Fuzzy Science

Researchers brush up on the biology of hair

By RICK WEISS

Grown long, it became a hallmark of hippies. Neatly trimmed and moussed, it has become the trademark of yuppies. Women sprouting yellow ones have been said to have more fun. And men in whom it's thinning become obsessed with its disappearance, supporting a booming industry of ointments, transplants and toupees.

Among humans, at least, hair carries symbolic significance far beyond what one might expect from a collection of dead appendages.

In the United States alone, style-conscious mammals unwilling to accept their follicular fates spend more than $40 billion each year to cut, perm, tame or otherwise alter this peculiar vestige of a furrier past. Still, for all the attention lavished upon it, hair remains one of the least understood components of the mammalian body.

Recently, however, scientists have begun to lift hair's shroud of mystery. Recognizing that hair may hold the answers to some long-standing questions in cell biology, researchers have focused renewed attention on this evolutionary equivalent of feathers and scales.

In many cases, hair research is financed by pharmaceutical and textile companies hoping to profit from the basic science. At its strangest, the new work has led to the development of laboratory culture systems that allow scientists to cultivate small amounts of hair from follicle-rich slabs of artificial skin. But despite substantial research expenditures, no one has managed to grow significant amounts of hair anywhere but on the body itself — a fact that offers testimony to hair's bewildering biology.

"One of the reasons people have avoided looking at hair is because it's so complex," says Howard Baden, who studies the molecular biology of hair at Harvard Medical School in Boston. "Now scientists are recognizing that it's a very good model for looking at some basic biological problems."

Indeed, hair biology has attracted researchers from several scientific disciplines. Cancer specialists explore hair and its follicles because these are the only parts of the body that repeatedly die and self-regenerate throughout life. For these scientists, hair promises insights into the cellular controls that go awry in skin cancer and other proliferative disorders.

For developmental biologists, the lifelong cycle of hair death and regeneration provides a series of remarkable repeat performances that allows them to examine and reexamine in a single animal the stages of cell growth and differentiation.

Textile developers hope that an understanding of hair growth at the molecular level will lead to genetically engineered sheep bearing improved varieties of wool — a motivation that explains the large proportion of hair research performed in Australia. And for cosmetic and pharmaceutical manufacturers, every new finding related to hair regeneration holds the prospect of enormous profits from a population of aging men unwilling to accept nature's plans for their pates.

"This was a nonfield just a few years ago. There were very few people studying hair and follicle growth," says Stewart Yuspa of the National Cancer Institute in Bethesda, Md. Now, he says, "a lot of the basic questions in skin cell biology have been answered, and people are looking for new challenges. The hair follicle is it."

Uno

Stumptailed macaques at ages 4, 4.3, 4.7 and 7 years, showing the progressive balding typical of the species.

As a trait unique to mammals — and one intimately involved in sexual communication — hair has attracted plenty of scientific attention on the macroscopic level. Its functions are myriad: As fur it provides camouflage and insulation; as whiskers it offers tactile sensitivity; as eyelashes and nasal hairs it protects against dust.

About 100,000 of the fibers grace the scalp of the average human. Seen in cross section, hairs appear oval in Caucasians, flat in blacks and circular in Asians. In humans, the few patches of body hair that have survived evolution serve primarily as social cues between the sexes, says Kurt S. Stenn of the Yale University School of Medicine.

Of particular interest to biologists is the observation that hair grows in cycles. In humans, for example, individual hairs grow for periods of two to five years, then rest for four to six months. Growth involves the rapid proliferation of cells inside the hair follicle, a specialized involution of skin.

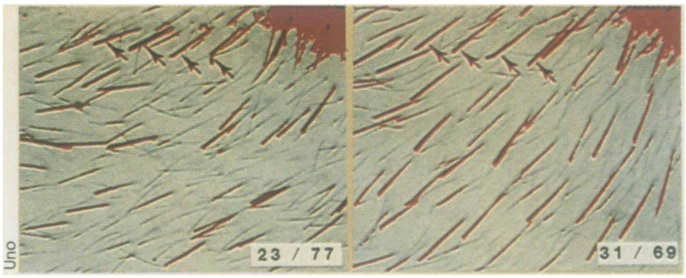
Production of a hair within a follicle resembles a miniature assembly line. As dividing hair cells push older hair cells upward and out of the skin, pigmented cells called melanocytes enter the developing fiber to provide color. At the same time, a series of polymerizing reactions cross-links 10 different kinds of protein molecules, or keratins, within the hair cells to create the tough, finished product. All this goes on while the new hair emerges at a rate of about one-third millimeter per day, or about half an inch per month.

During the resting phase, growth comes to a halt and many cells in the follicular bulb wither and die. But all is not lost. A supply of so-called papilla cells, capable of reseeding the follicle, remains hidden in a portion of the deflated follicle. Later, in response to molecular signals secreted by surrounding cells, the follicle springs to life again. Papilla cells migrate to the bottom of the follicle and begin to divide, and a new hair shaft grows upward, pushing out the old hair as it goes.

In humans — in contrast to animals with seasonally synchronized molts — the growth and rest cycles of individual hairs are uncoordinated, so that at any given time, 90 percent of the hairs are growing while the rest are not. But hair growth cycles, especially in men, get shorter with age, until the amount of time each follicle spends resting exceeds the amount of time spent growing. Moreover, the follicles become smaller and shallower with age, squeezing out finer and finer hairs. For many men completing their third or fourth decade, a look in the mirror provides evidence of "male pattern baldness" — a receding hairline and thinning crown.

Scientists hope that by studying the hair cycle they will learn to control the growth and regeneration of hair and skin. But whether the goal is to slow the balding process in men, increase wool production in sheep or stop skin cell proliferation in cancer patients, the key lies in understanding the molecular signals that regulate the cycle of growth and rest.

The hair cycle, says Yuspa, "is extremely well controlled, based on the appearance and disappearance of regulatory molecules and the presence or absence of receptors within each follicle." But to rewrite the score of this regulatory symphony, researchers need a way of testing the effects of individual hormones and cellular growth factors in a controlled fashion. Thus, much of the recent work on hair biology has focused on the development of laboratory-grown hair.



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Computer-enhanced photographs ease objective comparisons of hair size and density before and three months after treatment with 5 percent minoxidil.


Uno

Female (white) and male (tan) "fuzzy rats." These hybrids bear fine hairs resembling those on the heads of balding men, providing useful models for studies of human hair growth.

Until recently, the only way to test the effects of drugs or naturally occurring cell-growth factors on hair was to spread the lotions and ointments on furry animals. Indeed, a few animals remain popular for such studies.

Southeast Asian stumptailed macaque monkeys (*Macaca arctoides*), for example, predictably and progressively go bald between their fourth and seventh years, providing a "speeded up" model of baldness in humans. Early experiments with minoxidil, today's only FDA-approved hair-regenerating drug, were performed on stumptails, and scientists continue to use the animals to test other experimental hair thickeners.

Another popular animal model for hair growth is the so-called fuzzy rat – the hybrid progeny of a hairy albino rat and a hairless, normally pigmented rat. The fuzzy rat's tiny follicles sprout fine filaments resembling the thinning hairs in balding men. "Fuzzy rats have fuzz, and bald [human] heads have fuzz," observes Hideo Uno, who works with the rats and macaques at the University of Wisconsin-Madison. "So if a drug makes the fuzzy rat's fuzz get thicker, then that's the bottom line, right?"

To test candidate hair growth enhancers, Uno takes 4-millimeter skin biopsies from the scalps of test animals and compares the proportion of growing and resting follicles before and after application of experimental compounds. He is also developing a computer system that provides enhanced views of animal scalps to ease objective comparisons of hair density.

But in many respects, living animals make poor models for hair growth experiments. The constant circulation of hormones, immune factors and other metabolic variables confound interpretation of an already complicated phenomenon. So researchers are increasingly turning to *in vitro* systems to decipher the molecular signals that trigger hair growth.

In one approach, researchers remove a few hair follicles from human skin and extract from each follicle about 10,000 outer root sheath (ORS) cells, which surround the hair root. They culture these cells along with dermal fibroblasts – a type of skin cell – gaining about 1 million ORS cells within two to three weeks.

These cells, when grown on a slab of collagen (a protein common in skin) and nourished with hormones and growth factors, differentiate into several kinds of cells, including trichocytes, or hair cells. But as with several other petri dish systems, the trichocytes fail to develop further into true hairs, reports skin researcher Alain Limat of Cosmital SA in Marly, Switzerland. Limat described his research in January at a conference on the molecular and structural biology of hair, sponsored by the New York Academy of Sciences.

In another approach, Michael P. Philpott and his colleagues at Cambridge University in England dissect follicles from the human scalp and culture them in tiny wells filled with a cocktail of nutrients. In what appears to be the first successful growth of hair filaments *in vitro*, the team has kept the system alive for up to 10 days, during which time the disembodied follicles produced hair shafts up to 3 millimeters long.

The researchers used their system to test the effects of cell-stimulating compounds such as epidermal growth factor, transforming growth factor alpha and transforming growth factor beta-1. Many scientists suspect that these and other factors, produced by various cells in the body, play regulatory roles in the hair growth cycle.

Indeed, Philpott's initial results suggest that at least some of these compounds are key elements determining the timing and duration of hair growth, although the details remain obscure. But not everyone agrees that Philpott's system represents true hair growth.

"I think you can be fooled very easily," comments one scientist, noting that previous *in vitro* hair growth "successes" have turned out to be nothing more than a bunch of epithelial cells lining up in formation.

"The problem is, epithelial cells have this habit of moving," says Harvard's Baden. "So there's always this question of whether there's really a new population of cells being created or whether these cells are just changing their shape or position."

In upcoming experiments, the Cambridge group plans to look for a wave of DNA synthesis moving up the length of the hair strand, which may settle questions of the system's validity, Philpott says.

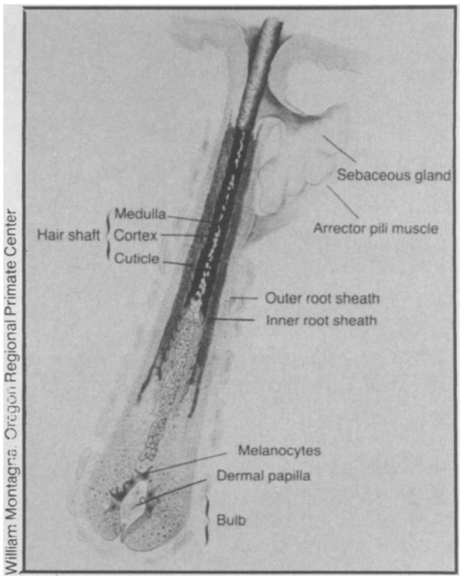
Meanwhile, a third technique shows some promise. Karen A. Holbrook of the University of Washington School of Medicine in Seattle places small pieces of human tissue from aborted 10-week fetuses in a liquid growth medium. After several days, the skin swatches naturally gather themselves into hollow, seamless balls and continue to grow.

In the following couple of weeks, the skin cells differentiate into the major cell types and tissue layers typically seen in developing fetuses, with hair follicles appearing on the outer surface. So far, Holbrook says, these follicles produce only "hair pegs" – stubby precursors to true hairs. But ongoing studies may suggest ways to push their development further, she adds.

With laboratory models of hair falling short of anything that might reasonably be called hirsute, other researchers argue that for now, at least, live animals remain the best systems for studying the biology of hair.

In one of the more bizarre attempts to study hair growth in rodents, researchers at the University of Dundee in Scotland have transplanted one foot pad from each of six rats onto the rodents' backs to make the hairless pads more accessible. (Foot pads don't have follicles.) Then they transplanted dermal papilla cells into each of the transplanted pads. All five foot pads that survived the procedure developed hair follicles, and three of the pads sprouted "beautiful hair fibers," says Dundee biologist Colin Jahoda.

"A lot of people want to grow more hair on their head," Jahoda says. "But we think that having produced hair fibers here, where hair never grows, is actually more significant." He says the work strengthens the argument that dermal



William Montagna, Oregon Regional Primate Center

papilla cells "contain the information that says, 'Make a hair,'" but it remains unclear whether dermal papilla cell transplants represent a practical means of adding hair to human heads.

In other experiments that may shepherd in a new era of rational textile design, Australian researchers at the CSIRO Division of Animal Production in Blacktown, New South Wales, have begun altering the DNA of mice and sheep in hopes of learning how to enhance wool production. "Our ultimate aim is to produce transgenic sheep that produce more wool and also to make fibers with new chemical and physiological properties for the textile industry," says CSIRO researcher Graham Cam.

Cam and his colleagues are experimenting with genes that increase follicular production of glucose and sulfur-containing amino acids critical to keratin formation. By placing these genes under the control of other hair-related genes, they hope to boost wool production using the animals' own genetic machinery.

Recently, the Australian team inserted a cell-proliferation gene called N-myc alongside a gene that regulates keratin synthesis in mice. But the genetically supercharged DNA proved fatal to most members of the first experimental litter, and the two surviving mice showed no obvious improvements in coats.

With failures like these far outnumbering successes, researchers concede they face tough challenges as they investigate the nature of hair and attempt to control its growth. The picture appears even more complicated, some note, as evidence accumulates that some hormones and growth factors that stimulate hair growth at certain times or in certain parts of the body also *suppress* that growth at other times or in other parts of the body.

But in the long run, the work promises a host of human benefits that extend beyond the development of anti-balding agents. Not least of these, says Yuspa of the National Cancer Institute, is the resolution of several cancer-related problems.

"We got into the field out of the question of whether epithelial cancers originate in the follicle cell or the [surrounding] skin cells," he says. "This has been a question that has been nagging us for 20 years."

Hair studies may shed light on other aspects of cancer, too. "Hair growth resembles tumor growth," Yuspa says. For example, when follicles regenerate after a resting phase, they penetrate the outer layers of skin in much the same way as cancer cells invade surrounding tissues.

Insights into the mechanisms of follicular invasion and the regulatory molecules that limit its extent may help scientists block the uncontrolled epidermal invasion characteristic of skin cancers, Yuspa says. "Ultimately, cancer is our goal. But you can't understand cancer unless you understand normal."

Then again, when it comes to hair, "normal" isn't always desirable. Should baldness – normal among aging men – be considered a "problem"?

"I don't really think it's a problem," Yuspa says. But a look at his thick-cropped head of hair suggests to some that he may not be the best judge. □

Hair in hibernation

While some scientists scratch their heads wondering what makes hair grow, others seek to learn what makes it stop. Most researchers believe that cyclic changes in circulating hormones trigger the periodic resting phases experienced by all hairs. But Walter Gibson has another idea.

Gibson, a senior scientist at Unilever's Colworth Laboratory in Sharnbrook, England, proposes that immunologic factors may lie at the heart of hair's periodic hibernation. The evidence remains largely circumstantial, but Gibson points to several findings consistent with the hypothesis.

For example, many diseases of hair growth have an immunologic basis – including alopecia areata, which leaves patches of baldness on parts of the scalp and face. And the immune-damping drug cyclosporin A stimulates hair growth in many people who take it, suggesting the immune system might help suppress hair growth.

Last January, at a scientific meeting on hair growth biology, Gibson described some of the latest and perhaps best evidence for immune involvement in hair's resting stage. Using a panel of antibodies that detect and label immunologic markers on cells, Gibson found that during the resting phase, hair cells in the follicle sprout class II MHC antigens – cell-surface markers that can trigger an attack by the immune system. Around the same time, connective tissue surrounding the follicle becomes disrupted, and scavenging white blood cells called macrophages move in very close to follicular cells. These findings suggest that hair cells, in response to some unknown signal, sprout markers that induce their own demise.

Gibson adds that he's puzzled by an apparent lack of class I MHC antigens on rapidly dividing hair cells during hair's growth phase.

"This is a very intriguing finding," since almost every other kind of cell in the body – with the notable exception of some cancer cells – bears these antigens, he says. The markers essentially tell the immune system: Don't attack us; we belong to this body.

Gibson suggests that the body's routine toleration of these antigen-lacking cells may indicate that the hair follicle remains immunologically "privileged" during hair's growth phase, sealed off from routine immune surveillance. In this scenario, the breakdown of the follicular wall and the apperance of immune-antagonizing antigens at the end of a growth period may represent key hair-growth-suppressing events, suggesting that scientists may someday use immune-altering drugs to prevent baldness or enhance hair growth in people and other animals. – *R. Weiss*