be a secondary phenomenon that results from the initial autoimmune attack on the hair bulb, such abnormalities could affect the course of the disease, especially the follicle's capacity to regenerate itself.

Neurotransmitters and neuropeptides that are released from sensory nerve fibers provide a wide range of "trophic" (i.e., growth-supporting) influences on peripheral tissue homeostasis (7, 619). The recognized role of

the nervous system in immunomodulation (222, 466), especially in skin (7, 391), may be relevant to immunological hair growth controls and the neural influences on perifollicular mast cells and macrophages (see sect. x). For example, the neuropeptide substance P, stored in perifollicular sensory nerve endings, acts as a potent hair cycle modulator in mice and stimulates mast cell degranulation in murine skin organ culture (319, 414, 419). Because the murine hair cycle is characterized by striking, hair cycle-dependent fluctuations in mast cell-nerve fiber contacts (42), and because mast cell degranulation appears to be functionally important to both anagen and catagen development in mice (319, 419), sensory nerve fibers may well affect hair follicle cycling by the release of mast cell-activating neuropeptides. However, formal proof for this axis of indirect piloneural communication (420) is still needed.

Added to the complexity of any neural contribution to hair growth control is the neuroendocrine influence on hair growth, long attributed to neurohormones, such as prolactin, melatonin, and ACTH (94, 106, 404, 516). Although these controls cannot be discussed here in depth, it is of note that the hair follicle is not only a prominent target for hypothalamic and pituitary hormones, but it also expresses cognate receptors in a hair cycle-dependent manner. Moreover, the pilosebaceous unit itself is a source of such neurohormones such as corticotropin releasing hormone, ACTH, α-melanocyte stimulating hormone, and β-endorphin, whose production fluctuates over the hair cycle (408, 479, 521, 526). Because these neurohormones also have neurotrophic functions (619), we are learning that there exists a highly complex, interacting piloneural system (408, 423).

After initial indications from skin organ culture assays that NGF has hair growth-modulatory properties (418), it became clear that neurotrophins and their receptors are key elements in the control of both hair follicle morphogenesis and cycling and that the hair follicle is both a major source and peripheral target tissue for the neurotrophins, NGF, neurotensin (NT)-3, NT-4, and brain-derived neurotrophic factor (BDNF) (36, 40, 46, 48). Interestingly, the functional effects of neurotrophins differ between keratinocyte subpopulations (e.g., epidermal versus hair bulb keratinocytes; Refs. 43, 47, 447) and change during defined stages of skin and hair follicle maturation (36, 46). For example, while NT-3 promotes hair follicle morphogenesis and epidermal keratinocyte proliferation in mice (36, 43), it also promotes catagen, i.e., it is an apoptotic agonist (46). In addition, there are important differences in the hair growth-modulatory roles of various members of the NGF family and their high- and low-affinity receptors (45, 48). Most recently, distant members of the TGF-β superfamily with neurotrophic properties, i.e., glia-derived neurotrophic factor and neurturin, as well as their receptors, have surfaced as part of the complex controls of hair growth by neurotrophic factors (47).

The role of neurotrophins in hair cycle control is interesting for at least three reasons: *1*) neurotrophins are prominently expressed by perifollicular Schwann cells at the level of the isthmus/bulge region (37, 40, 46, 51), and they can stimulate their cognate receptor in the follicle epithelium and mesenchyme. *2*) Hair cycle-dependent production of neurotrophins by the follicle itself is likely to affect the remodeling of its innervation (41). *3*) Follicle- or glia-derived neurotrophins may alter the (hair cycle-modulatory) functions of perifollicular mast cells and macrophages (420).

Taken together, all these lines of argumentation make it quite reasonable to expect that the nervous system plays a, direct or indirect, role in hair cycle control under physiological circumstances, even though it has proven exceedingly difficult to experimentally pinpoint the most relevant pathways of piloneural communication in vivo. Specific neuropeptide, neurotrophin, and/or neurotransmitter receptor agonists, as well as antagonists, may well be clinically exploitable as hair cycle manipulatory agents (420).

X. ROLE OF THE IMMUNE SYSTEM ON THE CYCLE

That the immune system, or at least some of its cellular protagonists, is somehow involved in hair growth control is a fairly old idea (e.g., Refs. 351, 417). This is based on several observations. *1*) Synchronized hair follicle cycling in rats and mice is associated with quite substantial alterations in the skin immune status, namely, in the number, location, and/or activation of perifollicular mast cells, macrophages, Langerhans cells, and T cells (see sect. xii*D*). A key proinflammatory adhesion molecule, ICAM-1, which is differentially expressed by selected follicle compartments during defined hair cycle stages, may be connected with the hair cycle-dependent accumulation of perifollicular macrophages (356). So, it is possible that changes in the activities, location, and number of perifollicular mast cells and macrophages have an impact on hair cycle control (319, 321, 419, 428, 590). *2*) Several forms of abnormal human hair loss are associated with a prominent inflammatory cell infiltrate that attacks the hair follicle. Generally, this causes reversible damage if the bulb is the target (e.g., in alopecia areata, Refs. 139, 425) and irreversible damage if the isthmus and bulge region and/or the sebaceous gland are assaulted (e.g., in scarring alopecias; cf. Refs. 182, 410, 538). Such a macrophage-driven attack of the isthmus/bulge region may also be used for deleting malfunctioning hair follicles (see sect. viii; Ref. 112). The transformation of terminal to vellus hair follicles in some forms of androgenetic alope-

cia is also associated with a perifollicular macrophages and mast cell infiltrate, which has been proposed to be inherent to the terminal-to-vellus switch (see sect. XI) itself (224, 276). All this raises the question whether these components of the skin immune system (SIS) are also involved in hair growth control under physiological conditions. *3*) Potent immunosuppressive drugs are among the most powerful hair cycle-manipulatory agents known to date. Although the immunophilin ligands cyclosporin A and FK506 induce anagen and inhibit catagen in rodents (322, 409, 426, 555), potent topical glucocorticosteroids do the opposite: they inhibit anagen development and induce catagen in mice (412, 536). This has been interpreted as support for immunological controls of hair follicle cycling (417, 426). *4*). Many of the endogenous hair cycle-modulatory agents identified to date have defined immunomodulatory properties. This is particularly evident for recognized hair growth modulators like TGF-β1, IL-1, IGF-I, TNF-α, TGF-α, ACTH, substance P, and PDGF (129, 222). However, a second interpretation may be that any of the hair cycle-associated fluctuations in the skin immune status, and in the expression patterns of adhesion molecules like ICAM-1, may simply reflect hair cycle-associated changes in the local cytokine milieu; that is, the skin immune parameter changes could be a consequence of the cycle unrelated to the primary controls of hair growth.

Despite the above associations to date, there is little more than circumstantial evidence supporting a role of the immune system in hair cycle control. To that point, considerable investigation is currently ongoing regarding the role of perifollicular mast cells and macrophages in hair cycle control. For decades perifollicular mast cells have been thought to operate as "central switchboards of tissue remodeling" during hair follicle cycling (321). Not only is the perifollicular dermis and subcutis one of the preferred sites of connective tissue-type mast cells, but the mast cell number, degranulation activity, histochemical staining characteristics, histamine/heparin skin content, and physical mast cell-nerve fiber contacts all fluctuate significantly during synchronized hair follicle cycling in rodent skin (42, 44, 319, 321, 351, 419). Light and electron microscopic evidence suggests that perifollicular mast cells degranulate around and during the earliest stages of telogen-anagen as well as during the anagen-catagen transformation. Because mast cell secretagogues can prematurely induce both anagen and catagen in mice, while inhibitors of mast cell degranulation block both anagen and catagen development, these constitutive changes in mast cell activity appear to be functionally relevant to hair cycle control (44, 219, 419). Despite these observations, surprising observations have been made with the mast cell-deficient mouse who has normal-appearing hair follicle development and growth (544). Nevertheless, histomorphometry has revealed that mast cell-deficient mice with a defect in c-*kit*-mediated signaling show a discrete, but significant, retardation of catagen development (319). In addition, selected mast cell products exert hair growth-modulatory effects in vitro (organ culture) (403), and systemic administration of histamine or serotonin receptor antagonists retards anagen development in vivo (mice) (419). A functionally important role for mast cells in hair cycle control awaits to be conclusively documented by "knock-in" experiments, namely, by rescuing the normal phenotype from the mast cell-deficient mouse after replacing normal mast cells.

In addition to mast cells, macrophages have also long attracted the interest of hair researchers. Ultrastructural studies during the anagen-catagen transformation in rats reveal an increased number of activated macrophages in the direct vicinity of the regressing hair bulb and its thickened, undulating basement membrane, with some of these macrophages apparently phagocytosing excess basement membrane collagen (399). Interest in the hair growth-modulatory role of macrophages was further stimulated by phenomenological studies implicating these cells in the pathogenesis of some forms of AGA (224, 276). Westgate et al. (590) postulated that an attack of macrophages on MHC class I negative hair bulb keratinocytes toward the end of anagen VI might be instrumental to the induction of catagen. Unfortunately, no convincing functional evidence for a role of macrophages in catagen control has as yet been presented. The theory is challenged by the fact that macrophages are not capable of recognizing MHC class I negative cells within a defined area of "immune privilege" (590), and the anagen hair bulb represents such a MHC class I negative area of immune privilege (418, 420). Such an attack would be the perogative of natural killer cells (406, 420). In normal human and mouse skin, there are very few natural killer cells detectable in or around the hair follicle, and there is certainly no increase in their number/activity during catagen; finally, the anagen-catagen transformation is actually associated with a decline in the number of detectable perifollicular macrophages, not an increase (73, 428). It is interesting, however, to note that IL-1, TNF-α, and FGF5, three signals now widely held to be critically involved in catagen induction (see sect. V), are all secreted products of macrophages (129, 222, 402). As mentioned above, the fact that FGF5 plays an important role in murine catagen control (179, 434, 482, 548, 549) and that a short FGF5-neutralizing form is expressed in perifollicular macrophages, may give some support to a macrophage role. One challenge is to determine how other recognized catagen modulators, such as dexamethasone and cyclosporin A, alter these putative catagen-inducing secretory activities of perifollicular macrophages, and which other, less toxic topical drugs may be exploited to manipulate them therapeutically.

XI. VELLUS-TO-TERMINAL SWITCH

Lanugo hairs, the first body hairs formed in the embryo, are vellus in character, but often longer than the vellus shafts of the adult. The vellus hair shaft is short, thin, fine, lightly pigmented, and with no medulla (32). A vellus follicle is defined as a small follicle that extends no deeper than the upper dermis and produces a shaft no wider than its IRS. Although vellus follicles may lack arrector pili muscles in some areas, vellus follicles are associated with these structures on the face (366). With maturity and exposure to androgens, regional human hair follicles switch in morphology to terminal follicles that produce terminal hair shafts. The inverse terminal-to-vellus switch occurs on the scalp of the genetically susceptible (AGA) individual after exposure to androgens (158).

The hair cycle appears to be central to the vellus-to-terminal hair follicle switch because phenomenologically the cycle appears to initiate that process; the follicle must cycle in order for the switch to occur (348). We do not yet know how the cycle is related to this transformation, although it may be due to a gradual change in the size of the papilla with the completion of each cycle. Relatively little attention has been given to this switch phenomenon mechanistically; in fact, even the follicle that characteristically switches has not yet been fully characterized. Although there are very few examples of the follicle switch phenomenon in animals, aside from humans (e.g., the macaque, Ref. 569), one is attracted to the possibility that the conversion of underhair to overhair (544) might provide a viable animal model for the phenomenon in humans.

It has long been appreciated that androgens are paramount to human hair follicle/shaft patterning (329, 462). Sexual maturity is heralded by the development of body hair in adolescence. Hamilton (158) demonstrated that, in the absence of testosterone, men neither develop body and facial hair nor grow bald. The wide response range of hair to androgens reflects inherent differences of hair depending on body site. There is a graded response of regional hairs to androgen levels; inguinal and axillary follicles, for example, are stimulated to grow under low levels of androgen, and facial hair to high levels, while deep temporal/occipital scalp and eyebrow/eyelash hair are insensitive to androgen levels altogether. This principle underlies the success of scalp hair transplants for male pattern balding, where androgen-insensitive hairs (occipital area) are transplanted to sites of androgen-sensitive hairs (frontal, parietal, coronal areas) (381). Thus one must distinguish between hairs that are androgen dependent (axilla), androgen insensitive (eyebrow), and androgen independent but androgen sensitive (scalp vertex in susceptible individuals). Ultimately, these interfollicular and interregional differences must stem from the way a given follicle responds to androgen stimulation, its androgen target genes, and the nature of its androgen receptor-mediated signal transduction events. Unfortunately, these parameters have not yet been dissected.

The chemistry of androgen processing and hair growth has been reviewed (248, 462). Many attempts have been made to localize the expression of the major enzymes and receptors of the androgen system in the pilosebaceous apparatus. Enzymes that reduce androgenicity, by aromatizing testosterone and androstenedione to estrogens localize immunologically to the ORS (*P*-450 aromatase complex, Ref. 494). Enzymes that convert the relatively inactive testosterone to the highly active dihydrotestosterone (DHT), the 5α-reductases (5α-R type 1 and 5α-R type 2), localize to the papilla and ORS (109, 495). 5α-R type 1 localizes to the nucleus of cells and 5α-R type 2 to the cytoplasm (109). Patients with the genetic absence of 5α-R type 2 grow hair in the pubic and axillary areas, suggesting that the testosterone to DHT conversion is not necessary for androgen-dependent follicles in these sites (205).

Although interpretation is not unequivocal, in vitro studies show that there are regional differences between follicles with respect to 5α-R activity (157). Grown in tissue culture, papilla cells from axillary or pubic follicles, for example, liberate testosterone in the medium, whereas papilla cells from beard follicles produced DHT (157). 5α-R activity in human beard papilla cells was found to be three to five times as high as that of reticular dermal fibroblasts and papilla cells from occipital scalp follicles (209).

To respond to androgens, follicles must express androgen receptors (ARs). In androgen-sensitive skin the FP, ORS, dermal sheath cells, sebaceous gland, and eccrine glands express androgen receptors (70, 183, 210, 495). Papillae arising from androgen-sensitive follicles (beard, pubis) have more ARs than androgen-insensitive follicles (nonbalding scalp) (463). The AR has been most convincingly localized to the nuclei of papilla and dermal sheath cells in situ (70) and in papilla cell in vitro (463). However, the whole skin organ differs in this respect from site to site, since, for example, in genital skin ARs are expressed in epidermis, dermal fibroblasts, smooth muscle cells, and endothelial cells; in nongenital skin, ARs are found in basal and glandular cells of the sebaceous gland, the ORS, and eccrine sweat glands (29). Differences between various hair follicle populations at the level of androgen receptor expression or in the activity of androgen-metabolizing enzymes can hardly explain why the same androgen (e.g., DHT) produces diametrically opposed effects rather than a graded response in the same direction (vellus-to-terminal switch vs. terminal-to-vellus switch). This paradox is seen in closely located follicle regions of the skin (e.g., beard vs. parietal scalp).

Androgens act on beard papilla cells in culture, which in turn produce IGF-I (210); this effect is antago-

nized by antiandrogens and antibody to IGF-I (210). Moreover, papilla cells from androgen-sensitive follicles (beard) in culture are stimulated to produce stem cell factor by testosterone (183). In the macaque, testosterone stimulates papilla cells, from androgen-sensitive follicles, to produce a factor that suppresses the growth of ORS epithelial cells in culture (373). That androgens appear to act on follicular mesenchyme is consistent with findings in other epithelial-mesenchymal interacting systems (e.g., mammary, Ref. 265).

Although androgens are often hailed as the ". . . main known hormonal regulators of human hair . . ." growth (462), in fact the androgen effect is not fundamental to hair growth but is critical to hair patterning. For example, hair continues to grow on the body (vellus, eyebrow, eyelashes) of the patient with complete absence of functional androgen receptors (270). This suggests that androgens are modifiers and not factors basic to all hair growth or even to hair follicle cycling as such.

XII. HAIR FOLLICLE INFLUENCE ON SKIN BIOLOGY

A. Introduction

Heretofore, we have discussed how the body and skin environment influence hair growth; the converse also is true, namely, the hair cycle influences the character of the skin. It has long been appreciated that the whole skin organ is influenced by the hair cycle (66, 163, 342, 427). Earlier than most other hair researchers of his time, Chase recognized that hair follicle cycling has a profound impact on its surrounding tissue environment (66). This is particularly evident in rodents with highly synchronized cycling patterns, where the entire skin architecture changes whenever thousands of hair follicles more or less simultaneously pass from one hair cycle stage to the next. With anagen the epidermis and dermis thicken, dermal vascularity and stromal content increase, and the subcutis layer increases in depth (163). Sebaceous gland size and function also appear affected by the cycle: they grow faster in anagen (345), allegedly larger in telogen (in some areas) (66, 400), and show varied gene and neuropeptide expression, proliferation, and apoptosis over the cycle (e.g., Refs. 161, 523, 617). How the hair follicle impacts growth of the skin organ is not apparent.

Further effects of hair follicle cycle on skin biology are seen from wound healing and delayed-type hypersensitivity studies. There is accelerated healing of porcine wounds during anagen (W. Eaglstein and R. Paus, unpublished data) and, conversely, suppression of contact allergen sensitization (189, 190).

B. Reparative Role

It has long been appreciated that skin appendages contribute substantially to epithelial wound closure (7, 113, 141, 281). The upper ORS provides epithelial cells, which cover ulcerated wounds. The distal ORS in humans may also serve as a reservoir for relatively immature antigen presenting cells (Langerhans cells) that can repopulate the epidermis from the follicular location after the intraepidermal Langerhans cell pool has been depleted by ultraviolet irradiation (140).

In addition to its contributory role to wound closure and epidermal restoration, the hair follicle has inherent regenerative properties. This is best manifest in its ability to regenerate itself with the initiation of each cycle; throughout life the follicle retains its ability to regenerate its inferior cycling portion. This regenerative potential is demonstrated clearly after massive damage to the follicle in the course of chemotherapy (322, 413, 525). If the lower follicle is truncated surgically below the level of the sebaceous gland, without destroying the permanent portion or the surrounding fibrous sheath, the follicle can regrow (206, 218, 377, 378). Throughout adult life, the follicle possesses the capacity to regenerate sebaceous glands after the glands are experimentally destroyed (345). In addition, as mentioned above, cells dissociated from perinatal follicular buds and the papilla or lower CTS mesenchyme have the capacity to regenerate the total skin organ as well as hair follicles in a murine transplant (292, 457, 458, 473).

That the follicle contains cells that have regenerative properties (83, 84, 292, 457) suggests that the connective tissue cells of the follicle may also play a role in dermal repair. It has been found that the fibroblasts of the connective tissue sheath have the ability to regenerate a new papilla (198, 206, 377, 378). This regenerative ability of the follicle and the inductive property of its cells extend beyond the newborn period into maturity (122) and likely into senescence.

C. Angiogenesis During Hair Follicle Cycling

One aspect of hair follicle influence on skin physiology relates to cutaneous vasculature (63, 104, 444, 510, 531, 600), in particular as to whether genuine angiogenesis occurs during each anagen development. If the latter were the case, this should offer an unusually attractive model for studying how physiological angiogenesis is controlled by a complex E-M interacting system in vivo. At the same time, the therapeutic inhibition of perifollicular angiogenesis and/or induction of vascular involution would appear useful for the treatment of unwanted hair growth (hirsutism) (325).

A priori, it is logical that small, metabolically "rest-

ing" telogen follicles have considerably lower perfusion requirements than larger, rapidly growing, anagen hair follicles. That synchronized hair follicle cycling affects skin perfusion and blood vessel arrangement was noted decades ago, primarily on the basis of dye injection studies (104, 116, 348). In rat and rabbit skin, these studies revealed substantial changes in the caliber, apparent density, and spatial arrangement of peri- and interfollicular blood vessels during synchronized anagen development (104), whereas a "degeneration" of capillaries was reported within the catagen papilla of human hair follicles (116). The dermis in the vicinity of anagen follicles appears more vascular than that around telogen follicles, and endothelial cell DNA synthesis is found exclusively within the papillae of anagen follicles, primarily during anagen IV (510). Interestingly, the epithelial hair bulb, rather than the papilla, of rat vibrissae follicles in anagen was shown to be angiogeneic in the classical rabbit corneal pouch angiogenesis assay (531); however, we recognize that both papilla fibroblasts and ORS keratinocytes contain angiogenic factors such as vascular endothelial growth factor (VEGF) (144, 264, 271, 272).

The above studies suggested that the blood vessel changes in the dermis over the cycle are orchestrated by the follicle: the follicle calls forth its own blood supply and, conversely, dermal vessels do not control the cycle. However, these studies do not definitively establish whether new vessel formation from preexisting blood vessels, angiogenesis, occurs during the cycle. Such proof has only recently become available, using depilation-induced anagen development in the C57BL/6 mouse (66, 427, 542). With the use of standardized quantitative histomorphometry, electron microscopy, and CD31 [platelet endothelial cell adhesion molecule-1 (PECAM-1)] immunohistochemistry as an endothelial cell marker, it was shown that the cutaneous microvasculature is substantially rearranged during anagen development, that there is endothelial cell proliferation, and that there is an increase in endothelial cell number in anagen (325). Taken together, these studies suggest that anagen development, at least in species with a synchronized hair cycle, is associated not only with a rearrangement of the skin vasculature and a concomitant increase in skin perfusion, but also with genuine and substantial angiogenesis.

What we do not know from these and previous studies is what cellular or molecular elements control these vascular changes. Likely candidates as cellular sources for angiogenic factors are papilla fibroblasts, which have been identified as sources of at least two important angiogenesis stimulators, i.e., VEGF (264, 271, 272) and HGF/SF (297). However, the hair follicle epithelium is also a source of angiogenic factors in vivo (531); VEGF antigen is found in the human ORS (264). Because HGF/SF can stimulate keratinocyte VEGF expression in vitro (139a), it is also possible that papilla-derived factors like HGF/SF (297) stimulate ORS cells to secrete other angiogenic factors, like VEGF. Furthermore, the balance of pro- and antiangiogenic factors such as endostatin, angiostatin, and angiopoietin-2 (160) deserves careful analysis, since this balance very likely shifts during anagen-associated angiogenesis and catagen-associated partial blood vessel involution.

D. Hair Cycle-Associated Changes in the Skin Immune System

In addition to its dramatic effects on skin architecture and the proliferation, differentiation, and apoptosis of many extrafollicular cell populations (see above), synchronized hair follicle cycling has profound effects on standard skin immune parameters (406, 420). During both cyclosporin A- and depilation-induced anagen development in mice, the numbers of intrafollicular Langerhans cells, γ/δ-TCR+ lymphocytes, and perifollicular macrophages fluctuate significantly, e.g., more MHC class II+ perifollicular macrophages are found around anagen VI follicles compared with telogen follicles (428). That these hair cycle-associated alterations in standard skin immune parameters are functionally relevant has recently been observed. In a standard mouse model of contact and photocontact sensitization to picryl chloride, an efficient sensitization against the allergen could only be obtained through back skin when all the follicles were synchronized in telogen, whereas hardly any sensitization could be obtained through anagen skin (192). A similar, anagen-associated suppression of type IV skin immune responses was seen in a photocontact allergy variation of this mouse model (564).

Subsequent studies showed that synchronized anagen development over a large region of the skin (back) even suppressed contact hypersensitivity in telogen skin (abdomen), suggesting that hair cycle progression into anagen is associated with secretion of a systemic, immunosuppressive activity (193). Synchronized hair follicle cycling in mice even goes along with changes in splenocyte proliferation ex vivo. Although the nature of the anagen-associated immunosuppressive activities remains speculative, it is reasonable to suspect that they are related to the anagen-coupled intrafollicular generation and secretion of potent immunosuppressive agents like ACTH, α-MSH, TGF-β1, and IL-10 (39, 123, 408, 564, 588).

Another fascinating aspect of hair cycle-associated changes in the skin immune system is that each entry of a hair follicle into anagen generates a large territory of relative "immune privilege" in the proximal hair follicle epithelium of the anagen hair bulb. This intriguing feature of the hair follicle cycle was first proposed by Billingham and Silvers (cf. Ref. 26) and defined by more recent work (174, 427, 590). The follicular immune privilege is charac-

terized by an absence or downmodulation of MHC class I expression, antigen-presenting cells, and the local production of potent immunosuppressants in the follicle epithelium (73, 408, 418, 428, 486, 590). This immune privilege may be established to sequester antigenic peptides derived from melanogenesis-related proteins, which are generated only during anagen III-VI in the proximal hair bulb (418, 425, 486). It has been hypothesized that the immune privilege of the epithelial anagen hair bulb ceases early on in the pathogenesis of alopecia areata and that MHC class I expression becomes abnormally upregulated, thus presenting melanogenesis-related autoantigens to preexisting, autoreactive CD8+ T cells. In the presence of appropriate costimulatory signals and help from CD4+ T cells, this autoreactive process would presumably initiate a sequence of secondary immunopathological processes that would eventually culminate in the development of the full-blown disorder (425). This hypothesis has been given support by the recent observation that alopecia areata can be transferred to human scalp transplants on SCID mice by CD8+ T lymphocytes, which recognize only MHC class I-presented autoantigens (139).

Irrespective of the true function of the putative follicular immune privilege, the fact that every hair follicle entering into anagen establishes such a unique territory of restricted antigen presentation, recognition, and response along with anagen-associated suppression of contact hypersensitivity illustrates that hair follicle cycling has a profound impact on the skin immune system and its functional properties (420).

XIII. CONCLUSIONS: CHASE IN PROSPECTIVE

Chase (63) described for us the biology of hair of his day. Although the major tools of the workers of his generation limited studies to gross and light microscopic levels, they generated models and insights that have withstood the test of time. Their greatest contribution was the recognition and description of the hair cycle itself. Chase appears to have appreciated the most important theme in modern hair biology, namely, that the follicle is a regenerative structure that utilizes the molecular and mechanistic tools of the embryo during each hair cycle over the lifetime of the individual.

Since that time until the mid 1980s, we gathered more insight into the cell biology and the structural and metabolic biochemistry of the follicle. In the mid 1980s, for reasons that are not entirely clear (perhaps the availability of a drug that actually did stimulate hair growth as well as new and revolutionary insights into developmental biology and molecular biology), considerable interest in hair biology arose and has resulted in profound new insight into hair growth. These findings include the recognition of stem cell populations in the follicle, the powerful inductive properties of the papilla, systems for studying the follicle in culture, the recognition of families of morphogenetic and mediator molecules in the developing and cycling follicle, and the integral role of the sebaceous gland. Currently, the investigative challenges in hair follicle biology involve all the major questions of modern biology: organogenesis, stem cell biology, epithelial-mesenchymal interactions, pattern formation, organ cycling, and cell differentiation.

The current generation of researchers has its work cut out for them. In fact, there is plenty of work for several generations of scientists, and the expected findings will undoubtedly impact other fields of biology and medicine. In closing, we would like to propose a challenge to workers in the field, as a sort of "hit list" for our generation of hair researchers. *1*) Our work begins with better systems to analyze and assay hair growth. Needed are in vitro systems that measure anagen induction, vellus-to-terminal switch or vice versa, the terminal-to-vellus switch (the androgen effect), and pattern formation. *2*) We need systems for generating follicles in vitro from dissociated cells. *3*) We have to know more about stem cells, both epithelial and mesenchymal, how to propagate them in culture, and how to orchestrate their differentiation to pilosebaceous structures in culture. *4*) We have to learn how to deliver genes to the stem cells of the follicle to influence hair growth. *5*) We have to identify and place in perspective all the genes important to hair follicle growth and shaft formation. *6*) We need to know more about the controls for inducing each of the phases of the cycle-anagen, catagen, telogen, and exogen and, in particular, the role of apoptosis in the cycle. *7*) We need to elucidate the dynamics of telogen and establish what is going on within this apparently "resting" structure. *8*) We need to know the controls of pigmentation and of melanocyte differention, propagation, and death as well as its relationship to the follicular growth cycle. *9*) Finally, we desperately need a central database, accessible to investigators worldwide, that will help us tabulate and integrate the huge amount of data, past and present, that we will need to understand this deceptively simple organ.

It is humbling to end this essay with many of the same questions Chase had as he closed his discussion. However, with the legacy he left us and the tools we now have on hand, there is no doubt those questions will be very different 50 years from now.

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