HEALTH AND STRESS

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LIPITOR, MEMORY LOSS & LEAPING LIKE LEMMINGS

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Lemmings are little furry creatures best known for traveling in huge herds to some site of self-destruction, usually by drowning. They inhabit cold climates in the Northern hemisphere, subsist on grasses, roots and possibly insects and reproduce very rapidly. Folk lore accounts of mass extinction stem from the fact that every three or four years, the population explosion is so great in some species that hordes of lemmings are forced to swarm out in all directions in search of food. They can swim across some rivers and streams but may drown *en masse* on reaching a large lake or the ocean.

Since lemmings up front quickly consume most of the food in their path, those in the rear constantly try to leap forwards or sideways to gain a better position. This results in a very erratic migratory route that seems to have no purpose and can be lethal for huge herds trying to traverse insurmountable bodies of water.

Lemming is often used as an adjective to denote large groups of people who blindly follow the dictates of some doctrine or person. It also has the connotation that such unswerving allegiance may have calamitous or possibly cataclysmic consequences. The Jonestown massacre and the mass suicides seen in certain cults might be considered to fall into this category.

What does any of this have to do with Lipitor, a widely prescribed medication that has been found to be extremely effective in reducing deaths from coronary heart disease? It is also represented as having a fairly satisfactory safety profile so what's the problem? My concern is not with Lipitor or other statin medications per se, but rather the recent quasi-governmental guidelines concerning the indications for treatment and determination of dosages to be used. Some believe that this report has been engineered by manufacturers eager to further increase their lucrative profits from statin sales. It is important to question the origins, safety and validity of these new guidelines. As will be seen, following them blindly like lemmings could be dangerous or even disastrous.

ALSO INCLUDED IN THIS ISSUE

According to the Director of one popular public advocacy group, which has blown the whistle on other Federal and FDA finagling, **"This whole program has the flavor of a drug industry/NIH cabal."** And with good reason.

The Clout Of The Cholesterol Cartel

The revised set of guidelines was issued by the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. The panel consists of "top cholesterol experts" convened by the National Heart, Lung and Blood Institute, most of whom have strong financial ties to pharmaceutical companies who manufacture cholesterol lowering drugs and products. As the director of the Institute admitted, **"If these guidelines are followed, about 65 million adults will be on dietary treatment and about 36 million will be prescribed a cholesterol-lowering drug."**

Essentially, what this boils down to is that the number of prescriptions for statin medications would triple to almost one in five U.S. adults. Statins would now be indicated in any individual at "high risk". In addition to patients with evidence of heart disease, elevated cholesterol or LDL, this would include anyone with diabetes, evidence of atherosclerosis in other arteries or multiple risk factors (cigarette smoking, hypertension, low HDL, family history, or age (men over 45 and women over 55). **The problem is that these are really "risk markers" that are associated with rather than *bona fide* causes of heart attacks.**

Half of heart attack patients do not have high LDL or any of the standard risk factors. The seven year MRFIT (Multiple Risk Factor Intervention Trial) study showed no reduction in cardiac mortality by eliminating elevated cholesterol, hypertension and cigarette smoking and a subset of hypertensives given diuretics actually had increased death rates. There are some 300 "risk factors" for heart attacks, including a deep earlobe crease, premature vertex baldness or a potbelly, but these are simply statistical associations, not causes.

The National Cholesterol Education Program (NCEP) for the detection and treatment of high blood cholesterol has an interesting history. It evolved from a prior educational effort designed to stamp out hypertension. The general premise underlying this program was that the lower your blood pressure, the healthier you would be and the longer you would live. That turned out to backfire when aggressive attempts were made to reduce blood pressure to lower levels and was especially disastrous for many elderly individuals.

The first NCEP report was issued in 1988. By a miraculous coincidence, it was timed to the introduction of Mevacor, Merck's new cholesterol lowering drug. In an unprecedented action, it was also released to the public directly, weeks before doctors could read the scientific information on which it was based. Prior to this, clinical trials with available cholesterol lowering drugs had shown some reduction in coronary events but not in overall mortality rates. In addition, they were associated with a variety of adverse side effects, including violent behavior, suicide, and possibly an increase in deaths due to cancer. Mevacor (lovastatin) was the first of a new class of statin drugs that reduced cholesterol, seemed safer, and reduced deaths from heart attacks without any increase in mortality from other causes.

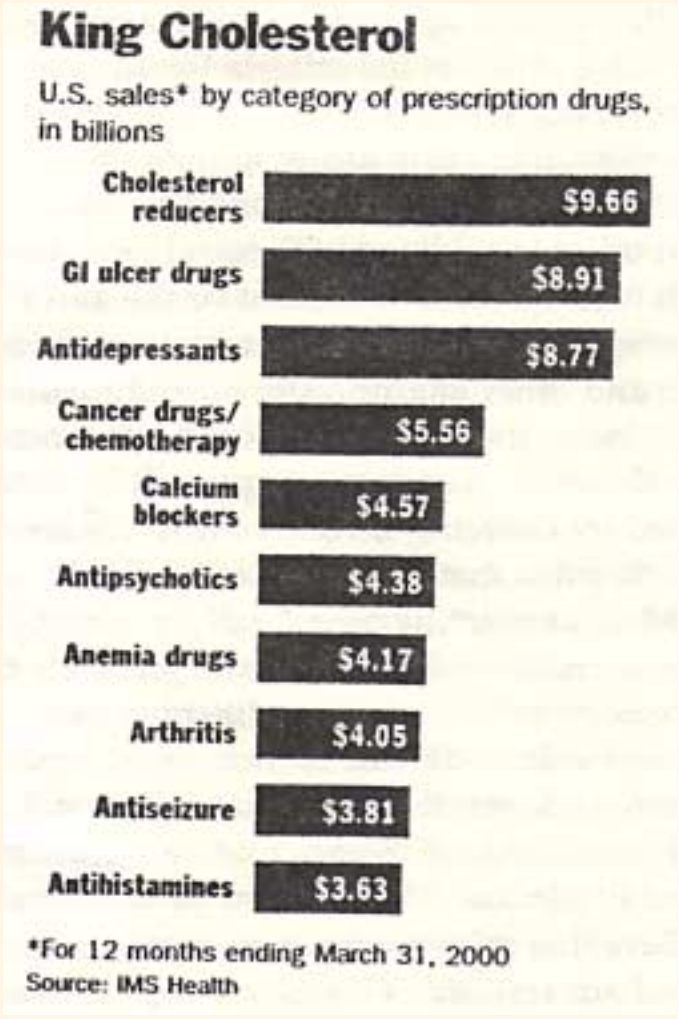
While newer statins like Lipitor may be superior, **these revised guidelines are based more on speculation than solid scientific research studies**. While the ostensible goal is to reduce coronary deaths, one wonders how much increasing corporate profits may have played a role in this recent pronouncement.

Public Health Or Private Profits?

As *The Wall Street Journal* noted, "**Rarely have so few doctors recommended so many drugs for so many people - virtually overnight**. For the first time in eight years, the government has published new cholesterol standards. If the more rigorous guidelines are widely followed, doctors could wind up writing a stack of prescriptions that would nearly triple - to 36 million people - the number of Americans on cholesterol-lowering drugs. **The recommendations**

would put fully 18% of Americans on 'statin' drugs like Pfizer Inc.'s Lipitor, Merck & Co.'s Zocor and Bristol-Myers Squibb Co.'s Pravachol. **And the new guidelines could theoretically triple U.S. sales of these medicines to $30 billion a year.**"

Proponents and pharmaceutical manufacturers argue that these drugs will ultimately lower health care costs because the number of heart attacks, strokes and diabetic complications will be reduced. Sounds good but this remains to be proven. What we do know is that **despite a sluggish economy, spending on prescription drugs has been rising nearly 19% a year and is even higher for cholesterol drugs, which lead the pack as noted below**.



Lipitor is already the nation's leading prescription drug with sales of $4.5 billion last year, and it is no wonder that Pfizer would like to see this triple. Spending hundreds of millions of dollars to promote it ethically as well as covertly may seem like a lot of money, but is actually a paltry investment in view of the immense potential returns.

While cholesterol has been the biggest bonanza, drug companies have been busy finding ways to push other products; hypertension is a good example. Last January, the American Diabetes Association decided to issue new and lower blood pressure standards. The result is that more diabetics will now be taking antihypertensive medications and those already on them may have to take more. In addition, over the past few years, experts have recommended that several drugs should be used to lower elevated pressure rather than the usual practice of simply increasing the dose of one that has not achieved the desired effect. Manufacturers are jockeying for position for the over 70 products to choose from, including calcium channel blocking agents, diuretics, beta blockers and others. Conflicting claims for superior efficacy and safety can be confusing, especially since manufacturers increasingly advertise directly to the public. All patients who have had a heart attack are now also advised to take beta blocker drugs to avoid a recurrence, even if blood pressure is normal.

The immediate financial repercussions of these aggressive promotional efforts are staggering and there is little doubt that the costs will be passed on to consumers. As one expert noted "Managed care is no longer trying to control costs. Insurers will simply take whatever they have to pay for these drugs and pass that cost along directly to employers, who will raise co-payments and deductibles for their workers." According to another, the health and financial benefits of increased prescription drug use, such as heart attacks and strokes prevented, could be years away. Managed care companies will be asked to provide more expensive treatment that ultimately might reduce Medicare and Medicaid costs, but there is no guarantee of when or if this will happen.

Are LDL Levels The Best Criterion?

The available evidence suggests that statin drugs like Lipitor can significantly reduce the incidence of coronary events and

deaths due to heart attacks in susceptible individuals. **However, these benefits may be entirely unrelated to their ability to lower cholesterol or LDL levels as the new guidelines claim.** If this were the reason, why don't other drugs that also lower LDL or cholesterol provide the same clinical rewards? What's the difference?

As emphasized in previous Newsletters, cholesterol is a large inert molecule and it has always been difficult to understand how it could infiltrate the arterial wall. In addition, the lipid laden lesions seen in animals force fed on high fat diets bear little resemblance to the obstructive atherosclerotic plaque seen in coronary artery disease. These **plaque deposits are more reminiscent of the type of response one might see to an infection, with foam cells and other stigmata of inflammation**. Support comes from studies showing that patients with heart attacks and stroke due to obstructive atherosclerosis have higher than normal antibody titers to chlamydia and other common microorganisms and chlamydia has also been cultured from these lesions obtained during surgery or at autopsy.

In addition, these patients have higher than normal blood levels of C-reactive Protein (CRP). In the absence of an acute infection such as tonsillitis, a significantly elevated CRP appears to be an independent risk factor or marker for the arterial inflammation associated with atherosclerotic plaque. Using a new highly sensitive assay now available at most academic medical centers, CRP levels over 2.0 mg./L correlate with increased risk provided that other causes of elevation can be excluded.

The reason that statins reduce risk for heart attacks and strokes is because they reduce inflammation, not LDL or cholesterol. The vast majority of coronary thromboembolic events occur when fissures in plaque cause segments to be dislodged. This tendency is reduced by the stabilizing actions of statins, which occur fairly rapidly after onset of therapy and long before effects on LDL are seen.

A recent double blind study published in *Circulation*, an American Heart Association journal, showed that **all three major statin drugs have potent anti-inflammatory effects**. It involved 22 individuals, average age 48, with elevated LDL or "bad" cholesterol and high triglycerides who followed a low fat diet and were given the three drugs alternately for six weeks. CRP concentrations were measured three times at the beginning of the study and twice after each six-week treatment period. CRP levels were lowered in 73 percent of patients taking Pravachol (pravastatin) and in 82 percent of those taking Lipitor (atorvastatin) or Zocor (simvastatin). The average reduction ranged from 20 to 28 percent. Although cholesterol and LDL were also lowered, **there was no correlation between the reduction in LDL and reduction of CRP**.

While a high LDL seems to be more associated with coronary events than a high cholesterol, **a normal or low LDL hardly predicts protection**. LDL contributes to atherosclerosis when it becomes oxidized by bombardment with free radicals and generates foam cells in an inflammatory reaction that attracts macrophages and other scavenger cells that gradually build up plaque. Thus, **atherosclerosis also satisfies the criteria for an autoimmune reaction** and is often accelerated in such disorders, including lupus, antiphospholipid syndrome and rheumatoid vasculitis. **Elevated antibodies to oxidized LDL correlate not only with future heart attacks and stroke, but also subsequent blockage of blood vessels in bypass and other angioplastic procedures.**

Under the new guidelines, the dosage and duration of statin therapy will be determined by reducing LDL to new lower levels. This implies that **most patients will be advised to take statins perpetually, probably in ever increasing doses**. That's great for the drug companies, but is not likely to result in corresponding clinical improvement since it does not address the infectious, inflammatory and autoimmune factors that cause atherosclerotic plaque. **There is also good reason to believe that this practice may cause unanticipated adverse side effects.**

Side Effects, Toxicity And Safety

All medications have side effects. In some instances, it may be difficult to determine if an unsuspected or undesired reaction or even a favorable response is due to the drug, as opposed to a nocebo or placebo response. That's why the gold standard for clinical trials is a double blind study in which the active agent is compared with something that appears identical but is inert, and neither physician nor patient is aware of what is being administered.

Drugs with potent effects in one area are also apt to have more side effects not related to their therapeutic activity. All drugs also have toxic effects when excessive amounts are taken and the ratio between effective and toxic doses can vary considerably. In many instances, adverse side effects are not detected in clinical trials and may not surface until a medication has been in widespread use for a long period of time. Penicillin appeared to be a panacea for pneumococcal pneumonia and other infections when it first became available and was generally considered to be completely safe, even in massive doses. It took years to recognize that it could cause serious allergic reactions and even anaphylactic deaths in sensitized individuals. Phenylpropanolamine was recently removed from numerous popular prescription and nonprescription products because of its link with stroke. **It had been in widespread use for over five decades before this was recognized!**

Cholesterol is a basic building block for steroids and other vital compounds and the vast majority of brain structures are composed of lipids. It would be naive to assume that drugs affecting its makeup or metabolism would be completely innocuous. While statins enjoy a good safety profile, it is not unlikely that undesirable or even dangerous side effects will emerge with the widespread and indiscriminate long term use that is mandated by these new guidelines. **This would be more likely to occur if the dosage and duration of therapy is determined by LDL levels that have no correlation with efficacy of treatment. If LDL continues to be high, doctors will simply increase the dose of the drug.**

Such problems may have already started to surface. Last April, a reputable syndicated health column reported the following: "Several weeks ago we received a letter from a reader with impeccable credentials. **A retired family doctor and former astronaut started taking Lipitor for elevated cholesterol and six weeks later had a six-hour episode in which he couldn't remember anything and didn't even recognize his wife.** A full diagnostic workup did not show any neurologic problems so he stopped the Lipitor.

According to 'Spacedoc', (who has devoted a web site to this at www.spacedoc.net) **'Believing that must have been a simple coincidence, I decided a year later to restart Lipitor. Six weeks later I was brought to the ER with a 12-hour episode of total global amnesia.'** Again he lost his memory.

One 39-year-old man reported: 'Six weeks ago my doctor doubled my dose of Lipitor from 20 mg. to 40 mg. For the past four weeks I have had trouble with memory. I couldn't remember my brother's phone number, I couldn't remember a recent trip or a restaurant I ate in, and I forgot to attend an important meeting. This is totally out of character for me.'

A woman reported that soon after starting a cholesterol-lowering drug she experienced pain in her chest, neck and jaw. This was followed by six hours of disorientation. **'I could not remember things that were very ordinary such as names of friends, their addresses or phone numbers (including my own).'** She stopped the drug and memory gradually returned with no further episodes.

Others have experienced muscle pain and weakness. Although blood tests were normal, many found they could not longer exercise as they used to. According to one patient: 'I became more and more inactive until I hardly had the strength to get up in the morning and bathe. When I became debilitated with tremendous joint pain, I stopped the medication. Since then, my energy level has increased a hundred fold. **As I see it, this medicine ruined the quality of my life. It caused severe bouts of depression, short spells of memory loss and debilitating pain**.'"

Other Observations, Including My Own

I found this column intriguing for several reasons. If so many unsolicited complaints had been submitted to this one source, how many others of a similar nature were out there that had not been reported? And just how significant were these anecdotal observations? After all, Lipitor and statin drugs are particularly apt to be prescribed for patients already at increased risk for small strokes and transient ischemic events that could include temporary memory loss. With so many elderly people taking these medications, it would not be unusual for such complications to occur. The only way to determine if statins were responsible would be to discontinue the drug to see if the problem quickly disappeared and then resume it to determine if it recurred. However, few people would take such a risk.

I decided to correspond with "Spacedoc", who turned out to be Duane Graveline, a retired physician board certified in Family Practice as well as in Preventive Medicine. His concern was that doctors would attribute any adverse reactions to age or senility rather than statins and said that he would never take another cholesterol-lowering drug. In his opinion, "An event may be rare by any definition, but when millions take it, even a one-in-a-thousand incidence creates swarms of cases." A former member of the astronaut program, **he is especially fearful that doctors may prescribe statins to people where memory loss might be disastrous not only for them, but possibly others, as could be the case for an airline pilot or school bus driver**.

I also talked with one of the investigators at the University of California, San Diego, who is involved in a study of the central nervous system effects of statins. The results will not be available until 2004, but she said they were actively investigating several disturbing reports of memory loss and unusual fatigue while taking statins that improved on cessation of therapy. She also indicated that there was some evidence that recovery was more rapid following the administration of Coenzyme Q-10, a powerful antioxidant that blocks free radical damage, which makes sense.

Since starting his statin web site, "Spacedoc" has received numerous communications that confirm his concerns that side effects may be much more common than previously suspected. Most complained that it had never occurred to them that the problem might be due to statin therapy. Even when this possibility was raised, it was usually dismissed by their doctor or neurological consultant as extremely unlikely.

Some examples include, "I have been a physician for 25 years. I have high cholesterol and three years ago started on Lipitor. It lowered my cholesterol level from 261 to 141 within months. A year ago, I noticed severe calf pain and a progressive loss of stamina in my legs while jogging or playing tennis. I feared I was developing intermittent claudication, a decrease in blood flow to the muscles of the leg. An angiogram demonstrated that my leg blood vessels were clean and wide open. A surgeon friend ruled out spine disease. I finally did some research on Lipitor and found that it could cause rhabdomyolisis, or destruction of muscle cells. My doctor and I agreed to discontinue Lipitor. Within weeks my muscle pain was completely gone. Now leg cramps never interrupt my tennis matches. **I am convinced that Lipitor was causing my problem and worry that others may suffer needlessly**."

Lipitor is not the only offender and muscle pain, amnesia and fatigue are not the only side effects. One housewife wrote, "On Zocor I experienced drastic mood swings and literally kicked my dog and two cats as they were waiting to be fed. **I was yelling at my husband for no reason. I was also having problems with my short-term memory. I told my husband that I would kill myself if the rest of my life had to be like that.** My doctor switched me to Pravachol after two weeks off Zocor. During that time the mood swings and memory lapses improved greatly and I did not feel violent. Within a month of starting on Pravachol, however, I felt extremely fatigued. I began to have migraines almost daily. All of my arthritis spots acted up at once, and I had head-to-foot body aches. Before long, I was fighting insomnia, muscle weakness and short-term memory loss.

Worst of all, I felt detached from myself, a very spacey, lost feeling. I returned to my doctor and refused to take any more of these drugs. Over the next several months the migraines disappeared, the arthritis came under control and the muscle aches and weakness left. My mood is back to normal. I am happiest that **I am again mentally normal, with no more foggy, spaced out feelings. I am 57 going on 45 in looks and actions. While taking Zocor and Pravachol, I felt like I was going on 90 instead!"**

I have never been a proponent of the high fat diet-high cholesterol-heart attack hypothesis. We have included several sessions at our annual International Congress on Stress to debunking this widespread misconception by distinguished authorities in the field including Stewart Wolf, George Mann, William Stehbens, and most recently, Ray Rosenman. Stewart Wolf, our first Hans Selye Award recipient and a respected cardiologist, had a cholesterol that approached 600 in his college days and has always been elevated ever since. Although now well in his eighties, he has no cardiovascular problems and actively continues his clinical research.

My wife, Marguerite, had been taking Lipitor for about a year and after reading all these accounts, I recalled that she had also recently complained of increasing fatigue as well as memory lapses. The latter were laughingly dismissed as "senior moments", even though she is still not eligible for Medicare. Like many others of Mediterranean extraction, Marguerite has always had a high cholesterol but with a high HDL that puts her in the very lowest risk category for a heart attack. I had previously reassured her that no treatment was necessary but when a preoperative blood test for a colonoscopy caused concerns, her physician correctly prescribed Lipitor. Her cholesterol fell slightly and the dosage had been increased.

Since stopping Lipitor several weeks ago her feelings of fatigue have definitely diminished. There is also some suggestion that her memory complaints have also improved but this is difficult to substantiate. Based on the UCLA research group's comments, she also takes Coenzyme Q-10 in addition to her daily dose of Vitamins C and E, and this may be a factor.

Putting Things In Perspective

As originally emphasized, statins are a very promising class of medications that can undoubtedly benefit millions at high risk for coronary heart disease. **However, this is not due to lowering of LDL or total cholesterol but rather their ability to reduce inflammation and increase blood flow by stimulating nitric oxide induced vasodilatation.**

In patients who have had a myocardial infarction, **mortality rates for those treated with statins over the next twelve months are less than half of non-treated controls, regardless of LDL and total cholesterol effects. This rapid reduction in risk is achieved by stabilization of plaque lesions rather than reduction in lipid atherogenesis, which would take years to achieve.**

Atherosclerosis is a complex process that involves bombardment of LDL with free radicals to create an inflammatory reaction that the body's immune defenses respond to, resulting in plaque formation. The process of plaque fissuring and rupture is responsible for the vast majority of coronary events and statins are effective because they prevent this, not because they lower LDL.

The amount of statins required to stabilize plaque may be much less than that required to reduce LDL to the new lower levels that have been arbitrarily selected. Aspirin has similar cardioprotective effects and it is now clear that the effective dose is a small fraction of the previously recommended amount used for most indications.

If physicians use LDL levels or even HDL-cholesterol ratios (which correlate better with coronary events) as the target goal for determining statin dosage, numerous patients are apt to suffer adverse effects needlessly. CRP concentrations are superior predictors but are influenced by too many factors not related to coronary atherosclerosis. What we need is a more specific and sensitive measure of arterial inflammation. Until this is available, prophylactic statin therapy should be considered cautiously on an individual basis, rather than blindly following blanket guidelines like lemmings.

Customer Relationship Management (CRM) & Pharmaceutical Marketing

When I entered practice over four decades ago, prescription drugs were never promoted directly to the public and the only information about them was usually from a physician, or possibly the *Merck Manual*, which was available in most public libraries. Doctors generally learned about new drugs from pharmaceutical representatives who supplied them with samples and promotional literature and sometimes pens, flashlights, knives or other items containing the name of the drug to keep reminding them about it. I was reminded about that last week on a plane flight, when my meal tray included an advertisement for Allegra, which included a rebate for up to $10.00 on any Allegra prescription and urging me to ask my doctor about the drug or to call 1-800-Allegra for further details. Today, patients can quickly become just as informed as their physician about any drug by consulting a PDR or surfing the web, including free access to all scientific publications in the National Library of Medicine. Radio and TV ads abound not only to promote drugs, but medical equipment, hospitals, as well as ophthalmologists offering the latest laser surgery.

Customer Relationship Management (CRM) is a euphemism to describe the complex process that now enters into promoting pharmaceuticals. It involves deciding how much to allocate to direct media advertisements, sales representatives who call on physicians, what medical journals or web sites to advertise in, etc. These priorities are constantly changing as physicians are no longer the sole source of information for patients, and in recent years, Direct To Consumer promotion has approached $2 billion annually. However, since physicians usually have the final say, statin manufacturers have launched an all out campaign to provide them with rewards. As *The Wall Street Journal* recently noted, "Many insurers now grade doctors' performances and dole out monetary bonuses and penalties based on measuring and improving patients' cholesterol levels. And the fastest and easiest way for doctors to lower cholesterol is to prescribe a powerful statin like Pfizer Inc.'s Lipitor. Insurance provides all kinds of incentives for that behavior. You get a bonus payment that is about 20% of what you are otherwise paid for care." Drug companies enlist doctors as "consultants" even at smaller community hospitals and pay for medical conferences. At the recent American College of Cardiology meeting Pfizer was the leading sponsor at a cost of $822,000, in addition to handing out thousands of Lipitor logo bags to physicians. Sales reps bring pizza or lunch for the office staff, treat physicians to dinner, etc.

With the imminent introduction of new statin drugs, competition will be fiercer and patients and physicians will be bombarded with offers and contradictory claims that are bound to be confusing. As will be discussed in a future Newsletter, many doctors are fighting back at www.nofreelunch.org. Legislation is also being considered to ban misleading media ads that do not provide full disclosure of adverse side effects. Stay tuned to see how Marguerite makes out.

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