The findings infuriated a lot of people—consumers as well as those in the $7 billion-a-year vitamin business. A systematic review of all antioxidant clinical trials found that beta carotene, vitamin A, and vitamin E increase mortality, though things are still unclear regarding vitamin C and selenium. Unlike prescription drugs, vitamins do not have to be proven safe or effective before they go on the market.

Much of the enthusiasm for antioxidants comes from observational studies that showed people who take them have a lower rate of heart disease. But it has long been known that healthy people are the people most likely to take vitamins. Over the last two decades, most of the clinical trials that randomly assigned people to take either antioxidants or placebos failed to find that antioxidants prevent heart disease or cancer (with the possible exception of prostate cancer).

The new systematic review includes trials that reported the deaths of all participants. This review, conducted by the independent international organization called the Cochrane Collaboration, is not the first to find an increased death rate for people taking antioxidant vitamins. Sixty-eight trials are included in this Cochrane review published in the February 28 issue of the Journal of the American Medical Association.

“This is one of the most intensely studied topics in the world,” said one of the co-authors, Christian Gluud, MD, of the Cochrane Hepato-Biliary Group, Rigshospitalet, Copenhagen University Hospital. On an Australian radio show, Dr. Gluud explained how mortality became the focus of interest. Years ago, the same team of Cochrane reviewers assessed all trials that had explored the question of whether antioxidants reduced the rate of cancers in the gastrointestinal tract.

“When we looked at the best quality studies, we saw a trend toward increased all-cause mortality,” he explained. “And when we focused on the trials with the best methodological design [least likely to produce erroneous results], we were surprised to see a significant increase in mortality.”

That finding, published in the international medical journal Lancet in 2004, led to the topic of this article—the Cochrane review of all antioxidant trials that had randomly assigned participants to receive a synthetic antioxidant (or antioxidant combination) or a placebo. The 232,606 participants ranged in age from 18 to 103 years.
Antioxidants continued

(mean age, 62 years). All identifiable trials were included. That proved problematic because the initial search of the published scientific literature pulled up 815 trials. Due mainly to rampant duplication (publishing the same trial in multiple journals) or trials without any mortality measured, that number was eventually reduced to 68.

When the Cochrane reviewers put the results of all 68 trials together, they concluded that antioxidants had no effect on mortality. But when they separated out the 47 trials with the highest methodological standards, the increases in mortality became apparent. These trials, which had the lowest risk of erroneous results and a combined total of 180,938 participants, showed the following increases in mortality per antioxidant: 7% for beta carotene; 16% for vitamin A; and 4% for vitamin E.* The Cochrane reviewers concluded that ongoing trials looking at vitamin C and selenium should continue.

Criticisms Addressed

Now for the criticisms leveled at this review—and there were many. Contrary to one popular assertion, it was not funded by the pharmaceutical industry to counteract public enthusiasm for vitamins. “The sole sponsor of this review is the Copenhagen University Trial Unit, a publicly funded, not-for-profit clinical research center,” wrote Dr. Gluud in an e-mail response to inquiries, “in addition, we all gave a number of hours from our free time.” And about 90% of the trials in this review, he explained, were funded by companies that make vitamins.

Some U.S. doctors criticized the review for combining trials of long and short duration, as well as primary (healthy people) and secondary (people with cancer, heart disease, etc.) prevention trials. “The whole idea of doing systematic reviews and meta-analyses of randomized clinical trials is to increase the power and precision. That is why we included both primary prevention trials and secondary prevention trials,” explained Dr. Gluud, who attributed much of the criticisms to a lack of understanding of the methodologies involved in a systematic review.

“There was no significant influence of primary or secondary prevention on our estimates of increased mortality,” Dr. Gluud wrote in response to an e-mailed question. “That is, the examined supplements seem to exert their detrimental effects irrespective of whether you gave them to healthy persons, or persons with a previous diagnosis. We saw similar effects in both populations that do not differ significantly. Accordingly, if we had split our review into two, we would have reached the same conclusions regarding the healthy participants. Also, we did not observe any beneficial effects among those with previous diseases.”

Who exactly is defined as healthy is also an issue in a population with a mean age of 62 years. “Most of the primary prevention trials included 'healthy persons', but this is not the same as saying they did not have any disease,” explained Dr. Gluud. “Their atherosclerotic vascular disease or their precancerous lesions may just have been undetected at the time they entered the trial.”

As for combining trials with short durations (less than a year) with those of long duration (up to 14 years), “We included all trials we could find, irrespective of duration because there is no scientific argument against combining trials with short duration and trials with long duration.” The mean duration of the primary prevention trials is 2.7 years, Dr. Gluud continued, “Duration of supple-

*The trials tested a wide range of doses. For example, Vitamin A doses ranged from 2,000 IU/day to 200,000 IU/day.
Antioxidants continued

mentation was not significantly associated with the observed significant increase in mortality. That is, the examined supplements seem to exert their detrimental effect irrespective of the duration of administration. We cannot exclude the possibility that they may be even more harmful if used for longer than the duration of the trials included in our systematic review.”

This caution appears at the end of the review: “Because we examined only the influence of synthetic antioxidants, our findings should not be translated to potential effects of fruits and vegetables.”

The findings of this Cochrane review lend support to those who argue against isolating certain nutrients and taking them in high doses. “…even the simplest food is … a virtual wilderness of chemical compounds, many of which exist in complex and dynamic relation to one another,” according to nutrition writer Michael Pollan.

Any take-home messages from this antioxidant review? “Vitamins are not non-toxic,” answered Dr. Gluud. “Anything sold to consumers should be tested beforehand. And it is mandatory that governments require the registration of trials,” referring to the worldwide movement among researchers and medical journal editors that would require sponsors of all trials to register them from the onset on a publicly available database. “It has taken us years to reach this conclusion because these 68 trials were published in 385 different places.”

Maryann Napoli, Center for Medical Consumers © 2007

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Each condition comes with four to eight quality measures. With a click of the mouse up comes the percent of heart attack patients who, for example, were given a percutaneous coronary intervention within 120 minutes of arriving at the hospital. (Longer than that amount of time would make this coronary artery-opening procedure less effective in limiting heart muscle damage.)

There are surprises to be found in this Web site. For example, St. Luke’s Roosevelt Hospital, widely perceived as one of New York City’s best cardiac hospitals, had a lower percent (48%) of heart attack patients getting a PCI within 120 minutes than the average for all reporting hospitals in the U.S. (69%) and in New York State (72%).

Most of us cannot recognize high-quality acute medical care, so it helps that this Web site provides explanations. The surgical wound care section, for example, describes steps that should be taken to reduce the risk of infection, such as preventative antibiotics for surgery patients one hour before incision. After the majority of procedures, the antibiotics should be stopped within 24 hours after surgery “to avoid side effects and other problems associated with antibiotic use.”

There is much more we need to know about hospitals—like the rate of hospital-borne infection (currently available for Pennsylvania hospitals only)—but this Web site is a pretty good start.
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