Probiotics – An Important Therapeutic Concept Awaiting Validation

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The concept that lactobacilli might be useful in displacing and replacing harmful microorganisms on mucosal surfaces was presented a century ago [1]. Three decades ago, it was suggested that probiotics constitute the other half of the antibiotic story [2], and was defined as organisms and substances that contribute to a better intestinal microbial balance [2]. Later, probiotics was defined as a live microbial food supplement that beneficially affects the host animal by improving its intestinal microbial balance [3]. The definition was broadened to include microorganisms that benefit humans or animals by improving the properties of the indigenous microflora [4]. A still later definition emphasized living microorganisms, which, upon ingestion in certain numbers, exert health benefits beyond the inherent basic nutrition [5]. Currently, probiotics is broadly defined as the preparation of a product containing viable, defined microorganisms in sufficient numbers that alter the microflora by implantation or colonization in a compartment of the host and exert beneficial health effects in the host [6].

The complex gut ecosystem is inhabited by 50 genera and over 400 separate microbial species [7]. More than 75% of the wet weight of fecal output is composed of bacterial cells, each gram containing approximately 1 x 10^{11} microbes [7]. The microbial community differs in composition along the length of the gut, with the colon containing increased numbers of indigenous microbes [7]. Relatively, the large intestine contains the most complex and diverse microbial populations [7]. The microbes are comprised of rapidly transmitting and relatively persistent bacteria [8]. The physiologic environments of the microbes vary from acid conditions in the stomach to an alkaline pH in the small bowel, in addition to changes in motility, sloughing of epithelial cells, epithelial mucin secretions and secretions of bile, exocrine pancreas, gut-associated lymphatic cells and secretory immunoglobulins [9]. The gut microflora is metabolically adaptable and is dependent on the availability of substrates like carbohydrates [10].

An important energy source for the colonocyte is short chain fatty acids (acetate, propionate and butyrate) produced from colonic microbial fermentation of undigested complex carbohydrates [11]. The competition among bacteria for nutrients and space contributes to the microbial composition of the ecosystem. One of the theoretic considerations for adding probiotics such as

Lactobacillus acidophilus is its supply of short chain fatty acids as the main luminal energy source for the colonocyte [12]. A second theoretic consideration is its provision of a salvage pathway for lactose malabsorption and intolerance, through hydrolysis of lactose by lactobacilli in the colon, thereby ameliorating the symptoms resulting from the ingestion of dairy products [13].

In this issue of *IMAJ*, Chermesh and Eliakim [14] discuss the concept of using probiotics for Crohn's disease and ulcerative colitis. One of the reasons for using lactobacilli in active Crohn's disease is that the gut flora is rich in *Escherichia coli* and depleted of bifidobacteria [15]. In their review of probiotic use in gastrointestinal disease, Chermesh and Eliakim [14] present the rationale for its application in lactose intolerance, antibiotic-associated diarrhea, viral gastroenteritis and travelers' diarrhea. One of the key questions is what kind of probiotic preparation to use. The authors cite the study of Gionchetti et al. [16], who treated chronic relapsing pouchitis with four strains of lactobacilli, three strains of bifidobacteria, and one of *Streptococcus salivarius*. The success of the treatment might have been due to the generation of short chain fatty acids, which provided a luminal source of energy to the enterocyte [12]. The hypothesis that correcting the bacterial imbalance causes an immune response was suggested as a mechanism of action of probiotics, but it has yet to be proven.

Also presented in the current *IMAJ* issue is the possible use of probiotics for other mucosal systems. Shalev [17] reviews the use of lactobacilli for bacterial vaginosis in pregnancy. Conceptually, he posits, by altering the mother's intestinal flora with probiotics we can influence the habitation of the microflora in the offspring and possibly prevent certain infections and diseases.

Nonetheless, the possibility of side effects should not be overlooked. Dunne et al. [18] articulate the prerequisites for successful probiotic use: namely, the bacteria of the human host, their non-pathogenic behavior, viability during gut passage, ability to adhere to the colonocyte, and resistance to gastric acidity, bile, pancreatic enzymes, etc. In addition, the prospect that the probiotic may produce antimicrobial substances, modulate immune response and influence metabolic activity should be considered and might be of great benefit in health and disease.

However, the picture is considerably more complex since methodologic problems arise when attempting to prove specific benefits of probiotics. There are inherent problems in the study design with regard to different probiotics. Multiple probiotic agents have been suggested and tested, but repeated studies have not yielded uniformity. Moreover, different dosing patterns of bacteria have been used in various studies. Acceptable endpoints to prove efficacy among the many study designs are rarely attainable. Finally, many uncontrolled variables are overlooked in the design of probiotic studies, yielding inconclusive results.

Presumably in the future, once we have acquired more information and a better understanding of gut microflora composition, colonization, interaction, translocation and immunomodulation, we might comprehend the probiotic effect in different diseases. It will be difficult to promote the concept of probiotic treatment without a carefully designed study – one that must include specific probiotic agents, fixed bacterial species and dosage, null hypothesis, inclusion and exclusion criteria, appropriate sample size, etc. Furthermore, based on extensive research of the human host bacteria, we might be able to develop innovative biotechnology-based probiotic products tailored to promote health and prevent specific diseases. Until then, we have an excellent preventive and therapeutic concept that has yet to be proven.

References

1. Metchnikoff E. The Prolongation of Life: Optimistic Studies. New York: GP Putman's Sons, 1908:161–83.
2. Parker R. Probiotics, the other half of the antibiotic story. *Anim Nutr Health* 1974:29:4–8.
3. Fuller R. Probiotics in man and animals. *J Appl Bacteriol* 1989:66:365–78.
4. Havenaar R, Huis in't Veld JHJ. Probiotics: a general view. In: Wood BJB, ed. The Lactic Acid Bacteria in Health and Disease. New York: Chapman & Hall, 1991:209–24.
5. Guarner F, Schaafma GJ. Probiotics. *Int J Food Microbiol* 1998:39:237–8.
6. Schrezenmair J, De Verse M. Probiotics, prebiotics synbiotics approaching a definition [Review]. *Am J Clin Nutr* 2001:73(Suppl):361–4s.
7. Conway PL. Microbial ecology of the human large intestine. In: Ginson GR, Macfarlane GT, eds. Human Colonic Bacteria: Role in Nutrition, Physiology and Pathology. Boca Raton:CRC Press, 1995:1–24.
8. Mackie RI, Sghir A, Gaskins HR. Developmental microbial ecology of the neonatal gastrointestinal tract. *Am J Clin Nutr* 1999:69:1035–45.
9. Falk PG, Hooper LV, Midtvet T, et al. Creating and maintaining the gastrointestinal ecosystem: what we know and need to know from gnotobiology. *Microbiol Mol Biol Rev* 1998:62:1157–70.
10. Roberfroid MB, Bornet F. Bouley C, et al. Colonic microflora: nutrition and health. *Nutr Rev* 1995:53:127–30.
11. Cummings JH, Macfarlane GT. Role of intestinal bacteria in nutrient metabolism. *Clin Nutr* 1997:16:3–11.
12. Firmansyah A, Penn D, Lebenthal E. Metabolism of glucose, glutamine, n-butyrate and beta-hydroxybutyrate in isolated rat colonocytes after acute fasting and chronic malnutrition.*Gastroenterology* 1989:97:622–9.
13. Penn D, Lebenthal E. Intestinal mucosal energy metabolism. A new approach to therapy of gastrointestinal disease. *J Pediatr Gastroenterol Nutr* 1990:10:1–4.
14. Chermesh I, Eliakim R. Probiotics – scope and promise in inflammatory bowel disease. *IMAJ* 2002.;4:353–6.
15. Giaffer MH, Holdsworth CD, Duerden BI. The assessment of faecal flora in patients with inflammatory bowel disease by a simplified bacteriological technique. *J Med Microbiol* 1991:35:238-43.
16. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double blind, placebo-controlled trial. *Gastroenterology* 2000:119:305–9.
17. Shalev E. Ingestion of probiotics: optimal treatment of bacterial vaginosis in pregnancy. *IMAJ* 2002;4:357–60.
18. Dunne C, O'Mahony L, Murphy L, et al. In vitro selection criteria for probiotic bacteria of human origin: correlation with in vivo findings [Review]. *Am J Clin Nutr* 2002:73:386–92s.

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