ABSTRACT
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Clinical Trials for Benefits: Evidence-Based Medicine or Nutrition?

During the last decade, approaches to evidence-based medicine, with its heavy reliance on randomized clinical trials (RCTs), have been adapted to nutrition science and policy. However, there are distinct differences between the evidence that can be obtained for the testing of drugs using RCTs and those needed for the development of nutrient requirements or dietary guidelines. Although RCTs present one approach toward understanding the efficacy of nutrient interventions, the innate complexities of nutrient actions and interactions cannot be adequately addressed through any single research design.

Certain features of evidence-based medicine are ill-suited to the nutrition context because of the differences between the evaluation of drugs and nutrients. For example, medical interventions with drugs are designed to cure a disease not produced by their absence, while nutrients prevent dysfunction that result from their inadequate intake. Also, it is not usually feasible to design ethical studies requiring nutrient depletion or avoiding the provision of diets considered fully adequate. Drug effects are generally intended to be large and with limited scope of action; in contrast, nutrient effects are typically polyvalent in scope and, in effect size, are typically within the normal range of biological variability. Efficacious drug actions tend to be monotonic with response varying in proportion to dose, while nutrient effects are often of a sigmoid character, with useful responses occurring only across a portion of the intake range. Drug effects can be tested against a non-exposed (placebo) contrast group, whereas it is impossible and/or unethical to attempt a zero intake group for nutrients. Moreover, therapeutic drugs are intended to be efficacious within a relatively short term while the impact of nutrients (or whole foods or dietary patterns) on the reduction of risk of chronic disease may require decades to demonstrate, a difference with significant implications for the feasibility of conducting meaningful RCTs, especially for primary prevention.

The requirements for nutrients are traditionally focused on single organ system endpoints, usually the earliest signs of a deficiency syndrome. However, determining the optimal intake for the prevention of a chronic disease requires recognition of the multiplicity of a nutrient's effects throughout the body. For example, the intake of dietary folate necessary to reduce the risk of neural tube birth defects is greater than that necessary to prevent macrocytic anemia, and the amount of vitamin D required to reduce the risk of falls and hip fracture in the elderly is greater than that required to prevent rickets or osteomalacia.

Because of the limitations inherent in RCTs of nutrients, policy decisions will have to be made using the totality of the available evidence. This will require implementation of new policies at a level of certainty different from that needed in the evaluation of drug efficacy. Similarly, the level of confidence needed in defining nutrient requirements or dietary recommendations to prevent disease can be different from that needed to make recommendations to treat disease. Advancing evidence-based nutrition will depend upon

research approaches which include RCTs but go beyond them. Also necessary to this advance will be the assessment in future human studies of covariates such as biomarkers of exposure and response and the archiving of samples for evaluation by emerging technologies such as the “-omics”.