

# The LifeLink Letter

Volume 1, Number 1

Because good health isn't an accident.

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## Imagine If Everything You Knew about Aging Was Wrong!

### Part 1: The Common Basis of Aging and Diabetes

#### *In This Issue*

##### **Tanned Like Leather: Aging Is Just Diabetes, Only Slower** *Page 2*

Aging and diabetic deterioration are caused by sugar binding, or crosslinking, with proteins. Many conditions—organ and skin hardening, heart disease, blood-vessel damage, cataracts, kidney failure, etc.—can be reduced, eliminated, and even reversed by preventing or breaking these sugar-protein bonds.

##### **Which Crosslinking Inhibitors and Breakers Are Right for You?** *Page 6*

Inhibiting and breaking crosslinked bonds can prevent damage and even undo it. We'll tell you which of these drugs and supplements are safe and effective, and which are risky and unproven.

##### **Everything You Always Wanted to Know about the Maillard Reaction... But Were Afraid to Ask!** *Page 11*

Sugar binds to your body's proteins and destroys them using the same chemistry that browns a roast and makes caramel. Learn why cooked food tastes good, and how your body is like an oven.

*The accepted "wisdom" about the inevitability of aging and diabetic deterioration is wrong, and new compounds can slow both down and even reverse some effects.*

Much of the difference between youth and old age is a combination of factors: diet and exercise, risk factors like drinking and smoking, environmental toxins and the sun's ultraviolet rays, highly reactive molecules routinely produced in the body, diseases like diabetes, and, yes, genetics. The conventional view is that one must accept gradual deterioration as an inevitable part of life as nothing can be done. This belief is not only totally wrong, it condemns us to suffer needlessly.

Juan Ponce de Leon devoted his life to the search for eternal youth, and died never having found a way to evade the ravages of time; with the right combination of supplements he would have achieved, if not eternal youth, a biologically "younger" body in far better condition.

The *LifeLink Letter* explores theories about health; examines various medical conditions and what you can do to slow them down or even, in some cases, stop or reverse them; and how to be healthier, feel better, and hopefully live a longer, happier life.

Some topics are complicated. Some involve terminology. Some even require a little biochemistry. I'm sorry, but medical issues aren't always simple. LifeLink will try to explain issues in enough detail so you can make highly informed decisions about your health, but not so much that you give up. I can't guarantee that our newsletter will always be easy to read, but I can guarantee that it will *always* be worthwhile.

When he reached his one hundredth birthday Eubie Blake said, "*If I'd known I would live this long, I would have taken better care of myself.*" LifeLink hopes you'll start doing something today to slow down or roll back the aging clock, instead of waiting until it's too late.

*David Blanco*

David Blanco  
President and Founder, LifeLink



# Tanned Like Leather: Aging Is Just Diabetes, Only Slower

## The LifeLink Letter

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Aging, diabetes, toast, and roast beef all have something in common: *crosslinking*.

To a *chemist*, this means that sugars—from starches, carbohydrates, fruits, and other sources—have reacted with cellular components like amino acids, fats, proteins, and DNA.

To a *chef*, it means that the *Maillard reaction* (see article in this issue) has browned a roast or caramelized onions.

To a *doctor*, it means that your arteries, organs, and cells have been hardened or damaged, causing cardiovascular disease, neurological disorders, vision loss, kidney problems, or chronic inflammation.

To *you*, it means premature aging, diabetes, and lowered quality of life.

### Joined at the Hip

The basis of crosslinking is what chemists call *intermolecular bonding*, which means that molecules bond to other molecules. (Bonding inside the same molecule is called *cyclization*.)

Crosslinking is very useful: leather is tanned (crosslinked) skin, paint is cured (crosslinked) polymer films, plastics are polymerized (crosslinked) oils, and tires are made from vulcanized (crosslinked) rubber. Many of the natural products that we enjoy—fibers, wool, fur, and feathers, to name just a few—depend upon crosslinking.

Nearly *anything* can crosslink, which creates both opportunities and problems for the body.

### A Double-Edged Sword

Crosslinking is a lot like Janus, the two-faced Roman god of doorways. With it we age, but without it we can't live at all. Consider collagen, a critical protein in connective tissue, skin, tendons, ligaments, cartilage, bone, and even the cornea of the eye.

Crosslinked collagen is hard, which creates a host of problems: skin deterioration (wrinkles, sagging, stiffness), connective-tissue rigidity (often misdiagnosed as arthritis), bone problems, organ stiffening (heart problems, bladder incontinence, lung issues), etc.

But collagen is an example of the crosslinking's two faces; too much destroys collagen's function, yet some is crucial for connective-tissue strength. Without this web of interlocking we'd fall apart.

Our hair and fingernails are a type of crosslinked protein called *keratin*. (Hair straightener and depilatories rely on breaking such crosslinks.)

Any solution to the crosslinking problem must target the unwanted type—those causing damage—while leaving the remainder alone. This is not always easy to do, and understanding how crosslinking originates explains why.

### Literally Tied Up in Knots

Consider a strand of protein as a flexible piece of rope. Imagine two adjacent strands of rope (protein) fixed only at the ends, such that each has total freedom to bend and move, independent of the other.

As more and more horizontal pieces of twine are tied from one rope to the other, the flexibility of

movement declines until the two have become somewhat rigid. As the joining twine contracts, as often happens in crosslinked molecules, the ropes pull together simplifying the addition of new crosslinks.

This is exactly what happens in the body as proteins and other molecules bind together. This changes their shapes and biological properties, altering normal functioning.

Chemists call changes like these “denaturing,” since the original properties of the molecule have been altered. This isn’t always bad; cooking a steak denatures the proteins, making them far more digestible, and much tastier, too!

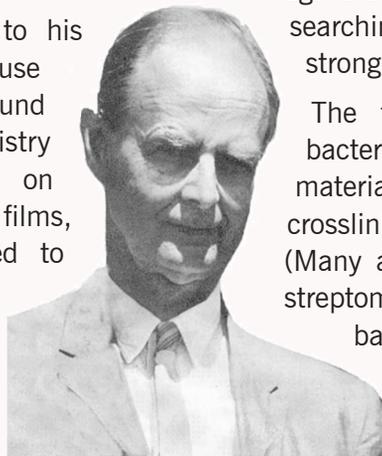
The idea that crosslinking causes aging is hardly a new one; back in 1941, Dr. Johan Bjorksten, a Wisconsin chemist, first proposed that undesirable bonding gradually damages proteins, fats, DNA, vitamins, etc.

These damaged molecules bind together into sticky tangles; over time, these blobs grow and wrap around other molecules, growing and posing more and more of a problem.

### Leather, Hectographs & Aging

Bjorksten came to his discovery because of his background in leather chemistry and his work on hectograph films, which were used to duplicate pages prior to the invention of the photocopier.

This wet process, which dates



**Johan Bjorksten**

back to the late 19th century, uses a gelatin film to transfer ink to paper, much like a printing press. It was good for about fifty copies from the same sheet. (Remember this the next time you use fast, inexpensive, and dry copier technology.)

The problem plaguing Bjorksten was how to stop the gelatin films from hardening with age and use. He quickly identified the

*“Many of these cross-linked molecules lead to agglomerates which cannot be broken down by any body enzyme, but will increase in the cell and gradually crowd out other constituents, thereby causing continued decline in the cell’s activity and the ability to cope with stresses.” —Johan Bjorksten*

culprit as protein crosslinking, and noticed that the hard gelatin films were remarkably similar to damaged skin. He concluded that the same chemical processes must be at work in both cases and that inhibiting crosslinking would prevent many human diseases and disorders, and thus extend life.

### Cracking Bonds with Enzymes

Bjorksten started by taking vitamin E, the only anticrosslinking agent available to him, and began searching for a means to crack the strong bonds with proteins.

The first approach used soil bacteria—a rich source of raw material for pharmaceuticals—fed crosslinked protein, exclusively. (Many antibiotics, like the potent streptomycin, originated with bacteria from dirt.)

The bacteria that survived would, of necessity, produce enzymes capable of breaking

protein bonds. Bjorksten felt that these enzymes could then be used in humans.

### The Real World Intrudes

Facing him were two big problems: science and funding. Every single enzyme he found that could break protein crosslinks was so toxic it couldn’t be used in lab animals, let alone humans. Beyond the science, however, the debate over extending the human life span was as contentious as today’s debates over stem-cell research, and this made funding his work controversial.

Bjorksten also contributed to the controversy, including a proposal that the United States Department of Defense fund development of a “rapid-aging spray” to be used against enemy soldiers during wartime. The military’s reaction was, needless to say, not enthusiastic.

Running out of money and concluding that the search for enzymes was hopeless, at least in any timeframe that would benefit him—Bjorksten’s parents suffered from Alzheimer’s disease, which exhibits much crosslinking—he abandoned the crosslinking breaker approach for a new idea.

### Cracking Bonds with Chelation

Moving to chelation agents like ethylenediaminetetracetic acid (EDTA), Bjorksten reasoned that if these compounds can break bonds with metals, they would prevent, or even break down, the protein tangles in the body.

There is evidence that copper and iron catalyze reactions between sugars and proteins, particularly in cataracts and Alzheimer’s disease, and that eliminating excess metal

ions may slow crosslinking. (This topic is complex enough that it needs its own article.)

### A Theory Now Accepted as Fact

Bjorksten's work on the "crosslinking theory of aging" provides an explanation for aging and diabetes making perfect sense; the body's proteins do harden over time. One example is the leathery skin of cowboys and habitual beachgoers. His theory is accepted today as a crucial component in aging and disease, especially diabetes.

### Origins of the Ties That Bind

Crosslinking is caused by such diverse factors as: intermolecular bonding (metabolic by-products), ultraviolet light (sun, tanning salons), acetaldehyde (alcohol, cigarette smoke, pollution), ozone (pollution), ketones (diabetes, high-protein/low-carb diets), metal ions (lead, cadmium, mercury, copper, iron, aluminum), X-rays, and free radicals (normal metabolism, rancid or overheated oils and fats).

It wasn't until 1965, however, that one of the leading culprits in crosslinking and aging was identified: sugar bonding to protein via the "*Maillard reaction*." (See the article in this issue.) This is the mechanism causing diabetics to age prematurely, and it explains why otherwise healthy people need to protect themselves from even typical blood-sugar levels.

Other types of crosslinking, such as between proteins, lipids (fats), or involving metals like copper and iron, are very important as well. So are the sulfur-sulfur (disulfide) bonds made between the sulfur-bearing amino acids in proteins. Sugar, however, seems to be the leading cause of damage and aging, even in nondiabetics.

Increases in blood sugar happen after consuming starches and carbohydrates—these are broken down into simple sugars—as well as fruits and vegetables, which also contain sugars and carbohydrates.

The problem is that sugar is a biochemical straightjacket. Before it can be metabolized it damages molecules crucial for routine cellular function and creates toxic compounds as a by-product.

### Marrying Sugar to Protein

The overall process is very simple, but sounds a little complicated because of terminology. All you *really* need to know is in the next two paragraphs. (The sidebar on page 5 explains the details.)

It all begins when sugar oxidizes, giving it a reactive carbon-oxygen (*carbonyl*) group that binds to proteins in a process called *glycation*. These glycated, or sugared, proteins eventually form stable, long-lived, and highly damaging *Advanced Glycation End-Products (AGE)*. This is the key phrase to remember, because the crosslinking theory of aging is basically all about AGEs.

Similar results occur when fats and proteins bond together. Reactions between proteins, sugars, and fats explain why sautéed food is tastier than steamed, and why sauces are made from browned bones (reacted proteins, fats, and sugars), roasted vegetables (caramelized carbohydrates and natural sugars), and butter (fat). (See the page 11 article on the Maillard reaction.)

### How Sweet It Isn't

Arteries and the fine capillaries in the retina and kidney are particularly vulnerable to sugar-protein reactions because, unlike other cells, they cannot break down certain forms of sugar, like

sorbitol. These sugars then attack the proteins in the blood-vessel and capillary walls, leading to damage and AGEs.

Artery-clogging plaque is nothing more than globs of crosslinked AGEs made from a variety of materials—sugars, proteins, lipids and fats like cholesterol, metals, fibrin, etc.

### You're Showing Your AGE

Over time, AGEs crosslink the inside of your body like a browned roast, causing diseases like cardiovascular hardening and heart attacks, retinal deterioration, cataracts, glaucoma, peripheral nerve damage, kidney failure, osteoarthritis, stroke, scleroderma, and atherosclerosis.

Once a long-lived protein (such as those in the eye's lens or the collagen in skin and joint cartilage) is damaged it usually remains so. This is why levels of the AGE-product pentosidine in an eighty year old's joint cartilage have been measured at thirty times those of a twenty year old.

Implicated in many diseases, AGEs are known to activate a variety of inflammatory cytokines, or messenger molecules, including tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin, even in otherwise healthy people.

### Stop Doing That Right Now!

A variety of prescription drugs and nutritional supplements with anticrosslinking effects are readily available. (See "Which Crosslinking Inhibitors and Breakers Are Right for You?" in this issue.)

Nearly a thousand such compounds are known, but many of them, as Bjorksten discovered a long time ago, are completely unsuitable for use in the body.

Crosslinking *inhibitors*—available as both prescription and supplement—typically interfere with the binding of the carbonyl groups (just a carbon-oxygen bond) on sugars to amino acids and other molecules. Some inhibitors are sacrificial, binding to an active site on the sugar before it can disrupt an amino acid in a protein.

The aptly named crosslinking *breakers* crack the bond between the sugar and the protein, undoing some of the damage and allowing repair. This is more difficult,

and many of the breakers target bonds—like those giving cartilage its strength—which must remain untouched.

### Breaking Sugar’s Hammerlock

Supplement-based compounds are known to break existing AGE bonds without serious side effects. Prescription drug breakers are still relatively new, however, and have limited safety histories. Until their long-term and even short-term effects are better known and understood, nonprescription

supplements offer a safe, effective, and very affordable alternative.

### Conclusion

Toast, roasts, and caramelized onions can be delicious, but you certainly don’t want the same reactions occurring in your body.

So, if you have diabetes or just want to put the brakes on your age-related deterioration, you’ll definitely want to add crosslinking inhibitors and breakers to your supplement list. *Do it before your body gets tied up in knots!*

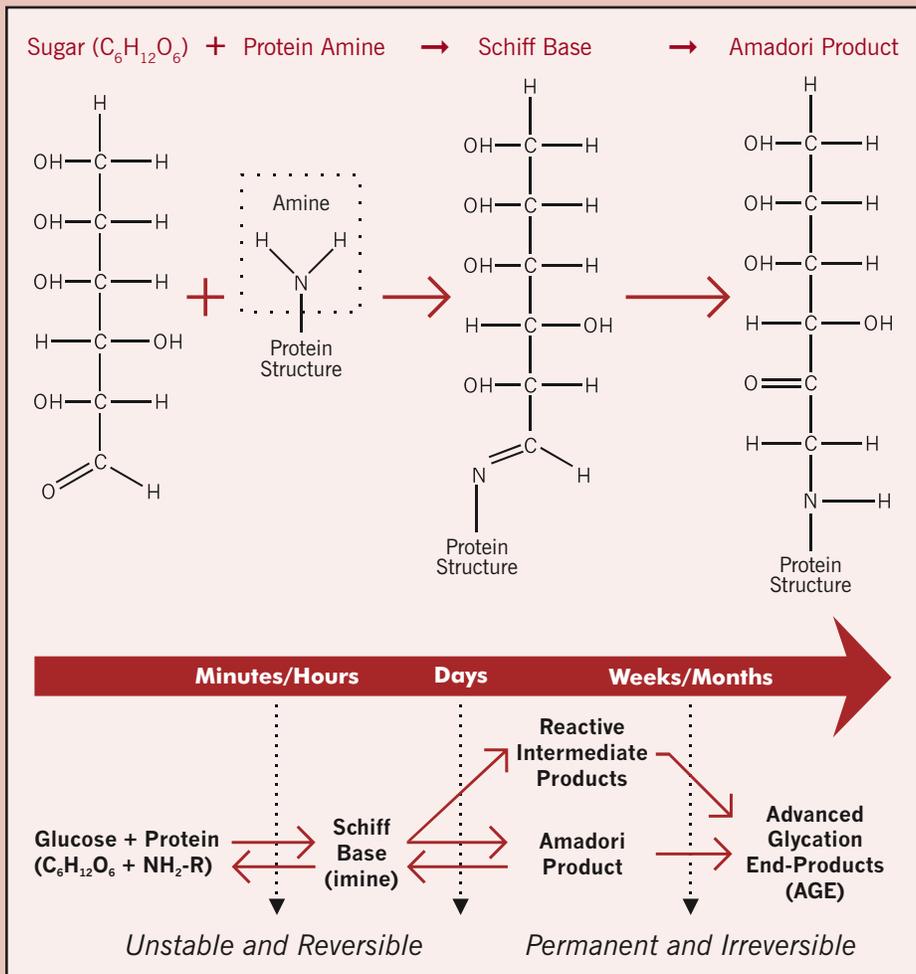
## The Dance of Sugar and Protein (a Brief Chemistry Lesson)

AGE formation starts with sugar molecules,  $C_6H_{12}O_6$ , floating around in your bloodstream, cells, and eyes. After oxidizing, these sugars acquire a reactive carbonyl group that binds to one of the free amine ( $NH_2$ ) groups in a protein, typically at the ends.

Antioxidants—such as lipoic acid, vitamins C and E, and n-acetyl-cysteine—interfere with glucose’s oxidation, preventing carbonyl formation. This slows, but does not stop, early-stage AGE production.

The resulting sugar-protein hybrid is called a *glycoprotein*, a member of a class of molecules called a *Schiff base*. The process of binding sugar to a protein is (typically) called *glycoxidation*, *glycation*, or *glycosylation*.

Schiff bases are unstable in water, so a portion revert to their original molecules. Most of the glycoproteins, however, either become highly reactive compounds—like triosephosphates and



oxoaldehydes—that attack lipids, proteins, and even DNA—or solidify, over days or weeks, into a stable *Amadori product*. Both the reactive

intermediates and the Amadori products are converted, over weeks to months, into AGEs, which are stable, long-lived, and essentially permanent.

# Which Crosslinking Inhibitors and Breakers Are Right for You?

## Acarbose

*Acarbose (precose or glucobay)* interferes with *alpha-glucosidase*, an enzyme key in breaking down complex carbohydrates into simple sugars. This reduces blood-sugar levels, inhibiting crosslinking and AGE formation. It does not, however, interfere with the actual binding of sugars to proteins.

Lowering blood-sugar levels protects organs with many delicate blood vessels—such as the retina, kidney, brain, etc.—from damage.

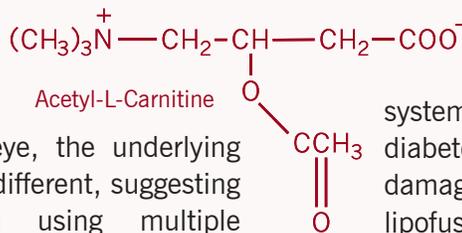
The problem with acarbose is twofold: The long-term effects of suppressing carbohydrate breakdown are unknown, and it leaves high levels of unabsorbed carbohydrates in the intestines, causing pain, cramps, bloating, and diarrhea. Given the risks and problems, it is unsuitable as an antiaging compound.

## Acetyl-L-Carnitine

*Acetyl-L-carnitine* protects the eye's lens from cataracts. (Its numerous antiaging properties will be covered in a future issue of the *LifeLink Letter*.)

The protective effect comes from the acetyl group potential binding sites; aspirin and n-acetyl-cysteine contain an acetyl group and have a similar effect.

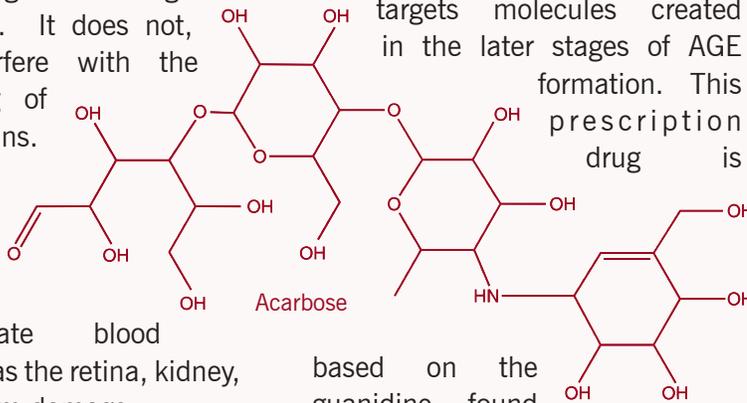
While taurine also protects the lens of the eye, the underlying mechanism is different, suggesting benefits from using multiple



inhibitors. No such protection was seen for the unacetylated L-carnitine, since it cannot preempt the binding sites.

## Aminoguanidine

*Aminoguanidine (pimagidine)* targets molecules created in the later stages of AGE formation. This prescription drug is



based on the guanidine found in French Lilac (aka Goat's Rue), a bushy perennial.

Diabetics have used French Lilac since medieval times, but were limited to small amounts because the plant contains the toxic molecule galegine.



Protecting collagen against crosslinking, aminoguanidine shields the skin and connective tissue from stiffening and wrinkling, and muscle, like the heart, from hardening. Typical dosages do not inhibit the routine collagen crosslinking required for strength.

Preventing crosslinking between proteins and fats, aminoguanidine spares the arteries from clogging.

By protecting small arteries feeding the peripheral nervous system, it reduces age- and diabetes-associated nerve damage. It also prevents lipofuscin (age spots),

a signature sign of aging and crosslinking.

Aminoguanidine is among the most effective crosslinking inhibitors, with vitamin B-6 comparable. *But don't rush out to get a prescription quite yet!*

The drug has numerous side effects, including anemia and autoimmune disorders. While a potent inhibitor of diabetic complications, aminoguanidine is not safe enough to justify its use by nondiabetics.

## Aspirin (Acetylsalicylic Acid)

Originally isolated in tree bark, *salicylic acid* has been used for millennia for fever and inflammation; the famed physician Hippocrates praised its benefits.

The addition of an acetyl group—done twice in the 1800s by two different chemists—finally eliminated much of the harsh side effects on the stomach, increasing its popularity and therapeutic potential. Aspirin is now *the* most commonly prescribed drug.

More recently, aspirin has been discovered to interfere with the post-Amadori reaction because the phenol ring provides antioxidant properties and the physical structure chelates iron and copper.

Both of these metal ions have been implicated in crosslinking; the beta-amyloid plaques found in Alzheimer's disease, for example, contain both AGEs and complexes with copper and iron.

Aspirin, like acetyl-L-carnitine and taurine, also protects the lens of the eye from cataracts. Experiments



using eye lenses submersed in sugar solutions show a profound reduction in cataract formation when aspirin is added.

**Benfotiamine** (*S*-benzoylthiamine-*O*-monophosphate) is a fat-soluble vitamin B-1 (*thiamine*) derivative that prevents crosslinking and inhibits AGE formation. The body metabolizes it into *thiamine pyrophosphate (TPP)*, vitamin B-1's active form.

An allithiamine—it is found in the allium family of vegetables, including garlic, onions, and leeks—benfotiamine is a fairly old compound, having been discovered in 1951. (Alteon Pharmaceutical's *alagebrium* is derived from B-1.)

Its original application was in the treatment and prevention of a variety of conditions in both diabetics and nondiabetics: nerve damage, including neuropathy, sciatica, and shingles; cardiovascular damage, including heart, kidneys, and eyes, and high blood pressure; and general aging-related disorders.

Diabetes damages blood vessels through four chemical pathways, and benfotiamine completely blocks three of them. It also converts the toxic triosephosphates to the more benign pentosephosphates.

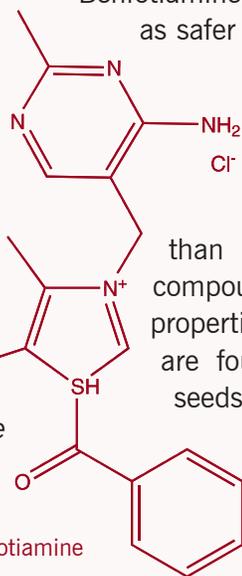
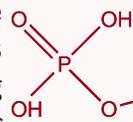
Absorption of B-1 is so poor that supplements often contain far more than is usable. Benfotiamine uptake, however, can exceed one hundred times that for B-1.

Reducing AGE levels—preventing retinopathy, renal damage, etc., even in the healthy—benfotiamine can *undo* damage, substantially

improving nerve function while profoundly reducing pain.

Benfotiamine is widely regarded as safer than the already-safe vitamin B-1 it is derived from.

**Benfotiamine**



**Bioflavonoids**

A family of more than four thousand compounds with antioxidant properties, *bioflavonoids* are found in citrus, grape seeds and skins, green tea, cranberries, pine bark, and fruits. Common

bioflavonoids are polyphenols, proanthocyanidin, and quercetin.

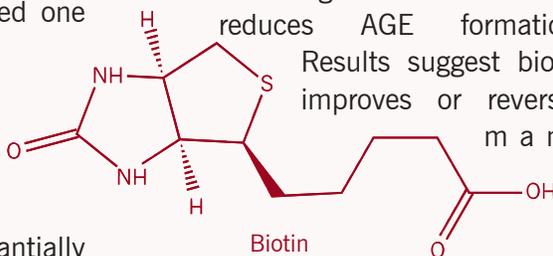
Bioflavonoids inhibit oxidation and aldose reductase, reducing conversion of glucose into the more damaging sorbitol. Pairing with taurine and n-acetyl-cysteine reduces crosslinking far more than these compound do alone.

**Biotin**

*Biotin* has a crucial role in the metabolism of sugar, moving glucose into cells, stimulating the release of insulin, and increasing the conversion of glucose into fatty acids burned for energy and glycogen for stored energy.

Diabetics taking 10–15mg. of biotin daily have significantly lower fasting blood-sugar levels—*nearly fifty percent lower*—and can reduce the size and frequency of their insulin injections. Lowering levels of sugar in the blood also reduces AGE formation.

Results suggest biotin improves or reverses many



symptoms of diabetes. It has no known toxicity even in very high dosages.

**BHT**

Widely used as a food preservative, *butylated hydroxytoluene (BHT)* is also a potent antioxidant. Like other antioxidants—vitamins C and E, lipoic acid, and rosmarinic acid—it inhibits oxidation of glucose and thus prevents the formation of the Schiff bases, which start the AGE creation cycle.



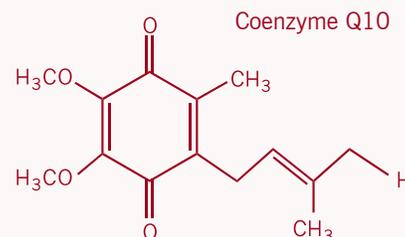
BHT is technically approved for use *only* as a food preservative, so supplement sellers market it only for that purpose.

**Chromium**

The body uses the element *chromium (chromium picolinate, glucose tolerance factor, GTF)* in combination with insulin to regulate blood-sugar levels. Chromium deficiencies are common, and supplementing reduces blood-sugar levels and AGE formation.

**Coenzyme Q10 & Idebenone**

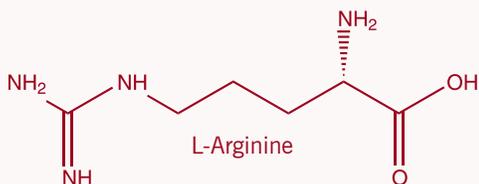
As potent antioxidants and metabolic enhancers, *coenzyme Q10 (CoQ10)* and *idebenone* reduce AGE formation and lower blood-sugar levels by stimulating insulin, improving the metabolism and preventing the oxidation of glucose.



CoQ10 and idebenone are regarded as very safe and well tolerated.

## L-Arginine & L-Lysine

The amino acids *L-arginine* and *L-lysine* inhibit glycation and AGE formation by sacrificially reacting with carbonyls, ketones, aldehydes, and metal ions, saving the body's proteins from attack.



In large doses, L-arginine can lower blood pressure and increase viral replication, particularly for the herpes family. L-lysine, however, suppresses L-arginine's effect on viral replication. Together, the two slow or prevent AGE formation.

## L-Carnosine

Made by the body and found in muscle and nervous system tissue, *L-carnosine* (*beta alanyl-L-histidine* or *n-acetyl-L-carnosine*) is composed of two amino acids: *alanine* and *histadine* and has several important roles.

By binding to free carbonyl groups, it inhibits sugar binding to proteins and DNA, and reduces protein-protein and protein-DNA crosslinking. As an antioxidant, it preserves the body's primary antioxidant, glutathione. Finally, by breaking the bonds in crosslinked proteins it undoes damage.



Known to reduce levels of AGEs and free radicals in the body, L-carnosine prevents and even removes age-related cataracts. (It may also benefit age-related eye conditions like glaucoma.)

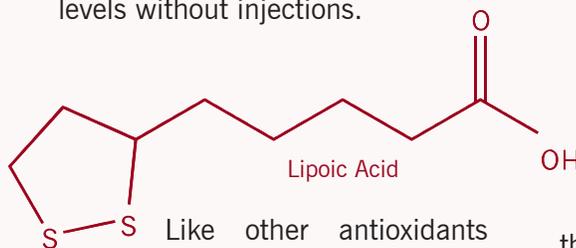
Combining L-carnosine with AGE breakers like benfotiamine may eliminate newly liberated carbonyls before they can bind to other proteins.

L-carnosine is regarded as safe in normal amounts. Large dosages—typically more than one gram per day—have been linked to histamine-type allergies.

## Lipoic Acid

A potent sulfur-bearing antioxidant, *lipoic acid* (*thioctic acid*) inhibits glucose oxidation, Schiff-base formation, lipid peroxidation, and the binding of fats to proteins.

Complexing excess metal ions, lipoic acid reduces AGE formation. It also recycles oxidized vitamin C, preventing it from producing the reactive carbonyls leading to AGEs. Finally, lipoic acid works like insulin, lowering blood-sugar levels without injections.



Like other antioxidants lipoic acid is an early-stage inhibitor. It pairs nicely with mid- and late-stage inhibitors like L-carnosine, PABA, vitamin B-6, and benfotiamine.

## Metformin

*Metformin* (*glucophage*) is a prescription drug for diabetes. A slightly modified double guanidine, the drug prevents the liver's breakdown of carbohydrates into glucose—thereby lowering blood-sugar levels—and inhibits the formation of AGEs, particularly those involving collagen in the heart, connective tissue, and skin.

Like L-carnosine, metformin binds to carbonyl groups, interfering

with crosslinking. It also ties up binding sites on the fibrin proteins responsible for coagulation and, like aspirin, reduces the risk of heart attack and stroke.

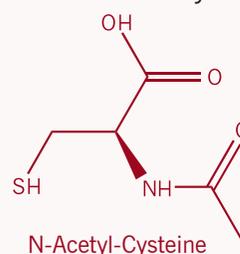


Metformin, unfortunately, has serious side effects: lactic acidosis, liver and kidney damage, and decreased folate and vitamin B-12 levels. Drops in these vitamins are known to raise the homocysteine levels associated with heart and circulatory system damage.

The chemically similar drug *phenformin* killed a number of patients before being removed from the market. Given the risks, metformin is too risky to use as an antiaging compound.

## N-Acetyl-Cysteine

*N-acetyl-cysteine* is a powerful antioxidant with wide antiaging properties. (These will be discussed in a future issue of the *LifeLink Letter*.) By preventing the oxidation of glucose, it slows down early-stage AGE formation.



Like aspirin and acetyl-L-carnitine, *n-acetyl-cysteine* acetylates potential binding sites, preventing AGE formation. It

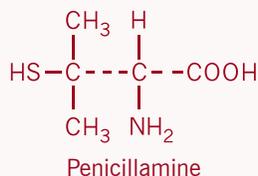
pairs nicely with inhibitors like L-carnosine, PABA, vitamin B-6, and benfotiamine.

## Penicillamine

A distinct molecule from the antibiotic, *penicillamine* (*dimethyl cysteine*) inhibits crosslinking, but not particularly well. Its primary use is in chelation, like EDTA, since

it complexes metals and reactive molecules. It also interferes with routine metabolism.

Known side effects include immune system suppression, impaired collagen synthesis, lupus, aplastic anemia, and myasthenia gravis. Given the serious risks, penicillamine is suitable only for life-threatening illnesses on a short-term basis.



### PABA (Para-Amino Benzoic Acid)

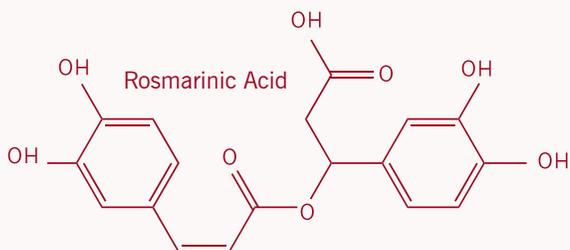
A vitamin B cofactor, *PABA* (*para-amino benzoic acid*) is an antioxidant and crosslinking inhibitor. It is the active ingredient in many sunscreens.



PABA is generally safe and well tolerated, even up to several grams daily. Some users find it disagrees with them, even in small quantities, so some caution is required. The typical side effects of high dosages are nausea and diarrhea, which vanish upon dosage reduction.

### Rosmarinic Acid

A potent antioxidant, *rosmarinic acid* inhibits the oxidation of glucose, slowing the formation of the Schiff bases created in the early stages of AGE formation. It also is a strong anti-inflammatory, which may prevent autoimmune reactions to AGEs and the tissues containing them.



As an inhibitor of aldose reductase, rosmarinic acid prevents the conversion of glucose into sorbitol. Many cells, like those in the eye, cannot metabolize sorbitol, and suffer damage. (See taurine for details.)

### Selenium

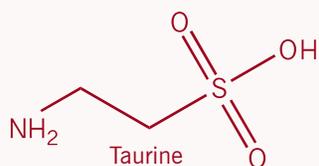
The element *selenium* (*selenomethionine*, *sodium selenate*) is a key ingredient in the antioxidants made by the body that prevent the oxidation of glucose, thereby inhibiting AGE formation.

### Taurine

The amino acid *taurine* (*2-aminoethane sulfonic acid*) is several times better at inhibiting AGE formation than the risky prescription drug aminoguanidine.

Taurine is believed to work by binding to sugar, sparing the proteins in the eye's lens. This has particular value when it comes to protecting sight.

About the size of a shirt button, the eye's lens is made of transparent protein that focuses light onto the retina. When crosslinked by the sun's ultraviolet rays or by sugar, it turns cloudy with cataracts, causing a loss of vision.

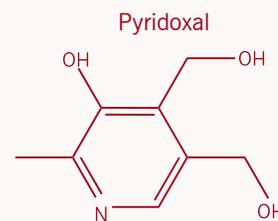
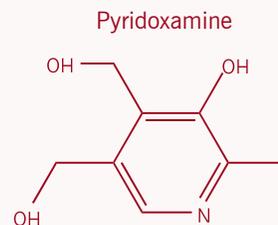
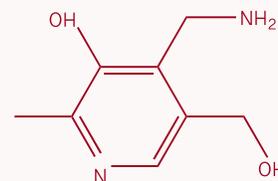


The high taurine levels in the eye protect the lens by preferentially bonding to sugars. In addition to taurine, high levels of vitamins C and E are known to halve the risk of cataracts.

### Vitamin B-6

*Vitamin B-6* is crucial for metabolism of proteins, carbohydrates, and fats. It is found in three different forms: *pyridoxal* (*pyridoxal-5-phosphate*, *P5P*, and *PL*), *pyridoxine* (*PN*),

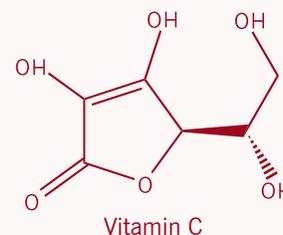
and *pyridoxamine* (*PM*). The best crosslinking inhibitor is *PM*.



Trapping carbonyls and acting as an antioxidant, B-6 inhibits AGE formation better than aminoguanidine, but without the risk of injury or death.

### Vitamin C

Like other antioxidants, *vitamin C* inhibits glucose oxidation, reducing Schiff-base formation. An early-stage inhibitor, it pairs nicely



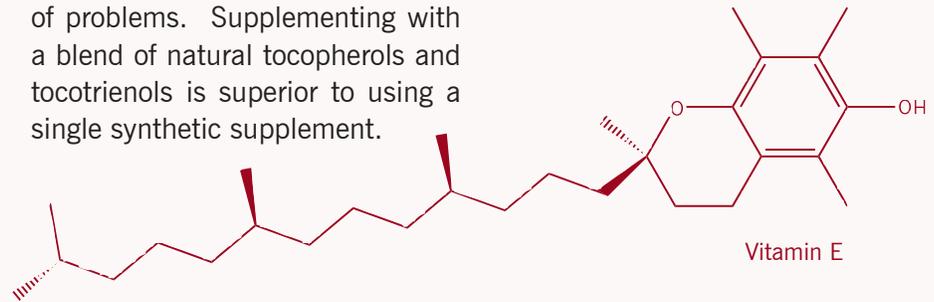
with mid- and late-stage inhibitors like L-carnosine, PABA, vitamin B-6, and benfotiamine.

### Vitamin E

*Vitamin E* (*tocopherol*, *tocotrienol*) is a family of antioxidants that, among its other benefits, prevents the oxidation of glucose, reducing the formation of Schiff bases. It also slightly inhibits

carbonyl formation. Using a single synthetic supplement like DL-tocopherol will not deliver optimal protection from oxidation and AGEs; evidence suggests synthetics are inferior to natural vitamin E and can cause a variety

of problems. Supplementing with a blend of natural tocopherols and tocotrienols is superior to using a single synthetic supplement.



### Crosslinking Inhibitors and Breakers at-a-Glance

Name	Availability	Mechanism	Inhibitor	Breaker	Stage	Risk Factor
<b>Acarbose</b>	Prescription	Reduces blood-sugar levels	Yes	No	Early	High
<b>Acetyl-L-Carnitine</b>	Supplement	Acetylates glycation sites, enhances metabolism	Yes	No	Mid-Late	Very Low
<b>Aminoguanidine</b>	Prescription	Antioxidant, traps carbonyls, aldehydes, ketones, metal ions	Yes	No	Mid-Late	Moderate-High
<b>Aspirin</b>	Over the Counter	Antioxidant, acetylates glycation sites, traps metal ions	Yes	No	Mid-Late	Low
<b>Benfotiamine</b>	Supplement	Antioxidant, traps carbonyls, aldehydes, ketones, metal ions	Yes	Yes	Mid-Late	Low
<b>BHT</b>	Supplement	Antioxidant	Yes	No	Early	Low
<b>Biotin</b>	Supplement	Lowers blood-sugar levels	Yes	No	Early	Very Low
<b>Bioflavonoids</b>	Supplement	Antioxidant	Yes	No	Early	Low
<b>Chromium</b>	Supplement	Lowers blood-sugar levels	Yes	No	Early	Low
<b>Coenzyme Q10 &amp; Idebenone</b>	Supplement	Antioxidant, enhance metabolism, lowers blood-sugar levels	Yes	No	Early	Very Low
<b>L-Arginine</b>	Supplement	Traps carbonyls, aldehydes, ketones, metal ions	Yes	No	Mid	Low-Moderate
<b>L-Carnosine</b>	Supplement	Antioxidant, traps carbonyls, aldehydes, ketones, metal ions	Yes	Yes	Mid-Late	Low
<b>L-Lysine</b>	Supplement	Traps carbonyls, aldehydes, ketones, metal ions	Yes	No	Mid	Very Low
<b>Lipoic Acid</b>	Supplement	Antioxidant, traps carbonyls, aldehydes, ketones, metal ions, lowers blood-sugar levels	Yes	No	Early	Very Low
<b>Metformin</b>	Prescription	Antioxidant, traps carbonyls, aldehydes, ketones, metal ions	Yes	No	Mid-Late	Moderate-High
<b>N-Acetyl-Cysteine</b>	Supplement	Antioxidant, traps metal ions	Yes	No	Early-Late	Very Low
<b>PABA (Para-Amino Benzoic Acid)</b>	Supplement	Traps carbonyls, aldehydes, ketones, metal ions	Yes	Yes	Late	Low-Moderate
<b>Penicillamine</b>	Prescription	Traps carbonyls, aldehydes, ketones, metal ions	Yes	No	Early	Very High
<b>Rosmarinic Acid</b>	Supplement	Antioxidant, inhibits aldose reductase	Yes	No	Early	Very Low
<b>Selenium</b>	Supplement	Antioxidant	Yes	No	Early	Low
<b>Taurine</b>	Supplement	Traps carbonyls, aldehydes, ketones	Yes	No	Early-Late	Very Low
<b>Vitamin B-6</b>	Supplement	Traps carbonyls, aldehydes, ketones, metal ions	Yes	No	Late	Very Low
<b>Vitamin C</b>	Supplement	Antioxidant, inhibits aldose reductase	Yes	No	Early	Very Low
<b>Vitamin E &amp; Tocotrienols</b>	Supplement	Antioxidant, traps carbonyls, aldehydes, ketones, metal ions	Yes	No	Early-Late	Very Low

## Everything You Always Wanted to Know about the Maillard Reaction... But Were Afraid to Ask!

Ever since Prometheus brought fire to mankind and cooking began, humans have enjoyed the results of the Maillard reaction; without it cooked or fermented foods would lack much color and taste. But the reaction has a dark side, and causes deterioration of the body.

### Beer, Food & Chemistry

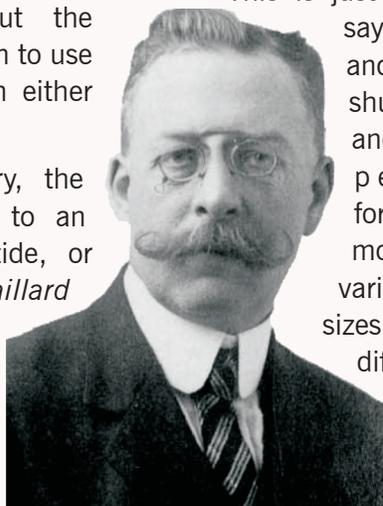
In 1908, the English chemist A.R. Ling was trying to explain how beer obtained its color. He deduced that the reaction involved sugar and protein, but was unable to determine the precise mechanism.

Across the English Channel, the French chemist Louis Camille Maillard was investigating how individual amino acids linked together to form proteins. (Proteins are just long chains of amino acids glued together and then folded into compact shapes.)

Maillard discovered, in 1912, when he combined sugar and amino acids in water and then heated the mixture it turned a yellowish-brown. This was the first time anyone was able to initiate nonenzymatic browning using well-defined materials.

When people talk about the Maillard reaction, they often to use the word “sugar” to mean either sugars or carbohydrates.

In honor of his discovery, the process binding a sugar to an amine, amino acid, peptide, or protein is known as the “*Maillard reaction*.” Familiar to chefs for centuries, it was not until 1953, however, that the complex web of underlying reactions was finally deciphered.



Louis Camille Maillard

### Why the Maillard Matters

The reaction is of crucial importance, and not just in chemistry. Crosslinking between sugars and amino acids, among others, produces much of the color and taste we associate with cooked or fermented foods. More ominously, crosslinking also forms many mutagenic, carcinogenic, and otherwise toxic compounds.

The very same reaction occurs in the body, as the proteins making up collagen, muscle tissue, bone, organs, eyes, etc. are hardened, distorted, corrupted, and otherwise rendered nonfunctional by sugar.

Understanding the Maillard reaction leads not just to safer—and *tastier!*—food, but also to longer, healthier living.

### What Happens

A chemist explains the reaction as one of the reactive carbonyl groups in the sugar molecule binding with the amino acid’s nucleophilic-amine group, yielding a variety of interesting, and frequently uncategorized, low-molecular-weight organic compounds.

This is just a fancy way of saying that sugars and amino acids shuck off their shoes and join together permanently, forming new molecules, in a variety of small sizes, each with different chemical properties. The end products of the reaction, called

“*melanoidins*,” have different colors and tastes, and have such variety that many have never been categorized, let alone studied.

### What’s All That Brown Glop?

The brown residue left over after sautéing meats, commonly used to make sauces—aka “*deglazing the pan*”—is concentrated residue from the Maillard reaction.

So are: the color and taste of roasted coffee and cocoa beans; the crunchy, browned surface of toast; the caramelized tomato and sugar hybrids in barbeque sauce; the sweet, rich taste of roasted vegetables and caramelized onions; the crunchy goodness of crème brûlée; the sticky, brown caramel formed when milk proteins and sugar combine; the taste and color of whiskey and beer; and even artificial maple syrup.

### Yuck! That Smells & Tastes Bad!

The Maillard reaction, however, isn’t always pleasant. During World War II soldiers complained that powdered eggs were an unappetizing brown and tasted spoiled. This was of great concern to everyone since an army marches on its stomach.

Investigation showed that the eggs were dehydrated and stored at room temperature, which should have made them quite stable. It turned out that the egg’s sugars were reacting with the amino acids in the proteins and creating some most unpalatable results.

Only after a fermentation process was adopted to eliminate glucose from raw eggs did the powdered version finally obtain a shelf life beyond a few weeks.

**Smile for the Camera!**

A related problem exists with old photographs. More than eighty percent of 19th-century photographs are “albumen prints” using an egg-white fixative. These prints have yellowed, in what is now known to be a Maillard-based process identical to the spoiled powdered eggs during WWII.

For a long time, scientists and food experts focused solely on shutting down the Maillard reaction in food to prevent exactly this sort of spoilage, but quickly realized the potential for improving both food and food safety.

**Cooking Up Taste or Trouble**

The chart to the right shows the major categories of flavors and aromas used by the food industry; about half depend upon the Maillard reaction.

Literally thousands of different results depend upon the raw ingredients and how they are cooked together: a dozen types of carbohydrates or sugars (ranging from simple to complex, including fructose, glucose, lactose, maltose, maltotriose, pullulan, sorbitol, starch, sucrose, and trehalose); twenty different amino acids; a variety of reaction temperatures, a wide spectrum of pH (acid or base); and variable reaction times.

For example, dry-toasting malt for beer yields a cereal flavor whereas heating wet malt delivers more of a caramel taste. The raw ingredients are identical; the only difference is the amount of water. The flavors we associate with meat, nuts, coffee, and even chocolate originate with pyrazines and guaiacols containing nitrogen,

oxygen and sulphur groups. Not very glamorous, perhaps, but chemistry deals with explanations, not poetry.

The melanoidins may have unpleasant flavors or odors—bitter, burnt, or rancid—or pleasing ones like bread, caramel, malt, or roast meat. The same goes for a wide range of colors; from Maillard’s original yellowish-brown to nearly pitch black.

Maillard-Derived Flavors	
Flavor	Maillard-Derived
Green, Grassy	No
Spicy	No
Herbaceous	No
Fruity, Citrus	No
Tropical	No
Black Currant, Cassis	No
Floral	No
Vegetable	No
<b>Caramel</b>	<b>Yes</b>
<b>Nutty</b>	<b>Yes</b>
<b>Woody</b>	<b>Yes</b>
<b>Smoky</b>	<b>Yes</b>
<b>Burnt, Roasted</b>	<b>Yes</b>
<b>Beef</b>	<b>Yes</b>
<b>Meat (Pork, Lamb, Chicken)</b>	<b>Yes</b>
<b>Savory, Bouillon</b>	<b>Yes</b>
<b>Fatty, Rancid</b>	<b>Yes</b>
<b>Dairy, Buttery</b>	<b>Yes</b>
Earthy (Truffle, Mushroom)	No
Sulfurous (Garlic, Onion)	No

**No Oven Needed**

The surfaces of roasted meats undergo extensive Maillard reactions because of exposure to high temperatures. The interior is largely unchanged because it is cooler, and the reaction proceeds far too slowly to yield significant results during the short cooking time. Low sugar levels and high water concentrations in the interior also slow down the reactions.

While the Maillard normally occurs above 285°F (140°C)—as in an oven or on a stove—it does occur at room temperature, only slower. This is why beer browns, pasta darkens during drying, and human tissue crosslinks, all at relatively “cool” temperatures. These cooler reactions take weeks or months instead of minutes, but they do occur, just the same.

**Other Uses**

Artificial tanning solutions, such as *dihydroxyacetone (DHA)*, react with the arginine in the *stratum corneum*, the outermost layer of skin. The result is a brown “tan” at room temperature, with the darkness determined by exposure. Such tans are purely cosmetic since they have only minimal UV-blocking effects.

Soybeans for cattle feed are now treated with a Maillard process to enhance digestibility and nutritional value.

**Role in Diabetes & Aging**

An article in this issue (“Tanned Like Leather: Aging Is Just Diabetes, Only Slower”) explains how damage from aging and diabetes is directly attributable to Maillard crosslinking. The basic problem is sugar bonding to proteins and ruining them.

**Conclusion**

Understanding the Maillard reaction improves food’s taste and color, increases food safety, and provides ways to slow down or undo the effects and damage caused by aging and diabetes. Maillard’s discovery is thus still important and highly relevant more than one hundred years later—even if you don’t cook!