HEALTH AND STRESS

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CORONARY DISEASE: LOOKING IN THE WRONG PLACES?

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A woman came across a man who was on his hands and knees under a street lamp, frantically searching for something. When she asked what he was looking for he explained that he had lost an important key and she offered to help. After five frustrating minutes crawling around under the bright light the woman inquired, "Where were you when you lost your key?" Pointing to a nearby dark alley, the man answered, "over there". "Then why aren't you looking there?" she asked. "Because the light's much better here," he replied.

The search for the cause of atherosclerosis has similarly been conducted in areas illuminated by scores of researchers focusing on the role of cholesterol and other lipids. The current concept proposes that atherosclerosis and coronary heart disease are caused by increased concentrations of LDL (low-density-lipoprotein) and that their development can be retarded by lowering LDL with drugs and/or diet.

While this seemed to be confirmed by several statin drug trials showing a reduction in LDL as well as coronary events, there is no convincing evidence that statins influence the rate at which atherosclerosis develops. **Lower coronary morbidity and mortality rates resulted regardless of the initial LDL levels or their degree of decline.** Benefits were sometimes seen within a few months, making it unlikely that they were due to reducing atherosclerosis.

If statin drugs don't achieve their cardiovascular benefits by lowering LDL or other lipid effects, what is their mechanism of action? As previously emphasized, obstructive atherosclerotic plaque is quite different in appearance and location than the fatty deposits seen in experimental animals force-fed on high cholesterol diets. The lipid-laden lesions of plaque are much more reminiscent of an inflammatory process and **there is good reason to believe that statins, like aspirin, are effective because of their anti-inflammatory actions rather than any influences on lipids**.

ALSO INCLUDED IN THIS ISSUE

Homocysteine promotes arterial inflammation. High blood levels are a powerful predictor of accelerated coronary atherosclerosis and can be corrected quickly and safely by vitamin B supplements for a few cents a day compared to costly statins that can have disturbing side effects. Have we been looking in the wrong location? Are there more productive places to search for the causes of atherosclerosis?

The Fatty Diet → Atherosclerosis Fable

I couldn't help hearing the following conversation while waiting for my turn at a Jewish delicatessen store last month. A middle-aged corpulent customer at the counter told the clerk, "I want a corned beef sandwich on rye with mustard, but make sure you give me only first cut and trim off all the fat you can. Otherwise, my cholesterol will skyrocket and I could die of a coronary on the spot. I'll pay extra."

The notion that increased fat consumption leads to elevated cholesterol, which in turn is what causes heart attacks, is a popular conviction. It is difficult to dispel since it dates back over 150 years, when it was proposed that the precipitation of fatty substances onto arterial walls was what caused atherosclerosis. These fats, and especially cholesterol, somehow irritated surrounding arterial tissues resulting in a proliferative reaction that could clog vessels and impede blood flow.

Whether cholesterol came from elevated blood levels that resulted from high fat intake was impossible to determine since there was no way to measure blood cholesterol or dietary fat intake at the time. In addition, there was not much interest in this since most people didn't live long enough to die from coronary heart disease or obstructive atherosclerotic lesions.

Around 90 years ago, the Russian physician Anichkov demonstrated that he could produce atherosclerotic lesions in rabbits by feeding them a high cholesterol diet. Further support came during World War II when it was observed that severely restricted meat and dairy products during food rationing resulted in a drop in deaths from coronary heart disease in Britain and Norway. Another report showed that Japanese and other populations who consumed much less animal fat than we do had almost 90% lower heart attack rates.

Probably the most convincing study was done by Ancel Keys a half century ago in which he showed a direct correlation between saturated fat intake and coronary heart disease in seven countries. This was widely heralded as definitive proof of a causal link, leading one authority to proclaim, "No other variable in the mode of life beside the fat calories in the diet is known which shows such a constant relationship to the mortality rate from coronary or degenerative heart disease". Yet, some scientists were skeptical since there were serious flaws in this reasoning as well as the methodology used to reach this conclusion.

In the first instance, rabbits are vegetarians and do not have the mechanisms to metabolize meat that humans do. The marked elevations of blood cholesterol in rabbits resulting from a high fat diet are not seen in patients with coronary heart disease. **The fatty arterial lesions that are produced do not resemble atherosclerotic plaque and do not cause obstruction of vessels or death. They are often visible on the inner lining of arteries within a few weeks, whereas infiltrative and occlusive plaque can take many years to develop.**

The seven countries Keys picked to prove his point were the U.S., Japan, Finland, Greece, Italy, Yugoslavia and The Netherlands, even though he had statistics from 15 others. Had he selected others, the results would be quite different. **Indeed, figures from Israel, Sweden, Germany and France would have led to the opposite conclusion, namely, that the more saturated fat and cholesterol that was consumed the lower the incidence of coronary heart disease.** The so-called "French Paradox" is a prime example.

Some Fatty Diet Flaws And Fallacies

In addition, within the countries that had been "cherry picked", even though fat consumption was fairly uniform throughout, the incidence of coronary heart disease varied considerably from region to region with as high as a seven-fold difference in

parts of Greece. To further prove his point, Keys fed middle aged men a very high cholesterol diet but found that their blood cholesterol was no different than a control group who consumed less than half as much. **Twenty years later, he admitted, "There's no connection whatsoever between cholesterol in food and cholesterol in blood. And we've known that all along. Cholesterol in the diet doesn't matter at all unless you happen to be a chicken or a rabbit."**

The diet-heart disease hypothesis got its biggest boost from the Framingham study, which was responsible for establishing the three leading risk factors for coronary disease as cholesterol, hypertension and smoking. The study began in 1948 when residents of this small Massachusetts manufacturing town were intensively investigated for anything that might conceivably influence the development of coronary heart disease, including blood concentrations of sugar, cholesterol and other chemicals, fat consumption, smoking, degree of obesity, physical activity and exercise levels. These were periodically monitored for decades and based on autopsy studies, it was concluded that blood cholesterol was the best predictor of risk of death due to coronary heart disease.

By the 1980's, this was so widely accepted that the American Heart Association had launched its "Lipid Hypothesis" campaign to emphasize that cholesterol was a killer. It was also promoting a "prudent diet" program designed to convince the public to reduce dietary fat intake as much as possible by replacing butter with margarine, bacon and eggs with cereal, steak with skinless chicken, and switching to low fat food products. The NIH had already issued similar guidelines and in 1988, the Surgeon General's office announced it was joining the battle and would shortly be publishing a definitive report showing the health hazards of fat consumption.

Nothing happened. Eleven years and four project officers later this definitive document was still not available and an NIH official quietly admitted it was being abandoned because "it had been initiated with a preconceived opinion of the conclusions, but on investigation the science behind those conclusions was nowhere near as solid as it was expected to be." The Framingham study conclusion was also erroneous since it simply reiterated that people with familial disorders characterized by marked elevations of cholesterol had a higher incidence of deaths due to coronary artery disease. **A review of the data revealed no difference in cholesterol levels in men who ate the most cholesterol and those who ate the least and women with the least fat intake had higher cholesterol levels than controls with high intakes.** In 1992, the Director stated that the study actually showed that "the more saturated fat one ate, the more cholesterol one ate, the more calories one ate, the lower people's serum cholesterol. People who ate the most cholesterol, ate the most saturated fat and ate the most calories, weighed the least and were the most physically active."

At least five other large studies over the past two decades have confirmed a lack of any correlation between fat consumption and serum cholesterol. A few also found that blood levels were higher in low fat diet subjects compared to those with above average intakes. However, there are millions to be made from low fat and no cholesterol substitutes since some 15,000 have appeared on store shelves in the past decade or two. Sales of these and other reputed cholesterol-lowering products rose further following reports that a high saturated fat diet would also raise risk of breast cancer by increasing estrogen production.

Not only is there no good evidence that this is true, but a recent Harvard study in postmenopausal women found just the opposite. Those on low fat diets had the highest estrogen levels and as fat consumption increased, hormone levels fell. Claims that saturated fat also causes endometrial, colon and prostate cancer and shortens life expectancy in other ways have also not panned out.

Cholesterol → Atherosclerosis Is Kaput!

The "Lipid Hypothesis" proposes (1) that dietary fat increases blood cholesterol, (2) elevated blood cholesterol eventually causes obstructive atherosclerosis in the

coronary arteries. The second step in this chain of events has now been shown to be just as erroneous as the first. Autopsy studies do not confirm any consistent correlation with elevated cholesterol or LDL except in people with very high values due to genetic defects. **If hypercholesterolemia was the culprit one might expect that the longer it had persisted the greater the severity of atherosclerosis one could demonstrate on coronary angiography. Five studies failed to find this and two showed that atherosclerosis progression was associated with a decrease rather than increase in cholesterol.**

Electron beam angiography detects calcified plaque regardless of its location. Since vessel occlusion often occurs at sites other than those suggested by routine angiograms this technique may be a better predictor of coronary events. However, total plaque content shows no correlation with cholesterol or any blood lipid fraction. Despite this and mounting evidence from other studies and large scale clinical trials, the conviction that total cholesterol or "bad" LDL cholesterol is the root problem continues to be the focus of research.

Coronary heart disease is not a specific disease like tuberculosis because the atherosclerotic plaque that produces coronary events can have multiple causes. The *causa vera* or true cause of tuberculosis is the tubercle bacillus since the disease cannot occur in its absence. Prior to its discovery tuberculosis had been thought to be due to close and unsanitary living conditions because it occur-red much more frequently under these circumstances. Such statistical associations do not prove a direct causal relationship unless they are always present and at least half of heart attack victims have normal cholesterol and LDL levels. Cholesterol, hypertension and smoking are considered to be "risk factors" for coronary disease, which implies a causal effect. "Risk marker" would be a more accurate description since these are simply statistical observations.

If you get people to stop smoking you will significantly reduce the incidence of emphysema and cancer of the lung because cigarettes contribute to these disorders. Treating hypertension lowers the likelihood of stroke for the same reason. However, as with cholesterol, neither intervention significantly affects future heart attack or coronary mortality rates. The MRFIT study of some 13,000 men divided those with hypertension, elevated cholesterol and/or smoking habits into two groups: one that received medication and counseling to reduce these leading risk factors and controls who did not. At the end of seven years there was no significant difference in coronary mortality rates and total death rates were higher in the intervention group. **After eleven years the intervention group actually had more deaths from coronary disease and cancer. In other words, removing or reducing these risk factors did nothing to lower actual risk.**

In addition to cholesterol, hypertension and smoking, there are some 300 other "risk factors" for coronary disease ranging from various lipid abnormalities, a deep earlobe crease, abdominal obesity and premature male type baldness to living in Eastern Finland. These are simply statistical associations that are markers, not causes of increased risk. Removing them does not influence the rate, severity or course of coronary events, but that doesn't stop vested groups from implying otherwise.

This approach has been aggressively promoted and perpetuated by the cholesterol cartel of pharmaceutical and low fat food manufacturers despite the lack of any supportive scientific proof and abundant evidence to the contrary. It is not likely that things will change because so much money is at stake. **Statin sales exceed $16 billion annually and Lipitor has now become the best selling drug in the world.** Thousands of low fat food products are available and an avalanche of new ones is in the wings despite the fact that they provide no benefits and in some instances have proved harmful. The continued success of the cholesterol cartel is almost assured because they spend megabucks to barrage consumers with misleading commercials about the dangers of dietary fat and elevated blood cholesterol.

Inflammation And Atherosclerosis

Support for cholesterol as the culprit in coronary disease has come in recent years from studies with statins which, unlike their predecessors, have been shown to reduce total as well as coronary deaths. Since this is presumably due to their ability to lower blood levels of "bad" LDL cholesterol, the criterion for dosage and duration of therapy is decreasing concentrations of LDL to a level that has been arbitrarily established as safe. **However, this is obviously not why statins work since patients with normal LDL's receive the same benefits and these rewards are seen too rapidly to be attributed to retarding or reversing the development of atherosclerotic plaque.**

It's easy to visualize that excess blood cholesterol spills over to line the inner walls of arteries with fatty material much like deposits that precipitate out in plumbing systems eventually restrict the flow of water. The problem is that arteries are not lifeless passive pipes but contain cells that are in constant communication with each other and their environment. In addition, **the buildup of atherosclerotic plaque starts within the arterial wall rather than its surface. Coronary events are usually due not to severe obstruction of blood flow but rather rupture of a plaque that causes clot formation that can occlude vessels**. This explains why heart attacks and strokes often occur without any prior warning and why the prompt administration of clot busters can be so successful in such situations.

Inflammation is what causes the development of atherosclerotic lesions in arterial walls as well as the rupture of plaque into the circulation that leads to obstructive clots and thrombi. **Statins are effective primarily because they reduce inflammation and the likelihood of plaque fragments breaking off into the blood stream.** LDL is an inert molecule that does not cause inflammation unless it is oxidized, which is why vitamins E, C and other antioxidants may have cardioprotective effects. Statins may also help to stabilize plaque by preventing LDL oxidation and inhibiting the proliferation of smooth muscle that is commonly seen in plaque lesions.

Further evidence of an inflammatory process comes from studies showing that seemingly minor infections with various microorganisms can cause or accelerate atherosclerosis. These include herpes viruses and *Chlamydia pneumoniae*, a common cause of mild "flu" and upper respiratory infections. Chlamydia antibodies indicative of past infection are much more frequent in hospital patients admitted for coronary disease compared to other complaints. Those with the highest antibody titers are twice as likely as patients with the least to have more serious atherosclerosis. Chlamydia has been identified by DNA testing and cultured from plaque removed from heart attack and stroke patients.

It is believed that when this and other microorganisms enter the blood stream the immune system is activated and macrophages carry them to locations where there is evidence of inflammation, such as arterial injury due to atherosclerotic plaque, where they continue to reproduce. This intensifies the inflammation attracting other macrophages carrying microbes that further aggravate the problem. In one study of 61 patients hospitalized for an acute heart attack, throat cultures and blood tests were taken on admission and one month later. Tests for chlamydia showed chronic infection in 23, acute reinfection in 12 and 20% reported respiratory infections within the three weeks prior to admission.

CRP (C reactive protein) is a chemical that rises when the immune system reacts to destroy microbial intruders and CRP levels can reflect the degree of this inflammatory response. In one study of physicians taking part in a large trial to determine the cardioprotective effects of aspirin, CRP measurements were obtained on entry. Over the next eight years the 25% with the highest CRP levels had twice as many strokes and three times more heart attacks as controls who had remained healthy. Harvard researchers reported that **people with high CRP levels and normal cholesterol have the same risk for heart attack as those with the highest lipid and lowest CRP levels. Numerous studies also confirm that statins reduce inflammation and that this has little to do with lowering LDL or cholesterol**.

Stress And Atherosclerotic Heart Disease

What about the contribution of stress to coronary heart disease? We have devoted several Newsletters and sessions at our International Congresses to the role of emotions, behaviors, acute and chronic stress to various aspects of this complex subject. As indicated, anxiety, depression, anger and hostility increase risk for coronary and especially recurrent coronary events. Type A behavior has been shown to be as significant as cholesterol, hypertension and smoking, severe shocks such as learning of the unexpected death of a loved one can cause sudden death and the chronic stress of loneliness, frustration or bigotry is associated with higher coronary mortality rates.

These effects are mediated via multiple mechanisms ranging from exaggerated sympathetic or parasympathetic nervous system reactions, as in the "fight or flight" response and "voodoo death" to prolonged cortisol suppression of immune system defenses. A strong link between emotions and the heart has been recognized since antiquity. Aristotle taught that the heart rather than the brain was the seat of emotions, the Roman physician Celsus noted that "fear and anger and any other state of the mind may often be apt to excite the pulse". The Bible tells us that "A merry heart doeth good, like medicine, but a broken spirit dries the bones" and Shakespeare similarly wrote, "A light heart lives long". Not being able to "get things off your chest", "taking things to heart", 'brokenhearted", "heartsick", "heartache", "eat your heart out", "stone hearted", "faint of heart", etc. are expressions that still reflect our beliefs in varied heart-mind interrelationships.

William Harvey, who in 1628 discovered that the heart was a pump, described a man with heart disease as "Overcome with anger and indignation, and unable to communicate it to anyone." John Hunter, a keen observer who elevated surgery from a mechanical trade to a science in the eighteenth century suffered from angina and complained, "my life is in the hands of any rascal who chooses to annoy and tease me". This was an accurate prophecy since an argument with a colleague did precipitate his sudden death from a heart attack.

Napoleon's physician, Corvisart, wrote that **heart disease was due to the "Passions of the mind, such as extreme anger, fear, jealousy, terror, despair, love, joy, jealousy, greed and ambition**. One hundred and thirty-five years ago, Von Dusch, a German physician emphasized that excessive involvement in work and similar behaviors were characteristic of people who developed heart disease. A few decades later, Sir William Osler, arguably the greatest diagnostician that ever lived, described the coronary-pone individual as "an ambitious man, the indicator of whose engines are set at 'full speed ahead."' In the 1930's, Karl Menninger referred to this as being "strongly aggressive" and Flanders Dunbar, who introduced the term "psychosomatic" into American medicine, characterized coronary candidates as being authoritarian with an intense drive to achieve unrealistic goals.

The fact is that every physician who has commented on coronary heart disease up until 60 years ago has called attention to the causal role of certain emotions and/or behavioral traits. Subsequent scientific studies, including those dealing with Type A behavior and the demand/ control model of job stress have corroborated the correctness of their suspicions. Everyone knows that stressful emotions such as fear and anger often cause angina in coronary disease patients. A recent report on over 1,000 Johns Hopkins medical students who were followed for several decades found that those who quickly reacted to stress with feelings of anger were three times more likely to have developed premature heart disease.

One would suspect that if diet played a crucial role it would have been mentioned by astute physicians who carefully observed patients. For what it is worth, stress has far more effects on cholesterol than fat intake as has been shown in students before final exams and tax accountants who similarly show a sharp increase prior to April 15 despite any change in diet. Increased stress is also associated with greater atherosclerosis in human and animal studies. However, it's not likely that the role of stress will be publicized until someone finds a way to make it profitable financially.

Why Does The Lipid Hypothesis Persist?

I suspect the reasons for this are already quite apparent. The most obvious is that there are so many billions to be made from cholesterol lowering drugs, nutritional supplements and low fat/ no cholesterol food products that any effort to disturb the status quo will be fiercely opposed. However, it's unlikely that this gravy train will be slowed down much less derailed by anyone. The cholesterol cartel has powerful influence if not control over academic institutions, governmental agencies, Congress, cardiologists and scientists who establish guidelines and media resources responsible for the dissemination of this information to the public and health professionals.

Those with contrary views find it difficult to get them published. Funding for continued research not only vanishes but individuals who might pose a challenge, like Kilmer McCully, are actively persecuted. Around 30 years ago, as a young pathologist at Harvard, McCully proposed that the culprit in coronary disease might not be cholesterol but a chemical called homocysteine. Studies in rabbits showed that elevated homocysteine levels acted like sandpaper to irritate the inner lining of arteries and initiate an inflammatory process that could result in atherosclerotic plaque in a matter of weeks. This was subsequently demonstrated in baboons, making the results more relevant for humans. In 1976, Australian researchers reported a definite correlation between high homocysteine blood levels and the degree of coronary atherosclerosis in patients.

Despite this and other supportive studies, his NIH grants were not renewed, other sources of funding mysteriously dried up, his staff was cut down and his lab was moved to tiny quarters in the basement of Massachusetts General Hospital. The hospital Director later told him to leave and "never to come back" since he had not proven his theory. His tenure at Harvard was also terminated in 1978 since it was dependent on this hospital appointment. Although well trained and an ideal candidate for many positions that were available it took him two years to find another job because of persistent persecution.

Following a television interview after his dismissal he received a call from the Public Affairs Director of the hospital telling him to "shut up" and that they "didn't want the names of Harvard or Massachusetts General Hospital to be associated with my theories". Although he thought he did very well on numerous interviews he was surprised to hear nothing further. When he and supporters made appropriate inquiries there was a stone wall of science save for repeated rumors of "poison phone calls" from Harvard. After he sought assistance from a prominent Boston attorney things suddenly changed and he promptly obtained a position at the Providence VA Hospital.

The above might sound like paranoia, but there's nothing worse than being paranoid and being right. McCully's findings have now been confirmed by numerous researchers all over the world, showing that high homocysteine levels are associated not only with increased coronary atherosclerosis, stroke and peripheral arterial disease, but Alzheimer's disease and possibly certain cancers as well. Nevertheless, the "hypothesis" that fat and cholesterol are the cause of coronary disease not only persists, but has become dogma.

Uffe Ravnskov, an independent Swedish physician with a Ph.D. in chemistry has also experienced the persecution of the cholesterol cartel. By 1990, he had published over 40 papers and letters, based on scientific studies, in peer reviewed journals demolishing claims that high-fat foods increase cholesterol and coronary disease, high cholesterol causes atherosclerosis and blocks arteries. He summarized and expanded on these views 10 years ago in *The Cholesterol Myths*, which included hundreds of references from prestigious publications. Many of these were from the very same articles cited to prove the lipid theory that actually showed little or no support.

Cholesterol proponents in Finland were so incensed that they went on TV where they literally burned the book in protest. Despite all the vitriolic rhetoric, nobody has been able to discredit Ravnskov's allegations or seems willing to debate him, probably because recent findings indicate he is correct.

Why Official Guidelines And Recommendations Can Be Hazardous To Your Health

Although the government's campaign to restrict fat consumption has been successful, the promised rewards have not materialized. Over the past three decades, the percentage of fat intake dropped from 40% to 32% and over 90% of adults now eat low or reduced-fat foods and fat substitutes. However, heart disease has more than quadrupled and as fat consumption has decreased, obesity, which remained constant from the early 1960's to 1980, has also skyrocketed. The percentage of obesity increased from 14% to over 22% and a recent study reveals that more than one in four Americans who are 36 years old are already obese. It is no coincidence that the current epidemics of obesity and diabetes started when the government began bombarding Americans with the "Cholesterol is a killer" and low fat propaganda. A low fat diet encourages increased carbohydrate consumption which raises triglycerides and LDL, lowers HDL levels, and leads to insulin resistance and Metabolic Syndrome X. Syndrome X is now found in 30% of adult males and up to 15% of postmenopausal females. It is associated with a marked increase in coronary disease and deaths, even in patients whose LDL levels are well within normal limits.

We are told to avoid meat and dairy products because their saturated fat raises cholesterol. Steak contains equal amounts of protein and fat but half the fat is the monounsaturated type found in "good for the heart" olive oil. A third of the remainder is stearic acid, which also raises "good" HDL cholesterol. Although animal fat consumption has increased in Mediterranean regions over the past three decades, heart disease rates have continued to fall. We were also urged to switch from butter to "heart healthy" margarine. However, margarine is high in trans fats that are known to cause heart attacks, stroke and cancer. Olestra, a fat substitute used in potato chips and other snack foods reduces the absorption of fat-soluble antioxidants like vitamins A, and E that may help protect against coronary disease. Most people are also not aware that many low fat foods actually contain more calories than those they are intended to replace because of increased carbohydrates.

We are constantly asked "Do you know your cholesterol count?", which reminds me of a sign in Albert Einstein's Princeton office that read ***"Not everything that counts can be counted, and not everything that can be counted counts."*** A "cholesterol count" illustrates the latter and with respect to the first half, coronary heart disease is a complex disorder that can have many causes. It is not likely that all of them have been "counted". As Hippocrates first noted, ***"Many times it is much more important to know what kind of patient has the disease than what kind of disease the patient has."*** For some, elevated homocysteine or CRP levels may suggest the most appropriate treatment. For others, reducing coronary prone Type A behavior, depression, anxiety or learning how to cope with stress may prove more productive than trying to lower cholesterol with dangerous diets and drugs that could have adverse long term consequences. Stay tuned for more!

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