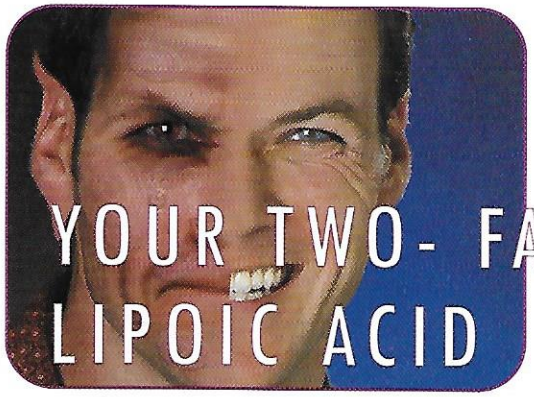


YOUR TWO- FACED LIPOIC ACID

Half your Lipoic Acid is Working *Against* You. How to stop it.

While it's not something that *anybody* will have heard of, like echinacea or vitamin C, health-conscious folks have become more and more familiar with **lipoic acid** (or **thioctic acid**) over the last few years. It's best known as an antioxidant – but it's *not* just another free radical quencher. And even among antioxidants, lipoic acid has an unique place, as the central hub of the body's **antioxidant network.**

While many antioxidants – from beta-carotene to grape skin polyphenols – are found in the diet, and play powerful roles in supporting optimal health, conventional antioxidants are like facial tissue: use it once, and it's no good to you any more – so get rid of it. Not so with the antioxidant network. While other antioxidants work in isolation, the five members of the antioxidant network work *together* to form the indispensable core of the body's free-radical defense and "recycling" system.[1-3] That is, the body uses network antioxidants as a *team* to protect you against rampaging free radicals. These specific antioxidants team – whose other members are the vitamin E complex (tocopherols plus tocotrienols), vitamin C, Coenzyme Q_{10}, and glutathione (GSH) – complement each others' strengths, and make up for each others' weaknesses. Above all, **network antioxidants have the unique ability to "recharge" one another into their active, antioxidant forms when they fall down in the fight against free radical marauders.**

Of that elite, free-radical counterterrorist strike force, **lipoic acid is the least-known ... yet it plays the *most* important role.** Lipoic acid's place at the heart of the network springs from its remarkable versatility. This powerful nutrient is the only network antioxidant which is active in both cellular membranes *and* watery cellular fluid; which retains some of its antioxidant powers even after stepping in to block free radical damage; and which can directly or indirectly "recycle" *all* of the other members of the network back to their active antioxidant form when they become neutralized in taking down free radicals.[4] On top of this – as we'll see – lipoic acid is the *only* antioxidant you can get from diet and supplements that will actually restore the youthful efficiency and energy-producing potential of the body's cellular "power plants" (**mitochondria**). It's literally the most crucial antioxidant for a person to take.

Combine lipoic acid's dynamic antioxidant role with the controlled trials which show that it provides powerful support for healthy blood sugar metabolism,[5] and protects and even restores the functioning of nerves[6] and perhaps kidneys[7] damaged by years of high blood sugar exposure from diabetes – and you know that anyone serious about their health and longevity will look further into this remarkable nutrient.

Yes, lipoic acid is a nutrient with awesome potential. But if you're taking the form of lipoic acid found in almost all supplements currently on the market, then we advise you to sit down before continuing with this article. Because what you'll learn may startle you. If you're taking a conventional lipoic acid pill, then the health-promoting, anti-aging benefits associated with this nutrient are only being delivered by *half* of your supplement. The other half is worse than useless: it actually *antagonizes* the effects of the *good* half of the supplement. To put it bluntly: **the lipoic acid you're taking harbors both a hero ... and an "evil twin."**

The Evil Twin

It's an old story. You've heard it a million times.

There's this well-intentioned, usually good-looking, and always sympathetic main character, who suddenly has his or her life turned upside-down by a look-alike impersonator with a score to settle ... or maybe just a mean disposition. Think of the German *doppelganger* legends ... or of "Data" and "Lore" on *Star Trek: The Next Generation* ... or of Dostoevski's *The Double: Two Versions.* And, of course, there's Robert Louis Stevenson's *Dr. Jekyll and Mr. Hyde,* which is the same tale – but told with a twist. You can find the "evil twin" theme across the whole range of human storytelling, from high-brow literary classics to the daytime soaps.

But keep reading. *This* "evil twin" story is no fairy tale.

Let's start with the fact that **many molecules in nature, including many nutrients and microscopic components of the body, have a "handedness"** (technically, **"chirality"**), just like your left and right hand. Both of your hands have palms and five fingers, but because of the way those components are put together – because of the way their parts are oriented relative to the body and to each other – they still aren't the same in structure or function. Likewise, the biological effects of many key molecules are defined not just by the *sequence* of the atoms that make them up, but their *three-dimensional structure.*

Putting the wrong isomer into your body can actually harm you.

One example of a molecule whose "handedness" is important to its function is **alpha-tocopherol.** As most health-conscious folks know, the alpha-tocopherol found in natural foods is "***d*-alpha tocopherol.**" But the synthetic form found in many drug-store supplements is "***dl*-alpha.**" The molecules in *d*- and *dl*-alpha-tocopherol are made up of the same atoms, put together in the same order; the difference is that the atoms in the molecules of the *dl*- mixture are twisted in different directions in space, just like

you can twist the shafts in a tinker-toy chain to get many different patterns from the same basic building blocks. These different "handednesses" are referred to as different **"isomers"** (EYE-so-mers) of the molecule.

Your body is designed in such a way that it can often make much better use of the natural isomer of a molecule than it can do with that molecule's synthetic look-alikes. Again, alpha-tocopherol is a great example: milligram for milligram, the *d-* form of the molecule is much better used and retained by the body than is the *dl-* mixture. Still, in the case of *dl*-alpha-tocopherol, there's nothing particularly *dangerous* about having those extra, synthetic isomers in your supplement: they're just weaker, less effective imitations of the real thing. In other words, the *dl-* form is not so much an "evil twin" as a geeky kid sibling.

In other cases, however, **putting the wrong isomer into your body can actually harm you.**[8] An example that's becoming better and better known is ***trans*-fatty acids.** Again, most health-conscious people have heard of *trans-* fats, but few people understand what they are, or why they're dangerous. Found in large quantities in most margarines, but also sprinkled throughout the processed-food universe, synthetic *trans*-fatty acids are actually just unnatural *isomers* of natural polyunsaturated fats. When you expose the **natural *"cis-"* isomer** of a polyunsaturated fat to a great deal of heat and pressure (as is done in the partial hydrogenation of vegetable oils), you can literally *twist its structure*, rearranging the molecule's orientation in space. Thus the synthetic *trans-* isomer is born.

Changing a fatty acid from the *cis-* to the *trans-* form is a matter of a simple rotation of orientation ... yet it completely alters the effects of the fat on your body. The crucial difference between the natural *cis*-isomers of polyunsaturated fats and their synthetic *trans*-forms was shown in a large study of the diet and health of over 80 000 female nurses in the United States.[9] This study found that the total *amount* of fat in the nurses' diets did not affect their odds of heart attack or of heart disease death. Instead, it found that it's the *kind* of fat that a person puts into his or her body that affects heart health.

When a woman in the study took 5% of the carbohydrate Calories in her diet, and replaced them with Calories from polyunsaturated fats in their natural *cis-* form, she cut her odds of a heart attack or a heart-disease death by an impressive 38%. But **when a woman replaced just 2% of her carbohydrate Calories with *trans*-fatty acid isomers, she nearly *doubled* her risk of heart attack or death from heart disease** (a 93% higher relative risk)![9] Frighteningly, scientists studying the same group of women have found that **a similar pattern exists for risk of diabetes:** the natural isomer is protective, while the artificial isomer puts a person at greater risk.[10]

Mirror, Mirror ...

If you look on the label of conventional "lipoic acid" supplements, you'll see just that: "lipoic acid" or "alpha-lipoic acid," and the number of milligrams per capsule or tablet. What the label *won't* tell you is that **you're actually getting a 50/50 mixture of two *different*, mirror-opposite *isomers*** of lipoic acid in such supplements. When a molecule exists in two isomers which are one another's *exact* opposites – as is the case with lipoic acid – the two isomers are called **"enantiomers."**

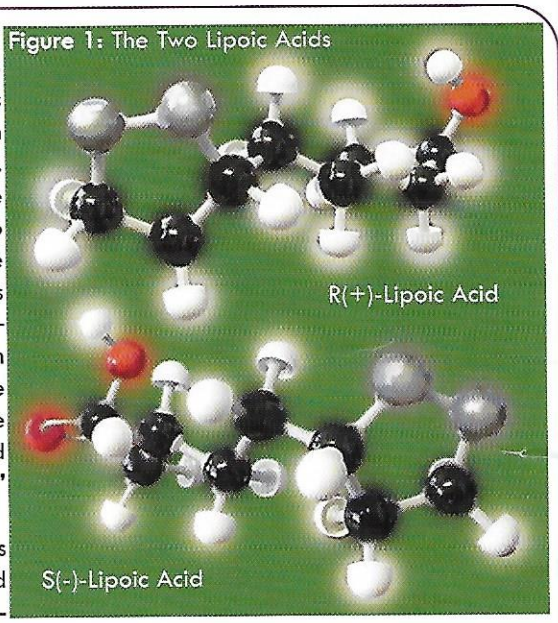


Figure 1: The Two Lipoic Acids

Of the two forms of lipoic acid present in conventional supplements, the isomer which is identical to the one made by living things for their use – **the *natural* form of lipoic acid – is the "R(+)-enantiomer," or "R(+)-lipoic acid." "S(-) lipoic acid" is a purely artificial molecule:** it does not exist in nature but is produced as a byproduct in the normal method of producing commercial lipoic acid (see **Figure** 1). A 50/50 mix of two enantiomers is called a "racemic compound" or "racemate," and the proper, scientific designation for lipoic acid in this form is "*rac*-lipoic acid," "R,S-lipoic acid," or "(±)lipoic acid." But because of industry conventions – and because, until recently, lipoic acid was only available as the racemate, except in tiny quantities for scientific research – lipoic acid supplement labels don't bother to tell you that you're getting a racemic compound, rather than the pure, natural R(+)-form of the nutrient.

Regular lipoic acid supplements are a 50/50 mixture of two *different*, mirror-opposite *isomers*

Well, thanks for the terminology lesson, you may think, *but so what? We already know that lipoic acid supplements provide health benefits. So does the fact that my lipoic acid is a "racemate" actually affect the value of the supplement? Does the presence of the S(-) form make any real difference?*

You bet it does. The S(-)-form that's taking up 50% of your supplement is not just a weaker cousin of the real thing, like the "other" isomers of alpha-tocopherol in the *dl-* product. In fact, **S(-) lipoic acid is the R(+)-enantiomer's "evil twin."** When he reported his findings about the opposing effects of the two forms of lipoic acid on the energy-producing powers of mitochondrial particles, for instance, Dr. Guido Zimmer stated that **"The S(-)-enantiomer ... part of the racemate, which is present as about a 50% *impurity* [our emphasis], needs to be eliminated."**[11]

When you look at the differences between the R(+)- and S(-)- forms of lipoic acid in terms of their effects on the body's **metabolism of blood sugar,** or their **protective and antioxidant activities,** or their **effects on mitochondria** (the cellular "power plants" – see **Figure 2**), and the preliminary evidence on their effects on **the aging process itself,** we expect you'll come to agree with Dr. Zimmer and other lipoic acid researchers (see sidebar: **What Researchers Say**). There *are* cases where the S(-)-enantiomer is merely *less effective* than **R(+)-lipoic acid** –

and also cases where, at worst, the S(-)-form is just totally *ineffective*. But as you dig into the lipoic acid story, you'll also see many cases in which **the S(-)-enantiomer actually *counteracts* the benefits of R(+)-lipoic acid!**

The Bottom Line

- Many molecules used by the body have a specific "handedness" (**chirality**). For example, alpha-tocopherol, or essential fatty acids.
- In some cases, synthetic versions of these molecules have a different "handedness" than the natural molecule.
- Some of these unnatural molecules are merely *less potent* than the natural forms, such as *dl*-alpha-tocopherol. Others are actually *harmful* — for example, *trans*-fatty acids.
- Unless they specify otherwise, "lipoic acid" supplements are a 50/50 mixture of the natural **R(+)-lipoic acid**, and the synthetic S(-)-lipoic acid. These mixtures are called "**racemates**."
- In some cases, S(-)-lipoic acid — or the racemate in nearly all supplements — is simply *less* effective than R(+)-lipoic acid. In other cases, the S(-)-form actually acts *in opposition to* the effects of R(+)-lipoic acid.

Part One

Glucose Metabolism

Transit Strike!

To function properly, cells need a steady fuel supply. Blood sugar is the key fuel for most cells in the body, and the body produces the hormone **insulin** precisely in order to help get energy to the cells that need it. Insulin is like a "key" that turns on the glucose transport "ignition" (**insulin receptor**) which is located on the surface of the cell (see **Figure 3**). When the "key" (insulin) activates the "ignition" (the insulin receptor), it turns on the engines of the "tanker trucks" (**GLU**cose Transporters, or **GLUT**s) that do the work of hauling glucose (blood sugar) out of your bloodstream and into your cells. So to get your cells the energy they need – and to keep blood sugar from building up to dangerously high levels – insulin has to *tell* your cells to take up blood sugar ... and the cell also has to *listen* to the signal, and mobilize the GLUT transporters.

The system is efficient and remarkably adaptable, but it has its limits. The fact is that there's only so much blood sugar that your cells can *take in* at a time. And as soaring rates of diabetes show, North Americans have been overtaxing those limits for generations. Our fast-paced lifestyles and processed-food diets cause most of us to take in more Calories – and, especially, more carbohydrate – than our bodies can handle. After years of being asked, by insulin, to take in more glucose than they can use, eventually **your cells stop responding properly to insulin's signal.**

The *natural* form of lipoic acid is the R(+)-enantiomer, or R(+)-lipoic acid. S(-)-lipoic acid is a purely artificial molecule.

Think of an old car starter whose pins have been so worn down by years of friction against the key's teeth that you have to juggle and twist at the key to get the car to start. When the same thing happens to your body's glucose transport system, **your body becomes *resistant* to the action of insulin.** Insulin is still being produced, but the cells no longer respond properly, and fail to mobilize GLUTs in response. As a result, cells don't take in glucose, and blood sugar levels climb.

Thus begins a vicious circle. Because high blood sugar is bad for you, the body responds to insulin resistance by producing *more* insulin. In the short term, this does the trick, forcing your cells to take in more glucose. But if insulin levels are persistently too high, your cells eventually become even *less* interested in hearing insulin's cries to take in excessive glucose, and respond by producing even *less* GLUTs ... which makes your cells even *more* insulin resistant.

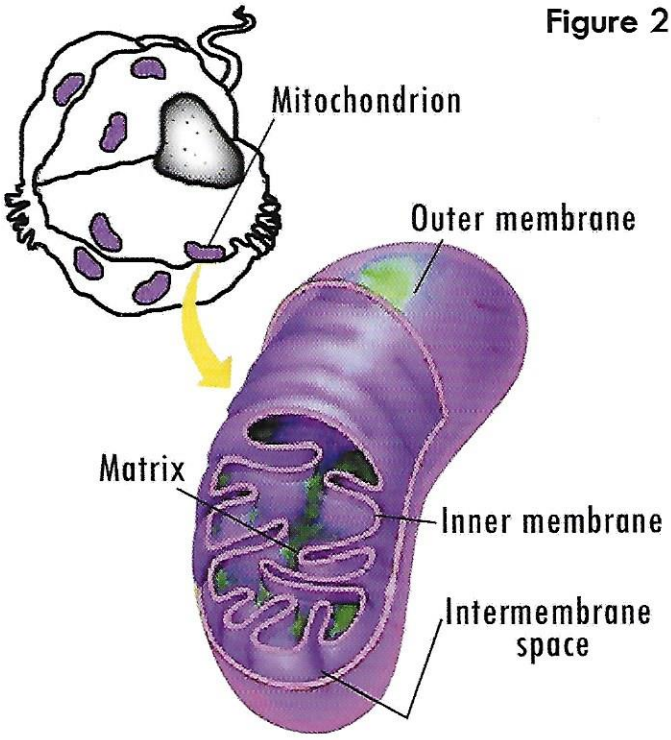
Something has to give. If the insulin-producing cells of the pancreas just can't produce enough insulin to keep blood sugar levels under control in the face of increasing insulin resistance, then the cycle ends in **adult-onset diabetes.** On the other hand, if the brute-force strategy of keeping blood sugar levels at manageable levels by cranking insulin levels higher and higher succeeds, a metabolic disorder known as **insulin resistance syndrome**, or "**Syndrome X**" ensues.[12] And while full-blown, clinical "Syndrome X" is not diagnosed in most people, **almost everyone develops some degree of insulin resistance as part of the "normal" aging process.**

Resistance is Deadly

Even though the blood sugar of most people with insulin resistance may be within the normal range, their health is still in jeopardy, because **insulin resistance *itself* is a potential killer.** The key reason: one of insulin's functions is to control the release of **free fatty acids** from your tissues into your bloodstream ... with the result that, when your body doesn't respond properly to insulin, your plasma levels of free fatty acids rise higher.[13] High free fatty acids keep your blood vessels squeezed up tight by interfering with the action of **nitric oxide,** the molecule that helps your blood vessels to relax;[14] as a result, their **high free fatty acids cause insulin resistant people to have high blood pressure.**[12]

High levels of free fatty acids from insulin resistance also create a distinct and deadly cholesterol pattern.[12] Through a complex series of interactions,[13] high free fatty acid levels cause people with insulin resistance to have *low* levels of ***H*DL cholesterol** (HDL is the "good" cholesterol: think "H" for "healthy") and high blood fats (triglycerides). And while they may have perfectly normal *total levels* of ***L*DL cholesterol** (think "L" for "Lethal" – the "bad" cholesterol), people with insulin resistance end up with a greater *proportion* of

Figure 2



their LDL in the especially deadly form of small, dense LDL particles. "**Many experts believe that syndromes characterized by small, dense LDL are, in aggregate, the *most common* recognized cause of coronary artery disease** [our emphasis]."[13]

So it's no surprise that a recent study[15] found that **how insulin resistant you are is a powerful predictor of your odds of cardiovascular disease.** When a group of otherwise healthy people of normal weight were tested for insulin resistance, the most insulin-resistant third of people were *seven times* as likely to develop cardiovascular disease, and over twice as likely to develop hypertension *plus* cardiovascular disease, over the next five years, as compared to the third of people with only moderate insulin resistance. And the *least* insulin-resistant folks? *Not one* of the third of individuals whose bodies were the most responsive to the insulin signal developed cardiovascular disease over the course of the study!

A similar increase in risk of cardiovascular disease is seen when you look directly at free fatty acid levels themselves;[14] and just as alarmingly, a recent study[16] found that **healthy, middle-aged men who did *not* have heart disease were *70% more at risk of sudden death* if their free fatty acids were in the highest fifth** as compared with the men with the lowest levels.

So what does all of this have to do with lipoic acid?

R(+)- vs. S(-)- in the Sugar Struggle

Controlled trials[5,17,18] prove that even *racemic* (R,S)-lipoic acid helps people become more sensitive to insulin – that is, *less* insulin resistant. But research shows that **only the R(+)-lipoic acid half of conventional "lipoic acid" supplements makes the body's cells more responsive to insulin.** In fact, in some ways **the S(-)-form actually makes it *harder* for your body to healthily process blood sugar!**

Even when no insulin is available, cells can still open their doors to a small amount of glucose. This ability is called the cell's **basal glucose uptake,** and it can be tested by isolating a cell from the influence of insulin and other bodily signals in a test tube. Under these artificial conditions, R(+)- lipoic acid effectively increases cells' basal uptake of glucose[19] whereas the S(-)-form has been found to be either totally ineffective,[20] or just half as effective as **R(+)-lipoic acid,**[19] depending on what kind of cell you look at.

But the ability to increase cells' glucose uptake when there's no insulin around is more of a laboratory curiosity than a medical breakthrough. In a living, breathing organism, insulin *is* present – and restoring the cell's ability to respond to insulin's signal is the key factor in controlling both blood sugar and the witches' brew of risk factors that come with "Syndrome X." So the key question is not what effects the two enantiomers have on *basal* glucose uptake, but how they affect the interplay between insulin, sugar, and the cell.

What Researchers Say About the Two Lipoic Acids

"We're finding – and others are, too – that the R(+)-form – the natural form – is much more powerful than the racemic mixture ... Hopefully ... companies are going to be producing on more of a clinical scale the R(+)-form of lipoic acid, because we're finding very significant effects using this, as opposed to the racemic mixture."

*Dr. Tory Hagen, in **Mitochondrial Decay in Aging.***[27]

"We have presented in this study new information indicating that this enhancement of glucose metabolism is sterospecific, with the R(+)-enantiomer being much more effective than the S(-)- enantiomer."

*Dr. Ryan Streeper and colleagues, in **The American Journal of Physiology.***[21]

"Lipoic acid sold in a health food store is a synthetic mixture, a racemic mixture. And R[+]- is the natural form and S[-]- is an unnatural one ... And in our hands R[+]- works and S[-]- doesn't."

*Dr. Bruce Ames, in **Strategies for Engineered Negligible Senescence.***[86]

"R[+]-LA [that is, R(+)-lipoic acid], and not a racemic mixture of R[+]-and S[-]- LA, should be considered a choice for therapeutic applications."

*Dr. Lester Packer and colleagues. in **Free Radical Biology and Medicine.***[67]

"The S[-]-enantiomer ... part of the racemate, which is present as about a 50% impurity, needs to be eliminated."

*Dr. Guido Zimmer and colleagues, in **Methods in Enzymology.***[17]

There *are* cases where the S(-)-enantiomer is merely *less effective* than **R(+)-lipoic acid ...** but also many cases in which **the S(-)-enantiomer actually *counteracts* the benefits of R(+)-lipoic acid!**

To get answers to this question, scientists compared the response to insulin in the muscle cells of insulin-resistant lab animals injected with either straight S(-)-enantiomer, or pure **R(+)-lipoic acid.**[21] It immediately became obvious that

R(+)-lipoic acid was superior. Using a special, "traceable" form of glucose to monitor the two enantiomers' effects, the very first treatment with **R(+)-lipoic acid caused the animals' muscle cells to take up 31% more glucose in response to insulin,** which was 64% more glucose than under basal (non-insulin-stimulated) conditions. By contrast, **S(-)-lipoic acid caused *no* significant increase in muscle cell glucose transport.**

R(+)-lipoic acid caused the animals' muscle cells to take up 31% more glucose in response to insulin. S(-)-lipoic acid caused no significant increase in muscle cell glucose transport.

Next, the scientist looked at the longer-term effects of the two enantiomers. One group of animals was fed a regular diet, while two other groups' chow was supplemented with one of the two enantiomers. The results were essentially the same. Compared to animals which ate an unsupplemented diet, the muscle cells of animals which were given pure **R(+)-lipoic acid** were able to take up 34% more blood sugar in response to insulin, or 65% more than they did under basal conditions. By contrast, feeding animals the same amount of "lipoic acid" in the artificial S(-)-form had no effect on the animals' ability to clear blood sugar.

In fact, **even giving the animals two-thirds *more* S(-)-enantiomer than had been effective when using R(+)-lipoic acid, *still* led to no clear-cut improvement:** while there did appear to be an increase in the animals' muscle cells' glucose uptake under the influence of insulin, the scientists found that the apparent increase was not strong enough, as compared to their *basal* intake, to rule out a statistical fluke.[21] And the numbers were about the same (145 vs. 150 pmol/mg muscle mass) when they *further* upped the dose of the S(-)-form to one that was *three times* more than what was needed to get clear-cut results with **R(+)-lipoic acid**!

At the same time, **insulin levels in animals that were supplemented with R(+)-lipoic acid were pushed down by 17%,** proving that the vicious circle of insulin resistance was being put into reverse. By contrast, **S(-) lipoic acid actually caused insulin levels to soar 15% *higher*.**[21] Another clear sign that the animals were made less insulin resistant was the fact that **animals given R(+)-lipoic acid experienced reductions of free fatty acids of greater than a third** – an extremely important result, granted the role of increased free fatty acids in causing the high blood pressure[14] and killer cholesterol profile[13] seen in "Syndrome X,"[12] and their place as a risk factor for cardiovascular disease[14] and sudden death.[16] It was a different story in the other group: **free fatty acids in animals fed S(-)-lipoic acid showed no significant change.**

Looking down at these animals' cells, scientists could see what had happened. The **amount of GLUT-4, the muscles' main glucose transporter, was actually *reduced* by 19% by S(-) lipoic acid supplementation!**[21] Granted **R(+)-lipoic acid**'s ability to increase the cell's responsiveness to insulin, you might expect that it would increase GLUT-4 levels. In fact, *levels* of GLUT-4 were not affected one way or the other by the R(+)-form. Instead, other studies[19,22,23] have shown, **R(+)-lipoic acid helps the cell to *mobilize* its glucose transporters**, without affecting GLUT *levels*. These studies found that S(-)-**lipoic acid either has no effect on,**[23] **or actually *interferes with*,**[19] **the cell's ability to mobilize GLUTs.**

Other aspects of the response to insulin were also improved by R(+)-, but not S(-)-, lipoic acid, including a 33% restoration in the ability to burn glucose for fuel and a 26% increase in the formation of **glycogen,** the long-chain molecules used to store carbohydrates for quick use by the liver and muscles.

In short, when you take a racemic mixture of R(+)- and S(-)-enantiomers found in conventional "lipoic acid" supplements, **R(+)-lipoic acid improves insulin resistance, while the S(-)-form actually makes it *worse*.** The results that are seen in clinical trials using the racemate, then, are the *net effects* of combining the powerful benefits of **R(+)-lipoic acid**, with the sometimes weaker, and sometimes even *harmful*, effects of the S(-)-form.

R(+)-lipoic acid, in other words, is not just fighting against insulin resistance: it's fighting against the "evil twin" present in most commercial supplements. Getting rid of the "fifth column" in your supplement frees up the full potential of **R(+)-lipoic acid,** allowing its full strength to be unleashed in the battle to restore healthy sugar metabolism.

The Bottom Line

- Insulin resistance, in which the cells of the body stop responding properly to the hormone insulin, happens to some degree in almost all of us as we age.
- Insulin resistance causes higher levels of insulin, blood sugar, and free fatty acids, all of which are threats to your health.
- Lipoic acid has been used to support healthy blood sugar metabolism.
- The "lipoic acid" in common supplements is a 50/50 mixture of two different "lipoic acid" molecules: the natural R(+)-lipoic acid, and the unnatural S(-)-form.
- Animal experiments have compared the effects of the two "lipoic acid" molecules seperately.
- R(+)-lipoic acid fights all of the major effects of insulin resistance. The S(-)-form either does not help in these areas, or makes things worse.
- Common "lipoic acid" supplements are thus like a house at war with itself. The S(-)-form should be removed from supplements.

Part Two

Antioxidant Activity

When you swallow a racemic lipoic acid tablet – the kind you get in nearly all "lipoic acid" supplements – both the S(-)- and the **R(+)-lipoic acid** are taken up into your blood[24] and then transported to your cells.[25] Already at this point, another advantage of **R(+)-lipoic acid** becomes clear: the **R(+)-lipoic acid is dramatically more bioavailable than the S(-)-form.** The *peak* concentration of plasma lipoic acid obtained from **R(+)-lipoic acid** is *twice* as great as from an equal amount of the S(-)-form,[26] and the *total* **R(+)-lipoic acid** delivered into the plasma over the course of time is 60 to 85% greater than the total amount of the S(-)-form which ultimately reaches the plasma as well.[27,28] More importantly, studies show that **R(+)-lipoic acid** is taken up *into the tissues* to a greater degree than the S(-)-form. In one study,[29] scientists gave lab animals the R(+)-, the S(-)-, or the racemate form of lipoic acid – providing it *by injection,* so as to bypass the differences in absorption in the digestive system, and thus start the animals off on a level playing field. As expected, lipoic acid levels were the same in all three groups within the first hour as the injected lipoic acid made its way through the circulation. But three hours later, the **animals which had received R(+)-lipoic acid had *two to seven times more* lipoic acid in the lenses of their eyes than animals given the same amount of the S(-)-form,** and three times as much as the animals given the racemate form!

Impressive as these results are, an even more important difference emerges only *after* the different forms of lipoic acid have been taken into your cells.

An Antioxidant ... and its Antagonist

Despite what you hear, lipoic acid *itself* – whether we're talking about the natural R(+)-enantiomer or the artificial S(-)-form – is not much of an antioxidant. The *real* free-radical fighter in the lipoic acid story is **dihydrolipoic acid (DHLA** – see **Figure 4**).[30] Lipoic acid and DHLA are like the two alter egos of some superheroes. If lipoic acid is Billy Batson, then DHLA is Captain Marvel. One (lipoic acid) is the day-to-day identity of the hero: courageous and smart, but limited to the strengths of a mere mortal. But when the hero puts on a ring or says a magic word, the day-to-day identity is shed in a flash of light, as the hero is charged with fabulous powers.

Insulin levels in animals that were supplemented with **R(+)-lipoic acid** were pushed down by 17%, **S(-)-lipoic** acid actually caused insulin levels to soar 15% higher.

R(+)-lipoic acid is dramatically more bioavailable than the S(-)-form.

Lipoic acid is "charged up" into its DHLA "superhero" identity as part of its function in transforming *food* energy into *cellular* energy in the mitochondrial enzyme complex **pyruvate dehydrogenase (PDH** – see **Figure 5**). Usually, mitochondria have to synthesize their own lipoic acid,[31] which is an "expensive" process ... so there's *just* enough lipoic acid available to meet the mitochondria's energy needs. When you make *extra* lipoic acid available by taking a supplement, the mitochondria "charge up" lipoic acid into DHLA, whereupon the extra DHLA is released into the rest of the cell and into the surrounding fluid[32] ... and free radicals tremble in their boots.

So what are the "superpowers" that make DHLA the real hero of our tale? **DHLA is both a more *potent* antioxidant than lipoic acid (R(+)- or S(-)-), and has a wider *range* of antioxidant actions.**[30] For instance, one key property of lipoic acid that we've already mentioned is its ability to "recharge" the complete antioxidant network, giving new life to molecules of vitamin C, E- complex vitamins, and glutathione,[30] as well as CoQ_{10},[33] when they fall down in the fight against free radicals. But it's actually DHLA, and not lipoic acid *itself,* that has this ability.[30] Likewise, most studies find that DHLA can take out **superoxide,** the main free radical made by the cell's mitochondria,[34] and DHLA appears to even prevent the *formation* of superoxide by the mitochondria.[35] Lipoic acid *itself* lacks this ability. And most remarkably, whereas conventional antioxidants just *prevent* free radical damage, DHLA is actually able to help *repair* free-radical damage to some types of bodily proteins, by enhancing the activity of a protein repair enzyme.[36]

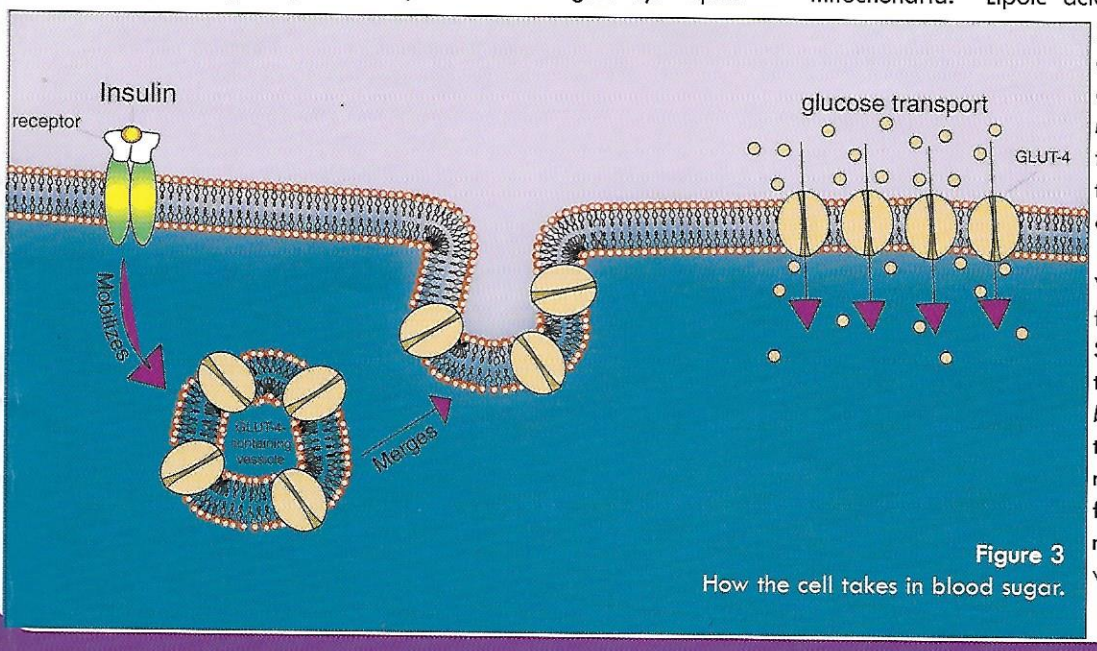


Figure 3
How the cell takes in blood sugar.

What difference does this make to the form of lipoic acid you choose? Simple. Remember, **R(+)-lipoic acid** is the form of the molecule *actually used by your body.* **R(+)-lipoic acid,** and not the S(-)-form, is made by your mitochondria, and is essential to their function. So it's no surprise that the mitochondrial enzyme complex (PDH) which is *specifically* responsible for

converting lipoic acid into DHLA "prefers" the orthomolecular R(+)enantiomer to the foreign S(-)-form: **R(+)-lipoic acid** is the "key" made by your body to open this "lock," while the S(-)-form is a warped counterfeit.

In fact, the **mitochondrial PDH enzyme complex converts R(+)-lipoic acid into DHLA at a rate *at least twenty-four times faster* than the S(-)-form.**[37,38] In some human cell types, the mitochondrial enzyme won't accept S(-)-lipoic acid at all.[38] Worse: at high concentrations **the S(-)-enantiomer actually *interferes* with the mitochondrial enzyme's ability to make DHLA from R(+)-lipoic acid!**[37] Fortunately, it's unlikely that anyone taking racemate lipoic acid supplements is in danger of getting such high concentrations of the S(-)-enantiomer into their bodies.

R(+)-lipoic acid is transformed into DHLA six to eight times more quickly than is the S(-)-form.

There are, however, places *other than* the mitochondria where the body can make some DHLA from either form of lipoic acid. As a result, when you look at the *total* DHLA formed in the cell, as opposed to just what's made in the PDH complex, the S(-)-enantiomer is still clearly inferior to the R(+)-, but the gulf is not quite so extreme: in the heart, for instance, **R(+)-lipoic acid** is "only" transformed into DHLA six to eight times more quickly than is the S(-)-form.[39]

Even this, however, makes the S(-)-form look *more useful* than it really is, because the main way that the S(-)-form gets powered up into DHLA is by *hijacking* the activity of an enzyme which was never designed for the purpose: **glutathione reductase.** You may know **glutathione (GSH)** as another player in the antioxidant network , which is known specifically for its ability to protect the liver against toxins and drugs and to fight lung infections.[40] Glutathione reductase is an enzyme whose *purpose* is to recycle used-up **glutathione (GSH)** into its active form.

Well, there's only so much an enzyme can do at a time! Every moment that glutathione reductase is kept sidetracked by S(-)-lipoic acid is a moment during which it *can't* do the job it was *designed* to do – namely, again, to keep *glutathione* cycling smoothly through the cell's defense system. So when S(-)-lipoic acid takes over this enzyme, a bit more DHLA is made ... but a bit less glutathione is recycled, too. Bottom line: **the S(-)-enantiomer robs Peter (GSH) to pay Paul (DHLA),** giving with one hand while taking with the other. It's one step forward, one step back. **R(+)-lipoic acid** has no such problems, being strongly taken up by the mitochondrial enzyme as it was designed to do, and having a much weaker tendency to waste glutathione reductase's time.

But enough molecular babble (for now!). What does all of this *mean,* in terms of real-world antioxidant defense? Scientists have been asking themselves this question for some time, and have made some discoveries that users of lipoic acid need to know about. Let's have a look at their findings.

One study[41] looked at the effects of aging – and of the two forms of lipoic acid – on the vulnerability of liver cells to ***tert*-butylhydroperoxide (t-BuOOH),** a chemical that causes the cell's mitochondria to churn out more free radicals. As had been seen in other studies, older animals' cells were much more susceptible to the toxin than were those from young animals: an amount of t-BuOOH that half of the cells from young animals managed to survive, was enough to kill all but 12% of the cells from older ones.

Astoundingly, when the cells of old animals were given one of the two forms of lipoic acid in advance of t-BuOOH, **R(+)-lipoic acid *completely protected* the cells from the free radical assault,** so that the cells given **R(+)-lipoic acid** *and* the toxin survived as often as did cells which were *not given the toxin at all.* And, on the opposite extreme, S(-)-**lipoic acid provided *no significant protection* against rampaging free radicals,** such that cells were equally doomed by the toxin *whether or not* they also got the S(-)-form (see **Figure 6**).

In another study, [42]nerve cells from different parts of the brain were exposed to enough **buthionine sulfoxamine (BSO)** to destroy half of them. (BSO is a chemical that makes cells more vulnerable to free radicals by depleting the cell of antioxidant defenses). **Providing the cells with R(+)-lipoic acid saved between one half and one third of the brain cells** that would otherwise have died from necrotic cell death (depending on what kind of brain cells were involved). By contrast, **neither the S(-)-form, nor the *racemate* (R,S)-lipoic acid found in common supplements, offered any significant protection.**

The ineffectiveness of S(-)-lipoic acid is not terribly surprising, granted that the body converts so little of the artificial enantiomer into DHLA as compared with what's achieved using **R(+)-lipoic acid.** But it's surprising to see the impotence displayed by the *racemate.* After all, (R,S)-lipoic acid contains *50%* **R(+)-lipoic acid** by weight ... and yet the presence of an equal amount of **the S(-)-enantiomer not only failed to lend a helping hand to the R(+)-lipoic acid which is present in the racemate, but actually rendered the racemate *useless*** in protecting cells from a toxin against which **R(+)-lipoic acid** *alone* provides an effective shield! But we've already seen a couple of reasons why this might happen. The S(-)-form could have interfered with the supercharging of **R(+)-lipoic acid** to DHLA; it could also have further contributed to the imbalance in antioxidant defense created by BSO, by interfering with the recycling of glutathione.

R(+)-lipoic acid *completely protected* the cells from the free radical assault, so that the cells given R(+)-lipoic acid *and* the toxin survived as often as did cells which were *not given the toxin at all.*

S(-)-lipoic acid provided *no significant protection* against rampaging free radicals.

Even more unexpected results were seen when the same research team decided to find out how much of the racemic form of lipoic acid, or of each of the two enantiomers, is needed to protect

nerve cells against **homocysteic acid,** a byproduct of the toxic amino acid **homocysteine.**[42] It was no surprise when the scientists found that **the R(+)-lipoic acid was able to protect nerve cells from the cortex of the brain against homocysteic acid at less than half (38%) of the concentration required by the S(-)-form.** What *was* a surprise was the finding that **the racemate was not only less potent than R(+)-lipoic acid, but was even weaker than the S(-)-enantiomer** in protecting against this toxin! In fact, it took *six and a half times* as much of the racemate as had been needed by **R(+)-lipoic acid** to provide the same level of protection.

Also strange was the fact that the three forms of lipoic acid were about *equally* effective in protecting nerve cells from a different part of the brain (the hippocampus) against this toxin.[42] Then there are the results of experiments testing the ability of the different lipoic acid in protecting the lenses of lab animals' eyes from treatment with BSO.[29] *All* of the animals given the toxin by itself developed cataracts. **Providing the animals R(+)-lipoic acid slashed the number of animals that developed cataracts by nearly half,** to just 55% of the group, while the same amount of **the S(-)-form provided no protection.** Yet the protection provided by an equal amount of the racemate was not significantly different from what was seen with **R(+)-lipoic acid.**

Clearly, different forms of lipoic acid vary in their protective powers, depending on the part of the body under attack and the nature of the threat. But it's also clear that, *overall,* **R(+)-lipoic acid is far superior to both the S(-)-enantiomer, and the (R,S)-form available in common "lipoic acid" supplements** in providing antioxidant protection. Indeed, when you find out about results like these, the S(-)-lipoic acid that's taking up half of your supplement starts to look more and more like the worst kind of "third wheel."

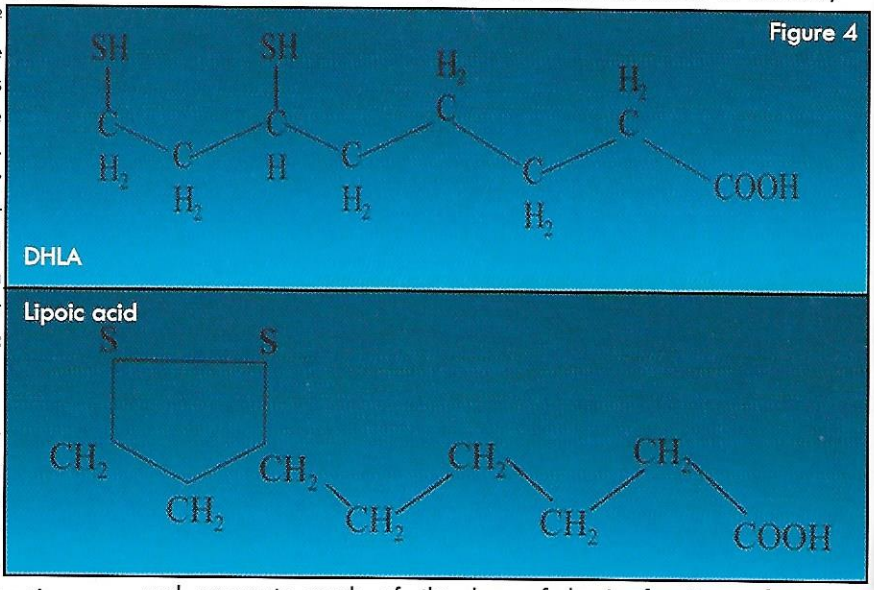
The Bottom Line

- Lipoic acid is known as a powerful and versatile antioxidant.
- The "lipoic acid" in common supplements is a 50/50 mixture of two different "lipoic acid" molecules: the natural R(+)-lipoic acid, and the unnatural S(-)-form. This mixture is called the "racemate."
- R(+)-lipoic acid is more easily absorbed and taken into the cells than S(-)-lipoic acid.
- Both forms of lipoic acid can be made more powerful by upgrading them into their DHLA form. R(+)-lipoic acid is upgraded much more rapidly than S(-)-lipoic acid.
- Many studies have found that R(+)-lipoic acid provides much more effective protection than S(-)-lipoic acid or the racemate. In some cases, the S(-)-lipoic acid actually *counteracts* the effects of R(+)-lipoic acid.

Part Three

Neurological Function

We've already seen some examples of how **R(+)-lipoic acid** can protect nerve cells from free radicals and toxins, even in cases where the racemate – or the S(-)-form alone – cannot. In animal studies, lipoic acid has also been shown to protect rodents from a variety of toxins, from amphetamines[43] to the chemotherapy drug cisplatin[44] and excitotoxic amino acids like aspartate.[45] Furthermore, lipoic acid improves an animal's chance of survival,



and prevents much of the loss of brain function, after a simulated "stroke" (created by blocking off the arteries which supply the animals' nerve cells with oxygen and then letting oxygen flood back in),[45] and prevents age-associated reductions in **long-term potentiation,** the mechanism whereby the brain moves short-term memories into long-term storage.[46]

"Blood and Iron"

Part of the reason for this protection is, of course, the fact that lipoic acid – especially when at the height of its powers as DHLA – effectively neutralizes free radicals. But there's more to lipoic acid's antioxidant protection than simply attacking free radicals as they come along, the way children stomp on ants coming out of an ant hill. Lipoic acid also provides a kind of *proactive* defense against some of the worst kinds of free radicals by binding up unbound **"transition metals"** such as copper, iron, and cadmium.

Transition metals are not free radicals *themselves,* but when they're put in contact with **hydrogen peroxide** (a *relatively* harmless free-radical-like substance), they can tear the molecule apart, forming *two* molecules of the toxic **hydroxyl radical** (a process known as the **Fenton reaction**). By keeping transition metals safely bound away, lipoic acid prevents Fenton reactions from happening, and thereby keeps some of the nastiest kinds of free radicals from materializing in the first place.

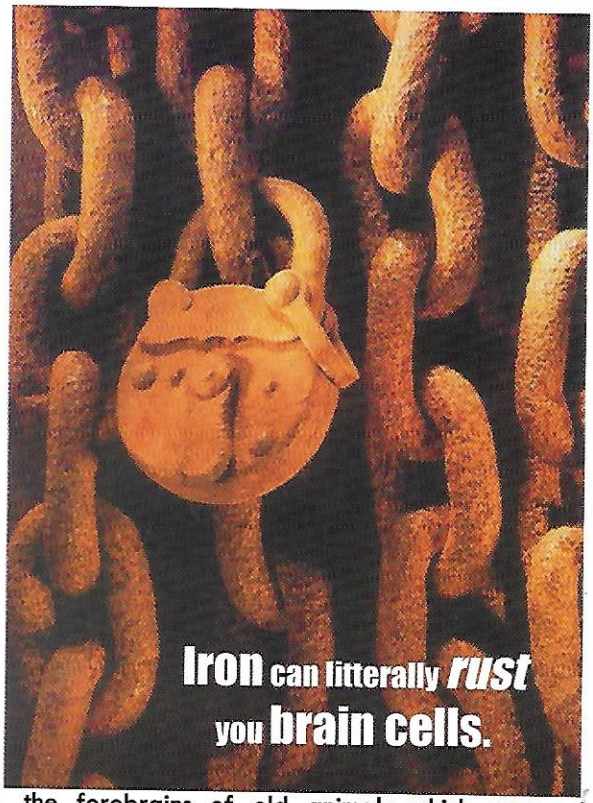
Aside from the *general* role of transition metals in free radical damage, there's a significant amount of evidence to suggest that **an excess of transition metals in various areas of the brain is**

a central factor in many neurological disorders.[47] For instance, people with **Parkinson's disease** have high levels of iron in exactly those cells of the brain which are affected by the disease (the **substantia nigra**);[48] likewise, scientists have found high concentrations of iron in disease-specific parts of the brains of victims of **Huntington's disease**[49] and **Friedreich ataxia.**[50] There are similar stories to be told with copper in **primary dystonia** (a genetic disorder which causes involuntary muscle contractions, leading to "freezing," spasming, or cramping of the muscles involved)[51] and **Alzheimer's disease.**[52,53]

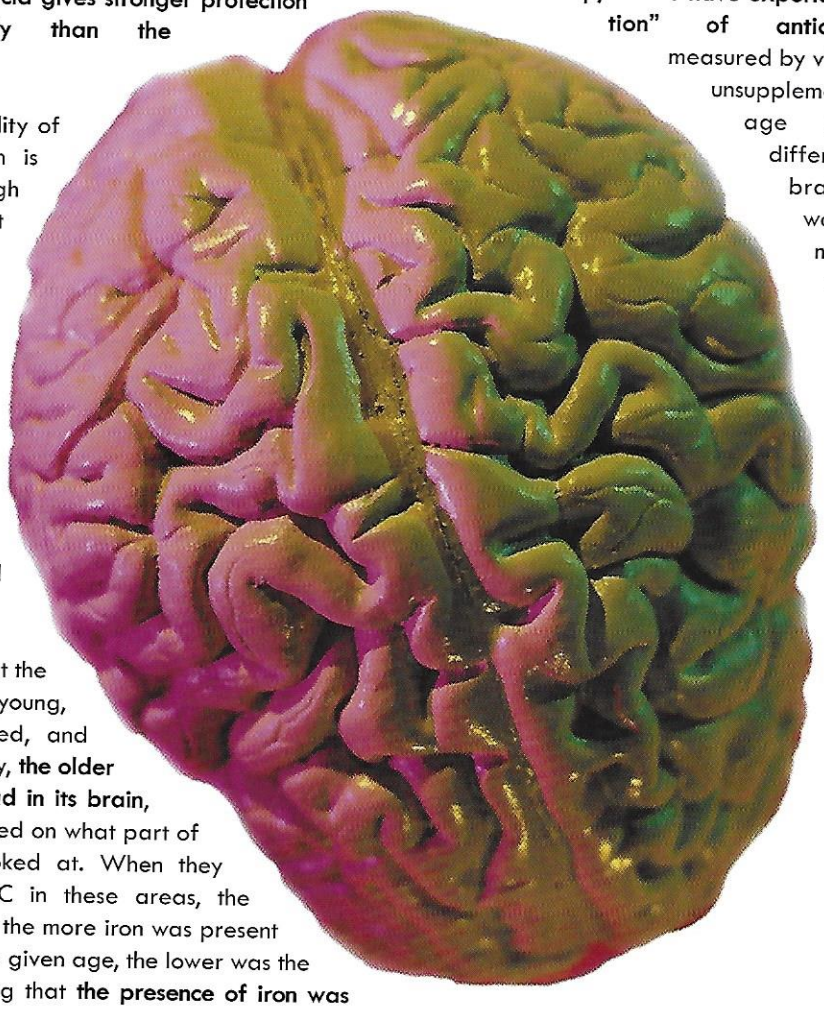
As mentioned above, lipoic acid chelates transition metals, binding them tightly and preventing them from going on a "Fenton frenzy." More specifically, **R(+)-lipoic acid is superior to the S(-)- in controlling the acceleration of free**

The S(-)-enantiomer which is present in the racemate actually rendered the racemate *useless*.

radical damage by copper.[54] Likewise, lipoic acid can protect cells from the toxic heavy transition metal cadmium through chelation, but it only becomes effective when charged up into its DHLA form;[55] since the body makes DHLA from **R(+)-lipoic acid** much more quickly than happens with **the S(-)-form,**[37,39] **that should mean that R(+)-lipoic acid gives stronger protection against cadmium toxicity than the S(-)-form.**



And what about iron? The ability of the racemate to tie up iron is well-established,[30] although unfortunately no studies that we know of have *compared* the iron-chelating protection provided by the racemate with the powers of **R(+)-lipoic acid.** But there's only been *one* study to see if lipoic acid might be able to protect the brain of a living, breathing organism against damage from excessive iron buildup – and that study used **R(+)-lipoic acid.**[56]



In this study,[56] scientists looked at the levels of iron in the brains of young, middle-aged, late-middle aged, and old lab animals. Not surprisingly, **the older the animal, the more iron it had in its brain,** though how *much* more depended on what part of the brain the researchers looked at. When they looked at levels of vitamin C in these areas, the scientists consistently found that the more iron was present in a given part of the brain at a given age, the lower was the level of vitamin C – suggesting that **the presence of iron was depleting the brain of its antioxidant defense forces.**

Remarkably, at the end of an experiment that lasted just two weeks, **the forebrains of old animals which were given R(+)-lipoic acid in their food were found to have 60% less iron buildup, and to have experienced a "substantial restoration" of antioxidant defenses** (as measured by vitamin C levels) compared to unsupplemented animals in the same age group. No significant differences were seen in other brain areas; however, one wonders if a mere two weeks may simply not have been enough time to mobilize the iron accumulation from structures located deeper within the brain. Either way, this study – combined with the other knownneuroprotective effects of lipoic acid (and especially the R(+)-form) – suggests that **R(+)-lipoic acid** shows promise in the prevention (and, perhaps, even the treatment) of several devastating neurological diseases.

The Bottom Line

- Lipoic acid is known for its ability to protect brain and nerve cells.
- The "lipoic acid" in common supplements is a 50/50 mixture of two different "lipoic acid" molecules: the natural R(+)-lipoic acid, and the unnatural S(-)-form. This mixture is called the "racemate."
- Excessive levels of "transition metals" such as iron, copper, and cadmium are believed to play an important role in many neurological disorders.
- An animal study using R(+)-lipoic acid found that it was able to significantly reduce age-related buildup of iron in the brain. Other studies suggest that S(-)-lipoic acid will not work as well.

Part Four

The Mitochondrion

Twenty years ago, if you'd mentioned **free radicals** to the average person, they would probably have thought you were talking about campus political dissidents. Today, almost everyone has at least some familiarity free radicals and their harmful effects – which is why health-conscious people always have their ears perked up for news on the latest antioxidant to hit the market.

The forebrains of old animals which were given R(+)-lipoic acid in their food had 60% less iron buildup, and had experienced a "substantial restoration" of antioxidant defenses.

But even after a generation of attention on the role of free radicals in health and disease, many health-conscious people still don't know that, while *some* free radicals come into the body from the environment (such as from smog, rancid fats, and ultraviolet radiation), *most* free radicals are actually produced by the body itself. Some free radicals are used by the body's immune cells to kill off invaders. Others are produced by the enzymes that help your body break down toxins. Even the ability of your blood vessels to relax and allow blood to flow is dependent on production of a kind of free radical (nitric oxide).

At Ground Zero

And in fact, **the single biggest source of free radicals in your body are its *mitochondria*.**[57] Elsewhere in this article, we've referred to mitochondria as the cell's "power plants." But "*nuclear* power plants" might be a more precise image. Because as part of the process of energy production, both nuclear plants and mitochondria also produce deadly, high-energy waste. In the case of mitochondria, that waste is a free radical called **superoxide.**

This means that the body's cellular power plants are the site of an ongoing "reactor leak," exposing them to the biggest load of free radical marauders in the body. And unfortunately, while your body produces antioxidant enzymes which can partially protect the *rest* of the cell from free radical damage, these enzymes are much less able to protect the mitochondria.

A striking example of the greater vulnerability of mitochondria to free radical damage is the extent of the damage suffered by their DNA, which is separate from the DNA of the rest of the cell. While health-conscious people are rightly concerned about free radical damage to the DNA blueprints of the cell as a whole, the number of hits to the *main* genetic code pales next to the level of damage suffered by *mitochondrial* DNA. When you look at the cells of key organs like the brain and heart – the long-lived cell types that normally must last a lifetime – you see that **mitochondrial DNA suffers seven to eleven times more damage from free radicals than does the DNA for the rest of the cell.**[58-60]

The picture doesn't get any prettier when you look at the *working parts* of the mitochondria – a system we've only recently begun to truly understand. Remarkably, as scientists have pieced together the mechanism whereby mitochondria generate energy, it's become clear that **mitochondria create power using almost identical principles to the ones used by hydroelectric dams** – right down to the turbines (see **Figure 7**)![61,62]

In simple terms, mitochondria take energy from food, and use it to build up a "reservoir" of hydrogen ions (H^+) behind a "dam" (the **mitochondrial inner membrane**). The buildup of ions behind the "dam" creates a force drawing them to the "downhill" side of the mitochondrial inner membrane, just as water behind a dam is drawn downward by gravity. The "dam" leaves only one route for the ions to flow: through a quite *literal* turbine called "**Complex V**" (or the "**F0/F1 ATP synthase**"). The flow of ions through Complex V literally causes its turbine to *spin*, and this motion drives the joining of a carrier molecule (adenosine *di*phosphate, ADP) with a high-energy phosphate bond, to create

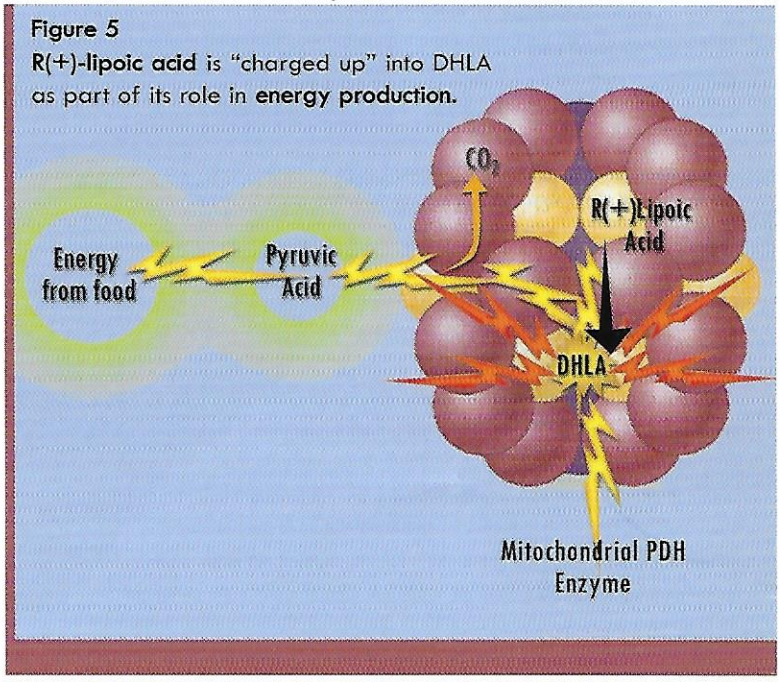


Figure 5
R(+)-lipoic acid is "charged up" into DHLA as part of its role in **energy production.**

the "universal energy molecule" of life: ATP (adenosine *tri*phosphate).

So guess what happens when the moving parts of your turbine start to wear out, and you start getting cracks in your hydro dam?

You get the picture. **With age, the mitochondrial "dam" literally becomes *leakier*,** allowing hydrogen ions to escape across the mitochondrial inner membrane without powering the Complex V turbine.[63] A key part of this loss of membrane function is free radical damage in the proteins of the mitochondria, which slowly creeps up with age.[64] Just as a leaking dam reduces the water levels behind it (and thus, the potential energy which is available to drive the dam's electrical turbines), so a leaky mitochondrial inner membrane reduces the amount of force available to push ions through the ATP turbines of Complex V.

As a result, **old organisms' mitochondria have less membrane energy potential than do young ones, and produce less ATP**[63] (a fact which can be measured using mitochondrial oxygen use). In addition to seriously compromising your cellular energy supply (and especially the ability of the cell to *increase* energy output to meet unusually high energy demands under stressful conditions), this mitochondrial energy inefficiency has another cost. Remember, the process of maintaining the ion "reservoir" creates waste, in the form of superoxide free radicals. When there are leaks in the "dam," it takes more and more "pumping" of ions to create a given amount of energy, because fewer of the ions that are moved into the "reservoir" will ultimately generate energy by passing through the Complex V turbines.

The consequence: **old animals' mitochondria "burn" their fuel less and less *cleanly*, churning out more and more free radical waste per unit of useable energy produced.**[63,65,66] It's a vicious circle: as mitochondria decay, the cell's power situation looks more and more like a California brown-out, even as the cell's *need* for energy is increased by the greater and greater load of choking free radicals ... which come precisely from its increasingly polluting "power plants."

Less energy. More free radicals. The flames of life grow smoky and dim. Without energy, the cell can't perform its essential functions in the body. Proteins aren't made; chemicals aren't detoxified; hearts don't pump; wounds don't heal. Youth fades. Organisms age ... and die.

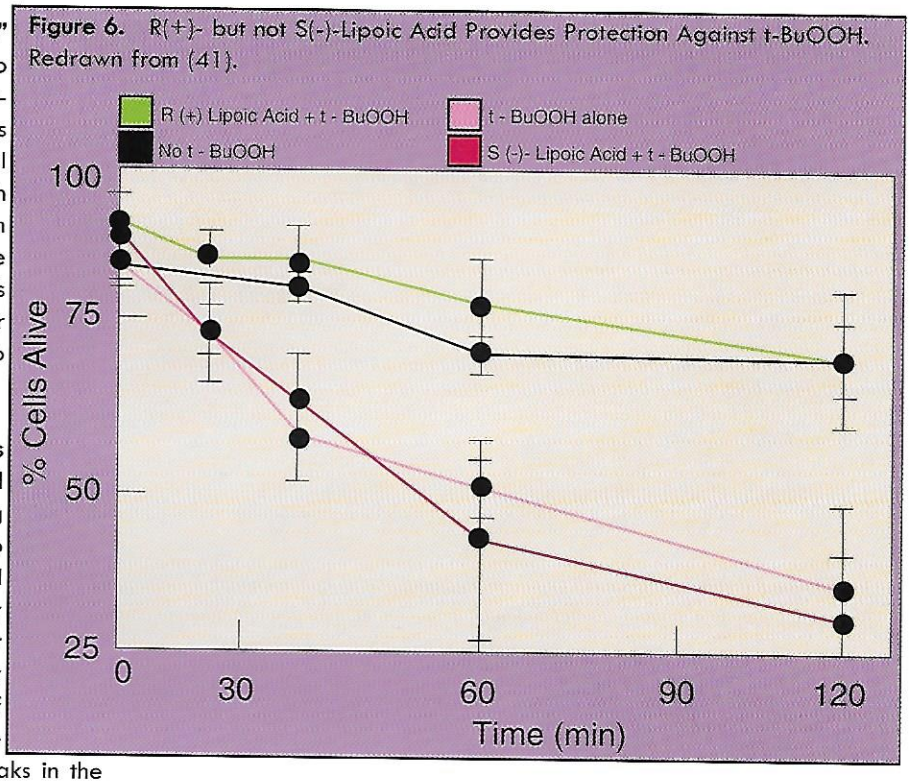
How can you get that youthful energy production back?

The Turbo Charger Must Fit *Your* Car!

As we've already seen, **R(+)-lipoic acid** has a key place in mitochondrial energy production, springing from its role in the **pyruvate dehydrogenase enzyme complex (PDH)** – the same enzyme complex which "charges up" lipoic acid into DHLA (see **Figure 5**). PDH extracts energy coming into the mitochondria bound up in pyruvic acid (which is made in the cell from glucose) and gives that energy to carrier molecules. This energy is ultimately used to create the mitochondria's ion "reservoir."

So you'd expect that boosting levels of **R(+)-lipoic acid** might increase the mitochondria's ability to make ATP. (And you'd be right – but, as we'll see, for the *wrong reason*). And because the S(-)-form is only poorly used as an energy coenzyme by the mitochondria – and, indeed, can actually *interfere with* the mitochondria's ability to use **R(+)-lipoic acid** for this purpose! – it also makes sense to look and see if the two lipoic acid enantiomers might have different effects on energy production and use.

Figure 6. R(+)- but not S(-)-Lipoic Acid Provides Protection Against t-BuOOH. Redrawn from (41).



While R(+)-lipoic acid revs up mitochondria's cellular fuel production, the S(-)- form does not.

When researchers have looked into these questions, they've found the same sorts of answers we've been seeing with the use of the two enantiomers for support of healthy glucose metabolism and as antioxidants. **While R(+)-lipoic acid revs up mitochondria's ability to make cellular fuel, the S(-)- form does not – and in some critical situations both S(-)-lipoic acid *and the racemate* may actually *deplete* the cell's energy supply!**

Since PDH needs **R(+)-lipoic acid** as a coenzyme for its function, you might expect that giving cells extra **R(+)-lipoic acid** would make PDH extract even *more* energy from pyruvic acid. Not so: when a team of scientists provided cultured cells with **R(+)-lipoic acid**, it was found to have no effect on PDH's ability to help process pyruvic acid.[67] That might seem strange, but it actually does make sense, since the cell normally has all the **R(+)-lipoic acid** it needs for PDH activity. It's precisely because it has no *need* for extra lipoic acid that, after "charging up" supplemental **R(+)-lipoic acid** into its more potent DHLA form, PDH readily *releases* the extra DHLA into the cell and the rest of the body, where it can lend its potent antioxidant assistance.

But when the same scientists provided the cells with **R(+)-lipoic acid**'s "evil twin," they found that S(-)-**lipoic acid actually *suppresses* the ability of cells to use pyruvate in energy production,** reducing its activity by 25 to 30%! The obvious explanation: S(-)-**lipoic acid was actually getting in the way of the natural R(+)-form of lipoic acid, which is *needed* for PDH to do its job.** Looking at their results, the scientists concluded that **"R(+)-LA [that is, R(+)-lipoic acid], and not a racemic mixture of R(+)- and S(-)-LA, should be considered a choice for therapeutic applications."**[67]

Exposing these mitochondria to either the S(-)- form *or* the racemate actually *slows* their rate of ATP synthesis!

But hold on. If **R(+)-lipoic acid** doesn't increase PDH activity, doesn't this mean that **R(+)-lipoic acid** is useless for boosting mitochondrial energy production? No – because the effects of **R(+)-lipoic acid** on mitochondrial energy production go well beyond PDH, and into the very heart of the activity of the mitochondria's ATP turbine.

This was first shown by German scientists, in early experiments using mitochondria which had literally been turned inside out to study their functioning.[11] These researchers found that providing these special mitochondria with **R(+)-lipoic acid boosts their ATP production.** But they also found that the two forms of lipoic acid showed "decisive differences" in their effects on mitochondrial ATP. **Exposing these mitochondria to either the S(-)- form or the racemate actually *slows* their rate of ATP synthesis!**

Why would **R(+)-lipoic acid** tubocharge mitochondrial function, while the S(-)-enantiomer undermines it? Remember that the "leakiness" of the mitochondrial membrane is in large part caused by damage to the proteins it contains. One critical kind of damage that these proteins undergo is the handcuffing together **(crosslinking)** of key proteins' sulfur-rich **cysteine** amino acids, which creates **disulfide** (sulfur-to-sulfur) bonds between two sulfur atoms. These disulfide handcuffs change the structure of the membrane itself and of its functional proteins – including the all-important Complex V turbines. It's these structural changes that create the "holes" in the "dam" of the mitochondrial inner membrane, rendering the mitochondrion an inefficient and "dirty" energy producer.

Preventing the crosslinking of sulfur groups is therefore a key part of keeping the mitochondrial inner membrane intact, and its proteins functional. But in order to maintain the structure and function of this system, a molecule must be able to interact with the complex 3-dimensional structures of the proteins themselves. So it's easy to see why scientists studying the effects of the two forms of lipoic acid have concluded that **the *specific* three-dimensional design of R(+)-lipoic acid allows it to favorably interact with mitochondrial proteins – including the turbines of Complex V – while the mirror-opposite architechture of the S(-)-form cannot.**[11,68,69]

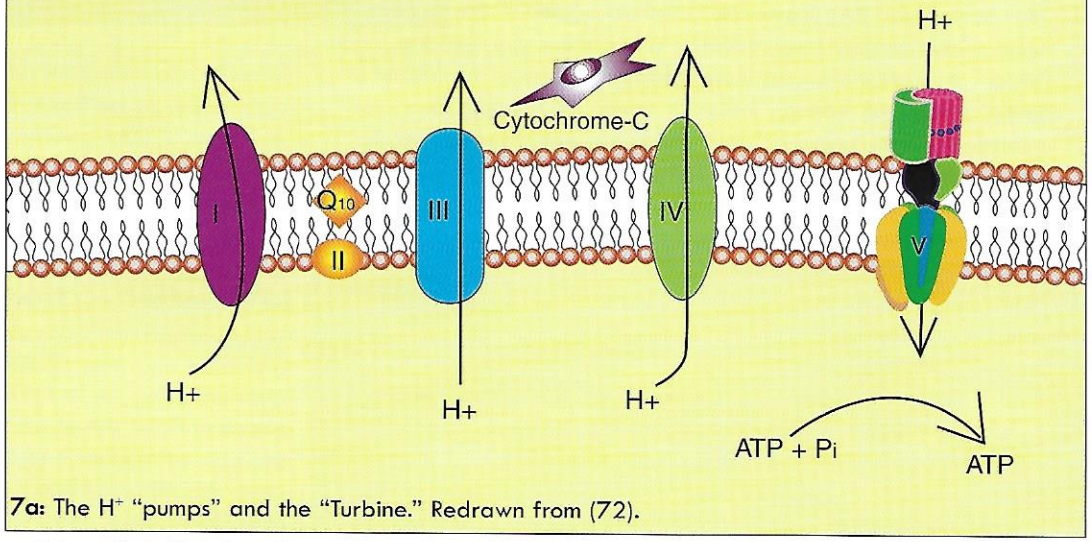
In other words, you won't get anywhere trying to install a turbo charger in your car if it isn't compatible with your engine. Trying to install the wrong unit might even *sap* your engine's power.

Energy In Crisis

To see if the strikingly different effects of the two lipoic acid enantiomers they had observed in isolated mitochondria would also be seen in living organisms, the same group of scientists next tested the two forms of lipoic acid in animals undergoing a simulated heart attack.[69] It's in these critical moments, when the heart is starved for life-giving oxygen and the fuels in the bloodstream, and when free radicals roar through the cells as oxygen floods back in, that the production of energy can spell the difference between life and death – both for the cells of the heart, and for the living body they support.

By opening up the chests of unconscious lab animals, the research team was able to first cut off, and then reintroduce, the heart's supply of blood – which is exactly what happens in a heart attack. And by infusing the hearts with one of the two forms of lipoic acid, they were then able to see how they would affect the mitochondria's ability to maintain energy production in the crisis and get the heart pumping blood again.

Figure 7: How Mitochondria Make ATP.

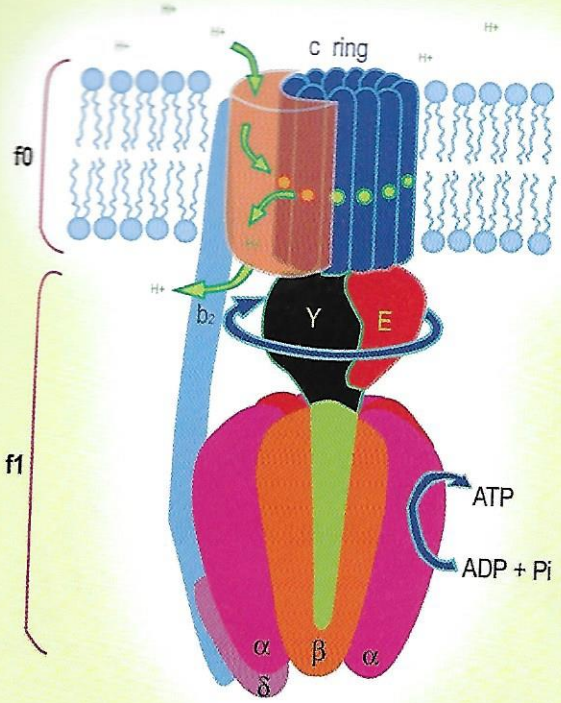


7a: The H^+ "pumps" and the "Turbine." Redrawn from (72).

When the animals' hearts' blood supply was cut off, the flow of blood to the aorta dropped like a rock. As blood and oxygen came back online, the hearts of control animals (those whose hearts had not been provided with *either* form of lipoic acid) crept up slowly and weakly, and were only able to pump half as much blood into the aorta as they had before the "heart attack." But **when the animals' hearts were infused with R(+)-lipoic acid, a "much steeper increase of aortic flow" resulted, along with a more complete recovery of heart function,** so that their hearts were pumping 36% more blood than animals not given lipoic acid.

By contrast, **the same amount of the S(-)-enantiomer yielded no benefit,** so that blood flow recovered no more quickly or com-

7b: The Complex V "Turbine." Redrawn from (61) and (62).



pletely than in the controls (see **Figure 8**). In fact, in later tests, the scientists found that while **R(+)-lipoic acid** was able to improve blood flow into the aorta at extremely low concentrations, **it took a dose of the S(-)-enantiomer which was as much as *twenty times* as great to provide any significant advantage over *no treatment at all*** – and even then, the benefit of the S(-)-form was still *less* than was seen at the twentyfold *lower* concentration of **R(+)-lipoic acid!**[69]

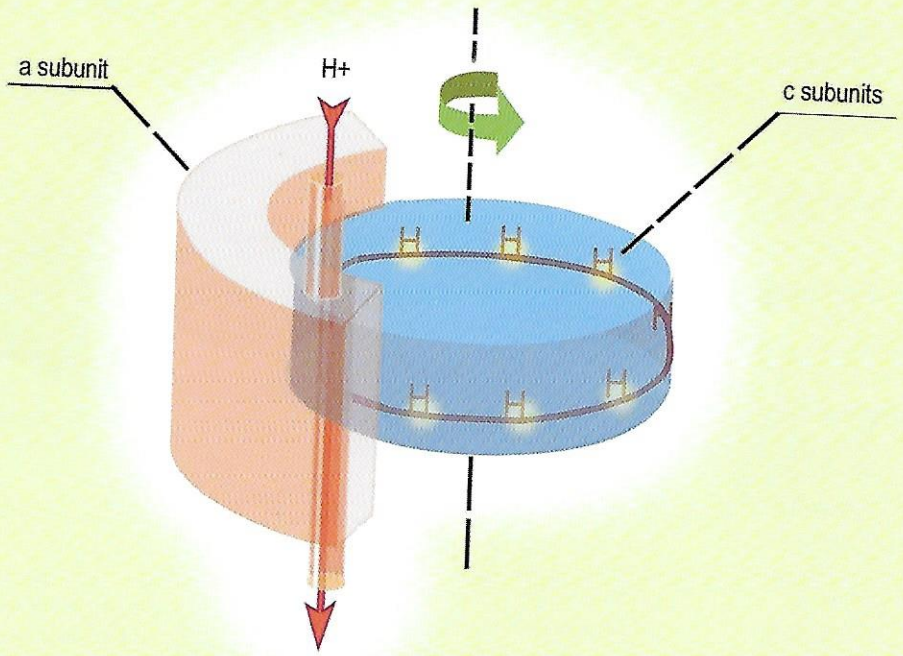
Deep down in the mitochondria, the contrast was even more profound. When the scientists isolated the mitochondria from the animals' hearts after the "heart attack," having infused the hearts of different animals with different concentrations of either R(+)- or S(-)-lipoic acid, they found that **mitochondrial energy production was boosted at even tiny concentrations of R(+)-lipoic acid,** and continued to climb as the dose was increased. By contrast, ***no* amount of the S(-)-form was found sufficient to increase the production of ATP.**

But if the S(-)-enantiomer was unable to jumpstart mitochondrial energy production at *any* concentration, then how did it manage the weak increase in *blood flow* seen in the animals infused with extremely high levels of the compound? To answer this question, you have to understand that **under certain conditions, the complex V turbine can actually be made to run in *reverse*, tearing down ATP** to make the low-energy carrier molecule, ADP. When this happens, the mitochondria actually *consume* ATP more than they *make*, so that the cell *loses* the very energy the mitochondria are *supposed* to be producing.

So how did the two forms of lipoic acid affect this potentially disastrous tendency? By now, you've probably got a pretty good guess. At realistic concentrations, **R(+)-lipoic acid slowed down the tendency of mitochondria to cannibalize their own ATP; by contrast, the S(-)-enantiomer *accelerated* it.**[69] The same effect had previously been seen in the isolated, "inside-out" mitochondria.[11] But at the extremely high concentrations of the S(-)-form at which a small benefit to blood flow was seen, the pattern *reversed* itself, so that at these ultrahigh levels the R(+)-enantiomer no longer inhibited the teardown of ATP, while the S(-)-form *began* to do so.

If you're thinking that this means that the S(-)-enantiomer might actually *benefit* you, if you could only take *enough* of it – or that you'll *lose* one of the advantages of **R(+)-lipoic acid** if you take *too much* of it – think again. The concentrations that were needed to achieve this curious inversion were *dozens* of times greater than those achieved in humans after *injecting* them with 1200 mg of racemate lipoic acid.[24] In a nutshell, this is a

When the animals' hearts were infused with R(+)-lipoic acid, a recovery of heart function the same amount of the S(-)-enantiomer yielded no benefit.



7c: How Ions Spin the "Turbine." Redrawn from (61) and (62).

property of the S(-)-enantiomer you're never going to get from a supplement in the real world.

That Youthful Spring in the Step

Obviously, it's vital to protect energy production in crisis situations like the simulated heart attack in these experiments. But when you take the long view, what's of even greater significance is maintaining – or, if possible, *restoring* – the energy supply you have every day. Damage to mitochondria, and loss of mitochondrial function with age, is now believed by almost all investigators into the biology of aging to be central to the loss of function and resilience that we experience as "aging."[57,70-72]

When older people feel their get-up-and-go has got up and went, it's no illusion: it's a real loss of cellular bioenergetics, spread across the entire organism. And because ATP is required for essentially *all* cellular functions, this loss of energy impacts all aspects of life, from the shaping of vital enzymes to the repair of the thousands of injuries, great and small, that we suffer every day. We've already seen the effects of **R(+)-lipoic acid** in a *crisis*. How does it impact the quiet desperation and *gradual* loss of function – the quiet desperation – of aging?

Dr. Tory Hagen and his fellow researchers at the Molecular and Cell Biology department of UC Berkeley asked themselves just these questions – and decided to find out.

Dr. Hagen says, "these animals are *looking* a whole lot better."

The Hagen team[73] first determined just how big a gap there was between young and old lab animals, so that they could later determine how much of a difference **R(+)-lipoic acid** would make in the old animals. As you'd expect, the old animals looked like they were running on empty, at all levels.

Down at the cellular level, the "depth" of older animals' mitochondrial "reservoirs" was less than half (40%) of what it was in young animals. As a result, their mitochondrial production of ATP (which can be measured using cellular oxygen consumption) was also about half (58.5%) of what it was in youths. And, as you'd expect by now, the old animals' mitochondria had become very polluting sources of energy for the cell: for every unit of ATP produced, old animals were producing nearly *twice* as many free radicals as young animals did.

The increase in free radical production exacted a serious toll on the overall antioxidant defense system of old animals, lowering their levels of reduced glutathione by nearly a quarter (23%) and slashing their vitamin C levels in half. You can't solve the problem *just* by supplementing with more vitamin C and glutathione precursors like **n-acetylcysteine (NAC)**, by the way: Dr. Hagen and his research team have indicated that the evidence suggests that the ability of the cell to both *take in*[74] and effectively *recycle*[75] vitamin C (which happens using enzymes in the mitochondria[76]) and the glutathione precursors,[77] is weakened with age.

As a result of the increased production of – and relative defenselessness against – free radicals, the membranes of old animals' cells were literally *turning rancid*, as measured by levels of **malondialdehyde (MDA)**, a chemical marker of lipid peroxidation. MDA levels were *five times* higher in old animals' cells, as compared to young ones. In later work,[74] Hagen's team showed that **free radical damage in the DNA of old animals' hearts was also considerably higher**, being almost exactly *double* that seen in young animals.

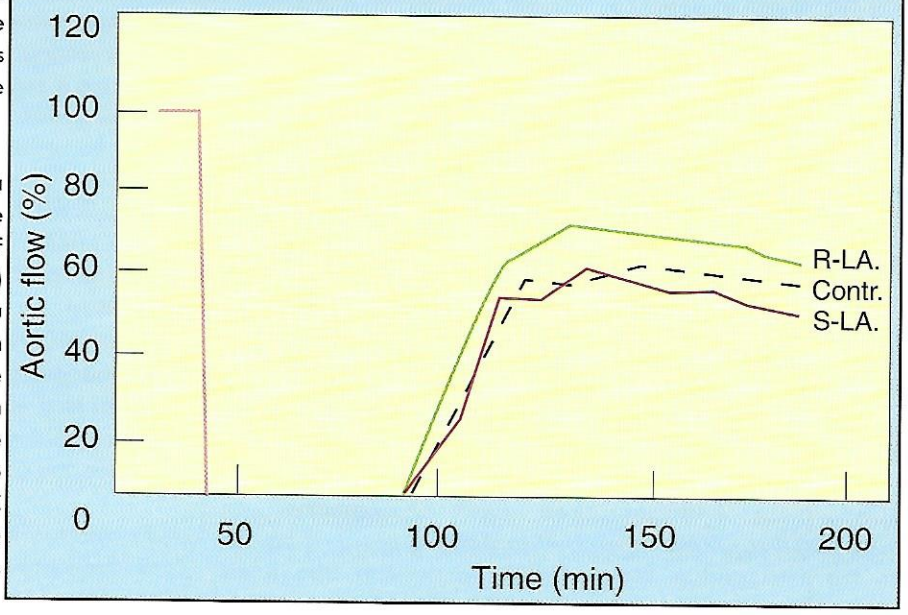
After just two weeks on an R(+)-lipoic acid supplemented diet, the old animals' mitochondrial function and antioxidant defenses were dramatically improved.

Meanwhile, up at the level of the whole organism, scientists monitored the activity of the animals using video cameras linked to computers running special digitizing software. This monitoring system revealed the real impact of reduced mitochondrial function in the old animals: they were hardly moving. While young animals actively sniffed about in their cages, traveling an average of more than 500 centimeters each hour, old animals were only managing to get up the energy to haul their aging bodies a third as far. They also appeared to be less active in other ways, such as in spending less energy in grooming themselves.

R(+)-lipoic acid changed all that.

Hagen's group specifically used **R(+)-lipoic acid**, because (in their words) of the "evidence that (R)-lipoic acid supplementation may be more potent than either the racemic mixture (the form sold commercially as alpha-lipoic acid) or (S)-enantiomer". **After just two weeks on an R(+)-lipoic acid supplemented diet, the old animals' mitochondrial function and antioxidant defenses were dramatically improved.** Their levels of reduced glutathione

Figure 8
R(+)- but not S(-)-Lipoic Acid Helps Heart Function Recover. Redrawn from (69).



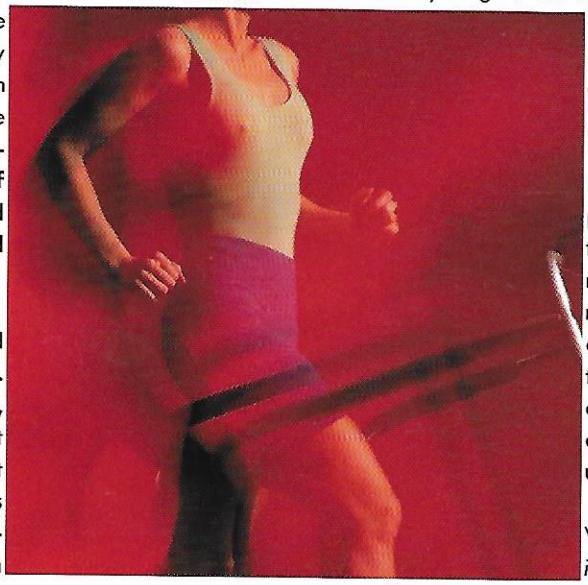
and vitamin C were no longer significantly different from the young animals'.

R(+)-lipoic acid is like installing a mitochondrial turbocharger.

Dr. Hagen link this restoration back to lipoic acid's known ability to increase recycling of these antioxidants, but has also now stated[77] that his group – and Dr. Lester Packer – have found evidence that **R(+)-lipoic acid also increases the ability of cells to *abosorb* vitamin C from the plasma.** And even *more* excitingly, **consuming supplemental R(+)-lipoic acid brought the level of free radical *production* in old animals down to levels not significantly different from the young ones.**

This change was reflected in levels of fatty peroxidation, as MDA levels dropped by over 40%. In a new study published just this spring,[74] Hagen's team not only confirmed these results, but also showed that **supplementing old animals with R(+)-lipoic acid also wiped out the age-associated increase in DNA damage in the heart,** bringing levels back to those seen in young animals!

ATP production had been boosted, too, so that the mitochondrial ion "reservoir" of animals getting the **R(+)-lipoic acid** supplements was fully half again as high as it was in unsupplemented animals. In parallel, the cellular oxygen consumption data indicated that the **mitochondria of R(+)-lipoic acid supplemented old animals produced as much ATP as did young animals.**



The change could be seen in the old animals' appearance and in their activity. "Anecdotally," Dr. Hagen has stated, "these animals are *looking* a whole lot better."[77] And they were *acting* a lot healthier, too: **old animals supplemented with R(+)-lipoic acid doubled the amount of exploring they did in their cages,** and also appeared to be otherwise more active than the animals eating an unsupplemented diet.

Bottom line: **giving old animals R(+)-lipoic acid is like installing a mitochondrial turbocharger,** which soups up the engine's power while making it run more cleanly and efficiently. All the evidence says that S(-)-**lipoic acid does not have this power, and may even be counterproductive.**

The Problem with Leadfoot

With **R(+)-lipoic acid,** in short, the old animals got *back* their get-up-and-go. But there's *another* possible solution to the problem of fading energy production with age, in the form of the compound **acetyl-L-carnitine (ALCAR).**

ALCAR is a better-absorbed form of **carnitine,** an amino-acid-like substance involved in shuttling energy from fat into the mitochondria. More: ALCAR supplements also boost levels of **cardiolipin** in mitochondria. Cardiolipin is a fatty substance found only in mitochondria. It's needed for the functioning of several of the energy transporters and "pumps" that help create the ion "reservoir" whose force drives ions through Complex V turbines to create energy.

As a result, adding ALCAR to the diets of old animals increases the activity of several mitochondrial energy transporters and ion pumps[78-81] and the mitochondria of old animals fed ALCAR supplements produce as much energy as those of young.[80,82] And, again as is seen with **R(+)-lipoic acid,**[73] **old animals fed ALCAR *double* the amount of distance they cover when running around in their cages.**[82]

Results in humans show that this isn't just a lab-rat result. Many short-term studies using even "standard" **L-carnitine supplements have shown improvements in exercise performance in people** with cardiomyopathy (weakened and structurally abnormal hearts), vascular disease,[83] heart failure,[84] or whose hearts have been damaged by a heart attack.[85]

But if this makes it sound as if you should rush out to buy ALCAR supplements for mitochondrial function, there's just two little details you'll want to know. The first has nothing to do with science, and everything to do with the right of the individual to make decisions about his or her own health: "Health" Canada has decided that you can't have ALCAR or standard L-carnitine supplements.

But the second, and more important, problem is that, while ALCAR increases the transport of fuel into the mitochondria – thereby increasing mitochondrial energy production – it doesn't improve the *efficiency* with which that energy is produced. In fact, **old animals receiving ALCAR actually produce 30% *more* free radicals for every unit of energy that they produce.**[82]

We've already seen how much aging *itself* makes the mitochondria of young animals burn "dirtier" than those of young ones.[73,74] Making the mitochondria even *more* polluting using ALCAR can be expected to have a serious impact on the cell, and the long-term health of the organism. Indeed, we've seen how the age-related increase of free radical production impacts the levels of vitamin C and reduced glutathione in these animals.[73,74,75] Well, **giving old animals ALCAR supplements actually lowers antioxidant defenses even *further,*** slashing vitamin C by an *additional* 50% and cutting an extra 30% off of their reduced glutathione supplies!

In other words, **giving old animals ALCAR is like flooring the gas pedal on a worn-out old Cadillac:** sure, the car goes faster ... but it *also* belches out more pollution. And the harder you push the engine, the dirtier its exhaust.

By contrast, you'll recall, **R(+)-lipoic acid** not only increases old animals' energy *production,* but also *reduces* the amount of free

radical waste created in the process, and restores more youthful antioxidant defenses.[73,74] So what would happen if you *combined* the two supplements, creating (one might expect) a vehicle which both runs more cleanly and powerfully per unit of fuel consumed (as with **R(+)-lipoic acid**), *and* is running more fuel through the engine (as in ALCAR)?

The study has been done,[73,82,86] although the actual *numbers* have yet to be properly published. The results: **supplementing old animals' diets with a combination of ALCAR and R(+)-lipoic acid simultaneously gives a boost to mitochondrial metabolism, while resulting in no increase in free radical stress.** (To find out just *how much* more energy the mitochondria of old animals receiving *both* supplements produce, as compared to the extra juice they get from either supplement *alone*, we'll have to wait for the full publication of their results).

And crucially, free radical researcher Dr. Bruce Ames of UC Berkeley, who has been a leading force in the ALCAR research from the beginning, has recently revealed that **only R(+)-lipoic acid has these effects.** In his words, "Lipoic acid sold in a health food store is a synthetic mixture, a racemic mixture. And R[+]- is the natural form and S[-]- is an unnatural one ... And **in our hands R[+]- works and S[-]- doesn't.**"[86]

Astonishing results. Results that force us to ask daring, even radical questions about the role of this orthomolecule in the fundamental processes of life.

The Bottom Line

•The biggest source of free radicals in your body are your cellular "power plants, "the mitochondria. They are both the origin, and the target, of most of the free radical damage in the body.
•As we age, our mitochondria become less and less efficient "power plants," generating less and less energy while creating more and more free radicals.
•The "lipoic acid" in common supplements is a 50/50 mixture of two different "lipoic acid" molecules: the natural R(+)-lipoic acid, and the unnatural S(-)-form. This mixture is called the "racemate."
•R(+)-lipoic acid, in animal experiments and in test-tube studies, makes mitochondria more efficient, so that they produce more energy and create fewer free radicals. S(-)-lipoic acid does not have these effects.
•These benefits extend to the whole organism. Old animals supplemented with lipoic acid look better and are more active.
•Acetyl-L-Carnitine (ALCAR) also boosts mitochondrial energy production. However, it does not make the mitochondria run more efficiently.
•As a result, old animals supplemented with ALCAR create more energy, and are more active, in the short term, but they suffer even more free radical damage.
•Animals supplemented with *both* ALCAR and R(+)-lipoic acid get the benefits of ALCAR without the increase in free radical stress. S(-)-lipoic acid does not have these effects.

Part Five

Fundamental Aging

Dr. Denham Harman was confused.

Harman had become interested in aging as a student, after reading a *New York Times* article about the work of a Russian biogerontologist. He continued to puzzle away over riddle of aging while completing his medical education, and through fifteen years of laboratory work — much of it involving the chemistry of free radicals. Then, one morning in November of 1954, while working at the UC Berkeley's Donner Laboratory of Medical Physics, his three interests — medicine, aging, and free radical chemistry — suddenly became fused in his imagination. I

Out of nowhere, it dawned on Dr. Harman that aging *itself* might be caused by the kind of uncontrolled, damaging chemical reactions he had seen time and again in his laboratory work. Looking at animals which had been subjected to heavy X-ray treatment seemed to prove him right: bombarding these animals with radiation caused free radicals to rage through them, and their young bodies suddenly seemed old in every way you could test.

And his insight, first published in 1956[105] also seemed to suggest a way to escape the ravages of old age. If aging was a disease caused by free radicals, then *antioxidants* should cure the diseas, just as it protected animals from radiation exposure.

So why didn't it work?

An Education through Failure

By 1972, Dr. Harman had invested fifteen years of his life into testing antioxidants as potential anti-aging therapies.[105a-c] He'd tried a host of them, from natural ones like cysteine,[105b] hydroxylamine,[105b] and vitamin E[105a] to potent synthetic "radioprotectors" like diaminoethyldisulfide[105b] and 2-mercaptoethylamine[105b]

Time and time again, Dr. Harman got the same results. Again and again, the supplements made the animals *healthier*, with longer *life expectancy* ... but none had any significant impact on the **maximum lifespan** of the species – the length of years which members of the species never exceed if they are allowed to live out their "natural" lives.

The failure was crucial. An organism may get a specific *disease* because of a toxic environment, or a poor lifestyle, but the rate of *aging* is a function of fundamental aspects of the design of the organism itself. That fact is reflected in the existence of maximum lifespan. So if you're really impacting on aging *itself,* you should see clear changes in this crucial parameter. Animals on a true anti-aging program should see increases in maximum lifespan.

Generations of scientists after Harman have reported the same results. They've tried combinations of beta-carotene, alpha-tocopherol, vitamin C, selenium, zinc, and the flavonoid

rutin,[99] or of alpha-tocopherol, glutathione, melatonin, and polyphenol-rich strawberry extract.[100] They've tried CoQ_{10},[101,102] and they've tried a host of synthetic antioxidants.[103] The result is the same. The animals live *better* — but not remarkably *longer*.

Likewise, later researchers have found that there's *also* no consistent relationship between maximum lifespan and the levels of the various antioxidants that occur *naturally* in the bodies of animals.[104]

The more free radicals a species' mitochondria produce; the shorter is that species' maximum lifespan.

The question was, why? Was the theory wrong — did the raging cellular damage caused by free radicals really have nothing to do with aging? That seemed almost impossible. But if so, then **why do conventional antioxidants not protect these animals from aging itself?**

In 1972, Dr. Harman had his second breakthrough.

The Mitochondrial Free Radical Theory

The scientific world knew little about mitochondria in 1972, but Dr. Harman's intuition caused him to zero in on them astonishing precision. Granted the mitochondria's essential role in energy production, and their precarious role as both the *origin* of most of the body's free radical load, and the prime *target* of those free radicals, a picture began to emerge in his mind.[106] What if the antioxidants "troops" he was sending in to protect his animals were not reaching this critical free radical battlefield?

As later studies would show, his intuition was correct. **Standard antioxidants – including even the "mitochondrial antioxidant," CoQ_{10}[98],[109,110] – fail to protect the mitochondria when taken as supplements.** And when the mitochondria fall, so must the cell. Without energy, or with an impossibly high free radical burden, life cannot continue. Dr Harman concluded that **mitochondria are the nexus of the fundamental process of aging.**[106]

Since Dr. Harman made his radical leap in 1972, evidence has piled up in favor of this view, and some form of "***mitochondrial* free radical theory of aging**" is now widely accepted as being critical to any understanding of aging.[51,70-72a,96]

One powerful piece of support for the key role of mitochondria in the aging process is the fact that the levels of free radical damage *created and suffered* by mitochondria vary from species to species — and there's a consistent relationship with the maximum lifespan. **The more free radicals a species' mitochondria produce;[107] the more easily damaged the species' mitochondrial membranes are;[108] the more free radical damage suffered by the species' mitochondrial DNA;[61] the shorter is that species' maximum lifespan.** And another, extremely powerful piece of evidence has come from **the *one* anti-aging therapy that has actually been proven to *work*.**

The Only *Proven* Anti-Aging Therapy

If free radical production in the mitochondria causes aging, then any intervention which can preserve youthful mitochondrial function should slow aging *itself*, rather than just alleviating its symptoms. Fortunately, there *is* one *proven* "anti-aging" therapy —and, indeed, it keeps mitochondria burning clean and bright.

That intervention is **caloric restriction (CR).** Simply put: provide an animal with a diet which contains fewer Calories than its body *thinks* it needs, while ensuring that you provide it with adequate amounts of protein, essential fats, vitamins, and minerals, and you will dramatically *slow down the intrinsic aging process of the organism*. And as a result, mammals on calorically restricted nutritional plans routinely live lives dramatically longer than their normally-fed cousins ... and, more excitingly, many exceed the *species maximum lifespan* as well.[88,89,90] In other words, **an animal eating a calorically-restricted lives longer than that animal is *"supposed" to be able to live.***

In experiment after experiment, by criterion after criterion, CR animals live longer, live healthier, and live *younger* than any other animals in the world. They don't just add more "old" years onto the ends of their lives: instead, **the added years are *healthy* ones.** CR animals are smarter, faster, more energetic, and better-looking at ages where animals fed conventional diets are entering the gloomy twilight of their lives.[89,90] (For more on the effects of CR, and human practice, see "The Road to Aging is Paved with Calories," The Holistic Lifestyle 1(5), and Dr. Roy Walford's landmark **Beyond the 120 Year Diet**[91]**).**

As you might expect from a true anti-aging therapy, CR reduces free radical damage – but it accomplishes this in a way that's quite different from what can be achieved with conventional antioxidant supplements. E-complex vitamins, melatonin, vitamin C, and the rest do a reasonable job of cleaning up the mess created by free radicals, but they can't prevent them from being formed *in the first place*.

By contrast, **the age-related loss of energy efficiency in the mitochondria – which, as we've noted, is the prime source of free radicals in the body – is dramatically slowed by CR.**[93-98]

Lower free radical production results in less mitochondrial free radical damage,[66] protection of the mitochondrial DNA,[98,111] and the preservation youthful mitochondrial structure and function with age.[112-115] As a result, most researchers now believe that caloric restriction's unparalleled anti-aging power is due in large part to the fact that it actually makes mitochondria "burn" more cleanly, producing fewer free radicals in *the first place*.[92,96]

Is this starting to sound familiar?

The Elixir of Life?!

R(+)-Lipoic Acid is unique among known antioxidants. No other dietary supplement is known to take old mitochondria – which are the cellular equivalent of beat-up old Oldsmobiles: hulking, unreliable beaters with no acceleration – and make them roar with new power while cleaning up their tailpipes.

So a question has to arise in the heads of anyone comparing the effects of caloric restriction with those of **R(+)-Lipoic Acid.** Are its effects on mitochondria *fundamentally* the same as those of caloric restriction? If so, will this dynamic nutrient have the same bottom-line impact on fundamental aging as the only anti-aging therapy we know? Is **R(+)-Lipoic Acid** like caloric restriction in a pill? **Will R(+)-Lipoic Acid extend species maximum lifespan?**

The answers are coming. Soon. And preliminary evidence suggests that the answer may very well be "yes."

The preliminary evidence dats from the mid-1990s, before the effects of the different enantiomers of lipoic acid on mitochondrial function were reported. At that time, researchers tested the effects of racemic, S(-)-, and **R(+)-Lipoic Acid** on lifespan, solely on the basis of their known antioxidant effects.[106] The researchers chose the NMRI mouse as their study animal. These mice lack a thymus, which drastically impairs their immune function. As a result, they're more susceptible to dying of things which have nothing to do with aging – such as simple bacterial infections. But you can make up for this problem, in large part, by giving them strong antibiotics and raising them in a carefully-designed, nearly germ-free environment not unlike a less extreme version of the ultra-sterile environments in which children with Severe Combined Immunodeficiency (SCID – the "bubble babies") require in order to survive.

Why would researchers want to intentionally use such a fragile organism for a life extension study? Well, once you've taken steps to protect the animals from the simple risk of disease, some researchers think the NMRI mouse is an excellent *accelerated* model of important aspects of the "normal" aging process.[116,-118] That's because the immune system abnormalities in these animals – in particular, the tendency for the animals to develop an insidious, systemic *autoimmunity* – in some ways mimic the tendency of the body's immune system to turn against us as we age, even if we escape the more obvious autoimmune diseases like rheumatoid arthritis and lupus. A whole theory of aging has been built up around the changes the body undergoes because of this subtle autoimmune attack.[119]

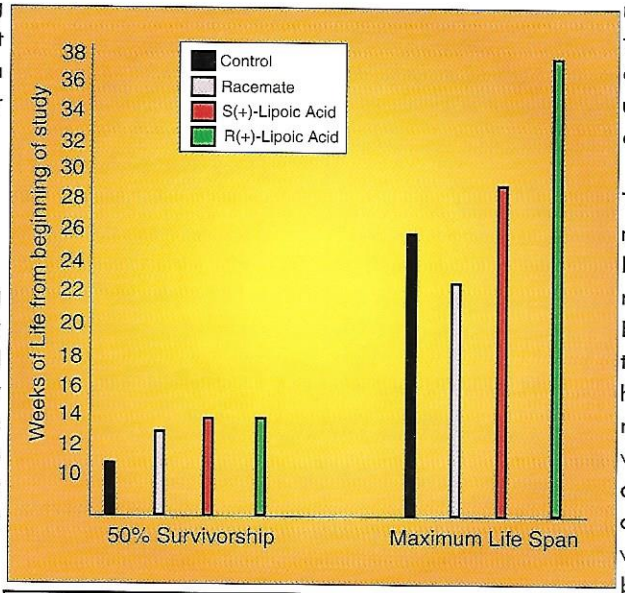


Figure 9
Lives of NMRI Mice Receiving R(+)- Lipoic acid Supplements vs. Other Forms. Redrawn from (116).

The advantage of using an accelerated model of aging is that their short lifespans allow researchers to get quick results, especially when funding is tight. But the disadvantages can be serious, too. When the results do come in, it's hard to ever be sure what a the final result *means*, because there's no sure way to tell what parts of the results are due to a therapy's effects of *aging*, and the therapy's effects on the *disease* which makes them so short-lived to begin with. But with that understanding, let's have a look at the study.

The scientists fed the animals either a basic lab animal diet, or one supplemented with equal doses of one of the three forms of lipoic acid, starting from the time they were ten weeks old and continuing for the rest of their lives.[116] The results of this experiment can be seen in **Figure 9**. The time it took for half of the animals in each group to die was not changed by any form of lipoic acid, suggesting that none of the supplements had any effect on simple things like short-term vulnerability to an infection or parasite. But among the animals who made it past the halfway point, a dramatic difference emerged.

Animals whose diets were supplemented with the racemic compound lived no longer than they would have if they had just received the basic, unsupplemented diet – if anything, they might have lived lives that were a little shorter, although the difference was not strong enough to rule out a simple statistical fluke. Similarly, the animals who got the S(-)-enantiomer seemed to live a little longer than the unsupplemented animals – but, again, not long enough for the difference to be a statistically meaningful result. In short, **neither the racemate form of lipoic acid you get in common supplements, nor straight S(-)-lipoic acid, seems to have done anything notable to these animals, for better or for worse.** They may as well have been eating regular lab chow.

Mice with supplemental R(+)-lipoic acid in their diets exceeded, by a huge margin, the maximum lifespan of animals left to live out their normal lifespans.

But now have a look at the results in the animals who were given access to a diet enriched in **R(+)-Lipoic Acid.** Here, the results were undeniable. The longest-lived animals in this group lived *dramatically* longer lives than those in any other cohort. In fact, the **mice with supplemental R(+)-lipoic acid in their diets exceeded, by a wide margin, the maximum lifespan of animals left to live out their normal lifespans (Figure 9).**

And these were realistic doses of the supplement, too. The researchers fed the animals supplements at a concentration which, in a human, would only be about 630 mg – not at all out of line with what human users are taking. In fact, these scientists also tried out some considerably higher doses of lipoic acid in their study, but interestingly, they had no effect on lifespan – with the bizarre exception that, **at extremely high dosages, the racemic compound actually *shortened* the animals' lifespan** to a maximum of ten weeks.

It's important to note that the animals' weights did not differ significantly by group – so we can rule out the effects of "hidden" caloric restriction in these results. That is, if the animals eat less food, the resulting caloric restriction might slow aging, and the anti-aging effect of caloric restriction be misattributed to the therapy. That kind of mistake won't explain these results.

At extremely high dosages, the racemic compound actually *shortened* the animals' lifespan.

The use of the NMRI mouse means that the researchers got *fast* results ... but it's hard to say for sure what those results *mean*. They *might* mean that the core processes of aging are dramatically slowed by the **R(+)-Lipoic Acid** – and not by the racemate or the S(-)-enantiomer. But even the longest-lived of these mice still lived a short life, compared to a *normal* mouse given nothing but regular lab chow. So maybe the supplement merely protected them against some aspect of their unusual genetics.

These are crucial questions. It's a little giddying to even ask them. And as we'll see, answers will not be long in coming. But in the meantime, we can shortly expect to hear results from *another* lifespan experiment — an experiment with a fatal flaw.

The Wrong Molecule

Several years ago, scientists with the University of California's Riverside campus, and with the University of Wisconsin at Madison, began a lifespan study using lipoic acid in a long-lived strain of mouse.[120] Unfortunately, the study was begun before the drastic differences between the two enantiomers became widely understood ... and before the dramatic effects of **R(+)-Lipoic Acid** on mitochondrial function were available. As a result, the researchers used the common racemate for their "lipoic acid" supplement.

The results of this study have not been published, but the word in the research halls is that we won't be hearing of any miracles. That's just what you'd expect, based on the results from the *first* lifespan study.[116] But the health and nutrition reporter for your local TV news won't know the difference. So the headlines – if there are any – will likely read, "No Effect of Lipoic Acid On Lifespan of Mice."

Just like the average commercial supplement, the headline will only tell you *half* of the story. It *should* read, "No Effect of Common Racemate Lipoic Acid On Lifespan of Mice."

We'll still be left with questions that demand answers. And, fortunately, we're going to get them. After looking at the astounding rejuvenation of mitochondrial function achieved by researchers using **R(+)-Lipoic Acid** – and especially the **R(+)-Lipoic Acid**/ALCAR cocktail – **the National Institutes on Aging are now convinced of the need for a new lifespan study, using R(+)-lipoic acid in the diets of a long-lived strain of rat.**[77,86]

It's taken Hagen and Ames some time to get started. There were problems getting the animals, and also problems getting the **R(+)-Lipoic Acid:**[86] until very recently, the only sources in the world were two German pharmaceutical companies, who have been very jealously guarding the precious stuff. But the funding is in place, the animals are housed, and the diets prepared. In a few years, we should know if users of **R(+)-Lipoic Acid** are drinking from the Fountain of Youth.

A "One-Mouse" Experiment

No matter what the results of the Riverside/Madison experiments turn out to be, they'll give us the *wrong answer* – because they'll have asked the *wrong question*, having used the wrong molecule. In the place of **R(+)-Lipoic Acid** – the *true* lipoic acid, crafted by untold generations of evolution for use in the body, and made , in tiny amounts, by *your* body every day – these experiments have used a schizoid supplement, with two personalities warring within it. No great good can come from a supplement which contains a stowaway which undoes the very wonders it works. No one can be healed by a medicine which is laced with an opposing poison.

So we're still left searching for answers to fundamental questions. Will **R(+)-Lipoic Acid** live up to its full promise? Can it truly step in to stop the slow, steady sinking into oblivion we all face with age? Will **R(+)-Lipoic Acid** extend *maximum lifespan*? **Does R(+)-lipoic acid slow down the aging process itself?**

The experiments which will yield answers to these questions are already underway. But in the meantime, there's *another* experiment to be run: the grand experiment of life. We don't yet know if **R(+)-lipoic acid** slows intrinsic aging. But we *do* know a lot about what it *can* do, from improving glucose metabolism, to providing powerful antioxidant protection, to preventing damage associated with neurological dysfunction, and on to restoring the vigor of functioning cellular "power plants." **R(+)-Lipoic Acid** has proven itself again and again to be powerful support against the countless imperceptible injuries that we face every day – injuries that surely keep us from savoring sweet drops of life's nectar.

After years of only being available to academic institutions in the tiny quantities required for biochemistry purposes, **R(+)-Lipoic Acid** is now available as a dietary supplement for humans. You have to wait to hear what the rodents will tell us – but not to see what your own body can experience.

You're the scientist – and the guinea pig. *You* choose which supplement gets used in this experiment. And you won't just read about the results — you'll live them.

"Evil twins" belong in soap operas — not in your body.

The Bottom Line

•Nearly all researchers into the biology of aging agree that the decay of mitochondrial function is a major engine of the aging process.

•Caloric restriction, with adequate nutrition, is the only proven way to slow down the fundamental aging process in mammals.

•Lipoic acid has a reputation as an "anti-aging" supplement.

•The "lipoic acid" in common supplements is a 50/50 mixture of two different "lipoic acid" molecules: the natural R(+)-lipoic acid, and the unnatural S(-)-form. This mixture is called the "racemate."

•Many of the benefits of R(+)-lipoic acid closely mimic those of caloric restriction.

•R(+)-lipoic acid's effects on mitochondrial function are the most striking and unique in this regard.

•A study in a short-lived strain of mouse demonstrated that R(+)-lipoic acid can dramatically increase its lifespan. Neither S(-)-lipoic acid, nor the racemate, had this power.

•The National Institutes on Aging are currently funding studies to see if lipoic acid can truly slow down the aging process itself.

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Volume 2 * Issue 1

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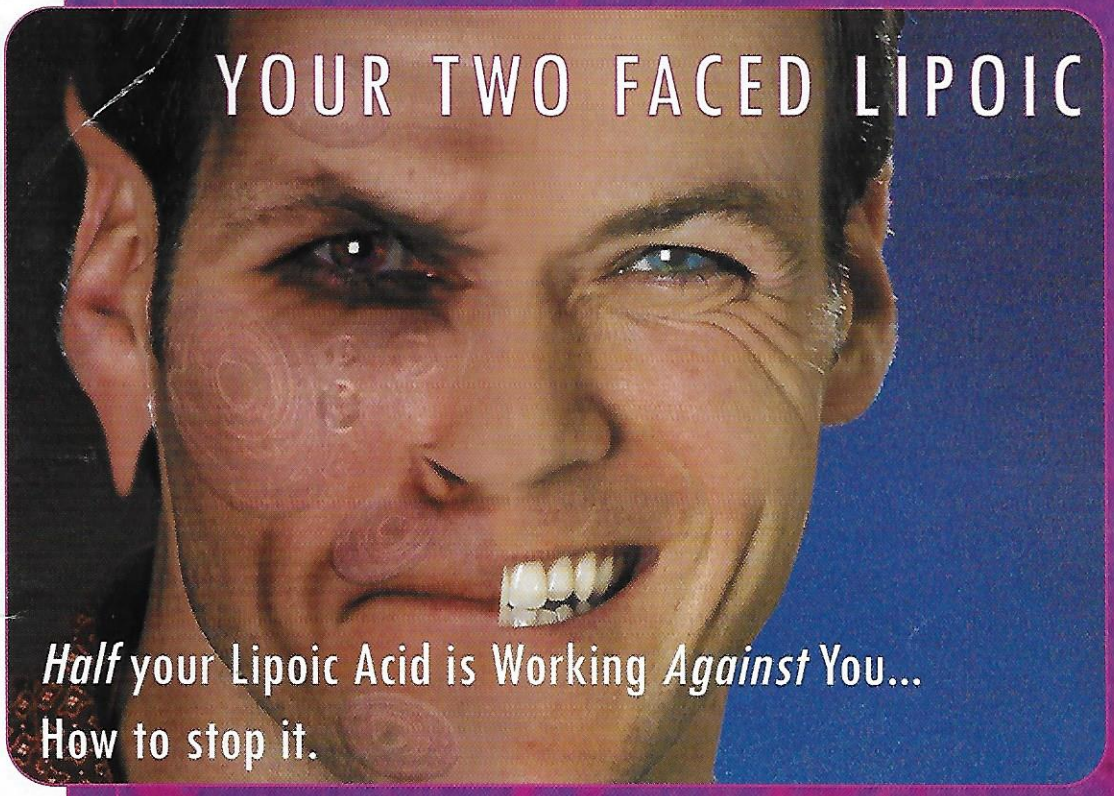

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How to stop it.

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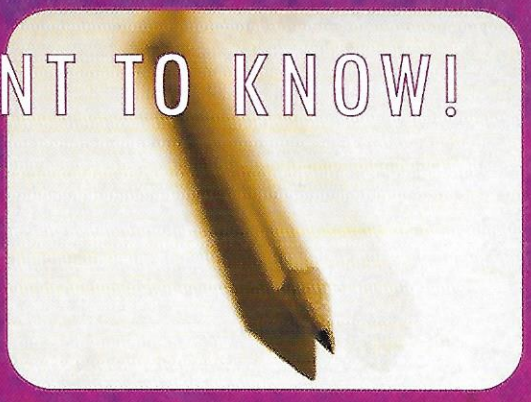

evidence-based botanical integrative orthomolecular breakthrough