

Dr. Mark Babizhayev is one of the principal Russian researchers behind the development and use of N-acetylcarnosine or NAC eye-drops, which are being heralded as a breakthrough in the treatment and prevention of senile cataract. In this interview, Dr. Babizhayev discusses with Phil from International Anti-Aging Systems (IAS) some of the results of his research.

Phil: "Dr. Babizhayev thank you for being kind enough to undertake this interview for the IAS Anti-Aging Bulletin.

Dr. Babizhayev: "You're welcome."

Phil: "Perhaps I could start by asking you to please tell our readers how many years you have been involved in the research with NAC?" [Ed.- n-acetylcarnosine].

Dr. Babizhayev: "We started our work on N-acetylcarnosine as a potent ophthalmic drug in 1991, after we concluded the contract relations with the executives Dr. Edoardo Bozzo Costa and Mr. Ovidio Caveri of Bruschetini S.r.l., Genoa, Italy."

Treatment of human cataract with the eye drops of 1% n-acetylcarnosine for the period of 5 months.



Left image shows the appearance of cataract which resembles a bat in its form.

Right image shows that this opacity has disappeared after the cited period after treatment with n-acetylcarnosine is completed. The lens has become clearer.

Phil: "In all that time, when did you first realize that NAC was something special for the treatment of cataract?"

Dr. Babizhayev: "We initially realized that NAC was promising for the treatment of human cataracts when the first pharmacokinetic studies were completed. They showed that NAC can act in-vivo as a pro-drug of L-carnosine in ophthalmic application, as an antioxidant." [Ed.- Clin. Chim. Acta 1996, 254, 1-21].

Phil: "Presumably, your first experiments were undertaken with animals? Would you like to elaborate on some of the results you obtained?"

Dr. Babizhayev: "The NAC anti-cataract eye drops have been carefully tested in animals. We have processed the treatment of age-related cataracts in canines and experimental models of cataract in rabbits. The most striking results have been obtained using a 1% NAC instillation in canines with age-related cataracts. We have determined the efficacy of cataract treatment, and we have revealed a new phenomenon of melting snow upon the instillation of NAC, for the chronic treatment of cataract within only 1-month [Ed.- see photos]. The cortical appearance of cataract reversal starts from the periphery and then the lens becomes more transparent. This is then accompanied by the improved visual behavior of the animal. Rigorous computerized image analysis have been supplied to support the evidence of the cataract treatment in rabbits [Ed.- see photos]. The striking results of reversing cataract and the prevention of the lens opacities are clear, and have been revealed in traumatic and liposome-induced types of modeling cataract."

Phil: "Later of course, you were also involved with NAC eye-drops in human trials, what kind of results did you get there?"

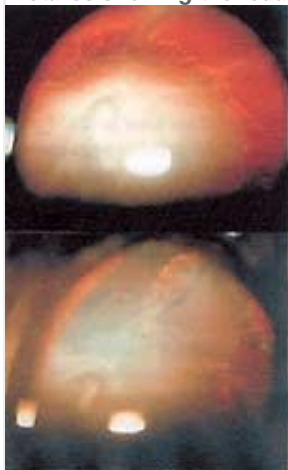
Dr. Babizhayev: "First we developed sensitive measurements for the lens opacities in humans. These were original techniques of glare tests [Ed.- see figure]; they are very sensitive to even tiny changes of the lens opacities and we also tested the macular function, which is the vision behind the cataract. We have also utilized stereocinematographic slit-image and retro-illumination photography, with subsequent interactive digital image analysis and 3D computer graphics for the lens light scattering, or absorption. The intra-reader reproducibility of the measuring techniques for cataractous changes were good. One group of patients were the control reference group, they demonstrated the variability in densitometric readings of lens clouding and they had negative advance in glare sensitivity at 6 months, and a gradual deterioration of visual acuity and gross transmissivity of lenses at 24 months, these results were compared at baseline and 6-month follow-up examinations. However, when compared with baseline examination at 6 months, 41.5% of the eyes treated with NAC eye drops presented a significant improvement in visual acuity of 7-100% and 88.9% of the eyes ranged a 27-100% improvement in glare sensitivity. Topographic study demonstrated less density and corresponding areas of opacification in posterior subcapsular and cortical morphological regions of the lens. That is consistent with visual acuity up to 0.3. The total study period was over 24 months and it revealed that the beneficial effect of NAC is sustainable."

Image analytical readings of lenses indicated that no cases resulted in a worsening of visual acuity for the NAC-treated group of patients, and in most of the patients drug tolerance was good. Statistical analysis revealed significant differences between 6 and 24 months as an overall cumulative and positive change of the characteristics of cataracts in the NAC-treated group, when compared to the control group. The synthesized N-acetylated carnosine eye drops are therefore proposed as an effective and physiologically acceptable drug for non-surgical treatment of age-related and senile cataracts."

Phil: "Were there any side-effects noted in the human trials?"

Dr. Babizhayev: "For most of the patients treated, drug tolerance was good and no side effects were specifically associated with the application of 1% NAC. What is more, no recurrence of cataract development occurred during the period of NAC application."

Pictures showing the reduction of cataract in canine eyes.



Top picture: this shows the canine cataract before treatment with n-acetylcarnosine eye drops.
Bottom picture: this shows the results of the treatment after only 1 month. Already we begin to see the break-up of the impaired proteins - an effect that for obvious reasons has been described as "melting snow".

Phil: "Have you drawn any conclusions on why NAC is able to treat cataract so successfully? Is NAC breaking existing cross-links of proteins as well as inhibiting them? Or are there other forces at work here too?"

Dr. Babizhayev: "The therapeutical indication for NAC to treat senile cataract can lead to diminishing of light-scattering units in the lens, probably by prevention of the oxidative modification of crystallins and utilization of lipid peroxides, that promote lens opacities. Most known biological antioxidants that can prevent oxidative damage to biological molecules show some specificity in their mechanism of action, and so they can provide only one type of protection. N-acetylcarnosine and its bioactivated analog L-carnosine may exert their antioxidant properties by removing high reactive peroxide compounds from the lipid phase of the lens, i.e. the fiber cellular membranes. We assume the advantage of NAC is as a universal antioxidant, which relates to its ability to give efficient protection against lipid peroxidation, both in the lipid phase of biological membranes and in the aqueous environment. We maintain the hypothesis that NAC assists the proprietary lens antioxidant systems including glutathione, and the enzymatic antioxidant systems of the lens, to provide their operation most effectively. Glutathione in conjunction with glutathione-related systems, like glutathione reductase, can partially reduce the S-S bonds in the cross-linked lens proteins. Besides, we agree that NAC can prevent and reverse the cross-linking of the lens proteins, including crystallins induced by lipid hydroperoxides and their secondary breakdown molecular products, like aldehydes. This mechanism can be prominent to reverse and prevent lens opacification that is related to the glycation reactions of the lens proteins, and as you know they are also associated with complications of diabetes."

Phil: "To-date what is the longest period that anyone has been continuing to receive NAC eye-drops?"

Dr. Babizhayev: "Usually, we only provide well-controlled randomized trials. Accordingly, we have no personal experience of clinical evaluations lasting more than 2 years of therapy. We have always avoided any substance materials that have originated from uncertain sources, so recently we developed the precise cGMP manufacturing process for NAC."

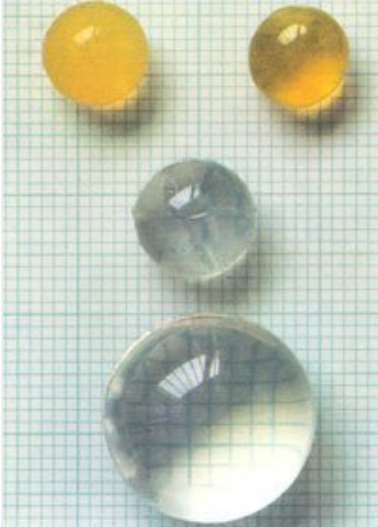
Phil: "So are the benefits of NAC eye-drops being preserved in these long-term patient trials?"

Dr. Babizhayev: "Again, the total study period over 24 months revealed that the beneficial effect of NAC is sustainable."

Phil: "I appreciate that your work has focused on the treatment of patients with cataract, but do you envisage that NAC may also have a role to help prevent cataract?"

Dr. Babizhayev: "Oh yes! We usually pursue the following therapeutical strategy for the treatment of human cataracts with NAC. Firstly, we expect to obtain the maximal effect of improvement of visual acuity within the first 3-5 months of therapy, then the clinical strategy is to maintain the received visual outcome for a lasting period. In this connection, NAC does indeed help to prevent human cataracts."

Picture showing human cataract and normal human eye lenses.



Cataract is caused by the nuclear matter of the elderly human lens hardening and taking on a yellowish/ brown color.

Phil: "Of course it has also been documented that L-carnosine, the sister to NAC, is able to help prevent cross-links from occurring, yet I believe you do not advocate L-carnosine as an eye-drop. Could you please explain to our readers why?"

Dr. Babizhayev: "Topical administration of pure L-carnosine to the eye does not lead to accumulation of this compound in the aqueous humor within a reasonable amount of time, or in a concentration exceeding that of the placebo-treated eye. Exogenous L-carnosine entering the organism topically to the eye, intravenously, intraperitoneally, or with food is not accumulated by the tissues, but is excreted or destroyed by carnosinase, a dipeptidase enzyme that is present in blood plasma and in the aqueous humor of the anterior chamber of the eye. With a topical eye application, L-carnosine releases the toxic compound, histamine, which can severely promote oxidation reactions. Compared to L-carnosine and due to its relative hydrophobicity, NAC appears to penetrate through the cornea gradually, thus maintaining a longer active therapeutic concentration of L-carnosine in the aqueous humor and the lens of the treated eye. Importantly, NAC is highly resistant to hydrolysis by carnosinases. Different techniques of ocular administration with NAC prove its efficacy for the treatment of cataracts, combined with excellent tolerability to the eye, safety, and the lack of possible side effects."

Pictures showing the reduction of cataract in rabbit eyes.



Top picture: shows the cataract in the rabbit eye large in the center of the eye, before treatment with n-acetylcarnosine eye drops.

Center picture: shows the cataract in the rabbit eye greatly diminished after 3 months of treatment with n-acetylcarnosine eye drops.

Bottom picture: shows the cataract even further diminished after 6 months of treatment.

Phil: "Please allow me to recap. Your results indicate that L-carnosine when used as an eye-drop could be dangerous. However, some NAC breaks down into L-carnosine, but presumably NAC is not causing any side effects because it only breaks down into L-carnosine at a later stage; which is then not dangerous to the eye. Is that basically correct?"

Dr. Babizhayev: "Yes that is correct. Specifically, L-carnosine is first hydrolyzed with carnosinase and histamine and is released postponed from its histidine moiety via the activity of histidine decarboxylases in tissues. As the aqueous humor of the eye is a flow system, L-carnosine can be released from the NAC ophthalmic vehicle in the eye and becomes active as an ophthalmic antioxidant. L-Carnosine released in situ from its ophthalmic pro-drug NAC enters the lens, which is not equipped with carnosinase activity and concurrently L-carnosine is washed out with the aqueous humor flow, this then allows the chronical application of NAC for the treatment of human cataracts over years."

Phil: "I also understand that you have acquired the proprietary process of producing a high-purity NAC for eye-drop use. Did you find that normal production of NAC was in some way inferior?"

Dr. Babizhayev: "Thank you for this important question. The application of NAC for the treatment of cataracts has been protected by the PCT patents by our group."

[Ed.- They are as follows: Babizhayev MA, Bozzo Costa E. Composizioni farmaceutiche contenenti N-acetilcarnosina per il trattamento della cataratta. Italian Patent A61K gruppo37/00 20122 MI, Priority 15.10.1993 and Babizhayev MA, Bozzo Costa, E. Pharmaceutical compositions containing N-acetylcarnosine for the treatment of cataract. Patent PCT/EP 94/03340 SCB 238 PCT, 10.10.1994].

"However, we advise competitors not to rush forward. There are many carnosines with little or abandoned biological activities. This strongly varies with the content of transition metals in the peptide moiety, admixtures of hydrazine and other impurities dependent to the type of obtention and/or synthesis. We have developed the important cGMP manufacturing process for NAC which demonstrates its extraordinary biological anti-cataract activity in humans. We have provided the chemical-functional correlation of the NAC properties and ensured the clinical anti-cataract efficacy of the product for human lenses. But if NAC is extremely pure this also abandons the antioxidant and biological activities of the peptide product. Innovative Vision Products, Inc., of Delaware, keeps secret their know how on the processing and permanent biological and analytical controls, in order to manufacture the effective anti-cataract NAC bulk material. This technology has been envisaged by cooperation and extensive studies with a Japanese manufacturing facility."

Phil: "This is obviously an important breakthrough in anti-aging medicine and I can foresee numerous attempts to copy your innovation. How can patients be sure that they are getting your particularly pure NAC eye-drops when purchasing such material?"

Dr. Babizhayev: "They should ensure that the label tells them that the product was formulated by Innovative Vision Products [Ed.- IVP]. If it does not state that, it isn't our high-purity NAC and will either be ineffective or possibly even dangerous for eye-use."

Phil: "I congratulate you Dr. Babizhayev on your incredibly important work. It certainly appears that NAC eye-drops are a major contribution to the control and indeed the eradication of cataract, which by itself is clearly an age-related disorder. Do you believe that NAC may be useful for any other eye disorders?"

Dr. Babizhayev: "We think that further attention should be directed to ophthalmic application of NAC to treat cataract, ophthalmic manifestations of diabetes, ocular inflammation, primary open-angle glaucoma, and retinal disorders which involve the pathological mechanisms associated with oxidative stress."

Phil: "I think this is one of the most exciting anti-aging products to emerge in recent years and I believe it is a clear example of anti-aging medicine at its best. I wish you all success with this project and your future projects."

Dr. Babizhayev: "Thank you."

Phil: "Will you come back and tell the readers of the IAS Anti-Aging Bulletin about any further developments and breakthroughs you have?"

Dr. Babizhayev: "Of course, my pleasure."

Authors

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