• Foods are readily available to the total population, in non-limited amounts. Zero intake for a control group in a study may not be attainable.

• Foods must be considered as part of an overall healthy diet.

• Choice of a control product can be difficult when assessing functional ingredients in foods. The food without the functional ingredient is a likely choice for a control, but the control food itself may contribute to a physiological effect (e.g., conventional yogurt compared to a probiotic yogurt). The choice of a control product is driven in part by the research question being asked; however, to achieve blinding in a study on functional food, a control comprised of the food matrix must be used.

• Generally the anticipated magnitude of effect is smaller than for drugs.

• Unlike pills, food formulations can change frequently (new flavors, functional ingredients, levels of macronutrients, targeted formulations for different geographical regions). An important consideration for research on foods is determining when a new food formulation differs substantively from the researched food, requiring confirmatory efficacy studies.

• Profit margins are lower for foods than for drugs. This leads to a disparity with research investment possible by food compared to drug companies.

• Foods are most often natural rather than synthetic products, not produced under drug manufacturing practices, and are more likely to show batch-to-batch variability.

It should be noted that although dietary supplements are generally considered within food regulations, some of the differences highlighted above between foods and drugs do not pertain to dietary supplements. For example, formulation of an inert placebo for a dietary supplement is generally a straightforward choice, supplements do not contribute calorically to consumers' diet, matrix effects may not be as variable for supplement formulations and zero-intake may be easy to establish for subjects in studies.

Studies on foods should be of high-quality and well-controlled. But differences between foods and drugs compel recognition that the type of evidence required for efficacy may be different. For example, Blumberg et al.[20] recently questioned the appropriateness of randomized controlled trials for foods.

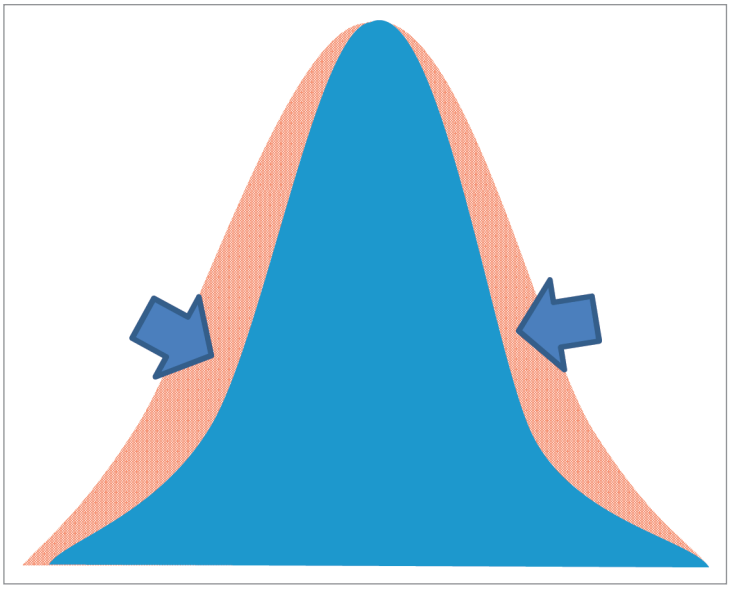

Figure 2. Visualization of the concept of improved homeostasis. An intervention able to minimize the variation around the mean for a specific measure, even in the absence of changing the mean, would be a demonstration of improved homeostasis.

A regulatory framework that recognized the existence of the above-described continua would provide an environment where the full role of foods (including nutritional supplements) in promoting health, reducing the risk of disease and managing health conditions could be realized.

Implementing such a regulatory framework would present numerous challenges, but in the end consumers may benefit from such changes. However, one unintended consequence of this regulatory approach that would need to be considered is the risk of therapy substitution. Many health conditions require medical intervention, for which foods cannot substitute. Consumers are attracted to the ready availability, economy and lack of side effects from foods, but must be adequately informed by clear labeling when foods cannot substitute for needed medical intervention.

Homeostasis and Health: A Statistical Approach

One sizable challenge due to the current regulatory frameworks is how to conduct meaningful studies on probiotics or prebiotics in healthy humans. How does one show that health is improved—or even more challenging, maintained—in a healthy person? What does "maintained" mean as a study outcome? One approach is demonstration of reduced incidence of disease or illness. Such a study would be conducted in healthy people, but it may be prohibitively expensive due to low incidence or long latency, depending on the endpoint being examined. Tracking the incidence of dental caries is an example of an endpoint that may be successfully undertaken with a manageable budget and time frame. But measuring the impact on immune function with concomitant demonstration of reduced common infectious diseases, for example, would be a much more expensive and lengthy study. Another approach, which would not require tracking a disease or illness endpoint, would entail measurement of homeostasis, as suggested by D. Tancredi. From a statistical point of view, if an intervention were able to minimize the variation around the mean for a specific measure (even in the absence of changing the mean; **Fig. 2**), it could be a reflection of improved health, assuming a biological rationale exists that tighter control of the parameter is physiologically advantageous. In other words, lessening the fluctuation around an individual's biomarker could

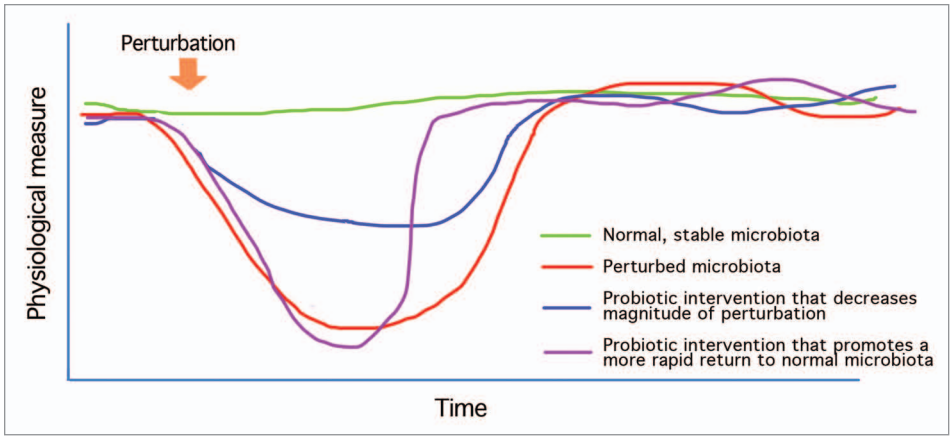

Figure 3. The concept of homeostasis as expressed by reducing the magnitude or duration of fluctuations. Such a study could be conducted in healthy people, by collecting repeated measures of the physiological measure and comparing intervention and control groups on summary measures of the amount of within-person fluctuation. The study design could also include a timed sequence of challenges designed to disturb the measure, allowing between-group comparisons on resistance to perturbation. Modified after Ger Rijkers, personal communication.

be interpreted as contributing to improving health. This novel idea emphasizes the importance of homeostasis as a focus of studies on health, and provides a rationale based in solid statistical theory as a way to measure this.

One challenge to demonstrating the value of this approach is to identify appropriate biomarkers that could be studied. The following properties would be important to a biomarker:

- maintaining moderate levels of the biomarker is associated with good health;
- high or low values are associated with ill health;
- biomarker levels in the same person can fluctuate over time; and
- reducing the magnitude or duration of such fluctuations in healthy people is considered desirable (**Fig. 3**).

Such a biomarker could be an individual endpoint or be formed as a ratio of two other biomarkers, when maintaining the same relative amounts of the two component biomarkers would be desirable.

Assuming a biomarker with the above properties is available, it could be used as the outcome measure in a randomized controlled trial to provide evidence that the experimental food is able to improve the maintenance of health in humans. Statistically, the trial would be set up to address the hypothesis that the experimental substance is associated with lower variation in biomarker levels, compared to the control arm, in subjects who were healthy at baseline. Such a trial would be able to use information on within-person variations in biomarker levels, even those who did not become ill. Partly as a result of the more efficient use of study data, such a trial would require far fewer subjects than an intervention that instead addressed the hypothesis that treatment is associated with fewer healthy persons becoming ill.

A mounting understanding of the value of stability of the colonizing microbial communities makes this endpoint an attractive one to consider. Perturbation of gut microbiota is associated with intestinal dysfunction, as illustrated during antibiotic treatment. Specific probiotics have been shown to promote a quicker rebound from antibiotic-induced microbiota disruption, including a study on *Lactobacillus rhamnosus* GG (LGG).[21] This paper concludes "…that a key mechanism for the protective effect of LGG supplementation on the subsequent development of allergic disease is through the promotion of a stable, even and functionally redundant infant gastrointestinal community."

However, it would be useful to define additional biomarkers that would be appropriate targets for this type of investigation.

In pediatric nutrition, the measurement of metabolic homeostasis has become a standard approach when developing infant formulas.[22] The concept of homeostatis as a model to distinguish between foods (including food supplements) and medicinal products was explored by the Council of Europe,[23] and is an interesting correlate to the above hypothesis.

Economic Impact

According to a 2006 World Bank report on health enhancing foods, "cost-effectiveness of functional foods in reducing disease burden and lost productivity is an important research gap."[24] While there is a growing interest in evidence-based health care, evidence on cost-effectiveness is often lacking. The pharmaceutical industry and the medical community have introduced science-based economic evaluation of health management programs and care protocols as well as standardized treatment protocols. These studies have established the principles of cost-benefit and cost-effectiveness assessments, evaluating not only the health spending but also the economic benefits.[25,26] Such benefits could include, for example, the public health savings induced by health management programs. Approaches that establish procedures for the assessment of the role of food with particular beneficial effects on health, well-being and quality of life in our society are needed. Such assessment would provide important perspective on the economic impact of a regulatory framework that encourages research and communication on the health benefits of foods, and the subsequent broad implementation in the diet of target populations.

Conclusions

A reassessment of the regulatory approach to functional foods in general, and

probiotics and prebiotics in particular, is needed. Promulgated in the interest in protecting the consumer from fraudulent claims or from unsafe products, in some cases the regulatory standards being implemented have the unintended consequences of keeping valuable information from being communicated to consumers and healthcare providers, and perhaps more worrisome, may effectively discourage investment by food companies in research to explore the health benefits of their products. Success with research is never guaranteed, but companies seek clarity on a research path that at least should have the potential to result in a favorable assessment by regulators. Harmonization of different approaches globally would simplify requirements for industry, decrease consumer confusion and improve the scientific framework for the research community to set up appropriate research pathways. Conversations among all stakeholders to work toward regulatory frameworks more consistent with accepted scientific concepts of "continuum" and "suboptimal" are needed. The "continuum" approach does not seem fully possible without a change in law, as the current law clearly separates products, health conditions and evidence into discrete entities. A more flexible approach could contribute to better informed choices, increased consumer protection and encouragement of scientific innovation leading to improved health of the targeted populations. In addition, there are few endpoints for human studies that will satisfy the restrictive nature of endpoints that are physiologically meaningful but allowable in the current regulatory environment for probiotics and prebiotics. Development of new approaches for measuring health, such as the proposed assessment of homeostasis, is needed.

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