

LE Magazine April 2004

## COVER STORY

### A Partial Reversal of Skin Aging

A new delivery system overcomes a long-standing obstacle to effective skin care



*In recent years, people's perception of the Life Extension Foundation has changed in an interesting way. As word has spread about our commitment to products backed by solid research, the quality of the proposals we get from inventors has improved. This self-selection process has weeded out many dubious products since the promoters realize they will not get past our rigorous evaluation process.*

*Yet even now, dozens of companies offering so-called "revolutionary" health products knock on our door each month. The majority of these products fail our initial peer review, and the few that look promising usually do not pass the in-house clinical testing we perform. As a result, only a select number of inventions ever demonstrate the efficacy needed to meet our exacting standards. This month, Life Extension introduces a patent-pending product that addresses an important issue for all of us who are getting on in years: the declining condition of our skin.*

*Skin aging is a complex process determined by individual genetic endowment as well as by environmental factors.<sup>1</sup> We have all seen people whose skin looks younger than their chronological age and others whose skin appears older than their years. Of course, you cannot go back and order new parents, but you can take the initiative and minimize the impact of the environmental factors under your control. You can also utilize effective therapies to counteract changes in the skin that occur over time.*

Collagen is an integral part of the skin's fabric. It forms a mesh-like structure that helps to support new cells as they grow while providing needed flexibility. There is more collagen in the skin than any other protein, but it is not inert. There is continual collagen synthesis and degradation, and the balance between them determines whether you have a collagen deficiency.<sup>2</sup>

Collagen's significance in maintaining healthy skin has been known for decades. Women have long gone to dermatologists to have collagen injected under their skin. This treatment, first performed in 1982, augments the skin's natural network of collagen in areas where it has become depleted, immediately removing fine lines and wrinkles, and temporarily restoring a smoother, softer, and more youthful appearance to their skin.

There is no question that these injections are effective. As with natural collagen, however, the injected supply diminishes, so continued treatments are required. This entails substantial financial expenditures that over time can easily add up to thousands of dollars. There is also the pain associated with the injections after the anesthetic wears off. And, of course, most people do not want to be pricked with needles, especially around their eyes, or be inconvenienced by a dermatologist's waiting room.

As news about the success of collagen injections spread, many cosmetics companies rushed to take advantage of the commercial opportunity. They introduced collagen creams and advertised that their creams could produce anti-aging effects similar to those of injections. Regrettably, collagen molecules are too large to pass through the upper layer of the skin on their own, so the only benefit of the creams was to moisturize the surface of the skin, leaving unchanged the fundamental issue of declining collagen levels in the underlying layers. The regular use of vitamin C-fortified creams facilitates collagen synthesis beneath the skin,<sup>3-5</sup> but the age-related degradation of collagen can overwhelm the ability of vitamin C to generate new collagen.



Until recently, little else could be done. Botox® injections are able to improve the worry lines that occur on the upper face when frowning and squinting. The injections are also effective for diminishing crow's feet and forehead lines. Once again, however, the issue of pain and needle pricks presents itself. Also, Botox® is a toxin that works by paralyzing the small muscles involved in facial expressions. As a result, the lines may disappear, but there can be a diminished expressiveness of the face. And, of course, the injections only last a few months, requiring continued hassle and expense to maintain the improvement.

### First Transdermal Collagen Delivery System

A few months ago, the inventors of a new transdermal collagen-delivery system approached the Life Extension Buyers Club and suggested that the product be offered to Foundation members. This patent-pending delivery system enables very large molecules such as collagen to pass through the

upper layer of the skin. This allows the collagen to be delivered directly to the third layer of the epidermis—a feat achieved previously only by injection. The inventors presented several scientific studies to the Life Extension staff and showed stunning before-and-after photographs demonstrating this liquid's efficacy. Finally, it seemed, there was a topical liquid that produced many of the effects of injections without the pain and huge expense.

While the specific structure of this delivery system is a closely guarded secret until the patent is issued, Life Extension has learned that it involves a supersaturated formulation with a unique releasing component that incorporates dissolving polymers. Researchers have recently developed models for controlling drug delivery that have enabled them to understand the physics of drug release from polymers.<sup>6</sup> This has permitted scientists to deliver beneath the skin substances such as collagen that could not be effectively transported there before.

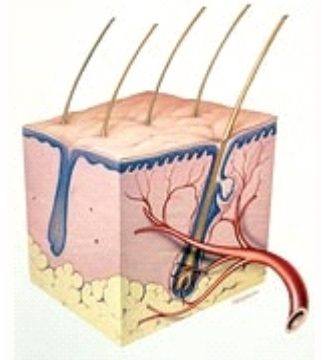
In addition, these scientists have produced a way to supersaturate the liquid formulation in a way that further enhances skin permeation.<sup>7</sup> They have found a way to maintain the concentration of a substance at supersaturated levels, which enhances the driving force for future transdermal drug delivery by increasing penetration through the skin layer. While collagen is not a drug, getting it to where it is needed most could easily produce drug-like effects.

### Studies Confirm the System's Efficacy

The new transdermal collagen liquid is called Hydroderm®. It consists mainly of type I marine collagen, though it contains small amounts of 29 other nutrients that contribute to its effectiveness, including vitamins, minerals, and hydrating proteins.

In the first study to demonstrate the product's efficacy, scientists tested the ability of their new delivery system to penetrate the third layer of the epidermis. They applied Hydroderm® to human cadaver skin and a cellulose acetate skin model following the instructions on the product insert. Penetration studies were performed in a diffusion chamber and the results were recorded at 10 minutes, 20 minutes, 30 minutes, and an hour later. The researchers found that 40% of the Hydroderm® dose penetrated the upper three layers of the epidermis within 10 minutes. Penetration rates increased to 60% after 20 minutes, 75% after 30 minutes, and 95% after an hour. Therefore, virtually all of the Hydroderm® made it to the desired location. Electro-phoresis and immuno-precipitation analyses confirmed that the product molecule was intact after skin penetration.

Scientists then performed a study to determine the benefits of Hydroderm® on live human subjects. Five volunteers ranging in age from 25 to 88 had their wrinkle status determined based on micrometer readings and digital photography. They then applied the liquid to half of their faces for 21 days. The results were impressive. As expected, the two volunteers in their twenties showed the least benefit due to the still-substantial amounts of natural collagen in their skin. Even including those two subjects, however, the total average reduction in wrinkle measurement was 17.4% around the eyes and 15.2% on the temporal cheek. Although there was less improvement in the chin and mouth areas (9.8% and 9.1%, respectively), the overall effectiveness of the product on the entire facial region was a dramatic 10.3%. The only side effect was a slight burning sensation for three to five minutes after the product was applied. This sensation was temporary, however, and no longer occurred by the end of the second week. According to the researchers, the product "softened the facial skin" of the volunteers and "induced a clearer facial appearance." Considering how many years it took to develop those wrinkles, a 10% reduction in three weeks is great news indeed.



Medical illustration of the epidermis, dermis, and subcutaneous layer of the skin, shown with the arterial blood supply.

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While the results of these two studies are impressive, we at Life Extension have learned to be skeptical of what can turn out to be hyped claims. Therefore, we asked for samples to try on people that we know personally. The initial results have been encouraging. One woman who regularly used Botox® injections stated that Hydroderm® worked just as well. We then requested more samples so we could conduct our own clinical study and ascertain whether the product was really effective. We gave 10 people of various ages a jar of this transdermal collagen liquid and instructed them to use it on only one side of the face for 30 days. The results in some of the study participants were significant. There were visible age-reversing effects, including a reduction in fine lines, diminished bags under the eye, and removal of irregular pigmentation.

One older study participant could not wait for the clinical trial to finish, as she looked somewhat disfigured because one side of her face looked younger than the other. Younger volunteers, on the other hand, did not notice a significant improvement. Most of the participants, however, were extremely satisfied with the product and eagerly awaited the completion of the study so they could use Hydroderm® on the other side of their faces as well.

In line with its commitment to vigorous research, Life Extension will conduct another clinical study on Hydroderm® in the near future. This time, however, it will be restricted to older women with visible signs of skin aging. The conclusions of this research will, of course, be included in a future issue of this magazine. In the meantime, we are offering this product so that Life Extension members can take advantage of its benefits at the earliest possible time.

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#### How Hydroderm® Works

Collagen fibers primarily exist in dense bundles, but the density and horizontal orientation of these bundles decline as you get older.<sup>8</sup> Collagen forms part of the extracellular (outside the cell) matrix, which maintains the integration of cells in the skin tissue. Along with elastin and proteoglycan, and various structural glycoproteins, collagen directly influences the behavior of the skin's cells.<sup>9</sup> This is why it is so important to ensure an optimal supply of collagen throughout your life.

To understand how the Hydroderm® liquid works, you need a bit of background on the structure of the skin and how it ages. While people sometimes think of the skin as an inert layer, it is actually the largest organ of the human body. The skin is in a constant state of change. In fact, the cells of the top layer, known as the epidermis, are completely replaced an average of once every two weeks.

The epidermis consists of three layers, with the very top layer in direct contact with the environment. This layer has a very low permeability that only small molecules can pass through, which is why most collagen creams are unable to penetrate it. While topical collagen creams help moisturize and reduce dryness and scaling, they do nothing to alter the basic supporting structure beneath the skin.

Beneath the upper layer of the epidermis are two more layers that are critical for the skin's structural integrity and contain substantial amounts of collagen. The Hydroderm® delivery system enables topically applied collagen to penetrate the upper layer of the epidermis and nourish the underlying structures of the skin.

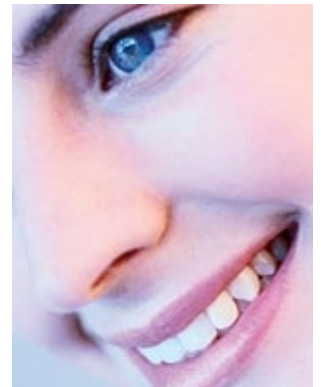
#### Many Factors Involved in Skin Aging

In the last 50 years, tremendous progress has been made in understanding the mechanisms and mediators involved in the slow but steady deterioration of the skin.<sup>10</sup> We now know that the anatomical changes in aging skin result in altered function and susceptibility to disease.<sup>11</sup> There are alterations in immune surveillance and a reduction in the skin's vascular supply. Impairments of thermal regulation, tactile sensitivity, and pain perception also occur as one ages. At the same time, the dermal-epidermal junction becomes flatter, giving the appearance of atrophy.<sup>12</sup> This occurs due to a reduction in the dermal cell population as well as changes in the quantity and characteristics of the collagen and elastin fibers in the skin.<sup>13,14</sup>

While many factors are involved in the aging of skin, most are associated with one major mechanism: the synthesis of intercellular (between the cells) adhesion molecules under the top layer of the skin.<sup>15</sup> These aging factors directly or indirectly induce a micro-inflammatory cycle, leading to the secretion of collagenase, an enzyme that eats away at collagen, as well as reactive oxygen species (free radicals). The end result is that the matrix supporting the skin is slowly destroyed, producing a variety of visible and invisible changes to the skin layer.

While people often focus on ultraviolet radiation and cigarette smoking as causes of skin aging, it also occurs naturally due to the body's metabolic requirements and the passage of time. For example, nearly all of your body's cells use glucose (blood sugar) for fuel. Sometimes, however, glucose binds to proteins in a reaction known as glycation. This process results in the formation of advanced glycation end-products that can cross-link the proteins they bind with—including collagen. Studies have shown that glycation impairs the assembly of collagen macromolecules.<sup>16</sup> Glycation end-products also keep type IV collagen molecules from forming a normal network-like structure.<sup>17</sup> Since type IV collagen is responsible for the mechanical stability of the skin's scaffolding known as the basement membrane, glycation accounts for a significant amount of skin deterioration. Just as you have to eat to live, you can take steps to replenish the collagen that is destroyed by this regrettable, albeit natural, process.

Skin aging also appears to have a hormonal component. A Spanish study of women aged 35 to 60 found a dramatic decline in type IV collagen in the basement membrane, which decreases the strength of this important foundation for the skin.<sup>18</sup> This decline in collagen levels can be partially reversed when women take supplemental estrogen. Therefore, the natural reduction in estrogen levels that occurs with age is partially responsible for the observed changes to skin, at least in women.<sup>19</sup> The health risks associated with estrogen drugs have caused many health-conscious women to stop using them. Fortunately, there are some natural alternatives such as DHEA, which has demonstrated anti-aging effects when consumed orally or applied topically.<sup>20,21</sup>





Physical stress taxes the skin as well. The force of gravity exerts a continuous stress on the extracellular (outside the cell) matrix, which triggers the production of the superoxide radical by the mitochondria of the affected cells. This results in free-radical damage and other biological events that lead to the inflammatory response mentioned earlier, resulting in collagen degradation. Other factors contributing to skin aging include psychological stress and limits on cell division known as cell senescence.<sup>22</sup>

Of course, sun exposure plays a role in the reduction in collagen levels over the years. The absorption of ultraviolet radiation type A (UV-A) generates reactive oxygen species that oxidize the proteins, lipids, and DNA in the skin, damaging their cellular structure and reducing their antioxidant capacity.<sup>23</sup> Meanwhile, UV-B absorption by DNA causes the cross-linking of the adjacent proteins, wreaking havoc. The end result is an increase in a destructive enzyme known as matrix metalloproteinase and a reduction in type I procollagen, the precursor molecule to collagen. The rise in matrix metalloproteinase activity also degrades the dermal connective tissue, resulting in a fourfold increase in partially degraded collagen. The combination of these factors produces long-lasting damage to the skin. While these changes occur to some extent in sun-protected skin due to the effects of naturally generated free radicals, they dramatically increase in severity when the skin is exposed to UV radiation. So for your skin's health, be sure to use sunscreen liberally. UV rays do a lot more than cause skin cancer.

### **A Multipronged Attack on Skin Aging**

For decades, women have gone to dermatologists to have collagen injected under their skin. The immediate effect is the removal of fine lines and wrinkles and a temporary restoration of a more youthful appearance to the skin.

Collagen is a naturally occurring protein that provides support and flexibility to the skin. It forms a mesh-like structure that supports new cells as they grow. Collagen levels diminish with age, resulting in skin sagging, loosening, and losing resiliency. When collagen is injected into the skin, it increases the supportive layer under the skin so that scars, lines, and wrinkles can be filled in. As a result, skin looks younger and smoother.

Cosmetics companies have taken advantage of the known benefits of collagen injections to claim that their collagen creams produce similar anti-aging effects. Regrettably, collagen molecules are too large to efficiently pass through the upper layer of the skin, so collagen creams provide little benefit.



For the first time, a patent-pending delivery system has been developed that enables very large molecules (such as collagen) to pass through the upper layer of skin. When this new transdermal system is combined with collagen, the collagen molecules are delivered directly to the third layer of the epidermis—an effect achieved previously only by injection.

Collagen replacement is one important component of an anti-aging skin program. The good news is that scientists have published findings indicating that people may have more control over the rate at which their skin ages than over any other organ of the body.

To slow skin aging and partially reverse it, an individual must take a comprehensive approach to gaining control over all the factors that have been identified in the skin degeneration process. Life Extension members have taken advantage of this wealth of knowledge by using the multi-ingredient Rejuvenex® and/or Dream Cream® face creams. Both of these formulas contain stabilized forms of vitamin C, which has been shown in published studies to facilitate the natural synthesis of collagen beneath the skin and induce anti-aging effects.

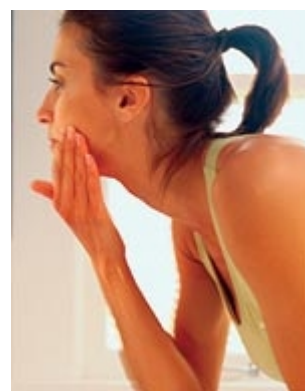
With the availability of Hydroderm® liquid drops, far more collagen can now be restored beneath aging skin. For optimal results, we suggest applying Hydroderm® liquid drops immediately after the face is cleansed while the pores are open for maximum assimilation of the collagen into the lower layers of the skin. Wait 15 minutes for the Hydroderm® to dry, and then apply Rejuvenex® or Dream Cream® to provide your skin with a complete armamentarium of age-defying nutrients.

## Taking Control of Your Appearance

For many years, a debate raged in the dermatological community as to whether topically applied anti-aging preparations really slowed or reversed skin aging. The scientific literature now indicates that the daily application of a variety of agents can have a profound effect on both the health and appearance of the skin.

While the concept of controlling cellular aging remains controversial, no one disagrees that individuals can significantly influence the rate at which their skin ages. For instance, if a person wants to accelerate skin degradation, all they have to do is expose themselves to lots of ultraviolet radiation, cigarette smoke, and ethanol. Even second-hand cigarette smoke prematurely ages the skin.

Hydroderm® liquid drops have become an incredible success story. Word-of-mouth advertising has resulted in an enormous number of jars being shipped monthly to regular users. Based on our review of the scientific reports and the results of our own clinical study, Hydroderm® has demonstrated efficacy in reversing the signs of certain aspects of skin aging, primarily in people over the age of 40.



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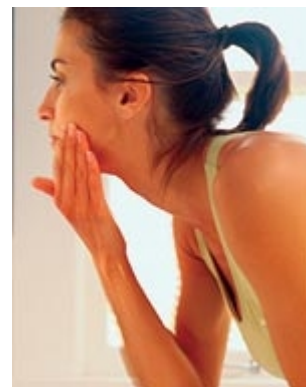
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