

Vital Information

"No conspiracy is required to keep unconscious people in ignorance."

--Robert Burkhalter

Medical Disclaimer: Information provided in this article is for educational purposes only. The author makes no claims or representation regarding treatment, cure, or mitigation of any specific disease or condition. Please consult your own doctor, healthcare practitioner, and/or pharmacist for any health problem (before deciding to self-treat or making any changes to your prescribed medications). If you are ill, I recommend you see a qualified health professional.

When I was 13 years old, I sensed that people were dieing of heart disease needlessly. I kept my eyes open and watched for some hint of what would be the cure. For a long time I thought exercise might be the key. And after my mother had a heart attack and survived, I really wanted her to become physically active and use exercise to heal herself. She had her own ideas and died a few months later of some kind of aneurism.

Then Jim Fixx, a famous and dedicated runner, died of a massive heart attack while running. If exercise was presumed to be the key, I thought, he just proved it might not be.

When Douglas Adams (the author of the Hitchhiker's Guide to the Galaxy) died in his 50's of a heart attack, I remember saying to one of my colleagues, "If his doctor was surprised, he had the wrong doctor. And if his doctor WASN'T surprised, he had the

wrong doctor."

Then, I began to assemble the facts. It takes me a while, but eventually I sort things out. And when Tim Russert (host of Meet the Press) died, I had enough of the details of what really is happening with heart disease to realize the medical profession had conned him. The proof of it wasn't just that they had pronounced him a good patient, but that they really started thrashing around in the aftermath, claiming that "no physician can guarantee that you aren't going to have a heart attack".

Well, I'm no physician. And I think they are wrong. I believe it is possible to rule out the possibility of a heart attack.

Just as I was getting the details of what I'm about to tell you in this article, my Father-in-law perished a few days after sustaining a massive stroke. When I spoke to his son some months later, and shared with him what I am about to share with you, he said, "My father could have lived if he had this information." It took me by surprise when I realized my mother could probably have also lived much longer for the same reason.

About a year before the conversation with my brother-in-law, I got the first bit of confirmation that I was literally being handed the cure for heart disease. A friend of mine who had coronary bypass surgery had followed one of my suggestions and six months after had gotten some raised eyebrows from his physician. The physician was expecting the usual closing of the arteries at this checkup. Instead they had opened (improved).

I quizzed my friend carefully. I asked if he had done only what I had suggested and nothing more. He said, "Trust me, Bob. That's the only change I made."

This was music to my ears. Anecdotal yes. But a positive, and speedy, confirmation that I MIGHT be on the right track.

As much as I would love to force-feed you this information, I realize it's against spiritual law. Your state of consciousness, and your set of beliefs, are part of your sacred space. If you're going to find out something from these words I write

that will benefit you, you must be open to the possibility that I might be speaking more than just MY truth.

Gordon's Story

A friend of mine, Gordon¹, told me he was scheduled to have surgery to clear a blockage in one of the arteries that fed his heart. And as he was discussing it with the surgeon, he realized he didn't like the guy's eyebrows. Gordon's like that; the littlest "wrinkle" in a process will cause him to get a handle on what his gut has been trying to tell him.

So he cancelled the surgery. The surgeon said, "But you'll die." Gordon said, "No, I won't".

He told me he went home and cleared it himself.

Two years pass and I find this book (see link below). In it, I read about this cure for heart disease that was granted a patent in 1994. I phone Gordon and say, "Is this what you did?" He says, "Yes!". I ask, "And did it take 90 days or less, like it says in the book?" He says, "No. It took me 4 months."

And then he says, "When about 6 months had passed since my meeting with the surgeon, I went back to the cardiologist who recommended the surgery, and he did the tests again. The cardiologist told me there was no evidence of blockage NOR any evidence that there EVER WAS any blockage. In short, he pronounced what I had accomplished a complete fix."

Gordon then told me this: "The head of the outpatient cardiology clinic took me aside and said, 'I know what you did works. And if our other patients had your discipline, we would use it.'" When I heard this, I had to tell you because every time they admit it works, we save a few more lives.

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I wrote this because I thought you would like to know about this. I purchased the book. It's called "[Practicing Medicine Without A License](#)" by Owen Fonorow. Click [here](#) to order it from Amazon.Com.

This seems like a really good way to skip stroke and to simply avoid heart disease. I firmly believe this isn't about lowering

¹ Gordon Bell exists. It's my pleasure to call him a friend. His web sites are accessible at www.gordonbell.org.

your risk for these two killers; it's about removing the CAUSE.

Apparently, for the last several years, when doctors refuse to do a bypass because the patient has had several bypass surgeries and they don't seem to help, or they think they cannot successfully make it happen, they tell the patients to seek alternative medicine. The patients go to the web and find these two sites,

www.practicingmedicinewithoutalicense.com

www.sallyjewell.com

And according to the hundreds of testimonials posted at those sites, folks do the simple, inexpensive, self therapy my friend did that's described in the book. Typically, their chest pain disappears in 10 days, they are able to play with their kids again in about a month. And after 3 months, they are out jogging, or doing the vigorous sports they know will help the rest of their body.

The Underlying Science

The underlying science behind how heart disease "works" is very simple. And the model I'm about to share with you is the only one that is supported by all of the evidence. The other models, the ones the vast majority of medical professionals embrace, is seriously flawed and produces 780,000 deaths a year in the USA alone. The model I'm about to share with you would bring that number virtually to zero. Read on.

There are three classes of mammals that suffer from scurvy: guinea pigs, fruit bats, and primates (humans and monkeys). Scurvy, as most people know it, is characterized by bleeding gums, and bruises that won't heal. And if not treated, it leads rather quickly to a horrible death. This is the way many British sailors died before the admiralty tried feeding the crew fresh vegetables. I say "tried" rather than "discovered that" feeding fresh vegetables would avoid scurvy.

Captain Bligh [Vice-Admiral William Bligh FRS RN (9 September 1754 - 7 December 1817)] (made famous by the true story Mutiny on the Bounty) "discovered" that feeding his crew fresh vegetables eliminated scurvy, and recorded this in his log. The admiralty, knew he "claimed" this, and it took them only 50 years to give it a "try". And that little experiment ended the needless deaths.²

I mention this "delay" the Brits went thru before they ended the needless deaths related to Vitamin C deficiency, because we're in a similar position now. Physicians categorize what most people call "scurvy" as "frank scurvy", meaning "open", or scurvy that's "not hidden". And we know, at this point in time, that it can be avoided by 60 mg of Vitamin C per day. And this dosage is easily obtained either by supplementation or from food.

There is another scurvy. And it's not frank. It's categorized as "chronic". And it's relatively hidden. In this case, it requires no less than 3000 mg of Vitamin C daily to avoid it. And that dosage cannot be obtained from food; it requires supplemen-

² It took many years later to establish the fact that the three classes of mammals that suffer from scurvy do so because they lack the enzyme necessary to manufacture their own Vitamin C.

tation.

And now the shocker: The symptoms of chronic scurvy are heart disease and ischemic stroke.

In case you doubt this, let me state that there are only three classes of mammals that exhibit heart disease: guinea pigs, fruit bats, and primates. That's the same group that gets scurvy. That's the same group that must obtain its Vitamin C from sources outside the body.

As soon as you've absorbed that statement, here's the model:

With each heartbeat, your arteries crack. And, as you might guess, your body does a continuous job of repairing them. If there is enough Vitamin C (ascorbic acid) in your blood, the repair is un-noticeable. The wall of the artery is completely restored to its original state because the collagen formed by this type of repair is a perfect match for what cracked.

It's like the repair you make when someone cracks one of your counter-top tiles. You go into the garage and get one of the "extra" tiles the contractor left and use it to replace the one that's cracked so there's never a hint that anything was replaced.

However, if there isn't any ascorbic acid (Vitamin C) available, your body doesn't wait. It repairs it with a substance it produces for just such an emergency.

The alternate substance the body uses to make the repair when it is lacking Vitamin C is called "lipoprotein(a)"³. It's one of the many identified types of cholesterol. And, when you're lack-

³ To underscore the validity of this model, researchers have recently verified that the only cholesterol in arterial plaques, is indeed lipoprotein(a). And it's common knowledge that the plaques occur at the site of the greatest arterial stress, which is closest to the heart. This latter fact debunks the "theory" that the cause of arterial plaques is elevated cholesterol. If it were elevated cholesterol that caused the plaques, the plaques would be everywhere in the arteries instead of in just this one localized area. And of course it raises serious questions about the sanity of taking drugs to reduce cholesterol.

ing Vitamin C, your body produces more of this vital type of cholesterol.

The problem with this process is that these "emergency" patches made of cholesterol eventually fill, and close, the artery. If that closed artery happens to be one of those feeding your heart, you have what's called a heart attack. The other problem is that the patches break off and float up into the brain. That's called a stroke.

So, when you think about this, you might be pleased, and shocked at the same time, to know there is no medication available to lower the amount of lipoprotein(a) available for emergency patches in your blood. It's also a fact that Statins (the flagship drug in the alleged war on heart disease) increase the amount of lipoprotein(a). I smell a class-action lawsuit brewing here. But I digress.

So, if you've been following all of this, you should have two questions: 1) Why is it necessary to take so much vitamin C, and 2) How should I take it. Well, there's a third question: Why doesn't my doctor know about this?

The answer to number three is "S/he does!". That's why, over the last 10 years, when someone with heart disease isn't a "good candidate" for yet another bypass surgery, some doctors refer the patient to the internet to seek "alternate therapies". I'll give you the link to two sites that discuss what I've outlined here, and they have lots of posted testimonials from folks who do the therapy themselves and usually start their testimonial like this: "Ten days after starting on the Vitamin C and Lysine, my chest pains went away..."

To answer the second question, I'll come right to the point. I take 2000 mg of Vitamin C three times a day. I use a mixture of powdered ascorbic acid and powdered sodium ascorbate. I'll list the sources below. I mix those two because taking only ascorbic acid seems to be too much acid for my stomach.

In keeping with the protocol from Fonorow's book, and summarized below, I also take 1000 mg of Lysine three times a day. That's a total of 6000 mg of Vitamin C and 3000 mg of Lysine every day.

The sodium ascorbate (another form of Vitamin C), reduces the acidity of the ascorbic acid. Sodium ascorbate is so benign that it's what's used when people want to inject Vitamin C directly into a person's artery.

Incidentally, I read recently that some folks (doctors included) actually think Vitamin C can be toxic if taken in large doses. This is not true. If you doubt me, check with the Academy of Science. They are the folks you have to contact to allow you to run tests in which you give your test subjects (humans and animals) doses of substances. Vitamin C is one of the few substances for which the Academy of Science does not impose a limit.

The patent

In 1994, Pauling and Rath received a patent⁴ for reversing heart disease. The procedure involves using vitamin C and Lysine. Remember, Pauling got the Nobel Prize the first time for his work with proteins. So when he said that Lysine would bond with the lipoprotein(a) and make it less sticky, and more-easily replaced by the ascorbic acid as the arteries heal, he wasn't just guessing.

If you understand that the arterial plaque that many doctors are worried about is the result of a long-term shortage of vitamin C, and NOT the result of the fat you eat, not only does your life become simpler, but your fears diminish. And so should your trust (diminish) of anyone trying to cut your "risk factors" rather than simply removing the cause.

I've kept this brief. If you need more details, get Fonorow's book below. He presents a more thorough description of the model and a lot more details. If you can read, and have an IQ greater than 90, you will have all the proof you need. There's also the fact that Life Extension Foundation did an investigation to see if Vitamin C had any effect on a person's arteries. I think their work is so valuable, and pertinent to this discussion, that I'm including not only a link to it, but I've also reproduced it in the Appendix B.

⁴ US Patent No. 5230996 Pauling/Rath (1993). A Procedure for the Cleansing/Removal of Atherosclerotic Plaque from Human Organs During Transplant Surgery.

If you have a stent, and especially a drug-eluting stent, I suggest you get Fonorow's book because it contains a lot of information you need to know. I am not able to summarize this part of his book at this time. I need to understand it more; so I suggest you read it yourself.

The links

The book

["Practicing Medicine Without A License"](#) by Owen Fonorow. Click [here](#) to order it from Amazon.com.

And the web sites with the testimonials and more information:

www.practicingmedicinewithoutalicense.com

www.sallyjewell.com

Resources

I take the vitamin C as a mixture of ascorbic acid and sodium ascorbate (half and half). It seems to cut the acidity. And I'm using powder (crystals) form. It's much cheaper than tablets.

You can get powdered ascorbic acid (Vitamin C) at Trader Joe's for something like \$4 a pound. But since not everyone has access to that physical store, just do a search on Google for "cheap Vitamin C". It's pretty hard to botch Vitamin C manufacturing.

I once had someone tell me that she didn't want to take a lot of Vitamin C, and that she thought the quality and "naturalness" of it was important, so she was taking hers from some source like acerola cherries. I'm not saying that is a mistake, except, she took a very low dosage, and there's research to indicate that anything less than 2000 mg daily isn't going to give you the results I'm talking about in this paper.

Remember, if several thousand milligrams of ascorbic acid is too much acid in your stomach, use powdered sodium ascorbate. Someone once told me that he was afraid of adding sodium to his diet with sodium ascorbate. So he used Calcium Ascorbate. I tried it and didn't like the taste at all.

I found a good source of Lysine at

www.nutrabio.com/Products/lysine.htm?gclid=CLym4rX3yp0CFRcjawodPEDDqw

Here's an excerpt from chapter 7 of the book that summarizes the therapy:

[Practicing Medicine Without A License](#) by Owen Fonorow
From the summary close to the end of chapter 7 (p106-107)

Pauling Therapy Summary

Therapeutic

Vitamin C (6,000 to 18,000 mg)
Lysine (5,000 to 6,000 mg)

Pauling Therapy Enhancements

Proline (260 to 2,000 mg)
Coenzyme Q10 (100 to 300 mg)
Magnesium (150 to 1,500 mg)

Preventives

Vitamin C (3,000 to 10,000 mg)
Lysine (2,000 to 4,000 mg)

Follow Pauling's Other Heart and Cardiovascular Recommendations

Vitamin E - 800 to 3,200 IU
Vitamin A - 20,000 to 40,000 IU
Super B-Complex - 1 or 2
Daily multiple vitamin and mineral
Drink plenty of water

Additional Enhancements

Eliminate trans fatty acids from the diet
Introduce unprocessed Omega 3 and Omega 6 oils
Eat salt, but only unrefined salt
Reduce manganese intake (see the warning below)
Eliminate ordinary sugar and refined carbohydrates
Supplement with vitamin K
Avoid supplemental calcium
Supplement with amino acids taurine, arginine and car-

nitine (1 to 3 grams)

Supplement with vitamin D3 (2,000 IU), especially in the winter months

Supplement with melatonin (3 to 6 mg) before bedtime

end of exerpt

A BIGGY: at another place in the book, it states that the United States Department of Agriculture found, and issued a bulletin that states, that excessive amounts of manganese (NOT magnesium) can cause heart rhythm irregularities. Decreasing to a safe amount and waiting as much as 90 days will allow the rhythm to return to normal. The safe amount: 2-3mg per day. The toxic amount, causing the irregular rhythm: 20mg per day.

What makes this a biggy is that some multi-vitamins actually have this toxic dose of manganese in them. Be aware.

I take the vitamin C and Lysine in powder form 3 times a day (6am, 2pm, and 10pm). Statements in the book indicate 6am, 10am, 2pm, 6pm, 10pm would be ideal, but because I'm on a "prevention" protocol and not a "therapeutic" protocol, I feel ok with that.

Related thought:

If the model the general public uses is correct (proposed by the drug companies), claiming that cholesterol is the cause of arterial blockage, then there would be no place in the patient's body to harvest clean arteries for a bypass. If their model were correct, no matter where you looked in a patient's body, the arteries would be in deep trouble. But that is not the case, the blockages are always where the greatest amount of stress to the system is -- nearest the "pump", even though "demon cholesterol" is everywhere in the system.

This suggests that intense flexing of the arteries, which occurs closest to the heart, causes the damage. And the repair fol-

lows as I described. You don't have cholesterol clogging up the arteries just because it's present in the system. Cholesterol clogs the arteries when it's the only substance available for repair.

One little gotcha:

In Dr. Michael Eades's book [Protein Power Lifeplan](#) (click [here](#) to get it from Amazon), he mentions that the human body stores iron more efficiently if a person takes the amount of Vitamin C discussed in this article. Indeed, accumulated iron from a lifetime of iron-enriched foods can be a problem. He suggests getting a blood ferritin (iron) test and then indicates how many units of blood one must donate to get that iron down to a safe level. He says the damage done during a stroke, or heart attack, is increased by several orders of magnitude if there is too much iron stored in your body. This item alone is worth the price of his book. I'm on my second reading of it.

And this warning:

Keep your body free of infections. Whenever you have an infection, that infection consumes a lot of the Vitamin C in your blood. And that leaves precious little to properly repair arteries and veins.

That's why the medical establishment will tell you that if you have gum disease, you are at higher risk for a heart disease. They won't tell you the underlying reason like I just did. We can talk later about why they don't tell you, but just keep it in mind: if you've got an infection, add more Vitamin C to your diet until you're sure the infection is gone.

If you don't know if you've got an infection, or if your dental situation is kind of iffy, you can increase your Vitamin C intake by 1000 mg every day until you get loose stools. Then you can choose to reduce your Vitamin C intake just a bit. Or you can leave it like that if constipation might be an issue. This should guarantee that you are getting enough for your body and any infections that you might not be aware of.

One last item:

I would like to make this document "responsive" to criticism (both positive and negative). So if you can think of something I should add, or if you've got a question, I'd like to add the answer to that question to this document (because I'm sure others will have the same question), and, if your input can help me improve this document so it speaks clearly to more people, I would appreciate your feedback.

Please send any feedback to info@robertburkhalter.com. Please say if you would like a response and I'll do my best.

Thank you for reading. I hope this information will benefit you and yours.

May the blessings be.

Robert Burkhalter
March 12, 2010

Appendix A

What follows is taken from this web page

www.drrathresearch.org/lab_research/study_hd_unified_theory.html

Unified Theory of Human Cardiovascular Disease Leading the Way to the Abolition of This Disease as a Cause for Human Mortality (1992)

Rath M, Pauling L.

Journal of Orthomolecular Medicine, 6: 139-143.

Summary (Abstract)

Until now therapeutic concepts for human cardiovascular disease (CVD) were targeting individual pathomechanisms or specific risk factors. On the basis of genetic, metabolic, evolutionary, and clinical evidence we present here a unified pathogenetic and therapeutic approach. Ascorbate deficiency is the precondition and common denominator of human CVD. Ascorbate deficiency is the result of the inability of man to synthesize ascorbate endogenously in combination with insufficient dietary intake.

The invariable morphological consequences of chronic ascorbate deficiency in the vascular wall are the loosening of the connective tissue and the loss of the endothelial barrier function. Thus human CVD is a form of pre-scurvy. The multitude of pathomechanisms that lead to the clinical manifestation of CVD are primarily defense mechanisms aiming at the stabilization of the vascular wall.

After the loss of endogenous ascorbate production during the evolution of man these defense mechanisms became life-saving. They counteracted the fatal consequences of scurvy and particularly of blood loss through the scorbutic vascular wall. These countermeasures constitute a genetic and a metabolic level. The genetic level is characterized by the evolutionary advantage of inherited features that lead to a thickening of the vascular wall, including a multitude of inherited diseases. The metabolic level is characterized by the close connection of ascorbate with metabolic regulatory systems that determine the risk profile for

CVD in clinical cardiology today.

The most frequent mechanism is the deposition of lipoproteins, particularly lipoprotein(a) [Lp(a)], in the vascular wall. With sustained ascorbate deficiency, the result of insufficient ascorbate uptake, these defense mechanisms overshoot and lead to the development of CVD.

Premature CVD is essentially unknown in all animal species that produce high amounts of ascorbate endogenously. In humans, unable to produce endogenous ascorbate, CVD became one of the most frequent diseases. The genetic mutation that rendered all human beings today dependent on dietary ascorbate is the universal underlying cause of CVD.

Optimum dietary ascorbate intake will correct this common genetic defect and prevent its deleterious consequences. Clinical confirmation of this theory should largely abolish CVD as a cause for mortality in this generation and future generations of mankind.

Full Study

"An important scientific innovation rarely makes its way by gradually winning over and converting its opponents. What does happen is that its opponents gradually die out and that the growing generation is familiar with the idea from the beginning."

Max Planck, Nobel-Laureate in Physics

This publication is dedicated to the young physicians and medical students of this world.

Introduction

We have recently presented ascorbate deficiency as the primary cause of human CVD. We proposed that the most frequent pathomechanism leading to the development of atherosclerotic plaques is the deposition of Lp(a) and fibrinogen/fibrin in the ascorbate-deficient vascular wall (1,2). In the course of this work we discovered that virtually every pathomechanism for human CVD known today can be induced by ascorbate deficiency. Beside the deposition of Lp(a) this includes such seemingly unrelated processes as foam cell formation and decreased reverse-cholesterol transfer, and also peripheral angiopathies in diabetic or homocystinuric patients. We did not accept this observation as a

coincidence.

Consequently we proposed that ascorbate deficiency is the precondition as well as a common denominator of human CVD. This far-reaching conclusion deserves an explanation; it is presented in this paper. We suggest that the direct connection of ascorbate deficiency with the development of CVD is the result of extraordinary pressure during the evolution of man. After the loss of the endogenous ascorbate production in our ancestors, fatal blood-loss through the scorbutic vascular wall became a life-threatening condition. The resulting evolutionary pressure favored genetic and metabolic mechanisms predisposing to CVD.

The Loss of Endogenous Ascorbate Production in the Ancestor of Man

With few exceptions all animals synthesize their own ascorbate by conversion from glucose. In this way they manufacture a daily amount of ascorbate that varies between about 1 gram and 20 grams, when compared to the human body weight. About 40 million years ago the ancestor of man lost the ability for endogenous ascorbate production. This was the result of a mutation of the gene encoding for the enzyme L-gulonolactone oxidase (GLO), a key enzyme in the conversion from glucose to ascorbate. As a result of this mutation all descendants became dependent on dietary ascorbate intake.

The precondition for the mutation of the GLO gene was a sufficient supply of dietary ascorbate. Our ancestors at that time lived in tropical regions. Their diet consisted primarily of fruits and other forms of plant nutrition that provided a daily dietary ascorbate supply in the range of several hundred milligrams to several grams per day. When our ancestors left this habitat to settle in other regions of the world the availability of dietary ascorbate dropped considerably and they became prone to scurvy.

Fatal Blood Loss Through the Scorbutic Vascular Wall - An Extraordinary Challenge to the Evolutionary Survival of Man

Scurvy is a fatal disease. It is characterized by structural and metabolic impairment of the human body, particularly by the destabilization of the connective tissue. Ascorbate is essential for an optimum production and hydroxylation of collagen and elastin, key constituents of the extracellular matrix. Ascor-

bate depletion thus leads to a destabilization of the connective tissue throughout the body. One of the first clinical signs of scurvy is perivascular bleeding. The explanation is obvious: Nowhere in the body does there exist a higher pressure difference than in the circulatory system, particularly across the vascular wall. The vascular system is the first site where the underlying destabilization of the connective tissue induced by ascorbate deficiency is unmasked, leading to the penetration of blood through the permeable vascular wall. The most vulnerable sites are the proximal arteries, where the systolic blood pressure is particularly high. The increasing permeability of the vascular wall in scurvy leads to petechiae and ultimately hemorrhagic blood loss.

Scurvy and scorbutic blood loss decimated the ship crews in earlier centuries within months. It is thus conceivable that during the evolution of man periods of prolonged ascorbate deficiency led to a great death toll. The mortality from scurvy must have been particularly high during the thousands of years the ice ages lasted and in other extreme conditions, when the dietary ascorbate supply approximated zero. We therefore propose that after the loss of endogenous ascorbate production in our ancestors, scurvy became one of the greatest threats to the evolutionary survival of man. By hemorrhagic blood loss through the scorbutic vascular wall our ancestors in many regions may have virtually been decimated and brought close to extinction.

The morphologic changes in the vascular wall induced by ascorbate deficiency are well characterized: the loosening of the connective tissue and the loss of the endothelial barrier function. The extraordinary pressure by fatal blood loss through the scorbutic vascular wall favored genetic and metabolic countermeasures attenuating increased vascular permeability.

Ascorbate Deficiency and Genetic Countermeasures

The genetic countermeasures are characterized by an evolutionary advantage of genetic features and include inherited disorders that are associated with atherosclerosis and CVD. With sufficient ascorbate supply these disorders stay latent. In ascorbate deficiency, however, they become unmasked, leading to an increased deposition of plasma constituents in the vascular wall and other mechanisms that thicken the vascular wall. This thickening of the vascular wall is a defense measure compensating for the im-

paired vascular wall that had become destabilized by ascorbate deficiency. With prolonged insufficient ascorbate intake in the diet these defense mechanisms overshoot and CVD develops.

The most frequent mechanism to counteract the increased permeability of the ascorbate-deficient vascular wall became the deposition of lipoproteins and lipids in the vessel wall. Another group of proteins that generally accumulate at sites of tissue transformation and repair are adhesive proteins such as fibronectin, fibrinogen, and particularly apo(a). It is therefore no surprise that Lp(a), a combination of the adhesive protein apo(a) with a low density lipoprotein (LDL) particle, became the most frequent genetic feature counteracting ascorbate deficiency (1). Beside lipoproteins, certain metabolic disorders, such as diabetes and homocysteinuria, are also associated with the development of CVD. Despite differences in the underlying pathomechanism, all these mechanisms share a common feature: they lead to a thickening of the vascular wall and thereby can counteract the increased permeability in ascorbate deficiency.

In addition to these genetic disorders, the evolutionary pressure from scurvy also favored certain metabolic countermeasures.

Ascorbate Deficiency and Metabolic Countermeasures

The metabolic countermeasures are characterized by the regulatory role of ascorbate for metabolic systems determining the clinical risk profile for CVD. The common aim of these metabolic regulations is to decrease the vascular permeability in ascorbate deficiency. Low ascorbate concentrations therefore induce vasoconstriction, hemostasis and affect vascular wall metabolism in favor of atherogenesis. Towards this end ascorbate interacts with lipoproteins, coagulation factors, prostaglandins, nitric oxides, and second messenger systems such as cyclic monophosphates (for review see 1, 3-5). It should be noted that ascorbate can affect these regulatory levels in a multiple way. In lipoprotein metabolism low density lipoproteins (LDL), Lp(a), and very low density lipoproteins (VLDL) are inversely correlated with ascorbate concentrations, whereas ascorbate HDL levels are positively correlated. Similarly, in prostaglandin metabolism ascorbate increases prostacyclin and prostaglandin E concentrations and decreases thromboxane levels. In general, ascorbate deficiency induces vascular constriction and hemostasis, as well as cellular and extracellular defense measures in the vas-

cular wall.

In the following sections we will exemplify the role of ascorbate for frequent and well established pathomechanisms of human CVD. In general, the inherited disorders described below are polygenic. Their separate description, however, will allow the characterization of the role of ascorbate on the different genetic and metabolic levels.

Apo(a) and Lp(a), the Most Effective and Most Frequent Countermeasures

After the loss of endogenous ascorbate production, apo(a) and Lp(a) were greatly favored by evolution. The frequency of occurrence of elevated Lp(a) plasma levels in species that had lost the ability to synthesize ascorbate is so great that we formulated the theory that apo(a) functions as a surrogate for ascorbate (6). There are several genetically determined isoforms of apo(a). They differ in the number of kringle repeats and in their molecular size (7). An inverse relation between the molecular size of apo(a) and the number of synthesized Lp(a) molecules has been established. Patients with the high molecular weight apo(a) isoform carry fewer LDL particles in their Lp(a) fraction. Vice versa, patients with the genetic pattern of low apo(a) isoform have more LDL particles in their Lp(a) plasma fraction and thus have increased Lp(a) plasma levels. In most population studies the genetic pattern of high apo(a) isoform/low Lp(a) plasma level proved to be the most advantageous and therefore most frequent pattern.

In ascorbate deficiency Lp(a) is selectively retained in the vascular wall. Apo(a) counteracts increased permeability by compensating for collagens, by its binding to fibrin, as a proteinthiol and antioxidant, and as an inhibitor of plasmin-induced proteolysis (1). Moreover, as an adhesive protein apo(a) is effective in tissue-repair processes (8). Chronic ascorbate deficiency leads to a sustained accumulation of Lp(a) in the vascular wall. This leads to the development of atherosclerotic plaques and premature CVD particularly in individuals with genetically determined high plasma Lp(a) levels. Because of its association with apo(a), Lp(a) is the most specific repair particle among all lipoproteins. Lp(a) is predominantly deposited at predisposition sites and it is therefore found to be significantly correlated with coronary, cervical, and cerebral atherosclerosis but not

with peripheral vascular disease.

The mechanism by which ascorbate resupplementation prevents CVD in any condition is by maintaining the integrity and stability of the vascular wall. In addition, ascorbate exerts in the individual a multitude of metabolic effects that prevent the exacerbation of a possible genetic predisposition and the development of CVD. If the predisposition is a genetic elevation of Lp(a) plasma levels the specific regulatory role of ascorbate is the decrease of apo(a) synthesis in the liver and thereby the decrease of Lp(a) plasma levels. Moreover, ascorbate decreases the retention of Lp(a) in the vascular wall by lowering fibrinogen synthesis and by increasing the hydroxylation of lysine residues in vascular wall constituents, thereby reducing the affinity for Lp(a) binding (1).

In about half of the CVD patients the mechanism of Lp(a) deposition contributes significantly to the development of atherosclerotic plaques. Other lipoprotein disorders are also frequently part of the polygenic pattern predisposing the individual patient to CVD in the individual.

Other Lipoprotein Disorders Associated with CVD

In a large population study Goldstein identified three frequent lipid disorders, familial hypercholesterolemia, familial hypertriglyceridemia, and familial combined hyperlipidemia (9). Ascorbate deficiency unmasks these underlying genetic defects and leads to an increased plasma concentration of lipids (e.g. cholesterol, triglycerides) and lipoproteins (e.g. LDL, VLDL) as well as to their deposition in the impaired vascular wall. As with Lp(a), this deposition is a defense measure counteracting the increased permeability. It should, however, be noted that the deposition of lipoproteins other than Lp(a) is a less specific defense mechanism and frequently follows Lp(a) deposition. Again, these mechanisms function as a defense only for a limited time. With sustained ascorbate deficiency the continued deposition of lipids and lipoproteins leads to atherosclerotic plaque development and CVD. Some mechanisms will be described in more detail.

Hypercholesterolemia, LDL-receptor defect

A multitude of genetic defects lead to an increased synthesis and/or a decreased catabolism of cholesterol or LDL. A well

characterized although rare defect is the LDL-receptor defect. Ascorbate deficiency unmasks these inherited metabolic defects and leads to an increased plasma concentration of cholesterol-rich lipoproteins, e.g. LDL, and their deposition in the vascular wall. Hypercholesterolemia increases the risk for premature CVD primarily when combined with elevated plasma levels of Lp(a) or triglycerides.

The mechanisms by which ascorbate resupplementation prevents the exacerbation of hypercholesterolemia and related CVD include an increased catabolism of cholesterol. In particular, ascorbate is known to stimulate 7 α -hydroxylase, a key enzyme in the conversion of cholesterol to bile acids and to increase the expression of LDL receptors on the cell surface. Moreover, ascorbate is known to inhibit endogenous cholesterol synthesis as well as oxidative modification of LDL (1).

Hypertriglyceridemia, Type III hyperlipidemia

A variety of genetic disorders lead to the accumulation of triglycerides in the form of chylomicron remnants, VLDL and intermediate density lipoproteins (IDL) in plasma. Ascorbate deficiency unmasks these underlying genetic defects and the continued deposition of triglyceride-rich lipoproteins in the vascular wall leads to CVD development. These triglyceride-rich lipoproteins are particularly subject to oxidative modification, cellular lipoprotein uptake, and foam cell formation. In hypertriglyceridemia non specific foam cell formation has been observed in a variety of organs (10). In the vascular wall foam cell formation, although a less specific repair mechanism than the extracellular deposition of Lp(a), may have also conferred stability on the ascorbate-deficient vascular wall.

Ascorbate resupplementation prevents the exacerbation of CVD associated with hypertriglyceridemia, Type III hyperlipidemia, and related disorders by stimulating lipoprotein lipases and thereby enabling a normal catabolism of triglyceride-rich lipoproteins (11). Ascorbate prevents the oxidative modification of these lipoproteins, their uptake by scavenger cells and foam cell formation. Moreover, we propose here that, analogous to the LDL receptor, ascorbate also increases the expression of the receptors involved in the metabolic clearance of triglyceride-rich lipoproteins, such as the chylomicron remnant receptor.

The degree of build-up of atherosclerotic plaques in patients with lipoprotein disorders is determined by the rate of deposition of lipoproteins and by the rate of the removal of deposited lipids from the vascular wall. It is therefore not surprising that ascorbate is also closely connected with this reverse pathway.

Hypoalphalipoproteinemia

A frequent lipoprotein disorder is the genetically determined decreased synthesis of HDL particles. HDL is part of the 'reverse-cholesterol-transport' pathway and is critical for the transport of cholesterol and also other lipids from the body periphery to the liver. In ascorbate deficiency this genetic defect is unmasked resulting in decreased HDL levels and a decreased reverse transport of lipids from the vascular wall to the liver. This mechanism is highly effective and the genetic disorder hypoalphalipoproteinemia was greatly favored during evolution.

With ascorbate resupplementation HDL production increases (12), leading to an increased uptake of lipids deposited in the vascular wall and to a decrease of the atherosclerotic lesion. A look back in evolution underlines the importance of this mechanism. During the winter seasons, with low ascorbate intake, our ancestors became dependent on protecting their vascular wall by the deposition of lipoproteins and other constituents. During spring and summer seasons the ascorbate content in the diet increased significantly and mechanisms were favored that decreased the vascular deposits under the protection of increased ascorbate concentration in the vascular tissue. It is not unreasonable for us to propose that ascorbate can reduce fatty deposits in the vascular wall within a relatively short time. In an earlier clinical study it was shown that 500 mg of dietary ascorbate per day can lead to a reduction of atherosclerotic deposits within 2 to 6 months (13).

This concept, of course, also explains why heart attack and stroke occur today with a much higher frequency in winter than during spring and summer, the seasons with increased ascorbate intake.

Other Inherited Metabolic Disorders Associated with CVD

Beside lipoprotein disorders many other inherited metabolic diseases are associated with CVD. Generally these disorders lead

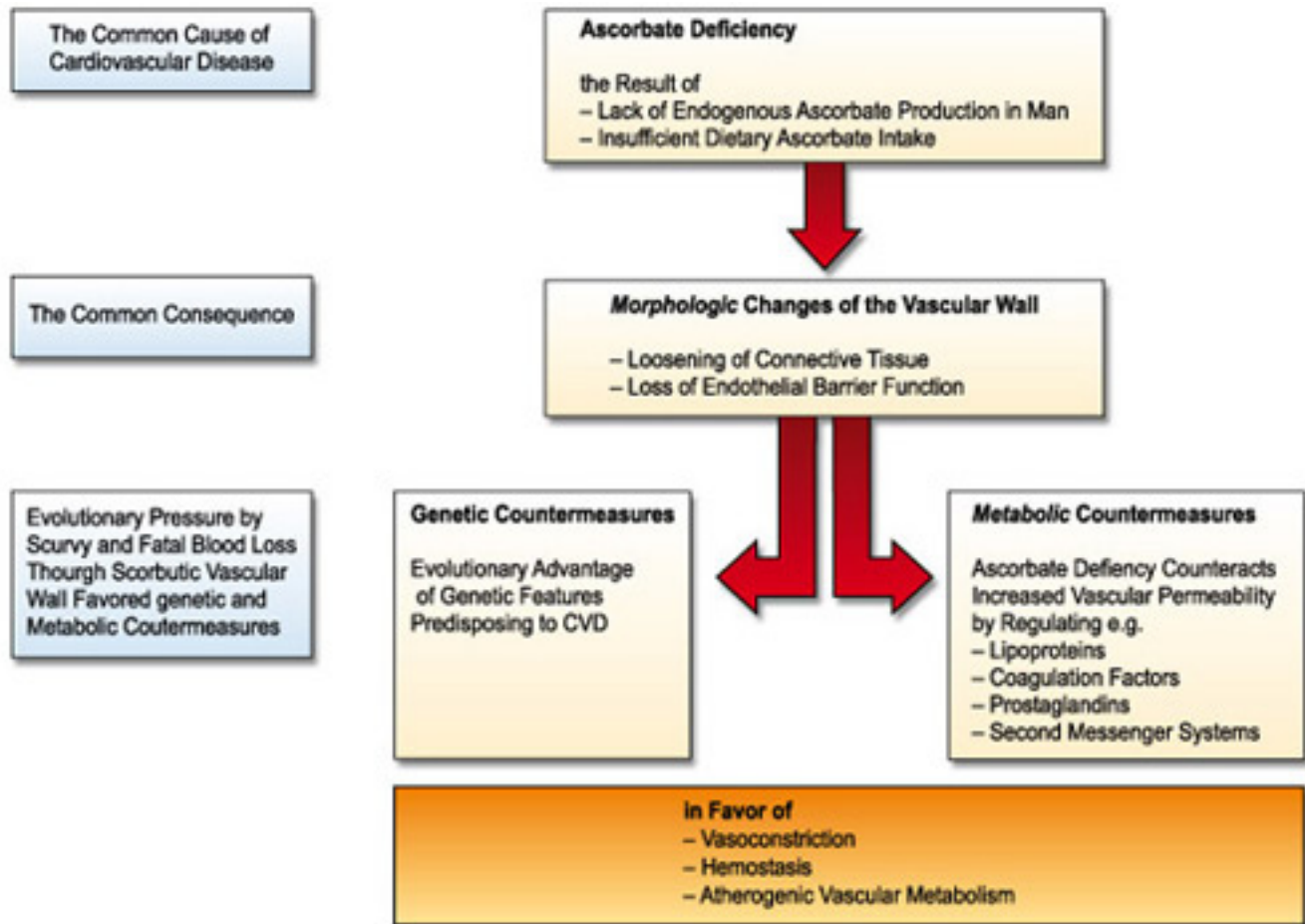


Figure 1.

Ascorbate deficiency is the precondition and common denominator of human CVD. Ascorbate deficiency invariably leads to an increased permeability of the vascular wall. The evolutionary pressure from fatal blood-loss through scorbatic vascular wall over million of years favoured genetic and metabolic countermeasures. The genetic level (A) is characterized by an evolutionary advantage of genetic features predisposing to CVD. The evolutionary pressure in favour of these predisposing genetic features was so great that CVD became one of today's most common diseases. The metabolic level (B) is characterized by the regulatory effect of ascorbate on factors determining the clinical risk profile for CVD in cardiology today including lipoproteins, coagulation factors, prostaglandins, and others. Ascorbate deficiency counteracts increased vascular permeability by inducing vasoconstriction, hemostasis, and atherogenic vascular metabolism.

to an increased concentration of plasma constituents that directly or indirectly damage the integrity of the vascular wall. Consequently these diseases lead to peripheral angiopathies as observed in diabetes, homocysteinuria, sickle-cell anemia (the first molecular disease described (14)), and many other genetic disorders. Similar to lipoproteins the deposition of various plasma constituents as well as proliferative thickening provided a certain stability for the ascorbate-deficient vascular wall. We illustrate this principle for diabetic and homocystinuric angiopathy.

Diabetic angiopathy

The pathomechanism in this case involves the structural similarity between glucose and ascorbate and the competition of these two molecules for specific cell surface receptors (15,16). Elevated glucose levels prevent many cellular systems in the human body, including endothelial cells, from optimum ascorbate uptake. Ascorbate deficiency unmasks the underlying genetic disease, aggravates the imbalance between glucose and ascorbate, decreases vascular ascorbate concentration, and thereby triggers diabetic angiopathy.

Ascorbate resupplementation prevents diabetic angiopathy by optimizing the ascorbate concentration in the vascular wall and also by lowering insulin requirement (17).

Homocystinuric angiopathy

Homocystinuria is characterized by the accumulation of homocyst(e)ine and a variety of its metabolic derivatives in the plasma, the tissue and the urine as the result of decreased homocysteine catabolism (18). Elevated plasma concentrations of homocyst(e)ine and its derivatives damage the endothelial cells throughout the arterial and venous system. Thus homocystinuria is characterized by peripheral vascular disease and thromboembolism. These clinical manifestations have been estimated to occur in 30 per cent of the patients before the age of 20 and in 60 per cent of the patients before the age of 40 (19).

Ascorbate resupplementation prevents homocystinuric angiopathy and other clinical complications of this disease by increasing the rate of homocysteine catabolism (20).

Thus, ascorbate deficiency unmasks a variety of individual genet-

Genetic Countermeasures

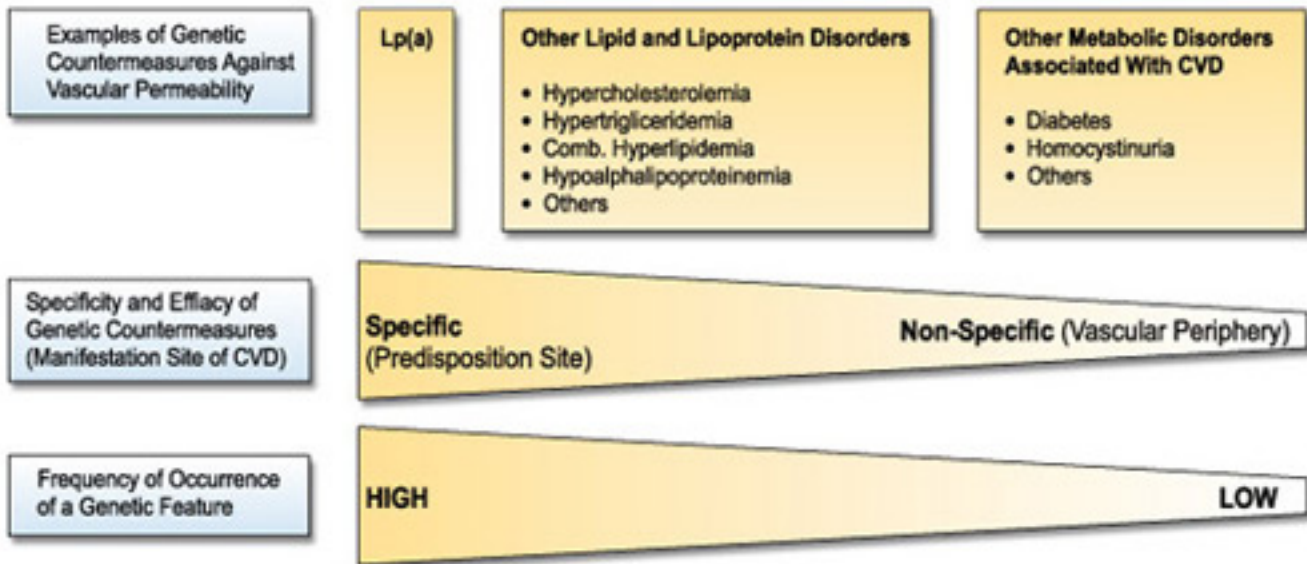


Figure 2.

Genetic countermeasures and the relation between their efficacy and the frequency of their occurrence. The more specifically a genetic feature counteracts the increased permeability of the vascular wall the more it was favoured during evolution and the more frequently it occurs today. The deposition of Lp(a) in the vascular wall is the most specific and therefore most frequent mechanism. Because of the specificity of Lp(a) the sustained accumulation of this lipoprotein during chronic ascorbate deficiency leads to CVD at predisposition sites. Diabetic and homocystinuric angiopathies are typical non-specific mechanisms. Their clinical exacerbation in chronic ascorbate deficiency leads to peripheral vascular disease. With the exception of Lp(a), most other lipoprotein disorders are rather non-specific countermeasures. They either follow the deposition of Lp(a) and aggravate CVD mainly at predisposition sites or they lead to peripheral vascular disease, such as in Type III hyperlipidemia. Figure 2 schematically summarizes these principles. This scheme, of course, can not reflect the multitude of polygenic variations in individual patients.

ic predispositions that lead to CVD in different ways. These genetic disorders were conserved during evolution largely because of their association with mechanisms that lead to the thickening of the vascular wall. Moreover, since ascorbate deficiency is the underlying cause of these diseases, ascorbate resupplementation is the universal therapy.

The Determining Principles of This Theory

The determining principles of this comprehensive theory are schematically summarized in Figures 1 to 3.

1. Cardiovascular disease is the direct consequence of the inability for endogenous ascorbate production in man in combination with low dietary ascorbate intake.

2. Ascorbate deficiency leads to increased permeability of the vascular wall by the loss of the endothelial barrier function and the loosening of the vascular connective tissue.

3. After the loss of endogenous ascorbate production scurvy and fatal blood loss through the scorbutic vascular wall rendered our ancestors in danger of extinction. Under this evolutionary pressure over millions of years genetic and metabolic countermeasures were favored that counteract the increased permeability of the vascular wall.

4. The genetic level is characterized by the fact that inherited disorders associated with CVD became the most frequent among all genetic predispositions. Among those predispositions lipid and lipoprotein disorders occur particularly often.

5. The metabolic level is characterized by the direct relation between ascorbate and virtually all risk factors of clinical cardiology today. Ascorbate deficiency leads to vasoconstriction and hemostasis and affects the vascular wall metabolism in favor of atherogenesis.

6. The genetic level can be further characterized. The more effective and specific a certain genetic feature counteracted the increasing vascular permeability in scurvy, the more advantageous it became during evolution and, generally, the more frequently this genetic feature occurs today.

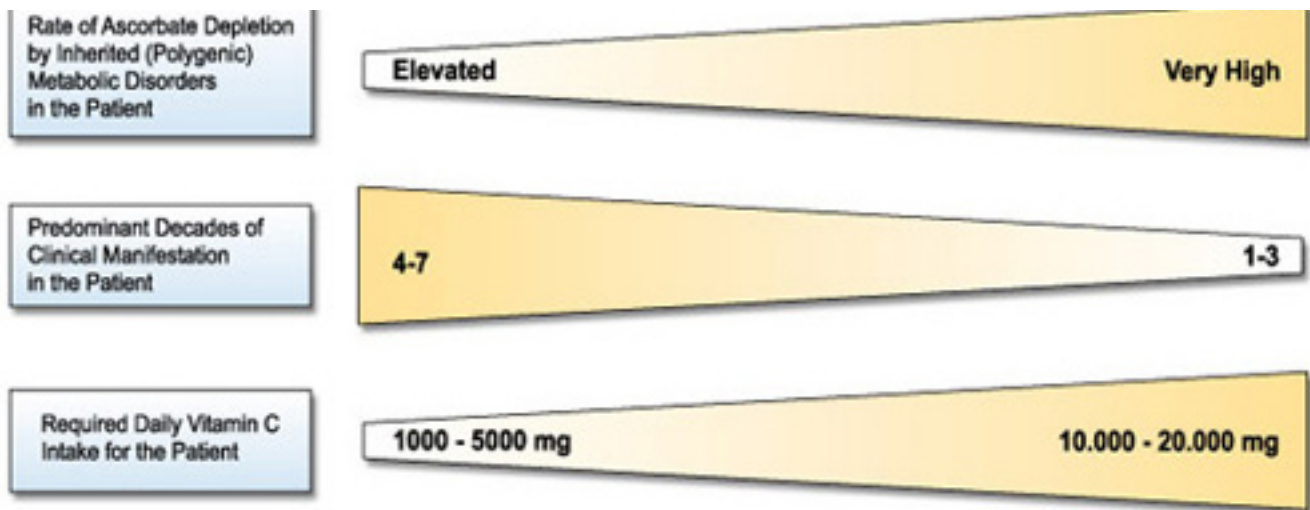


Figure 3.

The relation between ascorbate depletion and the onset of clinical symptoms in the patient. As a result of most genetic defects the rate constants for certain metabolic reactions are decreased. Ascorbate is destroyed in the attempt to normalize these decreased rate constants and in compensatory metabolic pathway. 1,22 The overall rate of ascorbate depletion in an individual is largely determined by the polygenic pattern of metabolic disorders in an individual (and to some extent also by exogenous risk factors). The earlier the body ascorbate reserves are depleted without being resupplemented the earlier the clinical manifestation occurs. Consequently, the higher the probability of early clinical onset of a latent genetic predisposition, the higher is the amount of required ascorbate intake to prevent this onset. For patients at high risk dietary ascorbate intake is recommended in the range of 10,000 to 20,000 mg/d. This corresponds to the amount of ascorbate our ancestors synthesized in their bodies before they lost this ability. The validity of Figure 3 is not limited to CVD. Ascorbate deficiency, of course, also unmasks latent disorders predisposing to cancer and to autoimmune and other diseases.

7. The deposition of Lp(a) is the most effective, most specific, and therefore most frequent of these mechanisms. Lp(a) is preferentially deposited at predisposition sites. In chronic ascorbate deficiency the accumulation of Lp(a) leads to the localized development of atherosclerotic plaques and to myocardial infarction and stroke.

8. Another frequent inherited lipoprotein disorder is hypoalphalipoproteinemia. The frequency of this disorder again reflects its usefulness during evolution. The metabolic upregulation of HDL synthesis by ascorbate became an important mechanism to reverse and decrease existing lipid deposits in the vascular wall.

9. The vascular defense mechanisms associated with most genetic disorders is unspecific. These mechanisms can aggravate the development of atherosclerotic plaques at predisposition sites. Other nonspecific mechanisms lead to peripheral forms of atherosclerosis by causing a thickening of the vascular wall throughout the cardiovascular system. This peripheral form of vascular disease is characteristic for angiopathies associated with Type III hyperlipidemia, diabetes, and many other inherited metabolic diseases.

10. Of particular advantage during evolution and therefore particularly frequent today are those genetic features that protect the ascorbate-deficient vascular wall until the end of the reproduction age. By favoring these disorders nature decided for the lesser of two evils: the death from CVD after the reproduction age rather than death from scurvy at a much earlier age. This also explains the rapid increase of the CVD mortality today from the 4th decade onwards.

11. After the loss of endogenous ascorbate production the genetic mutation rate in our ancestors increased significantly (21). This was an additional precondition favouring not only the advantage of apo(a) and Lp(a) but also of many other genetic countermeasures associated with CVD.

12. Genetic predispositions are characterized by the rate of ascorbate depletion in a multitude of metabolic reactions specific for the genetic disorder (22). The overall rate of ascorbate depletion in an individual is largely determined by polygenic

pattern of disorders. The earlier the ascorbate reserves in the body are depleted without being resupplemented, the earlier CVD develops.

13. The genetic predispositions with the highest probability for early clinical manifestation require the highest amount of ascorbate resupplementation in the diet to prevent CVD development. The amount of ascorbate for patients at high risk should be comparable to the amount of ascorbate our ancestors synthesized in their body before they lost this ability: between 10,000 and 20,000 milligrams per day.

14. Optimum ascorbate resupplementation prevents the development of CVD independent of the individual predisposition or pathomechanism. Ascorbate reduces existing atherosclerotic deposits and thereby decreases the risk for myocardial infarction and stroke. Moreover, ascorbate can prevent blindness and organ failure in diabetic patients, thromboembolism in homocystinuric patients and many other manifestations of CVD.

Conclusion

In this paper we present a unified theory of human CVD. This disease is the direct consequence of the inability of man to synthesize ascorbate in combination with insufficient intake of ascorbate in the modern diet. Since ascorbate deficiency is the common cause of human CVD, ascorbate resupplementation is the universal treatment for this disease. The available epidemiological and clinical evidence is reasonably convincing. Further clinical confirmation of this theory should lead to the abolition of CVD as a cause of human mortality for the present generation and future generations of mankind.

Acknowledgments

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References

1. Rath, M, Pauling L. Solution of the puzzle of human cardiovascular disease: Its primary cause is ascorbate deficiency, leading to the deposition of lipoprotein(a) and fibrinogen/fibrin in the vascular wall. Journal of Orthomolecular Med 1991;6:125-134.

Appendix B

Copied from web page

http://www.lef.org/featured-articles/may2000_vitamin_c_01.html

The news media has disseminated several articles over the last few months implying that dietary supplements are useless and dangerous. The basis for these articles are press releases from mainstream supported groups such as the American Heart Association and American Cancer Society. These organizations receive financial grants from the pharmaceutical industry, and have openly expressed their bias against dietary supplements in court briefs filed in support of FDA regulatory restriction.

Negative media hype against dietary supplements is nothing new, as the popular press has displayed a historical prejudice against dietary supplements that dates back to the 1940's. For instance, in 1984 the press warned against taking vitamins because conventional doctors said that high potency supplements could cause liver and kidney damage. The Life Extension Foundation reacted immediately to these allegations by testing the blood of 200 members who had been taking massive doses of supplements for years. These blood tests showed there to be zero toxicity in healthy people taking high potency supplements, and the press never again published this fictitious information that had no basis in fact to begin with.

The Life Extension Foundation has continued its reactionary tradition by conducting larger scale blood screening tests of Foundation members. Last year we published an article based on original research at our diagnostic laboratory showing that 50% of our members were not taking enough TMG or vitamin B6 to adequately suppress homocysteine to guard against atherosclerosis. (For specific details, refer to the October 1999 issue of Life Extension magazine.) In response to the American Heart Association's most recent attack on vitamin C, we are proud to present the following article based on actual high resolution carotid ultrasound tests of Life Extension Foundation members who have been taking high potency supplements for many years.

Refer to the Abstracts section for reprint rebuttals to the American Heart Association's attack on vitamin C from the Linus

Pauling Institute, The Vitamin C Foundation and Dr. Robert Cathcart.

**A pilot study to ascertain
carotid artery status in high
potency vitamin C supplement takers**

by Paul Wand, M.D. Neurologist

Atherosclerosis is an insidious disease that begins in youth, but often accelerates as humans age resulting in the manifestation of cardiovascular disease. 1,2,92,93 Vitamin C has been explored as an agent that may protect against atherosclerosis and cardiovascular disease. 3-14 The most significant finding came from a published study involving 11,348 adults over a 10 year period. This study showed that males taking the highest amount of vitamin C had a 45% reduction in all cause mortality, a 22% reduction in cancer incidence and a 42% reduction in heart attack risk.¹⁵

An in-depth analysis of published studies on vitamin C and cardiovascular disease, however, makes it difficult for the vitamin C user to extrapolate how the results may apply to them individually. For instance, some studies define high-dose as only 250-500 mg a day of vitamin C, 16-19 whereas the serious vitamin user often consumes between 2,000 and 12,000 mg a day of vitamin C.

To put this into perspective, we conducted a Medline search to evaluate published studies showing the effects on humans of various doses of vitamin C as it related to any parameter of cardiovascular disease risk. This database search covered the time period of January 1, 1990 to April 25, 2000. Table 1 reveals the results of this search as it relates to vitamin C dosage and cardiovascular risk factors.

Table 1. Effects of Vitamin C on Cardiovascular Disease Risk

1 study showed favorable response when under 500 mg was administered 53

- - -

30 studies showed favorable response when over 500 mg was administered 54-83

- - -

3 studies showed no response when under 500 mg was administered 84-86

- - -

4 studies showed no response when over 500 mg was administered 87-90

Based on the published literature over the last ten years, it would appear that higher potency vitamin C supplements have some effect in reducing cardiovascular disease risk, whereas potencies lower than 500 mg a day may have no effect. It is important to note that the human studies presented on Table 1 on the following page do not include the published molecular research of Linus Pauling, Matthias Rath and others who are largely responsible for convincing health conscious people that supplementation with greater than 2000 mg a day of vitamin C reduces cardiovascular disease risk. More on the research of Linus Pauling, et al will appear later in this article.

When attempting to assess the benefits in humans who take very high doses of supplements, such as those taking in excess of 2000 mg a day of vitamin C, a serious gap exists in the published literature. A significant confounding factor is that people taking in excess of 2000 mg a day of vitamin C usually take other nutrients that have been shown to reduce the risk of cardiovascular disease such as coenzyme Q10, 20-25 vitamin E, 91,176,177 vitamin B12, 27 vitamin B6, 28,29 and folic acid. 30-40 It therefore becomes difficult, using epidemiological data, to

ascertain the real effects of very high dose vitamin C supplementation on human populations who are taking a wide variety of nutrients in addition to vitamin C.

Why some people take very high doses of vitamin C

An impressive body of research indicates potential health benefits when very high doses of vitamin C are taken over an extended time period. We will define every high dose from here on out as vitamin C intake in excess of 2000 mg a day.

Some of the notable doctors and scientists who have endorsed very high dose vitamin C supplementation include Linus Pauling, Abram Hoffer, Robert Cathcart, Matthias Rath, Irwin Stone, Frederick R. Klenner, Durk Pearson and Sandy Shaw and host of others. These doctors and scientists have authored books and scientific papers that document the benefits of very high dose vitamin C supplementation. In response to these publications, a sub-fraction of the American public has chosen to personally consume 2000 to 12,000 mg a day of vitamin C.

A consistent theory among doctors endorsing very high dose vitamin C supplementation is that it works by specially defined mechanisms to reduce the incidence of artery disease. Linus Pauling, along with his associate Matthias Rath, MD, have published data showing that arteries harden in the absence of sufficient vitamin C. They cite research showing that when the dietary intake of vitamin C is low, collagen production is limited, and arteries tend to become thinner and weaker from wear and tear. Plaque deposits (atherosclerosis) then form to compensate for this weakness. The Pauling/Rath theory, published in both conventional and alternative medicine circles, holds that the root cause of atherosclerotic plaque deposits is a chronic vitamin deficiency.

94-98

Given the credentials of the doctors and scientists advocating very high dose vitamin C supplementation, and the widespread dissemination of their publications in the United States, a sub-fraction of the American population believes that very high dose vitamin C supplementation (along with nutrients such as vitamin E, B6, folate, coenzyme Q10, etc.) will reduce the formation of atherosclerotic plaque and the subsequent development of common forms of cardiovascular disease.

Why conventional doctors doubt the value of vitamin C

The medical profession has traditionally been biased against dietary supplements for a variety of economic and political reasons. As mentioned earlier in this article, there are published studies that show that vitamin C fails to confer a protective effect in reducing cardiovascular disease risk. While the majority of studies (31 favorable studies compared to 7 showing no response) indicate that vitamin C supplements reduce cardiovascular disease risk factors, it appears that the few studies showing no benefit carry great weight in the medical profession. Conventional physicians also tend to be unenlightened about 76 additional human studies published since 1990 showing that vitamin C confers other health benefits such as lowered risks of cancer and other diseases. 99-174

Mainstream organizations have a propensity to look at studies showing no health benefit when vitamin C is consumed in low doses, and then make a public announcement that insufficient evidence exists to recommend widespread vitamin supplementation. The news media is quick to report on studies that show that vitamin C may not protect against cardiovascular disease, without presenting the counter view that not enough vitamin C was consumed in the particular study to provide the expected benefit.

So, despite a rather intensive amount of research that has occurred over the past 10 years, we are still without a scientific consensus as to whether vitamin C is protective against cardiovascular or other diseases, ergo the continued debate over the value of vitamin C supplementation.

The latest controversy

At a meeting of the American Heart Association held on March 2, 2000, a presentation was made of an unpublished trial indicating that those who consumed high amounts of vitamin C supplements had increased carotid intima-media wall thickening over an 18-month time period. 41 The doctors who made this presentation described high amounts of vitamin C as up to 500 mg a day. This presentation contradicts previous published studies showing that vitamin C protects against carotid atherosclerosis and intima-

media wall thickening. 42

In response to this unpublished American Heart Association presentation, The Life Extension Foundation asked me to oversee a pilot study of 30 people who had been taking very high doses of vitamin C (and other nutrients) for at least four years.

The objective of this study was to ascertain whether those who have consumed more than 2000 mg a day of vitamin C have a greater or lesser degree of carotid artery wall thickening and atherosclerotic plaque in relationship to their age and other risk factors.

The subjects in our test group ranged from age 45 to 81 years, with a median age of 61. Our test subjects were significantly older than the group tested by the American Heart Association.

The procedure used to evaluate the carotid arteries of these 30 subjects was a high resolution ultrasound of the carotids with doppler evaluation. Multiple sonographic scans were obtained through the area of the right and left carotid systems. This test enabled me to ascertain if there was atherosclerotic plaque present, the degree of intima-media thickening if any, blood flow velocity and the percentage of stenosis (narrowing or blockage), if any. I routinely use this test to help determine if neurologic deficit is caused by carotid artery disease. It is not uncommon for me to detect 60% to 90% blockage in the carotid arteries of patients, along with significant increase of carotid blood flow velocity and severe intima-media thickening. Lay readers should know that increased blood flow velocity is indicative of greater carotid artery stenosis (narrowing).

I was surprised that the doctors who made the presentation at the American Heart Association conference only tested for carotid intima-media thickening. This is only one of four parameters that can be evaluated via carotid ultrasound testing. I believe the American Heart Association doctors should have also checked for carotid atherosclerotic plaque, stenosis and blood flow velocity, in addition to intima-media thickening. Of all parameters that can be evaluated, intima-media wall thickening is the least important factor. Atherosclerotic plaque, stenosis and blood flow velocity are far more important indicators of underlying carotid disease.

The results of The Life Extension Foundation™s four-pronged carotid ultrasound test showed that in 23 out of 30 of these very high vitamin C supplement takers, there was no evidence of carotid plaque formation, obstruction (stenosis) or intima-media thickening. Blood flow velocity through the carotids was completely normal in these 23 subjects.

In seven cases, there was some evidence of carotid pathology, but the extent of disease was insignificant with the exception of two persons who showed carotid stenosis of 30% and 40%. Based on the advanced age of these two subjects, the 30 and 40% stenosis observed was not considered abnormal and was not indicative of a clinically significant disease state.

In the seven cases showing some evidence of carotid pathology, preliminary follow up has at the time of this publication revealed elevated levels of homocysteine, LDL cholesterol and/or glucose as potential causative factors. Additional blood testing of these seven subjects will be conducted to evaluate serum iron, Creactive protein, LDL particle size, fibrinogen and other potential risk factors for carotid stenosis. When adjusting for age and other confounding factors such as high cholesterolhomocysteine, the slight to moderate carotid pathology detected in these 7 out of 30 subjects is below what would be normally expected.

Overall, this group of very high vitamin C supplement takers showed remarkably healthy carotid arteries, with 23 out of 30 having absolutely no sign of intima-media thickening, blood flow restriction, atherosclerosis or stenosis.

Our pilot study of 30 subjects differed from the American Heart Association study in the following ways

The American Heart Association tested people aged 40 to 60. We thought age 40 was too young to observe significant carotid artery disease in asymptomatic people, so we tested people beginning at age 45. We had no upper age cutoff limit, and tested many people in their 60s, 70s and one 81-year-old.

The American Heart Association only tested for carotid intima-media thickening, while we tested for carotid atherosclerosis,

stenosis and blood flow velocity, in addition to intima-media thickening. Atherosclerotic plaque, stenosis and blood flow velocity are far more important indicators of underlying disease than intima-media thickening.

The upper limit for vitamin C intake was apparently 500 mg in the American Heart Association study. Our subjects, on the other hand, consumed well over 2,000 mg a day of vitamin C along with potent doses of other nutrients purported to reduce risk of atherosclerosis and cardiovascular disease.

If we had set a cutoff of 60 years of age like the American Heart Association did, we would have found that none of our test subjects would have shown clinically significant carotid artery pathology. In other words, had we used the same narrow parameters (under age 60) that were presented at the American Heart Association meeting, we would have had no carotid artery pathology to report in this group of people who take very high doses of supplements.

Since aging is a risk factor in the development of carotid artery disease, we choose to evaluate a much older group (45 to 81 years) of people consuming greater levels of vitamin C and other nutrients. By testing an older age group, we obtained a more clinically significant picture of the carotid artery status of people who have consumed very high doses of vitamin C and other nutrients for long periods of time.

Additional considerations

It is well established that excess iron accelerates atherosclerosis, and one study specifically showed that high levels of iron cause carotid atherosclerosis 43 . It is therefore possible that the people in the American Heart Association study who were taking low potency vitamin C supplements were consuming a multi-vitamin that contained a relatively high level of iron. There is also a possibility that these relatively low-potency vitamin C supplements were causing excess iron absorption from food, but not enough vitamin C to protect against iron-induced LDL cholesterol oxidation that could have contributed to the intima-media thickening observed in the American Heart Association presentation.

Previously published research shows vitamin C as either having a protective effect, or no effect in the development of carotid artery disease. The most significant positive study was published in the American Heart Association™s own journal 42 and measured the relationship between the intake of dietary and supplemental vitamin C, vitamin E and provitamin A carotenoids and average carotid artery wall thickness. In 6,318 female and 4,989 male participants 45 to 64 years old, carotid artery intima-media wall thickness was measured as an indicator of atherosclerosis at multiple sites with ultrasound testing. Among men and women over age 55 who had not recently begun a special diet, those in the high vitamin C intake group showed significantly less average carotid artery wall thickness adjusted for age, body mass index, fasting serum glucose, systolic and diastolic blood pressures, HDL and LDL cholesterol, total caloric intake, cigarette use, race and education. Vitamin C showed an 81% protective effect in women and a 65% protective effect in men. The doctors concluded by stating:

"These data provide limited support for the hypothesis that dietary vitamin C and alpha-tocopherol may protect against atherosclerotic disease, especially in individuals over 55 years old."

Carotid endarterectomy is a surgical procedure used to remove atherosclerotic plaque in the carotid artery. In a study of 45 people undergoing this procedure, the lower the plasma content in vitamin C over a 12-month period, the higher the percentage of vessel re-narrowing after endarterectomy. This study implies that even in advanced cases of carotid stenosis, supplemental vitamin C may be of benefit in preventing further occlusion. 44

Another study involved the feeding of oxidized lab chow along with vitamin C and iron to rabbits for four weeks to induce experimental atherosclerosis. These rabbits had been fed a trans-fatty acid rich diet for 36 weeks prior. Administration of coenzyme Q10 after the feeding of a trans-fatty acid-rich diet showed a decrease in coronary atherosclerosis, artery plaque size and atherosclerosis scores when compared to the placebo group. 45 This study indicates that supplemental coenzyme Q10 may be required when people take vitamin C and iron supplements.

While Linus Pauling, Matthias Rath and others make a good case

that vitamin C protects against atherosclerosis, there are studies suggesting that garlic, 46 homocysteine-lowering nutrients folate, 30-38 B6, 28 B12, 26,27 TMG (trimethylglycine), 47-50 and calcium regulating nutrients such as vitamin K 51 provide even greater benefits. One study on people with elevated homocysteine showed that supplementation with folic acid, vitamins B12 and B6 resulted in a regression in carotid artery stenosis within one year as measured by ultrasound testing. 52

Conclusions

Our direct observation, based on carotid ultrasound testing, show that very high vitamin C supplement users have remarkably healthy carotid arteries. When adjusted for other factors such as age, elevated homocysteine, LDL cholesterol and glucose, these very high vitamin C takers as a group appear to have less carotid pathology than the general population. A review of previously published findings indicates that consuming a wide variety of very high potency dietary supplements, combined with blood screening to monitor cholesterol, homocysteine, glucose, iron and other atherogenic risk factors, confers a significant protective effect against the development of carotid artery disease.

References

1. Oalman MC, et al. Atherosclerosis in youth: are hypertension and other coronary heart disease risk factors already at work? *Pediatr Nephrol* 1997 Feb;11(1):99-107.
2. Celermajer DS, et al. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. *J Am Coll Cardiol* 1994 Aug;24(2):471-6.
3. Siow RC, et al. Vitamin C protects human vascular smooth muscle cells against apoptosis induced by moderately oxidized LDL containing high levels of lipid hydroperoxides. *Arterioscler Thromb Vasc Biol* 1999 Oct;19(10):2387-94.
4. Frei B. On the role of vitamin C and other antioxidants in atherogenesis and vascular dysfunction. *Proc Soc Exp Biol Med* 1999 Dec;222(3):196-204.
5. Siow RC, et al. Induction of antioxidant stress proteins in

- vascular endothelial and smooth muscle cells: protective action of vitamin C against atherogenic lipoproteins. *Free Radic Res* 1999 Oct;31 (4):309-18.
6. Kanani PM, et al. Role of oxidant stress in endothelial dysfunction produced by experimental hyperhomocyst(e)inemia in humans. *Circulation* 1999 Sep 14;100(11):1161-8
 7. Gokce N, et al. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1999 Jun 29;99(25):3234-40
 8. Clemetson CA. The key role of histamine in the development of atherosclerosis and coronary heart disease. *Med Hypotheses* 1999 Jan;52(1):1-8
 9. Carr AC, et al. Vitamin C protects against and reverses specific hypochlorous acid- and chloramine-dependent modifications of low-density lipoprotein. *Biochem J* 2000 Mar 1;346 Pt 2:491-9.
 10. Valkonen MM, et al. Vitamin C prevents the acute atherogenic effects of passive smoking. *Free Radic Biol Med* 2000 Feb 1;28(3):428-36.
 11. Jialal I. The effect of antioxidant dietary micronutrients on LDL oxidation: Implications for atherosclerosis prevention. *Canadian Journal of Cardiology (Canada)* 1993, 9/SUPPL. B (11B-13B).
 12. Singh RB, et al. Usefulness of antioxidant vitamins in suspected acute myocardial infarction (the Indian Experiment of infarct survival-3). *Am J Cardiol* 1996 Feb 1;77(4):232-6.
 13. Ness AR, et al. Vitamin C and cardiovascular disease: a systematic review. *J Cardiovasc Risk* 1996 Dec; 3(6):513-21.
 14. Wilkinson IB, et al. Oral vitamin C reduces arterial stiffness and platelet aggregation in humans. *J Cardiovasc Pharmacol* 1999 Nov;34(5):690-3.
 15. Enstrom JE, et al. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology* 1992 May;3(3):194-202
 16. Azen SP, et al. Effect of supplementary antioxidant vitamin intake on carotid arterial wall intima-media thickness in a controlled clinical trial of cholesterol lowering. *Circulation* 1996 Nov 15;94(10):2369-72.
 17. Galley HF, et al. Combination oral antioxidant supplementation reduces blood pressure. *Clin Sci (Colch)* 1997 Apr;92(4):361-5.
 18. Mosca L, et al. Antioxidant nutrient supplementation reduces the susceptibility of low density lipoprotein to oxidation in patients with coronary artery disease. *J Am Coll Cardiol* 1997

Aug;30 (2):392-9.

19. Paolini M, et al. The nature of prooxidant activity of vitamin C. *Life Sci* 1999;64(23):PL 273-8.

20. Kogan AKh, et al. [The antioxidant protection of the heart by coenzyme Q10 in stable stenocardia of effort]. *Patol Fiziol Eksp Ter* 1999 Oct-Dec;(4):16-9.

21. Singh RB, et al. Serum concentration of lipoprotein(a) decreases on treatment with hydrosoluble coenzyme Q10 in patients with coronary artery disease: discovery of a new role. *Int J Cardiol* 1999 Jan;68(1):23-9.

22. Singh RB, et al. Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction. *Cardiovasc Drugs Ther* 1998 Sep;12(4):347-53

23. Hanaki Y, et al..Coenzyme Q10 and coronary artery disease. *Clin Investig* 1993;71(8 Suppl):S112-5.

24. Kato T, et al. Reduction in blood viscosity by treatment with coenzyme Q10 in patients with ischemic heart disease. *Int J Clin Pharmacol Ther Toxicol* 1990 Mar;28(3):123-6

25. Langsjoen PH, et al. Effective and safe therapy with coenzyme Q10 for cardiomyopathy. *Klin Wochenschr* 1988 Jul 1;66(13):583-90.

26. Siri PW, et al. Vitamins B6, B12, and folate: association with plasma total homocysteine and risk of coronary atherosclerosis. *J Am Coll Nutr* 1998 Oct;17 (5):435-41.

27. Verhoef P, et al. Homocysteine metabolism and risk of myocardial infarction: relation with vitamins B6, B12, and folate. *Am J Epidemiol* 1996 May 1;143(9):845-59.

28. Shimakawa T, et al. Vitamin intake: a possible determinant of plasma homocyst(e)ine among middle-aged adults. *Ann Epidemiol* 1997 May;7 (4):285-93.

29. Chasan-Taber L, et al. A prospective study of folate and vitamin B6 and risk of myocardial infarction in US physicians. *J Am Coll Nutr* 1996 Apr;15(2):136-43

30. Woodside JV, et al. Published erratum appears in *Am J Clin Nutr* 1998 Sep;68(3):758 Effect of B-group vitamins and antioxidant vitamins on hyperhomocysteinemia: a double-blind, randomized, factorial-design, controlled trial. *Am J Clin Nutr* 1998 May;67(5):858-66

31. Selhub J, et al. Relationship between plasma homocysteine, vitamin status and extracranial carotid-artery stenosis in the Framingham Study population. *J Nutr* 1996 Apr;126(4 Suppl):1258S-65S.

32. Fenech MF. Folate, vitamin B12, homocysteine status and

- chromosome damage rate in lymphocytes of older men. *Carcinogenesis* 1997 JUL;18(7):1329-1336.
33. Verhoef P, et al. Homocysteine metabolism and risk of myocardial infarction: relation with vitamins B6, B12, and folate. *Am J Epidemiol* 1996 May 1;143(9):845-59.
34. Bottiglieri T. Folate, vitamin B-12, and neuropsychiatric disorders. *Nutr Rev* 1996 Dec;54 (12):382-390
35. Young PB, et al. Lipid peroxidation induced in vivo by hyperhomocysteinaemia in pigs. *Atherosclerosis* 1997 Feb 28;129(1):67-71.
36. Malinow MR, et al. Reduction of plasma homocyst(e)ine levels by breakfast cereal fortified with folic acid in patients with coronary heart disease. *N Engl J Med* 1998 Apr 9;338(15):1009-15.
37. Ubbink JB, et al.. Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia. *Am J Clin Nutr* 1993 Jan;57(1):47-53.
38. Ubbink JB, et al. Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia. *Am J Clin Nutr* 1993 Jan;57(1):47-53.
39. Robinson K, et al. Hyperhomocysteinemia and low pyridoxal phosphate. Common and independent reversible risk factors for coronary artery disease. *Circulation* 1995 Nov 15;92(10):2825-30
40. Verhoef P, et al. Folate and coronary heart disease. *Curr Opin Lipidol* 1998 Feb;9(1):17-22
41. James H Dwyer, et al. Vitamin C Supplement Intake and Progression of Carotid Atherosclerosis. the Los Angeles Atherosclerosis Study American Heart Association meeting presentation March 2000.
42. Kritchevsky SB, et al. Dietary antioxidants and carotid artery wall thickness. The ARIC Study. *Atherosclerosis Risk in Communities Study. Circulation* 1995 Oct 15;92(8):2142-50.
43. Kiechl S, et al. Body iron stores and the risk of carotid atherosclerosis: prospective results from the Bruneck study. *Circulation* 1997 Nov 18;96 (10):3300-7.
44. Mezzetti A, et al. Increased systemic oxidative stress after elective endarterectomy: relation to vascular healing and remodeling. *Arterioscler Thromb Vasc Biol* 1999 Nov;19(11):2659-65.
45. Singh RB, et al. Effect of coenzyme Q10 on experimental atherosclerosis and chemical composition and quality of atheroma in rabbits. *Atherosclerosis* 1999 Feb;148(2):275-82.
46. Koscielny J, et al. The antiatherosclerotic effect of *Allium sativum*. *Atherosclerosis* 1999 May;144 (1):237-49.
47. Duell PB, et al. Homocyst(e)ine: an important risk factor

- for atherosclerotic vascular disease. *Curr Opin Lipidol* 1997 Feb;8(1):28-34
48. Malinow MR. Plasma homocyst(e)ine and arterial occlusive diseases: a mini-review. *Clin Chem* 1995 Jan;41(1):173-6.
49. Mar MH, et al. Betaine in wine: answer to the French paradox? *Med Hypotheses* 1999 Nov;53 (5):383-5.
50. Wang JA, et al. Betaine:homocysteine methyltransferase--a new assay for the liver enzyme and its absence from human skin fibroblasts and peripheral blood lymphocytes. *Clin Chim Acta* 1991 Dec 31;204(1-3):239-49.
51. Jie KG, et al. Vitamin K status and bone mass in women with and without aortic atherosclerosis: a population-based study. *Calcif Tissue Int* 1996 Nov;59(5):352-6.
52. Hackam DG, et al. What level of plasma homocyst(e)ine should be treated? Effects of vitamin therapy on progression of carotid atherosclerosis in patients with homocyst(e)ine levels above and below 14 micromol/L. *Am J Hypertens* 2000 Jan;13 (1 Pt 1):105-10.
53. Khaw KT, et al. Interrelation of VITAMIN C, infection, haemostatic factors, and cardiovascular disease. *BMJ* 1995 Jun 17;310(6994):1559-63.
54. Gokce N, et al. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1999 Jun 29;99(25):3234-40.
55. Chambers JC, et al. Demonstration of rapid onset vascular endothelial dysfunction after hyperhomocysteinemia: an effect reversible with vitamin c therapy. *Circulation* 1999 Mar 9;99(9):1156-60.
56. Wilkinson IB, et al. Oral vitamin C reduces arterial stiffness and platelet aggregation in humans. *J Cardiovasc Pharmacol* 1999 Nov;34(5):690-3.
57. Jeserich M, et al. Vitamin C improves endothelial function of epicardial coronary arteries in patients with hypercholesterolaemia or essential hypertension--assessed by cold pressor testing. *Eur Heart J* 1999 Nov;20(22):1676-80.
58. Frei B. On the role of vitamin C and other antioxidants in atherogenesis and vascular dysfunction. *Proc Soc Exp Biol Med* 1999 Dec;222(3):196-204.
59. Nappo F, et al. Impairment of endothelial functions by acute hyperhomocysteinemia and reversal by antioxidant vitamins. *JAMA* 1999 Jun 9;281 (22):2113-8
60. McAuliffe AV, et al. Administration of ascorbic acid and an aldose reductase inhibitor (tolrestat) in diabetes: effect on urinary albumin excretion. *Nephron* 1998 Nov;80(3):277-84.

61. Solzbach U, et al. Circulation 1997 Sep 2;96(5):1513-9. Vitamin c improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients.
62. Ting HH, et al. VITAMIN C improves endotheliumdependent vasodilation in forearm resistance vessels of humans with hypercholesterolemia. Circulation 1997 Jun 17;95(12):2617-22.
63. Mosca L, et al. Antioxidant nutrient supplementation reduces the susceptibility of low density lipoprotein to oxidation in patients with coronary artery disease. J Am Coll Cardiol 1997 Aug;30 (2):392-9.
64. Levine GN, et al. Ascorbic acid reverses endothelial vasomotor dysfunction in patients with coronary artery disease. Circulation 1996 Mar 15;93(6):1107-13
65. Fuller CJ, et al. Effect of ascorbate supplementation on low density lipoprotein oxidation in smokers. Atherosclerosis 1996 Jan 26;119(2):139-50.
66. Valkonen MM, et al. Vitamin C prevents the acute atherogenic effects of passive smoking. Free Radic Biol Med 2000 Feb 1;28(3):428-36.
67. Schwille PO, et al. Postprandial hyperinsulinaemia, insulin resistance and inappropriately high phosphaturia are features of younger males with idiopathic calcium urolithiasis: attenuation by Ascorbic acid supplementation of a test meal. Urol Res 1997;25(1):49-58.
68. Zhang J, et al. A single high dose of vitamin C counteracts the acute negative effect on microcirculation induced by smoking a cigarette. Microvasc Res 1999 Nov;58(3):305-11.
69. Purkayastha SS, et al. Effect of vitamin C and E in modulating peripheral vascular response to local cold stimulus in man at high altitude. Jpn J Physiol 1999 Apr;49(2):159-67.
70. Chamiec T, et al. Effects of antioxidant vitamins C and E on signal-averaged electrocardiogram in acute myocardial infarction. Am J Cardiol 1996 Feb 1;77(4):237-41.
71. Weber C, et al. Increased adhesiveness of isolated monocytes to endothelium is prevented by VITAMIN C intake in smokers. Circulation 1996 Apr 15;93 (8):1488-92.
72. Gatto LM, et al. Ascorbic acid induces a favorable lipoprotein profile in women. J Am Coll Nutr 1996 Apr;15(2):154-8.
73. Singh RB, et al. Usefulness of antioxidant vitamins in suspected acute myocardial infarction (the Indian Experiment of infarct survival-3). Am J Cardiol 1996 Feb 1;77(4):232-6
74. Munoz JA, et al. Effect of VITAMIN C on lipoproteins in healthy adults. Ann Med Interne (Paris) 1994;145(1):13-9.

75. Tomoda H, et al. Possible prevention of postangioplasty restenosis by Ascorbic acid. *Am J Cardiol* 1996 Dec 1;78(11):1284-6.
76. Laskowski H, et al. Mortality and clinical course of patients with acute myocardial infarction treated with streptokinase and antioxidants: mannitol and Ascorbic acid. *Int J Cardiol* 1995 Mar 3;48(3):235-7.
77. Eriksson J, et al. Magnesium and Ascorbic acid supplementation in diabetes mellitus. *Ann Nutr Metab* 1995;39(4):217-23.
78. Gilligan DM, et al. Effect of antioxidant vitamins on low density lipoprotein oxidation and impaired endothelium-dependent vasodilation in patients with hypercholesterolemia. *J Am Coll Cardiol* 1994 Dec;24(7):1611-7.
79. Cerna O, et al. Plasma lipids, lipoproteins and atherogenic index in men and women administered vitamin c. *Cor Vasa* 1992;34(3):246-54.
80. Barta E, et al. Protective effect of alpha-tocopherol and L-ascorbic acid against the ischemic-reperfusion injury in patients during open-heart surgery. *Bratisl Lek Listy* 1991 Mar-Apr;92(3-4):174-83.
81. Salonen JT, et al. Effects of antioxidant supplementation on platelet function: a randomized pairmatched, placebo-controlled, double-blind trial in men with low antioxidant status. *Am J Clin Nutr* 1991 May;53(5):1222-9.
82. Hornig B, et al. Vitamin c improves endothelial function of conduit arteries in patients with chronic heart failure. *Circulation* 1998 Feb 3;97(4):363-8.
83. Heitzer T, et al. Antioxidant vitamin c improves endothelial dysfunction in chronic smokers. *Circulation* 1996 Jul 1;94(1):6-9.
84. Azen SP, et al. Effect of supplementary antioxidant vitamin intake on carotid arterial wall intima-media thickness in a controlled clinical trial of cholesterol lowering. *Circulation* 1996 Nov 15;94(10):2369-72.
85. Mayer-Davis EJ, et al. Vitamin c intake and cardiovascular disease risk factors in persons with noninsulin-dependent diabetes mellitus. From the Insulin Resistance Atherosclerosis Study and the San Luis Valley Diabetes Study. *Prev Med* 1997 May-Jun;26(3):277-83.
86. Calzada C, et al. The influence of antioxidant nutrients on platelet function in healthy volunteers. *Atherosclerosis* 1997 Jan 3;128(1):97-105.
87. Bostom AG, et al. The effect of high-dose ascorbate sup-

- plementation on plasma lipoprotein(a) levels in patients with premature coronary heart disease. *Pharmacotherapy* 1995 Jul-Aug;15(4):458-64.
88. Jacques PF, et al. Effect of VITAMIN C supplementation on lipoprotein cholesterol, apolipoprotein, and triglyceride concentrations. *Ann Epidemiol* 1995 Jan;5(1):52-9.
89. Kelly TH, et al. Response patterns and cardiovascular effects during response sequence acquisition by humans. *J Exp Anal Behav* 1991 Nov;56(3):557-74.
71. Weber C, et al. Increased adhesiveness of isolated monocytes to endothelium is prevented by VITAMIN C intake in smokers. *Circulation* 1996 Apr 15;93(8):1488-92.
90. Westhuyzen J, et al. Effect of preoperative supplementation with alpha-tocopherol and ascorbic acid on myocardial injury in patients undergoing cardiac operations. *J Thorac Cardiovasc Surg* 1997 May;113(5):942-8.
91. Pryor WA. Vitamin E and heart disease: basic science to clinical intervention trials. *Free Radic Biol Med* 2000 Jan 1;28(1):141-64.
92. Strong JP, et al. Early lesions of atherosclerosis in childhood and youth: natural history and risk factors. *J Am Coll Nutr* 1992 Jun;11 Suppl:51S-54S.
93. Strong JP, et al. Early lesions of atherosclerosis in childhood and youth: natural history and risk factors. *J Am Coll Nutr* 1992 Jun;11 Suppl:51S-54S.
94. Rath M, et al. Hypothesis: lipoprotein(a) is a surrogate for ascorbate. *Proc Natl Acad Sci U S A* 1990 Aug;87(16):6204-7
95. Rath M, et al. Immunological evidence for the accumulation of lipoprotein(a) in the atherosclerotic lesion of the hypoascorbemic guinea pig. *Proc Natl Acad Sci U S A* 1990 Dec;87(23):9388-90.
96. Matthias Rath, et al. Unified Theory of Human Cardiovascular Disease Leading the Way to the Abolition of this Disease as a Cause for Human Mortality. *Journal of Orthomolecular Medicine* (1992; 7: 5-15.).
97. Axel Niendorf, et al. Morphological detection and quantification of lipoprotein(a) deposition in atheromatous lesions of human aorta and coronary arteries. *Virchows Archives of Pathological Anatomy*, 1990, Number 417, Pages 105-111.
98. Matthias Rath, et al. Nutritional Supplement Program Halts Progression of Early Coronary Atherosclerosis Documented by Ultrafast Computed Tomography. *Journal of Applied Nutrition* (1996; 48: 68-78).

99. Tanaka H, et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch Surg* 2000 Mar;135(3):326-31.
100. Kodama N, et al. Cisternal irrigation therapy with urokinase and ascorbic acid for prevention of vasospasm after aneurysmal subarachnoid hemorrhage. Outcome in 217 patients. *Surg Neurol* 2000 Feb;53(2):110-7; discussion 117-8.
101. Sinclair S. Male infertility: nutritional and environmental considerations. *Altern Med Rev* 2000 Feb;5(1):28-38.
102. van Rooij J, et al. Oral vitamins C and E as additional treatment in patients with acute anterior uveitis: a randomised double masked study in 145 patients. *Br J Ophthalmol* 1999 Nov;83(11):1277-82.
103. Zollinger PE, et al. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. *Lancet* 1999 Dec 11;354(9195):2025-8.
104. Gorton HC, et al. The effectiveness of vitamin C in preventing and relieving the symptoms of virusinduced respiratory infections. *J Manipulative Physiol Ther* 1999 Oct;22(8):530-3.
105. Vermeer IT, et al. Effect of ascorbic acid and green tea on endogenous formation of N-nitrosodimethylamine and N-nitrosopiperidine in humans. *Mutat Res* 1999 Jul 16;428(1-2):353-61.
106. Reinhold U, et al. Treatment of progressive pigmented purpura with oral bioflavonoids and ascorbic acid: an open pilot study in 3 patients. *J Am Acad Dermatol* 1999 Aug;41(2 Pt 1):207-8.
107. Hemila H. Vitamin C supplementation and common cold symptoms: factors affecting the magnitude of the benefit. *Med Hypotheses* 1999 Feb;52(2):171-8.
108. Curhan GC, et al. Intake of vitamins B6 and C and the risk of kidney stones in women. *J Am Soc Nephrol* 1999 Apr;10(4):840-5.
109. Johnston CS. Biomarkers for establishing a tolerable upper intake level for vitamin C. *Nutr Rev* 1999 Mar;57(3):71-7.
110. Jarosz M, et al. Effects of high dose vitamin C treatment on *Helicobacter pylori* infection and total vitamin C concentration in gastric juice. *Eur J Cancer Prev* 1998 Dec;7(6):449-54.
111. McAuliffe AV, et al. Administration of ascorbic acid and an aldose reductase inhibitor (tolrestat) in diabetes: effect on urinary albumin excretion. *Nephron* 1998 Nov;80(3):277-84.
112. de la Fuente M, et al. Immune function in aged women is improved by ingestion of vitamins C and E. *Can J Physiol Pharmacol* 1998 Apr;76(4):373-80.

113. Allard JP, et al. Effects of vitamin E and C supplementation on oxidative stress and viral load in HIVinfected subjects. *AIDS* 1998 Sep 10;12(13):1653-9
114. Eberlein-Konig B, et al. Phototoxic lysis of erythrocytes from humans is reduced after oral intake of Ascorbic acid and d-alpha-tocopherol. *Photodermatol Photoimmunol Photomed* 1997 Oct-Dec;13(5-6):173-7
115. Alessio HM, et al. Exercise-induced oxidative stress before and after VITAMIN C supplementation. *Int J Sport Nutr* 1997 Mar;7(1):1-9.
116. Schwille PO, et al. Postprandial hyperinsulinaemia, insulin resistance and inappropriately high phosphaturia are features of younger males with idiopathic calcium urolithiasis: attenuation by Ascorbic acid supplementation of a test meal. *Urol Res* 1997;25(1):49-58.
117. VITAMIN C intake and susceptibility to the common cold. *Br J Nutr* 1997 Jan;77(1):59-72
118. Gustafsson U, et al..The effect of VITAMIN C in high doses on plasma and biliary lipid composition in patients with cholesterol gallstones: prolongation of the nucleation time. *Eur J Clin Invest* 1997 May;27(5):387-91.
119. Cohen HA, et al. Blocking effect of VITAMIN C in exercise-induced asthma. *Arch Pediatr Adolesc Med* 1997 Apr;151(4):367-70.
120. Jeng KC, et al. Supplementation with vitamins C and E enhances cytokine production by peripheral blood mononuclear cells in healthy adults. *Am J Clin Nutr* 1996 Dec;64(6):960-5.
121. Intake of vitamins A, C, and E and postmenopausal breast cancer. *Am J Epidemiol* 1996 Jul 15;144(2):165-74.
122. Reilly M, et al. Modulation of oxidant stress in vivo in chronic cigarette smokers. *Circulation* 1996 Jul 1;94(1):19-25.
123. Levy R, et al. VITAMIN C for the treatment of recurrent furunculosis in patients with impaired neutrophil functions. *J Infect Dis* 1996 Jun;173(6):1502-5.
124. Curhan GC, et al. A prospective study of the intake of vitamins C and B6, and the risk of kidney stones in men. *J Urol* 1996 Jun;155(6):1847-51.
125. McAlindon ME, et al. Effect of allopurinol, sulphasalazine, and VITAMIN C on aspirin induced gastroduodenal injury in human volunteers. *Gut* 1996 Apr;38(4):518-24.
126. Jarrar K, et al. [A case-control study for the recognition of nonoccupational risk factors for tumors of the lower urinary tract]. *Dtsch Med Wochenschr* 1996 Mar 15;121(11):325-30.
127. Boffa MJ, et al. A double-blind, placebo-controlled, cross-

- over trial of oral VITAMIN C in erythropoietic protoporphyria. *Photodermatol Photoimmunol Photomed* 1996 Feb;12(1):27-30.
128. Waring AJ, et al. Ascorbic acid and total VITAMIN C concentrations in plasma, gastric juice, and gastrointestinal mucosa: effects of gastritis and oral supplementation. *Gut* 1996 Feb;38(2):171-6.
129. Lonrot K, et al. The effect of ascorbate and ubiquinone supplementation on plasma and CSF total antioxidant capacity. *Free Radic Biol Med* 1996;21(2):211-7.
130. Nadgrodkiewicz K. [The effect of intravenous Ascorbic acid on urinary 17-hydroxysteroid excretion at an early stage of cerebral stroke]. *Neurol Neurochir Pol* 1996 Jan-Feb;30(1):49-56.
131. Wang H, et al. Experimental and clinical studies on the reduction of erythrocyte sorbitol-glucose ratios by Ascorbic acid in diabetes mellitus. *Diabetes Res Clin Pract* 1995 Apr;28(1):1-8.
132. Sharma DC, et al. Correction of anemia and iron deficiency in vegetarians by administration of Ascorbic acid. *Indian J Physiol Pharmacol* 1995 Oct;39(4):403-6
133. Paolisso G, et al. Metabolic benefits deriving from chronic VITAMIN C supplementation in aged noninsulin dependent diabetics. *J Am Coll Nutr* 1995 Aug;14(4):387-92.
134. Gastaldello K, et al. Resistance to erythropoietin in iron-overloaded haemodialysis patients can be overcome by Ascorbic acid administration. *Nephrol Dial Transplant* 1995;10 Suppl 6:44-7.
135. Vaxman F, et al. Effect of pantothenic acid and Ascorbic acid supplementation on human skin wound healing process. A double-blind, prospective and randomized trial. *Eur Surg Res* 1995;27 (3):158-66.
136. Wang H, et al. [Reduction of erythrocyte sorbitol by Ascorbic acid in patients with diabetes mellitus]. *Chung Hua I Hsueh Tsa Chih* 1994 Sep;74(9):548- 51, 583.
137. Herbaczynska-Cedro K, et al. Inhibitory effect of vitamins C and E on the oxygen free radical production in human polymorphonuclear leucocytes. *Eur J Clin Invest* 1994 May;24(5):316-9.
138. Lamm DL, et al. Megadose vitamins in bladder cancer: a double-blind clinical trial. *J Urol* 1994 Jan;151(1):21-6.
139. Lockwood K, et al. Apparent partial remission of breast cancer in "high risk" patients supplemented with nutritional antioxidants, essential fatty acids and coenzyme Q10. *Mol Aspects Med* 1994;15 Suppl:s231-40.
140. Cunningham JJ, et al. VITAMIN C: an aldose reductase inhib-

- itor that normalizes erythrocyte sorbitol in insulin-dependent diabetes mellitus. *J Am Coll Nutr* 1994 Aug;13(4):344-50.
141. Rifici VA, et al. Dietary supplementation with vitamins C and E inhibits in vitro oxidation of lipoproteins. *J Am Coll Nutr* 1993 Dec;12(6):631-7
142. Levy R, et al. Successful treatment of a patient with recurrent furunculosis by VITAMIN C: improvement of clinical course and of impaired neutrophil functions. *Int J Dermatol* 1993 Nov;32(11):832-4.
143. Zamah NM, et al. Absence of an effect of high VITAMIN C dosage on the systemic availability of ethinyl estradiol in women using a combination oral contraceptive. *Contraception* 1993 Oct;48(4):377-91.
144. Cahill RJ, et al. Effects of vitamin antioxidant supplementation on cell kinetics of patients with adenomatous polyps. *Gut* 1993 Jul;34(7):963-7.
145. Johnston CS, et al. VITAMIN C elevates red blood cell glutathione in healthy adults. *Am J Clin Nutr* 1993 Jul;58(1):103-5.
146. Roncucci L, et al. Antioxidant vitamins or lactulose for the prevention of the recurrence of colorectal adenomas. *Colorectal Cancer Study Group of the University of Modena and the Health Care District 16. Dis Colon Rectum* 1993 Mar;36(3):227-34.
147. Kataoka A, et al. [Intermittent high-dose VITAMIN C therapy in patients with HTLV-I-associated myelopathy]. *Rinsho Shinkeigaku* 1993 Mar;33(3):282-8
148. Dumitrescu C, et al. Effect of VITAMIN C administration on the ratio between the pro and antioxidative factors. *Rom J Endocrinol* 1993;31(1-2):81-4.
149. Karduss Urueta A, et al. [Results of the treatment of chronic idiopathic thrombocytopenic purpura with Ascorbic acid]. *Gac Med Mex* 1993 Jan-Feb;129 (1):23-5.
150. Dawson EB, et al. Effect of Ascorbic acid supplementation on the sperm quality of smokers. *Fertil Steril* 1992 Nov;58(5):1034-9.
151. Triana Mantilla ME, et al. [The effect of VITAMIN C on the lipolytic activity in type-II diabetics with angiopathy]. *Angiologia* 1991 Mar-Apr;43(2):77-81.
152. Reed PI, et al. Effect of Ascorbic acid on the intragastric environment in patients at increased risk of developing gastric cancer. *IARC Sci Publ* 1991; (105):139-42.
153. Beser E. The effects of short-term VITAMIN C on plasma bun, uric acid, cholesterol and triglyceride levels. *Acta Med Hung*

1991;48(1-2):73-8.

154. Bucca C, et al. Effect of VITAMIN C on histamine bronchial responsiveness of patients with allergic rhinitis. *Ann Allergy* 1990 Oct;65(4):311-4.

155. Hunt JR, et al. Ascorbic acid: effect on ongoing iron absorption and status in iron-depleted young women. *Am J Clin Nutr* 1990 Apr;51(4):649-55.

156. Johnston CS. Effect of a single oral dose of Ascorbic acid on body temperature and trace mineral fluxes in healthy men and women. *J Am Coll Nutr* 1990 Apr;9(2):150-4.

157. Holmes LG Effects of smoking and/or VITAMIN C on crevicular fluid flow in clinically healthy gingiva. *Quintessence Int* 1990 Mar;21(3):191-5.

158. Mai J, et al. High dose antioxidant supplementation to MS patients. Effects on glutathione peroxidase, clinical safety, and absorption of selenium. *Biol Trace Elem Res* 1990 Feb;24(2):109-17.

159. Park E, et al. Effects of multivitamin/mineral supplementation, at nutritional doses, on plasma antioxidant status and DNA damage estimated by sister chromatid exchanges in lymphocytes in pregnant women. *Int J Vitam Nutr Res* 1999 Nov;69 (6):396-402.

160. Mirvish SS, et al. Effect of ascorbic acid dose taken with a meal on nitrosoproline excretion in subjects ingesting nitrate and proline. *Nutr Cancer* 1998;31(2):106-10.

161. Howard DJ. Oxidative stress induced by environmental tobacco smoke in the workplace is mitigated by antioxidant supplementation. *Cancer Epidemiol Biomarkers Prev* 1998 Nov;7(11):981-8.

162. Seven A, et al. Biochemical evaluation of oxidative stress in propylthiouracil treated hyperthyroid patients. Effects of vitamin C supplementation. *Clin Chem Lab Med* 1998 Oct;36(10):767-70.

163. Girodon F, et al. Effect of a two-year supplementation with low doses of antioxidant vitamins and/or minerals in elderly subjects on levels of nutrients and antioxidant defense parameters. *J Am Coll Nutr* 1997 Aug;16(4):357-65.

164. Heuser G, et al. Enhancement of natural killer cell activity and T and B cell function by buffered VITAMIN C in patients exposed to toxic chemicals: the role of protein kinase-C. *Immunopharmacol Immunotoxicol* 1997 Aug;19(3):291-312.

165. Girodon F, et al. Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial. *Ann Nutr Metab* 1997;41(2):98-107.

166. Liyanage C, et al. Iron absorption from a traditional Sri

- Lankan weaning food and the enhancing effect of Ascorbic acid in adult male volunteers. *Ceylon Med J* 1996 Dec;41(4):135-40.
167. Duthie SJ, et al. Antioxidant supplementation decreases oxidative DNA damage in human lymphocytes. *Cancer Res* 1996 Mar 15;56(6):1291-5.
168. Pandey DK, et al. Dietary VITAMIN C and betacarotene and risk of death in middle-aged men. *Am J Epidemiol* 1995 Dec 15;142(12):1269-78.
169. Hunt C, et al. The clinical effects of VITAMIN C supplementation in elderly hospitalised patients with acute respiratory infections. *Int J Vitam Nutr Res* 1994;64(3):212-9.
170. Johnston CS, et al. Megadose of VITAMIN C delays insulin response to a glucose challenge in normoglycemic adults. *Am J Clin Nutr* 1994 Nov;60 (5):735-8
171. Bednar C, et al. Nitrate and VITAMIN C from fruits and vegetables: impact of intake variations on nitrate and nitrite excretions of humans. *Plant Foods Hum Nutr* 1994 Jan;45(1):71-80.
172. Levin ED, et al. Clinical trials using Ascorbic acid aerosol to aid smoking cessation. *Drug Alcohol Depend* 1993 Oct;33(3):211-23.
173. Maxwell SR, et al. Changes in plasma antioxidant status during eccentric exercise and the effect of vitamin supplementation. *Free Radic Res Commun* 1993;19(3):191-202.
174. Shah GM, et al. Effects of Ascorbic acid and pyridoxine supplementation on oxalate metabolism in peritoneal dialysis patients. *Am J Kidney Dis* 1992 Jul;20(1):42-9.
175. Kritchevsky SB, et al. Dietary antioxidants and carotid artery wall thickness. The ARIC Study. *Atherosclerosis Risk in Communities Study. Circulation* 1995 Oct 15;92(8):2142-50.
176. Stephens NG, et al. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study. *Lancet* 1996 Mar 23;347(9004):781-6.
177. Gey, KF. Vitamins E plus C and interacting conutrients required for optimal health. A critical and constructive review of epidemiology and supplementation data regarding cardiovascular disease and cancer. *Biofactors* 1998;7(1-2):113-74.

