

Roundoc Rx

Vitamins—the Good, the Bad, and the Ugly



Robert Rountree, MD

Vitamins are not only good for us, they are essential for our health and survival. On this, at least, I think we can all agree. Whereas vitamin deficiencies can cause disease and contribute to a variety of ailments, the flip side is that too much of any single vitamin, when taken as a megadose supplement, can be harmful and even toxic. As the saying goes, “one can have too much of a good thing.” Where the value and benefits of properly administered vitamin and mineral supplements for nutritional enhancement (the “good”), and the misguided, improper or excessive use of vitamin supplementation (the “bad”) cross over into the realm of the “ugly” is when we encounter the increasingly popular practice of vitamin-bashing.

This highly disturbing, yet pervasive trend takes several forms, attacking vitamins by asserting: that they are not protective against disease or the degenerative effects of aging; that vitamin supplements are not needed to prevent the oxidative damage caused by free radicals; that vitamins might not help people live longer or healthier lives; and that vitamins and other nutritional supplements may even increase people’s risk of developing serious diseases, such as cancer or heart failure. These types of biased generalizations are not based on sound data or scientific facts. These generalizations are at the core of an ugly agenda to delegitimize nutritional therapy.

In this column, I discuss how our views on oxidative damage, free radicals, antioxidants, vitamin and mineral supplements, and phytonutrients have changed in recent years. I present the challenges we face in meeting our nutritional needs through what is commonly thought of as a healthy diet. I share my approach to using vitamin supplements to treat patients with deficiencies that may be caused by diet, disease, lifestyle factors, or medication use. Finally, I explain why I recommend vitamins and increased phytonutrient intake to enhance antioxidant protection in people who are at increased risk of oxidative damage caused by smoking or environmental chemical exposures, for example.

What Is the Bias?

I am compelled to begin by responding to the strong bias I see against vitamins and other dietary supplements in the medical literature, in professional publications, and in the mainstream media. The pendulum of opinion on vitamins—their potential for maintaining health, minimizing the effects of injury and disease, and slowing the onset and progression of age-related wear-and-tear on the body—tends to swing back and forth over time. At present, it is at the far-negative end of the spectrum, and an ominous pall has arisen.

What is the source of this negative bias—the hidden agenda that seeks to discredit the benefits of dietary supplements and ignore all the exciting research that is being published in this field? In my opinion, a lot of it has to do with the ongoing failure of mainstream medicine to recognize nutrition research as legitimate science.

When I was in college back in the 1970s, classes in nutrition were taught under the academic umbrella of home economics. At that time, nutrition was viewed on the same level as sewing and soap making. Nutritionists were mostly women, whose ultimate roles were to design meal plans for their families or for cafeterias in schools, hospitals, and prisons. This was in contrast to the allegedly superior science of pharmacology, which was thought to hold the ultimate solutions to most acute and chronic diseases affecting humankind.

Fast-forward to the twenty-first century, where the public’s faith in the safety and efficacy of pharmaceuticals has been repeatedly challenged as one “approved” drug after another is taken off the market and as the price of commonly used medications has become astronomically expensive for no reason other than to increase profits. At the same time, dietary supplements have become increasingly popu-

lar, completely independently of the ups and downs of the world economy. In fact, research conducted by the Natural Marketing Institute found that supplement usage among U.S. adults increased from 62% in 2009 to 73% in 2013.* While the pharmaceutical industry is running out of ideas, the field of nutritional science is exploding with new discoveries and innovations.

It is no wonder that dietary supplements pose a threat to people who are deeply invested in conventional pharmaceutical-based medicine. The official message emanating from the lofty ivory towers of medical academia is that unscrupulous vitamin salespeople are duping a foolish and ignorant public. However, outside those towers an entirely different perspective has emerged among people who are able to think for themselves. This perspective posits that vitamins and other dietary supplements offer informed people a chance to regain control over their health by using nontoxic, less-expensive alternatives to drug therapy.

Unfortunately, the situation has devolved to the point where self-proclaimed academic “experts”—many of whom have very little formal training in nutrition—make negative assertions about vitamins and dietary supplements, often as publicly as possible. These assertions are not just uncalled for—they are scientifically unfounded. The latter is the key point here, and it is my main objection. When medical professionals make statements and generalizations that do not reflect the body of scientific data accurately, and when well-respected and far-reaching publications such as *The New York Times (NYT)* or *The Wall Street Journal (WSJ)* publish those assertions and opinions as if they were fact, they carry a certain weight and must be countered by evidence-based conclusions and science-driven realities. Reasonable and logical voices must prevail.

It is time to bring the conversation on the benefits of vitamins back into focus—to reset the pendulum to reflect a healthy and productive debate on when and how to recommend specific vitamin supplements to our patients. It is also necessary to continue to carry out well-designed, carefully managed, and properly analyzed clinical research

It is time to bring the conversation on the benefits of vitamins back into focus.

studies. I would urge all health care practitioners when they read a report or article in the media interpreting the results of a new study, or exhorting them to change long-held beliefs, or alter the treatment or advice they give to their patients, to read and analyze critically the study themselves and not to accept anyone else’s interpretation of the data at face value.

*See Supplement Use Is Up in News Briefs in this issue.

When the Data Do Not Add Up

Vitamin-bashing is certainly not new, and the current anti-vitamin crusade is broad-based and emanates from a variety of sources. The most recent written barrage—one that cannot go unchallenged—appeared in the June 8, 2013, *NYT* Sunday Review.¹ It was an Opinion piece written by Paul A. Offit, MD, a pediatrician, and the chief of the Division of Infectious Diseases of the Children’s Hospital of Philadelphia, Pennsylvania. Dr. Offit, who has no special expertise in the field of nutrition, says in the title of his article: “Don’t Take Your Vitamins.”¹ While stating that vitamins are essential for life—for converting food into energy—and that vitamin insufficiency causes diseases, such as scurvy and rickets, Dr. Offit concluded with the assertion that high doses of vitamins can increase the risk of cancer and heart disease and shorten lives.

He cited, for example, the results of a small handful of large studies in which subjects were given vitamin supplements to prevent diseases for which they were at increased risk, such as to prevent lung cancer in smokers or following asbestos exposure, or to protect people against the development of heart disease.^{2,3} When the study subjects who were taking the vitamin supplements did not fare better, and, in some cases, had higher rates of disease or death than people who were not taking vitamin supplements, the “logical” conclusion was that vitamin supplements are of no value and are even harmful.

A very similar opinion piece appeared in the *WSJ*, on March 6, 2006, with the title “The Case Against Vitamins,” and subtitled: “Recent Studies Show That Many Vitamins Not Only Don’t Help. They May Actually Cause Harm.”⁴ In this article, Ms. Tara Parker-Pope quotes Edgar R. Miller, MD, a cardiologist at the Johns Hopkins School of Medicine, who warns us about the dangers of taking vitamin E. Dr. Miller was the lead researcher for a 2005 meta-analysis of 19 clinical studies that found a higher risk of all-cause mortality among people who took more than 400 international units [IU] of vitamin E per day.⁵ (Dr. Offit also cited Miller’s study in his *NYT* Opinion piece.)

The Miller et al. study involved an extremely complicated statistical analysis of a highly complex set of data, based on which the researchers concluded that vitamin E supplements increased death rates by 4%–6%. If this is true, it means that taking vitamin E is more deadly than smoking! A fact not mentioned in the *WSJ* article was that Dr. Miller’s findings were thoroughly refuted by a comprehensive review written by 13 international authorities on nutritional science, who cited extensive evidence from published clinical trials showing that vitamin E supplements were generally safe in doses of up to 1600 IU daily.⁶ One cannot help but ask why the media did not mention this review article. The omission points again to a hidden agenda that denies the potential benefits of vitamins. In this case, is the agenda simply that positive news does not sell?

The negative conclusions drawn by Dr. Offit and Dr. Miller and the studies on which they are based—the design of the studies and what the data and outcomes actually mean—re-

quire a closer look. In most of these studies, thousands of people were given the same doses of one or more vitamins for years without any assessment of their individual needs for those vitamins. This “one-size fits all” approach to dietary supplements is not how I manage my patients, and neither is it how the nutritional practitioners I know practice.

When a person comes in with a set of signs and symptoms, objective tests are used to determine whether he or she has any specific vitamin or mineral deficiencies, based on direct measurement of blood or urine levels, functional biomarkers, or findings from a physical examination. These objective measures then guide treatment decisions. This is a very straightforward approach and is quite different from arbitrarily giving large numbers of people the same dose of a vitamin for a long period of time and saying, “let’s see what happens.”

The latter approach models the drug model of intervention more closely, in which everyone receives essentially the same dose, and is also how a drug candidate would typically be tested. The reality of drug trials is that some people respond, others do not, and side-effects are reported. Why should we be surprised when studies of single, high-dose vitamins show a similar pattern?

I will state in the strongest possible terms that vitamins and other dietary supplements are not “wonder drugs.” Supplements are not intended to be used out of context as single

Vitamins and other dietary supplements are not “wonder drugs.”

agents in high doses to treat illness. These supplements cannot replace good food choices and a well-rounded diet. Rather, vitamin supplements are adjunctive agents that are meant to be used as part of a comprehensive, personalized lifestyle management program. They are enhancements that can be used to correct deficiencies or optimize health. In a previous column, I provided many examples from published studies of how dietary supplements could enhance the effectiveness of pharmacologic therapy.⁷ Examples included folic acid for augmenting the effects of antidepressants, or α -lipoic acid and chromium to support hypoglycemic agents used to treat diabetes.

Consider another recent example of a study in which I believe that the conclusions reached by the authors—and displayed prominently in the media—were unsupported by the data.⁸ These conclusions are completely unfounded. It was “big news” that echoed around the world when the *Journal of the National Cancer Institute* published a study suggesting that omega-3 fatty acid supplements could increase men’s risk of prostate cancer. The study spawned headlines in the mainstream press such as: “Men Who Take Fish Oil Omega-3 Supplements at 71% Higher Risk of Prostate Cancer: Study.”⁹

In the study, the researchers analyzed omega-3 fatty acid levels in a single blood sample collected from each study subject, and then compared those levels among the men with

and without prostate cancer. These levels were only measured once in the course of the study, which lasted for many years, so they can’t be considered as representative of long-term dietary intake. However, the comparison that was based on this one data set led to the conclusion that men with high blood concentrations of omega-3 polyunsaturated fatty acids have an increased risk of prostate cancer and that these fatty acids are involved in prostate tumorigenesis. In a broader statement in a follow-up press report, one of the coauthors said, “use of nutritional supplements may be harmful.”⁹

Were the men in this study actually taking omega-3 fatty acid supplements? We have no way of knowing, as that information was not part of the study design. However, the data for this study were gleaned from the previously published Selenium and Vitamin E Cancer Prevention Trial (SELECT), in which men were given vitamin E and selenium (or placebo) in an attempt to prevent prostate cancer and were specifically told NOT to take additional dietary supplements.¹⁰

If some of the men were taking omega-3 fatty acid supplements against that advice, did they take them the day before their blood was drawn for the one-time test to measure their omega-3 fatty acid blood levels? We do not know that either. Did these men eat salmon or another fish high in omega-3 fatty acids that could have raised their levels in the blood draw?

It is also important to note that the study measured the plasma levels of omega-3 fatty acids, which only reflects dietary intake for the previous 24 hours.⁸ The mean level of omega-3 fatty acids in the group that developed cancer was 4.66% of total fatty acids, compared to 4.48% in the control group. In other words, there was only a 0.2% difference in omega-3 fatty acid levels in the two groups—a tiny variance that could have been affected by eating as little as one serving of fish. Given the complete lack of dietary data, it was astonishing to me that the researchers were able to make any comments at all about the potential risk of taking fish oil or nutritional supplements.

I would assert that these types of generalizations and far-reaching conclusions cannot be drawn from these data and this study design. No means of elaborate statistical analysis can extract meaningful conclusions from a weak data set. The researchers appear to have overlooked one of the basic tenets of epidemiology, which is that *correlation does not imply causation*. The data could just as easily have been interpreted to say that men who ate a fish taco on a certain date were at higher risk of developing prostate cancer many years later. If what the authors are saying is true, then we would expect the incidence of prostate cancer to be extremely high in places where people eat a lot of fish—such as Greenland, Scandinavia, and Japan. However, that is contrary to what the epidemiologic studies show.

I do not want to appear or become cynical. However, the poor design of studies like this one and the undiscerning acceptance of the results and their interpretation, combined with a lack of legitimate scientific discourse around these broader issues leads me to believe that these exercises are less about science and fact-gathering than about the predetermined agenda that I have discussed.

Vitamins for Health and Disease Prevention

There is an optimal amount of any vitamin that a person needs, and it has been well-established that ingestion of excessive amounts of some vitamins can cause toxicity. However, in many cases, our perspective of what is an optimal amount continues to evolve over time and with a growing body of experimental and observational studies. Amounts of vitamin supplements that might have been viewed as an overdose 10 years ago may now be considered a normal intake.

Consider vitamin D, for example. I have been prescribing daily doses of 1000–5000 IU of vitamin D to my patients for more than 15 years. In some situations, I have used even higher doses of up to 10,000 IU per day. During that time, several patients have needed to be seen by other specialists for various reasons, such as for presurgical evaluations. When the patient

I have been prescribing daily doses of 1000–5000 IU of vitamin D to my patients for more than 15 years.

shows a list of supplements he or she is taking to the other doctor, the reaction to seeing 5000 IU of vitamin D on the list is often: “That is way too much. You are overdosing.”

My response is: “Based on what theoretical information are you making that judgment?” The reality is that I have been regularly monitoring the patient’s blood levels of vitamin D, calcium, and phosphorus, and keeping them exactly where we want them to be. We might have tried a dose of 1000–2000 IU per day, but if the patient’s blood level was not adequate with that dose, I increased it to 5000 units per day. The patient is doing just fine without any evidence of toxicity. In other words, the idea that 5000 IU of vitamin D automatically constitutes an excessive megadose is based on outdated information, and the doctor who believes that this dosage is automatically a problem has not been keeping up with the medical literature.

It has been more than 57 years since the notion of biochemical individuality was first popularized by the brilliant biochemist Roger Williams, PhD. Dr. Williams was a true pioneer in the study of vitamins. In addition to discovering and/or characterizing many of the B vitamins—including pantothenic acid, pyridoxine, thiamine, and folic acid—he wrote numerous books for lay audiences on the topic of how specific nutrients affect our health. His strongly held opinion was that every human being has unique nutritional needs based on genetics and metabolic differences. Based on his research, he believed that a tailored program of diet and supplements could help correct many health problems.¹¹

Bruce Ames, PhD, a biochemist at the University of California, Berkeley, has continued the work of Dr. Williams in helping us understand disease pathways better and unravel the genetic basis of pathogenesis. As Dr. Ames and colleagues explained in a comprehensive review of the topic, at least 50

human genetic diseases caused by defective enzymes can be remedied or at least ameliorated through the administration of high doses of the vitamin component of corresponding co-enzymes.¹² Additional examples and reviews illustrating the use of vitamins for chronic disease prevention have been published.^{13,14} I would encourage the vitamin bashers to spend some time reading the extensive peer-reviewed journal articles by Dr. Williams and Dr. Ames before proclaiming that there is no evidence supporting the use of dietary supplements.

Views on Vitamins, Free Radicals, and Antioxidants Are Changing Radically

Our whole perspective on free radicals, the damage they cause to cells, and what an antioxidant is and the role it plays, have changed dramatically in recent years. In a nutshell, the previous notion held that all free radicals were bad, causing cells and bodily functions to break down because of damage to the cells’ DNA—specifically to the mitochondria that produce the energy needed to power the cells. Our bodies are not able to keep up with this ongoing oxidative damage as they age and are thus exposed to increasing numbers of free radicals. The damage is cumulative and seemingly irreparable. This concept has been called the free-radical theory of aging.

In contrast, current theory acknowledges a normal spectrum of free-radical activity in the body that represents a continuum of health rather than an all-or-nothing, good-versus-bad situation. A small amount of free-radical production is not only normal—it is healthy. Our bodies have evolved over millions of years in an oxygen-rich environment. We require oxygen to survive, and our bodies utilize it efficiently in the mitochondria in respiration, one result of which is the production of free radicals. The internal machinery of our cells is dependent on a certain level of free radicals—called the redox state—for proper function. Dr. Offit made this point in his *NYT* article—and I credit him for that. “Free radicals aren’t as evil as advertised,” he stated, then he added: “In fact, people need them to kill bacteria and eliminate new cancer cells.”¹

So, the concept that we have to eliminate as many free radicals from our bodies as possible by consuming a certain number of mg of vitamin C, β -carotene, or some other antioxidant is no longer widely accepted. The recommended doses of these “chemical antioxidants” were based on how much is required to neutralize a certain amount of free radicals in a test tube rather than what effect these chemicals have in the body.

However, I do fault Dr. Offit for failing to take the discussion to the next level. Whereas chronic, low-level production of free radicals may not be harmful, and is to some extent beneficial, higher amounts can damage cells. High levels of free radicals—a condition referred to as oxidative stress—can destroy cellular membranes. These free radicals also activate nuclear factor κ B, a transcription factor that is the final common pathway for inflammatory disease.

These effects are well-established in the medical literature. Who is more likely to have excessive free-radical production?

Some examples are: cigarette smokers; people who live in highly polluted environments and breathe in more sulfur dioxide and particulates; and individuals who are exposed to heavy metals or metalloids, such as arsenic. Elevated blood sugar can also generate free radicals—which explains why people with diabetes are prone to oxidative stress. In fact, excessive production of free radicals has been found in just about every type of chronic disease, including cancer, autoimmune disease, allergies and asthma, heart disease, and chronic kidney disease. In these situations, decreasing the production of free radicals is a good thing.

How do we do that? The answer to this question opens another evolving area of research and discussion in the nutritional therapy and emerging nutrigenomics field, which I reviewed in an earlier column.¹⁵ The body produces a number of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPX) that help to neutralize the free radicals produced in the mitochondria. These enzymes do not neutralize all of the free radicals—just enough to protect the cells from damage. Production of these enzymes rises and falls in response to changing levels of free radicals, in a dynamic process known as the adaptive stress response.

Consequently, the shift in thinking and practice in the nutrition field has been away from recommending high doses of chemical antioxidants such as vitamin C and β -carotene, and focusing, instead, on specific chemicals in plants—secondary metabolites known as phytochemicals—that reduce oxidative stress in the body. While these phytochemicals may not be particularly potent at neutralizing free radicals in a test tube, they are highly effective for activating the body's endogenous antioxidant system. They specifically activate DNA transcription to produce SOD, GPX, and a host of other enzymes capable of optimizing the redox state inside the cell. This concept of nutrients as “redox modulators” represents a completely different way of thinking about nutrients and their role in protecting the body against oxidative damage.

The effect of dietary factors on hormesis mechanisms, cellular stress responses, human health, and longevity represents an exciting, relatively young area of research. Numerous published studies support a role for phytochemicals in regulating gene expression associated with antioxidant enzymes and endogenous oxidant defense systems.^{16–19}

The “Eat Your Fruits and Vegetables” Conundrum

This new view on phytonutrients brings us to a final issue that cannot be overlooked as part of the broader discussion on dietary supplements. If the beneficial chemicals we need are naturally present in fruits and vegetables (such as the glucosinolates of broccoli, for example), then why can't people get all the protective nutrients they need from food, just by doubling down on the broccoli, green leafy vegetables, and blueberries they consume? I completely agree that we should strive to include as many fresh fruits and vegetables in our diet as possible.

However, I disagree with the argument that many conservative mainstream nutritionists and physicians have been making for years—that most people do not need dietary supplements because we can get all we need from eating a “healthy diet.” First, that concept presumes that we all have exactly the same dietary needs—a notion that Dr. Williams and Dr. Ames have clearly put to rest. Second, the notion of what constitutes a healthy diet is nebulous. The experts have been going around in circles about it for as long as I can remember. If the experts are confused, then the public is even more so. The reality is that many people have difficulty keeping up with even a basic level of nutrient intake, especially considering that the quality of our food supply has been increasingly called into question.

I would like to highlight an illuminating article in the *NYT* in which Jo Robinson clearly explained how we have been breeding the nutritional value out of our food.²⁰ “Studies published within the past 15 years show that much of our produce is relatively low in phytonutrients,” stated Ms. Robinson.

Advanced laboratory technologies have enabled accurate phytonutrient quantification. These analytical techniques show that decades of breeding to improve the taste, texture,

Advanced laboratory technologies have enabled accurate phytonutrient quantification.

and cooking qualities of crop plants are largely responsible for reducing their nutritional value. Much of our produce has been bred so that it can be shipped long distances around the world without rotting. Tomatoes that have been trucked in from hundreds—if not thousands—of miles away can bounce off the floor without breaking, but they simply do not have the flavor or the nutrient density of food that is grown locally. What this means is that eating several servings a day of fruits and vegetables does not guarantee that a person is getting an adequate supply of nutrients.

Conclusion

We need to recognize that some people make lifestyle choices or have genetic or medical conditions for which they might greatly benefit from a personalized program of nutritional therapy that includes vitamin or nutraceutical supplementation. Importantly, when we hear about negative (or positive) findings regarding nutritional research, we need to go to the source and read the actual studies. We need to learn how to think for ourselves and draw our own conclusions, instead of relying on the media or on supposed experts to interpret study data for us. Otherwise, we are letting other people guide our thinking and decision making toward these people's own biased perspectives. When it comes to vitamins, there is a not-so-hidden agenda, and it can get ugly out there. ■

References

1. Offit PA. Don't Take Your Vitamins. *The New York Times*, June 8, 2013. Online document at: www.nytimes.com/2013/06/09/opinion/sunday/dont-take-your-vitamins.html?pagewanted=all&r=0 Accessed August 2, 2013.
2. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994;330:1029–1035.
3. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150–1155.
4. Parker-Pope T. The Case Against Vitamins: Recent Studies Show That Many Vitamins Not Only Don't Help. They May Actually Cause Harm. *The Wall Street Journal*, March 6, 2006; reprint March 20, 2006. Online document at: www.mythyroid.com/documents/WSJVitamins.pdf Accessed August 29, 2013.
5. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005;142:37–46.
6. Hathcock JN, Azzi A, Blumberg J, et al. Vitamins E and C are safe across a broad range of intakes. *Am J Clin Nutr* 2005;81:736–745.
7. Rountree R. Roundoc Rx: Using nutraceuticals to complement drug treatments. *Altern Complement Ther* 2013;19:3–8.
8. Brasky TM, Darke AK, Song X, et al. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst* 2013;105:1132–1141.
9. Men Who Take Fish Oil Omega-3 Supplements at 71% Higher Risk of Prostate Cancer: Study. *Daily News*. Online document at: www.nydailynews.com/life-style/health/evidence-prostate-cancer-omega-3-link-article-1.1395853 Accessed August 1, 2013.
10. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2009;301:39–51.
11. Davis DR, Hackert ML, Reed LJ. Biographical Memoir, Roger John Williams. National Academy of Sciences, 2008. Online document at: www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/williams-roger.pdf Accessed August 28, 2013.
12. Ames BN, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K(m)): Relevance to genetic disease and polymorphisms. *Am J Clin Nutr* 2002;75:616–658.
13. Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: Scientific review. *JAMA* 2002;287:3116–3126.
14. Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: Clinical applications. *JAMA* 2002;287:3127–3129.
15. Rountree R. Roundoc Rx: The science of nutrigenomics. *Altern Complement Ther* 2009;15:104–108.
16. Mattson MP. Dietary factors, hormesis and health. *Ageing Res Rev* 2008;7:43–48.
17. Cornelius C, Perrotta R, Graziano A, et al. Stress responses and hormesis as critical determinants in aging and longevity: Mitochondria as a “chi.” *Immun Ageing* 2013;10:15.
18. Vendelbo MH, Nair KS. Mitochondrial longevity pathways. *Biochim Biophys Acta* 2011;1813:634–644.
19. Calabrese V, Guagliano E, Sapienza M, et al. Redox regulation of cellular stress response in aging and neurodegenerative disorders: Role of vitagenes. *Neurochem Res* 2007;32:757–773.
20. Robinson J. Breeding the Nutrition out of Our Food. *The New York Times*, May 25, 2013. Online document at: www.nytimes.com/2013/05/26/opinion/sunday/breeding-the-nutrition-out-of-our-food.html?pagewanted=all&r=1& Accessed August 1, 2013.

Robert Rountree, MD, practices family medicine in Boulder, Colorado.

To order reprints of this article, e-mail Karen Ballen at: Kballen@liebertpub.com or call (914) 740-2100.