

New Perspectives on the Role of the Intestinal Flora in Health and Disease*

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In centuries past, the intrinsic or commensal enteric flora, now often termed the microbiota, was regarded as a necessary evil which could, in certain circumstances, wreak havoc on the unwary host through the release of toxins (“vile humors”) and bacterial invasion. More recently, we have come to recognize, not only the importance of the gut flora in human homeostasis and the potential impact of alterations or perturbations of the normally symbiotic and highly beneficial relationship between the host and the microbiota, but have begun, through the use of prebiotics and probiotics, to attempt to restore balance and order where these have been lost (1).

The normal flora contains at least 500 different species and bacterial counts increase as one traverses the small intestine, rising most steeply on crossing the ileocolonic junction to reach counts of 10^{10} to 10^{12} on entering the colon (2). It is also notable that, reflecting the highly hypoxic environment that the colonic lumen provides, anaerobic species, such as clostridia, bifidobacteria and clostridia, predominate; it must be remembered, however, that many bacterial species within the colonic microbiota remain unculturable by conventional techniques. The beneficial impact of the normal flora is most dramatically illustrated by an examination of germ-free animals: in these animals, deprived of an indigenous flora, significant and deleterious effects are seen in the morphology and function of the intestinal mucosa, submucosa, vasculature, neuromuscular apparatus and gut- (or mucosa-) associated lymphoid tissue (GALT or MALT) (3). Clinical consequences of these changes include a failure to degrade intestinal mucus, shorter crypts,

impaired motility, a critical stunting of development of GALT and an inability to develop oral tolerance. We have also come to recognize other important functions for the microbiota in man, including: the production of arginine, glutamine and short chain fatty acids (an essential fuel for the colon), the deconjugation of bile acids, the prevention of colonization by pathogens and an important role in the metabolism of certain drugs. The clinical consequences of disruption of these functions are best illustrated by small intestinal bacterial overgrowth (SIBO) (1).

In health, therefore, a symbiotic and mutually beneficial dialogue (or “trialogue”) exists between the gut flora, the intestinal mucosa and the gut-associated lymphoid tissue. Disruption of this balance can lead to disease, as evidenced not only by SIBO, but also by such disorders as necrotizing enterocolitis, pseudomembranous colitis and urinary tract infections. It is also thought that more complex interactions between flora and host may be fundamentally relevant to inflammatory bowel disease; here a disordered recognition of components of the commensal flora, leading not to oral tolerance but to immune activation, seems highly likely (4).

We have a lot to learn of the subtleties of the interactions between the enteric flora/microbiota and the host; the advent and characterization of probiotics provides an opportunity to explore this field in some detail. Probiotics are currently defined as live microbial food ingredients that alter the microflora and confer health benefit. Given recent studies demonstrating probiotic-type effects for bacterial DNA (5,6) and supernatant from bacterial cultures (7), this definition may well require revision. After years of hype and inflated claims, science has, of late, come to bear on probiotics and has, in many instances, confirmed valuable properties. Clinical trials to demonstrate the translation of these properties or characteristics into real patient benefit have been less plentiful and often sub-standard in quality; here too progress has occurred, of late. A host of bacteriological experiments have clearly demonstrated that several probiotics (*lactobacilli* and *bifidobacteria* being the most widely studied) exert anti-pathogenic activity, not only by simple exclusion but also through the production of specific bacteriocins and the digestion of bacterial toxins. Much

* Lecture delivered on the occasion of the conferment of the title of Doctor Honoris Causa of the University of Medicine and Pharmacy Cluj-Napoca, Romania. December 8, 2005

interest has been generated by the demonstration of a host of immune-modulating effects for certain probiotics, including an enhancement of immunoglobulin A production and a modulation of the pattern of cytokine production by immune cells. These latter effects have been associated with an amelioration of mucosal inflammation in a variety of animal models of inflammatory bowel disease (8) and have even been shown to modify inflammatory processes distant from the gut, in the liver (9) and in the synovium (10). Probiotics have also been shown, again in animal models, to enhance gut barrier function and retard translocation of pathogens.

What is the relevance of this to the practicing gastroenterologist? It is now clearly established that probiotics can exert a beneficial impact on acute diarrhoeal illnesses, such as rotavirus-associated diarrhea, and that certain organisms appear effective in pseudomembranous (or, *C difficile*-associated) colitis. In human inflammatory bowel disease, the best evidence to date for efficacy of probiotics comes from pouchitis, where a probiotic cocktail, VSL#3, has been shown to be highly effective in both primary and secondary prevention (11). Studies in ulcerative colitis and Crohn's disease have, to date, been less impressive. It should come as no surprise that, given recent interest in the potential roles of prior bacterial infection and low-grade colonic inflammation in its pathogenesis, that probiotics have also been studied in irritable bowel syndrome (IBS). While many initial studies were underpowered and subject to criticism on the basis of study design, overall trends suggested benefit, especially, in relation to what could be generally referred to as "gas-related" symptoms (12). More recently, in two separate studies, we have demonstrated clear evidence of efficacy for one specific *bifidobacterium* (*bifidobacterium infantis* 35624) in improving all of the cardinal symptoms of IBS (13,14).

Certain important lessons have already been learnt from probiotic research. Organisms must be clearly characterized in terms of their morphology, immune activity, anti-bacterial properties and in vivo activity: not only do different probiotic bacteria exert possess different properties but, in some cases, their actions may be antagonistic and not synergistic! One cannot assume that two probiotics, even within the same species, will be the same; each must be meticulously characterized and studied. There is a great need for the application of the highest standards of quality control across all aspects of probiotic research. Probiotics can be powerful

tool to explore the physiology, immunology and therapeutic potential of the gut flora but this must be carried out with rigour, attention to detail and in keeping with the highest standards of clinical trials.

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