For: Pediatric Clinics of North America, 2002;49:127-141

Probiotics in Health and Disease

Jonathan E. Markowitz, MD and Stig Bengmark, MD

The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them—Sir William Bragg

Introduction

The idea that bacteria can affect health is not new. Much effort is directed at eliminating bacteria, through antibiotics, to improve the health of children. However, a different approach to bacteria, dating back to the early 20th century, is gaining popularity approximately 100 years later and may impact the way many diseases are treated in the future. This approach uses the idea of *probiotics*, a general term for nutritional supplements containing one or more cultures of living organisms (typically bacteria or yeast) that, when introduced to a human (or animal), have a beneficial impact on the host by improving the endogenous microflora[22].

Pasteur and Joubert observed over a century ago that there is an antagonistic interaction between bacterial strains, and even suggested that non-pathogenic bacteria should be used to control pathogenic bacteria[39]. Often credited as the first advocate for probiotics, Metchnikoff made the observation that lactic fermentation of milk products arrested putrefaction, and suggested that consumption of those products might offer the same protection to humans[34]. Today, research is directed towards developing specific strains of bacteria that are engineered to withstand the harsh environments of the stomach and proximal small intestine, to better allow colonization in the distal small intestine and colon. Further efforts are directed at developing foods that promote growth of probiotic strains of bacteria that can be administered alone (*prebiotics)* or in combination with the probiotic bacteria as one concoction (*synbiotics*).

Background

Each individual's gastrointestinal tract represents an ecosystem unto itself. The gastrointestinal lumen is a reservoir with an internal surface of approximately 200 m^2, 100 times the surface area of the skin[22]. This surface separates the host from approximately 10^{13} bacteria, 10 times more cells than exist in the entire human body[50]. There is constant interaction between the endogenous flora and potentially pathogenic microorganisms. Even under optimal conditions, bacteria, viruses, and toxins penetrate the intestinal barrier and invade the adjacent parts of the body. The integrity of the barrier can be dramatically altered by changes in the secreted antibodies, the mucus layer, and the immune system, as well as through direct and indirect inhibition of other organisms. The endogenous flora plays a major role in the control of each of these aspects of the mucosal barrier. In addition, alterations in the intestinal flora may impact the distal immune system and therefore can have effects beyond the gastrointestinal tract.

Probiotics in Health

Health and wellbeing depend on a complex and dynamic interplay between factors that control vital processes such as appetite, energy balance, metabolic rate, and

stress response. Lifestyle and eating habits are in part responsible for each individual's overall health status. Some well-known examples of how eating habits impact health include the negative impact by excessive intake of saturated fatty acids and cholesterol, refined sugars, and sodium. The typical "western" diet has been implicated in the development of diseases such as heart disease and cancer due to its content of saturated fats and sugars and relative lack of fruits and vegetables, as well as the desirable omega-3 fatty acids.

Perhaps an equally important factor that has been overlooked is intake of probiotic bacteria. Historically, fermentation was used as a method of preserving foods. Ingestion of these foods would expose the host to probiotic organisms, the same as or similar to those being used today. However, the typical "western" diet contains dramatically decreased numbers of fermented foods, exposing the host to as little as one millionth of the probiotic organisms our ancestors would have been exposed to. It does not seem to be a coincidence that astronauts, who receive a diet low in fiber and anti-oxidants return to Earth with significantly decreased counts of endogenous probiotic bacteria[28]. It may or may not be a coincidence that increases in inflammatory conditions, allergic conditions, obesity, heart disease, and cancers have paralleled the decreasing content of probiotics in the western diet.

Probiotics in Intestinal Disease

Probiotics have been best studied in the context of various gastrointestinal diseases. Intuitively, they would seem to have a role in diarrheal diseases thought to involve disorders of the endogenous intestinal flora, the most common of which include antibiotic associated diarrhea, *Clostridium difficile* associated diarrhea, and other enteric bacterial infections. There are many potentially probiotic strains of bacteria, but controlled research has not been conducted on more than a few. In pediatrics, the vast amount of research has been done with a particular strain of *Lactobacillus* known as *Lactobacillus GG*. This particular strain was isolated from human subjects and was found to survive oral administration and colonize healthy volunteers[20], and therefore has been often used in controlled studies.

Antibiotic-Associated Diarrhea

Diarrhea is a common side effect of antibiotic therapy[4, 12]. Up to 40% of children receiving broad-spectrum antibiotics experience diarrhea[13]. Given the large numbers of pediatric patients who receive antibiotic therapy each year, preventing even a proportion of the cases of antibiotic associated diarrhea may have a large impact.

Most of the cases of antibiotic associated diarrhea are not associated with an infectious pathogen, with the exact etiology unclear[29]. The mechanism behind the diarrhea likely relates to changes in the microbial flora with resulting alterations in metabolism of carbohydrates or other osmotically active substances[43, 46]. There are multiple trials of various probiotic preparations in antibiotic associated diarrhea that seemed to show some efficacy. Dating back to 1977, studies using the yeast *Saccharomyces boulardii* demonstrated that probiotics can reduce diarrhea in patients receiving antibiotics[2]. More recently, Surawicz, *et al.* [49] demonstrated a reduced rate of diarrhea in 116 patients receiving *S. boulardii* during antibiotic therapy as opposed to placebo.

Lactobacillus GG (LGG) has been extensively studied, and has been shown to have efficacy in children and adults. Two particular studies are worth noting. Armuzzi,

et al. [3] used LGG in a group of otherwise healthy adults undergoing treatment for asymptomatic *Helicobacter pylori* infection. This group represents a particularly interesting cohort, as they had no symptoms of disease prior to enrolling. They were treated with a triple therapy regimen including two antibiotics (clarithromycin and tinidazole) for one week and randomized to receive either LGG or placebo during that week. The treatment group experienced significantly less nausea and diarrhea than the control group throughout the week of treatment, with a relative risk for diarrhea of 0.1 in the treatment group. There was also a trend for less diarrhea among the treatment group for two weeks following discontinuation of both the antibiotics and the probiotic, but this difference did not reach statistical significance.

Vanderhoof, *et al.*[52] conducted one of the larger studies aimed at evaluating probiotics in antibiotic associated diarrhea in children. In this study, 188 children being treated with antibiotics for a variety of indications were randomized to receive LGG or placebo concomitantly with therapy. In the treatment group 8% of patients developed diarrhea, versus 26% in the control group. Duration of diarrhea was also shorter (by one day) among treated patients who developed diarrhea, but the clinical significance of a one day reduction is questionable.

These two studies show that probiotic bacteria are able to prevent diarrhea associated with antibiotic use. One may question the importance of the prevention of antibiotic induced diarrhea, given that most courses are self-limited and do not result in dehydration or hospitalization. However, one must not overlook the importance of maintaining a normal ecology in the intestines. Disruption of the normal intestinal flora represents a change to a delicately balanced system. Although diarrhea maybe the easiest manifestation to detect, there may be benefits beyond prevention of diarrhea. In addition, prevention of an unpleasant side effect—even one as benign as diarrhea—may greatly increase adherence to the medication regimen, although this particular aspect of probiotics has not yet been studied.

Probiotics in Infectious Diarrhea:

A very interesting aspect of probiotics is their ability to prevent and treat infectious diarrhea. Infectious diarrhea represents a worldwide health problem, especially among children[47]. While a major cause of mortality in developing nations, infectious diarrhea also has significant cost in developed nations in terms of hospitalization and lost time. Probiotics have been shown to be successful in the treatment or prevention of various types of infectious diarrhea, including rotavirus, *Clostridium difficile*, and traveler's diarrhea.

Saavedra, *et al.* [45] published a landmark study in the prevention of infectious diarrhea in children. Using children admitted to a chronic care facility, a standard infant formula was supplemented with two strains of probiotic bacteria (*Bifidobacteria bifidum and Streptococcus thermophilus*). Children up to age 2 years were randomized to receive either the probiotic-supplemented formula or standard formula and were followed for the development of diarrhea and the development of rotaviral shedding. Not only did subjects in the probiotic group develop diarrhea at a statistically lower rate than those in the control group (7% versus 31%), but rotavirus shedding was statistically decreased in the probiotic group as well (10% versus 39%).

A Peruvian study evaluated probiotics in a different, but also high-risk population[37]. In this case, 204 undernourished children received either LGG or placebo.

Again, a difference in rates of diarrhea was found, but although the treated group had statistically fewer episodes of diarrhea, the reduction was of questionable clinical significance (from 6 episodes/child/year to 5.2 episodes/child/year). Moreover, breast-fed children did not seem to benefit at all.

These studies demonstrated that prophylactic use of probiotics can successfully prevent non-specific diarrheal illness in a susceptible population. However, the effect on shedding of a specific viral pathogen is most interesting. The ability for supplementation with bacterial products to prevent infection with a viral agent seems to demonstrate an immune-modulating effect of probiotics, beyond simple barrier protection. This theory is further supported by the study of Isolauri *et al.*[24] whose group demonstrated that duration of hospitalization was significantly shorter in children with rotavirus diarrhea who were administered oral rehydration and LGG (both as a fermented milk product and as a freeze-dried powder), than in a similar group who received oral rehydration plus placebo. Another study of oral rehydration with and without LGG[21] in acute-onset diarrhea also showed decreased duration of diarrhea and of hospitalization among a large cohort of children who received active LGG versus those who received placebo. Four times as many children in the placebo group had admissions lasting one week or more. The difference was most pronounced among subjects with rotavirus or idiopathic diarrhea, with no significant difference among patients diagnosed with invasive bacterial pathogens, demonstrating a likely mechanism of action beyond simple antagonism of bacterial growth.

A possible explanation of this action in rotavirus diarrhea comes from Majamaa, *et al.*[31] In this study, 49 children with rotavirus gastroenteritis were randomly assigned to receive LGG, a similar strain of lactobacillus, or a combination of a streptococcus and lactobacillus. In this case, the patients receiving LGG had a decreased duration of diarrhea, but also showed a significant increase in the number of cells secreting IgA against rotavirus. The mechanism behind the improved antibody secretion in the LGG group is not known, but may indicate that certain probiotics have an immune modulating effect on the host.

Another aspect of the above study is the heterogeneous nature of probiotic bacteria. Two similar probiotic bacteria, LGG and another lactobacillus, had demonstrable differences in their effects. This aspect of probiotics is particularly important, as not every candidate probiotic will show efficacy, and not every probiotic will have efficacy in every disease. The science of probiotics is immature, and it is reasonable to believe that certain studies may have shown different results had a different probiotic or combination of probiotics been used. LGG is often chosen because of its ability to survive passage through the acid of the stomach and the bile of the duodenum and then to adhere to intestinal mucosa. It, however, is not the only probiotic with these properties, and future research will need to incorporate other candidates, such as *Lactobacillus plantarum* as they become available[7]. An entire subset of probiotic work may involve research directed towards identifying the appropriate organisms for use in particular diseases and in particular populations.

***Clostridium difficile* Diarrhea**

Clostridium difficile (*Cd*) has been associated with symptomatic diarrhea since it was identified as the pathogen responsible for pseudomembranous colitis[5]. It accounts for up to one-fourth of the cases of bacterial diarrhea, second only to *Campylobacter*

jejuni[30]. *Clostridium difficile* is a gram-positive, spore-forming bacillus that elaborates two toxins (A and B). Infection with *Cd* is often precipitated by antibiotic use that disrupts the endogenous flora that suppresses the growth of the organism under normal conditions. Although symptomatic disease was historically attributed to the presence of toxin A, both toxins are now recognized as important in disease physiology[30 11]. Symptoms of *Cd* infection can range from a mild, self-limited diarrhea to severe colitis with cramping, hematochezia, psudomembrane formation, and perforation[1]. Even though *Cd* usually responds well to treatment with oral antibiotics such as metronidazole or vancomycin, relapses are common and can be difficult to treat[6, 17]. Patients with a history of *Cd* seem particularly susceptible to recurrence during antibiotic therapy[15, 35].

As evidence that a normal bacterial flora can suppress the growth of *Cd*, patients have successfully been treated with fecal enemas leading to eradication of the infection[51]. Probiotic therapy could potentially treat *Cd* infection in a similar fashion. Biller, *et al.*[8] reported a series of four children with at least 3 recurrences of *Cd* prior to open label treatment with LGG. All patients responded, although two relapsed within 2 months. Retreatment in those individuals led to clearance of the infection without recurrence for a mean follow-up period of 11 months.

S. boulardii has been used preventively in *Cd* infection[33], but has been shown to decrease infection rate among only those subjects who have had a previous *Cd* infection. Of special note is that colonization was not reduced in subjects, while toxin production was. This may represent a mode of action for the yeast beyond inhibition of growth, although the exact etiology is unclear. **TABLE 1**

Traveler's Diarrhea

As evident in some of the studies of infectious diarrhea, probiotics seem to prevent viral induced diarrhea better than bacterial diarrhea. This may be the reason that probiotics have yet to be conclusively shown to decrease the incidence of traveler's diarrhea, although there is far less literature in this realm. In a study of Finnish tourists traveling to Turkey[38], there was a modest decrease in the incidence of diarrhea (41% for a group given LGG, 46.5% in those given placebo) with slightly better results in a group traveling to a particular area of Turkey. *L. acidophilus* was also not effective as prophylaxis for traveler's diarrhea in one study[26]. *S. boulardii* seems to show potential for preventing traveler's diarrhea, based on a double-blind, placebo-controlled trial where the treatment group developed diarrhea at a diminished rate (28.7% vs. 39.1% for placebo), but also showed variability depending on the region of travel[27]. It is of interest that *S. boulardii* seems to affect inhibition of bacterial growth, whereas LGG has been shown to be less effective against bacterial diarrheas. This may reflect different mechanisms of action between the yeast-based and bacteria-based probiotics. It also emphasizes that the term *probiotic* is best thought of as a general term and that one cannot assume that a specific probiotic will be effective for the same indications as another.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is the collective term used to describe Crohn's disease and ulcerative colitis. These diseases, although each with distinctive features, have in common inflammation in the gastrointestinal tract, which can lead to pain, diarrhea, and bleeding. The cause of IBD is unknown, and there is growing evidence that the diseases we call IBD actually represent a multitude of abnormalities that involve any of a number of body systems, which then result in the final, common pathway of chronic

intestinal inflammation[16]. There is also ample evidence that these diseases are multifactorial in etiology. Many, if not all, of the proposed factors affecting the development of IBD have a relationship with the endogenous bacterial flora.

A clinical scenario that implicates the role of endogenous flora in Crohn's disease is the finding that fecal diversion may prevent recurrence of Crohn's disease after colectomy, while reanastomosis precipitates recurrence[36]. Further support comes from an animal model of IBD, the IL-10 deficient mouse, that spontaneously develops colitis in the presence of normal colonizing bacteria, but does not in a sterile environment. The use of antibiotics with activity against the intestinal flora to treat IBD—tobramycin in ulcerative colitis[9] and metronidazole and ciprofloxacin in Crohn's disease[19, 41]—serves as more evidence that these diseases are in some part dependent on the host interaction with the gastrointestinal flora.

There is an increasing body of clinical data that supports a role for probiotics in the treatment of IBD. Pathmakanthan *et al.*[40] studied fresh biopsy specimens from patients with ulcerative colitis and quantified various aerobic and anaerobic bacteria such as *Bacteroides, Lactobacillus,* and *Bifidobacterium.* They found a significant reduction in mucosal *Lactobacillus* in inflamed tissue from ulcerative colitis patients. Similarly, Favier, *et al.*[14] demonstrated that patients with Crohn's disease had significantly decreased levels of *Bifidobacterium* versus normals.

More recently, clinical trials involving probiotic bacteria have shown evidence of efficacy in IBD. Rembacken, *et al.*[44] demonstrated that remission rates and maintenance of remission were not statistically different between ulcerative colitis patients receiving mesalazine, a mainstay of outpatient IBD therapy, and a probiotic consisting of a non-pathogenic strain of *Escherichia coli.* Venturi, *et al.*[53] found similar remission rates in a cohort of ulcerative colitis patients given a probiotic preparation consisting of 3 strains of bifidobacteria, 4 strains of lactobacilli, and 1 strain of streptococcus. Fecal concentrations of the probiotic organisms were increased in all patients at the close of the study. More recently, this same combination therapy was shown to have efficacy in preventing pouchitis in ulcerative colitis patients after colectomy[18].

In Crohn's disease there are less published studies, but one study of note found a trial of oral therapy with LGG resulted in increased numbers of IgA-secreting cells in children [32]. An especially intriguing possibility involves the development of so-called "turbo-probiotics" which are genetically engineered to deliver active compounds. An example is the probiotic bacteria *Lactococcus lactis* which was engineered to secrete interleukin-10, an anti-inflammatory cytokine which is currently undergoing study for its ability to treat active Crohn's disease[48]. In this experiment, the turbo-probiotic was able to reduce colitis in two different murine models of IBD.

Beyond the Intestine

Understandably, probiotics have been extensively studied in disorders of the intestine. However, a very intriguing aspect of these products revolves around their ability to affect other disorders as well. **TABLE 2.**

Helicobacter pylori

Probiotic bacteria may be antagonistic to *Helicobacter pylori*. *Lactobacillus salivarius* has been shown to inhibit the attachment of *H. pylori in vitro* and inhibits the ability of *H. pylori* to colonize the stomach mucosa of mice[25]. In clinical practice, an open-label randomized trial of triple therapy with or without the addition of *L.*

acidophilus was conducted among 120 patients with *H. pylori*[10]. Eradication rates were significantly higher (87% versus 70%) in the group supplemented with the probiotic. Further evaluation is needed, however these initial results are promising.

Allergy

A striking example of probiotic effects outside the intestine is their ability to reduce the symptoms of atopic dermatitis. Isolauri, *et al.*[23] studied infants who experienced eczema on exclusively breast-fed diets. They were randomized to receive a hydrolyzed protein formula with or without probiotics. Using an objective measure of atopic dermatitis activity, the group receiving probiotic supplementation had nearly complete to complete resolution of eczema, while the placebo group had minimal improvement. Explanation as to why this difference occurred may be increased production of the anti-inflammatory cytokine interleukin (IL)-10, as evidenced by a subsequent study showing increased IL-10 production in 9 children receiving supplementation with LGG[42].

Conclusions

Probiotics are truly a timeless concept. Initially a standard component of the human diet, potentially beneficial bacteria and yeast have been systematically eliminated through modern methods of preparing and preserving foods. Although the concept of probiotics is not new, the science of probiotics is in its infancy. Only recently have techniques been developed to consistently identify, culture, and produce the probiotics that are suitable for medical use. Furthermore, the potential uses for these organisms may extend far beyond what was originally thought. In no way should probiotics be thought of as a panacea for the diseases described above. However, when used appropriately they represent a potentially beneficial adjunct to other proven therapies, and have the added benefit of providing a stabilizing influence on the delicate balance between the ecosystem that consists of the human and its flora.

Table 1. Molecular effects of probiotics

Stimulates secretory IgA production
Inhibits IgE production
Modulates T-cell mediated responses
Modulates cytokine response
Stimulates nitric oxide production
Stimulates macrophage function
Stimulates natural killer cell activity
Activates the mucosal-associated lymphoid (MALT) system
Stimulates apoptosis
Promotes growth and regeneration
Reduces endotoxin production
Reduces mutagenicity
Produces antioxidants, nutrients, and various growth factors

Table 2. Potential uses of probiotics

Prevention of rotavirus diarrhea
Decreasing duration of infectious diarrhea
Promoting remission of IBD
Treatment of *Helicobacter pylori* infection
Treatment of recurrent *Clostridium difficile* infection
Treatment of atopic dermatitis
Prevention of colonic neoplasia*
Prevention of pancreatic sepsis in pancreatitis*
Prevention of sepsis after major surgery†
Prevention of sepsis in the intensive care unit setting†

*Animal studies †Preliminary data

REFERENCES

1. AAP: Clostridial Infections. *In*: Pickering LK, ed. 2000 Red Book: Report of the Committee on Infectious Diseases, 25th ed. Elk Grove Village, IL, American Academy of Pediatrics, 2000, pp 212-219
2. Adam J, Barret A, Barret-Bellet C: Essais cliniques controles en double insu de l'ultra-leure lyophilisee. Etude multicentrique par 25 medecins de 388 cas. Gaz Med Fr 84:2072-8,1977
3. Armuzzi A, Cremonini F, Bartolozzi F, et al.: The effect of oral administration of *Lactobacillus GG* on antibiotic-associated gastrointestinal side-effects during *Helicobacter pylori* eradication therapy. Aliment Pharmacol Ther 15:163-169,2001
4. Bartlett JG: Antibiotic-associated diarrhea. Clin Infect Dis 15:573-81,1992
5. Bartlett JG, Chang TW, Gurwith M, et al.: Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Engl J Med 298:531-4,1978

6. Bartlett JG, Tedesco FJ, Shull S, et al.: Symptomatic relapse after oral vancomycin therapy of antibiotic-associated pseudomembranous colitis. Gastroenterol 78:431-4,1980
7. Bengmark S: Immunonutrition: role of biosurfactants, fiber, and probiotic bacteria. [Review] [137 refs]. Nutrition 14:585-94,1998
8. Biller JA, Katz AJ, Flores AF, et al.: Treatment of recurrent Clostridium difficile colitis with Lactobacillus GG [see comments]. J Pediatr Gastroenterol Nutr 21:224-6,1995
9. Burke DA, Axon AT, Clayden SA, et al.: The efficacy of tobramycin in the treatment of ulcerative colitis. Aliment Pharmacol Ther 4:123-9,1990
10. Canducci F, Armuzzi A, Cremonini F, et al.: A lyophilized and inactivated culture of Lactobacillus acidophilus increases Helicobacter pylori eradication rates. Aliment Pharmacol Ther 14:1625-9,2000
11. Cleary RK: Clostridium difficile-associated diarrhea and colitis: clinical manifestations, diagnosis, and treatment. Dis Colon Rectum 41:1435-49,1998
12. de Roos NM, Katan MB: Effects of probiotic bacteria on diarrhea, lipid metabolism, and carcinogenesis: a review of papers published between 1988 and 1998. [Review] [80 refs]. Am J Clin Nutr 71:405-11,2000
13. Elstner CL, Lindsay AN, Book LS, et al.: Lack of relationship of *Clostridium difficile* to antibiotic-associated diarrhea in children. Pediatr Infect Dis 2:364-6,1983
14. Favier C, Neut C, Mizon C, et al.: Fecal beta-D-galactosidase production and Bifidobacteria are decreased in Crohn's disease. Dig Dis Sci 42:817-22,1997
15. Fekety FR, Shah AB: Diagnosis and treatment of *Clostridium difficile* colitis. JAMA 269:71-75,1993
16. Fiocchi C: Inflammatory bowel disease: etiology and pathogenesis. Gastroenterol 115:182-205,1998
17. George WL, Volpicelli NA, Stiner DB, et al.: Relapse of pseudomembranous colitis after vancomycin therapy. N Engl J Med 301:414-415,1979
18. Gionchetti P, Rizzello F, Venturi A, et al.: Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial [see comments]. Gastroenterol 119:305-9,2000
19. Gitnick G: Antibiotics and inflammatory bowel diseases. [Review] [18 refs]. Gastroenterol Clin North Am 18:51-6,1989
20. Goldin BR, Gorbach SL, Saxelin M, et al.: Survival of a Lactobacillus species (strain GG) in human gastrointestinal tract. Dig Dis Sci 371992
21. Guandalini S, Pensabene L, Zikri MA, et al.: Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial [see comments]. J Pediatr Gastroenterol Nutr 30:54-60,2000
22. Holzapfel WH, Haberer P, Snel J, et al.: Overview of gut flora and probiotics. [Review] [114 refs]. International Journal of Food Microbiology 41:85-101,1998
23. Isolauri E, Arvola T, x00Fc, et al.: Probiotics in the management of atopic eczema. Clinical & Experimental Allergy 30:1604-10,2000
24. Isolauri E, Juntunen M, Rautanen T, et al.: A human Lactobacillus strain (Lactobacillus casei sp strain GG) promotes recovery from acute diarrhea in children. Pediatrics 88:90-7,1991

25. Kabir AM, Aiba Y, Takagi A, et al.: Prevention of Helicobacter pylori infection by lactobacilli in a gnotobiotic murine model. Gut 41:49-55,1997
26. Katelaris PH, Salam I, Farthing MJ: Lactobacilli to prevent traveler's diarrhea? [letter]. N Engl J Med 333:1360-1,1995
27. Kollaritsch H, Holst H, Grobara P, et al.: [Prevention of traveler's diarrhea with Saccharomyces boulardii. Results of a placebo controlled double-blind study]. Fortschr Med 111:152-6,1993
28. Lencner AA, Lencner CP, Mikelsaar ME, et al.: [The quantitative composition of the intestinal lactoflora before and after space flights of different lengths]. Nahrung 28:607-13,1984
29. Lewis SJ, Freedman AR: Review article: the use of biotherapeutic agents in the prevention and treatment of gastrointestinal disease. [Review] [144 refs]. Aliment Pharmacol Ther 12:807-22,1998
30. Lyerly DM, Krivan HC, Wilkins TD: Clostridium difficile: its disease and toxins. [Review] [252 refs]. Clin Microbiol Rev 1:1-18,1988
31. Majamaa H, Isolauri E, Saxelin M, et al.: Lactic acid bacteria in the treatment of acute rotavirus gastroenteritis. J Pediatr Gastroenterol Nutr 20:333-8,1995
32. Malin M, Suomalainen H, Saxelin M, et al.: Promotion of IgA immune response in patients with Crohn's disease by oral bacteriotherapy with Lactobacillus GG. Annals of Nutrition & Metabolism 40:137-45,1996
33. McFarland LVP, Surawicz CMMD, Greenberg RNMD, et al.: A Randomized Placebo-Controlled Trial of Saccharomyces boulardii in Combination With Standard Antibiotics for Clostridium difficile Disease. JAMA June 22 271:1913-1918,1994
34. Metchnikoff E: The prolongation of life.: Optimistic Studies. London, 1907, pp
35. Nord CD, Edlund C: Impact of antimicrobial agents on human intestinal microflora. J Chemother 2:218-237,1990
36. Oberhelman HA, Jr., Kohatsu S, Taylor KB, et al.: Diverting ileostomy in the surgical management of Crohn's disease of the colon. Am J Surg 115:231-40,1968
37. Oberhelman RAMD, Gilman RHMD, Sheen PBS, et al.: A placebo-controlled trial of Lactobacillus GG to prevent diarrhea in undernourished Peruvian children. Journal of Pediatrics January 134:15-20,1999
38. Oksanen PJ, Salminen S, Saxelin M, et al.: Prevention of travellers' diarrhoea by Lactobacillus GG. Ann Med 22:53-6,1990
39. Pasteur L, Joubert J: Charbon et septicemie. C R Soc Biol 85:101,1877
40. Pathmakanthan S, Thornley JP, Hawkey CJ: Mucosally associated bacterial flora of the human colon: quantitative and species specific differences between normal and inflamed colonic biopsies. Microbial Ecology in Health and Disease 11:169-174,1999
41. Peppercorn MA: Current status of drug therapy for inflammatory bowel disease. [Review] [18 refs]. Compr Ther 11:14-9,1985
42. Pessi T, x00Fc, tas Y, et al.: Interleukin-10 generation in atopic children following oral Lactobacillus rhamnosus GG. Clinical & Experimental Allergy 30:1804-8,2000
43. Rao SS, Edwards CA, Austen CJ, et al.: Impaired colonic fermentation of carbohydrates after ampicillin. Gastroenterol 86:174-93,1988

44. Rembacken BJ, Snelling AM, Hawkey PM, et al.: Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial [see comments]. Lancet 354:635-9,1999
45. Saavedra JM, Bauman NA, Oung I, et al.: Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. Lancet 344:1046-9,1994
46. Simon GL, Gorbach SL: Intestinal flora in health and disease. Gastroenterol 86:174-93,1984
47. Snyder JD, Merson MH: The magnitude of the global problem of acute diarrheal disease: a review of surveillance data. Bull World Health Organ 60:605-13,1982
48. Steidler L, Hans W, Schotte L, et al.: Treatment of Murine Colitis by Lactococcus lactis Secreting Interleukin-10. Science August 25 289:1352-1355,2000
49. Surawicz CM, Elmer G, Speelman P, et al.: Prevention of antibiotic-associated diarrhea by *Saccharomyces boulardii*: a prospective study. Gastroenterol 96:981-8,1989
50. Tancrede C: Role of human microflora in health and disease. European Journal of Clinical Microbiology & Infectious Diseases 11:1012-5,1992
51. Tvede M, Rask-Madsen J: Bacteriotherapy for chronic relapsing *Clostridium difficile* diarrhoea in six patients. Lancet 1:1156-1160,1989
52. Vanderhoof JA, Whitney DB, Antonson DL, et al.: *Lactobacillus GG* in the prevention of antibiotic-associated diarrhea in children. Journal of Pediatrics 135:564-568,1999
53. Venturi A, Gionchetti P, Rizzello F, et al.: Impact on the composition of the faecal flora by a new probiotic preparation: preliminary data on maintenance treatment of patients with ulcerative colitis. Aliment Pharmacol Ther 13:1103-8,1999