Health Promotion and Disease Prevention: Philosophy, Observation, and Clinical Trials

Until the 1980s, dietary improvement and nutritional adequacy were of interest to policy makers and consumers primarily based on traditional models of health and nutrition. Good dietary patterns and adequate nutrient intakes based on the Recommended Dietary Allowances were considered the best guides to health, but chronic disease prevention through dietary modification was not a common topic of discussion, except for the American Heart Association's early championing of a relationship among saturated fat intake, blood cholesterol levels, and heart disease risk.

This situation began to change dramatically following publication of the 1977 report on *Dietary Goals for the United States*, prepared by the Senate Select Committee on Nutrition and Human Needs, positing a relationship between the affluent American diet and the incidence of numerous "killer diseases." (Senate Select Committee on Nutrition and Human Needs, 1977) This was followed by a cascade of other major reports on diet and disease, including the National Research Council's 1982 report *Diet, Nutrition and Cancer;* the Surgeon General's 1988 report *Nutrition and Health*; and the National Research Council's 1989 report *Diet and Disease.* (Department of Health and Human Services, 1988; National Research Council, 1982, 1989)

The reports asserted that improved dietary patterns, including increased intakes of fruits and vegetables and whole grains, could reduce the risk of chronic disease. They also featured extensive discussion of the components of these foods that were likely to be protective, including fiber and a number of antioxidant nutrients. The reports emphasized the importance of improved food patterns and downplayed the importance of increasing the intake of specific nutrients, but at the same time numerous clinical trials were undertaken specifically to evaluate the possibility that supplementation with some of the individual nutrients (especially antioxidants) might reduce the risk of cancer and heart disease. For example, by 1986 the National Cancer Institute was supporting more than 20 clinical trials on specific nutrients and potential cancer prevention. (Greenwald, Sondik, et al., 1986)

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DESIGN OF CLINICAL TRIALS

While countless epidemiological trials support the hypothesis that dietary improvement can reduce the risk of chronic disease, the design of clinical trials to test that hypothesis is a challenge. Nevertheless, many clinical trials have in fact demonstrated benefits against disease for specific nutrients. Calcium to protect against osteoporosis, folic acid to help prevent some birth defects, and omega-3 fatty acids to reduce the risk of heart disease are among these success stories. On the other hand, beta-carotene for cancer prevention, vitamin E for lowering heart disease risk, B vitamins for protecting against cardiovascular disease, and selenium and vitamin E for prevention of prostate cancer are among the disappointments, where clinical trials so far have largely failed to confirm the disease-related benefits suggested by earlier observational and other studies.

What factors in the design of clinical trials are responsible for success or failure? Does a negative trial mean the hypothesis of benefit has been disproven? Might a disappointing trial actually represent a failure to truly test the hypothesis suggested by epidemiology and other evidence? These are questions being intensely examined and vigorously debated within the scientific community. Some of the factors being considered are discussed in the following pages.

Clinical trials are done with single nutrients or a small number of nutrients:

The epidemiological evidence points to food patterns that are related to a lower risk of disease, but changing food habits over the long term is very difficult. Thus, researchers attempt to identify the specific nutrients that are most strongly associated with protective food patterns and then design clinical trials to test whether giving supplements of those nutrients will protect against disease. Is this a true test of the hypothesis? If diets rich in numerous carotenoids appear to be protective against lung cancer in the general population, does it follow that giving a single carotenoid (such as beta-carotene) for several years to older men who are lifelong smokers is likely to protect them against lung cancer?

Nutrients function in the body as an interdependent group, not primarily as individual stars. They play critical roles in metabolic systems, pathways, and cycles. Dr. Robert Heaney believes clinical trials and meta-analyses err when they focus on single nutrients without taking account of critical interactions. (Heaney, 2008) Dr. Frank Meyskens and Dr. Eva Szabo refer to the single-nutrient focus characteristic of clinical trials as the "four-legged stool problem." (Meyskens & Szabo, 2005) Nutrients are compared to the individual legs of a four-legged stool. Together, the four legs make a strong and functional unit, but tested individually, a single leg will not stand alone–and was never meant to stand alone. In order to design an effective nutritional intervention to be tested, it is necessary to understand which nutrients or other food components are essential to the overall functional package, and then to include all the limiting components in the intervention at appropriate levels.

Clinical trials are usually done in populations not screened for markers of nutrient status or markers of disease risk:

Subjects are generally recruited into clinical trials without regard to relevant markers of nutrient status, including for example their baseline blood nutrient levels, markers of antioxidant status, markers of inflammatory response such as CRP (C-reactive protein), or homocysteine levels. (Block, Jensen, et al., 2009; Jialal & Devaraj, 2005; Traber, 2007) Some have pointed out that this is equivalent to testing statins in people who do not have elevated cholesterol levels, or testing antihypertensive medications in people who do not have high blood pressure. (Halliwell, 2000; Heinecke, 2001)

Clinical trials are often done in diseased populations:

Even the leading causes of death from chronic disease occur at relatively low levels in the population. Thus, clinical trials are generally done in high-risk populations or in people who already have a disease, in order to increase the likelihood of having enough events over a period of several years to detect a difference

between the treatment group and the placebo group, if there is in fact a difference. Is this a true test of the hypothesis? If the hypothesis is that a lifetime of exposure to a nutrient (or a combination of nutrients) will reduce the risk of ever developing the disease, then testing the nutrient(s) in older or less healthy people within some brief window of time may not be a true test of prevention—and testing it in people who already have the target disease is definitely not. Is it close enough? That is the question. Some would say it is the best we can do. Others would say it is like the old story of the drunk looking for his keys under a street light. When a passerby stopped to help and eventually asked the drunk if he was certain he had dropped the keys in that spot, the man said, "No, I lost them over there, but the light's better here." Testing disease prevention in people who are already sick may be like looking for lost keys where the light is better, instead of where the keys are more likely to be found. (Drake & Colditz, 2009)

Clinical trials are often done in people already receiving state-of-the-art treatment for their disease:

The diseased or high-risk populations often selected for clinical trials have another characteristic that may limit the ability to observe an effect of a relatively mild intervention such as a vitamin supplement. These populations are already receiving all the medications considered to represent the standard of care for patients with their particular risk factors or diseases. Thus, in order to appear successful in a clinical trial, not only must the vitamin prevent progression of disease, it must provide benefits over and above those already being provided by the standard medical treatments the patients are receiving—and which they will continue to receive throughout the duration of the trial.

Combined primary endpoints:

Because of the relatively small number of deaths or serious events that are likely to occur during the course of a clinical trial, primary outcome measures are often combined events: death and nonfatal myocardial infarction (MI) and stroke, for example. In these cases, interventions will only be found successful if they have a benefit for the combined measure. If the intervention "only" prevents strokes, that may not be counted a success, but may only qualify as a secondary benefit. In some trials, the authors appear to bend over backwards to minimize some apparently real benefits, and an impression of failure is given where some success was actually observed.

Compliance and "intent to treat":

All subjects assigned to the treatment group are included in the analysis of effects of the treatment, whether or not they complied with the treatment regimen. This is the accepted statistical convention of analyzing data according to "intent to treat." Analysis of compliers is considered subgroup analysis and thus statistically questionable. Yet in the epidemiological studies that gave rise to the hypothesis, it was only the actual *use* of the supplement that contributed to the apparent benefit. Including noncompliers in the treatment group in analyzing clinical trials may be necessary for statistical purity, but may permit inappropriate conclusions to be drawn about the effects of nutritional treatments that are effectively applied. In some studies, beneficial effects have been shown in those people who actually took the assigned supplements. This is a meaningful result and should be recognized as such.

Relevance of epidemiologic data, apart from the results of clinical trials:

By the very nature of their design, most clinical trials test very narrow hypotheses—"a mile deep but only an inch wide," the saying goes. For example, a given

trial may test the effect of a single form of a single supplemental nutrient at a single dose, in a specific population, at a certain life stage, for a given period of time. All of the compromises that go into the design of clinical trials may, separately or together, make it more difficult or even impossible to detect a real benefit. While the current emphasis on "evidence-based medicine" tends to designate randomized clinical trials as the gold standard and minimize the relevance of even rigorously designed observational studies, the evidence for such a rigid hierarchy of study designs has been questioned. (Concato, 2004) It is important to recognize that failure to detect a benefit in a clinical trial does not necessarily negate the epidemiological data showing an apparent benefit, especially when the hypothesis tested in the clinical trial is not the same as the hypothesis suggested by the observational data.

Clinical trials travel in groups:

Strong epidemiological observations and thorough analysis of other supporting data is likely to result in the funding of not just one clinical trial, but numerous clinical trials—all initiated within a few years of each other and all being concluded within a few years of each other. Since the trials are concurrent, there is little or no opportunity for one trial to build on another in order to improve the study design.

Ethics of clinical trials:

In order for a clinical trial to be undertaken at all, there must be a critical balance between confidence and uncertainty. The treatment to be administered must be considered safe, and there must be enough confidence in a possible benefit to justify giving the treatment to thousands—often tens of thousands—of people. On the other hand, there must be sufficient uncertainty about a possible benefit so that it is not unethical to give half the subjects a placebo. Researchers undertake clinical trials in the expectation of finding a benefit. A trial that fails to find a benefit is a disappointment, but not necessarily the final word. As long as researchers in a subject area remain convinced of a likely benefit and as long as new trials are being initiated with a given substance or set of substances, the discussion is not over.

Terminology—"prevention" as a euphemism for "treatment":

In trials conducted in patients who already have the target disease, the administration of vitamins cannot truly be said to have the goal of "prevention." The term "secondary prevention" is commonly used to describe these trials in which an effort is made to prevent future progression or recurrence of the target disease. Realistically, "secondary prevention" is a euphemism for treatment effects. If the results of such trials are null, they do not indicate a failure of prevention, but a failure of treatment. The difference in terminology is important to the public perception of the findings. Hardly anyone would be surprised to tune in to the morning news and hear that a few B vitamins failed to be an effective treatment for MI or stroke. When the authors instead assert that the trial represents a failure of prevention, people are confused by this choice of language into believing that the trial actually tested prevention and that vitamins failed the test, when in truth the hypothesis of disease prevention with nutrients was likely not tested.

Where Next?

Many researchers remain convinced that improved dietary habits and some specific nutrient interventions are very likely to make large contributions to health promotion and disease prevention. Beneficial effects have already been demonstrated and are accepted as proven for calcium and vitamin D relating to bone health, for folic acid to protect against neural tube birth defects, and for dietary fiber and soluble fiber to

reduce the risk of cancer and heart disease. There is also persuasive evidence for an antioxidant cocktail to help prevent eye disease and for omega-3 EPA and DHA to reduce the risk of heart disease. At the same time, there is a dilemma posed by the series of null clinical trials relating to vitamin E and coronary artery disease, the B vitamins and cardiovascular disease, and antioxidants and cancer—trials apparently at odds with a large body of human observational evidence, supported by animal studies and a full understanding of the mechanisms by which these nutrients could be expected to have a beneficial effect.

Even after disappointing clinical trials on vitamin E and heart disease appeared, Dr. Daniel Steinberg expressed confidence in the antioxidant hypothesis, saying that the results "lead us to re-examine the question of what might be the appropriate nature of trials in humans, but they do not invalidate the large body of experimental evidence supporting the role for oxidative modification of LDL in atherogenesis." (Steinberg, 2000) Researchers such as Dr. Maret Traber and Dr. Balz Frei remain convinced that vitamin E is beneficial when taken before disease onset, as shown by some of the subgroup analyses in the Women's Health Study, and they also point out that 96 percent of American women and 93 percent of American men fail to consume even recommended amounts of vitamin E. (Traber, Frei, et al., 2008) They believe "the negative evidence regarding vitamin E supplements from randomized clinical trials is more a reflection of inadequate study design and methods of analysis than proof of failure of vitamin E in primary prevention." (Traber, Frei, et al., 2008)

Some researchers see disappointing clinical trials as a useful step toward better understanding of the questions to ask and the types of research designs to pursue in the future. While recognizing that "the most satisfying trials are those that deliver the goods," many researchers caution that null or unexpected results should not be viewed as failures, since such studies shed some light on the causes of disease and possible approaches to disease prevention. (Albanes, 2009)

Some researchers see disappointing studies as proof that clinical trials as presently designed are inappropriate for complex nutrient/disease interactions, and they call for some new thinking about the best way to scientifically evaluate such relationships. Some have wondered whether the scientific community is ready to rethink "the reductionist medical approach" when it comes to evaluating complex diet/disease or nutrient/disease relationships. (Meyskens & Szabo, 2005)

Dr. Heaney has been outspoken about the need for a new approach to research on nutrition and disease prevention, saying: "The field of nutrition must, I believe, apply the brakes to its mad, downhill rush to embrace a drug-based standard of proof, and instead, pause long enough to develop its own standards—standards that would involve both different designs and a differing approach to endpoints." (Heaney, 2008) He asserts that nutrition is important to health and to disease prevention, "despite the fact that the still growing number of failed trials of individual nutrients might suggest that no nutrient actually made much of a difference, a conclusion that is absurd on its face and ought to have alerted us to the possibility that there was something wrong with how we were investigating the matter." (Heaney, 2008)

Part of the solution, in Dr. Heaney's view, might involve the development of a global index of the various effects of specific nutrients on markers of health and disease—an outcome measure which would be complex but which would better reflect the multiple and related effects of nutrients on many metabolic systems. He argues that studying single nutrients apart from the host of other nutrients with which they interact is an exercise that is bound to fail. As a concrete

first step toward an improved nutrition research paradigm, he suggests that it "would be useful for the ASN [American Society for Nutrition], in collaboration with concerned governmental entities such as the USDA, to convene a workshop to address these structural issues." (Heaney, 2008) A workshop was convened at Creighton University in September 2008 to discuss these topics, and a report of the workshop appeared in *Nutrition Reviews* in 2010. (Blumberg, Heaney, et al., 2010)

The following sections will examine the concordance or discordance of epidemiologic evidence and clinical trials in several areas, including antioxidants and cancer, antioxidants and heart disease, and B vitamins and cardiovascular disease.

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