Health Condition: Heart, Blood, & Vessel Diseases

"I weighed about 228 lbs at my top and I'm only 5'9" or 10". My cholesterol profile was terrible. I had pre-diabetes, I had hypertension, I had arthritis, and I tried every diet in the world and was very successful at them for a couple of months. You name the diet, I was good at it."
—Steven Gundry, MD
Founder of the International Heart and Lung Institute
March, 2011

Who has heart, blood, and vessel diseases?

If we look at the global burden of hypertension from a worldwide perspective, overall we are going to see an estimated total number of adults with hypertension increasing from 972,000,000 in the year 2000, to over 1.56 billion people by the year 2025, a nearly 60 percent increase.[1] Hypertensive disorders are indicated through a normative value we call diastolic and systolic blood pressure. As an individual's blood pressure increases above a certain threshold level, there appears to be increasing risk to cerebral vascular and cardiovascular disease. The major form of hypertension is called essential hypertension, or idiopathic hypertension, meaning it has no known specific etiological agent that it is causing it. It is influenced by a complex shift in metabolic function that gives rise to changes in vascular endothelial compliance, leading less to vasorelaxation and more vasoconstrictive responses, which then elevates blood pressure. Essential hypertension accounts for about 95 percent of all cases of hypertension.

Essential hypertension has no single, organ-specific cause, but rather it is a complex, physiological dysfunction that we might say has its root origin in the alteration of the translation of messages from the environment producing altered gene expression, altered proteomics, and altered metabolomics at various tissue levels that produces what we see clinically as elevated blood pressure. We know there is a connection between sodium and blood pressure in individuals who have a genetic propensity towards what is called salt sensitivity. When it comes to dietary environment, primary hypertension and age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium chloride (salt) is less than 50 mmol per day. These are the people who don't use salt in food processing and they don't salt their foods. In fact, in the historical record, one of the major health risks among people who lived inland from the oceans was sodium deprivation back in the early days of human history, because salt was not prevalent or common. Individuals could get into a sodium deficiency situation and it was a very significant problem. That is why salt was so highly valued as a trading commodity in early civilization. We clearly know that's not the case today with the prevalence and plentiful nature of salt, which ends up being a food additive in our processed foods.

So in Western society today, we have a combination of high sodium diets and low potassium diets (potassium is higher in vegetable foods). We have cut down vegetable foods and increased salted processed foods, so the ratio of sodium to potassium in our diet now is extraordinarily high. We have almost completely reversed the ratio of sodium-to-potassium that was found in our indigenous diets, which were low sodium/high potassium, which influences the renin-angiotensin system and how it

influences (through the adrenal hormones) the retention of salt and retention of fluid, which then ultimately causes altered endothelial nitric oxide output, lowered vasodilation, and increased risk to high blood pressure.

We recognize there are many variables and many different messenger molecules that contribute to the concepts of vascular reactivity. Some of those variables relate to lipids. Cholesterol, in and of itself, be it either high or low, is not the be all and end all in determining exactly what is going on at the arterial wall relative to atherosclerosis. It is only a marker. Daniel Steinberg (from the University of California, San Diego and credited with the discovery of LDL oxidation) published an article in which he described high cholesterol and inflammation as "partners in crime" in the atherogenic process.[2]

The hypothesis that injury caused by inflammation may ultimately result in plaque formation historically dates back to the work of Rudolf Virchow in the 19th century. In looking at the coronary arteries of patients who had heart disease at the time of death, Dr. Virchow visualized the arteries as being injured. It looked like there was a wound and that the wound had tried to heal, forming a scab-like lesion that we now call a plaque. Virchow came to the concept that atherosclerosis was really an inflammatory condition, like a wound on the inside of the artery wall. In the early 20th century, a Russian physiologist by the name of Anichkov had a slightly different view of the origin of atherosclerosis. He was able to take white rabbits and feed them high-cholesterol and high-fat diets and induce plaque on the arteries that was associated with atherosclerosis. And so the cholesterol hypothesis was born out of the Anichkov work, and the injury and inflammatory model was born out of the observations of Virchow. From those two emerged the dominant intellectual lineage in terms of the origin, treatment, and prevention of vascular disease. The emphasis was more focused on the cholesterol hypothesis than on the inflammation hypothesis of Virchow's. For decades, cholesterol seemed to be the *sine qua non* for the etiology of atherosclerosis.

But then later, in the 1960s and 1970s, a pathologist at the University of Washington School of Medicine, Earl Benditt, talked about the monoclonal theory of the origin of atherosclerosis. Dr. Benditt proposed that if you looked at atherosclerotic lesions, they were monoclonal in origin, as if they had been induced by a single cell undergoing injury and then developing a clonal response as a dedifferentiated cell. He felt that this clonal response was a consequence of an injury to that cell, a mutagenic injury. It was not a cancer as such, but it was more like a benign tumor that we call the atheroma, which then caused alterations in vascular flow and activated the immune system, which ultimately led to infiltration of cholesterol and calcium and stage 3 atherosclerotic lesions. Dr. Benditt, along with his research group, published a number of papers about the monoclonal theory of hyperplasia. The theory was reminiscent (in part) of the Virchow model of inflammation and injury as the origin of atherosclerosis.

When the vascular smooth muscle cell undergoes a proliferative response as a consequence of an inflammatory message, it leads to the development of all sorts of alterations in the vascular wall in terms of its physiology and function. This can lead to things like restenosis after stents are placed, or bypass graft occlusion, or transplant vascularopathy, which are all secondary conditions of atherosclerotic risk associated with increased inflammatory burden. This inflammatory marker became

an important new component of the presumed etiology of atherosclerotic disease in the later 1970s, the 80s, and the 90s.

The macrophage converts itself into the foam cell. Once it infiltrates the artery wall, it undergoes a personality change with regard to its gene expression. It becomes, then, a cell type that is incorporated within the artery wall that engulfs a lipid. It engorges itself. It has a different physiological dynamic. The artery wall shifts into an oxidative chemistry. You get LDL oxidation and you start, then, getting this free radical oxidative process of inflammation and injury.

We need to then look at the processes that relate to cholesterol oxidation and lipid dynamics (moving in and out of the artery wall), including triglycerides as well as cholesterol, and the packaging of lipids into the various lipoproteins-lipoproteins that constitute LDL, HDL, VLDL, and the different forms within each of those because there are sub-fractions, as we now recognize, within each of those lipoproteins that are constituted by various percentages of different apolipoproteins.

Apolipoproteins have names like A, B, C, D, and E. Apolipoproteins are synthesized principally in the liver after messages come to the liver cells. These are proteins that have the principal responsibility for binding certain families of lipids and aggregating themselves into certain particles that then travel in the vascular fluid, allowing transport of lipids in a water matrix.

We can think of an apolipoprotein in a very simple way: as a detergent. It basically solublizes fats so they can be transported in the blood, which is principally water. That's a little bit overly simplistic, however, because these apolipoproteins like A, B, or E are not nonspecific detergents; they are very specific in the way they accumulate certain fats and how they assemble themselves with other proteins and other constituents (other active enzymes) to then transport that fat to specific receptor sites on the surface of the arterial wall. So they are not just kind of general and nonspecific; they have a very unique personality and therefore a lot of what we might consider the personality of atherogenesis is tied together with the personality of the apolipoproteins: how they are synthesized, and how they are transported, and how they are delivered to the cell at the surface of the arterial wall.

So, cholesterol is part of the story, but only part. It is like a snapshot or a surrogate view into a much more dynamic process that we need to take into account. If you have a high cholesterol (a low HDL and an elevated LDL), you want to take account as to why that is present as your snapshot in your blood chemistry. What are the dynamic processes that may contribute to that? Is it hyperinsulinemia? Is it related to allergy? Infection? Is it related to a toxic exposure? Many variables might influence changes in your lipid dynamics.

Diagnosis

In the chronology of cardiovascular disease assessment, there have been several significant milestones that have created current guidelines for standard of care. Jeffrey Bland, PhD, describes it this way:

> *"If we go back to Framingham and look at the work that was done in Massachusetts, it set the tone for risk factors and how that would be woven eventually into medical management, and then how that tied with blood cholesterol. Boehringer was the first company to develop a finger-stick cholesterol test that made it accessible at health fairs and suddenly the cholesterol number became a person's number because they could get it at their shopping mall. That technology, then, ultimately drove probably the largest singular drug family in the pharmacopeia today, the statin drugs."*

Marc Penn, Md, PhD, who is the Chief Medical Officer of Cleveland HeartLab, was interviewed by Dr. Bland in January 2012 and added his thoughts this way:

> *"Framingham set the tone for risk factors, recognizing that certain patients will be at a higher risk of developing disease. The other milestone I would put in your list is Russell Ross's response-to-injury hypothesis in '76, which really set the tone for studying lipids and how they induce injury, and then studying inflammation and how they propagate the disease. Brown and Goldstein, in their seminal work, recognized the lipid portion as inducing that injury, and perhaps driving the propagation. And then [Paul] Ridker, coming back and recognizing the inflammatory part of the pedestal, and recognizing that even in patients whose lipids are okay, if they have arterial inflammation they are still at risk."*

Framingham risk factors are still very viable and very valuable as gross determinants. But today the field cardiovascular risk factor assessment includes the study of extended risk factors (or biomarkers), which really relate to the very fundamental question of function. Rather than looking at overt pathology, these evaluative tools we call biomarkers are looking at aspects of disturbed physiological function or disturbed pathology. One might really view a biomarker in two respective ways. One is you might look at a biomarker that is analyzing the primary agencies that cause a specific dysfunction and contribute to the development of an ultimate disease. And the second is a biomarker that looks at secondary effects of that disease process; it's kind of the smoke that comes from the fire that tells us how severe the insipient disturbed metabolism or pathology is at that state in the patient's life cycle.

Why are extended risk factors important? Why are new assessments being sought when there are already so many? Dr. Marc Penn explains:

> *"What I recognize is that we have made tremendous strides in treating lipids in patients and decreasing the risk for heart disease, but now that about 50% of the patients who present with heart attacks have normal lipids, either treated to or naturally, I think it became clear that we needed to look under a different rock, if you will, in order to define who still has residual risk even though you've treated them to what the guidelines state for lipid management."*

In June 2012, Dr. Jeffrey Bland interviewed Mark Houston, MD, Director of the Hypertension Institute of Nashville and also an Associate Clinical Professor of Medicine at Vanderbilt University School of Medicine. Dr. Houston discussed a biomarker he feels is particularly significant, endothelial dysfunction (ED):

> *"When the blood vessel responds to one of these insults or one of these injuries, it is doing what it is supposed to do. It is an acute response that is the correct response. It is basically applying a defense mechanism against an invader. Now, when we do that acutely everything is fine. You take care of the problem, whether it is a microbe, or it's a toxin, or it has oxidized the LDL cholesterol, or whatever. But when you continue to respond to that insult you're continuing to insult the endothelium, and then it becomes what I call the innocent bystander of a chronic, dysregulated response, and it's the same three responses: inflammation, oxidative stress, and immune dysfunction. Over time, the body's normal response to injury becomes actually a dysfunctional problem, and later, as we progress, becomes a disease and we can put a name on it. But in that intervening period, which can be decades before we can actually define the disease, you will have endothelial dysfunction (ED), which becomes the best marker for predicting stroke, heart attack, coronary heart disease, congestive heart failure, renal disease, and a lot of other vascular problems. So the new movement in cardiovascular medicine is to be able to identify the insults, to identify ED with non-invasive basic testing, and start prevention and aggressive treatment before the patient develops a known disease related to cardiovascular illness."*

Inflammatory biomarkers, oxidative biomarkers, and lipid biomarkers interrelate one with the other. One of the tools that is used to look at this interconnection between HDL, inflammation, and oxidation is myeloperoxidase (MPO). MPO is a very interesting analyte to measure because it does helps predict aspects of endothelial dysfunction and increasing relative risk to inflammation-induced atherosclerosis. A paper was published a number of years ago in the journal *Circulation* looking at the interrelationship between serum MPO levels and demonstrating that they are independently able to predict endothelial dysfunction in humans.[3] There are a number of clinical laboratories that now are able to measure myeloperoxidase as a standard analyte in an extended cardiovascular risk factor profile.

Is there such a thing as too much testing? Are the various tests redundant and therefore unnecessary?

Dr. Marc Penn:

> *"The reason we focused on a panel approach at Cleveland HeartLab is the studies have demonstrated that these tests offer additive information. There is an elegant study by Heslop and colleagues out of Canada last year that showed that if you had a high MPO level your ten-year risk of mortality was significantly increased.[4] But what they also ended up showing was that if you had a low MPO and a low CRP, you did well. If either were high, you didn't do so well. If both were high you did yet worse. So it is hard to say that defining a MPO and a CRP are redundant or over testing. Similarly, we've looked at*

data in over 2000 patients from executive health programs and preventive cardiology clinics where about five-and-a-half percent of the patients will be at risk based on high MPO, and about four to four-and-a-half percent will at risk based on a high Lp-PLA2, but yet despite having well over 2000 patients, only six patients had both markers up. So it is hard to argue that those tests are redundant when you have such high discriminatory values."

Treatment

"Let's face it, the quality of life that we want to have in our later years and how long we live is extremely important to people like me who are part of the baby boomers. I don't want to live to 85, but by the time I am 75 years old have to deal with what would be 90% of my prescription bill during that particular time and not really have a high quality of life. There needs to be, I think, a dissecting of what we are doing in the healthcare system to make it cost effective and to also make it worthwhile for all of us to follow a certain way of how we live, the environment that we live in, the nutrition that we have, and, if we need medications, not take seven medications, but take only the ones that really need."

—Roger Newton, PhD
Co-developer of Lipitor
July 2007

All of the history leads us to lipid research intervention trials. Basically, there are two approaches that have been used. One approach is the use of diet, lifestyle, and exercise. There is a huge body of literature that supports the value of this primary therapy, and that becomes the basis of what the National Institutes of Health (NIH) now calls the first line of therapy, or the Therapeutic Lifestyle Change program (TLC program), which is recommended to physicians for use with patients who have hyperlipidemias prior to the onset of intervention with a lipid-lowering drug. This treatment approach involves dietary modification, exercise, stress management, smoking cessation, and ideal body weight achievement. This approach has a demonstrated success in primary prevention with limited to no adverse side effects. The other approach is pharmacotherapy, which is to intervene with a cholesterol-lowering pharmacological agent, most commonly the class of drugs known as statins.

The early history of statins and cholesterol goes back to Anitschkov, the Russian physiologist who did work with white rabbits, feeding them a diet enriched with cholesterol. The discovery of statins connects to red rice yeast fungal metabolites that were used as culinary agents in Japanese cooking. Japanese chemists were able to lower cholesterol levels in animals when they were fed certain red rice yeast metabolites. That led to the extraction, isolation, purification, and ultimate structure proof of these molecules, and they became antihypercholesterolemic agents, which then got derivatized and modified in structure to make new-to-nature molecules by the drug companies. From Lovastatin and Nevacor was birthed a whole family of new, improved versions of these cholesterol-lowering agents originally derived from natural products (from the red rice yeast). Lipitor has become the blockbuster

drug of our era for modulating cholesterol *de novo* biosynthesis. Statins have been made into over-the-counter (OTC) drugs in Britain, and there is even suggestion that they should be made available to children on a regular basis to bring their cholesterol levels down to levels that are considered ideal. These steps are being taken without a full understanding of exactly what we are we doing, what are we treating, what the long-term outcomes are-not just the biomarker change, but the actual health outcomes (morbidity and mortality).

In 2007, an editorial titled "The International Pandemic of Chronic Cardiovascular Disease" was published in the *Journal of the American Medical Association (JAMA)*.[5] During the final decades of the 20th century, even with the major medical advances made in the prevention of cardiovascular disease by the increasing application of statin drugs, there have been reductions in overall cardiovascular death rates, but the overall incidence of acute myocardial infarction (or heart attack) has not declined and has actually increased over this period of time among women. If we take that global, we see there is an ever-increasing epidemic of cardiovascular disease in cultures like China. The construct that we are winning huge battles against the war of cardiovascular disease by the application of these drugs like statins doesn't bear out when we look at the data.

Another paper that was published in *JAMA* in 2007 supports this. The authors of this article looked at atherosclerotic arterial disease mortality rates after one-year follow-up in both primary and secondary prevention-type studies. Their findings also indicate that the incidence of MI continues to increase while the number of sudden cardiovascular death cases goes down.[6]

What we end up with is an increase in the number of chronically diseased people who have had a first heart attack. We have to learn how to manage these people. Whereas before they may have expired with their cardiovascular event, now they are able to be kept alive. And so they are not a mortality statistic, but they are a chronic disease statistic, and now we have to learn how to manage that condition as a chronic disease after a heart attack. Secondary prevention becomes a very big part of the new medicine.

Statins have been used both for primary and secondary prevention, as have many other of the vascular-related drugs-the ACE inhibitors, the calcium channel blockers, the beta-blockers. What are some of the adverse risks associated with things like statin therapies? Patients often get diffuse neuromuscular symptoms: tingling and twitches, zips and zaps, and pains like a myalgia. In extreme cases, which are infrequent, we get rhabdomyolysis and loss of muscle; this is very serious and could even be life-threatening. For most patients, the symptoms are more subtle. They are musculoskeletal and neuromuscular issues. But there is another series of potential adverse side effects on the horizon for a population employing statins on a routine basis. In March 2012, the FDA came out with the requirement for a warning for statin users about memory loss and diabetes risk, which is certainly going to put a grey color on the implied safety of statins. This is going to change prescribing information that applies to the class of statins including not only atorvastatin (Lipitor), and rosuvastatin (Crestor), and simvastatin (Zocor), and simvastatin and ezetimibe (Vytorin), but also all the drugs in class that are cholesterol-lowering drugs of the statin family. This will warn patients and doctors that the drugs may cause a small

increase in blood sugar levels and type 2 diabetes, and also may have some adverse effects on cognitive function over time.[7]

In recent years, controversy has arisen over the appropriate use of statins. That is, the use of statins in primary prevention versus secondary prevention. James Wright, MD, PhD, who is a Professor of Medicine at the Department of Anesthesiology, Pharmacology, and Therapeutics at the Medical School, University of British Columbia, and his colleague, Jay Abramson, at Harvard Medical School, have written a number of articles on this subject.

For adults aged between 30 and 80 years old who already have occlusive vascular disease, statins can confer a benefit in total cardiovascular mortality. The controversy doesn't involve secondary prevention, but rather primary prevention (that is, people without occlusive vascular disease). Should people without occlusive vascular disease receive statins? With about three quarters of those who presently take statins in the category of primary prevention in the United States, the answer has huge economic and health implications.

In April 2008, following the publication of an article titled "Do Statins Do Any Good?" in *BusinessWeek* magazine, Dr. Jeffrey Bland had an opportunity to interview Dr. Wright about his statin research.[8]

Dr. Wright described it this way:

> *"Most of the people who were being offered the drug and who were taking the drug were actually people who had never had a heart attack, or a stroke, or had peripheral vascular disease. They were basically healthy people, and they were deemed to be at risk because they had had their cholesterol measured (or other things) and then were being told that they should be taking statins. We got involved in really looking at the evidence of the effectiveness of statins in that setting. When we really got into the data, we were quite surprised at how trivial the benefit is and that in most of those kinds of populations there really isn't any overall benefit. When you look at all serious adverse events and all hospitalizations, there is really no reduction in the people taking statins. That was initially quite surprising to us, but it convinced us that for most of the people who are basically healthy, there is no net health benefit."*

Dr. Wright continued:

> "For people who are healthy and in this primary prevention setting who are being considered for statins basically because they have risk factors, I think it makes much more sense for them to look at their risk factors and see how those could be modified by changing their lifestyle, changing their diet, increasing their amount of exercise, etc. That makes much more sense than hoping that taking the drug will resolve the problem for them when the potential benefit is so small and there are potential risks (some of which are unknown) , I think."

Indeed, even the co-developer of the blockbluster drug, Lipitor, agrees there is a greater need for individual assessment when it comes to determining the appropriate therapy for cardiovascular risk factors. Dr. Bland had the opportunity to interview Roger Newton, PhD, in July 2007. Dr. Newton said this:

> *"The original evaluation of LDL cholesterol and HDL cholesterol being respectively 'bad' and 'good' came from epidemiological studies years ago. These studies basically showed that in individuals who had risk for heart disease (and mostly through primary prevention and dietary means), that those folks who had higher HDL cholesterol seemed to be protected (most of the time), and those who had high LDL weren't. And so this yin-yang of LDL bringing cholesterol to the periphery and laying down that cholesterol to cause the nasty plaques that caused increased heart attacks (particularly when they are unstable plaques and they rupture), that link and the antagonism of HDL trying to remove that cholesterol and other lipids from the plaque, this is where the story became much clearer from a functional point of view…But really, that doesn't tell you about the real metabolism and physiology because it is a static measurement of a dynamic process…*
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> *As the individual biochemistry comes forward and we are able to evaluate this in a really meaningful way-people can better then judge what they should or should not do with their bodies, as well as realize that being on 4 or 5 or 6 medications where there are drug-drug interactions that occur and where there is this polypharmacy paradigm, that's not going to lead to optimum health.*
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> *I think understanding how each individual person can reach that potential is hopefully what will happen down the road with a multidisciplinary approach to health and to treating chronic disease."*

Personalized management of heart, blood, and vessel disorders

We have learned that our diet plays a very important role (as does our lifestyle) in signaling to our genes how they are expressed. Our genes are the templates that have pluripotentiality (meaning they can be expressed in multiple ways) to give different outcomes based upon the environmental messages that the genes are receiving. Although we can't change (as an individual) our genes, we can change the messages that are received by our genes and how that signals alternative function, in terms of what we call the phenotype (the outcome of the individual).

Diet plays an interesting role because it is not just the foods that we eat in the moment. The information from our diet washes over our genes and creates a phenotype that reshapes us—our physiognomy and our physiology—and this occurs over decades of living. People generally tend to eat diets that are consistent for many years, and so the shaping of gene expression patterns occurs as an outcome from that information that those foods are bringing. The information molecules in food are macronutrients. They are vitamins and minerals. They are accessory nutrients. They are phytochemicals. And they are all this rich tapestry of information sent to our genes over time.

In May 2009, Dr. Bland interviewed Ralph LaForge, MSc, who has been at the Duke University Medical Center, Division of Endocrinology, Metabolism, and Nutrition for a number of years, really looking at the role that therapeutic lifestyle change (and specifically diet, exercise, and stress management) has on health outcomes. Based on his many years of experience as a lipid educator, Mr. LaForge said this:

> *"Lifestyle changes (even modest), if they are adhered to, clearly reduce risk of diabetes, but also cardiovascular disease, through mechanisms other than just lipids and cholesterol reduction… The majority of us are in the high-end of low-to-moderate risk level, and many are taking prophylactic statins and other drugs to perhaps defer risk. That is where there is some question about the cost-effectiveness. For that group of people (including myself), sufficient energy expenditure per week/per day and the right choice of dietary behaviors (I'm not talking about a diet, per se, I'm just talking about the right choice of foodstuffs over the course of a day, a week, a month, or a year) would certainly be cost beneficial, especially from a cardiometabolic risk perspective. What I mean by that is that both the immediate risk of diabetes and metabolic disease and the later risk (usually it comes a little later) of cardiovascular disease are addressed."*

What does this look like in the real world? How do people make a difference in their health outcome using lifestyle approaches? Let's revisit Steven Gundry, MD, who was quoted at the start of this section. Even as a successful thoracic surgeon, Dr. Gundry openly admits he had bad markers of every kind, and in fact went on to write a book about his experiences titled *Dr. Gundry's Diet Evolution*. Dr. Gundry's perspective changed with one patient, an epiphany he described to Dr. Bland in March 2011:

> *"About ten years ago. A guy came into my office. I call him 'Big Ed' in the book. He's from Miami. Big Ed had inoperable coronary artery disease. Every one of his blood vessels was clogged up; so clogged up that you couldn't put stents in, and you couldn't do bypasses because there wasn't any place to land the blood vessels.*
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> *Ed had been going around the country looking for a surgeon who was crazy enough to operate him. I fit that bill. I'm famous for operating on people nobody else wants to touch. I looked at Big Ed, and I looked at the angiogram (the movie of his heart), and I said, 'You know, everybody who has seen you is right. I'd love to help you, but I just don't see how I'm going to do you any good.' Big Ed lets out a sigh and he says, 'Well, that's what everybody else says, but, look, here's what I've done. It's been six months since that angiogram was made, and I've gone on a diet, and I've lost 45 lbs.'*
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> *Now, Big Ed was still a big guy; he weighed 265 when I saw him. He says, 'I went to a health food store. I bought all these supplements.' He brings in, actually, a big huge shopping bag of supplements. He says, 'I've been taking these supplements every day. Maybe I did something with my weight loss and these supplements.' So I'm kind of scratching my professor beard and patting my big belly, and I said, 'Good for you for losing weight, but that's not going to change anything in your blood vessels. And I know what you did with all those supplements; you made expensive urine.' And I really truly believed that at that time. I said, 'At the most you've just wasted all your money.' He said, 'Well, I've come all this way. What do you say we get another angiogram? What would it hurt?' So I said, 'Okay.' We got another angiogram and then the next day I did a five-vessel bypass, because in six months' time he had cleaned out fifty percent of the*

blockages in his coronary arteries. He still had blockages, but now there were places to actually land blood vessels.

If I had known then what I know now, the last thing I would have done is operate on him, but I didn't know. After I operated I said, 'Big Ed, give me that bag of supplements.' I started looking through these supplements and a lot of them that he was taking I was using down in the laboratory in the form of intravenous solutions to protect hearts for heart transplant or to resuscitate hearts that had been dead. I was giving them through the veins of the heart; it never occurred to me to swallow them.

The other thing was I started talking to him about how he'd constructed his diet (because I loved diets). As he is describing it, light bulbs were flashing off in my head because, as you mentioned, I had a very fascinating major at Yale. For four years I investigated, basically, how we evolved from a great ape into a human based on social pressures and environmental pressures; basically, how our genes interacted with our environment and the foods we ate, and how that could turn a great ape into a human. I had a thesis that I got an honors for, and of course my mother had my thesis, so I called her and said, 'Still got it?' And she said, 'Oh yeah, absolutely.' She sent it up to me and I'm looking through my thesis and I said, 'Son of a gun, this is what I should have been doing for the last 20 years.'

I put myself on this diet, which is pretty well described in Dr. Gundry's Diet Evolution, and I started taking a ton of supplements. Not just willy-nilly—I actually started reading about them, which really, for me, would be the last thing I thought I'd be doing. I started sending my blood work up to Berkeley Heart Lab in northern California (it wasn't called that then). Lo' and behold, within a couple of months, my good cholesterol of 32 (which was terrible, my HDL) went up to 80 mg/dl, and my total cholesterol went from about 266 to 166 mg/dl, and my LDL went from 166 down to about 70 mg/dl. I said, 'Son of a gun. I was told that this is impossible.' Then several of my staff members started doing it, and the same thing happened on their blood.

So whoever I operated on at Loma Linda I would kind of enroll them into this program—teach them what they should eat and start giving them supplements—and the same thing started happening to them. Not only did their lipid profile get better, but a lot of these folks would call in a week or so and say, 'What supplement are you giving me that is making me dizzy?' I'd kind of look at my nurse (I didn't know much about supplements at this time) and I'd go, 'There's nothing in this that would make you dizzy. Get back into the clinic and let's see what's going on.'

Of course their blood pressure was like 80 over 50, and they were on two or three blood pressure medications, and I said, 'Well, son of a gun. I guess we better stop your blood pressure medicines.' 'Are you sure that's okay?' 'Well, look. It doesn't look like you need them anymore.' And then another patient would call and say, 'Gee whiz, I think my blood sugars are getting really low. What are you giving me that's making my blood sugar low?' 'Get back in here.' And sure enough, we have to start backing off on their insulin, or backing off on their metformin, or their glyburide.

This kept happening, so much so that after about a year of doing this at Loma Linda I looked at myself in the mirror one day and basically told myself I was in the wrong business. So I made a leap of faith. I moved to Palm Springs to set up an institute, which I called the Center for Restorative Medicine, where I basically teach people how to restore their health.

We enrolled these people in the trial. Every three months they had to have a complete set of Berkeley Heart Labs. We would check compliance by actually looking at how people's triglycerides were going. If I was going to get one blood test, that's the blood test I'd get on someone to predict their problems with heart disease. The lower the triglycerides the better. Most people will soon learn that the ratio of HDL to triglycerides is the best predictor of avoidance of heart disease or getting heart disease. That ratio should be at least 1:1, and the higher the ratio of HDL to triglycerides the better off you are. And yet most people walking around this country with normal levels of triglycerides and normal levels of HDL actually have a terrible HDL-to-triglyceride ratio. I think that's a huge cause of why we see so much heart disease in healthy living people.

At the end of five years, these people would be predicted, on the basis of very large (10,000 people) studies, to have somewhere in the range of 25 to 50 percent recurrence rates of heart disease (in other words, a new event—a new heart attack, a new bypass, a new stent, a new stroke, a new death). That's the standard of most tests, even on statins. Even on statins, the best statin trials still show an around 25% recurrence rate in 2 ½ years of a new event. So clearly this is not acceptable.

In our patients, in five years, 2 out of the 500 patients had a new stent put in, which is 0.4%. One other patient had a carotid artery endarterectomy, which I did (because he didn't listen to me), and one patient had a stroke who was in atrial fibrillation and refused to take Coumadin. So our overall cardiac event rate in five years in 500 patients was 4 out of 500 or 0.8%, so virtually nothing. This is 500 people with known coronary artery disease following a very simple diet and supplement program. This is not an irreversible process. This is not something that is going to happen to you. This is something that can be stopped. And the really exciting thing is we now have angiograms of people who have volunteered that show that the process is reversible, and it is reversible very, very quickly. I had the pleasure of showing you one of our more recent patients, who, in basically nine months, did a remarkable job of cleaning out his coronary arteries. The proof is in the pudding."

Fish Oils and Cardiovascular Health

When it comes to fish oils, literally thousands of articles have been published over the last 25 years since we first started hearing about the role that omega-3 fats have in cardioprotection and other immunological activities, so no discussion of heart, blood, and vessel health would be complete without a look at some of the research on this topic.

What has emerged recently is recognition that in our Western population, eating a standard Western diet, that we have seen a significant shift in the fatty acid profile of red cell membrane lipids (phospholipids). The Omega-3 Index, a concept and analysis developed by William Harris, PhD, is a

method of evaluating the relative levels of omega-3 fatty acids found in red blood cell membranes in comparison to omega-6 fatty acids. Dr. Harris, who is at the Lipid and Diabetes Research Center at the American Heart Institute at St. Luke's Hospital and the University of Missouri in Kansas City, has been looking at this extensively over many years. How do fish oils affect health? First, Dr. Harris explains why fish oils have always been a unique area of study:

> *"Fish oils were kind of an odd duck. Fish oils were--like vegetable oils--liquid at room temperature, and we knew liquid oils (vegetable oils) lowered cholesterol. But on the other hand, fish oils are also from an animal, and animal fats had been known to raise cholesterol, although they typically are solid at room temperature because of saturated fats. Fish oils are somewhere in the middle."*

Regarding how they work, evidence of this is only now becoming clear:

> *"How do omega-3 fatty acids work? Well, they work via affecting eicosanoid synthesis, or being a substrate for cyclooxygenase that competes with arachidonic acid. And that sort of was as complicated or as simple as it was until studies such as Olefsky's showing that the omega-3s can actually activate specific receptors, and that's a whole new concept rather than just competing with arachidonic acid for some other enzyme.[9] So I think the world is opening up. Along the same lines, we've now been able to discover that there are a whole host of metabolites of EPA and DHA that are made by cytochrome P450: epoxides, some mono- and di- and trihydroides, some ketones that are normal metabolites that we've just never been able to measure, and now we're discovering that a whole host of them exist, and the possibilities for how omega-3s actually are affecting health are continuing to expand as we discover these metabolites."*

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