

HAIR VITALITY LOSS, THINNING AND REPLENISHMENT

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The Hair Life Cycle

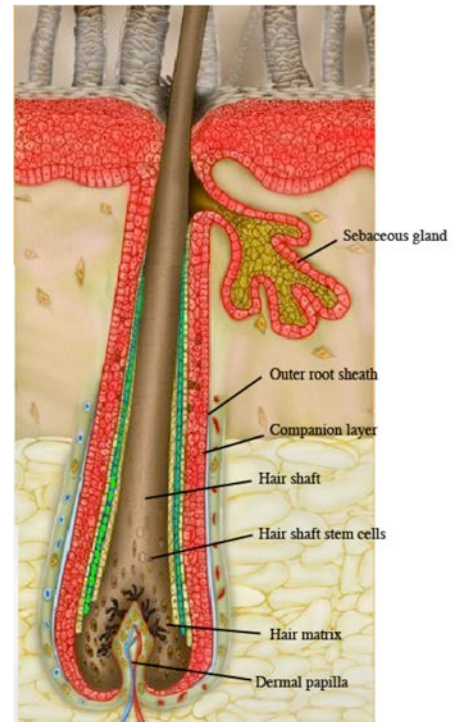
Hair follicles repeatedly go through stages in a cycle of growth and resting. It is the disruption of this cycle that results in excessive hair loss, or alopecia. The specialized cells in the follicle that become the hair shaft itself can be depleted during the resting or Latent phase in the hair cycle, resulting in fewer and fewer active follicles (and hair) over time.

ANAGEN. The hair growing stage is called Anagen. The bottom of the hair follicle (the bulb) is attached to the dermis and its blood supply through the dermal papilla. The precursor cells, called keratinocytes, and associated melanocytes multiply at the bottom of the bulb. The growing keratinocytes become part of the hair shaft. The upward pressure of the multiplying keratinocytes pushes the shaft up out of the follicle, where it appears as a hair. Hair grows outward from the bulb at about 1 cm per month. The Anagen phase lasts 3 years on average

but can vary from a few months to as much as ten years.

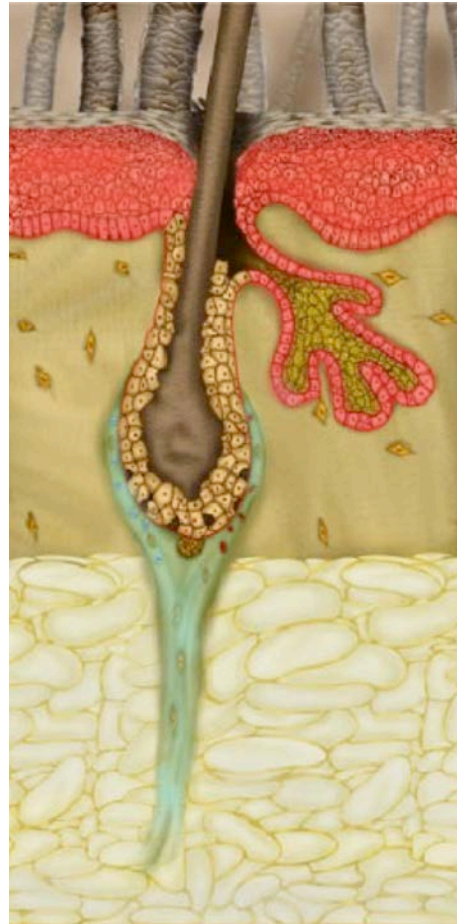
The length of time the hair follicle remains in Anagen, and keeps growing, depends on the signals it receives from the surrounding scalp and its blood supply. The cells that make up the hair follicle also communicate via the fibers in the Extracellular Matrix that provides the structure of the skin in the scalp. The hair follicle then enters the next phase of the cycle.

CATAGEN. When matrix cells in the hair follicle exhaust their proliferative capacity or chemical signals are received from the skin or blood, hair growth stops. The hair follicle begins to die and enters the CATAGEN phase. This process of programmed cell death or apoptosis, results in



the lower two-thirds of the hair follicle degenerating. The cells remaining form a pocket surrounding the old hair. This process occurs in a matter of a few weeks. The “bulb” of the hair follicle is drawn toward the skin surface via fibers in the Extracellular matrix, and essentially separates from the dermal papilla.

TELOGEN. In the Telogen phase, the remains of the hair bulb are inactive and the attached hair easily falls out. The telogen phase can last for 2 to 3 months. In the meantime, the dermal papilla remains attached to the remains of the bulb through the interconnecting network of the Extracellular Matrix. The fibers in this matrix maintain both a structural linkage and a chemical communication between the two components of the hair follicle.

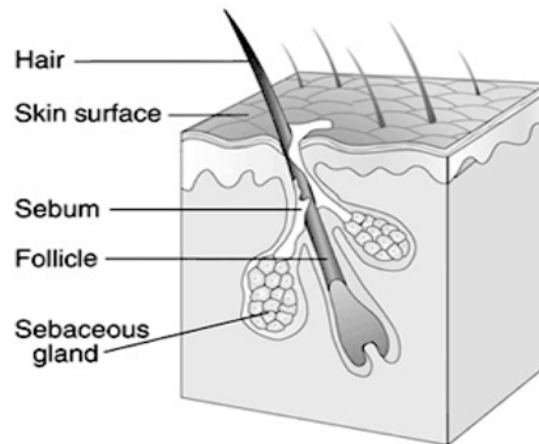


LATE TELOGEN. In the final phase of Telogen, lasting a few weeks, a chemical signal causes the “bulge” and dermal papilla to re-assemble within the scalp Matrix and form a new hair follicle around the empty follicle. Stem cells within their reservoir in the bulge begin to form new keratinocytes and the cycle starts over with a new Anagen phase. It is during the “re-awakening” process that stem cells can die and the hair follicles lose the capacity to form a new hair shaft. Preventing the loss of keratinocyte stem cells is extremely important to altering the course of hair loss and baldness.

What Causes Hair Loss?

The normal hair growth cycle is 2 to 6 years long. About 90 percent of the hair in the scalp is in a "growing" phase and 10 percent is in a "resting" phase. Some hair is lost every day as part of this growing and resting cycle.

Excessive hair loss is often caused by the male hormone testosterone which interacts in the scalp with the enzyme 5-alpha reductase to form the aging-bio-marker DHT, or Dihydrotestosterone. This transformed hormone signals the hair follicles in the scalp (by a mechanism that is not yet understood) to begin a process called follicular miniaturization. This course of hair thinness and loss sometimes begins as early as puberty, and about a quarter of men begin to show symptoms by age 30, while two-thirds of men over 60 are either bald or show a balding pattern. This form of "Pattern Baldness" is a primary cause of baldness, although exposure to environmental factors and UV light can also contribute significantly to hair loss.



Solar radiation and associated Reactive Oxygen Species (ROS) in the skin of the scalp activate a breakdown in the number of cells that produce hair, as well as the destruction of elastin and other Matrix Proteins surrounding and supporting the hair follicles. As these destructive elements impact the cells in the scalp, they trigger the initial effects of balding. The hair follicles become smaller. Hair loses its color, and the hair shafts become thin, fragile and begin to resemble peach fuzz. That's why it is important to maintain the health and vitality of your scalp and hair – it's much easier to keep the hair you have than it is to regrow the hair you've lost. NuLastin provides nutrients to your follicles that help maintain follicle health, including Recombinant Human Tropoelastin, or Elastatropin., to replenish the essential elastin in your scalp that supports, maintains and connects it's network of hair follicles and healthy head of hair.

Treatments for Baldness

Balding and baldness can be treated by topical and oral drugs, as well as surgery, weaves, wigs and hair pieces. The is also the widely-used, and derided, "comb-over" hair style. Propecia® (finasteride) is a once-a-day pill that is effective as a treatment for hair loss. This drug blocks the 5-alpha reductase enzyme responsible for the production of DHT in men showing the symptoms of male pattern baldness. Up to 3 months of daily dosing with Propecia can be required before results are evident. Taking Propecia can result in some side effects.

Women who are pregnant or may become pregnant cannot even handle Propecia tablets because of the risk of birth defects. Some men show a decrease in sexual desire, difficulty in achieving an erection, or a decrease in the amount of semen produced. Propecia is temporary. When Propecia is stopped, the patterns of former baldness return.

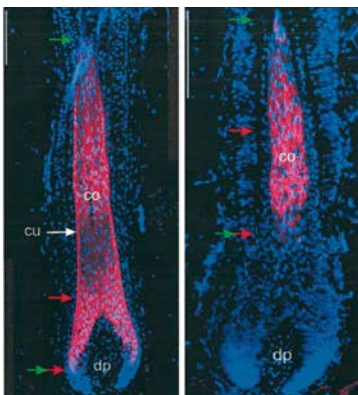
The topical medication Rogaine® (minoxidil) is applied directly to the scalp, avoiding the side effects of oral medication, and can be used by both men and women. You can expect to wait up to six months through twice-a-day applications before beginning to see results with Rogaine. Rogaine treatment is also temporary. Hair loss will resume if Rogaine treatment is stopped. Rogaine has a few side effects such as itchy scalp. More severe side effects, including headaches, low blood pressure and irregular heartbeat can occur if too much of the drug is used.

Hair transplants and other surgical procedures to treat balding are performed by a physician in a surgical environment. Hair transplants remove growing hair from one part of the head and transfer it to another area that has less hair cover. This is a somewhat painful and fairly expensive procedure, but has the advantage that it is usually permanent. Hair weaves, hair pieces, artificial hair replacement or changes of hair style may disguise hair loss. These are the least expensive and safest approach to hair loss. These approaches are also temporary and can look somewhat artificial. Hair pieces and other appliances are also inconvenient and occasionally embarrassing to use.

The Keratins

Keratins are a class of proteins called Intermediate Filament proteins. This is by far the most diverse type of protein with over 50 different forms of keratins, including the “soft” keratins, found in skin and within living cells, and the “hard” keratins such as those found in fingernails, hooves and hair. There are at least 9 different forms of keratins in the hair alone. Each special form of keratin is found only in its related type of tissue. The “hard” keratins mostly support the shape, strength and character of specialized structures such as hooves or claws.

Although it is obvious that keratins are involved in the growth of hair, since a shaft of hair is mostly made up of this protein, keratins are also associated with the regulation and production of hair itself by the hair follicle. So, a disruption of keratin production not only affects the shape or strength of hair shaft, it can also affect the growth and health of the hair itself.



The Figure on the left shows human hair follicles specifically stained (red) for the presence of 2 different types of hair keratins. This shows that

these keratins are only produced in the “bulb” portion of the hair follicle. The keratins do not appear in the hair shaft itself surrounding the bulb. This is strong evidence that keratins in hair are not simply inert “structural” proteins that contribute shape, strength and mechanical characteristics. The number and complexity of keratins and their production show that keratins also function in the control or regulation of hair growth itself, and therefore are important in the loss or thinning of hair and the health of the follicle. One class of keratins protects against apoptosis, which results in the death of the hair follicle and permanent hair thinning or baldness.

The Vital Link Between Elastin and Hair Thinning

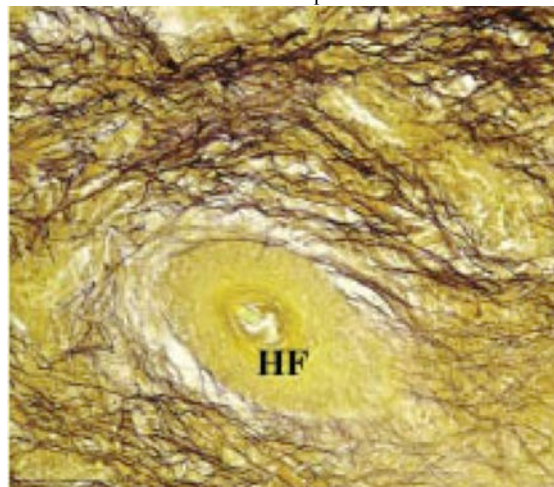
The loss and thinning of hair is a troubling experience for many men as they age, and even for some women. Male pattern baldness can begin in early adulthood for a few individuals, and leads to the eventual complete loss of hair except for a “fringe” around the sides of the head.

The causes of hair thinning are more diverse than most people realize although much attention has been focused on the activity of testosterone and dihydrotestosterone (DHT). Testosterone and DHT are known to be factors in male pattern baldness, but many men have high testosterone metabolite levels and never suffer from male pattern baldness. Some suggest that a combination of factors, including a person's genetic background and the impact of the environment are responsible for hair loss and thinning. What is known is that in some men, DHT causes an increase the length of time that the hair follicles are dormant, producing thinner, slower growing hair. The most widely used hair loss treatment, Rogaine®, does not block DHT or its activity. This drug stimulates production of the hormone Vascular Endothelial Growth Factor, and increases the vascularization (blood flow) in the dermal papilla.

Hair follicles in the scalp are intimately associated with and responsible for the production of scalp proteins such as elastin. The elastin fibers in the upper dermis are exclusively synthesized by the cells lining the root sheath in the hair follicle². This establishes an intimate connection between the hair follicles and the extracellular matrix that supports the follicles in the skin.

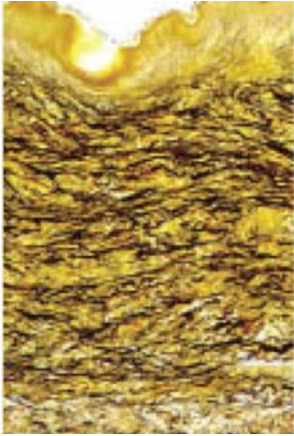
There is growing evidence that other factors affect thinning and

Follicle-associated elastin in the scalp of



of a human infant

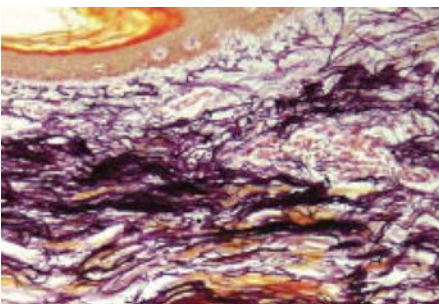
loss of hair, including damage to the proteins in the scalp from sunlight and also environmental conditions. This is a self-reinforcing problem, because as hair thins and becomes more sparse, greater amounts of sunlight, in particular in the UV range of the spectrum, can penetrate to the scalp and damage the proteins in the scalp matrix. For example, there are significant differences between the elastin in the scalp of infants compared to adults. The Figure below shows an elastin-stained section of skin from the scalp of a human infant, displaying organized bundles of elastin associated with the hair follicle³ (HF).



It is readily seen from these Figures that the elastin is both closely associated with and produced by the hair follicles themselves. The synthesized elastin forms dense, well organized bundles running through the epidermis and deeper into the dermis in the scalp of infants³.

The figure on the left shows a cross-section of elastin fiber organization in the scalp from a human infant.

Solar damage to elastin in the scalp of adults (solar elastosis) interferes with elastic fiber interactions with each other and with hair follicles, and may be a major contributor to hair thinning and loss. Sections of adult scalp show extensive elastin damage and loss of organization, presumably due to UV-induced changes in the elastin proteins themselves. These figures show a marked change in the elastin in the skin of adults compared to infant scalp skin³.



Section from adult scalp tissue showing hair follicle and elastin fibers.

Not only is elastin and its precursor, tropoelastin, synthesized by the cells in the hair follicles, but the follicles themselves appear to depend on elastin and the structure of its matrix for their function and vitality. A genetic defect in humans termed

Menkes' syndrome results in deficient uptake of dietary copper. Copper is essential for the enzyme that crosslinks elastin in the extracellular matrix, so sufferers of Menke's syndrome show abnormal arteries – arteries have very high elastin content – progressive neurological deterioration and early death⁴. Another effect of Menke's syndrome is brittle, fragile and sparse hair,

suggesting that the elastin structure in the scalp is important for normal hair follicle function and hair structure.

Further support for the idea that elastin structure in the scalp is linked to and supports hair growth is provided by a mouse genetic model called rough coat⁵. Mice with the rough coat genetic defect have significantly reduced levels and altered deposition of both elastin and collagen in their skin and internal organs. Rough coat mice also display progressive hair loss – similar to male pattern baldness in humans. These observations strongly suggest that elastin is both synthesized by and essential for the complete functioning of hair follicles. Elastin damage by aging processes and sunlight contribute to the loss and thinness of hair as we age.

One method of restoring elastin lost during aging would be the use of a small molecule that stimulates the body to synthesize more tropoelastin. No safe and effective molecules yet been found that stimulates elastin synthesis in skin. Another approach is to provide human elastin to the scalp in a formulation from an outside source. Human elastin is known from clinical trials⁶ to penetrate the skin on the face and become absorbed. We have recently evaluated the topical application of human tropoelastin, the precursor to elastin, to the scalp of a volunteer showing the signs of male pattern baldness. If damage to the structure and matrix of elastin in the scalp contributes to the thinning and loss of hair, then providing an external source of this human protein could help reduce ongoing hair loss and stimulate new hair growth.

What Is Elastin?

- Elastin is the protein in the extracellular matrix surrounding the skin, organs and connective tissues that gives these materials their strength and elasticity – it is the "rubber band" that causes our skin and other organs to maintain their shape and "snap back" if they are stretched.
- Elastin is produced almost entirely during development and early childhood – little or no elastin is made by adult tissues.
- Elastin is a major protein component of arteries and veins – About 30-50% of the aorta, 50% of elastic ligaments, and 2-5% of the skin are made of elastin.
- Elastin deficiencies cause certain diseases – elastin loss in major blood vessels leads to atherosclerosis and elastin loss in the lung leads to emphysema.
- Elastin is extremely durable in skin – it has a half-life of about 70 years, but is only slowly replenished.
- The skin gradually loses its elastin content over time, with about 10% of the elastin content of the skin lost over a lifetime.
- Elastin loss leads to decreases in the flexibility, strength and healing ability of skin; eventually thin, sagging and easily injured and bruised skin results.

Elastin loss also leads to a reduction in the vitality of hair follicles in the scalp.

- Tropoelastin is the water soluble precursor to elastin. Tropoelastin is the form of elastin made by the cells in the body. This elastin precursor is then exported outside the cells and becomes incorporated into the extracellular matrix as elastin.
- Elastin promotes wound healing and tissue regeneration; it has been used as a coating on collagen patches for injuries, tissue augmentation, as part of a gel or scaffold in wounds, and elastin helps recruit the cells that regrow new flesh to the site of a wound.
- Keracyte contains Elastatropin, a form of the human elastin precursor tropoelastin. It is made by inserting the gene for human elastin into plants and microorganisms. The human elastin is recovered from the cultures, purified and formulated into a skin care product.
- Elastatropin is much more available to the skin and active on the skin's surface and scalp than traditional forms of elastin, which is usually derived from animal sources.
- Laboratory studies have shown that some forms of human elastin (including the elastin in Keracyte) can penetrate into the surface of the skin, and become incorporated into the extracellular matrix surrounding the skin cells.
- NuLastin contains about 50 ug per ounce of human tropoelastin. This is a sufficient amount to replenish the elastin lost from the scalp in about one month.
- The addition of an active form of elastin to the skin's surface has the potential to reduce the requirement for drugs or cosmetic surgery procedures, making it a highly cost effective and safe alternative.

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