The American Institute of Stress

HEALTH AND STRESS

Your source for science-based stress management information

Volume 26 Issue 3 July 2014

REDUCE STRESS

PREVENT

HEART ATTACKS

The mission of AIS is to improve the health of the community and the world by setting the standard of excellence of stress management in education, research, clinical care and the workplace. Diverse and inclusive, The American Institute of Stress educates medical practitioners, scientists, health care professionals and the public; conducts research; and provides information, training and techniques to prevent human illness related to stress.

AIS provides a diverse and inclusive environment that fosters intellectual discovery, creates and transmits innovative knowledge, improves human health, and provides leadership to the world on stress related topics.

Your source for science-based stress management information

HEALTH AND STRESS

We value opinions of our readers.

Please feel free to contact us with any comments, suggestions or inquiries. Email: editor@stress.org

Publication Schedule

Health and Stress: January, April, July and October

Contentment: March, June, September, and December

Combat Stress: February, May, August and November

Health and Stress is a quarterly newsletter with news and advertising designed exclusively for AIS Members. However, it appeals to all those interested in the myriad and complex interrelationships between health and stress because technical jargon is avoided and it is easy to understand. Health and Stress is archived online at stress.org. Past issues can be purchased in the AIS Marketplace. Information in this publication is carefully compiled to ensure accuracy.

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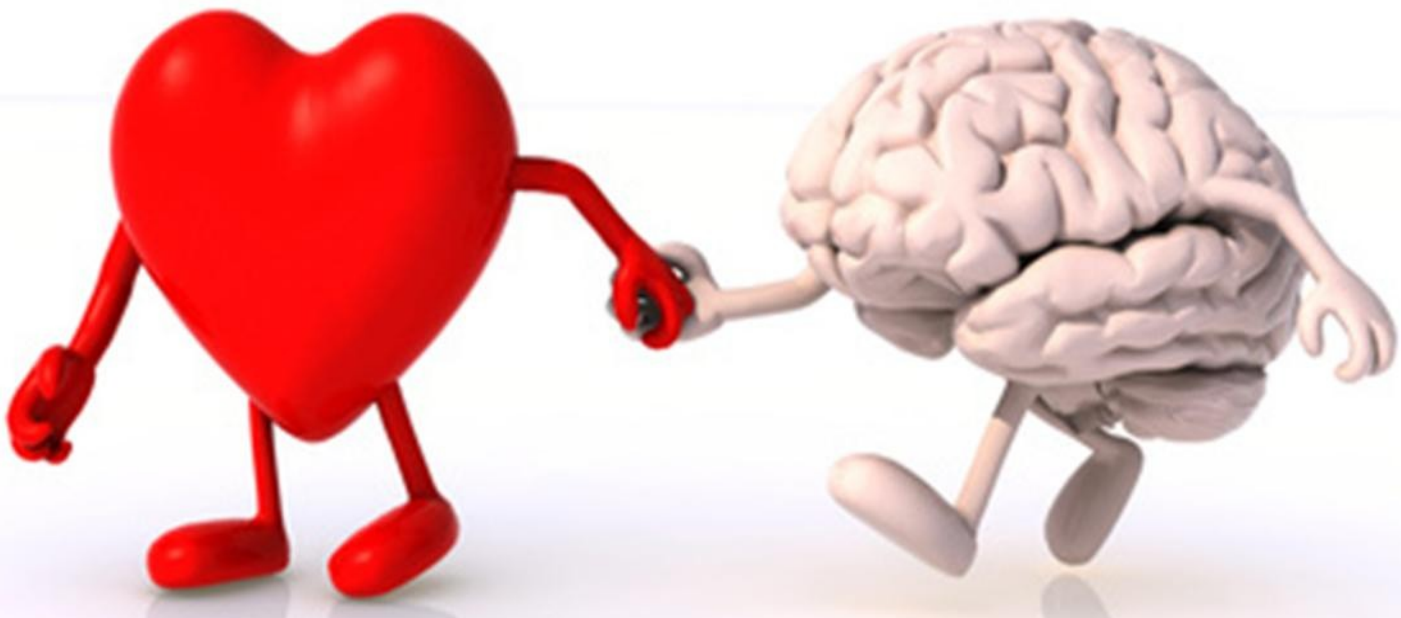

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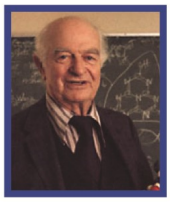
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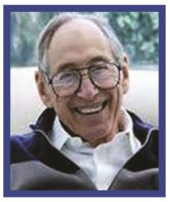
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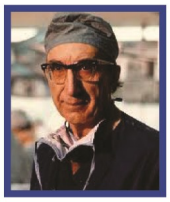
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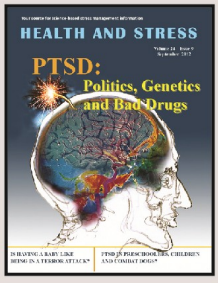

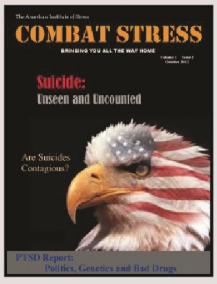

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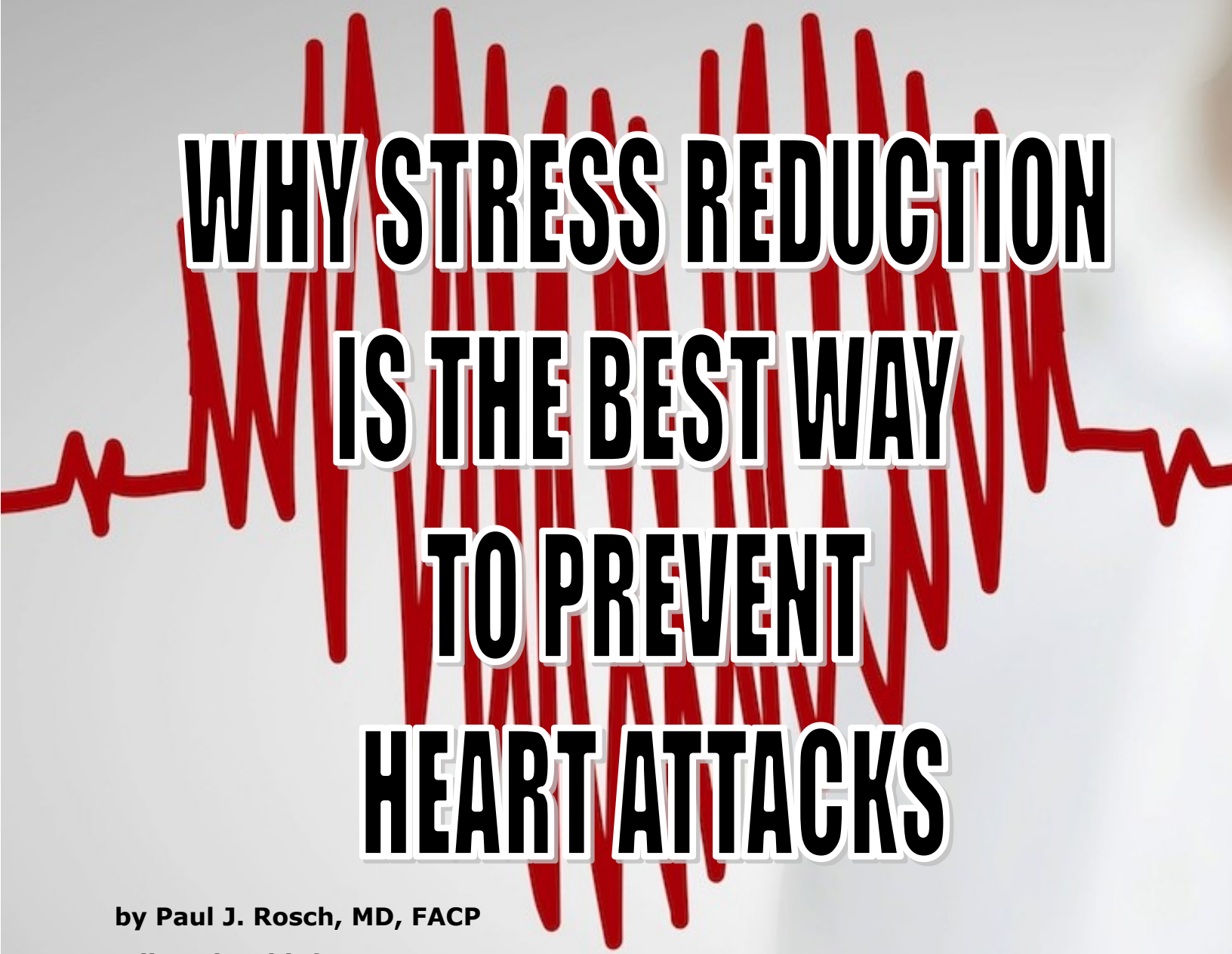
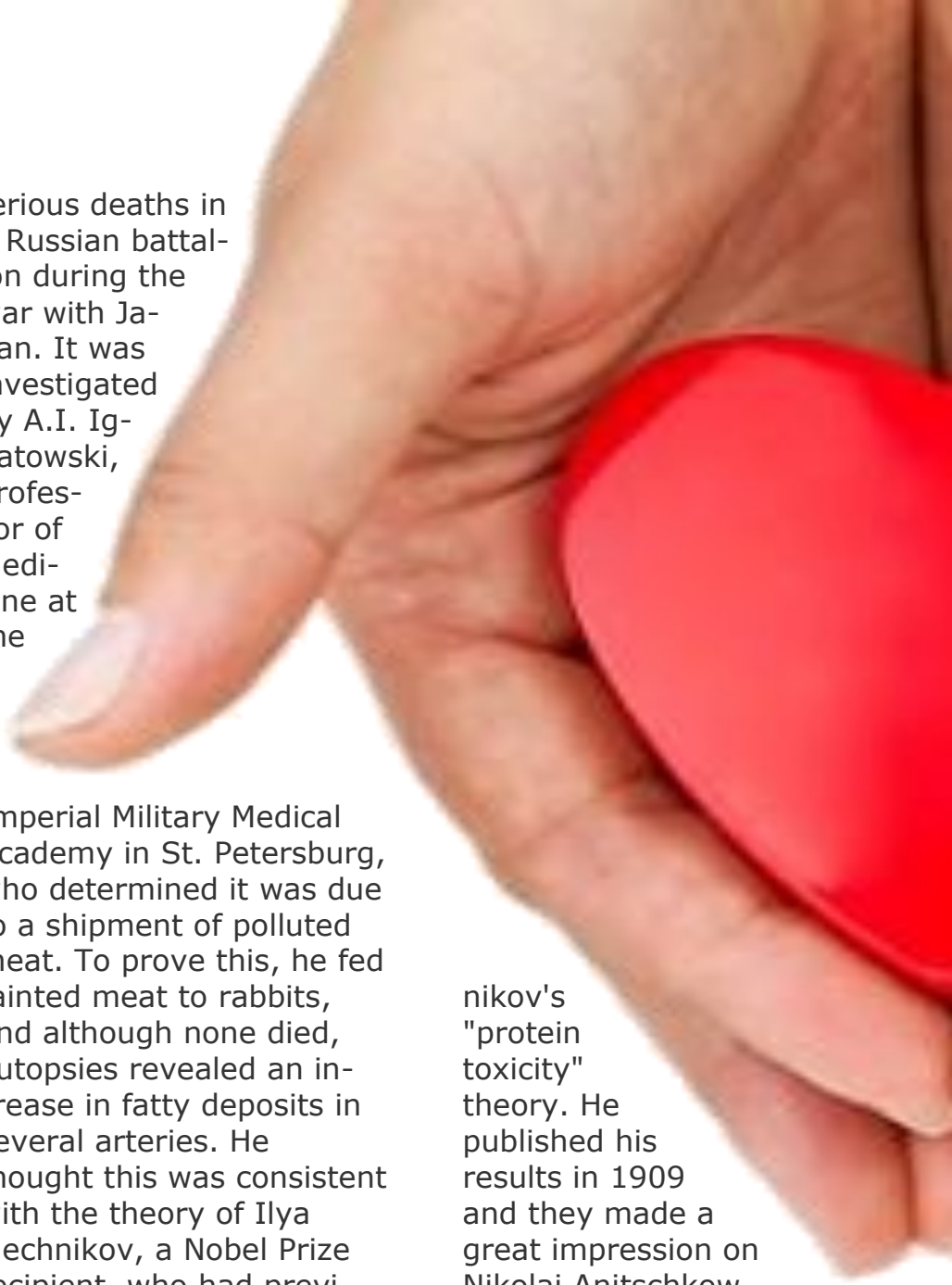


WHY STRESS REDUCTION IS THE BEST WAY TO PREVENT HEART ATTACKS

by Paul J. Rosch, MD, FACP

Editor–in-Chief


"That men do not learn very much from the lessons of history is the most important of all the lessons history has to teach."
Aldous Huxley



Ask anyone what causes heart attacks and the answer is likely to include an elevated cholesterol or LDL (bad cholesterol), which in turn comes from eating saturated fat. Although it has been proven that neither of these claims is true, they have been repeated so many times in articles and advertisements that they are accepted as gospel. As William James, the father of modern psychology noted, "*There's nothing so absurd that if you repeat it often enough, people will believe it*." Joseph Goebbels similarly said, "If you tell a lie big enough and keep repeating it, people will eventually come to believe it", and used this effectively in promoting Hitler's propaganda. So how did these fallacious notions about fat and cholesterol start and why have they been perpetuated for well over a century?

How The Lipid Theory Of Coronary Disease Began And Why It Persists

It all began in 1856 with Rudolf Virchow's discovery of cholesterol deposits in atherosclerotic plaque. Nobody paid much attention to this until over a half century later when there were a series of mysterious deaths in a Russian battalion during the war with Japan. It was investigated by A.I. Ignatowski, Professor of Medicine at the Imperial Military Medical Academy in St. Petersburg, who determined it was due to a shipment of polluted meat. To prove this, he fed tainted meat to rabbits, and although none died, autopsies revealed an increase in fatty deposits in several arteries. He thought this was consistent with the theory of Ilya Mechnikov, a Nobel Prize recipient, who had previously proposed that an excess of dietary protein accelerated hardening of the arteries and other aspects of the aging process.

Ignatowski then fed rabbits a protein rich diet of meat, egg and milk that caused cholesterol deposits reminiscent of atherosclerotic plaque in humans that seemed to confirm Mechnikov's "protein toxicity" theory. He published his results in 1909 and they made a great impression on Nikolai Anitschkow, who had just graduated from the same Military Medical Academy. He and Semen Chalatov, who was still a medical student, decided to develop an animal model of atherosclerosis in rabbits. After several experiments, they showed that simply feeding rabbits purified cholesterol obtained from egg yolks could reproduce the identical

changes Ignatowski described. In their 1913 paper, they reported that the earliest lesions appeared in the aortic arch and had vacuolated cells containing cholesterol.

Although this seemed to confirm that atherosclerosis was due to dietary cholesterol, there were several inconsistencies. When Virchow described atherosclerotic plaque, he termed it *endarteritis deformans,* to emphasize that it resulted from an inflammatory process that injured the intimal lining of arteries, as follows:

We cannot help regarding the process as one which has arisen out of irritation of the parts stimulating them to new, formative actions; so far therefore it comes under our ideas of inflammation, or at least of those processes which are extremely nearly allied to inflammation.

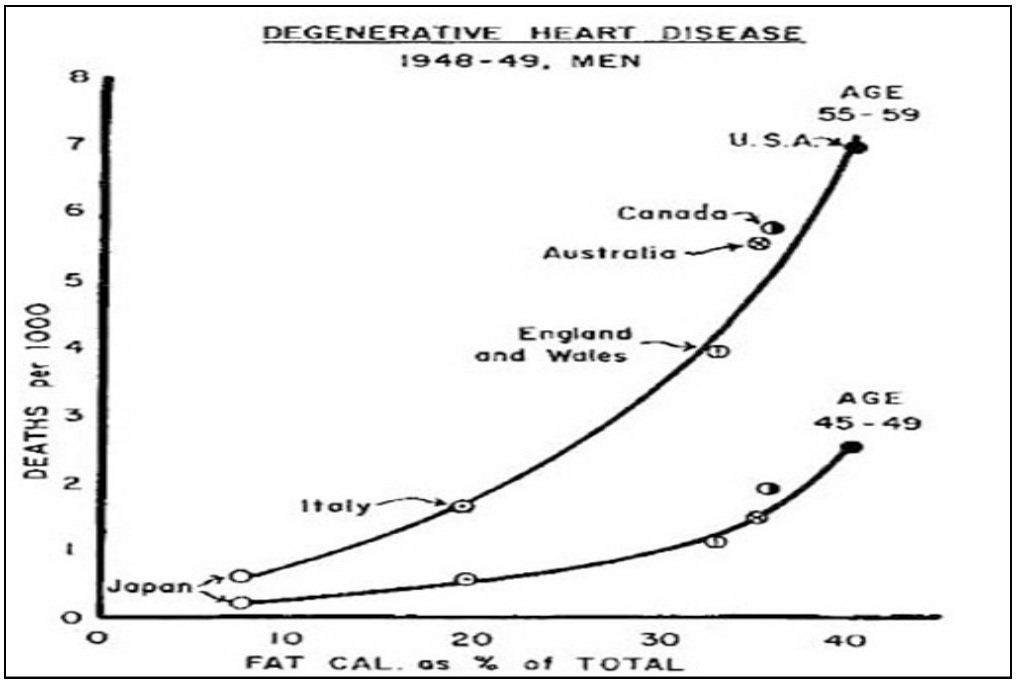
In other words, atherosclerotic plaque in humans was a response to injury or inflammation. The cholesterol deposits came later.

With respect to the studies conducted by Ignatowski, Anitschkow and others, since rabbits are herbivorous, cholesterol and fats are foreign substances that evoke a reaction. The cholesterol deposits they described did not show the characteristic features of atherosclerotic plaque seen in humans nor were they found in the same locations. More importantly, when these experiments were repeated in laboratory animals that were carnivores and regularly ate fats containing cholesterol, no atherosclerotic lesions were produced. In addition, few physicians were interested. Coronary heart disease was not a major problem since many people didn't live long enough to develop, much less die from it. And since cholesterol is a large and inert molecule, it was difficult to understand how it could infiltrate the inner lining of a coronary artery to incite an inflammatory response.

As a result, the high fat diet → elevated cholesterol → heart attack juggernaut did not start rolling until 60 years ago, when it was jump started by Dr. Ancel Keys. Prior to the 1920s, less than 10% of all U.S. deaths were due to heart disease, but by the 1950's this had esca-

lated to more than 30%. At a 1951 UN conference in Italy, a University of Naples professor told him that there was no such problem in his or nearby cities. Keys visited Naples and confirmed that there was almost no heart disease in anyone under the age of 60. The only exception was a class of wealthy people who ate meat almost daily. The general population ate pasta, vegetable and fruit and only had meat once a week and their cholesterol levels were also lower. Keys decided to investigate the relationship between fat intake and heart disease deaths by analyzing statistics from five other countries. He summarized his results at a 1955 conference with the following graph.

As can be seen, there is an almost straight-line correlation between fat intake and deaths from heart disease in men. The U.S. had more than seven times as many deaths as Japan and a corresponding increase in the percent of calories from fat intake. While most pronounced in the 55 -59 age group, it was still present in men ten years younger. To support his theory that fat increased cholesterol levels, which in turn caused heart disease, Keys then began a much larger study of these interrelationships in European and other developed countries around the world where such data could be retrieved. This confirmed his prior results with respect to fat intake and heart disease mortality.



The problem is that although he had data from 22 countries, he only reported the 7 that best supported his views and disregarded the others. Had he included all the countries that were available to him, the results would have been disastrous. For example, the death rate from heart disease in Finland was 24 times that of Mexico, even though fat consumption rates in the two nations were similar. **Also omitted were Sweden, Germany, France and Israel, where the higher the saturated fat and cholesterol intake, the lower the incidence of coronary deaths.**

Although critics pointed this out and their findings were not disputed, Keys' Seven Countries Study made international headlines and was heralded as the solution to heart disease. World War II K rations had been named after him and he was considered to be such a leading authority that his views became official NIH policy. He was featured on the cover of *Time* magazine in 1961, along with a four-page article hyping his

achievements. Despite mounting objections by numerous world-renowned experts, there was only one sentence that acknowledged Keys' dietary advice was "still questioned by some researchers."

As a result, the American Heart Association concluded in 1957 that the evidence that dietary fat correlates with heart disease "does not stand up to critical examination." However, they completely reversed this opinion in 1960 not as a result of any new evidence, but because Keys was now the lead author of their updated report. A massive national campaign was launched to lower cholesterol that emphasized the need to sharply reduce fat intake. This accelerated in the 1970's with the McGovern Senate Committee report advising everyone to eat less fat to prevent heart disease.

It was written by a single nutritionist who based his recommendations on Keys' advice and was entirely unaware of any controversy. The Department of Agriculture also used this report to draw up its national dietary guidelines, which emphasized that fat was bad. The NIH held a "consensus conference", which concluded there was now "no doubt that low-fat diets will afford significant protection against coronary heart disease for every American over the age of 2." The American Cancer Society as well as the Surgeon General also recommended a low-fat diet to prevent cancer.

The National Academy of Sciences disagreed, emphasizing that there was no compelling evidence to warrant recommending a low-fat diet for all Americans. Despite their stature and lack of any conflicts of interest, the authors were censured in the media and in Congressional hearings, as was anyone who denied the danger that had been proclaimed by the American Heart Association, the McGovern Report and various governmental agencies. At one hearing, Senator McGovern asked Dr. Edward Ahrens of Rockefeller University to reconcile his skepticism with a survey showing that *"low-fat recommendations were endorsed by 92 percent of the world's leading doctors*." Ahrens, whom Keys had previously cited as the leading authority on the influence of dietary fats on serum lipids, replied, "Senator McGovern, I recognize the disadvantage of being in the minority." He then went on to point out that the doctors surveyed were relying on secondhand knowledge because they didn't work in this field themselves. There was no solid evidence to support this view and some studies found contrary results. Like Keys, the nutritionist who wrote the report was not a physician and had not conducted any personal studies.

In contrast, George Mann, Sc.D., M.D. Professor of Medicine and Biochemistry at Vanderbilt

Saturated Fat Does Not Cause Heart Disease

Medical School had shown the exact opposite in his research on the Masai tribesmen in Kenya. He was co-director and nutritional consultant to the Framingham Study and reported that there was no relationship between fat intake, cholesterol or heart attacks. He later resigned after they refused to publish his findings. Mann was a harsh critic of the lipid hypothesis, and like Drs. Uffe Ravnskov and Kilmer McCully, was viciously persecuted by the cholesterol cartel. Some of Mann's comments are summarized in the first edition of Ravnskov's *The Cholesterol Myths*, which is now out of print, but can be seen at www.ravnskov.nu/myth7.htm. As noted in previous Newsletters, Ahrens, Mann, Stebhens, Rosenman and others mentioned in Ravnskov's review participated in several sessions dealing with this topic at our International Congresses on Stress in Switzerland two decades ago.

Since then, as noted in prior Newsletters, other evidence clearly disproves the lipid theory of heart disease that can be synopsized as follows:

1. Almost two-dozen

studies have reported that coronary heart disease patients ate less or the same amount of saturated fat as healthy controls. The huge World Health Organization project MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) that collected data from 21 countries for over 10 years failed to find any correlation between heart attacks and fat consumption or cholesterol. **Every single country with the lowest fat consumption had the highest mortality rates from heart disease and those with the most fat consumption had the lowest.**

2. The French consumed three times as much saturated fat compared to Azerbaijan but had one-eighth the rate of heart disease. The heart disease death rate in Finland was three times greater than in Switzerland, even though the Swiss ate twice as much fat. The Swiss have the highest cholesterol levels of any European country and their heart disease rate is one third that of the U.K. Australian aboriginals currently have the highest rates of heart disease in the world, 30 times that of France and 15 times that of the U.K. Yet, their cholesterol levels are the lowest of any population studied.

3. No dietary cholesterol lowering trial has ever shown a reduction in coronary disease or total mortality. In the "Prudent Diet" study of 49 to 59 year-old men, one group substituted margarine for butter, cold cereal for eggs, and chicken and fish for beef. Controls ate eggs for breakfast and meat three times a day. After ten years, there were eight deaths from heart disease in the low fat diet group, compared to none for the meat eaters. Keys also fed middle-aged men a very high cholesterol diet but found that their cholesterol levels were no different than a control group who consumed less than half as much. Decades later, he finally conceded, *"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."*

4. In the Framingham Study, which established cholesterol, hypertension and cigarette smoking as the three major controllable risk factors for coronary heart disease, a 26-year follow-up report found that 50% of cases occurred in people with below average cholesterol. There was a direct association between falling cholesterol levels over the first 14 years of the study and increased mortality rates over the following 18 years. For men above the age of 47, those with low cholesterol had higher mortality rates than those with elevated cholesterol levels. Subjects whose cholesterol had decreased spontaneously over 30 years were also at greater risk of dying from heart disease than those whose cholesterol had increased. In addition, the more saturated fat and the more cholesterol people ate, the lower their serum cholesterol was. Those who ate the most saturated fats also weighed the least.

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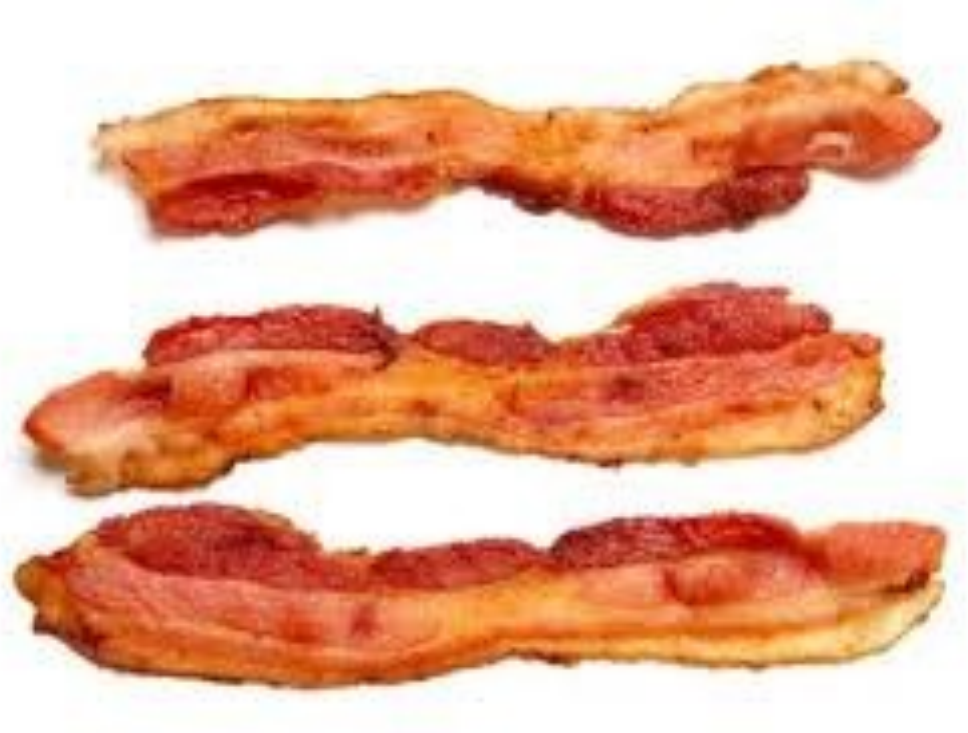
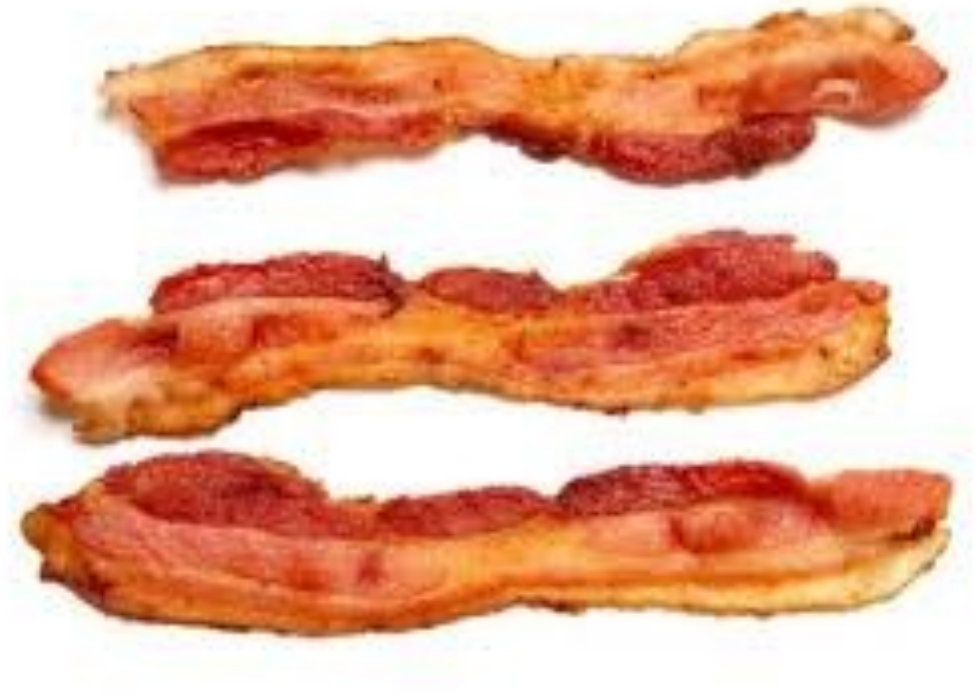


5. No association between cholesterol levels and the severity or extent of atherosclerosis has ever been found in autopsy studies of the general population. No clinical or imaging study has ever



found any correlation between the degree of cholesterol lowering and less atherosclerosis. In one angiography study in which blood cholesterol had been reduced by more than 25% in 24 patients, atherosclerosis was increased in 18 and unchanged in 8. A Mayo Clinic study similarly found that in all patients whose cholesterols had decreased by more than 60 mg., there was a significant increase in coronary atherosclerosis.

6. High cholesterol does not increase risk for heart attacks or coronary events in people over 65, women of any age, as well as patients with diabetes or renal failure. **Senior citizens with high cholesterols have significantly fewer infections and lived longer than low cholesterol controls.** In familial hypercholesterolemia, there is no evidence that the very high cholesterol and LDL levels are associated with a corresponding increased incidence or prevalence of coronary disease.

7. The huge and lengthy MRFIT study (Multiple Risk Factor Intervention Trial) was designed to prove the links between diet, cholesterol, and other risk factors with heart disease. Cholesterol consumption was cut by 42% and saturated fat consumption by 28%. While those on this diet had slightly lower heart disease death rates, this modest benefit was far outweighed by significantly increased total mortality rates, especially from hemorrhagic stroke, cancer, suicide, accidents and violence. **The risk of dying from a cerebral hemorrhage was 500% greater in those with low cholesterol compared to those with high levels**. In most other studies, the incidence of stroke was also higher in those who ate less saturated fat. The highest heart disease death rates were in hypertensive patients on thiazide diuretics and were most likely due to ventricular fibrillation resulting from low serum potassium levels.

8. Autopsy studies of vegetarians reveal that although they have lower serum cholesterol values than non-vegetarians, they have just as much atherosclerosis as meat eaters. In fact, **the International Atherosclerosis Project, which analyzed 31,000 autopsies from l5 countries, found no correlation between animal fat intake and degree of atherosclerosis or serum cholesterol level.** Dr. Michael DeBakey, the renowned heart surgeon, analyzed 1,700 patients with coronary disease and found no relation between levels of serum cholesterol and the degree of coronary atherosclerosis. Other U.S. studies, including the Vet-

erans Clinical Trial, the Minnesota State Hospital Trial, the Honolulu Heart Program, and the Puerto Rico Heart Health Study, all reported no significant relation between a diet high in cholesterol and saturated fats with coronary heart disease. George Mann accurately summed up the situation as follows:

Saturated fat and cholesterol in the diet are not the cause of coronary heart disease. That myth is the greatest scientific deception of this century, perhaps of any century. The diet-heart hypothesis has been repeatedly shown to be wrong, and yet, for complicated reasons of pride, profit and prejudice, the hypothesis continues to be exploited by scientists, fund-raising enterprises, food companies and even governmental agencies. The public is being deceived by the greatest health scam of the century.

Stents, Statins, PCSK9, Inflammation, Homocysteine And Infections

There are numerous other interventions and factors that are widely believed to prevent heart attacks despite lack of proof. Since most of these have been discussed at length in prior Newsletters, the following comments will be limited to a brief summary and update.

Stents to relieve a blocked coronary artery can be life saving for some patients who are experiencing an acute myocardial infarction. They are also useful in relieving anginal pain and improving the quality of life, especially in patients who have failed to improve on medication. However, stenting does not prevent heart attacks or prolong life. An article in *JAMA Internal Medicine* last month entitled "The whole truth about coronary stents: The Elephant in the room", cited a study involving 144,737 patients in over 1.000 U.S. hospitals, in which *almost half the stenting performed was deemed unnecessary.* Another report found that 88% of patients undergoing stenting for stable angina believed it would prevent a heart attack and that over 40% of cardiologists would continue to recommend stenting even when they thought it would not provide any benefits.

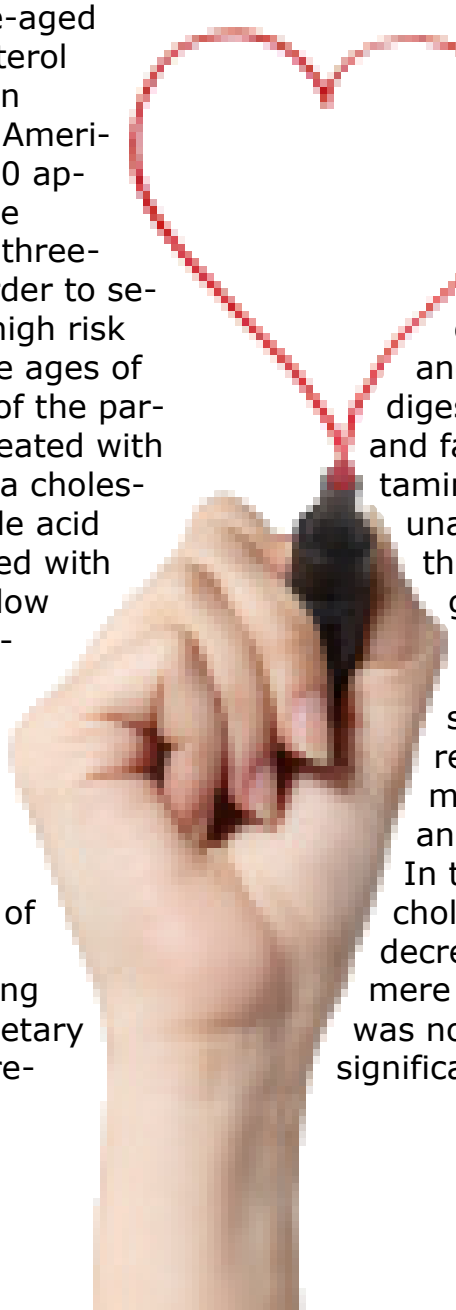
As the lead author noted, "For many patients, undergoing an invasive procedure may put their minds at rest due to the ignorance surrounding the benefit of stents, when in fact a worryingly large majority are undergoing a procedure that will bring absolutely no benefit to their long term prognosis."

Few patients are ever told that a stent would not prevent a heart attack or prolong life. Medicare payments for the procedure, which does not involve opening the chest, range from $10,000 to $19,000 and the cardiologist's fee is usually around $800 to repair one vessel, with an extra $200 to $300 for each additional vessel. Unnecessary stenting is

estimated to cost the U.S. healthcare system about $2.4 billion per year.

The massive campaign to stamp out heart attacks accelerated in 1973 with the NIH Coronary Primary Prevention Trial to prove that lowering blood cholesterol with a drug along with a low cholesterol, low saturated fat diet would reduce coronary heart disease and extend life. The participants were limited to middle-aged men with cholesterol levels higher than those of 95% of Americans and 480,000 applicants had to be screened over a three-year period in order to select 3,806 very high risk men between the ages of 35 and 59. Half of the participants were treated with cholestyramine, a cholesterol-lowering bile acid resin and provided with low cholesterol, low saturated fat dietary advice. The control group received an unpleasant tasting placebo consisting of an indigestible mixture of sand, sugar and food coloring along with the same dietary advice. It was predicted that blood cholesterol in the treatment group would be reduced by 28% and risk of heart disease by at least 50% after seven years.

The results reported in 1984 were disappointing if not disastrous. Some men stopped taking the foul tasting 4 to 5 packets of cholestyramine after a few days and many complained of severe constipation or other gastrointestinal complaints due to the lack of bile acids, which are made from cholesterol and aid in the digestion of fats and fat soluble vitamins. Most were unable to take the full 24 grams daily, so that relatively few stayed on the required regimen for seven and a half years. In those that did, cholesterol levels decreased by a mere 7%. There was no statistically significant difference in heart attacks between the two groups and their overall mortality rates were essentially the same. However, there were more deaths from cancer, intestinal disease, stroke, violence and suicide in the cholestyramine group. Little mention was made of this or the 21 cases and 8 deaths from gastrointestinal cancer in those taking the drug, compared to 11 cases and only 1 death in the control group.



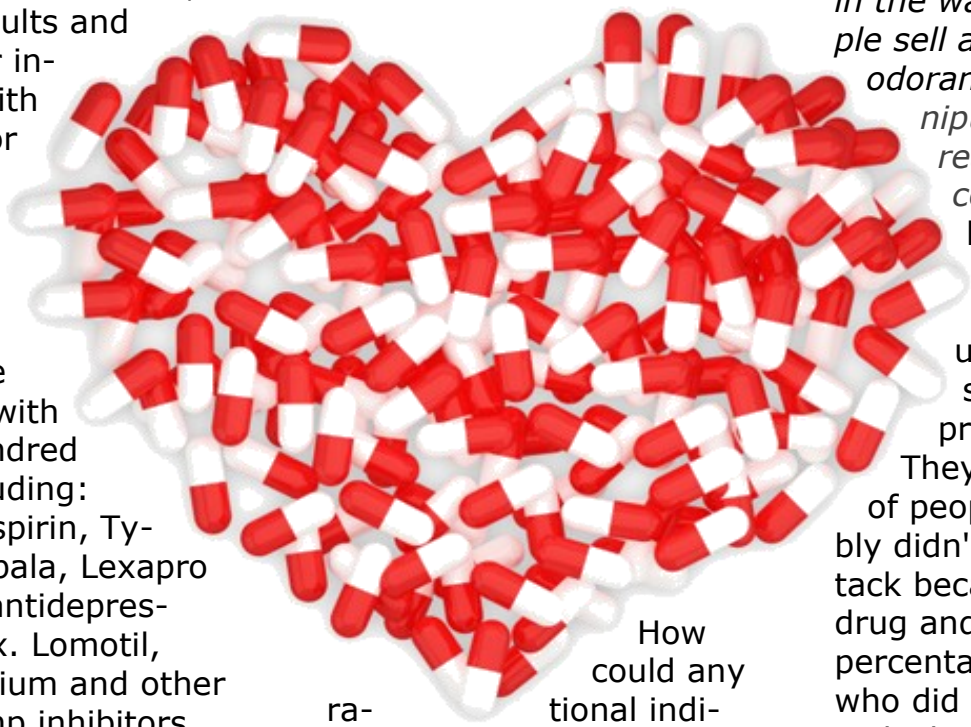
The biased and supportive media, as well as prominent medical journals, portrayed the study as the long sought proof that animal fats were the cause of heart disease. It was widely proclaimed that for the first time, "*It had been proven that lowering cholesterol would reduce the mortality from heart disease and lower the risk of having a heart attack*." And, according to the *Journal of the American Medical Association,*

> The trial's implications…could and should be extended to other age groups and women, and to others with more modest elevations of cholesterol levels. The benefits that could be ex-

pected from cholestyramine treatment are considerable.

This astounding recommendation was made despite the fact that the study group was limited to middle-aged men with unusually elevated cholesterols, many of whom had a rare genetic defect. It was not known what would occur if cholestyramine were given to women, senior citizens, younger adults and children, or individuals with moderate or lower cholesterol levels. In addition, cholestyramine interacted with several hundred drugs, including: low dose aspirin, Tylenol, Cymbala, Lexapro and other antidepressants, Lasix. Lomotil, Lyrica, Nexium and other proton pump inhibitors, Coumadin and other anticoagulants, Singulair, Synthroid, and Xanax. Nevertheless, even though the study failed to achieve any of its goals, the American Heart Association and NIH proudly proclaimed, **"Now we have proved that it is worthwhile to lower blood cholesterol; no more trials are necessary. Now is the time for treatment."**

It should be obvious that if cholesterol does not cause heart attacks, statins would be of little value in preventing them.



How could any rational individual possibly reach such a ridiculous and unsupportable conclusion? The controls had 158 (8.3%) nonfatal heart attacks compared to 130 (6.8%) in the treatment group. There were 38 (2.8%) fatal heart attacks in controls and 30 (1.6%) in the treatment group. These differences were not statistically significant even though the researchers had excluded "uncertain" nonfatal heart attacks from the treatment group but included them in the controls. Eminent authorities were severely critical and George Mann complained that NIH officials, "*used Madison Avenue hype to sell this failed trial in the way the media people sell an underarm deodorant*" and "*have manipulated the data to reach the wrong conclusions.*" What he referred to was that the researchers had used relative risk statistics to improve their results. They took the number of people who presumably didn't have a heart attack because of taking the drug and expressed it as a percentage of the people who did have heart attacks but didn't take the drug. The less than 2% absolute reduction in nonfatal heart attacks was reported as a 19% reduction in risk of a heart attack! The same tactic was used to claim a 24% reduced risk of fatal heart attack

rather than a 1.6% absolute risk reduction. The first law of statistics is that given enough statistics, you can prove anything. The second is that if the statistics do not prove your theory, you need more statistics.

It should be obvious that if cholesterol does not cause heart attacks, statins would be of little value in preventing them. Yet, they have become the best selling and most profitable drugs ever because they utilize the same statistical manipulations to hype their benefits and suppress their dangers in drug company sponsored studies. For example, your doctor tells you that there is a new statin drug with no side effects and that one study showed that if you take it every day for the next five years your **risk of heart attack will be reduced by 34%, but this is relative risk.** What you are not told is that after five years, 2.7% of patients taking this drug had a heart attack compared to 4.1% taking a placebo, an **absolute risk reduction of only 1.4%.** Nor are you told that 71 people would have to take this every day for five years to prevent one person from having a heart attack, but it is not known if that one person will be you. In addition, all the subjects in this study were presumably at increased risk because of elevated cholesterols, and there is no evidence that statins would benefit anyone with a normal cholesterol. If statins were effective in preventing or treating a heart attack, then one would expect to see some confirmation of a clear dose-response relationship. In other words, those patients who had the greatest lowering of cholesterol or LDL, which is used to assess the efficacy of therapy, should receive the most rewards, and this has never been demonstrated. The same minuscule amount of benefit was seen in subjects whose cholesterol declined minimally and those in whom it declined significantly and the same results were seen in participants with low and high baseline cholesterol levels.

These observations provide further proof that neither elevated LDL nor cholesterol cause heart attacks, which threatens the billions of dollars annually from statin sales. Lipitor alone brought in more than $140 billion while its patent was active and Crestor sales are now approaching $7 billion/year. The drug companies now publicly acknowledge that stain benefits are not related to cholesterol lowering, and LDL levels are no longer used to determine dosage. They now claim that statins prevent heart attacks by other "pleiotropic" effects such as anticlotting properties, about which more later. In addition, sales will skyrocket under recent guidelines released by the American Heart Association and the American College of Cardiology that will double the use of statins to 1 in 3 Americans from the current 16%. These now recommend that anyone diagnosed with heart disease, an LDL over 190 and every diabetic over the age of 40 and should be on statins regardless of their cholesterol. This despite the fact that statins are now recognized as causing Type 2 diabetes.

In that regard, as

noted previously, drug companies have successfully concealed the adverse side effects of statins in clinical trials. Proponents boast that their safety record is so superb, they should be added to drinking water. Baycol (ceruvastatin) was withdrawn in 2001 because of increased deaths due to rhabdomyolosis, a rare but serious muscle disorder. Since all statins cause this, it had to be listed on their warning labels along with muscle complaints and weakness. It was only in 2012 that the FDA added memory loss, diabetes, and liver damage, but these may just be the tip of the iceberg. All statins are carcinogenic in laboratory animals receiving doses comparable to those used in humans and it may take decades for the effects of carcinogens to surface. Skin and breast cancers would be the earliest malignancies to be diagnosed and both have now been shown to be increased in patients taking statins. There is also good evidence that Alzheimer's disease, peripheral neuropathy, an amyotrophic lateral sclerosis like disorder and congestive failure can result from statins. Just in the past six years, some 9,000 reports of transient global amnesia, 8,111 of rhabdomyolysis s with 811 deaths have been submitted to MedWatch, the FDA's adverse reaction data base. But the incidence of these and other complications may be much higher since well over 90% of adverse drug reactions are not recognized nor reported. To add to the confusion, there are also reports that statins actually improve memory and can prevent or delay the onset of cancer and Alzheimer's. As noted previously, an elevated cholesterol protects against infections, and the explanation may be that statins are usually given to patients whose high cholesterol for decades provided similar prophylactic benefits.

Trials to demonstrate that elevating HDL "good" cholesterol will prevent heart attacks have also failed miserably and some have been halted prematurely because of an increase in coronary morbidity and mortality. Nor has lowering LDL "bad cholesterol further by adding ezetimibe, which inhibits absorption of cholesterol, as evidenced by the failed Vytorin ENHANCE study. Nevertheless, the push to lower LDL as much as possible persists and the current emphasis is on a class of monoclonal antibodies called PCSK-9 (proprotein convertase subtilisin-kexin type 9) inhibitors. When given with statins, they can **lower LDL levels to less than 50**. At least 3 companies are said to be working at "warp speed" to gain quick approval. Interest in this is so great that at the recent American College of Cardiology conference, two days devoted to sessions on this approach were standing room only.

Statins work by blocking a liver enzyme needed to make cholesterol whereas PCSK9 inhibitors suppress a gene that regulates how much cholesterol the liver can filter out by binding to LDL receptors. It is important to note that these new drugs are not meant to replace statins but rather to augment their lipid lowering effects. No claims will be made that they prevent heart attacks or should be used for treatment, merely that they lower LDL. They are on the fast track for FDA ap-

proval and will probably be available in 2015 if there are no safety concerns. In that regard, complaints of neurocognitive disturbances have already surfaced in clinical trials, and FDA may now insist on tests to include this. LDL is essential for many key cellular processes and is an important component of the immune system and some authorities fear that PCSK9 inhibition will reduce resistance to viral infections such as HIV and hepatitis and lead to a fatty liver. In addition, the drug must be given by injection, probably every two weeks at a cost $3,000/month or $36,000/year. We have been brainwashed as to the evils of cholesterol and LDL and the need to lower them as much as possible. Cholesterol is a vital component of all cells, and most people are oblivious to the greater dangers of low cholesterol, such as suicides and cancer and I predict this new monoclonal antibody approach will be another disaster.

Inflammation has become the new buzzword and is allegedly the cause not only of coronary disease, but cancer and a host of other diseases. It is therefore not surprising that statin proponents now claim that their pleiotropic effects now include reducing inflammation as well as clotting tendencies. However, Vioxx, a powerful nonsteroidal anti-inflammatory drug was withdrawn because it was associated with an increase in heart attacks and over 60,000 deaths. Merck has already paid $6 billion to settle lawsuits; Pfizer paid $2.3 billion for illegal marketing of Bextra, its anti-inflammatory drug that was also withdrawn, and more suits will likely follow. If the combination of anti-inflammatory and anticoagulant activity provides some synergistic effect, then why not consider aspirin? It has been shown to prevent heart attacks and some cancers and is much less expensive.

In 1969, Kilmer McCully noted a connection between homocysteine (a sulfur-containing amino acid) and cardiovascular disease when he observed that people with a rare hereditary condition called homocystinuria were prone to develop severe cardiovascular disease in their teens. The disorder is due to an enzyme deficiency that causes homocysteine to accumulate in the blood and be excreted in the urine. Abnormal homocysteine elevation also occurs in people whose diet contains inadequate amounts of folic acid, vitamin B6, or vita—

min B12 but regardless of the cause, supplementation with one or more of these vitamins can lower plasma homocysteine at a cost of pennies/day. Subsequent studies linked elevated homocysteine to increased risk of premature coronary artery disease, stroke, and venous blood clots, even in those with normal cholesterol levels. It was thought this might be due to direct damage of the inner lining of arteries, increased clotting tendencies, oxidation of LDL, or some combination of these.

Since lowering homocysteine had been proven to reduce the risk of adverse cardiovascular events in people with homocystinuria, it was hoped it would provide similar benefits in others. However, randomized controlled trials of supplementation to prevent cardiovascular events have essentially had negative results. One reason may be that most participants in these trials had normal baseline homocysteine levels, especially since adding folic acid to white flour and cereal grains has been mandatory in the U.S. since 1998. A recent thorough review found no evidence to suggest that supplements of vitamins B6, B9 or B12 given alone or in combination would have

any value in preventing cardiovascular events.

There is growing evidence that infections can contribute to the development of atherosclerosis, especially with respect to *Chlamydia pneumoniae,* which causes a mild flu like illness, but can remain in the body for years without causing any symptoms. Half of all adults have had a C. pneumoniae infection but most are unaware of this. Patients with recent heart attacks had significantly elevated blood levels of antibodies to C. pneumoniae compared to healthy controls and in angiography studies, these antibodies were twice as high in patients with coronary artery disease. In patients with a history of coronary disease, increased antibody levels were associated with increased risk of a subsequent coronary event, or sudden death. Treatment with antibiotics lowered antibody levels and reduced adverse cardiovascular events. C. pneumoniae has been cultured or identified in atherosclerotic plaque from patients undergoing coronary bypass surgery, as well as atherosclerotic lesions in the carotid and peripheral arteries. The surface protein of chlamydia is very similar to the surface protein of blood vessels; so immune antibodies that attack chlamydia may also damage them. Cytomegalovirus accelerates atherosclerosis following heart transplants, other herpes viruses have been shown to cause atherosclerosis in animal studies. Epstein Barr virus infection has been specifically linked to coronary atherosclerosis.

Prior to the emergence of cholesterol, it was generally believed that atherosclerosis was caused by an infection. In 1908, Sir William Osler wrote of *"four great factors in the causation of atherosclerosis--the nor-*

mal wear and tear of life, the acute infections, intoxications [smoking, diabetes mellitus, obesity], and those combinations of circumstances which keep the blood tension high". Note that stress and infections came first and although smoking, diabetes, obesity and hypertension were listed, diet was not, since there were no trans fats. Numerous examples of the increased incidence of heart attacks and deaths following influenza epidemics have been cited as well as studies showing that experimental infections induced atherosclerosis at the site of arterial trauma. Heart disease mortality in Norway began to decline following the introduction of tetracyclines in the late 1950s, when dietary fat intake and smoking were still high and there was a similar fall in coronary deaths in Finland after the introduction of erythromycin and macrolide antibiotics that are effective against C. pneumoniae. Additional support for a causal relationship between influenza and heart disease comes from a recent report showing that flu vaccine provided a 50 percent reduction in the risk of a "major cardiac event" such as a heart attack, stroke or cardiac death, when compared to unvaccinated controls. Other vaccines that show promise in animal studies may be available for clinical use within the next five years.

Ravnskov and McCully have proposed that atherosclerosis and unstable coronary vessel plaque may be due to infection rather than cholesterol deposits. They point out that lipoproteins are part of a nonspecific immune defense system that binds and inactivates microbes and their toxins by the formation of complexes. This could explain why vulnerable plaque in the arterial wall contains lipids and microbes, why neutrophils are seen in the myocardium following an infarction, as well as the frequent occurrence of fever, diaphoresis, elevation of certain markers of inflammation like CRP and even bacteremia in some patients. In that regard, it is important to reemphasize that **inflammation does not cause disease. It is a response to injury**. Nanobacteria may also be a culprit. As its name suggests, nanobacteria are thousands of times smaller than bacteria and can only be seen with very high power electron microscopy. While originally identified in limestone and rocks containing calcium carbonate, they have now been isolated in blood, saliva, urine, atherosclerotic plaque, calcified coronary arteries and heart valves, as well as kidney and gallstones. What causes atherosclerotic plaque to calcify is not known but many believe nanobacteria are responsible because they surround themselves with a hard coat of calcium phosphate that protects them from antibiotics, radiation and the body's immune system defenses.

Geographical studies reveal a strong negative correlation between the availability of sunlight and coronary heart disease. Skin exposed to ultraviolet light synthesizes vitamin D3, and low vitamin D levels have been demonstrated to increase risk for heart attacks, strokes, peripheral arterial disease and accelerated atherosclerosis. However, there is no evidence that vitamin D3 supplementation provides any benefits. Dr. Stephanie Seneff, senior

scientist at MIT, believes this is due to a deficiency of sulfur that arteries require to function efficiently and is usually supplied by cholesterol sulfate. This form of vitamin D3 is water soluble and can travel via the blood stream throughout the body, in contrast to oral vitamin D3 supplements that are not sulfated. Atherosclerotic plaque is rich in cholesterol sulfate and Seneff believes this is nature's attempt to supply sulfate to the heart. Whether some form of sulfur or cholesterol sulfate supplementation will prevent heart attacks remains to be demonstrated.

Hereditary and other factors beyond our control also influence the development, extent and severity of atherosclerosis. Some of the initial signs of atherosclerosis can be seen in the arteries of infants in the same sites where atherosclerotic lesions tend to occur later in life. They consist of subintimal thickening without any evidence of cholesterol infiltration or inflammation. Atherosclerosis is a focal disease usually found in large and medium sized arteries and almost never in small arterioles, capillaries or veins. However, veins that are subjected to arterial pressures when used as bypass grafts or arteriovenous fistulas that are constructed for dialysis shunts often show rapid development of atherosclerosis. Atherosclerosis is frequently found in the arteries of the lower extremities but rarely in upper extremity arteries. These observations tend to negate the lipid hypothesis, since if atherosclerosis was caused by increased cholesterol or LDL blood levels there should be a more generalized or random distribution of lesions.

Moreover, within the large and medium sized arteries, lesions tend to localize at curvatures and branches where the flow is more turbulent, such as the inner sides of the bifurcation of aorta and the sharper curves of coronary arteries. While one side of an arterial segment may be severely affected, the opposite wall often shows no evidence of atherosclerosis. In other closed hydraulic system models with similar curves and Y shaped connections, there are greater negative pressures at these locations. In southern cities subjected to hurricanes, the palm trees lining an avenue will always be seen to be bending inward due to the negative pressure of high winds. Similarly, in the arterial system, negative pressure and shear stress on the inner lining of coronary vessels is greatest at such sites and repetitive insults would result in sufficient injury to initiate atherosclerosis. As the eminent pathologist Dr. Meyer Texon demonstrated well over a half century ago, plaque builds up on the convex surface of a curvature because a greater negative pressure stimulates endothelial cell proliferation.

How Stress Causes Heart Attacks And Coronary Atherosclerosis

As indicated initially, the best way to prevent heart attacks is to reduce stress. The reason for this is that stress is the most common cause of coronary heart disease morbidity and mortality. With respect to stressful life change events, loss of a spouse is at the top of the list and senior citizens have a 20 percent chance of dying, usually from a heart attack, in the 12-18 months after the death of a spouse. During the month

after the 9/11/2001 terrorist attacks on the New York World Trade Center, the rate of defibrillator firings was two to three times normal, even in patients living far from the catastrophe. In one review of work-related stressors, upcoming deadlines were associated with a six-fold increase in myocardial infarction. Other studies suggest that chronic work-related stress could carry a two to three times higher rate of coronary events, especially in employees who perceive little control over their jobs. In women with established coronary disease, those complaining of increased marital stress were three times more likely to experience recurrent events than controls with little marital discord. Caring for a sick spouse or relative at home nearly doubles heart disease death rates. There is also stress cardiomyopathy or "Broken Heart Syndrome" in which middle-aged or older individuals are admitted with severe chest pain and ECG changes suggestive of an impending massive infarction, but who have no angiographic abnormalities or enzyme changes indicating muscle damage. This usually occurs in women following some acutely stressful event that results in myocardial "stunning" due to increased secretion of stress hormones, and most patients recover spontaneously within 72 hours with no evidence of permanent damage.

- Other examples that support a link with heart attacks link included:

- Stress contributes to traditional risk factors such as hypertension, cigarette smoking, diabetes and obesity. For those who still subscribe to the lipid hypothesis, stress has a much greater effect in raising cholesterol than fatty food intake, as demonstrated in tax accountants as April 15 approaches and students on the eve of an important exam.

- Stress can cause costriction of the coronary arteries and increased-platelet stickiness and clumping. All of these promote clot formation.

- Stress increases homocysteine, CRP and fibrinogen, all of which areassociated with increased risk for coronary heart disease.

- Stress induced cortisol causes the deposition of increased deep abdominal fat, which releases cytokines that contribute to insulin resistance, Type 2 diabetes, hypertension and other features of metabolic syndrome and its deadly cardiovascular consequences.

- Increased cortisol secretion also lowers immune system resistance to infections associated with coronary atherosclerosis.

- In addition to stressful life change events, Type A behavior, hostility, excessive anger, depression, and anxiety have all been demonstrated to cause coronary heart disease.

- Stress induced catecholamine hormones and sympathetic nervous system stimulation can cause sudden death by triggering ventricular fibrillation. Rebound parasympathetic overdrive may also cause death due to asystole, an abrupt cessation of ventricular contraction.

- Stress increases free radical damage and inflammation, both of which have been incrimi-

nated as a cause of coronary disease.

- Stress can precipitate and/or worsen congestive heart failure.

- Stress reduces heart rate variability, an objective, accurate and sensitive measure of coronary disease and a powerful predictor of sudden death.

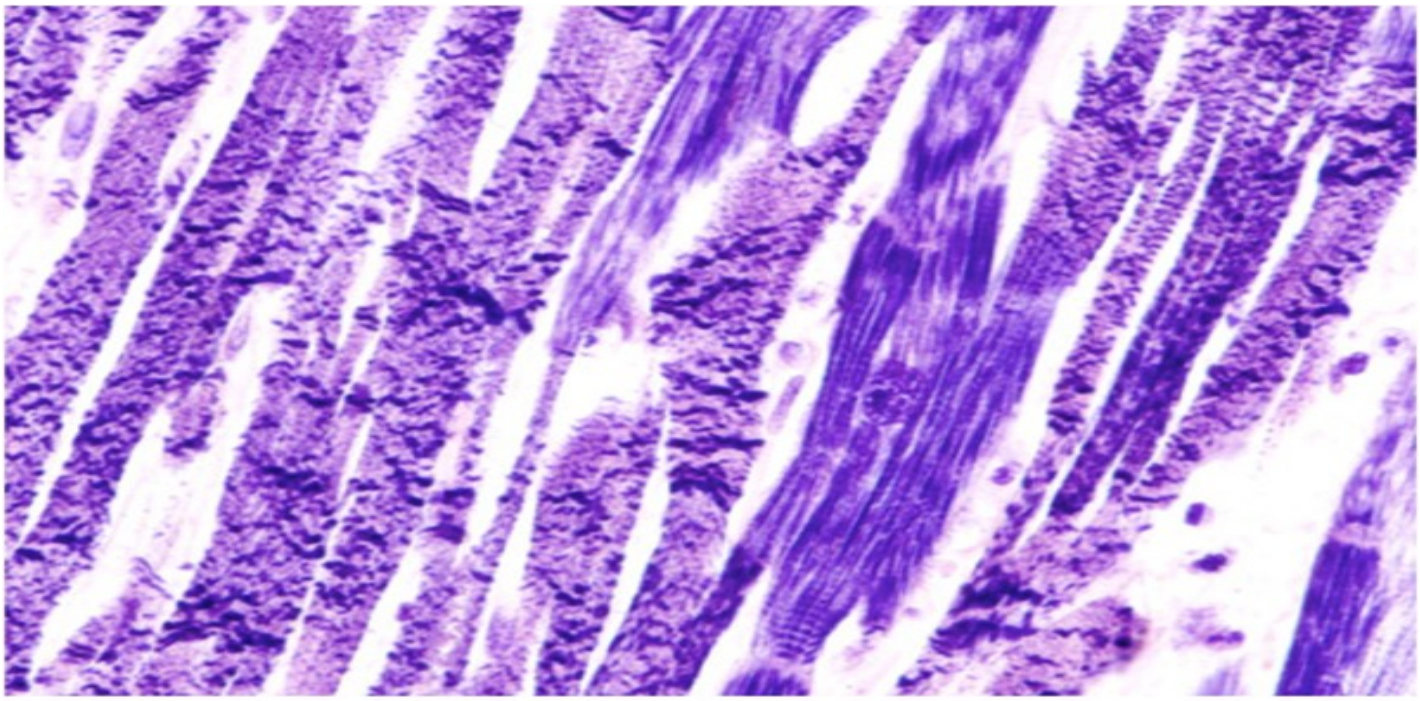
- Acute or severe stress can cause a heart attack in people with no evidence of coronary disease, including healthy teenagers, due to increased secretion of noradrenaline at nerve endngs in the myocardiu m. This produces a characteristic contraction band lesion that shows what is called coagulative myocytolysis, as illustrated below.

- Contraction band necrosis can be seen in sudden death following severe stress in healthy animals and people. It has been reported in pheochromocytoma patients who secrete excess amounts of catecholamines and can be induced in animals by giving intravenous norepinephrine. This lesion has none of the white cell infiltration or signs of inflammation that are usually seen acute myocardial infarctions due to coronary heart disease.

There is much more that could be said to support the opinion that avoiding stress or finding ways to minimize its damaging effects are the best ways to prevent heart attacks and possibly other disorders due to increased atherosclerosis. These will be discussed in the next Newsletter, along with a discussion of the commercial and political reasons that help to explain why they are not being implemented – so stay tuned!

Paul J. Rosch, MD, FACP

Editor-in-Chief



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