The AGE-Less Eye

A Breakthrough in Visual Health!

It took a while for the buzz to build.

For decades, it was known that **Carnosine** acted as a buffering agent in working muscles, and the only people paying attention to it were a few physiologists interested in its ability to keep muscles contracting. But as research into this simple dipeptide continued, the picture became more complex, and its biological role, once thought to be well-understood, suddenly became mysterious.[1]

First, it was found that **Carnosine** was also present in high concentrations in other tissues that last a lifetime but that don't require its buffering properties, such as nerve cells,[2] the cells of the retina,[3-5] and the lens of the eye[6] – and at only much lower concentrations in tissues that are constantly replaced, like skin cells and the lining of the intestines.

Other facts about the distribution of **Carnosine** were also intriguing. Researchers wondered why there's such a wide range of tissue **Carnosine** levels across the animal kingdom – and why it is that longer-lived animals tend to have more **Carnosine** in their cells than do shorter-lived species,[7] or that levels of **Carnosine** appear to decline with aging in humans (by 63% between the ages of 10 and 70).[8]

But the slow, steady pace of scientific investigation of **Carnosine** gave way to an explosion of new research in the mid-1990s, as astonishing new findings were reported in sober scientific journals. Reading the titles of some of the research papers on **Carnosine** can make you wonder if the pages of the *Annals of the New York Academy of Sciences* are being written by unemployed supermarket tabloid reporters. "**Carnosine**, the protective, anti-aging peptide."[9] "Use of **carnosine** as a natural anti-senescence drug for human beings."[10] "A possible new role for the anti-ageing peptide **carnosine**."[11] "Further evidence for the rejuvenating effects of the dipeptide L-**carnosine** on cultured human diploid fibroblasts."[12] And yet the recent scientific literature on **Carnosine** is positively *soaked* with this kind of language.

The fascination surrounding this nutrient began with a series of studies carried out at the Commonwealth Scientific and Industrial Research Organization (CSIRO), Australia's premier scientific research center,[12-15] and later verified by independent researchers.[16] Over the course of the last few years of the twentieth century, scientists painstakingly documented the unthinkable: that under culture conditions, **carnosine can not only slow down, but actually *reverse*, cellular senescence** – the process of "aging" at the cellular level.

Researchers have documented **Carnosine**'s "Striking effects on the cell morphology [shape and structure]," noting that "carnosine preserved a nonsenescent [youthful] morphology."[13] And adding **Carnosine** to the culture medium of aging cells doesn't just *slow down* cellular aging, but makes the cells *younger*: "These cells showed a remarkable rejuvenation, with regard to their morphology … and finally reached [ages] significantly greater than the control culture from which they were derived." **"Switching cells between media with and without carnosine also switches their phenotype [visibly observable properties] from senescent to juvenile, and the reverse."**[12] (see **Figure 1**).

Carnosine can not only slow down, but actually *reverse*, cellular senescence.

Based on their results, scientists "propose that carnosine is an important component of cellular maintenance mechanisms," and "favor the view that it may have a very important role in controlling cellular homeostasis"[12] – that is, in keeping cells in the tightly-regulated condition that optimizes their function.

Figure 1: a. Young Human Cells. b. Old Human Cells. c. Old Human Cells Bathed in Carnosine. With permission (12).

Taking Out the Trash

But *how* **Carnosine** exerts these effects remains a mystery. In test-tube studies, **Carnosine** protects cells and biomolecules against a sweeping range of toxic insults.[17] The one protective effect that's probably received the most attention in the life extension community is its ability to protect proteins against **glycation** – the process through which sugars bind to proteins and warp their structure, turning functional proteins into dysfunctional **Advanced Glycation Endproducts (AGEs)**.[18] But this effect has only been shown to happen in test tubes: it's not really clear that the same thing would happen in a living person, and in fact there's good reason to believe that it won't.[19]

But it appears that **Carnosine** may attack the same problem from a different angle, by actually boosting the cell's ability to *clear out* damaged proteins once they're formed. One of the problems with damaged proteins is that their mangled structures often don't give easy access to the enzymes that normally digest worn-out cellular components, making it difficult for the cell to maintain and renew themselves. Experimental studies have found that **Carnosine** reacts with proteins which have *already been damaged* by glycation[20,21] and other assaults on their structural/functional integrity,[20,22] forming "**carnosylated**" complexes which appear to be more easily removed than the original, warped protein.

Carnosine might actually help the body to *eliminate* glycated and other dysfunctional proteins.

At the same time, other such studies suggest that **Carnosine** revs up the **proteasome** – the cell's "recycling center" for malformed proteins.[15] Instead of *blocking* the formation of AGEs, in other words, **Carnosine might actually help the body to *eliminate* glycated and other dysfunctional proteins.**[20] (For more on the "anti-aging peptide," see "Of Carnosine and Cocoon" in *The Holistic Lifestyle* 1(5)).

The results at the *cellular* level are enticing. The question that begs to be answered next is: how do these effects translate out on a larger scale – on the health of our tissues and organs – when you supplement with **Carnosine**?

Eyes Syruped Shut

As already mentioned, the buffering role of **Carnosine** in the muscles was long thought to be its only biological purpose. So researchers were surprised to find it in such high concentrations in the eyes.[3-6] Misshapen proteins accumulate across the entire structure of the eye with "normal" aging,

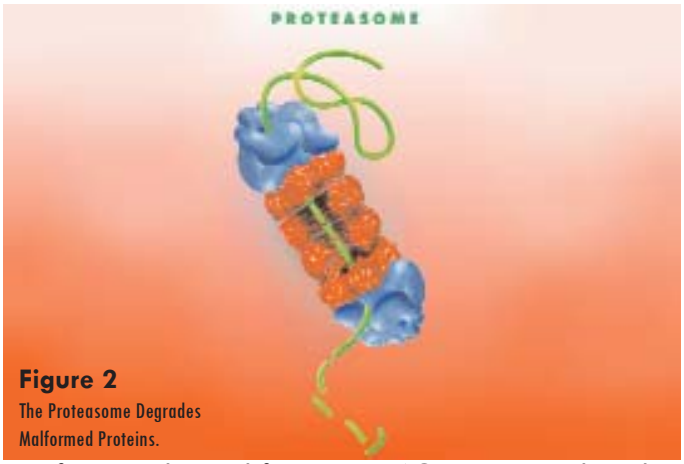


Figure 2
The Proteasome Degrades Malformed Proteins.

interfering with visual functioning. AGEs, in particular, play a major role in the universal age-related loss of eye structure and function, as well as in the more *specific* degenerative diseases of the aging eye, such as **cataracts**, **glaucoma**, and **age-related macular degeneration (AMD)**.[23] Granted its many protective roles, researchers began to wonder about the implications of **Carnosine**'s presence in the eye, how these effects might be exploited by the use of **Carnosine** as a *topical* supplement.

For example, glycation plays a role in the breakdown of the structure of the **vitreous fluid** – the Jell-O-like material that fills the eyeball (see **Figure 3**).[24,25] This breakdown leads to the gradual shrinking and liquefaction (**syneresis**)

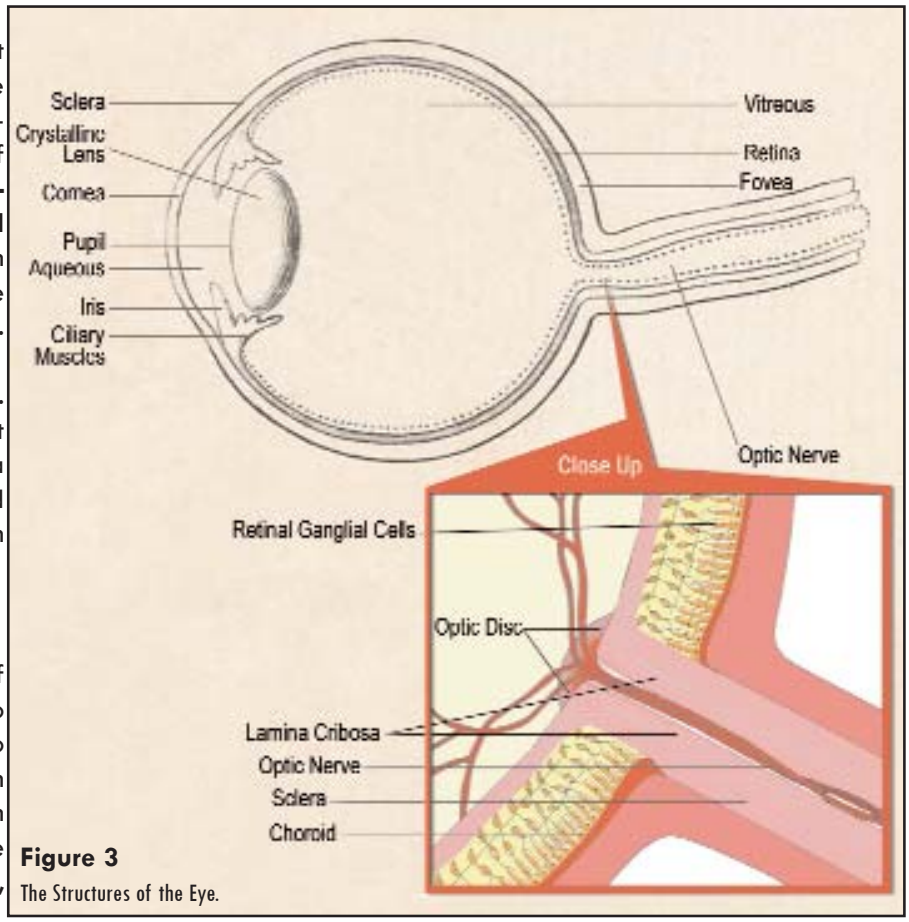


Figure 3
The Structures of the Eye.

of the vitreous, so that by the time the average person is in his or her nineties, nearly half of the vitreous has degenerated into unstructured goo.

Syneresis ultimately leads to tiny "cave-ins," in which the vitreous gel collapses away from the retina. These microcollapses often underlie "floaters" and light flashes, and they can ultimately cause the retina's sensory and pigment layers to tear apart (**retinal detachment**), causing devastating damage to the vision.[26] On top of that, new evidence has emerged to suggest that syneresis is also a contributor to the formation of **nuclear cataracts**.[27]

So test-tube studies showing that **Carnosine can prevent early glycation products from degrading the hyaluronan fluid of the vitreous gel,**[28] and animal studies showing that injected **Carnosine protects the lens of the eye from toxic lipid peroxide products in the vitreous,**[29] reinforce the idea that a topical **Carnosine** supplement might provide a powerful defense against the deleterious processes that age our eyes.

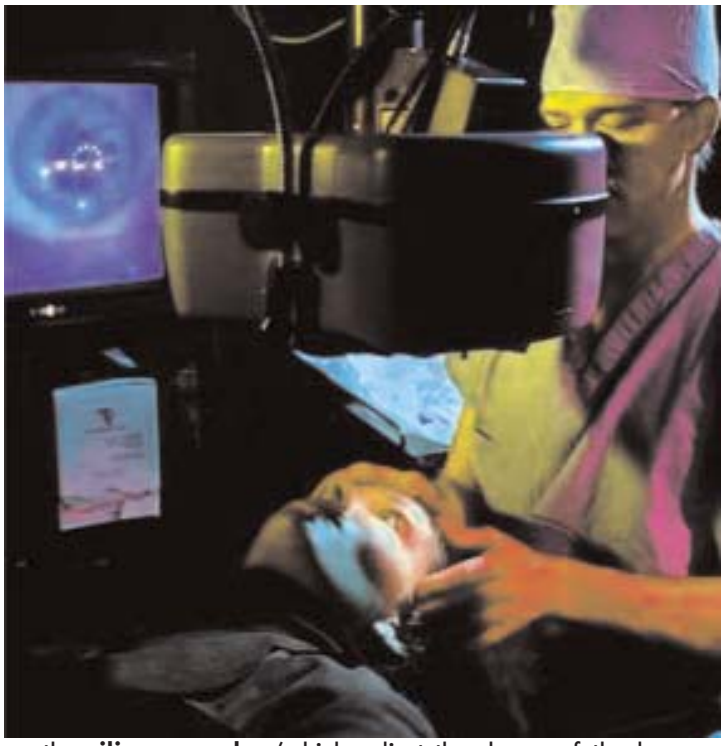
But *lots* of exciting-looking things happen in test-tubes or under irrelevant dosing conditions that never pan out in living, breathing human beings. And too often, companies sell people supplements based nothing more than on this kind of limited, preliminary evidence – supplements that actually do nothing to promote your health, however much they may cushion the company's bottom line. What we need to see is *real proof* that **Carnosine** is effective as a topical eye-health supplement: human studies (especially randomized, placebo-controlled trials) that document *in the body* the test-tube finding that **Carnosine** can protect against – and perhaps even actually *undo* – the damage to your eyes wrought by glycation and other protein-warping mechanisms of aging.

Those studies have been performed.

Flex that Lens!

The first human trials of topical **Carnosine** supplementation for eye health were performed in patients with **presbyopia**, by researchers at Harbin Medical University working in the late 1990s.[10] Presbyopia – the creeping, age-related loss of flexibility in the lens of the eye that leads to difficulty in focusing the eyes on close-up objects – is a major cause of the deterioration of sight that accompanies aging. The loss of flexibility, in turn, is in large part the result of AGE cross-links in the **crystallin** proteins of the lens.[23] So the test-tube and animal experiments showing that **Carnosine** can prevent – and perhaps even *reverse* – the accumulation of AGE and related damage to crystallin's structure[29-32] suggest that topical **Carnosine** supplements might restore lens flexibility, easing the strain

Topical Carnosine supplementation appears to alleviate eye tiredness and ... obviously improve eyesight.



on the **ciliary muscles** (which adjust the shape of the lens to focus on objects at different distances) and improving vision.

In an open study protocol, topical **Carnosine** supplements were used by patients in late middle age who had varying degrees of visual impairment, but no symptomatic cataracts.[10] Their results were consistent with **Carnosine**'s ability to protect the proteins of the eye from AGE damage – and perhaps even to help the body to *undo* it. Over the course of two to six months, the scientists observed that the use of **topical Carnosine supplementation "appears to alleviate eye tiredness and ... obviously improve eyesight**, giving more clear vision." Users found that topical **Carnosine** "could brighten and relax their eyes." The improvements were statistically significant.[10]

AGEs in the Cornea

Like the lens, the aging **cornea** (the transparent front portion of the eye – see **Figure 3**) also suffers structural damage with age. Much of this degeneration can be attributed to the warping of the **corneal stroma** – the collagen fibers whose specific structure and uniform layering is the foundation of the cornea's transparency.[23] At about the same time that the Harbin Medical University team was working with patients with "normal" eye aging, other researchers were reporting **success using Carnosine eyedrops against a variety of disorders of the cornea.**

In clinical studies involving 109 patients, these scientists found **Carnosine** to be effective in cases of primary and secondary **corneal dystrophy, corneal erosions, trophic keratitis,** and **bullous keratopathy,** as well as corneal

ulcerations and other damage wrought on the cornea by viral and bacterial infections.[33] The Russian government accordingly approved topical **Carnosine** supplementation for these uses as early as 1997.

"Set Phasers To *Haze*!"

People who have undergone **laser surgery** (both **Photorefractive Keratectomy (PRK)** and **LASIK ("LAser in-Situ Keratomileusis")**) are sometimes left with **corneal haze** – glare and haloes in their vision. *Temporary* corneal haze is normal in the early days after laser surgery, because the process actually *removes* the "skin" (**epithelium**) of the cornea, and the new epithelium which grows back over the site of the old corneal tissue is often temporarily opaque. But in some people, the damage is permanent.

Doctors usually try to reduce the risk of corneal haze in PRK by administering **steroid drugs**, whose anti-inflammatory effects cut down on the hazing of the new epithelium as it grows. But these drugs can cause problems of their own, including an increase in **intraocular pressure** (**IOP** – the fluid pressure that the vitreous exerts on the eyeball itself). Increased IOP can damage the eye and, in its extreme cases, cause nerve damage leading to **glaucoma**.

Because animal experiments have shown that **Carnosine improves wound healing after experimental surgery,**[34-37] and because previous trials had established the beneficial effects of **Carnosine** eyedrops on corneal structure and function,[33] a team of scientists with the Moscow Research Center decided to test topical **Carnosine** supplementation as a way to promote healthy regrowth of normal corneal epithelium after laser surgery, thereby reducing – or even *preventing* – corneal haze.

The Russian team first demonstrated that, when laboratory animals are treated with **Carnosine** eyedrops after experimental PRK, the corneal epithelium grows back more quickly and with less haze in than in eyes on which dummy eyedrops are applied.[38] Encouraged by this preliminary success, the investigators initiated two *human* trials in patients who had undergone PRK or LASIK.[38,39]

In the first trial,[39] 21 people who had suffered corneal haze following PRK (27 eyes were affected) were given topical **Carnosine** three times a day for two months. **Fully 57.9% of people using the Carnosine eyedrops experienced a reduction in corneal haze intensity, accompanied by an improvement in visual acuity;** only 14% of users' eyes continued to worsen. The positive results appeared in patients with low to moderate myopia, who had developed moderate haze (1 to 1.5 on a 3-point scale) within a month of surgery (there are no known treatments which are effective for late corneal haze of a higher grade than this).[39]

Users of topical Carnosine supplements following LASIK were one-third less likely to suffer corneal haze.

In a second, larger, and more rigorous trial,[38] patients who had just undergone PRK (41 patients (including 73 affected eyes)) or LASIK (34 people, 60 eyes) were given the same thrice-daily regimen of topical **Carnosine** as was used in the first trial, while corresponding control groups (41 PRK patients and 34 LASIK recipients) received **Carnosine**-free dummy eyedrops.

Because the regrowth of the corneal epithelium following laser surgery usually takes three to five days, it didn't take long for the researchers to see that users of topical **Carnosine** supplements experienced better outcomes than nonusers. Compared with people applying the placebo solution, **the healing of Carnosine eyedrop users' corneal epithelia regrew nearly *a day and a half* earlier** – a speeding of the regrowth process of roughly thirty to fifty percent! Even better, **users of topical Carnosine supplements following LASIK were one-third less likely to suffer corneal haze** than those using the unsupplemented eyedrops.[38]

Clearing the Lens

Cataracts are the most well-established form of havoc known to be wrought by AGEs and other damaged proteins in the eye.[23] The clarity of the lens depends on the precise molecular structure of the crystallin proteins of which it is made, and once these proteins have been twisted out of shape they can no longer transmit light. Over the course of decades of glycation and exposure to free radicals from ultraviolet light, crystallin becomes increasingly malformed, and its proteins begin to clump together into "**aggregates**," causing the lens to grow cloudy and dim. It's no surprise, therefore, to learn that *diabetes* is a major risk factor for cataracts … or that *aging itself* is the greatest risk factor of all.

Could there be a role for **Carnosine** in protecting the structure and function of the aging lens? Research has long suggested that it might.[40] **Carnosine** is found specifically concentrated in the lens, and is depleted in the lenses of

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cataract victims.[6,30] And as we've discussed, test-tube evidence suggests that **Carnosine** can not only *prevent* the disfigurement of the body's proteins by glycation and free radicals, but may even facilitate the body's *removal* of the wreckage,[15,20,22] clearing the way for healthy, new growth.

In the most remarkable of these studies,[32] researchers first glycated crystallin proteins in a test tube, causing it to form insoluble aggregates. At the molecular level, fluorescent polarization probes showed that the molecular

conformation of the glycated crystallin proteins had been warped by AGEs and carbonyl groups. Just like real cataracts, the glycated crystallin proteins could no longer transmit light properly, scattering about four times as much light as unglycated crystallin and increasing the opacity by about 20%. Then, they dropped a dilute **carnosine** solution into the medium.

The results were exciting. **AGE-related fluorescence quickly dropped by about 15% after exposure to Carnosine solution**, restoring the natural mobility of the previously AGE-shackled protein chains. For comparison, the scientists tested chemicals which can affect the same test in a non-AGE-specific way at the same concentration, and found no effect. And the *functional* impact was even more suggestive: **Carnosine solution *completely reversed* the increase in light scattering, and reduced the increased opacity of crystallin almost completely to normal baseline levels!**[32]

If those results panned out in the real world of the living body, the implications would be remarkable. It would mean that **Carnosine** was actually *undoing* the damage wrought over the decades by these deleterious biochemical processes – that the supplement could, in fact, *reverse* aspects of the aging of this tissue. In the case of the lens of the eye, it would mean that eyedrop-format **Carnosine** supplements would not only reduce a person's risk of *developing* cataracts, but actually help the body to *repair* and *remove* damaged crystallin proteins, *restoring* clarity to

Carnosine solution completely reversed the increase in light scattering, and reduced the increased opacity of crystallin almost completely to normal baseline levels!

the eye lenses of people with *existing* cataracts.

The potential of this approach created enough of a charge for some researchers to perform preliminary experiments using topical **Carnosine** supplements in animals with cataracts. When these studies showed that topical **Carnosine** could not only *prevent* model cataract formation,[29] but actually *clarify* the animals' *existing* cataracts,[30] the excitement of discovery must have been electric. And when two *human* trials – one using **Carnosine** itself topically[10] and another using a **Carnosine** metabolite as a deeper-penetrating delivery system for **Carnosine**[41] – demonstrated the same astonishing result in humans, there must have been *jolts* of juice arcing through the research centers.

The first human trial (an open investigation)[10] involved 96 senior citizens who had suffered with senile cataracts for periods ranging from as little as two years to as many as twenty-one. These individuals dropped topical **Carnosine** supplements into their eyes three or four times a day, for periods ranging from three to six months.

At the end of the study, the researchers found that **Carnosine eyedrops lead to improvements in eyesight and lens transparency** in the great majority of patients. They saw improvements in *every single one* of the people suffering with early-stage cataracts; and even in mature senile cataract, a remarkable *80%* of the topical **Carnosine** users experienced a benefit. The investigators went on to expand on these preliminary results with the sequential treatment of nearly a *thousand* cataract patients – to similar success, and with no side-effects observed.[10]

Carnosine eyedrops lead to improvements in eyesight and lens transparency.

In an innovative move, a second trial[41] used **N-acetyl-L-Carnosine**, a metabolite of **Carnosine** which the body slowly converts back into free **Carnosine**, instead

of **Carnosine** itself. (For the rationale for the use of this unique form of **Carnosine**, see the sidebar, **A "Penetrating" In-Sight**). In this randomized, double-blind, placebo-controlled study,[41] scientists affiliated with the Helmholtz Research Institute of Eye Diseases first evaluated the baseline state of cataract victims' eyes, testing their visual acuity and glare, as well as evaluating the lenses themselves using sophisticated imaging systems which allow for digital analysis of light-scattering and -absorbing centers. The trial included people with cortical, nuclear, posterior subcapsular, or combined cataract types.

The scientists then randomly handed out either topical **N-Acetyl-L-Carnosine** supplements (as a 1% solution) or an identical-looking placebo solution with no **N-Acetyl-L-Carnosine**, without anyone knowing who was getting which kind of eyedrop. Twenty-six people (with 41 cataract-afflicted eyes) used the genuine article, while thirteen individuals (21 eyes) received the bogus eyedrops. People in each group applied two drops of solution to their affected eyes twice a day, while a third group of cataract patients (10 patients, 14 eyes) received no eye-drops at all. For six months, everyone came back to the research center every alternate month to have their eyes re-evaluated; as well, a subgroup of the original patients joined a second trial which extended the original study to a total of two years, with checkups every six months.[41]

Ninety percent of the eyes of people supplementing with N-Acetyl-L-Carnosine eye drops saw their visual acuity improve.

After just six months, the differences between the two groups were striking. ***Ninety percent* of the eyes of people supplementing with N-Acetyl-L-Carnosine eyedrops saw their visual acuity improve**, with the strength of the effect ranging from a modest gain to a *full 100% recovery*.[41] In the same period, only *5.7 percent* of the eyes of people using the stand-in eyedrops were judged to have improved visual acuity – and over a third (34.7%) suffered a *worsening* of acuity, while most (60%) simply retained the same impaired vision with which they had begun the study.

What's more, **the two-year extension showed that N-Acetyl-L-Carnosine eyedrop users *maintain* their improved vision, while the eyesight of those not receiving the supplement continues to deteriorate.** By the end of the study, 87% of the eyes supplemented with topical **N-Acetyl-L-Carnosine** were still better than they had been before starting use of the eyedrops, and none were worse off than they'd been at the beginning; by contrast, a depressing 89.5% of the eyes of nonusers had lost acuity.[41]

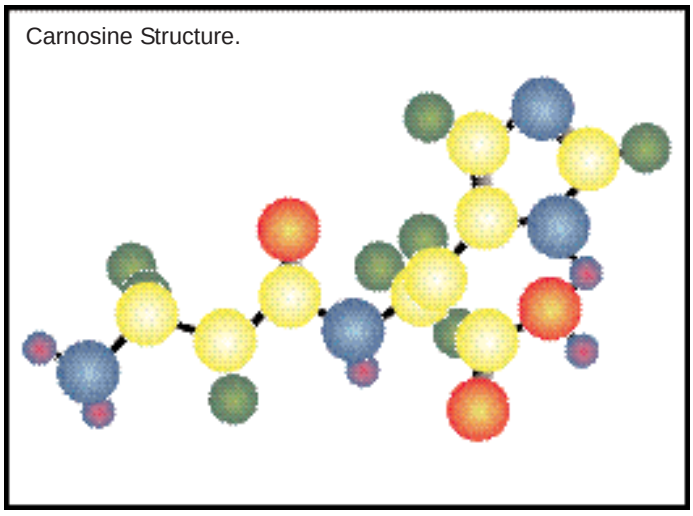
On top of the gains in visual acuity, researchers observed that **N-Acetyl-L-Carnosine topical supplementation also clearly improves glare sensitivity**, with 88.9% of **N-Acetyl-L-Carnosine** eyedrop users' eyes seeing improvements ranging from 27 to 100% after just six months; again, the divide separating supplementers from nonsupplementers was unequivocal, with over half (56.3%) of nonusers' eyes deteriorating and *none* getting any better.[41] The glare sensitivity tests were not repeated at the two-year mark.

The scientists were also able to *directly* evaluate the power of topical **N-Acetyl-L-Carnosine** supplementation on the actual opacification (clouding) of the lens, thanks to new medical imaging techniques. At the end of the full two-year trial, the image analyses showed that 47.8% of **N-Acetyl-L-Carnosine** topical supplement users' lenses were clearer than they had been at the beginning of the trial – and none had worsened. As you might expect, people whose eyedrops did not contain **N-Acetyl-L-Carnosine** suffered a dark mirror opposite of these sunny results: *none* of their eyes showed improvements on the image analysis, and a predictable 47.4% of the lenses continued the hazy slide into blindness.[41]

The results of these trials can only be described as revolutionary. For the first time, simple eyedrop treatments were proved to improve the vision of cataract victims, and to actually *reverse* the clouding of the lens. And the treatment was not a drug, but an orthomolecule: a substance *naturally present* in the body and essential to its health. And this is *on top of* the results observed in presbyopia, corneal disorders, and people whose vision has been damaged by laser surgery gone wrong.

With **Carnosine**'s wide-ranging powers, and **N-Acetyl-L-Carnosine**'s ability to bring those benefits to a wider range of eye tissues, what *else* might we expect from this remarkable new topical supplement?

Carnosine Structure.



A "Penetrating" In-Sight

You might be wondering why, after so many successful human[10,33,38,39] and animal[29,30,38] studies of topical supplementation using plain **Carnosine** for eye health, the Helmholz Eye Clinic team would instead use the **Carnosine** metabolite **N-Acetyl-L-Carnosine** in their studies.

These researchers' animal studies had shown the potential of **Carnosine** *injections* as a treatment for cataracts.[29,30] And some of these results they using *injected* **Carnosine** appeared to be the result of protecting the lens of the eye against lipid peroxides present in the **aqueous humor** of the eye – the clear fluid between the cornea and the lens (see **Figure 3**).

But research performed by this same group[31] and others[42] revealed that **conventional Carnosine eyedrops do not result in the accumulation of free Carnosine in the aqueous humor.** The most likely culprit in the case of the missing **Carnosine** is an enzyme in the body called **carnosinase,** which breaks **Carnosine** down into its constituent amino acids (beta-alanine and histidine).[43,44] (This carnosine-degrading action is also the reason why you need to take high doses of **Carnosine** (a gram or more, in human-equivalent terms) if you want to effectively increase tissue levels of **Carnosine** using an *oral* supplement,[45-47] and why such high doses are necessary to elicit **Carnosine**'s many protective benefits in living organisms).[48-52]

In order to get the *full* range fo benefits of **Carnosine** in the eye, these researchers wanted to find a way to increase free **Carnosine** levels in the aqueous, *without* the necessity of injection. To overcome the carnosinase problem, the Russian team looked to **N-Acetyl-L-Carnosine,** a natural metabolite of **Carnosine.**

N-Acetyl-L-Carnosine is one member of a family of **Carnosine**-related biomolecules found in the body. These compounds are concentrated in many of the same tissues as **Carnosine**: the brain contains roughly equal proportions of **Carnosine** and **N-Acetyl-L-Carnosine,**[53] and there's actually *more* **N-Acetyl-L-Carnosine** in muscle tissue than there is **Carnosine** itself.[54]

But **N-Acetyl-L-Carnosine** is resistant to the degrading influence of carnosinase.[43,44] So these investigators theorized that topical **N-Acetyl-L-Carnosine** might penetrate, *intact*, into the aqueous humor. Once there, **N-Acetyl-L-Carnosine** would then be slowly converted into **Carnosine,** thanks to enzymes in the body (**N-acetylesterase** and **N-acetyltransferase**) that interconvert these two forms of **Carnosine** as part of their normal biological function.[40] The liberated **Carnosine** would then be free to work its magic from within the aqueous humor.[31]

To cut a long story short: they tried it, and it worked. After applying **N-Acetyl-L-Carnosine** as a 1% solution to the eyes of the rabbits, **Carnosine** began to appear in the animals' aqueous humors within fifteen to thirty minutes, boosting **Carnosine** concentrations to 162% of their baseline levels.[31] These concentrations were similar to the ones which test-tube studies[29] suggested would achieve the specific effect that they were after – namely, the protection of the lens from lipid peroxides.

Does any of this really matter? That depends on how you look at it. The Russian researchers were looking to achieve a specific effect for a specific reason – to concentrate **Carnosine** into the aqueous humor, because of their theory about the importance of delivering **Carnosine** to this part of the eye to get its anti-cataract benefits. As other human studies show,[10] "regular" **Carnosine** achieves the same goal without penetrating into the aqueous, suggesting that this specific effect may not be a necessary – or even important – part of **Carnosine**'s *cataract*-fighting powers.

But the finding that topical **N-Acetyl-L-Carnosine** supplementation can increase **Carnosine** concentration in parts of the eye where regular **Carnosine** can't reach has broader implications. Because in addition to cataract patients, **Carnosine** eyedrops are also of interest as a supplement for people with *healthy* eyes, who would like to use topical **Carnosine** to *support* that eye health. For such people, this research shows that **N-Acetyl-L-Carnosine is the preferred topical supplement for *total eye health*,** because it can boost **Carnosine** levels in places where topical supplements using **Carnosine** itself would be ineffective. Topical **N-Acetyl-L-Carnosine** extends **Carnosine**'s benefits to regions of the eye which are inaccessible through conventional **Carnosine.**

Resisting the Pressure

A prominent example of a potential – but as-yet unproven – place for **Carnosine** in eye health is in **glaucoma.** Glaucoma is a major cause of vision loss, which results from damage to the nerve cells of the innermost layer of the retina (the **retinal ganglion cells** – see **Figure 3**). These neurons are located at the back of the eyeball to the brain, and come together to form the **optic nerve;** the spot where they come together to pass through the white outer coat of the eyeball called the **optic disk,** and the surrounding junction with the white of the eye is termed the **lamina cribrosa** (**Figure 3** again).

What, then, is the potential role of **Carnosine**? The nerve damage that underlies glaucoma is the result of excessive stress placed on the optic nerve by the fluid pressure inside the eyeball (**intraocular pressure**, or **IOP**); yet in about a third of people with glaucoma, the pressure in the eye is within the "normal" range. That's because vulnerability to glaucoma is also affected by factors other than IOP, such as age-related changes to the optic disk and the retinal ganglion cells.[23] AGE damage to the retinal ganglion cells themselves – or to supporting structures such as the lamina cribrosa, which accumulate AGE proportionately to a person's biological age – may be one such key factor.[23] In the diabetic animal model, the atrophy of the optic nerve can be prevented by inhibiting AGE formation.[55]

There's also evidence that **Carnosine** may help to support more normal, healthy IOP. **Carnosine** is a member of a group of compounds that run the molecular water pumps in at least some eye tissues,[56] a function critical to these cells' viability. When **Carnosine** is *injected* into the eyes of rabbits, IOP falls;[57] the use of **N-Acetyl-L-Carnosine** instead of regular **Carnosine** may again play a key role in ensuring that **Carnosine** gets where it has to go in order to exert this beneficial effect.

The Rest of Us

The results of the many human trials documenting the benefits of using topical **Carnosine** (and especially **N-Acetyl-L-Carnosine**) supplements for eye health are exciting – and they're probably just the tip of the iceberg. These studies appear to constitute proof-of-concept for the wider thesis that the use of topical **Carnosine** and **Carnosine** precursors can allow the body to remove dysfunctional proteins from the eye, facilitating the replacement of misshapen old proteins with fresh new ones and the rejuvenation of the tissue.

To date, clinical trials have demonstrated the ability of **Carnosine** – and especially the unique **Carnosine** metabolite **N-Acetyl-L-Carnosine**, a biological "delivery system" for **Carnosine** – to *treat* eyes damaged by a wide variety of *specific* disorders, from cataracts to corneal dystrophy, from improperly-healed corneal epithelia to presbyopia. But they bear an important implication for the rest of us. These studies clearly point to the potential of **Carnosine**/**N-Acetyl-L-Carnosine** eyedrops to support the maintenance of normal, healthy eye structure and function in people whose eyes are just fine – and whose owners want to keep them that way.

An Important Note About N-Acetyl-L-Carnosine Topical Formulations

In *all* of the clinical trials, **N-Acetyl-L-Carnosine** has been used by itself, with no added antioxidants or other ingredients other than formulants (such as buffering agents) required to make a viable **N-Acetyl-L-Carnosine** ophthalmic solution. The metabolism of **N-Acetyl-L-Carnosine** into **Carnosine** depends on enzymes in the body (**N-acetylesterase** and **N-acetyltransferase**) which accomplish this transformation as part of their normal biological function. The activity of these enzymes can be significantly changed by the presence of antioxidants other than **N-Acetyl-L-Carnosine** in the area.[58-60]

Therefore, mixing other antioxidants – such as vitamin A or alpha-tocopherol – into **N-Acetyl-L-Carnosine** eyedrops is asking for trouble. Under these circumstances, the conversion of **N-Acetyl-L-Carnosine** into **Carnosine** will be altered, with unpredictable results on the levels of free **Carnosine** delivered to different tissues within the eye.

The results observed in clinical trials flow from the natural, unmodified kinetics of these enzymes. **Products which adulterate N-Acetyl-L-Carnosine with unnecessary additional antioxidants are untested, potentially ineffective, and may theoretically even *damage* your vision in the long term** by leading to the inappropriate tissue-specific release of **Carnosine**, conversion to histamine, and resultant chronic, low-level inflammation. **Ensure that any N-Acetyl-L-Carnosine supplement you use is free of extraneous antioxidants.**

The Grand Vision

The DNA code lies coiled like the Serpent of Knowledge in the heart of your cells, untwisting to reveal its mysteries to the biological engines which build you up from its template. In a very real sense, you *are* the proteins that these enzymes make. And we age, in large part, because of the forces that degrade the integrity of these same proteins – and of the lipids and nucleic acids that many of these proteins exist to create.

The body is equipped with mechanisms that strive to keep this stochastic chemistry at bay, repairing damage and sopping up toxic molecules. But the repair is always imperfect, and the defenses limited. Slowly but surely, chemistry triumphs over biology.

Carnosine promises to intervene in this cycle in a fundamentally new way, making it easier for the body to rid itself of the cellular garbage that clogs our cells and creates structural deviations from the archetypal pattern laid out in the Code of Life. With **Carnosine** eyedrops, this potential may be delivered directly to the ocular proteins that need it; and with **N-Acetyl-L-Carnosine**, the power of **Carnosine** can be smuggled into the hidden recesses that **Carnosine** itself cannot reach.

The day is coming when radical new life extension technologies will undo the ravages of the aging process, creating an endless summer for the young and allowing the aged to slough off the ravaged husks of the years. As we've seen, topical **Carnosine** supplements may be the first, dawning glimpse of the regenerative medicine of tomorrow – and its users, the first to open their eyes to a new human potential.

The Bottom Line

• Research suggests that **Carnosine** may not only slow down, but actually *reverse*, some kinds of biomolecular damage. It may undo the clumping together of damaged proteins, increase the activity of cellular "garabage collectors," and make it easier for those "garbage collectors" to pick them up.

• Many vision problems are closely related to the accumulation of these damaged proteins. Therefore, it was suggested that topical Carnosine eyedrops might be helpful.

• ***N*-acetyl-L-Carnosine**, a metabolite of Carnosine which the body slowly converts back into free Carnosine, acts as a biological "delivery system" for Carnosine, allowing for slower, more thorough delivery of free Carnosine into the eye's tissues and access to areas of the eye where Carnosine itself cannot penetrate. Therefore, research suggests that ***N*-acetyl-L-Carnosine** is the superior form of Carnosine for use in topical supplements.

• Clinical trials have borne this out. Studies have found topical Carnosine and/or ***N*-acetyl-L-Carnosine** to be helpful in eye structure and function in people with **age-associated visual impairment**, primary and secondary **corneal dystrophy, corneal erosions, trophic keratitis, bullous keratopathy**, and above all **cataracts**. Other studies have reported more rapid and complete healing after **laser eye surgery** in people using Carnosine eyedrops.

• Because malformed proteins are implicated in nearly every aspect of age-related visual decline, these studies clearly point to the potential of **Carnosine**/**N-Acetyl-L-Carnosine** eye drops to support the maintenance of normal, healthy eye structure and function in people whose eyes are just fine – and whose owners want to keep them that way.

• In *all* of the clinical trials with ***N*-Acetyl-L-Carnosine**, the supplement has been used *by itself*, with no added antioxidants or other ingredients in the eyedrops other than other than the trace levels of formulants such as buffering agents required to make a viable **N-Acetyl-L-Carnosine** ophthalmic solution. The metabolism of **N-Acetyl-L-Carnosine** into **Carnosine** depends on enzymes in the body which accomplish this transformation as part of their normal biological function. The activity of these enzymes can be significantly changed by the presence of antioxidants other than **N-Acetyl-L-Carnosine** in the area.

• Therefore, although you can feel free to continue to take any *oral* antioxidant supplements while you use **N-Acetyl-L-Carnosine** eyedrops, *mixing* antioxidants (such as vitamin A or alpha-tocopherol) into the *eyedrops themselves* is asking for trouble. **Ensure that any topical N-Acetyl-L-Carnosine supplement you use is free of extraneous antioxidants.**

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