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Future Hair Loss Treatments

Future hair loss treatments address many of the limitations of the cosmetic, medical, and surgical treatment methods currently in use, and will include some entirely new treatment methods such as hair follicle cloning and gene therapy, both of which are methods that have the potential to actually "cure" inherited pattern baldness permanently.

But it also seems reasonable to ask why human society would spend precious biomedical research effort and limited funds on hair loss treatments, when deadly and debilitating conditions such as AIDS, cancer, diabetes, and heart disease also need solutions. While economic concepts such as a "free market" and "supply and demand" are a couple of answers, it also happens that the human hair follicle is a rich scientific model for understanding important aspects of human cell biology, organ system developmental biology, immune response medicine, the process of controlled cell regeneration and differentiation, and, especially, human genetics.

A unique feature of hair follicles is the way these miniature hair-growing organs cycle through growth and rest cycles. In addition to hairs being grown and then shed in these phases, the follicle itself disintegrates almost entirely by the end of the regression phase, and an almost entirely new follicle is created at the beginning of the next growth phase. The creation of a hair follicle at the beginning of each growth phase presents unique opportunities for applying advanced molecular biology medical techniques such as cloning and

gene therapy. The more we unravel the working of different parts of the human body, the more we find that everything is connected, and what we learn in one area of medicine can inevitably be applied to many other areas.

The Future of Cosmetic Treatments for Hair Loss

Cosmetic treatments for hair loss are by definition impermanent and reversible, so those aspects of cosmetic treatments will not change in the future. But other improvements will certainly be made. In the future, there will likely be hair-styling products that give a much more powerful appearance of a full head of hair, when compared to today's hair-thickening gels and hair shaft-coating mousses. Hairpieces and wigs currently have the disadvantage of expensive and time-consuming ongoing maintenance and replacement, and their use continues to include a significant fear of detection. In the future, cosmetic hair appliances such as hairpieces and wigs will likely be constructed of even finer and more durable materials, which will appear and feel even more genuine and be even less detectable. Attachment methods will continue to be very secure, but may also become easier and faster to release, reducing maintenance effort, and improving hygiene.

The Future of Medical Treatments for Hair Loss

Most of today's medicines for treating hair loss have limited effectiveness. Currently, we don't have a complete understanding of exactly why certain diseases cause hair loss. In many cases, we treat the symptoms, but not the causes of diseases. And often our ability to treat symptoms has limited effectiveness. There may be medications and treatments we are not yet aware of today that will be available in the near future. One may be treatment with a laser light apparatus or the laser comb. As of this writing, there are several reputable physicians who claim to have good results with this kind of apparatus. I have not been convinced thus far; time will tell. The same subject has been discussed with bogus treatments, Chapter 6.

Today's medications prescribed to counteract androgenetic alopecia (genetic pattern hair loss), require ongoing use for the benefits of treatment to continue, and these medications have only a limited effect on some patients. The cost of drugs, which must be taken on a continuing basis, adds up to a substantial lifetime expense. In the future, as physicians and scientists gain a better understanding of how the normal hair growth cycle is controlled and how various disease conditions affect hair growth, new medicines will be developed that more effectively target the cause of the hair loss and cause fewer side effects.

Perhaps the most promising near-future medical treatment for genetic pattern hair loss in men is GlaxoSmithKline's drug dutasteride, which as of this book's publication date has now received U.S. FDA approval as a prescription medication for treating enlarged prostate glands. Like Propecia, dutasteride is a 5-alpha-reductase inhibitor taken as a pill, and it has been shown to reduce dramatically the amount of testosterone in the blood from being converted into dihydrotestosterone (DHT). High levels of DHT in the blood over many years can cause enlarged prostate glands in men. DHT in the bloodstream also signals hair follicles to reduce hair growth, causing pattern baldness in people who have inherited hair follicles that are sensitive to DHT.

After three years of experience using dutasteride, more and more doctors are using it to treat patients who continued to lose hair when they were on Propecia. Those men who failed to stop their hair loss with Propecia, when put on Avodardt (which is dutasteride) have a greatly increased chance of stopping the balding process. Every man should be given the chance to be on finasteride (Propecia) first before transitioning to dutasteride. As stated earlier, women may well benefit from dutasteride because it effects type I alpha-reductase. No other medication we currently know of does that.

Reducing DHT in the blood causes the chemical message to "stop growing hairs" to become weaker, to a degree that it will not affect the susceptible hair follicles. The trick to reducing DHT levels is to use a medication to stop the 5-alpha-reductase enzyme from converting testosterone into DHT. If testosterone is not converted to

DHT, the DHT message never gets to the cells in the susceptible hair follicles, and these hair follicles will continue to grow new hairs.

There are two types of 5-alpha-reductase that convert testosterone to DHT. While Propecia effectively blocks the type-II 5-alpha-reductase enzyme, dutasteride has been shown to effectively block both type-I and type-II 5-alpha-reductase. While Propecia use typically results in a sixty to seventy percent decrease in DHT in the blood of men, dutasteride has been shown to decrease DHT in the blood by ninety percent or more. I am optimistic that dutasteride will work better for females with inherited pattern hair loss than any other medication currently available, as well as for men who did not get good results from Propecia. Side effects of dutasteride are believed to be similar to Propecia. The dosage appropriate for treating genetic hair loss has not been determined, and side effects are dosage-related.

One way to increase the effectiveness of hair loss medications, and simultaneously reduce side effects, is to target the cells causing hair loss. In the future we will have topical lotions applied to the scalp that more effectively block the DHT message from getting to hair follicle cells. Medications in pill form such as Propecia and dutasteride affect DHT levels in the blood, which in turn affects the amount of DHT in scalp tissue, which in turn affects DHT concentrations at the cellular level in hair follicles. As a result of treating the entire system with the medication, unwanted side effects can occur in areas other than the hair follicle cells.

In the future we will be able to better affect the DHT levels in the cells in the hair follicles, and as a result better control hair loss, and reduce unwanted side effects. Maybe medications of the future will be combined with shampoos or hair conditioners, and these products will become a common way to keep hair from falling out, just as fluoride in toothpaste is now used to help prevent teeth from falling out.

There will also be advances in medications for treating hair loss conditions other than genetic pattern hair loss. In the future we will develop new drugs that will more powerfully signal certain cells in the hair follicles to start or remain in the anagen (growing) phase, and continue to grow hair, even when they get other signals to shut down,

such as from sudden stressful events. And we will make advances in medications for treating diseases that cause both temporary and permanent hair loss.

Diseases and conditions that cause temporary hair loss are called non-scarring alopecias by doctors. These diseases do not seem to harm or scar the hair follicle in a permanent way. The hair is lost, but it either regrows all by itself, or with the right chemical signals, can be made to regrow. Alopecia areata is a non-scarring alopecia. Some alopecia areata patients have been able to regrow hair even after years of constant hair loss. Hair loss resulting from chemotherapy, and moderate doses of radiation treatment, are also non-scarring. Hair shafts that are pulled or plucked from the follicle do not permanently damage the follicle. After being plucked, the follicle rests and recovers, and a new hair bulb is grown, and it then grows a new hair.

Non-scarring alopecias affect the "bulb" portion of the hair follicle, which is located at the base of the follicle deep in the skin. The specialized cells in the bulb do the work of growing the hair shaft for four to six years during each hair growth cycle, but at the end of the growth cycle they seem to deteriorate as the hair follicle shrinks in size and enters the resting stage of the normal growth cycle. New hair follicle bulb cells are then produced at the beginning of the subsequent growth cycle. Future medications that effectively target or protect the cells in the bulb of the hair follicle may result in more effective treatment for alopecia areata, as well as less hair loss from stressful events and cancer treatments.

Diseases that cause permanent hair loss are called scarring alopecias, because the disease alters or scars the hair follicle in such a way that it loses the ability to grow new hairs. Some scarring alopecias, such as lupus erythematosus and lichen planopilaris, trigger an inflammatory immune response where the body's white blood cells attack cells in the "bulge" area of the hair follicle. The bulge area is located near the middle of the hair follicle, below the sebaceous (oil) gland and near the attachment point for the arrector pili muscle (the tiny muscle that allows hairs to "stand on end").

Androgenetic alopecia (genetic pattern hair loss) is also considered to be a scarring alopecia, as it diminishes hair follicle production over time until no new hairs are grown. New research has suggested

the area of inflammation in these permanent hair loss diseases is the "bulge" portion of the hair follicle, and certain cells in the bulge area are believed to be responsible for regrowing the hair follicle at the beginning of each new growth stage. It is believed that at the beginning of each growth stage, certain cells in the bulge produce the cells in the bulb, which in turn grow new hairs. When the cells in the bulge area are sufficiently injured, the hair follicle is not able to grow a new bulb, and no new hair is produced. In the future, medications that protect the cells in the bulge area of the hair follicle will more effectively treat permanent hair loss diseases, including genetic pattern hair loss.

The Future of Surgical Treatments for Hair Loss

Surgical treatments available today are limited in effectiveness because no new hair is added. Current surgical methods simply cannot produce a full head of thicker hair. The art of surgical hair restoration is rearranging the patient's existing DHT-resistant hair follicles for an appearance that looks fuller. But no new hair is added. Current surgical methods are very labor intensive and costly, and include the minor discomfort of recovery following surgery. The obvious key to improving surgical treatment is cloning hair follicles. Successfully cloning multiple hair follicles from a donor area follicle that is already programmed to continue to grow new hairs for a lifetime will result in a limitless supply of hair transplant grafts, which translates into limitless hair thickness. The cloned follicles may even be individually injected directly into the scalp, eliminating surgery altogether.

If scientists can already clone an entire sheep, why isn't human hair follicle cloning a commercial reality? The answer is somewhat complicated, and requires some explanation of cell biology, genetics, cell replication, and then a review of some of the different types of cloning that may apply in the future to mass duplication of human hair follicles.

Cell Biology

Cells are the basic units of all living organisms. Cells in a multicelled organism have specialized characteristics that enable them to

most efficiently do their particular jobs. Individual cells in an organism work together with other similar cells in tissue, or they work together with different types of cells in specialized cell structures called organs. For example, in a hair follicle, which is a miniature organ, there are several different types of cells working together to grow a hair.

Inside of just about every mature cell is a structure called a cell nucleus that contains chromosomes composed of double strands of twisted DNA molecules. DNA molecules contain information about creating particular types of proteins, and the cell uses that information to make the proteins that allow it to perform its particular function. Some proteins are structural, such as keratin protein in hair, while others have the function of sending messages, such as the hormone DHT, and some proteins such as the enzyme 5-alpha-reductase, help convert proteins from one form to another.

Genetics

Sections of DNA molecules that contain the code for particular types of proteins are called genes. That's all genes are: instructions for making specific proteins. There are no genes for particular body characteristics—such as "pattern baldness" or "green eyes" or "curly hair"—only instructions for making proteins. But the particular types of proteins that genes instruct cells to make, in turn determine characteristics such as inherited hair loss and eye color and hair curling. Usually many different genes, and many different proteins, together determine particular inherited body characteristics.

Unlocking the DNA information in mature specialized cells is an important aspect of some cloning techniques. This is because a remarkable feature of cells in a multi-celled organism is that each one contains in its chromosomes a complete DNA blueprint of all the genes for all the proteins for the entire organism. In theory, any cell from an organism could be used to clone the entire organism. But actually doing this with a mature specialized cell is very difficult. Individual cells only use the protein-making information that they need to do their particular job, even though they contain the protein-making information for the entire organism. For example, cells in the iris of the eye may make the proteins that express the characteristics

for green eyes, but not the proteins that could cause pattern baldness or curly hair. The information to make proteins that result in pattern baldness or curly hair is contained in the iris cells. They just don't express those proteins. Other cloning techniques require unspecialized cells called stem cells for the desired results. To understand the difference between using mature specialized cells or stem cells from cloning, we need to examine the process of cell replication.

Cell Replication

In a rapidly growing embryo, cells replicate by splitting in half and then growing to full size again. This process is called cell mitosis, and each half of a cell that splits containing a complete and exact set of the organism's DNA. As the embryo grows into a more fully functioning organism, its cells begin to take on more specialized characteristics, and begin to divide less. As cells become more specialized, cell replication shifts to special precursor cells called stem cells.

Mature specialized cells do not replicate easily, probably as a defense against cancer, which is characterized by uncontrolled cell division. But all cells wear out over time, and have to be replaced by new cells. Some cells only last for days; others for years, and others for decades, but eventually all cells wear out. The inability of mature cells to replicate themselves limits the body's ability to repair itself, to heal wounds and to replace aging cells. It also makes the process of cloning more difficult.

In mature organisms, undifferentiated cells called stem cells are responsible for replacing old or injured specialized cells. Stem cells are present in all self-repairing tissue, but most stem cells are difficult to detect in a mature living organism. Stem cells in a mature organism are like embryonic cells, in that they can create many different types of specialized cells. When stem cells are not actively making new cells, they divide infrequently, which reduces the risk of undesirable DNA mutations. But when they are signaled to make new cells of a particular type, they produce typically short-lived intermediate cells called transient amplifying cells, which in turn engage in rapid cell mitosis and create the specialized cells that the organism needs.

For a quick review, we've learned that cells make up tissue and organs, which make organisms. The DNA in cells contains genes that

are instructions for making proteins, and these proteins determine specialized cell characteristics and functions. Specialized cells in turn, determine characteristics of an organism, including inherited characteristics, such as resistance to the hormone DHT, for example. Specialized cells do not easily replicate themselves. When an organism needs new specialized cells, stem cells are signaled to create transient amplifying cells, which in turn make the needed specialized cells.

Types of Cloning

Cloning is the process of reproducing cells, organs, or entire organisms from a single parent, in contrast to sexual reproduction, which involves the mixing of DNA from both parents. Cloning results in offspring that have an exact copy of the DNA of the single parent. This is desirable if the parent's DNA has desirable characteristics, such as hair follicle cells resistance to DHT. There are many different types of cloning that may apply to hair follicles, including the DNA manipulation type that produced Dolly the Sheep; the "splitting hairs" method; the process of replicating mature cells; and growing new organs from stem cells. Each of these four methods will be described and evaluated as a possible basis for commercial hair follicle cloning.

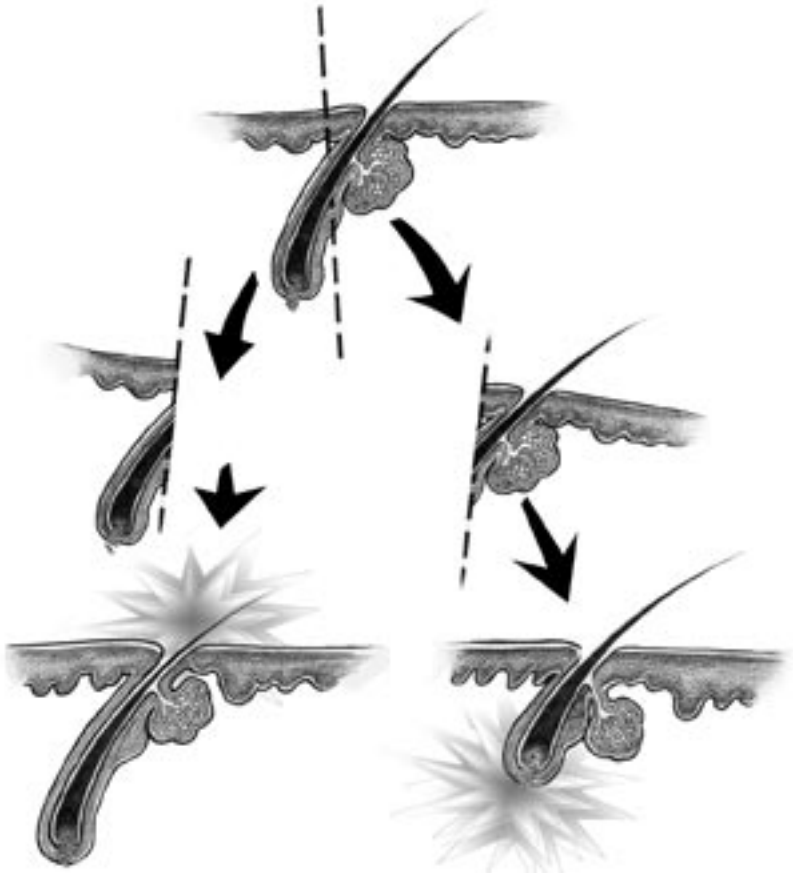
Dolly the Sheep Cloning Method

In 1997, Dolly the Sheep became the most famous cloned animal. DNA was removed from an unfertilized donor sheep egg cell, and then was replaced with DNA from a mature cell removed from Dolly's parent. An unfertilized egg has only half of the DNA needed to grow into an organism. The other half comes from the sperm cell. But Dolly's egg received a full set of DNA from a mature cell. The egg was fooled into thinking it was fertilized, and that it should grow into an organism. The egg cell grew into an embryo, and eventually into a sheep that was an exact genetic copy of Dolly's parent, since it had the exact same DNA. This was the first time a large mammal was grown from DNA taken from a mature cell, using that cell's entire DNA blueprint to make a new organism. The process is much more involved than this summary describes, and there were many failures

along the way. But if we just want some hair follicles, cloning an entire living organism from a donor cell is a bit excessive. While a fascinating genetic exercise, the Dolly the Sheep method is too complicated and costly for commercial hair follicle cloning. Another method, which is inadvertently used in almost every micrograft hair transplant procedure, is a lot easier.

The Splitting Hairs Method of Cloning

Hair restoration surgeons have long known about the "splitting hairs" method of cloning hair follicles, and it is a much less complicated process than the Dolly the Sheep method. Surgeons have observed that when a hair follicle is accidentally cut in half, one piece,



Cloning follicles by "splitting hairs"

and sometimes both pieces of the follicle, will survive and grow a new hair if the follicle is transplanted back into the donor. Micrograft surgeons routinely place cut follicles back into the patient's scalp, although they don't generally "count" the cut follicles as "grafts." Each fractional follicle is an exact DNA clone of the original, so if the original follicle is DHT-resistant, the clones will also be DHT-resistant.

If a follicle is cut in half to form top and bottom pieces, and both pieces are placed back in the scalp, the bottom half (with the hair bulb) will sometimes survive and grow a hair. The top half (with the bulge) will sometimes survive and grow a new bottom half containing a new hair bulb, and that half also eventually grows a new hair. This process is similar to the hair follicle creation that occurs at the beginning of the normal hair follicle growth phase. If the follicle is cut lengthwise, two surviving follicles can result, although they may produce finer hairs than the original full-size follicle.

Survival rates of transected hair follicles is lower than follicles that are not cut in half, so hair restoration surgeons continue to take great care to avoid cutting follicles. The reason the splitting hairs methods works when the cut follicle pieces are placed back into the scalp, is that other nearby hair follicle stem cells probably help with the cell regeneration process. But with improved methods to signal cell regeneration, and ultimately improved transected follicle survival rates, this crude cloning technique has some promise for the immediate future.

Mature Cell Cloning

Commercially cloning of undifferentiated stem cells for research purposes has been around for a few years. Recently the commercialization of cloning mature skin cells has been accomplished. On June 20, 2000 the U.S. FDA approved Organogenesis Incorporated's Apligraf, a skin patch product containing living human skin cells. To make an Apligraf patch, human skin cells derived from infant foreskins are cultured in a growth medium and are allowed to differentiate into some of the types of cells that form mature human skin. Apligraf skin does not contain pigment cells, blood vessels, sweat glands, or hair follicles, but it does have the types of cells that are

typically found in the upper and lower layers of skin. It is approved for use as a wound dressing for slow healing skin ulcers.

Replicating skin cells is much less complicated than replicating entire hair follicles. The approval and commercialization of this mature cell cloning process is very encouraging for future hair follicle cloning. Because hair follicles are miniature organs composed of several different types of specialized cells, they are difficult to clone and even more difficult to assemble properly. The trick to hair follicle cloning will be signaling hair follicle stem cells to make and assemble all the cells needed for a hair follicle.

In 1993, United Kingdom researchers Jahoda and Reynolds published a paper in *The Journal of Investigative Dermatology* describing their success in growing a rat whisker in a live rat from cultured rat dermal papilla cells. The dermal papilla cells are found in the hair matrix in the bulb of the hair shaft, and they are the cells that grow hairs. For many years it was believed that the hair follicle bulb contained the stem cells necessary for hair follicle growth. The researchers removed dermal papilla cells from a rat whisker hair follicle bulb, cultured the cells in a growth medium, and created thousands of dermal papilla cell clones. After they had enough dermal papilla cells, they implanted the cultured cells back into the rat, but they placed the cells in the skin forming the rat's ear (so they could better see any results). The cloned dermal papilla cells interacted with neighboring skin cells and made a hair follicle that eventually grew a rat whisker. The researchers patented this procedure of growing hair follicles in a living organism with cloned dermal papilla cells. (Jahoda and Reynolds, *Journal of Investigative Dermatology* (101:634-638, 1993) (also 115:587-593, 1992)

In 1994, *The Journal of Dermatological Science* published a paper by the same researchers, Jahoda and Reynolds, describing their success using a cell culture medium to grow a crude but functioning rat hair follicle from cultured adult hair follicle cells. The researchers cultured four different types of cells found in rat hair follicles, and using a framework of other living cells, assembled them into somewhat unusual hair bulb structures that grew irregular but recognizable hair shafts. This appears to be the first example of growing "test tube" hair follicles outside of a living organism.

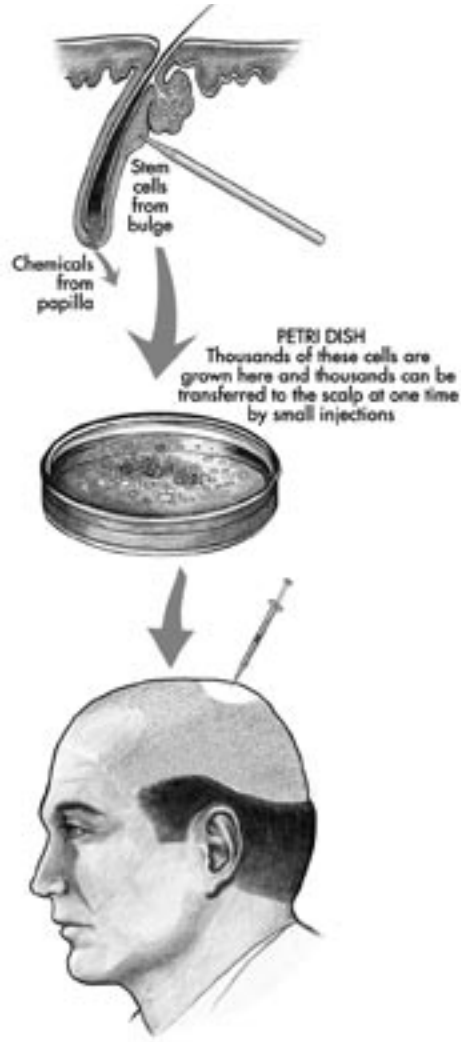
In 1996, hair restoration surgeon Jerry Cooley, MD successfully grew human hair follicles from cloned dermal papilla cells in a human. He cultured dermal papilla cells from hair follicle bulbs surgically removed from his own scalp, and after multiplying the cells in a culture medium, implanted the cloned cells back into his own forearm, and a new hair follicle formed and grew a scalp hair.

In 1998, Dr. Conradus Ghosal Gho of the Netherlands patented with the World Intellectual Property Organization, a "Method for the Propagation of Hair", in which he describes a method of plucking hairs in the anagen (growth) phase, and culturing the dermal papilla cells from the portion of the hair bulb at the end of the plucked hair. He describes using commercial cell culture media along with various beneficial additives such as amino acids, vitamins, trace elements, growth hormones, and antibiotics. His patent seems to imply that the best results are achieved by also adding cloned CD34+ progenitor cells, a type of stem cell, to the culture. Presumably these would be obtained by surgically removing a tissue sample from the donor, and culturing the stem cells separately, so they could be added to the dermal papilla cell culture. Alternatively, the CD34+ cells may be obtained commercially. After the dermal papilla cells and CD34+ cell mixture has multiplied and differentiated into the different types of cells that make up hair follicle, Dr Gho injects packets of the cloned cell mixture into the donor's scalp, where they develop into new hair follicles and grow new hairs. Dr. Gho also describes using an electronic repeating injection metering apparatus such as an insulin pen to rapidly and precisely insert the cloned cells into the scalp. Dr. Gho is currently working to refine and improve his method.

It seems that it won't be long before cloning thousands of whole human hair follicles in "test tubes" becomes a commercial reality. Or will it? There are still plenty of obstacles to overcome before commercial hair follicle cloning is a reality. The method of cloning dermal papilla cells from hair bulbs and injecting them back into the donor's scalp has not been perfected. Do the hair follicles created from cultured dermal papilla cells cycle through the normal growth cycles, and continue to grow new hairs for a lifetime? What are the chemical signals in living skin that tell the dermal papilla cells to grow into a hair follicle in the first place? If we knew more about how the hair

follicle growth cycle functioned, maybe we could improve the results of injecting cloned cells to make hair follicles. Or perhaps we could clone cells into entire hair follicles in "test tubes" and achieve better results than injecting packets of cloned cells.

The Wall Street Journal May 4, 2005 had an article on hair cloning in which they stated Dr. Unger of Toronto and Dr. Gho of the Netherlands both have patents on hair cloning and although it has worked in mice, "It's likely to be years before someone as bald as actor Bruce Willis will be able to walk into a doctor's office, donate a few hairs for multiplying, return for scalp injections ten days later and end up with a full head of hair in a matter of months."



More answers to the future of hair follicle cloning appear in work done over the last decade by Dr. Robert Lavker and his associate Dr. George Cotsarelis, both of the Department of Dermatology at he University of Pennsylvania School of Medicine.

In a paper published in 1990 in the journal *Cell,* Cotsarelis showed that hair follicle stem cells were located in the bulge area of the follicle, midway up the hair shaft, rather than in the bulb area at the base of the hair shaft. The bulge area is located near the middle of the hair follicle, below the sebaceous (oil) gland and near the attachment point

for the arrector pili muscle (the tiny muscle that allows hairs to "stand on end").

The April 2004 issue of *Nature Biotechnology* published research findings from the University of Pennsylvania School of Medicine that had isolated stem cells responsible for hair follicle growth within the follicle bulge. In studies involving adult mice, transplanted stem cells made new hair follicles that produced new hair within four weeks. According to research director Cotsarelis, isolating the stem cells responsible for hair growth—which are there throughout the lifespan of an organism and have tremendous capacity to regenerate and proliferate—is the first step to developing targets for manipulating hair growth. Researchers at the Penn Hair and Scalp Clinic hope to eventually isolate stem cells in adult humans and transplant those cells to other areas of the scalp, generating new follicles and hair growth, but the treatment is a good ten years away.

On behalf of the Trustees of the University of Pennsylvania, Lavker has registered several patents for methods for regulating hair growth. In a 1996 patent filed with the World Intellectual Property Organization (and cited by Dr. Gho in his patent two years later), Lavker describes a hair follicle bulge activation theory, in which the dermal papilla cells activate the stem cells in the bulge in the late telogen (resting) stage of hair growth. This is the point at which the dermal papilla cells move upwards and next to the bulge area of the follicle, after the follicle has shed the old hair and has shrunk in size. Once the stem cells are activated, a new hair follicle growth cycle begins, the follicle grows to full size, and a new hair bulb forms to grow a new hair.

Lavker states that the hair matrix cells are in fact transient amplifying cells; intermediate cells created by stem cells to rapidly grow other specialized cells, in this case those that make up a hair shaft. The 1996 patent describes growth-modulating molecules that are created by hair follicle cells and which undergo hair-cycle-dependent concentration changes in the hair follicle. One such molecule is a protein called glia-derived nexin 1, which has also been shown to play important roles in regulating a variety of types of cellular growth and differentiation.

Lavker's 1996 patent claims applications in modulating hair growth, as well as for growing hair follicle cells outside of a body with a selected growth-modulating molecule, and combining the expanded cells with selected dermal papilla cells to grow hair.

In a year 2000 paper published in *Dermatology Focus,* Cotsarelis reveals that he is working on cloning hair follicle stem cells in cultures, and that once the molecular events responsible for the cycle of hair follicle growth is unraveled, cloning entire hair follicles will be closer to reality.

This research suggests that the most likely method for commercial hair follicle cloning is not cloning dermal papilla cells, but the cloning of hair follicle stem cells collected from the bulge area of DHT-resistant hair follicles. These stem cells will be combined with proteins that provide the right molecular signals to tell the stem cells to generate transient amplifying cells in the form of a hair bulb, which in turn will grow a new hair.

Once these details are figured out, thousands of full-size "test-tube" grown hair follicles can be self-assembled from cloned DHT resistant stem cells. The cloned hair follicles could be grown in a standard size and shape, perhaps in a tray that can be directly loaded into an automatic graft placement device. Automated graft placement devices, such as Choi Transplanter developed by Yung Chul Choi, MD in Korea in 1990, use a hollow needle to create a tiny recipient site of the proper depth for the graft, and then automatically insert the graft into the opening.

There will still be some problems associated with cloning. One is an increased risk of cancer. The growth-inducing chemicals such as tetradecanoylphorbol acetate (TPA) used to stimulate cellular proliferation for cloning frequently promote tumors and cancer. While cancer risk is low for most cloned cell products, cloning hair follicle stem cells is riskier.

Dermatologists have observed that many basal cell carcinomas, a type of skin cancer that is the most common human tumor, seem to originate from the hair follicle. Cotsarelis notes in the 2000 paper presented in *Dermatology Focus:* "...the fact that basal cell carcinomas are slow-growing tumors composed of poorly differentiated cells that have the ability to differentiate into various adnexal structures

strongly suggests that the cell of origin is a pluripotent, slowly cycling stem cell with a highly proliferative potential." What he's saying is that molecular and genetic evidence points to the hair follicle stem cell as the source for this common form of cancer. Cloning hair follicle stem cells with cancer-inducing chemicals will require many years of study to assure the safety of the cloned follicles that result.

Hair Multiplication— Scalp Impregnation Therapy

This cell based, tissue engineered treatment for hair loss is touted as the "Holy Grail" of hair restoration. The term "hair multiplication" was coined by Dr. Gho of the Netherlands. In theory, this minimally invasive high tech surgical procedure should deliver an unlimited supply of donor hair to the patient. Hair cells are extracted from a small donor site in the scalp, then cultured and multiplied in a lab. Balding areas are then replanted with the cultured cells suspension. Dr. Carl Bazan of Mexico offers hair multiplication under the proprietary name "Scalp Impregnation Therapy." A twenty-minute impregnation session—administering cultured hair cells suspension quantified in ounces—claims to yield up to 6,000 hairs with negligible discomfort. As with any new medical breakthrough, the results are yet undetermined and cost for treatment is high—ranging from $22,000 to 36,000.

Research conducted by Colin Jahoda of the University of Durham in England in the early 1990s demonstrated that the cells at the base of a follicle can and do regenerate into self-contained, pre-programmed hair factories. These cells mature into hair follicles through a process known as *follicular neogenesis.* In theory, if this technology can be perfected, it will solve the supply and demand scalp-harvesting problem. To date, however, Dr. Gho's experiments find only twenty percent of implanted cells maturing into follicles.

Interesting to note, the molecules responsible for telling a hair to grow are in the same family of molecules that tell the liver, the kidney, or even a full limb to grow. If science can figure out exactly what turns on the regeneration of hair follicles, the field of tissue engineering will be advanced and science may one day be able to help an amputee grow a new limb.

Dr. Walter Unger recently presented information regarding an ongoing study on culturing hair matrix cells to produce unlimited donor hair. His work with Dr. D. N. Sauder to discover what is required to culture and reimplant hair matrix cells has shown that they can now be produced fairly rapidly for all patients. They will be doing studies on the cultured cells in mice and hope to start testing in humans, but this will require ethical permission from the governing medical boards. Likely this will be available to the public in ten years time.

Gene Therapy

An even more advanced technique for solving inherited hair loss in the future is gene therapy. Gene therapy is the process of changing genes of existing cells in the body, and thereby altering cell function. It is a medical treatment still in its infancy, and there have only been a few recent examples of gene therapy working. But it is a potential future baldness treatment method worth exploring.

Gene therapy requires learning how an inherited medical condition occurs at the DNA molecule level, and then going in and fixing it. With gene therapy, the hair follicles with DHT-sensitive cells could be changed into follicles with DHT-resistant cells, and the hair follicles would continue to grow new hairs for a lifetime. But gene therapy involves several very difficult steps. The first step is figuring out which of the tens of thousands of genes on strands of DNA are involved in the characteristic to be altered, and the second step is figuring out how exactly the target genes are to be changed, so that they give instructions for making the slightly different proteins that will achieve the desired effect. The third step is getting the target cells in the living organism to incorporate the new and improved genes as replacements for the old undesirable genes.

Gene Identification

Figuring out which genes are involved in the genetic condition to be changed is not an easy task. Despite all the advances in mapping genes in recent years, we are still very far away from knowing what most of these genes do. We certainly do not have a good understanding of all of the genes that affect the cycle of hair growth, and espe-

cially which genes are responsible for inherited hair loss. It is most likely that several genes are responsible for making proteins that cause certain hair follicles to be DHT-sensitive.

Future studies will likely involve comparing the genes and resulting proteins in different follicles from a single individual. In a given individual with androgenetic alopecia (pattern hair loss), some hair follicle cells will express the characteristic of DHT-resistance (the follicles at the back of the scalp), while other hair follicles on the same person will express the characteristic of DHT-sensitivity (at the hairline, for example). Both follicles contain cells with identical DNA, but they express different characteristics. So identifying the responsible genes will be tricky. And even after we identify these genes, we have to figure out how to change them ever so slightly so they will make proteins that create DHT-resistant hair follicles.

Scientists have been making progress in gene identification. To identify genes that may participate in a given response, gene arrays profiling is used to determine the genes that are differentially expressed. To use this molecular knowledge for enhancing protection and repair, it is necessary to over express the genes of choice. Future identification of genes that are important for protection and regeneration, along with improved gene transfer technology, will allow the use of gene therapy for treating a wide range of hereditary disease.

Modifying Genes

In a paper presented in the January 30, 1998 issue of the journal *Science,* researchers led by Angela Christiano PhD., identified a defect in a single gene responsible for a rare type of inherited baldness called generalized atrichia observed in a Pakistani family, in which affected individuals are born with infant hair that falls out and never grows back. Shortly after birth, affected individuals are completely hairless. The gene, called *hairless,* was mapped in humans to chromosome 8p21, and was the first example of a single gene defect being identified as a hair loss cause. Christiano was careful to point out that this was just a first step towards identifying genes that affect hair loss. (*Science,* January 30,1998, Vol. 279, No. 5351)

Later in the same year, in a paper presented in the September 11, 1998 issue of *The American Journal of Human Genetics,* Christiano's

team reported on members of a family of Irish Travelers who also exhibited congenital atrichia, in which affected individuals are born with infant hair that falls out and never grows back. Genetic analysis of the Irish Travelers revealed that a mutation of the hairless gene was again responsible for the hair loss condition. The mutation, however, was different from the one that resulted in hair loss in the Pakistani family.

In a paper reported in the November 25 1998 issue of *Cell,* researchers led by Elaine Fuchs PhD, induced the formation of new hair follicles in mice that were genetically engineered to constantly produce a stabilized form of a protein called beta-catenin. Beta-catenin is a multi-functional protein which signals a variety of cellular functions, but is normally quickly degraded within a cell after being produced. Researchers altered the mouse gene that contains instructions for making the beta-catenin protein in such a way that the beta-catenin produced was resistant to being broken down. The resulting accumulation of beta-catenin caused a massive growth of new hair follicles to grow in normal mouse skin, until there were hair follicles branching from existing hair follicles. Eventually the mice also developed hair follicle tumors as a result of over-expressing beta-catenin. (Fuchs, University of Chicago 1998) (Gat, *Dermatology Focus* Vol. 19, No. 2, Summer 2000).

In the October 1999 issue of *The Journal of Clinical Investigation,* researchers led by Dr. Ronald Crystal forced resting hair follicles of mice into the growth phase by exposing cells to larger than normal quantities of a protein produced by the Sonic Hedgehog Gene (abbreviated Shh).

The papers presented by these three groups of genetic researchers reveal the complexity of the task of understanding the genetic basis for inherited hair loss, and reveal the monumental task of figuring out how to correct the condition at the molecular level. In the first case, Angela Christiano's team identified a gene that can cause total hair loss when mutated in either of two different ways. In the second example, the team led by Elaine Fuchs mutated a gene in such a way that it coded for the creation of a slightly different protein that caused massive new hair follicle creation. And the third example showed that increasing the exposure to a naturally occur-

ring protein could signal hair follicles to shift from the resting phase into the growth phase. And while all of these genes and their respective proteins appear to play some role in hair follicles, they are also known to affect other cells and systems in the body. Genetics is very complicated.

But suppose that at some point in the future we develop an adequately complete understanding of how all the genes, and their respective proteins, affect inherited hair loss. And suppose that we can also determine how exactly we want to alter the genes so that the proteins they make result in hair follicles that are DHT-resistant, rather than DHT-sensitive, but without causing unwanted side effects.

Changing Genes in Living Cells and Living Organisms

The third challenge of gene therapy is delivering the new-and-improved genes to the target cells, and then to have those cells use the new genes to make the corresponding new proteins, and then to have the altered cells express the desired characteristic.

The correct target cells are critical to successful gene therapy. If mature cells are altered, the benefits of the gene therapy go away after those cells wear out and are replaced with new cells having the original DNA. For a long-lasting effect, stem cells are targeted. When successful, the altered stem cells will then create altered transient amplifying cells, which in turn will create altered specialized cells that will express the desired characteristics.

The most common altered gene-delivery method involves using crippled viruses to insert desired genes into the target cells. Outside of the laboratory, viruses are tiny organisms that infect cells by replacing some of the cell's DNA with virus DNA. After infection by a virus, a cell begin to make the proteins the virus DNA tells it to make, causing the expression of various diseases. Scientists use the virus infection mechanism to deliver desirable DNA.

First, they cripple the virus DNA so that it cannot reproduce or cause harmful effects, but is still able to insert new DNA into target cells. The desired genes are spliced onto to the virus DNA, and the

viruses insert the new DNA into the target cells. The viruses can be injected directly to the location where the stem cells are, or the stem cells may be cultured in a laboratory, altered by viruses containing the new DNA, and then the altered stem cells can be placed back into the organism.

There are many areas of gene therapy that need refinement. Identifying genes, determining exactly how to change them to code for the desired proteins, avoiding an immune response when the viruses are injected directly into the organism, getting an adequate quantity of target cells to take up the altered DNA regardless of how it is delivered, and getting the cells to express the characteristics coded by the altered genes, once the new DNA is inserted, all need more work. But progress is being made.

In summary, the future of hair loss treatment shows great promise, from new medications such as dutasteride to advances in cloning and gene therapy. But many of these treatments are years, and maybe decades away from commercial use. Current treatment methods, including cosmetic products, drugs such as Propecia, and surgical procedures such as follicular unit micrografts are available right now, if you really want to do something about your hair loss. Your first step should be scheduling an examination with a dermatologist knowledgeable about hair loss treatment.