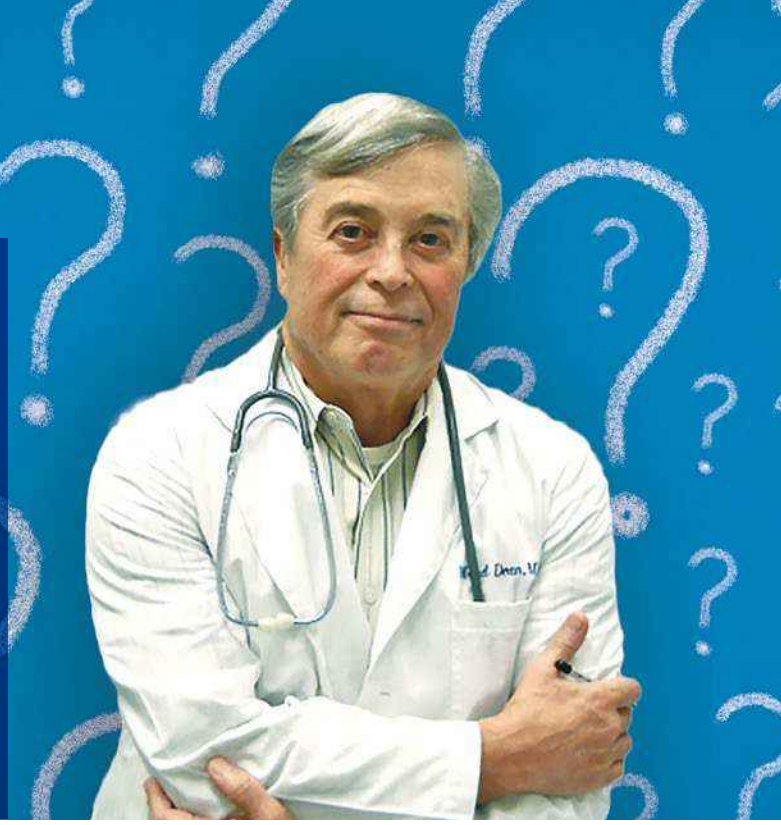
Dr Ward Dean answers your questions

We are delighted that Ward Dean, M.D., one of the world's foremost antiaging physicians, has agreed to answer our readers' questions. Full details about Dr. Dean can be seen at his website: **www.warddeanmd.com**



Dear Dr. Dean

Q. "I am most interested in the glycation theory of aging- whereby because of proteins cross-linking they become impaired etc. I am a 50 year old male who has been tested by BioCLIP™ and found to have hardening of the arteries. I also have mild cataracts and a potential pre-diabetic (type-II) development, (hence my interest in this theory!) Please advise me on any suitable strategies to reduce my glycated blood load."

B.A., Oregon

A. Dear B.A.,

The glycation theory of aging is a modern outgrowth of the venerable cross-linking theory of aging, first proposed by Johan Bjorksten in 1942.1,2 Bjorksten was a chemist from Finland, who earned his Ph.D. degree at the University of Wisconsin in 1937. He went to work for the Ditto Corporation of America, which was the 'Xerox' of the day.

Protein cross-linking as cause of aging

While at Ditto Corporation, one of the main problems Bjorksten faced was to develop a way to increase the ability of the Hectograph films to withstand summer temperatures, exposure to water, mechanical stretching and friction, and to prevent their drying out and cracking. The 'aging' of hectograph films was due to the cross-linking of protein molecules, which Bjorksten believed was also the cause of aging in humans. This was confirmed in a crude way by comparing the similarity between the shape of the mortality curve for humans (Fig. 1) with

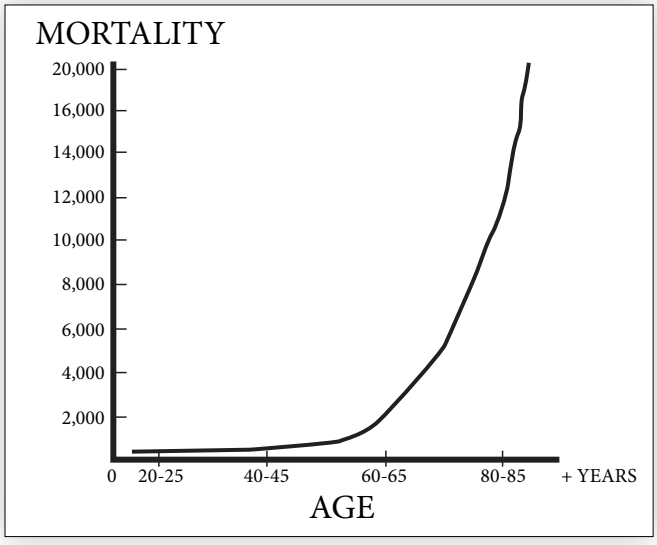


Fig. 1. Mortality rate plotted against time for white American males.3

a viscosity curve of gelatin during a cross-linking reaction (Fig. 2).3,4 The crosslinkage theory stated that the principal cause of aging was the linking together of two or more large molecules (macromolecules), which progressively linked with other molecules, impairing the functioning of cells, tissues, and organs, resulting in the aging of the organism.

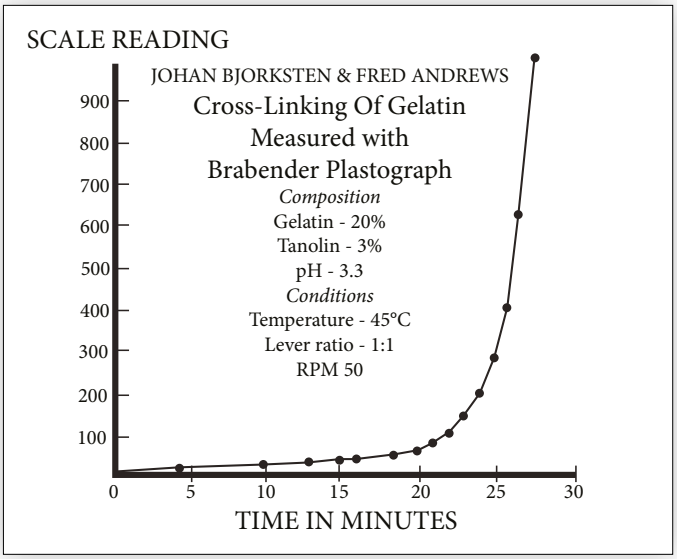


Fig. 2. Rate of progressive cross-linking of gelatin.4

Search for cross-linkage inhibitors

Bjorksten focused on a potential means of preventing and breaking up crosslinkages by using chelating agents that attach to metals within the body, enabling them to be excreted. Ethylene-diamine-tetra-acetic acid (EDTA) is a synthetic amino acid that removes metal-based crosslinkages by chelation, thereby "depolymerizing the gerogenic aggregates." 5 Chelating agents in current clinical practice besides EDTA (approved for use in the treatment of lead poisoning) are deferoxamine (Desferal® for acute iron intoxication), and DMSA (used to treat lead and mercury intoxication). Physician members of the American College for Advancement in Medicine (ACAM) are proponents of intravenous chelation therapy with EDTA as a treatment for many chronic degenerative diseases, like atherosclerosis, hypertension, diabetes, and Alzheimer's disease.6 Chelation with oral EDTA chelation is also becoming more widely used.

[Ed. - EDTA is available in BCI®, Beyond Clean 2® and Beyond Fiber®]

Other natural chelators include garlic, 7 chlorella, 8 lactic acid, citric acid, and malic acid. Bjorksten demonstrated that lithium was also an effective aluminum chelator and crosslinkage inhibitor, stating that "lithium continues to be the most effective electrolyte for aluminum detachment." 9

[Ed. – Lithium orotate is available from IAS]

Chelators as life-extending substances

A number of studies confirm that chelating agents, particularly, EDTA — may have life-extending properties. Scientists demonstrated the life-extending effects of EDTA on lowly rotifers (small multi-celled animals found in freshwater lakes and ponds).10-14 In the Soviet Union in the 1970s, Dr. T.L. Dubina performed a series of studies with EDTA on the life span of rats. In most of the studies, the mean life span of female rats treated with EDTA was increased by nearly 50%, and in one study the maximum lifespan increased 18-25% over the control animals. 15

Aluminum—a powerful cross-linker

Aluminum is a highly reactive metal that occurs freely in nature, and comprises over 8% of the earth's crust. Although it also occurs very widely in human nutrition, (most people ingest 10-100 mg of aluminum daily), it does not play a role in any known metabolic process. Aluminum is highly toxic, even in extremely small amounts, and although the neurotoxic effects of aluminum have been known for many years,16 scientists have recently shown that aluminum accumulation may contribute to Parkinson's disease17 Down's syndrome18 and Alzheimer's disease.19

Aluminum uptake increases with age

In 1955, during a talk on gelatin crosslinkages and aging at the Gerontological Society in Baltimore, Bjorksten discussed the relationship of aluminum to crosslinking. One of the attendees, Prof. H.H. Zinsser of Columbia University, was so interested in the concept that he and Bjorksten began a fruitful collaboration that was to last for seven years. Using spectrographic analysis, they examined the aluminum content of 84 persons, ranging in age from 10 to 90 years (Fig. 3).

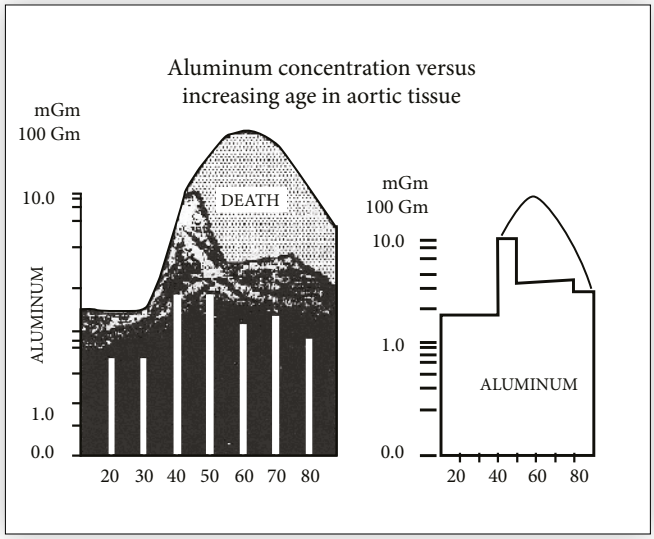


Fig. 3. Aluminium concentration versus increasing age in aortic tissue. Bjorksten, J. The crosslinking reaction in relation to aging, Life Chemistry Reports, 1988, 6:367-385.

They found peak levels at age 40-50, followed by a drop and then leveling off, indicating that those whose aluminum accumulation peaked in middle age most likely did not survive the next ten years. 20 Zinsser's data were confirmed independently by scientists who demonstrated a progressive increase of aluminum concentrations in the brain (Fig. 4).21

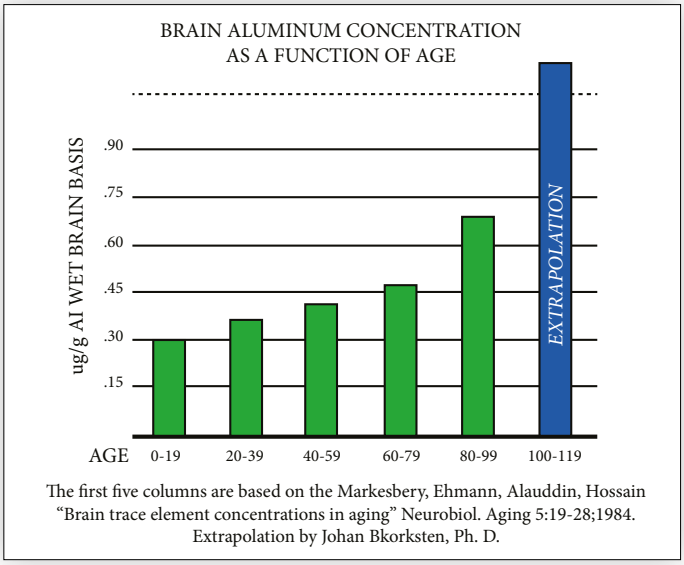


Fig. 4. Brain aluminium concentrations as a function of age. Bjorksten, J. The role of aluminium and age dependent decline, Environmental Health Perspectives. 1989, 31, 241-242.

Bjorksten concluded that the progressive increases of aluminum with age were of great importance, and believed that the aluminum mechanism alone would limit human lifespan to 110-120 years of age even if no other cause of death intervened.22

Preventing aluminum accumulation and crosslinking

Bjorksten and his staff evaluated the ability of chelating agents to remove aluminum-containing stains from the aortas of 5-6 month-old hogs (Fig. 5).23 it can be seen that EDTA was the most effective.

Lactic acid, similar to blood concentrations generated by exercise were moderately effective. Of interest was the fact that 0.5 % procaine—the active ingredient of Gerovital® (or GH3, the Romanian antiaging drug)—was also moderately effective in reducing the aluminum. This raises the question whether the metabolites of GH3—DMAE and PABA—might also have some effect in this regard.24 In fact, Drs. Imre Zs.-Nagy and Katalin Nagy demonstrated that both dimethylaminoethanol (DMAE) and centrophenoxine (CPH) are indeed able to diminish the extent of crosslinking in old rats.25

[Ed. – Original Gerovital-H3® and generic GH3-Pro® are available, as is centrophenoxine as Cent-Pro®]

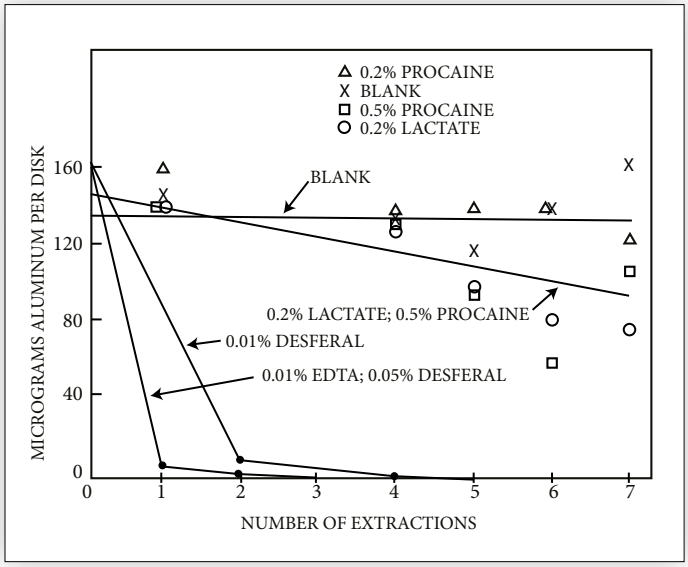


Fig. 5. Comparison of the ability of various chelating agents to remove aluminium from hog aorta. Schenk, R.U., Bjorksten, J., Lipert, R., Mortell, M. Extraction of aluminium from aorta tissues by chelating agents and lactic acid. Rejuvenation, 1981, VIII, 1, 4-10.

Bjorksten's team also evaluated the ability of various concentrations of lithium to remove tightly bound aluminum from tanned leather baseball covers.26, 27 Using a 0.05M concentration of lithium citrate, they completely demetalized the leather in approximately three months. Lithium is used clinically to treat manic depressive illness (MDI). Recent studies indicate that it may offer benefit in the prevention and treatment of Alzheimer's disease, as well. 28 Perhaps long-term treatments with low doses of lithium may be an effective way to displace crosslinked/protein bound aluminum in animals and humans. Lithium orotate as a dietary supplement is the safest, most effective form of lithium available. Bjorksten spent his entire career searching for the cause and cure of crosslinks, which he believed would result in the reversal of aging and maintenance of prolonged youth. He believed that one cause of the crosslinks was heavy metal poisoning, (especially aluminum), which could be prevented and reversed with chelation therapy. He also identified the loss of fluidity of cell membranes as a contributing factor, and supported the use of membrane fluidizers such as centrophenoxine, phosphatidylserine, choline and lecithin.

Advanced Glycation End Products of Aging (AGEs)

In 1965, Dr. H.B. Bensusan proposed that a process known as the Maillard reaction, (the non-enzymatic

chemical reactions between proteins and carbohydrates that cause cooked foods to turn brown) was what caused all long-lived proteins in the body to turn brown and become fluorescent, (under UV light), become more cross-linked, less soluble, less elastic, and less digestible by enzymes. In 1985, Monnier, Kohn and Cerami provided further details of the role of the Maillard reaction,1 and further developed the idea that the Maillard reaction causes premature aging and degenerative diseases such as diabetes and heart disease.29 In this regard, many scientists think the human body may be viewed as a 'low temperature oven' with a relatively long—approximately 75 year —'cooking cycle.'30 The Maillard reaction involves a chemical reaction between a sugar with a protein, into a complex known as a Schiff base. With continued exposure to the sugar, the Schiff base undergoes a 'rearrangement' known as non-enzymatic glycosylation that results in a more stable, less reversible substance, known as an Amadori product. In the human body, this process reaches equilibrium over several weeks (Fig. 6).31

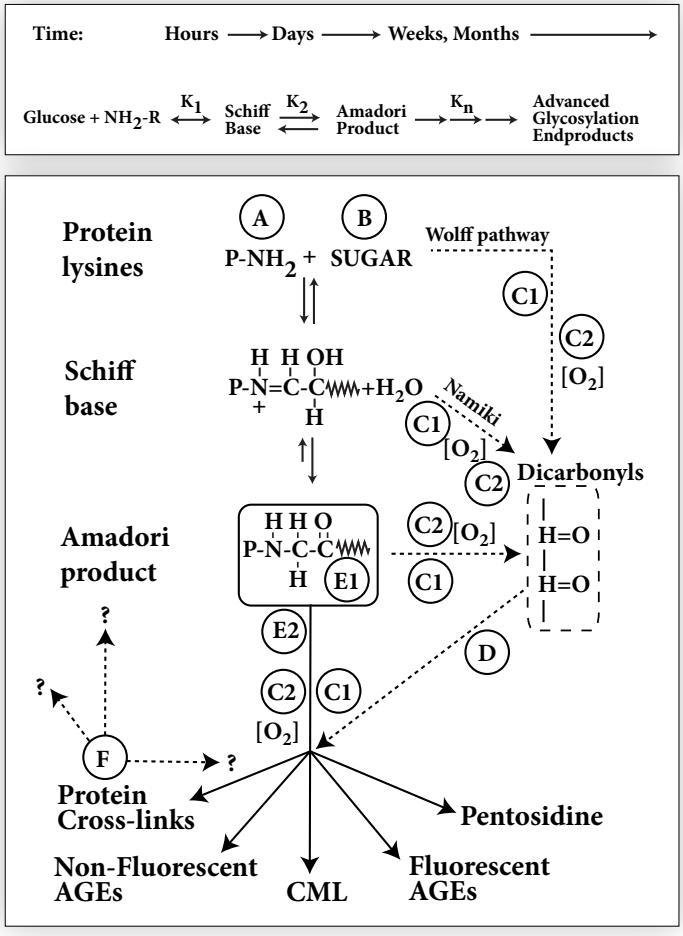


Fig. 6. Pathway of advanced glycosylation, from Schiff bases to AGEs over time. 31

The Amadori product further degrades irreversibly into a number of highly reactive carbonyl (C=O) compounds called Advanced Glycation End products, designated by the acronym AGE.32 AGE is a clever pun which reflects the proposed relationship of these reactive substances to aging and age-related diseases. AGEs can further react with other fats, proteins and nucleic acids to form largely indissoluble crosslinks. The age-related accumulation of these AGE products has been demonstrated in many tissues of the body (Fig. 7).33

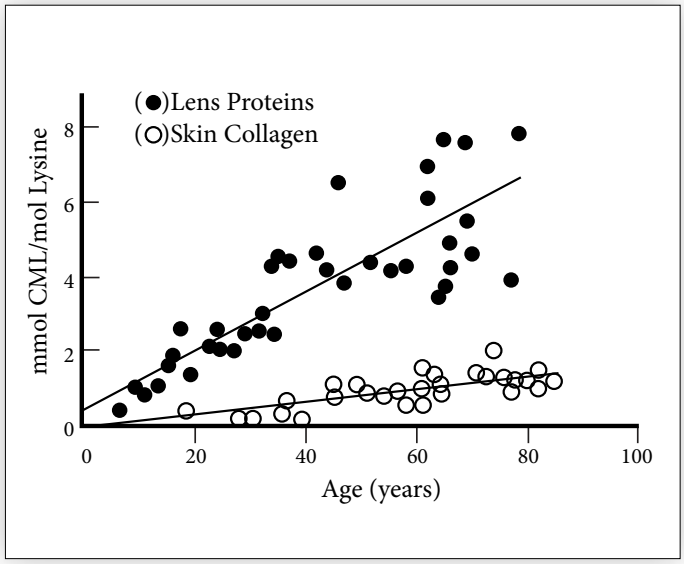


Fig. 7. Increased accumulation of AGEs (carboxymethyllysine [CML]) with age in human lens protein and skin collagen.32

During long-term hyperglycemia (elevated blood sugar), as in diabetics, glycation and AGE formation may be quadrupled! This explains why diabetics suffer the premature onset of a wide range of age-related complications including cataracts, retinopathy, neuropathy, nephropathy, atherosclerosis and osteoporosis.34, 35

Crosslinkage Theory Gets New Life

Bjorksten was a talented petroleum chemist. Had he been a food chemist instead, he may have appreciated this link between the Maillard Reaction and crosslinking much earlier, and made even greater progress in developing preventive and therapeutic approaches to crosslinkage-induced aging. Through their insightful work in understanding this process, scientists like Brownlee, Cerami and Monnier provided renewed impetus and a 'rebirth' for the crosslinkage theory. Unfortunately, they did this with little attribution to Bjorksten, who had doggedly pursued this approach to aging for over 50 years.