The hybrid science of diet, microbes, and metabolic health\textsuperscript{1–3}

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The inner world of the gut microbiota has become a focal point for investigators with seemingly disparate interests, including nutritionists, immunologists, epidemiologists, microbiologists, and specialists in metabolic medicine. This convergence is underpinned by several observations. First, it has long been known that the microbiota is a net contributor to the nutritional welfare of the host by metabolism of complex dietary carbohydrates, production of folate and B vitamins, and generation of short-chain fatty acids—the energy substrate for colonic epithelia. Second, the conditioning influence of the microbiota on the developing immune system has been evident since the first experiments with germ-free animals over a half-century ago, and more recently it has become clear that the host immune response has a reciprocal influence on the composition of the microbiota. Third, epidemiologic observations have suggested that diet and other elements of a modern lifestyle have an effect on the composition of the commensal microbiota and thereby may influence the increasing risk of immune-allergic and metabolic diseases in the developed world. Fourth, the pace of research linking these specialty interests has been greatly accelerated by technologic advances in molecular microbiology, such as metagenomics and high-throughput sequencing. These have circumvented the requirement for traditional cell culture conditions and have revealed remarkable diversity within the microbiota. In addition, metabolomic profiling has shown the relative contribution of microbial metabolism to the metabolome (the combined product of both the host genome and the microbiome) in health and disease.

However, until recently, interactions between diet, microbes, and the host might have been obscure for many nonspecialists. Now, the convergence of interests is arguably one of the hottest areas in medicine because of several exciting developments with therapeutic implications. These include new evidence linking dietary fat and intestinal microbial metabolism with the risk of atherosclerosis. This involves a previously unknown pathway, the first steps of which include microbial action on dietary phosphatidylcholine to generate proatherosclerotic metabolites (1). Other remarkable observations have provided compelling evidence linking the immune system with the microbiota and risk of obesity and diabetes. Disturbances of innate immunity can affect the microbiota and in turn may adversely influence the inflammatory response and risk of metabolic diseases.

Nonobese diabetic (NOD) mice deficient in MyD88, an adapter molecule required for sensing microbial signals by many Toll-like receptors (TLRs) within the innate immune system, are protected from development of type 1 diabetes but lose the protective effect when raised germ-free. It appears that some components of the microbiota may suppress the risk of autoimmune diabetes, whereas deficiency of MyD88 offsets this by changing the composition of the microbiota (2).

Experimental mice have also been used to uncover another layer of complexity in linking innate immunity and the microbiota with obesity and the metabolic syndrome. Mice lacking TLR5 develop obesity with many features of the metabolic syndrome, and this appears to be dependent on alterations in the intestinal microbiota (3). TLR5 is a component of the innate immune response; it is present on intestinal and immune cells and acts as an immunosensory receptor for microbial flagellin. The pathway by which TLR5 deficiency alters the makeup of the microbiota and the mechanism by which this leads to obesity are unclear. One suggestion is that the induction of proinflammatory cytokines by the disturbed microbiota leads to a desensitization of insulin receptor signaling with attendant hyperphagia and complications of obesity. This is conceptually appealing because obesity is known to be a proinflammatory condition.

A more direct mechanism linking diet, microbes, and risk of obesity could involve enhanced caloric extraction by the microbiota from dietary intake. Gordon et al (4), who rightly deserve credit for sparking much interest in this field, first showed that the gut microbiota represents an environmental regulator of fat storage by increasing absorption of monosaccharides from the gut and by promoting the deposition of lipid in adipocytes though the suppression of fasting-induced adipocyte factor (Fiaf), an inhibitor of lipoprotein lipase. This was followed by a series of provocative reports of a shift in the relative proportions of the 2 major divisions or phyla of bacteria within the gut microbiota (2).

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crobiota from obese animals they gained more weight than did mice that were colonized with microbiota from lean mice.

Whereas many researchers concur that the gut microbiota may influence fat metabolism and the risk of metabolic disease, the details are more complex than first considered (6–8). Whether alterations in the microbiota are a cause or consequence of obesity has become controversial. In addition, the age of the host and changes in the microbiota over time must be considered. Regardless, there is consensus regarding the primacy of diet among lifestyle factors influencing the composition of the microbiota.

The effect of diet on the fecal microbiota will be readily evident to anyone who has changed the diaper of a breastfed infant being weaned to formula foods. Comparative analyses of the fecal microbiota of children consuming a polysaccharide-rich, high-fiber diet in rural Africa compared with that of children in Europe showed marked differences (9). However, in contrast to experimental mice, there are considerable logistical difficulties in conducting controlled studies of the effect of dietary intake on the microbiota in humans. Therefore, the report by Jumpertz et al (10) in this issue of the Journal is welcome. They have linked comprehensive metagenomic analyses of the fecal microbiota with careful phenotypic studies of energy balance. This controlled and monitored nutrient intake and detailed physiologic phenotyping was lacking in earlier studies and shows that changes in nutrient load influences the fecal bacterial composition over a short time period. The microbial changes were correlated with stool energy loss in lean but not in obese individuals. The investigators rightly point out the limitations of the study, including the relatively small number of study subjects; however, as with all good research, the study raises new questions. How sustained are the effects of short-term changes in nutrient load on the microbiota? Do microbial communities adapt over time and is this different in lean and obese individuals? Is the fecal microbiota an accurate reflection of what is happening within other microbial niches of the gut? How do changes in nutrient load influence recently described clusters or enterotypes in the human microbiome (11)? In addition, a study of controlled over- and underfeeding on the basis of individual weight maintenance energy requirements is needed to confirm and clarify the apparent differences between lean and obese individuals.

There remains no doubt that the proximate cause of obesity is a surplus of energy consumption over expenditure, but the role of diet has become more complex and more intriguing by virtue of its effect on the microbiota and the role of the latter in modifying risk and protection from various metabolic and obesity-related disorders. Rigorous pursuit of this question in humans poses significant hurdles, but the report by Jumpertz et al represents a guide post for what may come.

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REFERENCES