The Vilification of Cholesterol (for Profit?)

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Those who have read my editorials over the years will know that I am not a wild-eyed, far-left anticapitalist. Nonetheless, the only justification I can see for the new cholesterol practice management guidelines (discussed below) is to print money for drug companies. Truly, how can anyone think we need to prescribe statins to 50% of the population older than 40?! In order to justify this extreme position, data had to be distorted and cholesterol vilified.

Cholesterol—a molecule critical to health—has been demonized in conventional medicine and the popular press as the major cause of heart disease. The research is clear that elevated cholesterol is indeed associated with cardiovascular disease. The real problem is not cholesterol but rather oxidized low-density lipoprotein (oxLDL) cholesterol. Elevated cholesterol typically also means elevated oxidized cholesterol, so it is, in reality, an indirect measure of the true problem (cooking cholesterol-rich foods in the presence of oxygen, excessive oxidative stress in the body, inadequate consumption of antioxidants, etc), which is discussed later.

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) "Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" significantly lowers the "safe" cholesterol blood levels. These new "standards" mean that many adults in the United States can be prescribed statins despite the dearth of documentation that they provide any benefit except for a small subset with very specific risk factors. As bad as, or even worse than, the costs will be all the adverse events and the real problem: the underlying causes are once again ignored in favor of treating the symptom—an elevated blood measure.

The New ACC/AHA Guidelines

The authors of the report of the ACC/AHA Task Force on Practice Guidelines certainly look prestigious.[1] And, as would be expected, the conventional medicine establishment almost universally praises their work (with notable exceptions discussed below). It is beyond the scope of this editorial to review all 78 pages of the treatise. It starts well enough by stating in the introduction that diet and lifestyle improvements should be emphasized. Unfortunately, the 84 words in the introduction are all they had to say about the actual causes of heart disease. Anyone who listens to radio or watches television will have experienced the ads that start with, "When diet and lifestyle have failed … prescribe this statin, etc," which typically means the patient was admonished once to improve their diet and lifestyle and then immediately prescribed statins. (Sorry, I know I am overstating this for dramatic effect—but the reality is that the current health care system provides doctors with neither behavioral change skills nor the time with patients to facilitate behavioral change if they had the skills.)

The authors assert, "… extensive and consistent evidence supporting the use of statins for the prevention of ASCVD [arteriosclerotic cardiovascular disease] in many higher risk primary and all secondary prevention individuals …"

For primary prevention, the guidelines to recommend statins have broadened to include those with at least a 7.5% 10-year risk of cardiovascular disease and consideration of statins for those with 10-year risks of 5.0% to 7.5%. Statins are already recommended for those with clinical ASCVD.

As I discuss later, these guidelines are predicated on a seriously flawed assumption of low incidence of adverse drug reactions (ADRs) and laughable numbers needed to treat (NNT). Less biased research shows they underestimate ADRs by a factor of 10 to as much as 100 and hundreds of people need to be treated for several years (depending on the study) for a single person to benefit! Considering only the benefit, ignoring the NNT, and discounting the damage result in invalid, possibly dangerous—but certainly very expensive—conclusions.

I want to be very clear that a subgroup clearly benefits and should be prescribed statins (along with serious

attention to diet, lifestyle, and appropriate supplements). The problem is not the appropriate use of statins—it is the overprescribing that results in more harm than good.

Let's start by looking at statins—their benefits and risks—and then consider cholesterol, its benefits and risks, why, and what to do about it.

Statins

More and more, I find that the concept of *number needed to treat* (NNT)—how many patients have to be treated to achieve a specific outcome excluding those who would have experienced that outcome without the intervention—very compelling when considering the risk/benefit of an intervention. All of a sudden, a drug ad that asserts a 36% reduction in heart attacks goes from seeming very good to being quite questionable when the NNT shows that 99.7 of people would need to take the drug for 3.3 years to prevent 1 heart attack (very little effect on mortality). Interestingly, this is the example given by Wikipedia on NNT using the drug atorvastatin for primary prevention of heart attack in patients with hypertension.[2] But it gets worse as the responsible clinician then needs to consider not only high cost, but all the adverse events (which I expand on later) that have been caused by that drug.

Statin Benefit

First, let's start with the benefits of statins, as there are certainly benefits for some individuals. The situation in which statins have been clearly shown to offer benefits is secondary prevention of a heart attack in those with a previous history of heart attack or stroke. But even for these patients, the NNT to prevent death is still at 83 for 5 years.[3] This analysis also shows that the NNT to cause diabetes is 50 and muscle damage 10.[i] Healthy diet, adequate exercise, and reducing oxidative stress are still far more beneficial, let alone cheaper, and suffer the only "ADR" of better health.

Statin Harm

As would be expected with 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, the reduction in the production of any molecule dependent on this enzyme, such as coenzyme Q_{10} (CoQ_{10}), can result in quite a diversity of adverse effects. In fact, with so many people on statins, that is what is found. Most likely, most of the ADRs from statins are secondary to mitochondrial damage from impairment in electron transport chain function (CoQ_{10} carries high-energy electrons from one complex to the next—see my editorial in the April 2014issue of *IMCJ*)—resulting in not only decreased ATP production but also increased oxidative stress.[4] As would be expected, statin ADRs are more likely to be seen in patients with other causes of mitochondrial dysfunction.

A big problem with accurately assessing the harm caused by statins is the systematic underreporting of statin ADRs. Experts unaffiliated with the pharmaceutical industry estimate 18% of statin users report ADRs and 20% stop taking statins because of decreased quality of life.

Underreporting of ADRs

Loukianos Rallidis, MD, FESC, and Maria Anastasiou-Nana, MD, FESC,[5] published a particularly articulate critique of the underreporting of ADRs by the 2013 ACA/AHA Guidelines. They assert that "… statin-related myopathy (SRM) has been greatly underestimated and this contrasts findings of observational studies which suggest that SRM is relatively common." Specifically, the report states SRMs are rare, occurring at the rate of approximately 0.01 cases per 100 statin-treated individuals per year. According to Rallidis and Anastasiou-Nana, they get to this very low number in several ways:

(1) Application of extremely strict criteria to define myopathy, such as creatinine kinase (CK) elevation >10 × the upper limit normal (ULN) with or without muscle symptoms (which is a rare manifestation of myopathy).
(2) Failure of many studies to systematically report symptoms of myalgia.
(3) Exclusion of patients most likely to suffer from myopathy.
(4) Exclusion of patients experiencing muscle symptoms during the open-label run-in phase of the trials. In some of them, up to 30% of the eligible patients were excluded.

In the real world of clinical practice, the authors assert 5% to 10% of patients will experience statin-related myopathy.

Statin ADRs

In addition to the myopathy, there are many more serious adverse effects such as cognitive loss, neuropathy, pancreatic and hepatic dysfunction, and sexual dysfunction. For example, one study found an increased incidence of amyotrophic lateral sclerosis-like conditions in the University of California, San Diego, Statin Effects Study, which was designed to better track statin ADRs. The study was able to contact and follow-up with 10 patients who had been diagnosed with formal or probable amyotrophic lateral sclerosis (ALS) in the context of progressive muscle wasting/weakness. All reported relief of symptoms when stopping their statin medications and immediate return when taken again. The authors hypothesized that ALS patients are particularly susceptible to the mitochondrial oxidative damage induced by statins.[6]

Risk factors for statin adverse events are listed in Table 1.

i. The Web site http://www.thennt.com is very interesting because it impartially looks at the NNT for many interventions.

Table 1. Risk Factors for Increased Risk of Statin ADRs[4]

Risk Factor	Notes
Dosage	The higher the dose, the greater the incidence of an ADR
Interacting drugs	Fibric acid derivatives, other lipid lowering drugs, macrolide antibiotics, azole antifungals, cyclosporine, calcium channel blockers, antipsychotics, amiodarone, antivirals
Frailty or small body frame	
Surgery	Increased energy production demands for recovery and tissue healing
Infection	Increased energy production demands for production of immune system cells
Heavy exercise	Increases mitochondrial activity, thus aggravating the effects of CoQ_{10} deficiency
Elderly	For those older than 65 y, the case can be made that the ADRs swamp the benefit in all subgroups
Asian ethnicity	
Female gender	The recent large study showing increased diabetes is but one example
Hepatic or renal insufficiency	Insulin resistance—NAFLD
Alcohol abuse	Alcohol is a mitochondrial poison
Hypertension	5.1-fold increased risk for hospitalization for myopathy
Diabetes	
Elevated triglycerides	Indication of insulin resistance, thus more likely to develop type 2 diabetes as statin ADR, also to use triglycerides to produce VLDL
History of CK elevation	More susceptible to statin damage
Thyroid disorders	
Family or personal history of muscle disorders	More susceptible to statin damage
Hyperkalemia	May be indicative of mitochondrial dysfunction
Specific genetic polymorphisms	Particularly those involved in drug detoxification and CoQ_{10} production
Vitamin D deficiency[7]	Cholesterol is used by the body to produce vitamin D; <30 ng/mL is correlated with double the risk of CVD mortality

CoQ_{10} Supplementation to Decrease Statin ADRs

Although most of the research on the benefit of CoQ_{10} supplementation to prevent or reverse statin ADRs shows benefit, the studies are inconsistent. Unfortunately, much of this inconsistency may be caused by poor quality or biologically unavailable CoQ_{10}.

Cholesterol

Let's look a bit more closely at this much-maligned molecule, cholesterol. This maligning of cholesterol has been going on for decades—I remember 40 years ago, when I was still in naturopathic medical school, my favorite, eccentric uncle telling me he had just been diagnosed with high cholesterol and asking what I thought of the drugs he was being prescribed and which high cholesterol foods he should avoid. I told him in no uncertain terms that elevated cholesterol was not the problem. Rather, the problem was a measure of his unhealthy diet and lifestyle, which the drugs could not fix. He took the drugs and went from apparently healthy to dead from heart disease in fewer than 10 years—and made a strong impression on me.

Cholesterol is Critical for Health

Cholesterol is essential for life. In fact, the body produces more of it each day (about 1 g) than most consume in their daily diet (typically 200-300 mg). It is used to make cell walls, insulate nerves, carry fats in the blood, make steroidal hormones, make vitamin D, make bile salts, repair injured tissues—the list is long. Interestingly, human breast milk contains a lot of cholesterol, typically making up 33% of the lipids. An infant consuming 600 mL of mother's milk in a day is taking in 50-100 mg of cholesterol.[8]

There is some very intriguing research showing that older people with higher levels of cholesterol have a lowered risk of death, depression, dementia, violent behavior, etc. This editorial is already going too long, so I did not dive into the research. (Perhaps a future editorial …)

Nonetheless, when cholesterol becomes oxidized, it becomes toxic in the body, particularly to the lining of the blood vessels.

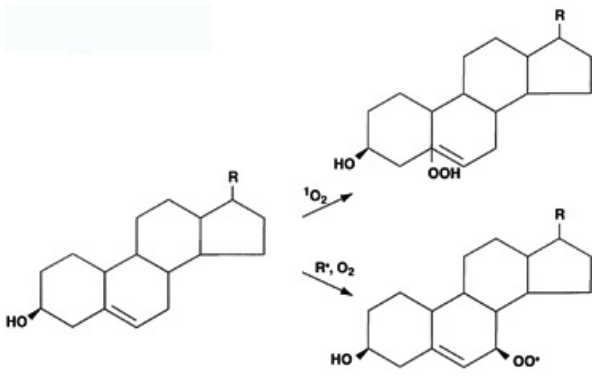
Oxidized Cholesterol

Although very high levels of cholesterol are probably not good for health (typically indicative of insulin

resistance), the primary problem is not the cholesterol itself, but rather when it is oxidized. More than half (52%) of the people suffering a heart attack have "normal" cholesterol levels (at least "normal" before the standards were changed).[9] This oxidation has more to do with inflammation than with cholesterol. C-reactive protein (hs-CRP), a marker of systemic inflammation, is a stronger predictor of cardiovascular events than LDL-cholesterol. Whereas those with the highest level of LDL-cholesterol have a 1.5 increased risk factor of heart attack compared with those with the lowest levels, those with the highest level of hs-CRP have an increased risk factor of 2.3 compared with the lowest.[10] **A person with high levels of LDL-cholesterol but low levels of hs-CRP has a lower risk of a heart attack than a person with low levels of LDL-cholesterol but high levels of hs-CRP.** The primary reason LDL-cholesterol correlates with cardiovascular disease is that it is more easily oxidized. In fact, patients suffering a heart attack have oxLDL twice as high as patients with angina but no heart attack and 4 × as high as healthy controls.[11] With most people, their elevated cholesterol is almost entirely composed of the more easily oxidized LDL cholesterol form—hence the apparent correlation of heart disease with elevated cholesterol. Interestingly, the reason statin drugs lower heart attack risk in some people may be more attributable to their anti-inflammatory activity than their lowering of LDL-cholesterol.[12]

Cholesterol has a double bond that is susceptible to oxidation leading to the formation of oxysterols. These oxidation products are formed in many animal foods during cooking or processing. They are cytotoxic, mutagenic, carcinogenic, and atherogenic. Eggs, milk, meats, and their products are the main dietary sources of oxysterols. Some natural antioxidants, such as alpha- and gamma-tocopherol, rosemary oleoresin extract, and quercetin inhibit the oxidation of cholesterol. Typically, approximately 1% of the cholesterol consumed in a Western diet is oxidized. oxLDLs[14] are directly involved in the initiation and progression of atherosclerotic lesions in coronary arteries that can result in atherosclerotic coronary artery disease (CAD).

Figure 1. Oxidation of Cholesterol[13]



Plasma levels of oxLDL are a sensitive biomarker of atherosclerosis. Elevated levels of oxLDL are associated with accelerated atherogenesis, CAD, acute myocardial infarction, and stable and unstable angina. Elevated oxLDL has also been associated with metabolic syndrome, impaired glucose tolerance/insulin resistance, and untreated overt hypothyroidism.

Low-density lipoproteins (LDLs), a major carrier of circulating cholesterol, are very susceptible to oxidation of the constituent apoB100 protein moiety by pro-oxidants such as metal ions, reactive oxygen radicals, oxidized macrophages, lipoxygenase, and peroxynitrite. When the LDL is oxidized it becomes antigenic and the oxLDL are taken up excessively by the "scavenger" or "oxLDL receptors" on monocyte-derived macrophages. oxLDL is present in macrophages in atherosclerotic lesions but not in normal arteries. Once macrophages breach the arterial endothelial barrier, the excessive uptake of oxLDL contributes to their entrapment in the subendothelial space. The trapped lipid-laden "foam" cells elicit biosynthesis and release of factors by the arterial wall that are proinflammatory and chemotactic for other monocytes, perpetuating the atherosclerotic process with injury to the arteries. Injury to the subendothelial vessel walls results in decreased production of nitric oxide and loss of elasticity of the arteries, and the damaged lipid-laden arteries eventually narrow, thereby restricting the flow of blood.

Oxidized cholesterol not only directly damages the blood vessels, it also serves as a marker of oxidative stress.

The Causes and Prevention of Oxidized Cholesterol

As can be seen in Table 2, cholesterol is easily oxidized both in the body and in food preparation. Replacing saturated fat with unsaturated fat results in an increase in oxidized cholesterol—which is probably why the campaign to eliminate saturated fat was such a failure.

LDL carries fat-soluble antioxidants, predominantly vitamin E and CoQ_{10}. One form of vitamin E, α-tocopherol, slows atherosclerosis in most animal models but has shown equivocal results in human trials. There is even the suggestion that it may increase LDL oxidation under some circumstances. I do not recommend supplementing with only 1 of the vitamin E family of 8 isomers. However, the first line of antioxidant defense in LDL is provided by CoQ_{10}. CoQ_{10} unequivocally reduces LDL oxidation in human subjects.

ii. Please note that I use oxLDL and oxidized cholesterol interchangeably. Although not technically correct, there is little practical difference.

Table 2. The Causes and Solutions for Oxidized Cholesterol

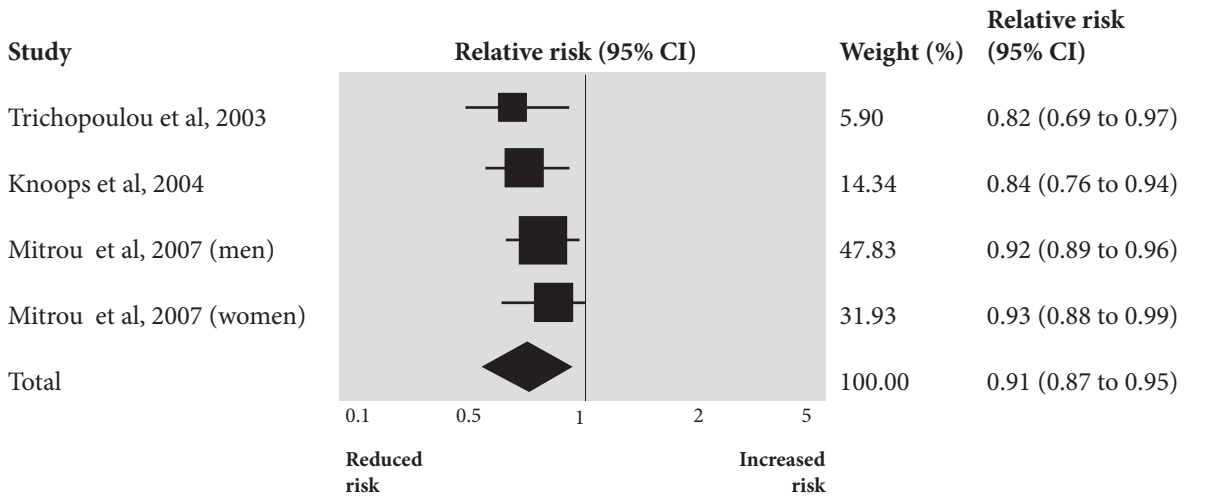
Cause	Solution
Cooking foods with cholesterol at high temperatures in the presence of oxygen	Bake and boil rather than fry and broil
Eating rancid oils (which oxidize cholesterol)	Keep oils rich in polyunsaturated fatty acids in dark bottles and protect from heat; eat more oils high in monounsaturated fatty acids (such as virgin olive oil)
Elevated homocysteine	Folic acid, B_6, B_{12}, and betaine
Elevated hs-CRP	γ- (not α-) tocopherol, selenium
Elevated cytokines	Nuts, dark chocolate
Insulin resistance	Achieve normal body weight; use high-viscosity fibers to normalize blood sugar; eat low-glycemic foods
Smoking	Stop smoking; vitamin C
Excessive alcohol (more than 59 mL in women and 88 mL in men)	Limit daily alcohol to 1-2 drinks for women and 2-3 for men
Excessive weight	Normalize body weight through diet and exercise
Deficiency of antioxidant nutrients	Proanthocyanidins, vitamins C and E, garlic, and dark-colored fruits and vegetables
Toxic metal exposure (lead, mercury, arsenic, and cadmium)	Environmental awareness and detoxification
Polychlorinated biphenyls (PCBs)—not only oxidize cholesterol but levels directly associated with carotid artery plaques[15]	Eat organically grown foods; at least avoid the "Dirty Dozen"[16]
Inadequate blood glutathione levels	*N*-acetylcysteine, whey, silymarin, and dealcoholized beer

CoQ_{10} levels are reduced in individuals with cardiovascular disease and high oxLDL. Whether this is cause or effect, it is difficult to say. However, supplementing with CoQ_{10} has been repeatedly shown to be effective for high blood pressure and congestive heart failure.[17,18]

Phenols in olive oil protect cholesterol from oxidation.[19] This protection is found only in virgin olive oil as the phenols are lost when refined. One study compared the effects of consuming virgin olive oil (629 mg phenols/L) versus refined virgin olive oil (0 mg phenols/L) on oxLDL in a crossover study in men. Not surprising that they found a strong negative correlations ($r = -0.30$; $P = .01$) between phenol levels and oxLDL.

The primary ways to decrease the amount of oxidized cholesterol is to decrease the consumption of cholesterol that has been damaged by cooking or storage and by preventing cholesterol in the body from being damaged.

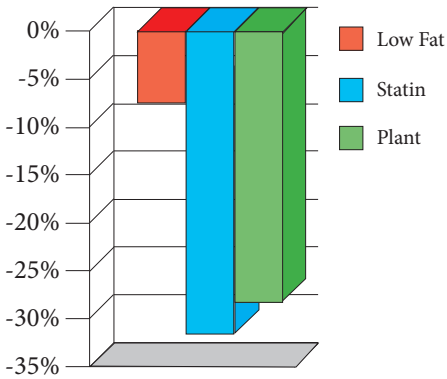
Figure 2. Decrease in Cardiovascular Risk with a Mediterranean Diet[20]



Reducing Cholesterol and Cardiac Risk Through Diet

The research is very clear that a Mediterranean or plant-based diet reduces elevated cholesterol. But more important it actually decreases cardiac events, stroke, risk of death—and even more potently, dementia and Alzheimer's disease (after all, what value is there in living longer if you can't recognize your children?).

Figure 3. Plant-based Diet as Effective as Statins in Lowering Cholesterol



As can be seen from the figure, if all that is being measured is a drop in cholesterol, a plant-based diet is as effective as statin drugs.[21] Of course, it is also cheaper and the side effects are less cancer, less dementia, less arthritis—the list is long.

Conclusion

The new guidelines for prescribing statins make no sense for all those newly included. Those experiencing ADRs will likely be 10-20 × higher than those who benefit. For patients with a history of a cardiac event, statins are indicated, but only if the ADRs are addressed. In these patients, great care should be taken to avoid or minimize the many factors listed in Table 1 that increase the risk of a statin-induced ADR. In addition, they should be supplemented with CoQ_{10} (100 mg/d).

Of course, the *actual causes* of their cardiovascular disease must be addressed! As discussed earlier, the primary problem is the oxidized cholesterol. Most of the causes of the oxidation can be controlled and many natural health products will decrease oxidative stress and protect cholesterol.

Finally, my apologies—there is so much about cholesterol and cardiovascular disease I did not address. This is my longest *IMCJ* editorial to date and I had to stop adding pages. With heart disease being the leading cause of death in Western societies, this critical topic needs considerably more attention.

In This Issue

Our clinician interview this month is with Alan Goldhamer, DC—in my opinion the world's leading expert in water fasting. I think water fasting is an extremely important therapy and am delighted we can bring you this fascinating interview. Having personally supervised hundreds of 4- to 30-day water fasts, I have seen remarkable results. However, if you are supervising a water fast longer than 4 days, you must first seek proper training—such as that offered at the TrueNorth Health Center. Although our bodies have many very effective mechanisms for not only adapting to but benefiting from fasting, in this toxic world with complex degenerative diseases and lowered vitality, great skills are required for patient safety and efficacy. Who should not be fasted, how to start, when and how to break a fast, what clinical signs need to be monitored—these are important issues that must be addressed with each patient. Dr Goldhamer is the lead author of the fasting chapter in the *Textbook of Natural Medicine* (Pizzorno J, Murray M; Elsevier, 2012). BTW, if you have not read our interview with Valter Longo, PhD, on how fasting makes chemotherapy more effective in treating cancer in both animals and cancer (December 2013 issue of *IMCJ*), I strongly encourage you to do so.

As I have stated in the past, true integrative medicine is more than natural health supplements combined with conventional drugs. We need to consider nonpharmaceutical approaches as well. Charlene M. Muhammad, MSHM, RYT500, CNS, RD, and Steffany H. Moonaz, PhD, provide us a compelling case report on the use of therapeutic yoga for adrenomyeloneuropathy, a condition not very responsive to conventional care.

Curcumin is quite a remarkable spice and medicinal food. The research on cancer prevention (even treatment), inflammation, etc, is very encouraging. The challenge is its poor availability. Doddabele Madhavi, PhD, and Daniel Kagan, PhD, provide us a study on the bioavailability of a novel form of curcumin designed to improve absorption. As always, a challenge to accept research from a company that benefits commercially from publication of a successful study, I want to assure readers we are very diligent in our review process. This typically means multiple revisions with the authors to improve the science and reduce the commercials. Nonetheless, I strongly encourage the companies who produce the products we need for our patients to engage in direct research of their own product rather than using borrowed research.

The more I study thyroid, the clearer it is that dysfunction is very common. In a corporate wellness program in Canada, I measured thyroglobulin in 200 oilfield workers and found iodine deficiency in 72%. So I am very pleased that our conference speaker interview is with Antonio C. Bianco, MD, PhD, who provides us important insights into not just T_4 production in the thyroid but the critical conversion to the 3 × as active T_3 in the cells. I fully concur with Dr Bianco—it is all about

tissue levels of T_3, which may have little relationship to serum T_4 or T_3.

Fortuitously, we have an interesting case history looking at adrenal and thyroid supplementation by Chistopher Wellwood, DC, and Sean Rardin, MD. I appreciate their thinking and successful efforts to comprehensively address a complex set of problems in a real patient.

I have to admit a high degree of skepticism seeing the title of John Weeks's column, "The US Medical Industry Turns Toward 'Health Creation.'" As this industry is based on disease treatment, in fact dependent upon it, addressing the actual causes of disease is not conducive to their bottom line. I remember quite vividly 3 conversations: (1) the president of a hospital who was fired because of political pressure from the medical staff when he tried to start wellness programs for the community; (2) a frank conversation with the vice president medical director of a large insurance company who pointed out that insurance companies depend upon health care becoming more expensive, as that is the only way to increase their profits, which are basically based on a percent of premiums; and (3) a debate with the recently retired dean of a conventional medical school who strongly asserted that wellness promotion was a bunch of "xxxx" and that the only proven interventions were to manage disease by controlling symptoms. Sorry about the cynicism. Nonetheless, I suspect most readers of *IMCJ* are fully committed to, indeed, converting today's disease-treatment system into a true health care system. The good news is that some of our concepts are leaking into the system …

As usual, Bill Benda, MD, in BackTalk courageously speaks the truth. Painful, unpopular, politically incorrect—but right on.

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