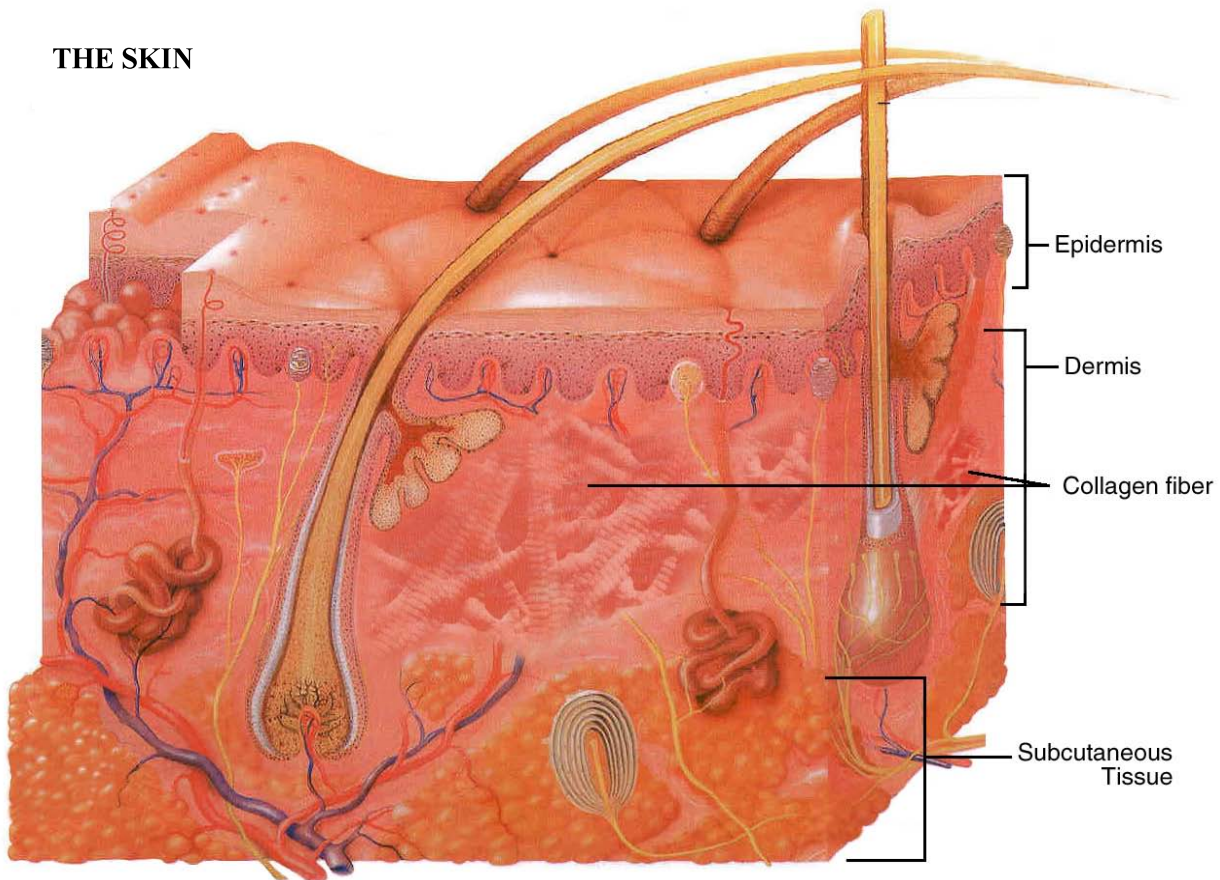


CollagenRX™

*Advanced Technology
for Skin Rejuvenation*

THE SKIN



INTRODUCTION

When I first started my medical training, and was attending medical school in Chicago, Illinois, one of my professors lectured on the subjects of embryology and histology.

During one of the lectures, the professor made a profound statement to the class. The professor articulated, “When all of you students become graduate physicians and enter your chosen field of medicine and surgery, always think and visualize what is happening at the cellular level.” His words have never been forgotten; I have carried them throughout my entire medical and surgical career as a General Surgeon.

During my many years as Surgical Director of a very large and busy wound-care hospital clinic in West Palm Beach, Florida, I continued to develop the cellular thought process that eventually helped to form the basis of my thesis in researching and investigating the advanced cosmeceuticals found in the CollagenRX™ formula. These advanced cosmeceuticals were developed through careful study of their molecular and bio-cellular effects on the epithelial and dermal layers of the skin.

In the normal skin, there are three basic layers: Epithelial, Dermal, and Sub-Cutaneous. In the clinical setting, patients that are admitted to be evaluated present a wound and/or ulcer in a chronic state of appearance. In this chronic state, the top epithelial layer is usually necrosed and destroyed; and the dermal layer is exposed. The advantage presented here to a trained surgeon, observing the skin with the first top layer gone and destroyed, is that the dermal layer is

where a great deal of cellular and kinetic energy and communication takes place between the cells. It is also the layer where Fibroblasts are very active producing collagen and elastin that makes the skin very durable from within. Collagen and elastin, under certain negative “Cellular Stress” which eventually leads to a sub-clinical state of inflammation, all cascade to the collagen being destroyed and other cellular functions being disrupted.

The CollagenRX™ anti-aging and anti-wrinkling cream–gel was developed as a result of many years of observing wounds and ulcers and through the knowledge of the biological and physiological activity that takes place at the dermal cell layer, as well as, the knowledge of the nutrients that are needed to nourish and stimulate the wound back to healthy and normal skin.

A great deal of credit to the final development of the cream-gel is extended to Tony Musso, Nutritionist, who contributed a very special pure form of hydrolyzed collagen.

Cells and Skin

Cells are the basic units of life, capable of performing fundamental processes. The size and shape of human cells vary depending on their particular function. Cells contain various structures such as a nucleus and mitochondria. Most human cells also contain small structures known as organelles (little organs), each of which performs a highly specialized task, such as manufacturing protein. Organelles are usually surrounded by a membrane and float in a jelly-like substance called cytoplasm. Ninety percent of cytoplasm is water; it also contains enzymes, amino acids, and other molecules needed for cell function.

This normal inter-relationship of cell structures takes place every day in the trillions of cells that are in the human body. These cells of the human body are destroyed by different etiological factors.

One of the most accepted theories to cell malfunction and damage is the free radical theory.

What is a Free Radical?

Free radicals are the products of oxidative reactions in the body. They are highly reactive compounds that take electrons from other molecules to stabilize themselves. In this process of electron “theft,” a new free radical is created, namely, the molecule from which the electron was taken. That new free radical then practices “theft” on another nearby molecule, and a chain-reaction cycle of cell destruction begins.

It is important to realize that oxidation is a normal part of life as are free radicals. Oxidation is what enables us to get and use energy from our food. When free radicals are produced in excess, however, they are so damaging that the body maintains a sophisticated antioxidant system to hold them in check.

However, when the body's prolonged exposure to oxidative factors causes an excessive output of free radicals that exceeds the body's ability to neutralize them (technically called "oxidative stress"), the body is put in an increasingly vulnerable position due to accelerated cell destruction.

Antioxidants are substances that neutralize free radicals. The most advanced antioxidants and nutraceuticals have been formulated along with other biotechnologies to develop an anti-aging and anti-wrinkling CollagenRX™ cream-gel.

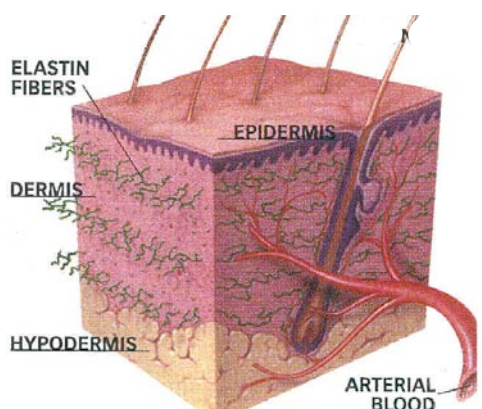
"CollagenRX™ reduces wrinkles of the face and hands through an advanced patented formula cream-gel that is the most advanced clinically proven cream-gel to nourish and revitalize the skin due to the aging process."

BACKGROUND

The Skin

The skin is the largest organ of the body. It is made up of three distinct layers: the *Epidermis*, the *Dermis* and the *Subcutaneous Tissue*. Each has its own unique function, yet are interrelated.

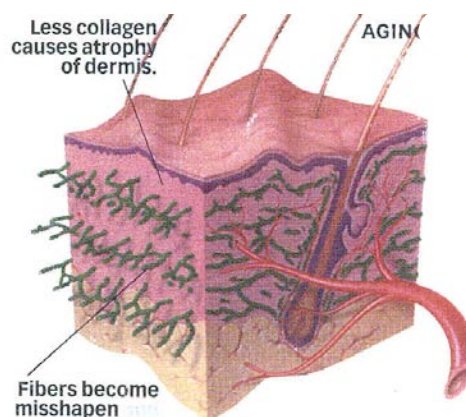
Young Skin



The *Epidermis*, the outer layer, acts as a protective shield. It is comprised of multiple cell strata that serve to regenerate the skin's protective function. The epidermis continuously sloughs keratinated cells of its outer layer, the *stratum corneum*, every thirty days or so. This regeneration occurs naturally through wear and tear such as bathing, friction from clothing and exposure to the environment.

The middle layer is the *Dermis*, through which blood vessels and nerve receptors penetrate to the epidermis. In this layer, chemical and enzymatic kinetic energy is constantly in motion. This motion allows cellular structures to communicate with each other whereby growth factors and stimulation of *Fibroblasts* produce **Collagen**, and provide strength and elasticity to the skin. Sebaceous glands furthermore produce protective oils in the form of an acid mantle onto the skin's surface to

Aging Skin



help protect from infections. Temperature and pain receptors along with blood vessels are also present.

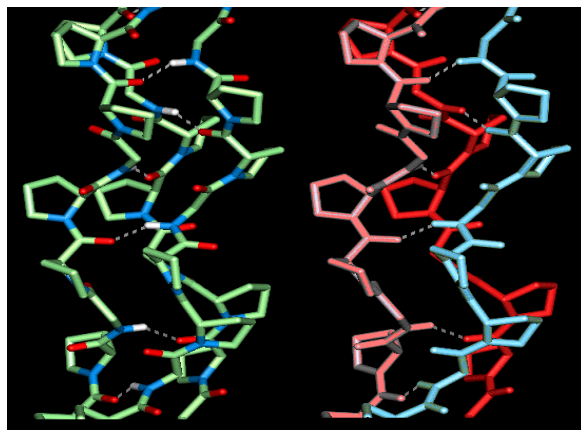
The third layer is the *Subcutaneous Tissue* or fatty layer. This fat layer serves to insulate the human body and helps the skin to be smooth and plump. It also acts as a binder between the dermis and underlying tissues, allowing the body to move as one.

BIOCHEMISTRY OF COLLAGEN METABOLISM

Metabolism

Collagen is found in all of our connective tissues such as the dermis, bones, tendons and ligaments; it also provides for the structural integrity of all of our internal organs.^{1,2} Because of its wide distribution throughout our bodies, it represents one of the most abundant naturally occurring proteins on earth.³ In addition to its natural abundance, over 1,000 commercial products are on the market today that contain collagen and collagen enhancers. These products are represented by body and hand lotions, nail treatments, firming gels, wrinkle injections, eye pads and even anti-cancer treatments, to name a few. In recent years, new high-tech wound dressing materials and skin substitutes have become available for the treatment of partial-thickness injuries, as well as full-thickness and chronic dermal ulcers.

There are close to twenty different types of collagen found in our bodies.^{4,5}



Each one of these collagens is encoded by a specific gene. The predominant form is Type I Collagen. This fibrillar form of collagen represents over 90% of our total collagen and is composed of three very long protein chains. Each protein chain is referred to as an *Alpha chain*. Two of the Alpha chains are identical and are called Alpha-1 chains, whereas the third chain is slightly different and is called Alpha-2. The three chains are wrapped around each other to form a triple helical structure called a *collagen monomer*. This configuration imparts tremendous strength to the protein. To understand the overall structure of the collagen molecule, picture the reinforcement rods called re-bar that are used in concrete construction. If one converts the molecular dimensions of the collagen molecule to measurements that we can relate to, the molecule when scaled up, would measure one inch in diameter to approximately seventeen feet long. Therefore, collagen is indeed nature's re-bar because it is responsible for the strength and integrity of all of our connective tissues and organ structures.

For the adult, the skin contains about 80% Type I and 20% Type III collagen. In newborns, the Type III content is greater than that found in the adult. The supposition is that the supple nature of the newborn skin, as well as the flexibility of blood vessels, is due in part to the presence of Type III collagen.

When degradation to the skin occurs, whether by age or injury, the platelets and inflammatory cells are the first to arrive, providing the key functions and signals needed for the influx of connective tissue cells and new blood supply. These chemical signals are known as growth factors or cytokines. The fibroblast

is the connective tissue cell responsible for the collagen deposition needed to repair the tissue injury. Collagen is the most abundant protein in the animal kingdom, as it accounts for 30% of the total protein in the human body. In normal healthy skin tissues, collagen provides strength, integrity and structure. When tissues are disrupted following injury, collagen is needed to repair the defect, and hopefully, restore structure and thus function.

Collagen Synthesis

The biosynthetic pathway responsible for collagen production is a very complex one.^{4,6} Each specific collagen type is encoded by a specific gene; the genes for all of the collagen types are found on a variety of chromosomes. As the messenger RNA (mRNA) for each collagen type is transcribed from the gene, or DNA “blueprint,” it undergoes many processing steps to produce a final code for that specific collagen type. This step is called the *rough endoplasmic reticulum* or *rER*. Like most other proteins destined for function in the extracellular environment, collagen is also synthesized on the rER.

A precursor form of collagen, called *procollagen*, is produced initially.⁷ Procollagen contains extension proteins on each end, called *amino* and *carboxy procollagen extension propeptides*. These nonhelical portions of the procollagen molecule make it very soluble, and therefore, easy to move within the cell as it undergoes further modifications. As the collagen molecule is produced, it undergoes many changes, termed *post-translational modifications*.^{4,6} These modifications take place in the Golgi compartments of the ER.

One of the first modifications to take place is the very critical step of hydroxylation of selected proline and lysine amino acids in the newly synthesized procollagen protein. Specific enzymes, called *hydroxylases*, are responsible for these important reactions needed to form hydroxyproline and hydroxylysine. The hydroxylase enzymes require Vitamin C and Iron as co-factors.⁸ The current recommended daily allowance for Vitamin C is 60mg; however, 200mg may be optimal. If a patient is Vitamin C deficient, then this reaction will not occur. In the absence of hydroxyproline, the collagen chains cannot form a proper helical structure, and the resultant molecule is weak and quickly destroyed.⁹

Some of the newly formed hydroxylysine amino acids are glycosylated by the addition of sugars, such as galactose and glucose. The enzymes that catalyze the glycosylation step, galactosyl and glucosyl transferases, require the trace metal manganese (Mn^{+2}). The glycosylation step imparts unique chemical and structural characteristics to the newly formed collagen molecule and may influence fibril size.¹⁰ It is of interest to note that the glycosylation enzymes are found with the highest activities in the very young, and they decrease as we age.¹¹

While inside the cell, and when the procollagen peptides are intact, the molecule is about 1,000 times more soluble than it is at a latter stage when the extension peptides are removed.¹² This high degree of solubility allows the procollagen molecule to be transported easily within the cell where it is moved

by means of specialized structures, called *microtubules*, to the cell surface where it is secreted into the extracellular spaces.¹³

As the procollagen is secreted from the cell, it is acted upon by specialized enzymes, called *procollagen proteinases*, that remove both of the extension peptides from the ends of the molecule.¹⁴ Portions of these digested end pieces are thought to re-enter the cell and regulate the amount of collagen synthesis by a feed-back type of mechanism.^{15,16} The processed molecule is referred to as collagen and then participates in the important process of fiber formation.

In the extracellular spaces, another post-translational modification takes place as the triple helical collagen molecules line up and begin to form fibrils and then fibers. This step is called *crosslink formation* and is promoted by another specialized enzyme called *lysyl oxidase*.¹⁷ This reaction places stable crosslinks within (intramolecular crosslinks) and between the molecules (intermolecular crosslinks). The crosslink formation is the critical step that gives the collagen fibers such tremendous strength. On a per weight basis, the strength of collagen approaches the tensile strength of steel!

One can visualize the ultrastructure of collagen by picturing the individual molecules as a piece of sewing thread. Many of these threads, called *fibrils*, are wrapped around one another to form a string. These strings then form cords; the cords associate to form a rope and the ropes interact to form cables. The structure is just like the steel rope cables on the Golden Gate Bridge. This highly organized structure is what is responsible for the strength of tendons, ligaments, bones and dermis.

Collagen Degradation

Of equal importance in the total picture of collagen metabolism is the complex process of collagen degradation. Normally, the collagen in our connective tissues turns over at a very slow and controlled rate of growth.

In normal healthy tissues where the collagen is fully hydroxylated and in a triple helical structure, the molecule is resistant to attack by most proteases. Under these normal healthy conditions, only specialized enzymes, called *collagenases*, can attack the collagen molecule.¹⁸ The group of collagenases belong to a family of enzymes, called *matrix metalloproteinases* or *MMPs*.

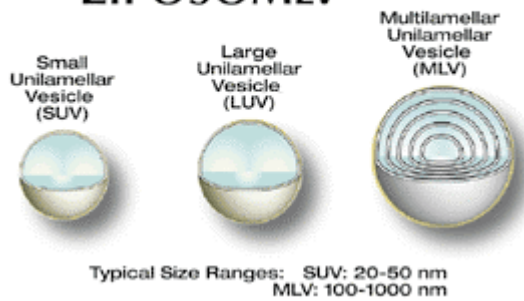
Many cells in our bodies can synthesize and release collagenase including fibroblasts, macrophages, neutrophils, osteoclasts and tumor cells. One of the reasons that some neoplastic cells can be so invasive is because they release potent collagenases and can break down the collagen around them. They then can break down the basement membranes of blood vessels and spread throughout the body.

BIOZONE

Leading Liposome Technology

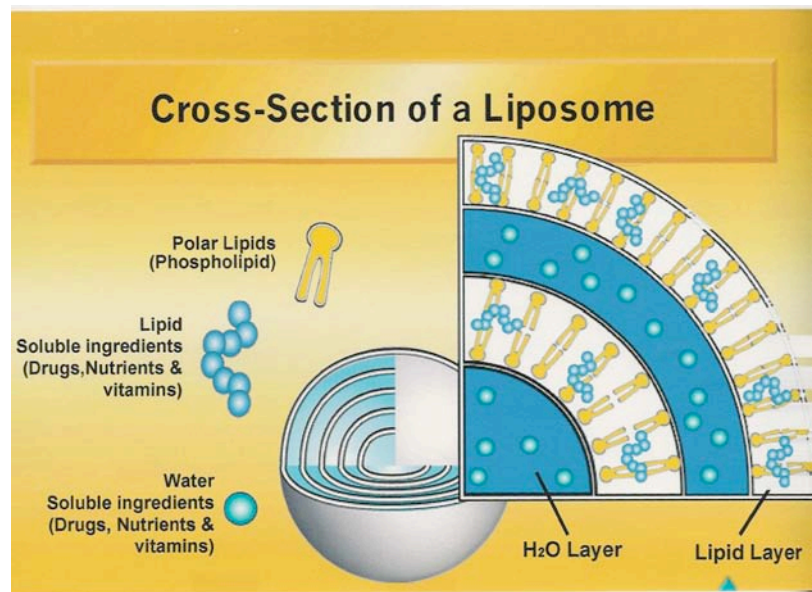
BioZone's revolutionary technology offers a unique alternative to conventional administration of cosmeceutical creams, gels, balms and sprays utilizing BioZone's proprietary liposome technology to microscopically encapsulate nutrients and cosmeceutical ingredients.

WHAT IS A LIPOSOME?



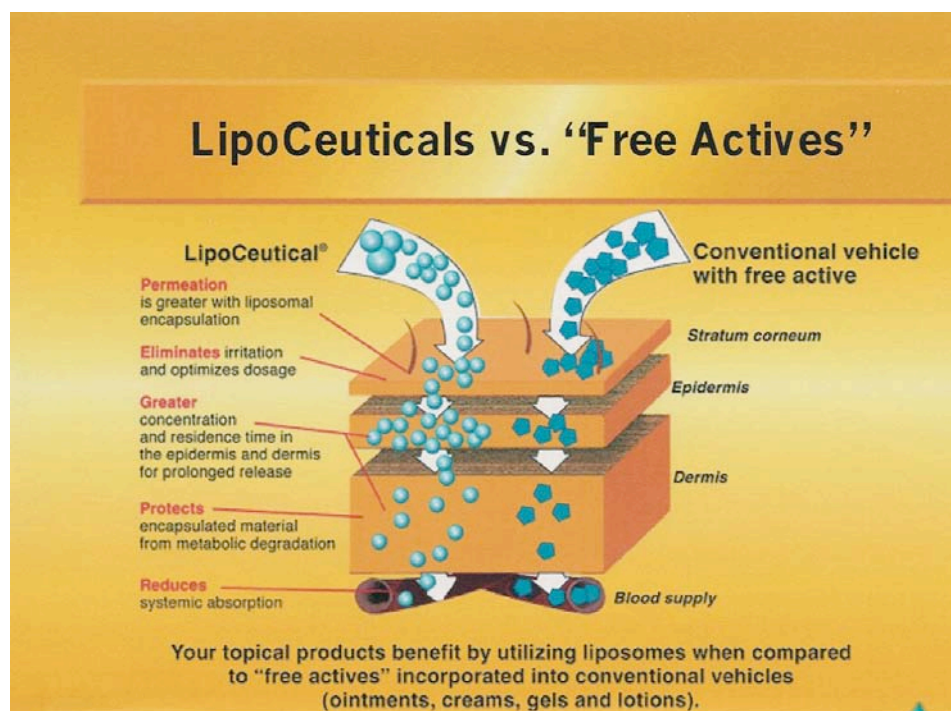
Liposomes were originally used by the pharmaceutical industry to deliver medications. Liposomes are highly complex microscopic lipid spheres, 1/50th the diameter of a human hair. The membrane of a liposome is made of highly purified natural lecithin that encapsulates water and the active ingredients. BioZone's liposomes are multi-layered to provide sustained delivery.

Increasing the level of active ingredients can actually flood or bombard the skin and cause irritation. The optimal method would be to protect the actives until absorbed into the lower layers of the skin where desperately needed, and then to time release the actives over a prolonged period of time.



Finally, a breakthrough in the developmental barrier. BioZone has developed a technology that delivers active ingredients to the lower layers of the skin, increasing the concentration of those actives in the epidermis and dermis, and then providing a prolonged time-release action throughout the entire day.

This revolutionary technology is called *LipoCeuticals*® and is so unique, it has achieved patents worldwide.



This technique was previously available only to the pharmaceutical industry. BioZone is leading the way by incorporating this pharmaceutical technique into cosmetic products, creating a true series of cosmeceutical products.

COLLAGENRX™

Patented Cream-gel

A newly patented cream-gel, to be applied to the face and hands, has been developed and clinically proven to improve the wrinkling of aging human skin in both women and men.

Mr. Tony Musso, Nutritionist, and I, Dr. Albert J. LaTorra, a General Surgeon, have formulated a compound consisting of accepted and approved vitamins, a special form of Collagen approved by the F.D.A., along with a biological carrier to transport our compound in the form of a cream and/or gel or spray to be applied to the skin of the face and hands. This compound will permeate the epithelial layer then the dermal layer of the skin where natural collagen is present and secreted by fibroblasts and other cellular interactions.

Several factors are considered concerning the basis of why skin ages, which include: genetics, declining hormones (men and women), gravity, sun exposure, smoking, diet, environmental elements and the eventual loss of collagen. Ultimately, the skin shrinks in thickness as it becomes drier and less flexible. As a result, the upper level of skin, the epidermis, becomes looser yielding “creases” and “wrinkles.”

By applying our formula in a cream-gel cosmetic base to the aging skin of the face and hands, the formula is able to rejuvenate the skin at the dermal layer where collagen fibers need to be replenished and nourished.

Clinical Trial

A clinical trial on twenty-four people, male and female, was conducted. Participants were instructed to apply the cream to the face and/or hands for two months. Color close-up photos of the face and hands were taken initially, at 30 days and at 60 days for scientific proof and evaluation. Two subjects in the clinical trial were extended to 90 days. The results proved very successful.

CLINICAL STUDY

Protocol

- **Human Volunteers** – 24
- **Test sites** – Subjects' face &/or hands
- **Test substance** – patented cream-gel with molecular enhanced collagen, and complementary advanced water and fat soluble vitamins (Vitamins A, C & E) acting as an antioxidant to combat free radical damage, coupled and transported with the aid of advanced fourth generation multi-layered sustained released liposome BioZone technology (*QuSomes*)
- **Application frequency** – applied sparingly and gently to the cleansed face and top of hands one hour prior to sleep
- **Test protocol** – subjects given one 2 oz. jar (57.6 grams) – color photos taken; close-ups of the full face, front, left and right sides; professional Nikon camera body & Nikon medical macro lens used; film - Fuji, super H.Q., A.S.A. fine grain 100 speed
- **Test subjects** – history of each patient was taken (i.e. present medication, etc). The twenty-two subjects selected were mixed, male and female, smokers & non-smokers, excessive amount of exposure to sun, pre-menopausal, peri-menopausal, menopausal females and aged skin of the face and hands
- **Aging skin** – subjects were 45 to 75 years of age
- **Results** – test subjects applied the cream-gel to the face for a total of 60 days. Two subjects applied cream-gel for 90 days. Test results revealed an estimated 55%-65% overall improvement in the reduction of wrinkles and skin tone

- **Work and testing done by** – Dr. Albert J. LaTorra, Board Certified General Surgeon and Wound Care Specialist, Columbia Hospital in West Palm Beach, Florida, USA

Summary

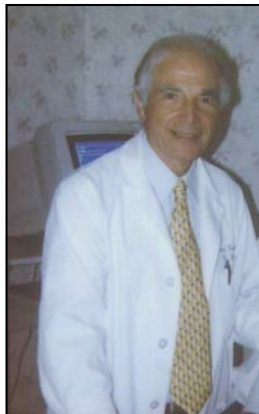
The “Skin” is the largest functioning organ of the human body. It is a complex structure carrying out many kinetic, chemical and enzymatic activities, one of which is the stimulation of fibroblastic cell relationship to produce collagen.

The skin ages due to many factors including genetics, sun exposure, smoking, declining hormones (male and female), gravity, diet and environmental elements resulting in degradation of the skin. This degradation leads to an inflammatory response of the cells, as well as breakdown of collagen and elastin, thereby producing wrinkles and aging skin. The free radical theory responsible for the above is perhaps the most universally accepted.

Tony Musso, Nutritionist, and I, Dr. Albert J. LaTorra, General Surgeon and Wound Care Specialist, collaborating with Dr. Brian Keller, co-founder of F.D.A. approved BioZone Laboratories, Inc., have formulated a patented cream-gel consisting of accepted and advanced complementary complex vitamins along with natural moisturizing ingredients for the skin to enhance its function. These ingredients include a special form of molecular structured hydrolyzed collagen, approved by the F.D.A., and a biological carrier. Our compounded formula cream-gel is applied to the face and top of the hands to be permeated through the epithelial layer and is then transported utilizing fourth-generation *QuSomes*, the most advanced state of the art biological technology.

This leading revolutionary liposome technology offers a unique alternative to conventional administration of cosmeceutical creams, gels, balms and sprays.

Utilizing BioZone's proprietary liposome (QuSomes) technology, our cream-gel microscopically encapsulates the water-soluble and fat-soluble cosmeceutical nutrients and complementary vitamin ingredients to be delivered by sustained release complex lipid spheres 1/50th the diameter of a human hair. The liposome (QuSomes), made of highly purified natural lecithin, is multi-layered to provide sustained release (i.e. time release) delivery of fat and water-soluble molecular elements over a long period of time. The skin responded by being nourished and moisturized, while the "natural" body cellular structures of the skin are replenished.



Dr. Albert J. LaTorra
Board Certified General Surgeon

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Bebe Bolton Pesenti
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MARTHA A. GOTTFRIED INC.
219 WORTH AVENUE
PALM BEACH, FL 33480

October 25, 2002

Dr. Albert J. La Torra
280C N. Flagler Drive
West Palm Beach, Fl. 33407

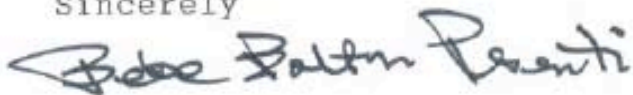
Dear Dr, La Torra:

First I want to thank you for introducing me to the wonderful product called CollagenRX.

As a Realtor I do face the public every day and since using CollagenRX I have seen a tremendous improvement in my skin. I have owned high fashion womens shops in New York, Called Bolton,s, in New York and I have been involved in the fashion industry for many years. I used many skin products and find the CollagenRX is now giving me excellant results.

Again, thank you and I do plan to continue to use this product which I feel is worth its weight in gold.

Sincerely



Bebe Bolton Pesenti
Realtor/Martha Gottfried, Inc.

SPECIALIZING IN CONDOMINIUMS & LUXURY YACHTS

Pamela M. Hall
DESIGNER

561-655-3367
561-833-1112 FAX

2800 N. FLAGLER DR.
SUITE 606
W. PALM BEACH, FL 33407

September 12, 2002

Dear Dr. LaTorra,

I started my career after college as a model. I then studied to become an Interior Designer. Now, even though I am officially retired, I still do special designing projects so it is very important that I look my best. You can imagine how delighted I was to see the results of **COLLAGENRX**. The texture and feel of this product was such a delight. I applied the cream gel to my face and, after half an hour to 45 minutes, I could feel it penetrating my skin.

Because of my very sensitive skin for years, no matter what cream I used around my nose, I always had red and peeling skin which was way hard to cover up—even with heavy makeup. Now I no longer have this unsightly problem, because I used **COLLAGENRX**.

Having such a sensitive and, you could say, allergic condition; I also could not wear some lovely and great fun costume earrings, without having to take them off after about an hour, as they hurt so much with peeling skin and, now and again, my ears would even bleed. After using **COLLAGENRX** I am able to enjoy not only my fine jewelry earrings, but fun ones as well.

On top of all these improvements, my friends keep telling me how great I look; naturally, I must say how really delighted and thankful I am for **COLLAGENRX** wonderful cream-gel.

Sincerely,



Pamela M. Hall