Clinical Trials Not Being Kind to Nutraceuticals

BY ERIK L. GOLDMAN

There seems to be a predictable pattern in nutritional supplement research: Epidemiologic or observational studies suggest that a particular nutrient or botanical might prevent or ameliorate a common chronic disorder, preclinical work describes a plausible physiologic mechanism, and small clinical studies give encouraging findings.

Then the National Institutes of Health or another major research establishment funds a large-scale “definitive trial,” and the data come up equivocal at best, negative at worst.

Over the last year or two, several disappointing nutritional/botanical studies have been reported. For example, vitamins C and E failed to reduce cardiovascular disease risk in the Physicians’ Health Study II (JAMA 2008;300:2123-33); selenium and vitamin E did not lower prostate cancer risk in the SELECT trial (JAMA 2009;309:39-51); and ginkgo biloba did not prevent dementia or Alzheimer’s in an elderly in the GEM trial (JAMA 2008;300:2253-62).

So why do big trials often return negative results when preliminary work looks positive? Is the epidemiology wrong to begin with, or were the trials improperly conducted? Are researchers and trial designs biased against natural products? Are the pilot trials biased in favor of “boasting” results?

“Some people in the supplements world take umbrage at randomized, controlled trials. But it is not impossible to do good RCTs with nutrients, and it doesn’t mean that negative results are wrong,” Paul M. Coates, Ph.D., director of the Office of Dietary Supplements (ODS) at the National Institutes of Health, said in an interview. “The RCT worked pretty well to document the impact of folate in preventing neural tube defects. No one seems to question this.”

Part of the problem in designing supplement trials is that researchers and the public often expect nutrients or botanicals to behave like drugs, with big, discrete, and easily detected benefits in a broad range of people. But nutrients and botanicals are not pharmaceuticals, and Dr. Coates said that he thinks expectations may be unrealistic.

“Generally speaking, few people in the United States have frank nutrient deficiencies (such as scurvy, rickets, or beriberi), so supplementation seldom results in dramatic effects,” he said.

Using vitamin C as an example, he said that although many people fail to get optimal amounts, few have scurvy. “If you give a lot of vitamin C to people who are more or less replete, you may not see much effect. The net effect was basically zero in the Physicians’ Health Study II. It’s going to be hard to see a strong signal because the effect size [on heart disease] is probably small to begin with, and the level of ‘noise’ is high.”

Vitamins exert subtle, nonspecific effects on multiple physiologic pathways, rather than strong effects on a relatively small number of pathways, which is how pharmaceuticals work, Jeffrey Bland, Ph.D., said at a meeting sponsored by the Scripps Center for Integrative Medicine.

“Most of the large-scale NIH-funded trials are based recommend- ations, or that epidemiologic signals engender unrealistic expectations. “Epidemiologic and observational studies cannot give cause-and-effect proof. They do provide clues about where to look. If the signals are strong enough, those clues should be followed and tested,” said Dr. Coates, whose job is to set the agenda for NIH-funded nutraceutical research.

Public interest in nutrition, botanicals, and supplements is strong, as is physicians’ need for scientific guidance, Dr. Coates said at a meeting sponsored by the Scripps Center for Integrative Medicine.

Solid evidence-based recommendations for dietary supplements are rare. Dr. Coates said that one of his primary responsibilities is to look closely at those unknowns and establish priorities based on public health needs. “This is a process—for better or worse—is driven by epidemiology.”

The recent vitamin E/C combination trial had its roots in population studies looking at heart disease risk in people with high versus low levels of serum markers of various vitamins, he explained. This led to trials designed around two of the possibly relevant nutrients. “We have to recognize that once we move to an intervention design, we cannot include everything that might be relevant,” he said.

In the widely anticipated SELECT trial, the impetus for studying selenium in prostate cancer came from an earlier selenium study that did not have prostate effects as a primary outcome, according to Dr. Coates.

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Vitamins exert subtle, nonspecific effects on multiple physiologic pathways, rather than strong effects on a relatively small number of pathways, which is how pharmaceuticals work, Jeffrey Bland, Ph.D., said at the conference. But many of the large-scale NIH-funded trials are premised on single-pathway thinking.

Future NIH trials should make greater use of the emerging science of nutrigenomics, which looks at how various nutrients and combinations of nutrients influence gene expression, suggested Dr. Bland, co-founder of the Institute for Functional Medicine, based in Gig Harbor, Wash. The larger trials would also be more clinically applicable if they controlled for or reported on variables like participants’ diets, oxidative stress status, and genetic predispositions for various metabolic states.

Beyond the domain of averting frank deficiencies, the effect of any given nutrient is largely determined by individual factors, such as how well someone digests and absorbs the nutrients, what nutrient-depleting or nutrient-blocking drugs are in a person’s system, and individual capacities to metabolize particular nutrients. Dr. Bland continued. Nutrition is definitely not a one-size-fits-all proposition, he stressed.

High-profile government-funded studies understandably carry a lot of weight with physicians, said Dr. Mary Hardy, medical director of the Center for Integrative Oncology at the University of California, Los Angeles. But all too often, “we just run with the top-line findings, we miss second, but important signals.” Although the SELECT trial did not show the hoped-for prostate protective benefit, it did show there were no major selenium-associated adverse effects after 6 years of continuous use, she pointed out, which is reassuring for anyone taking this mineral for other purposes.

Currently, the ODS is working with the federal Agency for Healthcare Research and Quality (AHRQ) and AHRQ’s Evidence-based Practice Centers to conduct a series of meta-analyses and systematic reviews, Dr. Coates said. Of the role of the ODS, Dr. Coates said, “We set the questions, and then we walk away. How the Evidence-based Practice Centers do the actual reviews.”

Future NIH trials will look at chroni- cally impaired insulin sensitivity; omega-3s for cardiovascular disease prevention; the effects of soy, B vitamins, and antioxid- ant phytotoxins on neurodegenerative diseases; and the health effects of vitamin D.

Biomedical Research Funding Growth Has Slowed Since 2003

BY MARY ANN MOON

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It appears that the “boom and bust” cycling of research funding of U.S. biomedical research, which enjoyed a “boom” between 1994 and 2003, has since slowed substantially.

The declines since 2003 may signal “a trend to favor incremental research rather than high-risk/high-reward endeavors,” they added.

Dr. Dorsey reported receiving research support from NIH, foundations, and industry. One other researcher reported relationships with advisory groups that work with foundations and industry.