SUPERNATURAL HEALTH WATCH

Probiotics and Prebiotics

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Note: **Submitted in part as a Commentary to the journal *Pediatrics***

The term "probiotic", as an antonym to the term "antibiotic" was originally proposed in 1965 by Lilley and Stillwell 1, to be used for *substances* which *favor* the growth of microorganisms. More than 20 years later, Fuller broadly defined them as "live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance" [2]. The concept is not new. At the turn of the century, Ilya Metchnikoff suggested that the consumption of live microbes in fermented milk products to maintain this balance between pathogenic and nonpathogenic bacteria may be, at least in part, an explanation for why certain ethnic groups lived longer [3].

Fermented milk products with live bacteria have been consumed for centuries; however, the interest in the use of live microbial agents for the purpose of health maintenance and disease prevention or treatment has exploded over the last few years. Many factors are probably responsible for this, but the recognition that the "oversterilization" of our environment, particularly our food supply, may ultimately have detrimental consequences, is part of this phenomenon. The search for "healthy foods" as well as treatment alternatives to antibiotics has been an additional incentive. Many of these organisms, under the generic name of probiotics, are being proposed as remedies for a broad number of gastrointestinal and other systemic conditions ranging from diarrheal disease to allergy to cancer prevention. Recently, several books and reviews have been dedicated to the topic [4-6].

The human body lives in a heavily contaminated bacterial environment and symbiosis with these microbes seems a condition to survival: a human individual has more prokaryotic organisms associated to skin, lung and gut surfaces, than human eukaryotic cells. The role and importance of the intestinal flora in the maintenance of the gut luminal milieu and its effects on colonic epithelium, mucosal integrity, vitamin and nutrient metabolism and absorption, etc. have been well described. A logical management approach to situations which alter our microbial environment (dietary, environmental, antibiotics, etc.) would be to deliberately increase our association with specific nonpathogenic organisms to counter that alteration. Thus, conceptually, the use of probiotics constitutes *a purposeful attempt to modify the relationship with our immediate microbial environment, in ways that may benefit human health.*

A well-documented example is that of improvement of tolerance to lactose in lactose malabsorbing individuals. When lactose is ingested with live lactase producing organisms such as *S. thermophilus*, *L. bulgaricus* (such as in yogurt) and other lactobacilli, luminal digestion is increased and absorption enhanced. Over the last few years, following the development of specific strains demonstrated to survive acid and bile digestion, clinical and basic research have lead to a series of studies demonstrating and suggesting many other benefits [45]. These include management of infectious and noninfectious diarrhea, inflammatory bowel disease and food allergies, as well as other gastrointestinal disorders, and vaginal infections. Preliminary investigation suggests some agents may also have hypocholesterolemic and anti-tumoral properties.

The use of antibiotics constitutes an assault to gastrointestinal flora, accepted as one of those risks taken to manage severe infections.

Probiotics would be a reasonable alternative to help the GI flora resist this aggression. *Lactobacillus GG* (*L. GG*) has been reported to decrease the recurrence of antibiotic associated diarrhea and C. difficile colitis in adult and children. And more recently, a few controlled trials have shown amelioration of diarrhea associated to antibiotic use in children who are prescribed antibiotics for several types of acute illnesses.

The alleged "maintenance of microbial balance" as a logical, albeit simplistic, mechanistic concept could be applied to the use of probiotics for control of gastrointestinal *bacterial* disease. For example, in controlled reports, *L. GG* has decreased the recurrence of *C. difficile* diarrhea [67]. However, there have been multiple studies documenting the effects of several probiotics on *viral* gastroenteritis [8]. In these studies *L. GG*, bifidobacteria and other Lactobacilli have been reported to prevent, or to shorten duration, and shorten viral shedding in rotaviral disease. The effects that a bacteria can have over viral illness suggests that the mechanisms involved are likely more than simply overwhelming the gut lumen with "friendly" bacteria [9]. In a study in undernourished children [10], *L. GG* decreased the incidence of diarrheal disease in non-breastfed children, but had little effect on those who were being breastfed, suggesting high risk groups may be the most benefited by the prophylactic use of probiotics for diarrheal disease.

Currently, many research efforts are pointed towards elucidating the effect that oral bacterial administration may have on gut immunologic response and its systemic consequences. The possibilities of receptor competition, increased mucin secretion, bacterial "priming" of gut associated lymphoid tissue (GALT), and immunomodulation of GALT response are all being considered. For example the secretory IgA component of the intestine to rotaviral infection or to enteral vaccination can be augmented with the concomitant ingestion of specific probiotics [11].

The exposure of gut epithelium to a large amount of specific nonpathogenic bacteria may in some ways counteract the bacterial environmental changes that we have induced with the advent of a more aseptic food supply. These changes have indiscriminately reduced or eliminated *all* microorganisms, rather than selectively weeding out only pathogens. Thus the possibility that probiotics may modify inadequate or exaggerated inflammatory responses (from intestines deprived of a "richer bacterial experience") such as in allergy or inflammatory bowel disease is now being explored, with encouraging results [12].

Unfortunately, the wide variety of microorganisms used, the multiple dosing patterns, and the different populations studied preclude blanket recommendations. Among the best demonstrated effects yet are those of the use of *L.GG* and bifidobacteria for the treatment and prevention of diarrheal disease 13. Other lactobacilli, and Saccharomyces boulardii (a probiotic yeast) have also been investigated, with positive results reported. But not all bacteria are created equal and their effects are not same. Thus, each "probiotic" strain or strains suggested for use must be carefully studied prior to making recommendations for the management of specific conditions; and evaluation of target populations, and cost- benefit analyses may be needed in some cases to justify their use.

Safety does not appear to be a significant concern. Centuries of use of these lactic acid producing bacteria and lack of significant adverse effects with most strains currently in use are reassuring. A recent review identified 143 human clinical trials that wee conducted between 1961-1998, involving more than 7,500 subjects, with no adverse events reported [14]. Nevertheless, we should remain vigilant.

The use of probiotic products for their potential beneficial effects has its cost. The development of candidate strains for specific effects, the clinical trials necessary to demonstrate these are all needed. In addition, adequate quality control of any products sold needed, but can be complex and costly. This, plus the relative safety of these agents has been at least in part responsible for the lack of regulation of the commercialization of probiotic products. Many over the counter probiotics now widely available in "health food stores" are neither reliable as products nor effective as remedies [15]. They are sold under the general umbrella of "probiotics", with disguised or sometimes overt claims.

Sensible regulation of products and claims, as well as responsibility on part of this industry is sorely needed.

Over the last few years, the concept of “prebiotics has arisen. This term is generally refers to non-digestible substances that preferentially enhance the growth of non-pathogenic strains which may have a probiotic effect [16]. Human milk contains galacto-oligosaccharides which have been demonstrated to favor the growth of Bifidobacteria, a commonly used probiotic.

Other non-digestible carbohydrates have been shown to have these properties in vitro and in vivo; the most widely studied being fructo-oligosaccharides. The advantages of developing prebiotic substances are significant, from the point of view of safety, and particularly cost, compared to live microorganisms.

Clinical studies have only recently begun, but the results are encouraging. In a recent controlled trial, we demonstrated a significant decrease in severity of diarrheal disease, in terms of fever and vomiting; in a group of children attending day care who received a daily average dose of fructo-oligosaccharide - supplemented cereal. These results will be presented at this meeting. Most interestingly, there was also a general decrease in acute febrile illness, and its consequences (absenteeism, medical attention, etc). These initial findings again support the concept that modification of the intestinal milieu, by orally administered bacteria, or, in the latter case by a dietary change may have systemic effects, possibly via modulation of the gut associated immune mechanisms.

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