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Part One: PLC - An Important New "Pillar" for Heart and Artery Health

An interview with Dr. Stephen T. Sinatra, M.D., F.A.C.C.

BY RICHARD A. PASSWATER, PH.D.

In this conversation with Dr. Sinatra, we will focus largely on a new form of heart-specific carnitine, Propionyl-L-carnitine (PLC), that improves heart function and, just as importantly, artery health. The new research showing tremendous benefit to artery health is tremendously exciting to many of us following the evolving science of endothelial function and the role of endothelial dysfunction in plaque formation. For more than 30 years, I have been writing about how arterial plaque (the so-called cholesterol deposits) are not related to either cholesterol in the diet or circulating blood cholesterol, but instead are related to a host of events ranging from oxidized-LDL, arterial inflammation, homocysteine and several other factors.

Stephen T. Sinatra, M.D., F.A.C.C., F.A.C.N., C.N.S., is a board-certified cardiologist and a certified bioenergetic psychotherapist, with more than 27 years of experience in helping patients prevent and reverse heart disease. He also is certified in anti-aging medicine. He is a fellow of the American College of Cardiology and former chief of cardiology at Manchester Memorial Hospital where he was director of medical education for 18 years. Dr. Sinatra is also assistant clinical professor of medicine at the University of Connecticut School of Medicine.

At his New England Heart & Longevity Center in Manchester, CT, Dr. Sinatra integrates conventional medical treatments for heart disease with complementary nutritional, anti-aging and psychological therapies that help heal the heart. He is uniquely qualified to give advice on nutritional supplements and the heart. Dr. Sinatra is one of the few medical doctors who formulate his own vitamins. He is expert in dosage, absorption, how to pick quality ingredients, and the effects of combining supplements with cardiac medications.

Dr. Sinatra has authored and/or co-authored several books on heart disease and is the editor of the monthly newsletter on heart health, *The Sinatra Health Report*. His most recent book is *The Sinatra Solution* (Basic Health Publications, Inc, North Bergen, NJ, 2005). Additional information can be found on his website at *www.drsinatra.com.*

Passwater: *We have been chatting about your evolution of metabolic cardiology over*

several months. Before we tie the advances all together and explore the fact that it is really the Adenosine triphosphate (ATP) levels in the heart and arteries that are more important than the oxygen levels, let's look at your latest breakthrough in the "Sinatra Triad" —Propionyl-L-carnitine (PLC). PLC is a nutrient that will bring a better quality of life to all heart patients.

Before we look at PLC specifically, let's review the role of carnitines in general.

Sinatra: I have been aware of the role of L-carnitine in the mitochondrial turnover of ATP since the late 1980s or early 1990s. The mitochondria are the energy factories of cells, and ATP is the primary energy storage compound of the body. However, the great amounts of ATP are needed to produce this stream of energy and the cells can't store this much ATP. Instead cells rely on a constant stream of replenishment of ATP. This is called ATP turnover. There have been many very interesting studies published on the carnitines in the cardiovascular journals since then about how heart cells deficient in carnitine and CoQ-10 cannot perform adequately, and how these nutrients can facilitate ATP turnover to restore the needed level of ATP. The heart needs a constant supply of ATP no matter how hard it has to work.

Passwater: *Perhaps we should discuss just why carnitines are so important to certain cells like the heart and artery lining. These tissues primarily burn fatty acids for their energy source, not glucose (blood sugar). Carnitine is needed to carry the acyl portion (a group of atoms having the general formula RCO, derived from the removal of a hydroxyl group from an organic acid) of fatty acids into the inner mitochondrial membrane for beta-oxidation and the production of energy.*

We get our energy from our food by using oxygen to convert carbohydrates and fats into ATP and then free energy. Carbohydrates are converted into ATP via the citric acid cycle (Krebs cycle) and oxidative phosphorylation. A molecule of glucose (blood sugar) or pyruvate can yield 38 molecules of ATP. Fats are converted to ATP via beta-oxidation. A molecule of fat such as palmitate, a 16-carbon fatty acid, produces 129 molecules of ATP via beta-oxidation in the mitochondria. However, medium-sized and long-chain fatty acids must first be converted into acylcarntines before they can enter the mitochondria.

I wonder why Nature chose carnitine for this function?

Sinatra: The first thought that comes to mind is that something needs to carry fatty acids into the mitochondria to be burned. About 60%-70% of the energy used by the heart comes from the breakdown of fatty acids in the mitochondria. Fat is the fuel for the heart, but a lot of people don't understand this. Most people think that sugar is the fuel for the body and it is certainly the fuel for the brain. A good example of the importance of blood sugar to the brain can be seen when someone has a donut and coffee and a half hour or hour later falls asleep. First the brain is fueled by the extra blood sugar and then when insulin rebound kicks in and the blood sugar drops, the brain runs low on fuel again and gets sluggish. The brain is very vulnerable to insulin spikes and that's why a lot of people get drowsy after a donut and coffee. Fortunately, the heart isn't that way! The heart uses primarily fat!

But how do the fatty acids get into the membranes of the mitochondria of muscle cells to produce this energy? What is this "something" to carry these fats there?

Figure 1 shows how carnitine transports fatty acids across the inner mitochondrial membrane where they can then be burned via beta-oxidation to produce energy via ATP.

Passwater: *Let me review this, since it is such an important point. Without carnitine, fats, which are the high-energy fuel for the heart, muscles and certain other body components including the endothelial cells of artery linings, cannot be converted into ATP. ATP is the energy of life. "Life" depends on the body utilizing energy. In the "living" process, "free energy" is released from the stored energy in ATP. Energy is a force, not a compound. The principal source of "free energy" in the body is in the high-energy bond phosphate group (P).*

In order for the biochemical reactions of life to occur, "free energy" must be liberated through a chemical reaction where ATP is split into adenosine diphosphate (ADP) and the high-energy bond phosphate (P) group (the source of free energy).

Sinatra: So I think Nature created carnitine to serve as a freight train or ferry boat to carry those fatty acids into the mitochondria. More importantly, it's not only the burning of fat in the mitochondria that fuels the energy for ATP, but the human being is a high-energy organism and because we are so high-energy we produce a lot of toxic waste This is where the carnitines are so absolutely phenomenal and instrumental—especially in cardiac health—is that not only do these carnitines shuttle in the fatty acids to be burned in the mitochondria, but they shuttle out the toxic metabolites.

That's why the carnitines—especially PLC—I've been using it now for intermittent claudication when it got released, and I have patients tell me in the last few weeks that the claudication had been improved remarkably. Again, not because the fat is burned easier, but when you have these harmful acyl groups—these metabolites of the burning of fat, and even lactic acid for that matter—they cause vasoconstriction and they are endothelial cell (flat epithelial cells that lines serous cavities, lymph vessels, and blood vessels) unfriendly and they cause spasms of the blood vessels. You can imagine if you have patients with lack of oxygen in the lower extremities such as caused by ischemia (reduced blood flow) in the leg muscles and now toxic metabolites build up, you have to get those toxic metabolites out of the cell and that's the magic of the carnitines.

So I think the carnitines were created by the body for a reason—to get those fats in and those toxins out.

Passwater: *No question, but as a biochemist, I was wondering what it is about the actual chemical structure of carnitine that made the body select it for these purposes. I have come to understand why the body uses selenium and silicon atoms for certain purposes that other atoms can't do, and how antioxidant structures are most efficient for quenching free radicals. I guess I always try to understand the "why" of structure vs. function. I like to envision the interaction of the electron clouds and charges to see how they affect their targets. There is nothing else really similar to the carnitines, and they are not easy to biosynthesize, so there must be a compelling reason for using their structure. (Figure 2: Carnitine structure). L-carnitine is often classified as an amino acid, but it isn't. L-carnitine can be thought of as a close cousin of amino acids, but technically it is a nitrogen-containing, short-chain carboxylic acid. It can also be described as a quaternary amine. Its*

chemical structure resembles choline, but there are important differences.

Let's move on.

It sounds as if athletes are going to be interested in PLC just as well. Endurance athletes are just beginning to attempt to burn fat—the most concentrated fuel to produce energy—but the enzymes needed to convert body fat back into free fatty acids are rate-limited and also as you just mentioned, lactic acid builds up and they have to discontinue.

Sinatra: I think every athlete should be using carnitine, CoQ-10 and D-Ribose. It just makes perfect sense. As I mentioned in one of our earlier chats, I used to wrestle in college at the Division 1 level and we used to wrestle a very tough schedule. We were a small school at F&M, of about 2,000 men and I have to tell you that if I knew about carnitine, CoQ-10 and D-Ribose back then, I would have done a heck of a lot better than I did.

When I was in my late 30s and early 40s, I used to coach a private high school team in wrestling—and if I knew about these nutrients back then, I think my wrestlers would have done really well.

Passwater: *Why the newer carnitines and especially PLC?*

Sinatra: I have been using the carnitines for 10 years. Specifically, I used L-carnitine at first, then began with acetyl-L-carnitine about five years ago, and now that PLC is available, I have found it to be especially helpful for my patients.

Passwater: *I see a study in your new book showing the response of one form was greater at the beginning and if the person took only that form the response was more immediate while another form was better long-term. But I get the impression that all three together would be more ideal, giving you a boot early and then another boost later, with L-carnitine providing the main thrust. Please tell us what that study showed.*

Sinatra: Researchers used MRI spectroscopy to measure the energy levels in the hearts of laboratory animals following a heart attack and found that all three carnitines markedly improved recovery of energy compounds in the heart. Acetyl-L-carnitine was stronger in the early response, but did not keep the energy level as high as L-carnitine over the entire study period. In the PLC group, the very early recovery was not as strong as either the acetyl-L-carnitine or L-carnitine groups, but by the end of the study, *the recovery was greater with PLC than either of the other carnitines.*

The study showed that the treatment with any of the carnitines tested improves the energetic state of the heart, which leads to increased ischemic tolerance. The study also showed that the carnitines also protect the heart against intracellular damage from the buildup of lactic acid that occurs during heart attacks. In fact, animals that were given any of the carnitines were able to tolerate up to four induced heart attacks in succession, whereas the controls not receiving supplemental carnitine were not able to do so. These results are

extremely important when considering treatment of ischemic heart disease.

In addition, other studies show that patients given carnitines after a heart attack end up with less damage as measured by infarct size, reduction in arrhythmias and in heart enlargement. Unfortunately, there were also more deaths in the placebo group than in those given carnitines. The study concluded that carnitine protects cardiac tissue as well as prevents cardiac complications of heart attack, including fatality.

Another study has shown that giving carnitine after a heart attack has a beneficial effect on preservation of the left ventricle, where most heart attack damage occurs and the left ventricle increases in size. This is of enormous importance as an increase in left ventricle size during the first year after a heart attack is an ominous predictor of future adverse cardiac events.

Passwater: *Let's chat some more about the triad of carnitines. There is L-carnitine, acetyl-L-carnitine which gets more into the brain than the heart, and there is PLC, which has a very fast half-life (the time required for something to fall to half its initial value) both in the bloodstream because it quickly enters into the muscle cells it gets inside the heart and also in the cells as it quickly is consumed doing its job of shuttling fatty acids into the inner mitochondrial membrane. PLC is selective for both peripheral muscle and cardiac muscle, and is considered to be a very heart-selective carnitine. Any of the carnitines will increase ATP turnover. That is why they are important in the Sinatra triad of metabolic cardiology.*

How should patients approach this newly expanded triad of basic L-carnitine, acetyl-L-carnitine and the new PLC? Is there reason to take one over the other? Is there a heart health benefit to go with the PLC alone? Is there a more cost-effective mixture? Or is there synergism in taking them together as a carnitine complex? Should they be taken together or separately?

Will people benefit most from selectively using each of the three carnitines or supplementing their diets with all three?

Sinatra: Actually, a complex of all three carnitines has an advantage. "Full-spectrum" carnitines or carnitine complex, I hope, will be the carnitine of the future. If consumers could take L-carnitine, acetyl-L-carnitine and PLC in one preparation, that means they would get full carnitine support that would help with ATP turnover whether it's in the heart, the brain, the eye, the ear … wherever.

In other words, you would get penetration of the carnitines in all of the tissues of the body. If we look at specific disease states, *acetyl-L-carnitine* will upgrade receptors in the ear as well as the eye. Animal laboratory experiments have shown that this is why animals given acetyl-L-carnitine can hear better. Acetyl-L-carnitine will also improve retinal receptors and it's been shown to improve macular degeneration. So acetyl-L-carnitine is clearly the most bioavailable form of the carnitines when we are talking about the blood-brain barrier.

Acetyl-L-carnitine would be more adept for people who want to improve their eyes, ears and brain. That would be for any individual who really wants to improve his or her mental activity.

Now I have patients who pre-Alzheimer's, I have patients with strokes, I have patients with full-blown Alzheimer's disease, patients with senile dementia—and I really like acetyl-L-carnitine. Acetyl-L-carnitine really makes a difference in these people. But again, I have to

use stronger dosages with these people. I usually start with a gram dose and go higher. You should always take carnitine, just like CoQ-10, in divided dosages, meaning two to four times a day. There are two principal reasons for this: 1. the efficiency of absorption is better when you take smaller dosages on multiple occasions; and 2. the half-life of the nutrient remaining in the body before it is removed from the blood and tissues and excreted, suggests that it should be replenished regularly throughout the day.

Now, I am excited about *PLC* because in patients with cardiomyopathy—especially angina and, more specifically, effort angina and patients with claudication, which I discussed earlier—PLC is soaked up by muscle. It's very specific for mitochondria, and with a very quick half-life it gets in very quickly. So PLC is better suited for the more symptomatic populations—such as people with coronary disease, claudication, and diabetes with ischemia. Even athletes should benefit from use of PLC because the turnover of ATP in exercising muscle is extraordinary. PLC is more conducive for people with more symptomatic heart disease as well as exercising athletes.

Passwater: *I understand your excitement about PLC and the heart itself, but what has captured my interest is PLC and endothelium function. This is extremely important to everyone.*

Sinatra: Yes, the endothelium is more than just a slippery surface to line the arteries and prevent the blood from clotting at the surface interface. Endothelial cells have four prime functions: 1. to form a barrier to exclude toxic substances from the artery wall; 2.to release factors into the blood to affect blood platelets—to activate them to tend to clump or not; 3. to sense the blood pressure and flow and help the artery adjust; and 4. to sense arterial injury and initiate repair. The repair process causes smooth muscle cells to migrate to the area of injury and blood cells to stick to the area of injury.

Passwater: *All of these functions interest me. The healthy endothelium strives to keep oxidized-low-density lipoprotein (Ox-LDL) out of the artery wall and thus prevent plaque formation. The repair process, if not done properly, also serves to initiate the so-called cholesterol plaque forming process. To me, this is the real importance to this story and deserves a discussion of its own later. Of course, platelet adhesion is critical as to whether or not a blood clot will form in damaged arteries and thus cause an acute myocardial infarction (common heart attack) or stroke.*

Sinatra: Research has shown that PLC is very important to the health and proper function of endothelial cells. PLC passes across the inner mitochondrial membrane to supply the carnitine needed for the production of ATP and energy in these cells. Remember that endothelial cells obtain about 60%-70% of their energy from fats, similar to cardiac cells. You're right, this is of great importance and also of immense interest to me, and I would like to follow up this point in a more detailed discussion later.

Passwater: *Yes, we can't cover everything about PLC and the other carnitines in an introductory discussion, so I will refer our readers to your book for more details. Let's get back to my questions concerning the forms of carnitines to take as supplements.*

Sinatra: To answer your question, I would like to see the carnitines as a complex or full-spectrum supplement because this way, you would get support of all of your major organs including heart muscle as well as the brain, eye, ear, etc.

As far as the various forms go, L-carnitine is best suited for liquid formulations requiring a high concentration of L-carnitine such as infant formulas, sports beverages and liquid nutritional supplements.

L-carnitine fumarate is the most stable and bioavailable carnitine salt. Because the fumarate is naturally present in the Krebs cycle, it optimizes the action of L-carnitine. L-carnitine tartrate is also a stable salt of L-carnitine used in tablets and capsules.

Acetyl-L-carnitine is a water-soluble L-carnitine derivative that rapidly absorbs into brain tissue. It is especially suitable for "brain health" preparations that enhance memory, learning and concentration, as well as anti-aging preparations.

PLC is most specific for cardiac tissue and has a short half-life and poses vasodilatory activities.

There is some interesting research out of Italy that shows that acetyl-L-carnitine, in high doses of three grams a day, is equivalent to testosterone in improving male libido and erectile potency.

Certainly the carnitines have a full-spectrum activity.

Passwater: *In your book,* The Sinatra Solution, *you describe an even newer generation of carnitines, the "AminoCarnitines."*

Sinatra: The "*AminoCarnitines*" are an exciting form of carnitines. The three carnitines that we have been discussing—L-carnitine, acetyl-L-carnitine and PLC—have been taken to a higher level. Now these carnitines have been combined with amino acids in order to give them some extra punch

The amino carnitine complex that I take personally is acetyl-L-carnitine arginate. This combines the acetyl-L-carnitine, which is good for the brain, eye, ear and heart, with arginine. Arginine helps support nitric oxide which is involved in maintaining the proper dilation of blood vessels. As a cardiologist, I understand that L-arginine can be a life-saver.

I want to stress that this is not just a simple mixture of acetyl-L-carnitine and arginine, but a specific patented complex that delivers L-carnitine along with a specific amino acid in one distinct molecule. Unlike an intimate mixture or blend of the two nutrients, there is no disparity in content uniformity during capsule formation. As dissociation of the specific AminoCarnitine occurs within the intestinal tract, molecule by molecule, a specific amount of amino acid becomes simultaneously available alongside the L-carnitine for metered absorption within the body.

The technology has evolved so that we can combine carnitines with vital amino acids such as taurine. With this combination, you can get incredible metabolic punch because the molecule of the amino acid will be absorbed in the gut next to the molecule of the carnitines. So you

are really getting tremendous metabolic efficiency when it's done this way.

Passwater: *With the newer carnitines becoming available, our readers may have a few more questions. Once, it simply was a matter of informing people about the health benefits of L-carnitine. Then, as our body of knowledge about L-carnitine expanded, the nuances between L-carnitine fumarate and L-carnitine tartrate emerged. Now it may seem quite complicated with the additional knowledge about acetyl-L-carnitine, PLC and AminoCarnitines.*

Please review with us what should we look for? How much of each form? Which form is preferred for which indication? Is L-carnitine obsolete?

What should one do at a bare minimum? Is it better for healthy people to go for the most economical form or the more efficient form?

Or, is effectiveness so much more important than cost among the ill that cost shouldn't be a factor unless out of desperation? What should people do?

Who should take carnitine supplements? Can you give us some guidelines and dosage ranges?

Sinatra: I think everybody on the planet should take some form of carnitine. And you don't need much. Basically, if you took 250 mg of L-carnitine on an empty stomach twice a day that would be more than enough of a dose for maintaining general health.

People really should take 500 mg (250 mg twice a day) because they are really not going to get enough in the diet to provide what the body really needs. I recommend 500 mg—250 mg twice a day—as the backbone of the carnitine supplementation program.

Passwater: *Are there drugs or health problems that increase this basic need for carnitine?*

Sinatra: If someone is taking Dilantin or any of the anti-convulsive medications—and a lot of people take Dilantin these days, not just for anti-convulsive activity but for other reasons as well, such as calming the thinking process—he or she will need even more carnitine. The anti-convulsive drugs will deplete carnitine in the body. The public needs to know that.

Anybody with renal insufficiency will have low carnitine levels in the body because it is the kidney is a major organ that makes carnitine. Remember that carnitine is made in the body and also received in the diet just like CoQ-10. Carnitine is made from L-methionine and L-lysine and the combination of these two amino acids leads to the formation of L-carnitine in the body. This production, however, can be disturbed by renal insufficiency. The liver also makes L-carnitine.

Passwater: *Well, that brings up the question, "Are there people who should take more than this basic amount?*

Sinatra: Now, if one has advanced cardiovascular disease or if you are compromised and you want to take higher dosages of carnitine, that is certainly valuable.

Here, quickly, are some of the people who should consider larger dosages:

* Anybody who drinks alcohol. Alcohol is toxic to the liver and carnitine will help prevent fatty infiltration and help spare the liver of the toxic effects of alcohol;

* Any athlete who needs to burn fat for energy—especially marathon athletes—or any world-class athlete;

* Anybody with cardiovascular disease;

* Anybody with renal insufficiency;

* Anyone with HIV Syndrome or is who is HIV-positive;

* Anyone with chronic fatigue syndrome;

* Anyone with Syndrome X;

* Anyone with fibromyalgia;

* Any male who has a difficult time impregnating his wife because of poor sperm motility. Relating to this last point, a study in Italy showed that three grams of acetyl-L-carnitine and PLC in combination was as good as testosterone. The combination improved the following penile functions—peak systolic velocity, end-diastolic velocity, resistive index, and the International Index of Erectile Function score.

The carnitines, particularly L-carnitine, will also upgrade the immune system. Some health professionals have begun using the carnitines in HIV syndrome as well as for chronic fatigue syndrome. Remember, chronic fatigue syndrome has a very complex aspect to metabolism. In fact, any chronic fatigue syndrome has faulty metabolism with ATP. With a lot of these syndromes—autoimmune as well—the carnitines have been very useful because they offer support to the immune system just like CoQ-10.

So, as you see, there are many reason reasons for taking carnitine supplements—not only for cardiovascular health, but also for general health.

Passwater: *Can someone take too much carnitine as a supplement?*

Sinatra: I have patients who go up to two to three grams of L-carnitine a day. When at this level, I check thyroid function, as high-dose carnitine could possibly interfere with iodination of the thyroid hormone and I have seen patients come down with a little hypothyroidism. Hypothyroidism is rampant in our culture today. It is, in fact, at epidemic levels, so I do watch thyroid levels when I have people on more than two grams of carnitine a day.

But certainly, L-carnitine is distributed throughout the body, and is affordable to most people.

Passwater: *Let's pause for now and continue next month with metabolic cardiology and how*

Adenosine triphosphate (ATP) and thus its precursors, the carnitines, CoQ-10 and D-Ribose, are the bottom line in heart health. Anybody with any type of cardiovascular disease has a heart that is always leaking ATP. The body can't make it back fast enough by de novo (from the beginning) synthesis! It takes too long and the ATP leakage is faster. It's all about ATP and less about oxygen! Cardiologists are always thinking about oxygen in the heart—and oxygen is important—but oxygen is only the stepping stone to ATP. Oxygen is only a tool—albeit a vital one—in the production of energy via ATP. But, it is not the oxygen that provides the energy of life—it's the ATP. Dr. Sinatra, perhaps at our next session, you will reveal how metabolic cardiology not only improves the energy of the heart, but also all of the life processes. This is important information for everybody. **WF**