

# Probiotics and Prebiotics: A Brief Overview

JoMay Chow, PhD\*

---

Probiotics and prebiotics are 2 food ingredients that confer physiologic effects through the gastrointestinal tract. *Probiotics* have been defined as viable microorganisms that (when ingested) have a beneficial effect in the prevention and treatment of specific pathologic conditions. These microorganisms are believed to exert biological effects through a phenomenon known as colonization resistance, whereby the indigenous anaerobic flora limits the concentration of potentially pathogenic (mostly aerobic) flora in the digestive tract. Other modes of action, such as supplying enzymes or influencing enzyme activity in the gastrointestinal tract, may also account for some of the other physiologic effects that have been attributed to probiotics. Conversely, prebiotics are nondigestible food ingredients that beneficially affect host health by selectively stimulating the growth and/or activity of 1 or a limited number of bacteria in the colon. The prebiotic, fructooligosaccharide (FOS), is found naturally in many foods, such as wheat, onions, bananas, honey, garlic, or leeks. They can also be isolated from chicory root or synthesized enzymatically from sucrose. Fermentation of FOS in the colon results in a large number of physiologic effects including increasing the numbers of bifidobacteria in the colon, increasing calcium absorption, increasing fecal weight, shortening of gastrointestinal transit time, and possibly lowering blood lipid levels. Other effects that have been observed in animal models include an increase in cecal weight and an increase in fecal nitrogen excretion. The increase in bifidobacteria has been assumed to benefit human health by producing compounds to inhibit potential pathogens, by reducing blood ammonia levels, and by producing vitamins and digestive enzymes.

© 2002 by the National Kidney Foundation, Inc.

---

THE NOTION that food could serve as medicine was first conceived thousands of years ago by the Greek philosopher and father of medicine, Hippocrates, who once wrote, "Let food be thy medicine, and let medicine be thy food."<sup>1</sup> However, during recent times, the concept of food having medicinal value has been reborn as *functional foods*, a term that refers to "any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains."<sup>1</sup> This article provides a brief overview of probiotics and prebiotics, 2 increasingly popular ingredients that can be found in functional foods and dietary supplements. The review first de-

scribes these ingredients and then explains how they are believed to work within the human body. Lastly, this article highlights some potential applications for these ingredients in patients with renal disease. For a more comprehensive treatment of these topics, the reader may consult several other articles.<sup>2-6</sup>

## Probiotics

### Definition and Strains

*Probiotics* may be defined as "viable microorganisms that (when ingested) have a beneficial effect in the prevention and treatment of specific pathologic conditions."<sup>7</sup> The most popular strains are represented by the following genera: *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* (Table 1), but other organisms including enterococci and yeasts have also been used as probiotics. Some of these strains were chosen based on selection criteria<sup>8</sup> that are believed to be important for efficacy such as origin of strain, in vitro adherence to intestinal cells,<sup>9-11</sup> and survival during passage through the gastrointestinal tract.<sup>12-16</sup> However,

---

\*Research Scientist, Strategic-Discovery Research and Development, Ross Products Division, Abbott Laboratories, Columbus, OH.

Address reprint requests to JoMay Chow, PhD, Strategic-Discovery Research and Development, Ross Products Division, Abbott Laboratories 105670/RP3-2, 625 Cleveland Ave, Columbus, OH 43215-1724.

© 2002 by the National Kidney Foundation, Inc.

1051-2276/02/1202-0001\$35.00/0

doi:10.1053/jren.2002.31759

**Table 1.** Microorganisms That Are Commonly Regarded as Human Probiotics

Species
<i>Bifidobacterium bifidum</i>
<i>Bifidobacterium breve</i>
<i>Bifidobacterium infantis</i>
<i>Bifidobacterium longum</i>
<i>Enterococcus faecalis</i>
<i>Enterococcus faecium</i>
<i>Lactobacillus acidophilus</i>
<i>Lactobacillus casei</i> Shirota
<i>Lactobacillus delbrueckii</i> subspecies <i>bulgaricus</i>
<i>Lactobacillus</i> GG
<i>Lactobacillus johnsonii</i>
<i>Lactobacillus reuteri</i>
<i>Lactobacillus rhamnosus</i>
<i>Lactobacillus plantarum</i>
<i>Lactobacillus salivarius</i>
<i>Saccharomyces boulardii</i> (yeast)
<i>Streptococcus thermophilus</i>

whether these properties are absolutely required for clinical efficacy has not yet been clearly established in the literature.

Enterococci such as *Enterococcus faecalis* and *Enterococcus faecium* are common inhabitants of the human gastrointestinal tract. Both species have been used as probiotics, but their safety has been questioned<sup>17</sup> because they have become an increasingly important cause of nosocomial infections.<sup>18</sup> The use of enterococci as probiotics is discussed in greater detail later in this review.

*Saccharomyces boulardii* is a nonpathogenic yeast that is sometimes used to treat *Clostridium difficile* diarrhea.<sup>19</sup> This organism, which was originally isolated from lychee fruit in southeast Asia, was used to treat diarrhea as early as the 1950s. Like other probiotic organisms, *S. boulardii* does not colonize the colon permanently; therefore, repeated dosings are needed to maintain detectable levels. Based on in vitro, animal, and human clinical studies, *S. boulardii* is thought to eradicate invasive pathogens by using multiple mechanisms including microbial interactions, antisecretory effects, inhibition of toxin binding to receptors, immunologic effects, and trophic effects on the intestinal mucosa.<sup>20</sup>

## History

The group of microorganisms most frequently regarded as probiotics, the lactic acid bacteria, has a long history of consumption by humans. These bacteria, which originally served to prevent spoilage of food by undesirable organisms, were con-

sumed in the form of fermented milk as early as 4000 BC. The consumption of fermented milk was first documented in the Old Testament, and ancient carvings indicated that humans purposely inoculated milk with cultures to produce sour milk as long ago as 2250 BC.<sup>21</sup>

During the modern era, consumption of fermented milk came into fashion during the early 1900s because of the efforts of Russian scientist Elie Metchnikoff. Metchnikoff first developed the notion that fermented milk products might have medicinal value. His hypothesis was based on the observation that Bulgarian peasants, who had extraordinary longevity, also happened to consume sour milk.

The consumption of fermented milk products fell out of fashion shortly thereafter, but growing concerns over antibiotic resistance and food safety have brought probiotics back into the spotlight of both animal and human health. Scientists from the US Department of Agriculture, in collaboration with Milk Specialties Bioscience (Dundee, IL), developed PREEMPT, a novel probiotic product for use in chickens. PREEMPT consists of 29 different microorganisms isolated from the intestines of adult birds and was the first commercial defined competitive exclusion culture against *Salmonella* colonization in poultry.<sup>22</sup> This product, which is sprayed on newly hatched chicks, was approved by the US Food and Drug Administration and introduced in 1998.

## Safety

Overall, traditional dairy strains of probiotic bacteria, particularly those belonging to the *Lactobacillus* and *Bifidobacterium* genera, are considered to be of low pathogenic potential when given to healthy humans.<sup>23,24</sup> Even after many years of use, probiotics have been linked to only 1 clinical infection.<sup>25</sup> In this case, a purulent viscous fluid specimen was aspirated from a hepatic abscess in a 74-year-old woman with a history of hypertension, non-insulin-dependent diabetes mellitus, mild abdominal discomfort, and mild fever. The aspirate contained virtually a pure culture of gram-positive coccobacilli. Results from enzymatic testing and molecular analysis (polymerase chain reaction assay and pulsed-field gel electrophoresis) of the culture aspirate were indistinguishable from those of *Lactobacillus* strain GG. An interview with the patient revealed that she had been ingesting approximately 0.5 L *Lac-*

*tobacillus* GG dairy drinks daily for 4 months before the onset of symptoms in an attempt to relieve abdominal discomfort.

In fact, aside from the involvement of some lactobacilli species in dental caries, microorganisms belonging to the *Lactobacillus* and *Bifidobacterium* genera, whether considered probiotics or not, have been largely regarded as nonpathogenic.<sup>17,26,27</sup> Members of both genera inhabit the human large intestine at concentrations exceeding  $10^9$  colony-forming units per gram dry feces.<sup>28</sup> However, these organisms occur infrequently in human infections, particularly when compared with members of the genus *Bacteroides*, which also inhabit the human digestive tract. For instance, Moore et al<sup>29</sup> isolated anaerobes from 81 consecutive clinical specimens that were submitted to their laboratory for culture. From these specimens, they cultured a total of 144 isolates, of which 33.3% were identified as members of the *Bacteroides* genus. In contrast, only 2.1% of the isolates were identified as members of the *Bifidobacterium* genus. Lactobacilli were not listed among the isolates, but some of the unidentified gram-positive nonsporing rods, which made up 2.1% of the total isolates, may have belonged to this genus. In a subsequent study, Saxelin et al<sup>30</sup> collected blood culture isolates over a 4-year period in Finland from cases of bacteremia. Of the 3,317 isolates that were detected, only 8 were identified as lactobacilli.

Although probiotic organisms have a long track record of safe consumption, a number of circumstances warrant caution when choosing a particular strain. First, the species of probiotic should be considered. With the exception of some lactobacilli, organisms belonging to the *Lactobacillus* or *Bifidobacterium* genera are very rarely pathogenic,<sup>31</sup> despite their ubiquitous presence in various body sites. Nevertheless, an extensive search of the literature suggests that certain species, such as *Lactobacillus rhamnosus* or *Lactobacillus casei* subspecies *rhamnosus*,<sup>32-37</sup> *Lactobacillus plantarum*,<sup>33,36-38</sup> and *Bifidobacterium dentium*<sup>39-41</sup> (formerly known as *Actinomyces eriksonni* or *Bifidobacterium eriksonni*), may have greater pathogenic potential than others.<sup>42</sup>

Organisms other than lactobacilli and bifidobacteria have also been used as probiotics, and these other organisms should be examined closely for potential pathogenicity because closely related strains may be known patho-

gens. As an example, enterococci have been implicated as the primary pathogen in a variety of infections including enterococcal meningitis, endocarditis, bacteremia, and urinary tract infections.<sup>17</sup> Hence, the use of enterococci, namely *E faecium* and *E faecalis*, as probiotics have fallen into disfavor because they have been found to be the third leading cause of nosocomial infections in the United States<sup>43</sup> and because they have acquired resistance to a large number of antimicrobial agents including vancomycin.<sup>18</sup> Perhaps the most worrisome development regarding this genus was the acquisition of vancomycin resistance and the possibility that the resistance genes could be transferred to other gram-positive pathogens such as *Staphylococcus aureus*.<sup>18</sup> Fortunately, the probiotic *E faecium* strain SF68 is sensitive to vancomycin, ampicillin, amoxicillin, chloramphenicol, and vibramycin; however, it is resistant to a large number of antimicrobials including erythromycin, gentamycin, neomycin, streptomycin, clindamycin, cloxacillin, cephaloridine, colicin, nitrofurantoin, nalidixic acid, and trimethoprim-sulfamethoxazole.<sup>44</sup>

Qualitative data collected from case studies suggest that lactic acid bacteria can act as opportunistic pathogens by producing infections almost exclusively in debilitated patients.<sup>45</sup> Thus, the relative risk to the patient should be assessed before the administration of probiotics. Patients who are immunocompromised because of extreme age (infant or elderly), use of therapeutics (eg, immunosuppressive agents), or presence of underlying disease may be at greater risk for infection by lactic acid bacteria.<sup>45</sup>

Additionally, patients who undergo dental procedures, have periodontal disease, or have underlying structural heart disease seem to be at increased risk for endocarditis.<sup>45</sup> Nonetheless, the risk of potential infection because of probiotic therapy should be weighed relative to the risk of side effects because of the administration of traditional medications, many of which are known to produce adverse effects.

The probiotic, *Lactobacillus acidophilus* strain NCFM, has been fed to a number of hemodialysis patients with end-stage kidney disease without adverse effects.<sup>46,47</sup> However, other members of the *Lactobacillus* genus including unspecified strains of *L acidophilus*<sup>48</sup> and *L rhamnosus*<sup>33,49,50</sup>

have been isolated from the peritoneal fluid of patients with peritonitis who were undergoing continuous ambulatory peritoneal dialysis. Each of the isolates was detected only after the patients had been treated with multiple antibiotics including vancomycin, and all of the isolates displayed resistance to this particular antibiotic. No attempts were made to identify the source of the lactobacilli, but the investigators<sup>33,48,50</sup> assumed that the organisms originated in another body site such as the gastrointestinal tract.

### Mechanisms of Action

The mechanisms by which probiotics exert biological effects are still poorly understood, but the nonspecific terms colonization resistance or competitive exclusion are often used to explain their mode of action. Colonization resistance or competitive exclusion describes a phenomenon whereby "the indigenous anaerobic flora limits the concentration of potentially pathogenic (mostly aerobic) flora in the digestive tract."<sup>51</sup> The concept of competitive exclusion was first developed during the early 1970s when it was discovered that the administration of mixed adult intestinal microorganisms conferred adult-type resistance against salmonella infection to newly hatched chicks.<sup>52</sup> Even more striking evidence of the protective effect of the normal intestinal microbiota comes from studies of *Clostridium difficile* pseudomembranous enterocolitis in both animal models<sup>53</sup> and in patients who experience multiple recurrences of diarrhea or colitis after discontinuation of successful antibiotic therapy.<sup>54-58</sup>

Some of the specific mechanisms by which the intestinal microbiota exclude undesirable organisms are thought to include the following:<sup>59,60</sup> (1) production of inhibitory substances, (2) blocking of adhesion sites, (3) competition for nutrients, (4) degradation of toxin receptor, and (6) stimulation of immunity. Although probiotic bacteria are thought to mediate their effects by using some of the same mechanisms as the native intestinal flora, probiotics may also work through other modes of action such as supplying enzymes or influencing enzyme activity in the gastrointestinal tract.<sup>59</sup> In fact, some studies have even suggested that probiotics, killed cells, or certain cell fractions exert antimutagenic<sup>61</sup> or adjuvant effects,<sup>62</sup> influence cytokine expression,<sup>63</sup> or influence the development of allergies.<sup>64</sup>

### Potential Applications for Improving Human Health

Given the wide variety of mechanisms by which probiotics are thought to work, scientists have proposed a variety of clinical applications for these organisms (Table 2). Much of the past research examined the application of probiotics to rotavirus diarrhea or lactose intolerance, but a number of intriguing results have also been published regarding probiotic use in antibiotic-associated diarrhea,<sup>65</sup> *Candida* vaginitis,<sup>66</sup> *Clostridium difficile*,<sup>67-69</sup> cryptosporidiosis,<sup>70</sup> *Helicobacter pylori* gastroenteritis,<sup>71</sup> hepatic encephalopathy,<sup>72</sup> inflammatory bowel disease,<sup>73</sup> necrotizing enterocolitis,<sup>74,75</sup> small bowel bacterial overgrowth in uremia,<sup>46,47,76</sup> suppression of chemically induced large bowel tumors,<sup>77</sup> and urinary tract infections.<sup>78,79</sup>

A unique application for probiotics in renal patients is the reduction of toxic metabolites, which are generated as a result of small bowel bacterial overgrowth during uremia.<sup>76</sup> These metabolites are thought to be responsible for some of the general symptoms of chronic renal failure, such as neurologic abnormalities, and they may also interfere with the absorption of nutrients from the gut.<sup>80</sup> In a pilot clinical study,<sup>47</sup> 19 patients with chronic renal failure ingested capsules containing 1 of 2 human strains of *L. acidophilus*, strain NCFM or strain BG2F04. Each capsule contained at least 10<sup>9</sup> colony-forming units, and 1 capsule was taken twice daily for an average of 76 ± 26 days. Results showed that oral ingestion of *L. acidophilus* reduced the serum levels

**Table 2.** Potential Applications for Probiotics and Sample References

Clinical Application	Reference
Antibiotic-associated diarrhea	65
<i>Candida</i> vaginitis	66
<i>Clostridium difficile</i>	67-69
Cryptosporidiosis	70
<i>Helicobacter pylori</i> gastroenteritis	71
Hepatic encephalopathy	72
Inflammatory bowel disease	73
Lactose intolerance	120
Necrotizing enterocolitis	74,75
Rotavirus diarrhea	121-123
Small bowel bacterial overgrowth in uremia	46,47,76
Suppression of chemically induced large bowel tumors	78
Urinary tract infections	79,80

of the marker compound, dimethylamine, from  $257 \pm 45 \mu\text{g/dL}$  to  $150 \pm 49 \mu\text{g/dL}$  ( $P = .001$ ), and blood nitrosodimethylamine levels decreased from  $236 \pm 69 \text{ ng/kg}$  to  $118 \pm 38 \text{ ng/kg}$  ( $P = .0053$ ). These results were subsequently reconfirmed in a placebo-controlled, double-blind, parallel study in patients undergoing hemodialysis.<sup>46</sup>

### Commercial Products

Many culture-containing dairy products such as yogurts and culture-added milks contain live microorganisms, but these products require refrigeration and have relatively short shelf lives that are measured in terms of weeks instead of months. On the other hand, freeze-dried microorganisms can remain viable indefinitely under ideal storage conditions. Therefore, because it has been assumed that viability is required for biologic activity, probiotic product forms have been largely limited to capsules, tablets, and powders. Even so, some commercial products, including those in tablet and capsule forms, display a marked discrepancy between the claimed and actual count of viable bacteria and/or a discrepancy between the species shown on the label and the actual species present in the product.<sup>81</sup>

A number of probiotic products are available in the United States. As an example, Lactinex (Becton-Dickinson; Franklin Lakes, NJ), a powdered or tableted product consisting of a mixture of *L acidophilus* and *Lactobacillus bulgaricus*, has been on the market since the early 1960s. However, clinical studies suggest that this preparation was ineffective for preventing or altering the course of enterotoxigenic *Escherichia coli* diarrhea in adults<sup>82,83</sup> and for reducing the incidence or duration of traveler's diarrhea.<sup>84</sup> In addition, a number of new probiotic-containing products such as Culturelle (*L GG* capsules; CAG Functional Foods, Omaha, NE) and Probiotica (*Lactobacillus reuteri* tablets; McNeil Consumer Healthcare, Ft Washington, PA) have been launched during recent years. Some of these organisms have undergone extensive clinical testing.

## Prebiotics

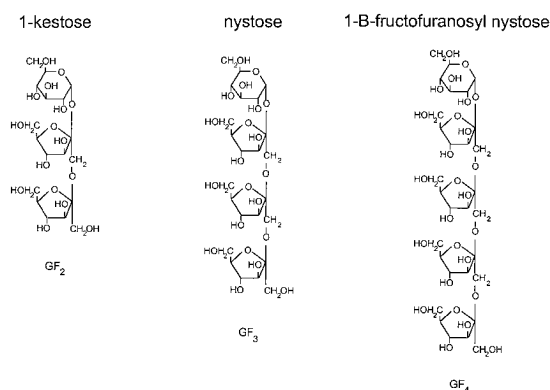
### Definition

The term *prebiotic*, first coined by Gibson and Roberfroid,<sup>5</sup> refers to "a nondigestible food in-

gredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health." At the present time, a large number of ingredients are known to escape hydrolysis in the small intestine, but only 4 ingredients also meet the criteria set forth for prebiotics in stimulating the growth of certain bacteria: transgalactosylated disaccharides, xylooligosaccharides, soybean oligosaccharides and fructooligosaccharides (FOSs). This review focuses solely on FOS because it was the first prebiotic oligosaccharide made available in the United States and because much more is known about it than other prebiotics.

### Structure of FOSs

FOSs are short- and medium-length chains of  $\beta$ -D-fructans in which fructosyl units are bound by  $\beta$  2-1 glycosidic linkages (Fig 1). Some molecules also contain glucose as the first moiety. These compounds occur naturally in many foods<sup>85</sup> including wheat, onions, bananas, honey, garlic, and leeks, but more purified forms may be purchased commercially. Long-chain fructan polymers, referred to as inulin (Raftiline [DRAFTI Active Food Ingredients, Tienen, Belgium] or Frutafit [Imperial-Suiker Unie, Sugar Land, TX]), are isolated from chicory root. These fructans can be partially hydrolyzed by enzymes to make a type of FOS known as oligofructose (Raftilose [DRAFTI Active Food Ingredients]). FOSs can also be synthesized from sucrose by using enzymes from *Aspergillus niger* to make Neosugar (Actilight [Beghin-Meiji Industries, Paris, France], Meiologo [Meiji Seika Kaisha, Tokyo, Japan], NutraFlora [GTC Nutrition, Westminster, CO]).



**Figure 1.** Chemical structure of Neosugar FOSs.

## Safety of FOSs

The US Food and Drug Administration has not yet approved FOS as generally recognized as safe (GRAS), but existing evidence suggests that the government will eventually grant this ingredient GRAS status.<sup>86</sup> As mentioned previously, FOSs occur naturally in a wide variety of foods. In fact, Americans consume approximately 2.5 g of inulin and oligofructose daily (range of 1 to 4 g), mostly from wheat and onions.<sup>87</sup> In addition, several US companies have already self-affirmed either oligofructose or Neosugar FOS as GRAS by having an expert panel review documentation regarding the safety of this ingredient. On a worldwide basis, NutraFlora FOS has been incorporated into at least 500 food products. In Japan, FOSs have been approved by the Minister of Health and Welfare as foods for specified health use (FOSHU) and have been included in at least 13 products that function as table sugar.

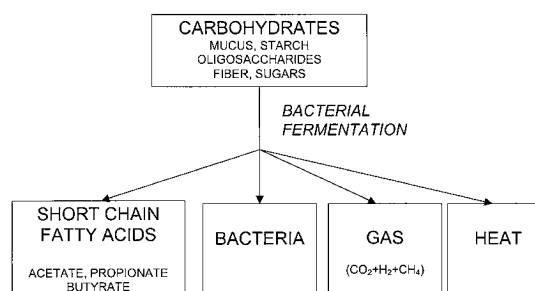
In terms of safety, the ingestion of FOSs cause few adverse effects, and the adverse effects are minor in nature.<sup>88</sup> Because FOSs possess many of the same physiologic properties as dietary fiber, the consumption of FOSs can lead to symptoms just like those encountered after a sudden increase in dietary fiber intake with the severity of symptoms related to intake level.<sup>88</sup> Common symptoms include flatulence, cramping, and diarrhea, but effects are only temporary.

The safety and tolerance of FOSs were actually measured in stable hemodialysis patients.<sup>89</sup> Seventy-nine normally nourished, stable, anuric, adequately dialyzed, adult outpatients with end-stage renal disease were randomized to 1 of 3 treatment groups in a prospective, controlled, single-blind, parallel study. The treatment groups included a standard medical nutritional and 2 renal nutritionals with one of the renal nutritionals containing added  $\beta$ -carotene and FOSs. During the 3-week long study, gastrointestinal symptoms and bowel habits were recorded during a 1-week baseline period and during 2 weeks of treatment. Subjects who were randomized to the FOS-containing treatment ingested an average of  $15.6 \pm 0.9$  to  $18.5 \pm 1.2$  g FOSs daily, and those in the other 2 groups did not ingest any FOSs. Results from the study showed that the number of instances in which gastrointestinal symptoms required treatment was not different between the renal nutritional without FOSs and the renal

nutritional with FOSs. Similarly, there were no differences between the 3 treatment groups regarding the number of patients who experienced symptoms that required treatment, the number of patients who withdrew because of gastrointestinal symptoms, the number of patients who experienced symptoms for at least 3 days, and the number of patients who had diarrhea that required treatment. On the other hand, significantly fewer of the patients who consumed the FOS-containing product experienced constipation that required treatment than those who received the renal product without FOS. Thus, the study showed indirectly that ingestion of as much as 18.5 g of FOSs daily was well tolerated by adult hemodialysis patients.

## Physiologic Effects of FOSs

Fructooligosaccharides resist degradation by human alimentary enzymes<sup>90</sup> and pass intact through the stomach and small intestine. Once these compounds reach the colon, anaerobic bacteria ferment them to obtain energy and carbon for their own growth (Fig 2). During the process, bacteria also generate short-chain fatty acids (SCFAs) gas, and heat. As a result of the fermentation, there is an increase in the concentration of bifidobacteria in the large intestine,<sup>88,91</sup> an increase in calcium absorption,<sup>92</sup> an increase in fecal weight,<sup>93</sup> a shortening of gastrointestinal transit time,<sup>94</sup> and a possible hypolipidemic effect.<sup>95</sup> Other effects observed in animal models include (1) an increase in cecal weight<sup>96</sup> because of the increased availability of energy in the form of SCFAs for the gut wall and (2) an increase in fecal nitrogen excretion<sup>97</sup> because of the additional capture of ammonia nitrogen as microbial mass and increased excretion of colonic bacteria in the feces. The increased numbers of bifidobacteria in



**Figure 2.** Fermentation of carbohydrates by colonic bacteria. Fermentation results in the production of SCFAs, bacteria cell growth, gas, and heat.

the colon have been assumed to positively benefit human health through a number of mechanisms<sup>6</sup> including (1) the production of strong acids<sup>98</sup> and other inhibitory substances<sup>99,100</sup> that inhibit the growth of potential pathogens, (2) the lowering blood ammonia levels by protonating ammonia in the colon,<sup>101</sup> and (3) the production of vitamins<sup>102</sup> and digestive enzymes.<sup>103</sup>

### Potential Application for Renal Patients

In populations that are frequently affected by diabetes, such as the end-stage renal disease population, FOSs could potentially serve as a sugar substitute. FOSs have 40% of the sweetness of sucrose, and they have no unpleasant aftertaste. Because FOSs are neither digested nor absorbed in the small intestine, their ingestion does not elevate blood glucose levels.<sup>104</sup> In addition, FOSs contain only 40% of the caloric content of hexoses (glucose or fructose) on a gram-for-gram basis (1.5 kcal/g for fructans *v* 3.9 kcal/g for hexoses<sup>105</sup>).

Chronic constipation is a common problem among the dialysis population,<sup>106–109</sup> with an estimated 40%<sup>108</sup> to 71% of patients<sup>110</sup> affected by this gastrointestinal disorder. The magnitude of the problem is not surprising given that this patient population carries many of the risk factors associated with constipation such as uremia, electrolyte imbalances, and restricted water intake.<sup>111</sup> In addition, the advanced age of these patients, inactivity, and comorbid conditions such as diabetes mellitus and cardiac disease adversely affect bowel function.<sup>111</sup> The administration of multiple medications including iron supplements, calcium- or aluminum-containing phosphate binders, and opioids and the dietary restrictions imposed on dialysis patients likely contribute to the problem.

FOSs could potentially serve to alleviate constipation in the dialysis population.<sup>112–116</sup> The mechanism by which FOSs is thought to alleviate constipation is likely to be similar to that of lactulose and sugar alcohols.<sup>116</sup> If the rate at which these undigested compounds enter the colon exceeds the colonic capacity to ferment them, excess molecules create an osmotic effect and draw water into the colon. In turn, the water drawn into the colon acts to soften stools. Moreover, because 30% of wet fecal weight is made up of bacteria,<sup>117</sup> these compounds may also increase

stool weight by supplying energy and carbon for bacterial growth. However, unlike lactulose and sugar alcohols, the severity of side effects associated with ingestion of FOSs, such as abdominal cramping, should be significantly less because of its lower osmolality on a weight-to-weight basis.<sup>116</sup>

Despite the presence of bacterial overgrowth in the small bowel of patients with chronic renal failure, FOSs would still likely reach the colon fully intact. Although the bacterial species present in small bowel bacterial overgrowth aspirates are similar if not identical to those found in the colon,<sup>118</sup> the mean concentration of bacteria in small bowel bacterial overgrowth is only  $10^8$  organisms per milliliter (*v*  $10^2$  colony-forming units per milliliter in healthy humans<sup>119</sup>), whereas the concentration of bacteria in the colon often exceeds  $10^{11}$  colony-forming units/mL. Thus, the concentration of bacteria in the colon would be at least 1,000 times greater than that in the small bowel. Consequently, fermentation should occur at a much slower rate in the small bowel than in the colon, even in small bowel bacterial overgrowth.

### Products Containing FOSs

In Japan, where FOSs have been officially recognized as a food for Specified Health use by the government, FOSs have been incorporated into numerous products including candies, beverages, and even infant formula. In contrast, the use of FOSs in the United States has been primarily limited to dietary supplements in which it frequently appears in combination with probiotics because of the belief that a mixture of these 2 ingredients would benefit the host “by improving the survival and the implantation of live microbial dietary supplements in the gastrointestinal tract, by selectively stimulating the growth and/or by activating the metabolism of one or a limited number of health-promoting bacteria, and thus improving host welfare.”<sup>5</sup> Only during the last several years have FOSs started to appear in food products. For example, inulin, a long-chain fructan polymer, was recently added to a commercial yogurt (Stonyfield Farm, Manchester, NH), and NutraFlora FOS has been added to a number of liquid nutritional formulas including 1 intended for use in people with end-stage renal disease.

## Conclusions

Probiotics and FOSs could potentially provide several benefits to renal patients. As an example, probiotics may reduce the levels of certain toxic compounds generated by the small bowel flora that are thought to contribute to some of the neurologic symptoms of uremia. On the other hand, FOSs, which also happen to have a very low glycemic index and lower energy content than glucose or fructose, could potentially function in the capacity of a dietary fiber supplement to help maintain regularity in this patient population or as a reduced calorie sweetener for diabetic patients.

## References

1. Institute of Medicine, National Academy of Sciences: Opportunities in the nutrition and food sciences, in Thomas PR, Earl R (eds): Washington, DC, National Academy Press, 1994, p 109
2. Gibson GR: Dietary modulation of the human gut microbiota using prebiotics. *Br J Nutr* 80:209-212, 1998 (suppl)
3. Rolfé RD: The role of probiotic cultures in the control of gastrointestinal health. *J Nutr* 130:396-402, 2000
4. Macfariene GT, Cummings JH: Probiotics and prebiotics: Can regulating the activities of intestinal bacteria benefit health? *Br Med J* 318:999-1003, 1999
5. Gibson G, Roberfroid MB: Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J Nutr* 125:1401-1412, 1995
6. Elmer GW, Surawicz CM, McFarland LV: Biotherapeutic agents: A neglected modality for the treatment and prevention of selected intestinal and vaginal infections. *JAMA* 275:870-876, 1996
7. Havenaar R, Huis in't Veld JHJ: Probiotics: A general view, in Wood JBJ (ed): *Lactic Acid Bacteria in Health and Disease* (vol 1). London, UK, Elsevier Applied Science, 1992, pp 151-170
8. Havenaar R, Ten Brink B, Huis in't Veld JHJ: Selection of strains for probiotic use, in Fuller R (ed): *Probiotics: The Scientific Basis*. London, England, Chapman & Hall, 1992, pp 151-170
9. Elo S, Saxelin M, Salminen S: Attachment of *Lactobacillus casei* strain GG to human colon carcinoma cell line Caco-2: Comparison with other dairy strains. *Lett Appl Microbiol* 13: 154-156, 1991
10. Conconner M, Klaenhammer TR, Kerneis S, et al: Protein-mediated adhesion of *Lactobacillus acidophilus* BG2FO4 on human enterocyte and mucus-secreting cell lines in culture. *Appl Environ Microbiol* 58:2034-2039, 1992
11. Bernet M, Brassart D, Neeser J, et al: Adhesion of human bifidobacterial strains to cultured human intestinal epithelial cells and inhibition of enteropathogen-cell interactions. *Appl Environ Microbiol* 59:4121-4128, 1993
12. Conway PL, Gorbach SL, Goldin BR: Survival of lactic acid bacteria in the human stomach and adhesion to intestinal cells. *J Dairy Sci* 70:1-12, 1987
13. Bouhnik Y, Pochart P, Marteau P, et al: Fecal recovery in humans of viable *Bifidobacterium* sp ingested in fermented milk. *Gastroenterol* 102:875-878, 1992
14. Goldin BR, Gorbach SL, Saxelin M, et al: Survival of *Lactobacillus* species (strain GG) in human gastrointestinal tract. *Dig Dis Sci* 37:121-128, 1992
15. Pochart P, Marteau P, Bouhnik Y, et al: Survival of bifidobacteria ingested via fermented milk during their passage through the human small intestine: An in vivo study using intestinal perfusion. *Am J Clin Nutr* 55:78-80, 1992
16. Kullen MJ, Amann MM, O'Shaughnessy MJ, et al: Differentiation of ingested and endogenous bifidobacteria by DNA fingerprinting demonstrates the survival of an unmodified strain in the gastrointestinal tract of humans. *J Nutr* 127:89-94, 1997
17. Aguirre M, Collins MD: Lactic acid bacteria and human clinical infection. *J Appl Bacteriol* 75:95-107, 1993
18. Centers for Disease Control and Prevention: Recommendation for preventing the spread of vancomycin resistance: Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 44(No. RR-12):1, 1995
19. McFarland LV: Biotherapeutic agents for *Clostridium difficile*-associated disease, in Elmer GW, McFarland LV, Surawicz CM (eds): *Biotherapeutic Agents and Infectious Diseases*. Totowa, NJ, Humana Press, 1999, pp 159-193
20. Buts J: Mechanisms of action of biotherapeutic agents, in Elmer GW et al (ed): *Biotherapeutic Agents and Infectious Diseases*, Totowa, NJ, Humana Press, 1999, pp 27-46
21. Kroger M, Kurmann JA, Rasic JL: Fermented milks—Past, present, and future. *Food Technol* 43:92-99, 1989
22. Hume ME, Corrier DE, Nisbet DJ, et al: Early *Salmonella* challenge time and reduction in chick cecal colonization following treatment with a characterized competitive exclusion culture. *J Food Protect* 61:673-676, 1998
23. Donohue DC, Salminen S: Safety of probiotic bacteria. *Asia Pacific J Clin Nutr* 5:25-28, 1996
24. Salminen S, von Wright A, Morelli L, et al: Demonstration of safety of probiotics—A review. *Int J Food Microbiol* 44:93-106, 1998
25. Rautio M, Jousimies-Somer H, Kauma H, et al: Liver abscess due to *Lactobacillus rhamnosus* strain indistinguishable from *L. rhamnosus* strain GG. *Clin Infect Dis* 28:1159-1160, 1999
26. Brook I, Frazier EH: Significant recovery of nonsporulating anaerobic rods from clinical specimens. *Clin Infect Dis* 16:476-480, 1993
27. Lidbeck A, Nord CE: Lactobacilli and the normal human anaerobic microflora. *Clin Infect Dis* 16:181-187, 1993 (suppl)
28. Moore WEC, Holdeman LV: Human fecal flora: The normal flora of 20 Japanese-Hawaiians. *Appl Microbiol* 27:961-979, 1974
29. Moore WEC, Cato EP, Holdeman LV: Anaerobic bacteria of the gastrointestinal flora and their occurrence in clinical infections. *J Infect Dis* 119:641-649, 1969
30. Saxelin M, Rautelin H, Salminen S, et al: Safety of commercial products with viable *Lactobacillus* strains. *Infect Dis Clin Pract* 5:331-335, 1996
31. Kandler O, Weiss N: Genus *Lactobacillus*, in Sneath PHA, et al (eds): *Bergey's Manual of Systematic Bacteriology* (vol 2). Baltimore, MD, Williams & Wilkins, 1986, pp 1209-1234
32. Davies AJ, James PA, Hawkey PM: *Lactobacillus* endocarditis. *J Infect* 12:169-174, 1986



33. Rao GG, Short A, Carmichael DJS: CAPD peritonitis caused by vancomycin-resistant lactobacilli. *Nephrol Dial Transplant* 5:235-236, 1990
34. Chomarat M, Espinouse D: *Lactobacillus rhamnosus* septicemia in patients with prolonged aplasia receiving ceftazidime-vancomycin. *Eur J Clin Microbiol Infect Dis* 10:44, 1991
35. Griffiths JK, Daly JS, Dodge RA: Two cases of endocarditis due to *Lactobacillus* species: Antimicrobial susceptibility, review, and discussion of therapy. *Clin Infect Dis* 15:250-255, 1992
36. Namnyak SS, Blair ALT, Hughes DF, et al: Fatal lung abscess due to *Lactobacillus ss rhamnosus*. *Thorax* 47:666-667, 1992
37. Bayer AS, Chow AW, Ishida K, et al: Therapy of experimental infective endocarditis due to antibiotic-tolerant *Lactobacillus plantarum* — Bactericidal synergy of penicillin plus gentamicin. *Chemother* 27:444-451, 1981
38. Sussman JI, Baron EJ, Goldberg SM, et al: Clinical manifestations and therapy of *Lactobacillus* endocarditis: report of a case and review of the literature. *Rev Infect Dis* 8:771-776, 1986
39. Sodeman TM, Schafer K, Bentz R, et al: Infection due to *Bifidobacterium eriksonii*. *Am J Clin Pathol* 59:143, 1973 (abstr)
40. Thomas AV, Sodeman TH, Bentz RR: *Bifidobacterium* (*Actinomyces*) *eriksonii* infection. *Am Rev Respir Dis* 110:663-668, 1974
41. Green SL: Case report: Fatal anaerobic pulmonary infection due to *Bifidobacterium eriksonii*. *Postgrad Med* 63:187-189, 1978
42. Scardovi V: Genus *Bifidobacterium*, in Sneath PHA, et al (eds): *Bergey's Manual of Systematic Bacteriology* (vol 2). Baltimore, MD, Williams & Wilkins, 1986, pp 1418-1434
43. Murray BE: The life and times of the Enterococcus. *Clin Microbiol Rev* 9:40-65, 1990
44. Martin SW, Heatherington AC, Elmer GW: Pharmacokinetics of biotherapeutic agents, in Elmer GW, et al (eds): *Biotherapeutic Agents and Infectious Diseases*, Totowa, NJ, Humana Press, 1999, pp 47-84
45. Gasser F: Safety of lactic acid bacteria and their occurrence in human clinical infections. *Bull Inst Pasteur* 92:45-67, 1994
46. Dunn SR, Simenhoff ML, Ahmed KE, et al: Effect of oral administration of freeze-dried *Lactobacillus acidophilus* on small bowel bacterial overgrowth in patients with end stage kidney disease: Reducing uremic toxins and improving nutrition. *Int Dairy J* 8:545-553, 1998
47. Dunn SR, Simenhoff ML, Fitzpatrick ME, et al: Reduction of an endogenous uremic toxin (dimethylamine) and a carcinogen (nitrosodimethylamine) and improvement of nutritional status in 24 dialysis patients treated with oral *Lactobacillus acidophilus*. *J Am Soc Nephrol* 9:145, 1998 (abstr)
48. Schleifer CR, Benz RL, McAlack R, et al: *Lactobacillus acidophilus* peritonitis in CAPD. *Peritoneal Dial Int* 9:222-223, 1989
49. Sanyal D, Bhandari S: CAPD peritonitis caused by *Lactobacillus rhamnosus*. *J Hosp Infect* 22:325-327, 1992
50. Klein G, Zill E, Schindler R, et al: Peritonitis associated with vancomycin-resistant *Lactobacillus rhamnosus* in a continuous ambulatory peritoneal dialysis patient: Organism identification, antibiotic therapy, and case report. *J Clin Microbiol* 36:1781-1783, 1998
51. Vollaard EJ, Clasener HAL: Colonization resistance. *Antimicrob Agents Chemother* 38:409-414, 1994
52. Nurmi E, Nuotio L, Schneitz C: The competitive exclusion concept: development and future. *Int J Food Microbiol* 15:237-240, 1992
53. Wilson KH, Silva J, Fekety FR: Suppression of *Clostridium difficile* by normal hamster cecal flora and prevention of antibiotic-associated colitis. *Infect Immun* 34:626-628, 1981
54. Bowden TA, Mansberger AR, Lykins LE: Pseudomembranous enterocolitis: Mechanism of restoring floral homeostasis. *Am Surg* 47:178-183, 1981
55. Schwan A, Sjolín S, Trottestam U, et al: Relapsing *Clostridium difficile* enterocolitis cured by rectal infusion of normal faeces. *Scand J Infect Dis* 16:211-215, 1984
56. Tvede M, Rask-Madsen J: Bacteriotherapy for chronic relapsing *Clostridium difficile* diarrhoea in six patients. *Lancet* 1:1156-1160, 1989
57. Paterson DL, Iredell J, Witby M: Putting back the bugs: Bacterial treatment relieves chronic diarrhea. *Med J Austr* 160:232-233, 1994
58. Borody TJ: "Flora power" — Fecal bacteria cure chronic *C. difficile* diarrhea. *Aust J Gastroenterol* 95:3028-3029, 2000
59. Fuller R: Probiotics in human medicine. *Gut* 32:439-442, 1991
60. Rolfe RD: The role of probiotic cultures in the control of gastrointestinal health. *J Nutr* 130:396-402, 2000
61. Reddy BS: Prevention of colon cancer by pre- and probiotics: Evidence from laboratory studies. *Br J Nutr* 80:219-223, 1998 (suppl)
62. Blocksma N, De Heer E, Van Dijk H, et al: Adjuvanticity of lactobacilli I. Differential effects of viable and killed bacteria. *Clin Exp Immunol* 37:367-375, 1979
63. Solis Pereyra B, Lemonnier D: Induction of human cytokines by bacteria used in dairy foods. *Nutr Res* 13:1127-1140, 1993
64. Majamaa H, Isolauri E: Probiotics: A novel approach in the management of food allergy. *J Allergy Clin Immunol* 99:179-185, 1997
65. Vanderhoof JA, Whitney DB, Antonson DL, et al: *Lactobacillus* GG in the prevention of antibiotic-associated diarrhea in children. *J Pediatr* 135:564-568, 1999
66. Hilton E, Isenberg HD, Sperlstein P, et al: Ingestion of yogurt containing *Lactobacillus acidophilus* as prophylaxis for candidal vaginitis. *Ann Intern Med* 116:353-357, 1992
67. McFarland LV, Surawica CM, Greenberg RN, et al: A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *JAMA* 271:1913-1918, 1994
68. Gorbach SL, Chang T-W, Goldin B: Successful treatment of relapsing *Clostridium difficile* colitis with *Lactobacillus* GG. *Lancet* 2:1519, 1987 (letter)
69. Bennett RG, Gorbach SL, Goldin BR, et al: Treatment of relapsing *Clostridium difficile* diarrhea with *Lactobacillus* GG. *Nutr Today* 31:35S-38S, 1996 (suppl)
70. Alak JIB, Wolf BW, Mdurvwa EG, et al: Supplementation with *Lactobacillus reuteri* or *Lactobacillus acidophilus* reduces intestinal shedding of *Cryptosporidium parvum* oocysts in immunodeficient C57BL/6 mice. *Cell Mol Biol* 45:855-863, 1999
71. Canducci F, Armuzzi A, Cremonini F, et al: A lyophilized and inactivated culture of *Lactobacillus acidophilus* increases *Helicobacter pylori* eradication rates. *Aliment Pharmacol Ther* 14:1625-1629, 2000
72. Loguercio C, Abbiati R, Rinaldi M, et al: Long-term

effects of *Enterococcus faecium* SF68 versus lactulose in the treatment of patients with cirrhosis and grade 1-2 hepatic encephalopathy. *J Hepatol* 23:39-46, 1995

73. Gionchetti P, Rizzello F, Venturi A, et al: Probiotics in infective diarrhoea and inflammatory bowel disease. *J Gastroenterol Hepatol* 15:489-493, 2000

74. Siu YK, Ng PC, Fung SCK, et al: Double blind, randomised, placebo controlled study of oral vancomycin in the prevention of necrotising enterocolitis in preterm, very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 79:105-109, 1998

75. Caplan MS, Jilling T: Neonatal necrotizing enterocolitis: Possible role of probiotic supplementation. *J Pediatr Gastroenterol Nutr* 30:18-22, 2000

76. Simenhoff ML, Dunn SR: Altered gut flora in uremia. *J Renal Nutr* 6:68-74, 1996

77. Goldin BR, Gorbach SL: The effect of oral administration of *Lactobacillus* and antibiotics on intestinal bacterial activity and chemical induction of large bowel tumors. *Dev Industr Microbiol* 25:139-150, 1984

78. Reid G, Chan RCY, Bruce AW, et al: Prevention of urinary tract infection in rats with an indigenous *Lactobacillus casei* strain. *Infect Immun* 49:320-324, 1985

79. Winberg J, Herthelius-Elman M, Mollby R, et al: Pathogenesis of urinary tract infection—Experimental studies of vaginal resistance to colonization. *Pediatr Nephrol* 7:509-514, 1993

80. Simenhoff ML: Role of the bowel in uremia. *Curr Nephrol* 9:107-148, 1986

81. Canganella F, Paganini S, Ovidi M: A microbiological investigation on probiotic pharmaceutical products used for human health. *Microbiol Res* 152:171-179, 1997

82. Clements ML, Levine MM, Black RE, et al: *Lactobacillus* prophylaxis for diarrhea due to enterotoxigenic *Escherichia coli*. 20:104-108, 1981

83. Clements ML, Levine MM, Ristaino PA: Exogenous lactobacilli fed to man—their fate and ability to prevent diarrheal disease. *Prog Fd Nutr Sci* 7:29-37, 1983

84. de Dios Pozo-Olano J, Warram JH, Gomez RG, et al: Effect of a lactobacilli preparation on traveler's diarrhea: a randomized, double blind clinical trial. *Gastroenterol* 74:829-830, 1978

85. Campbell JM, Bauer LL, Fahey Jr GC, et al: Selected fructooligosaccharide (1-kestose, nystose, 1<sup>F</sup>- $\beta$ -fructofuranosyl-nystose) composition of foods and feeds. *J Agric Food Chem* 45:3076-3082, 1997

86. Coussement PAA: Inulin and oligofructose: Safe intakes and legal status. *J Nutr* 129:1412-1417, 1999

87. Moshfegh AJ, Friday JE, Goldman JP, et al: Presence of inulin and oligofructose in the diets of Americans. *J Nutr* 129:1407-1411, 1999

88. Bouhnik Y, Vahedi K, Achour L, et al: Short-chain fructo-oligosaccharide administration dose-dependently increases fecal bifidobacteria in healthy humans. *J Nutr* 129:113-116, 1999

89. Cockram DB, Hensley MK, Rodriguez M, et al: Safety and tolerance of medical nutritional products as sole sources of nutrition in people on hemodialysis. *J Renal Nutr* 8:25-33, 1998

90. Molis C, Flourie B, Ouarne F, et al: Digestion, excretion, and energy value of fructooligosaccharides in healthy human adults. *Am J Clin Nutr* 64:324-328, 1996

91. Mitsuoka T, Hidaka H, Eida T: Effect of fructo-oligosaccharides on intestinal flora. *Die Nahrung* 31:427-436, 1987

92. Van den Heuvel EGHM, Muys T, van Kokkum W, et al: Oligofructose stimulates calcium absorption in adolescents. *Am J Clin Nutr* 69:544-548, 1999

93. Garleb KA, Snook JT, Marcon MJ, et al: Effect of fructooligosaccharide containing enteral formulas on subjective tolerance factors, serum chemistry profiles, and faecal bifidobacteria in healthy adult male subjects. *Microb Ecol Health Dis* 9:279-285, 1996

94. Roberfroid M: Dietary fiber, inulin, and oligofructose: A review comparing their physiological effects. *Crit Rev Food Sci Nutr* 33:103-148, 1993

95. Williams CM: Effects of inulin on lipid parameters in humans. *J Nutr* 129:1471-1473, 1999

96. Campbell J, Fahey Jr GC, Wolf BW: Selected indigestible oligosaccharides affect large bowel mass, cecal and fecal short-chain fatty acids, pH and microflora in rats. *J Nutr* 127:130-136, 1997

97. Younes H, Garleb K, Behr S, et al: Fermentable fibers or oligosaccharides reduce urinary nitrogen excretion by increasing urea disposal in the rat cecum. *J Nutr* 125:1010-1016, 1995

98. Ibrahim SA, Bezkorovainy A: Inhibition of *Escherichia coli* by bifidobacteria. *J Food Protect* 56:713-715, 1993

99. Meghrou J, Euloge P, Junelles AM, et al: Screening of *Bifidobacterium* strains for bacteriocin production. *Biotechnol Lett* 12:575-580, 1990

100. Gibson GR, Wang X: Regulatory effects of bifidobacteria on the growth of other colonic bacteria. *J Appl Bacteriol* 77:412-420, 1994

101. Rao AV, Koo MM: Effect of oral administration of bifidobacteria and Neosugar on plasma ammonia concentration in CF1 mice. *Int J Food Sci Nutr* 43:9-17, 1992

102. Krause LJ, Forsberg CW, O'Connor DL: Feeding human milk to rats increases *Bifidobacterium* in the cecum and colon which correlates with enhanced folate status. *J Nutr* 126:1505-1511, 1996

103. Jiang T, Mustapha A, Savalano DA: Improvement of lactose digestion in humans by ingestion of unfermented milk containing *Bifidobacterium longum*. *J Dairy Sci* 79:750-757, 1996

104. Hidaka H, Eida T, Takizawa T, et al: Effects of fructooligosaccharides on intestinal flora and human health. *Bifidobacteria Microflora* 3:37-50, 1986

105. Roberfroid MB: Caloric value of inulin and oligofructose. *J Nutr* 129:1436-1437, 1999

106. Stone WJ: Therapy of constipation in patients with chronic renal failure. *Dialy Transplan* 6:30-32, 1977

107. Chambers J: Bowel management in dialysis patients. *Am J Nursing* 83:1051-1052, 1983

108. Hammer J, Oesterreicher C, Hammer K: Chronic gastrointestinal symptoms in hemodialysis patients. *Wien Klin Wochenschr* 110:287-291, 1998

109. St. Peter WL, Clark JL, Levos OM: Drug therapy in haemodialysis patients: Special considerations in the elderly. *Drugs Aging* 12:441-459, 1998

110. Odaka K, Inamoto H, Sata K, et al T: Constipation and dietary fiber in dialysis patients. 2. Incidence and causative factors of constipation. *Japan Soc Dial Therapy* 22:995-998, 1989

111. American Gastroenterological Association: American Gastroenterological Association medical position statement: Guidelines on constipation. *Gastroenterol* 119:1761-1778, 2000

112. Chen H-L, Lu Y-H, Lin J-J et al: Effects of fructooligosaccharide on bowel function and indicators of nutritional status in constipated elderly men. *Nutr Res* 20:1725-1733, 2000

113. Hond ED, Geypens B, Ghooys Y: Effect of high performance chicory inulin on constipation. *Nutr Res* 20:731-736, 2000
114. Briet F, Achour L, Flourie B, et al: Symptomatic response to varying levels of fructo-oligosaccharides consumed occasionally or regularly. *Eur J Clin Nutr* 49:501-507, 1995
115. Hata Y, Nakajima K: Studies on relationship between intake of fructooligosaccharides and abdominal symptoms — Estimation of the maximum non-effective dose and 50% laxative effective dose. *Geriatr Med* 23:817-828, 1985
116. Clausen MR, Jorgensen J, Mortensen PB: Comparison of diarrhea induced by ingestion of fructooligosaccharide Idolax and disaccharide lactulose. *Dig Dis Sci* 43:2696-2707, 1998
117. Smith CJ, Bryant MP: Introduction to metabolic activities of intestinal bacteria. *Am J Clin Nutr* 32:149-157, 1979
118. Simenhoff ML, Saukkonen JJ, Burke JF, et al: Bacterial populations of the small intestine in uremia. *Nephron* 22:63-68, 1978
119. Williams RE, Hill MJ, Drasar BS: The influence of intestinal bacteria on the absorption and metabolism of foreign compounds. *J Clin Pathol* 24:125-129, 1971
120. Onwulata CI, Ramkishan Rao D, Vankineni P: Relative efficiency of yogurt, sweet acidophilus milk, hydrolyzed-lactose milk, and a commercial lactase tablet in alleviating lactose maldigestion. *Am J Clin Nutr* 49:1233-1237, 1989
121. Isolauri E, Huntunen M, Rautanen T, et al: A human *Lactobacillus* strain (*Lactobacillus casei* sp strain GG) promotes recovery from acute diarrhea in children. *Pediatr* 88:90-97, 1991
122. Isolauri E, Kaila M, Mykkanen H, et al: Oral bacteriotherapy for viral gastroenteritis. *Dig Dis Sci* 39:2595-2600, 1994
123. Shornikova A-V, Casas IA, Mykkanen H, et al: Bacteriotherapy with *Lactobacillus reuteri* in rotavirus gastroenteritis. *Pediatr Infect Dis J* 16:1103-1107, 1997