Fiber man meets microbial man1–3

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What a privilege it was to have attended a lecture by the late Denis Burkitt when audiences were fed large boluses of wit and wisdom. Even skeptics were impressed by his passion and persuasiveness. Tony Epstein found inspiration when he attended a seminar by Burkitt and credited it as a turning point in the discovery of the Epstein-Barr virus (1). The genius of this great Irishman included more than his rigorous epidemiologic insights into the lymphoma now bearing his name; he will probably always be linked with dietary fiber (2). Despite limitations, Burkitt’s epidemiology was more penetrating than simple risk factor epidemiology because he attempted a rapprochement of observations with disease mechanisms. However, great minds occasionally get things wrong, or so it seemed with Burkitt, when revisionists reassessed the role of dietary fiber in certain disorders of the digestive tract. For a time, it seemed fair game to criticize Burkitt’s health claims for fiber. In one critical commentary (3), the authors concluded that “fiber may appear in decline as a factor in a multitude of diseases, but do not count it out yet.” Curiously, a comprehensive understanding of the influence of dietary fiber on host pathophysiology has still not been achieved. Mechanistic explanations of the apparent health benefits of fiber have been simplistic, but perhaps we have been looking in the wrong place or at the wrong read-outs.

The article by Holscher et al. (4) in this issue of the Journal is welcome, in part because it represents a well-executed, appropriately controlled intervention with 2 forms of fiber (polydextrose and soluble corn fiber) in humans and because it looks at the microbiota beyond a description of composition toward functional capacity, showing the complexity of fiber effects, and has implications for the interpretation of previous studies. The study challenges the concept and definition of what constitutes a prebiotic effect. To their credit, the authors do not emphasize the term “prebiotic,” the definition of which is outdated and too narrow because it fails to encompass the effects of fiber on microbial composition and function that are not limited to lactobacilli and bifidobacteria (5).

Whole-genome shotgun sequencing showed that dietary fiber shifted the Bacteroidetes:Firmicutes ratio toward that previously associated with healthy lean rather than overweight subjects, and this was independent of caloric restriction. Both forms of added fiber altered microbial community structure rather than introducing or removing existing community members. As expected, enhanced metabolic function, particularly related to carbohydrate metabolism, was evident in the fiber-supplemented groups. Less predictable were the changes in genes involved in lipid and B-vitamin metabolism in addition to amino acid metabolism, including peptidases and transporters, which represented the largest enrichment in metabolic pathway genes after fiber supplementation. This provides a plausible explanation for the reduction in putrefactive compounds associated with fiber intake. Of course, the changes in functional capacity of the microbiome are complex and not all are seemingly beneficial. For example, the data of Holscher et al. (4) show a significant depletion of bacterial butyrate metabolism gene abundances in those individuals supplemented with both forms of fiber. This is again at odds with simplistic, unidimensional concepts of prebiotics.

Research on the human microbiome is growing rapidly, with contributions by investigators across disparate traditional disciplines. This enhances the collaborative potential and impact of sharing data but requires a level of standardization and consistency to ensure reproducibility of data. Hence, recommendations with regard to the adherence to fundamental methodology are timely (6). Accurate interpretation and avoidance of overstatement of data from microbiome studies also require an awareness of the limitations of current analytic technology. For example, Holscher et al. observed strikingly different results in quantifying the Bacteroidetes phylum when comparing their earlier 16S gene-based approach with their current whole-genome shotgun sequencing on the same samples (4). The investigators acknowledge the sources of bias in their own work and in metagenomic studies in general, which include not only methodologic variations but also an inherent potential bias in databases and analytic methods. At a clinical level, comparative and collaborative studies of the microbiome using samples from different populations will have to control for many environmental or lifestyle variables, the most important of which seems to be dietary. For example, the interpretation of a microbiome study in elderly humans in different living conditions would have been seriously confounded, and the dominant effect of food diversity would have been missed, if the details of dietary intake had not been recorded (7).

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The functional impact of dietary fiber on the human microbiome joins a growing list of diet-microbe-host interactions and underscores the intersection of microbe-host metabolic cascades. Of course, important questions remain. How much fiber is optimal? Fiber is no panacea; it adversely affects the symptoms of many patients with irritable bowel syndrome (3). Is there a clue here, and how may this be reconciled with fiber-induced functional changes to the microbiota? Does the functional effect of fiber vary depending on the age of the host? Although the 2 forms of fiber studied by Holscher et al. were similar in effect, variations in the fine structure of dietary fiber molecules may influence the evolution of host-microbe interactions and determine the diversity of the developing gut microbiome (8, 9). Limitations of many diet-microbiome studies include an over-reliance on fecal microbiota; fewer data are available on the microbiota at proximal sites. Finally, it may be informative to address the functional impact of fiber at a metabolomics level in conjunction with the whole-genome sequencing and compositional data.

It is time to re-examine Burkitt’s claims with the full range of modern technology, moving from descriptive assessments to functional analysis of the microbiota. In addition to discarding simplistic concepts of the mechanism of fiber-related health benefits, it is wise to resist becoming captive to restrictive language and outdated terms like prebiotics. Burkitt would have approved the new science of the human microbiome. Although he maintained that in science, as in life, “the heart takes precedence over the head” (1), he might now claim that the gut rules the heart and the head.

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REFERENCES