CHAPTER 8

Lactic Acid Bacteria and Plant Fibers
Treatment in Acute and Chronic Human Disease

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CONTENTS

8.1 WESTERN FOOD—THE THREAT TO HUMAN HEALTH

The modern Western diet is based on nutrients received from only a small number of plants; 80 percent of the nutrients come from 17 plants and 50 percent of the calories from 8 grains. Furthermore, the most Western food is extensively processed, which not only reduces the nutritional value of the food, but also increases the level of systemic inflammation in the body. Many nutrients and antioxidants do not sustain heating and drying; among them are the important amino acid glutamine and the master antioxidant glutathione. Furthermore, manipulation of food, especially heating, increases the content of unwanted proinflammatory ingredients. These include mutagens, oxidized fatty acids—trans-fatty acids—and dysfunctional and highly proinflammatory proteins, or Maillard products, which are most often advanced glycation and advanced lipoxidation end products; they are referred to as AGEs and ALEs (see Chapter 7). Among foods rich in AGEs and ALEs are dairy products especially powdered milk (frequently used in enteral nutrition and baby formulas, and in numerous foods such as ice cream), cheese, bakery products (bread crusts, crisp breads, pretzels, biscotti) and cereals (crisp rice), overheated (especially deep-fried and oven-fried) meat and poultry, as well as fish, drinks like coffee and cola, Chinese soy, balsamic products, and smoked foods in general; for further information, see Goldberg et al.[1,2] The consumption of such foods, often the main constituents in fast foods, has increased dramatically in recent decades, much in parallel with the endemic of chronic diseases. The anti-inflammatory effects of plant fibers and probiotic bacteria might not be strong enough to control chronically enhanced systemic inflammation, strongly associated with the global epidemic of chronic diseases.

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8.2 DERANGED AND DYSFUNCTIONAL IMMUNE SYSTEM

Numerous chemical substances, additives to foods and pharmaceutical drugs, seem to derange the immune system. In the past, priority was not given to investigation

of the eventual negative effects on the innate immune systems of consumed food additives and pharmaceutical drugs. It is clear, even if not fully investigated, that a large number of chemicals have a strong negative influence on the immune system and the body's resistance to disease when consumed. As an example, it has long been known that antibiotics suppress various immune functions, especially macrophage activities such as chemiluminescence response, chemotactic motility, bactericidal and cytostatic ability.[3,4] Recent experience suggest that H_2-blockers, commonly used in many diseases and in critically ill patients, exhibit strong procoagulatory and proinflammatory effects. Ranitidine, as an example, has been shown in animal studies to enhance the inflammatory response and increase the extent of tissue injuries, especially in the liver.[5–7]

Several other factors increase the degree of systemic inflammation in the body:

- *Impaired hormonal homeostasis* increases oxidative stress/release of free radicals, increases intracellular accumulation of "waste products," inhibits apoptosis, disturbs repair mechanisms, reduces gene polymorphism, increases premature shortening of telomeres, and reduces immune defense and resistance to disease, changes often observed in premature aging and in various chronic diseases.[8]
- *Low level in the body of vitamin D* and subsequent secondary hyperparathyroidism.[9,10]
- *Low levels in the body of antioxidants* such as folic acid and glutathione and increased levels of homocysteine.[11]
- *High levels in the body of estrogens*, especially 17β-estradiol, often induced by high consumption of hormone-rich dairy products.
- *High levels of angiotensin/rennin.*[12,13]
- *Larger intake of glutenoids.*[14,15]

The reason attempts to reduce inflammation with the use of probiotics have sometimes failed in the past might be that the proinflammatory pressure is simply too high due to underlying disease, but also due to consumption of too much of proinflammatory food and prescription drugs, all with inflammation-enhancing abilities. It is likely that in certain conditions additional measures are needed to achieve successful treatment with probiotics. Measures such as reduced supply of proinflammatory foods, restriction in use of pharmaceuticals, and increased intake of plant foods rich in anti-inflammatory vitamins and antioxidants, especially various polyphenols, might well be needed; see further below.

8.3 PLANT FIBERS REDUCE SYSTEMIC INFLAMMATION

Table 8.1 summarizes the content of fiber in some common plant-derived foods. It should be observed that various seeds, nuts, beans, and peas are especially rich in fiber, foods which no longer are eaten in the quantities they deserve. A common recommendation of minimum daily fiber intake is in the range of 30 to 35 g/day,[16,17] which roughly corresponds to about half a kilogram of fruits and vegetables, or, as often expressed, five to eight fresh fruits and vegetables per day. The recommendations for children above the age of 2 years are usually defined as age + 5 g/day.[18] No

Table 8.1 Content of Fiber in Common Plant-Derived Foods, g/100

Flax seeds	42	Cabbage	3.5
Sunflower seeds	21	Gooseberries	3.4
Passion fruit	16	Avocado	3.3
Soy flour	12	Fennel	3.3
Prunes	9	Savoy cabbage	3.2
Peanuts	8	Blueberries	3.1
Hazelnuts	6	Cauliflower	3.0
Blackberries	6	Bean sprouts	3.0
Green peas	6	Pears	2.8
Walnuts	5	Strawberries	2.4
Artichoke	5	Tomatoes	2.0
Black currents	5	Grapefruit	1.9
Onion	5	Orange	1.9
Beans	5	Apple	1.8
Brussels sprouts	4	Potato, cooked	1.4
Olives	4	Chili pepper	1.3/tsp
Kiwi	4	Turmeric	0.5/tsp
Raspberries	3.7		

precise recommendation exists yet about intake of fiber under different conditions of disease. The daily intake of dietary fiber is unsatisfactory in all Western countries, especially among people with a low level of education and low income. In the United States, for example, the estimated daily intake of fiber is approximately 14 to 15 g/day or about 50 percent of what is recommended, and far below the 60 to 80 g/day of substrate required to maintain a large bowel flora of 10^{14} microorganisms, which is known to be typical for a healthy and well-functioning human colon. Most Americans and Europeans have lost the ability to maintain a large proportion of what can be regarded as a natural flora.[19] A recent study in a northern European population found *Lactobacillus plantarum, L. rhamnosus,* and *L. paracasei* ssp. *paracasei* on the rectal mucosa of healthy humans in only 52, 26, and 17 percent, respectively.[20] The colonization rate with other, commonly milk-borne probiotic bacteria, such *L. casei, L. reuteri,* and *L. acidophilus* was in the same study only 2, 2, and 0 percent, respectively.

Commonly consumed cooked roots and other starchy vegetables; grains, consumed as bread, cereals, and porridge; and most fruit consumed in Western countries contain relatively little fiber, usually no more than 1 to 3 g/serving.[21] The largest amount of consumed plant fiber is provided by resistant starch (raw potato, unripe green banana, especially when allowed to cool after cooking, especially potato and whole-grain bread). However, the daily consumption of this type of fiber varies from

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one individual to another with several hundred percent (~8 to 40 g/day).[22] The second largest source of fiber is nonstarch polysaccharides (~8 to 18 g/day). The third group of fiber is oligosaccharides (onions, artichoke, banana, cecoria), which although AU: word okay? important to health, are today regrettably consumed in much too small quantities (~2 to 8 g/day).[22]

8.4 DIETARY FIBERS—FUNCTION AND DEFINITION

Dietary fiber is the collective name for pure fibers obtained from processing various plants. The term dietary fiber was coined some 50 years ago, and was then suggested to consist of cellulose, hemicellulose, and lignin,[23] all indigestible constituents of the cellular walls of plants. The concept was Some 20 years later, the concept was defined as "plant fibers and lignin, which are resistant to hydrolysis by the digestive enzymes of man."[24] A more recent definition by the American Association of Cereal Chemists (AACC) suggests that dietary fiber is "the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fibers include polysaccharides, oligosaccharides, lignin, and associated plant substances. Dietary fibers promote beneficial physiological effects including laxation, and/or blood cholesterol attenuation, and/or blood glucose attenuation."[25] According to this definition also some noncarbohydrates like waxes, phytate cutin, saponins, suberin, and tannins are included in the concept, substances sometimes referred to as associated with nonstarch polysaccharide and lignin complex in plants. Of the many substances known, only a few have been properly investigated as dietary fibers and for health purposes, for example, as medical fibers.

Supplemented fibers are associated with several health benefits. The best-documented physiological effects, in addition to providing energy and nutrients to the host and flora, are that they:

- Change in mucosal structure, increase mucosal growth, and improve mucosal function.
- Increase in intestinal flora, relieve constipation, reduce production of putrifactive gases, and provide resistance to invading microorganisms
- Reduce serum triglycerides, serum cholesterol, and very low density (VLD) lipoproteins
- Reduce the glycemic response to eating.
- Improve water and electrolyte balance and increase bioavailability and absorption of minerals such as calcium, magnesium, iron, and zinc.

Consumption of medical fibers should always be regarded as a surrogate for not consuming enough fresh fruits and vegetables. There is no solid information to support that supplementation of medical fibers to healthy individuals eating a diet rich in fruits and vegetables is associated with additional health benefits. Medical fibers are mainly needed because the individual has lost the ability to consume enough fresh

fruits and vegetables. This is often the situation in persons with severe allergy, in old and debilitated persons, and in persons with some gastrointestinal (GI) disorders, such as short bowel syndrome and advanced diverticular disease. This is also most often the condition for critically ill patients, for whom enteral supply of concentrates of medical fibers has become a most valuable clinical tool. It must, however, always be remembered that bioactive fibers during the processing have lost their content of numerous important antioxidants and nutrients, some of which when possible should be separately supplemented, and whenever possible complemented by supply of fresh fruits and vegetables.

8.5 DOCUMENTED HEALTH BENEFITS OF INCREASED FIBER CONSUMPTION

Significant information on beneficial effects from increased intake of plant fibers and prebiotics exists mainly for two large groups of diseases:

Blood glucose control/prevention of type 2 diabetes. Fiber is a slow-release system for delivery of glucose to the body. Sugar "entrapped" in plant cells is slowly released by fermentation and absorbed resulting in a controlled blood glucose and insulin response. It is well documented that the physical structure of starchy foods determines the glycemic index of that food. Fiber, regularly supplied to patients with diabetes, will significantly reduce the level of blood glucose and the need for insulin. Studies suggest that the most pronounced effects of fibers on glycemic index are obtained by water-soluble fibers. Guar gum is by far the most clinically used fiber and will, based on 15 different studies, induce a reduction in blood glucose to almost half (44 percent).[26]

Lipid control/prevention of coronary heart disease. Soluble fibers such as pectin, guar gum, betaglucans (oat) have repeatedly been shown to reduce blood cholesterol both in hypercholesterolemic and normocholesterolemic individuals, effects not found when nonsoluble fibers such as cellulose and wheat bran have been used. Common to water-soluble fibers is that they are gel forming. Soluble fibers are excellent substrates for production in the large intestine of short-chain fatty acids (SCFAs), known to reduce the level of cholesterol in the body. Studies both in animals and in humans suggest that it is especially propionic acid that is hypocholesterolemic.[27] A meta-analysis reports statistically significant protective effects against coronary heart disease in 14/16 studies.[28] In addition, fiber consumption is reported to reduce clotting and increase fibrinolysis, also important for prevention of building of arterial wall plaques and prevention of thrombosis formation.[29]

8.6 FIBERS COMMONLY USED IN CLINICAL NUTRITION

Substances, important to health—amino acids such as arginine, glutamine, histidine, taurine, various sulfur and related amino acids, polyamins, omega-fatty acids, numerous vitamins, and antioxidants—are all to a great extent supplied to the body

from plants. One cannot expect any significant amount of antioxidants to be delivered to the lower level of the GI tract, if not "hidden" in plant fibers. It is important to remember that key nutrients such as omega-3 fatty acids, glutamine, glutathione, and several other nutrients are heat-sensitive and do not tolerate processing or storage to any great extent. Plant fibers that have been dried, heated, or microwaved cannot be expected to contain any large amounts of these key nutrients; they mainly come from unprocessed foods. It is highly desirable that, whenever possible, the supply of commercial nutrition formulas is complemented by supply of fresh fruit and vegetable juices, produced as locally as possible. It is also desirable that several fibers are supplied in parallel, and that both soluble and nonsoluble fibers are used. For example, oat fibers are mainly metabolized in the proximal colon, whereas wheat fibers are known to be effective in the distal part of the colon, for example, the part of the colon where most cancers are localized. Oat has mainly shown sepsis-reducing effects while wheat has mainly been effective in cancer prevention. Among the fibers commonly used in clinical nutrition are the following.

8.6.1 Algal Fibers

Most of the algal fibers are resistant to hydrolysis by human endogenous digestive enzymes, but are fermented by colonic flora to various degrees. The soluble fibers consists in lamarans (a sort of β-glucan associated with mannitol residues), fucans (sulfated polymers associated with xylose, galactose, and glucoronic acid), and alginates (mannuronic and guluronic acid polymers). The insoluble algal polymers consist mainly of cellulose. Fermentation of alginates yields high levels of acetate (80 percent), while lamirans preferably yield butyrate (16 percent). It is most likely that algal fibers will be routinely used in clinical nutrition within a few years.

8.6.2 Fructans

Fructan starches and sucrose serve the plant as its energy reserve. These substances are also produced by bacteria and fungi. Fructans are said to enhance the tolerance of the plant to stressful conditions and make it possible for the plants to survive under harsh conditions, such as low temperature and draft. The most well known fructans are inulin (rich in chicory, artichoke, onions, banana) and phleins (rich in various grasses). Thus far, mainly inulin has been tried in human nutrition. Various oligosaccharides are reported to stimulate the flora and especially the growth of *Lactobacillus* and *Bifidobacterium* in the large intestine and to reduce the content of potentially pathogenic microorganisms (PPMs) in the intestine. Increase in the *Bifidobacterium* flora is regarded as especially favorable as bifidobacteria are known to produce important vitamins, among them thiamine, folic acid, nicotinic acid, pyridoxine, and vitamin B_{12}, which is of great importance for health. A fructan called neokestose, found in onion, is reported to have even better ability than inulin to promote growth of lactic acid bacteria (LAB).[30] Supplementation of fructans is also reported to reduce concentrations in serum of insulin, cholesterol, and triacylglycerol. It is also reported to promote absorption of calcium and other minerals.

Other oligosaccharides such as those extracted from peas and beans, especially soy bean oligosaccharide (raffinose and stachyose) and pyrodextrin, produced by pyrolysis of maize and potato starch, are also reported to be beneficial for human health.

8.6.3 Glycomannans

Glycomannan, a glucose/mannose polymer derived from a plant called *Amorphophallus konjak*, has several English names such as devil tongue, elephant yam, and umbrella arum. It has unique hydroscopic abilities and will swell and form a viscous gel on contact with water. Like other gels, this will delay gastric emptying and intestinal transit time. It has been shown to be effective in delaying absorption of digestible energy. It has thus far been used mainly in Japan and other Asian countries to treat diabetes, hypertension, and hypercholesterolemia. Dietary supply of konjak mannans has been shown to alter the flora and reduce tumorigenesis in experimental animals. It is also effective in controlling diarrhea in enteral nutrition, especially in elderly patients, and to increase the *Bifidobacterium* flora.

8.6.4 Oat Gum

Oat contains a series of interesting compounds, which is the reason an increasing part the world production of oat goes to the pharmaceutical and cosmetic industries. The amino acid pattern of oat is similar to that of human muscle (only that of buckwheat is more alike), and can thus be expected to deliver most of the amino acids needed to build muscles. Oat is rich in water-soluble fibers, β-glucans, known for their antiseptic properties. Oat is also rich in natural antioxidants, particularly ferulic acid, caffeic acid, hydrocinnamic acid, and tocopherols, and before synthetic antioxidants oat was available extensively and used to preserve foods: milk, milk powder, butter, ice cream, fish, bacon, sausages, and other food products sensitive to fat oxidation. Another ingredient richly available in oat is inositol hexaphosphate (phytic acid), a strong antioxidant, particularly known to enhance natural killer (NK) cell activity and to suppress tumor growth. Oat is also rich in polyunsaturated fats/polar lipids such as phosphatidylcholine, known for its protective effects of mucosal and cellular surfaces.

8.6.5 Pectin

Pectin is also an interesting fiber, extensively used by the pharmaceutical and food industries. It has a unique ability to form gels and is commonly used as a carrier of pharmacologically active substances; it is common in baby foods. An important finding is that pectin is a very strong antioxidant against the three most dominating oxidation damages induced by peroxyl, superoxide, and hydroxyl radicals. These effects might explain why pectin has the capacity to stimulate the gut-associated immune system and to prevent disruption of the intestinal microflora. In experimental studies, pectins have shown strong protective and healing effects on gastric and on intestinal mucosa, not inferior to that observed with H_2-blockers, proton

inhibitors, and surface-protection agents.[31,32] Pectin builds a protection layer in the stomach and facilitates maintenance of gastric acidity, important for prevention of colonization of the stomach by pathogens. Pectin is also an excellent substrate for microbial fermentation.

8.7 LACTIC ACID BACTERIA IMPORTANT FOR FERMENTATION OF FIBERS

Not all fibers are easily fermented in the gut. Among the more fermentation-resistant fibers are wheat fibers, which usually are not digested until they reach the descending colon. Also oligofructans (inulin or phleins) are difficult to ferment, and only a small minority of LAB are able to do so. When the ability of 712 different LAB to ferment oligofructans was studied, only 16 of 712 were able to ferment the phleins and 8 of 712 inulin.[33] Apart from *Lactobacillus plantarum* only three other LAB species, *L. paracasei* subsp. *paracasei*, *L. brevis,* and *Pediococcus pentosaceus,* were able to ferment these semiresistant fibers. Another study investigated the ability of 28 different LAB to ferment pure fructo-oligosaccharides (FOS). All *L. plantarum*, *L. casei,* and *L. acidophilus* strains studied and most *Bifidobacterium* utilized FOS, in contrast to yogurt bacteria such as *L. bulgaricus* and *Streptococcus thermophilus* and *Lactobacillus* strain *GG,* which were all unable to ferment these fibers.[34]

8.8 CLINICAL EXPERIENCE WITH SUPPLEMENTED PLANT FIBERS

8.8.1 Plant Fiber in Constipation

Chronic constipation is one of the most common disorders in Western countries. Its etiology remains unclear despite numerous clinical, pathophysiologic, and epidemiologic studies, but it is suggested that high intake of dairy products and intake of plant fibers plays a significant role in its pathogenesis. A randomized sample of 291 children with idiopathic chronic constipation was in a case control study compared with 1,602 healthy controls.[35] Constipation was clearly negatively correlated with low intake of cellulose and pentose fibers ($p < 0.001$). FOS may also have potential benefits in constipation, since they exhibit many soluble dietary fiber-like properties. In a study, a total of 56 healthy infants, age 16 to 46 weeks (mean age 32 weeks) were randomly assigned to receive either 0.75 g FOS or placebo added to a serving of cereals for 28 days.[36] The mean number of stools per infant was 1.99 ± 0.62 per day in the FOS-supplemented group compared with 1.58 ± 0.66 in the control group ($P = 0.02$).

8.8.2 Plant Fiber to Prevent and Treat Diarrhea

In a large randomized study in acutely ill medical and surgical patients, all requiring enteral nutrition for a minimum of 5 days, supplementation of hydrolyzed

guar gum was compared to fiber-free enteral nutrition. The incidence of diarrhea was 9 percent with fiber supplementation, compared to 32 percent with fiber-free nutrition ($p > 0.05$).[37] One of the effects of certain fibers is that they increase the bioavailability and absorption of zinc, which is especially shown for oligosaccharides. Zinc supplementation was proven effective to lower both the incidence of diarrhea and the duration of diarrhea in a randomized study in 3- to 59-month-old children in Bangladesh.[38] In another study from Bangladesh 250 g/L of green (unripe) banana (equivalent to two fruits) or 2 g pectin/kg food was supplemented to a rice diet in children suffering from persistent diarrhea.[39] The amounts of and frequency of stools, the duration of diarrhea, numbers of vomiting, use of oral rehydration, and amounts intravenous fluid solutions given were all significantly reduced with supplementation of both green banana and pure pectin. Recovery on the third day was seen in 59 percent in the green banana group and in 55 percent in the pectin group, compared to 15 percent in the rice only control group.

8.8.3 Plant Fiber to Support Mineral Absorption

It is well accepted that nutrition is of great importance for bone health. Most of the interest has thus far focused on calcium and vitamin D. Much less interest has been paid to other important nutrients such as protein, and especially to minerals such as phosphorus, potassium, magnesium and to vitamins such as C and K. Recent studies suggests that increased intake of plant fibers, fruits, and vegetables is associated with an increased bone mineral density, including in elderly subjects, both women and men.[40,41] Of the pure fibers available, the effects of oligosaccharides have primarily been studied, and mainly in experimental animals. Calcium absorption, bone calcium content, bone mineral density, bone balance, and bone formation/bone absorption index are reported to significantly increase after 3 weeks of supplementation of a mixture of inulin and FOS.[41]

8.8.4 Plant Fiber to Control Weight

No major effects on body weight by supplementation of prebiotic fiber alone have thus far been reported. The effects of dietary fiber on subjective hunger ratings and weight losses were studied some 20 years ago in members of a weight loss club. Of 135 members, 108 completed the trial: 23 controls, 45 on ispaghula granulate, and 40 on bran sachets.[42] Both fiber preparations reduced hunger at all meals. The mean (± SD) weight reductions during the trial were 4.6 ± 2.7 kg for the controls, 4.2 ± 3.2 kg for the ispaghula group, and 4.6 ± 2.3 kg for the bran group ($p > 0.05$ for both groups). Although supply of dietary fiber immediately before meals did reduce the feeling of hunger, it did not provide any additional benefits to the weight reduction. A more recent cross-over study compared the effect on satiety of supplementation of 27 ± 0.6 g/day of fermentable fibers (pectin, betaglucan) with similar amounts of nonfermentable fiber (methylcellulose). The daily satiety was significantly more increased with nonfermentable (methylcellulose) than with fermentable fibers (beta-

glucan, pectin) ($p = 0.01$), but no differences were observed in daily energy intake or loss of body weight or body fat.[43]

8.8.5 Plant Fiber in Inflammatory Bowel Diseases

Although patients with both inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) are known to underconsume dietary fibers, there is little evidence that lack of dietary fiber plays a role in the pathogenesis of these diseases. The ability of maintaining remission in patients with ulcerative colitis (US) by a daily supply of 10 g of *Plantago ovata* seeds (also called psyllium or ispaghula husk) was compared with daily treatment with 500 mg of mesalamine and a combination of the two.[44] The 12 months of treatment failed to demonstrate any difference in clinical benefits between the three groups. Germinated barley foodstuff (GBF), a by-product from breweries, rich in hemicellulose and in glutamine, was tried in 39 patients with mild-to-moderate active UC.[45] Daily supply of 30 g reduced significantly the disease activity, increased concentration of SCFAs, and increased the numbers of *Bifidobacterium and Eubacterium* in stool. It may well be that the observed effect was due more to increased supply of glutamine and other antioxidants such as various B vitamins than to the fiber per se as these compounds are known to be rich in by-products from breweries. Glutamine, as well as other antioxidants, are known to attenuate proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and to enhance release of heat shock proteins (HSP-72).[46] A controlled study using oat bran as fiber source was recently reported from a study in 22 patients + 10 controls with quiescent UC. Daily supply during 3 months of as much as 60 g of oat bran (equivalent to 20 g dietary fiber) resulted in a significant increase in fecal butyrate (average 36 percent) but also to a reduction in abdominal pain. All the treated patients tolerated well the large dose of fiber, and signs of relapse of disease were seen in none of the patients with colitis.[47] Butyrate has been shown to inhibit nuclear factor kappa B (NF-κB) activation of lamina propria macrophages, and to reduce the number of neutrophils in crypts and surface epithelia, as well as the density of lamina propria lymphocytes/plasma cells in patients with ulcerative colitis[48]—findings correlating well with the observed decreased disease activity. In a study, 20 patients with ileal pouch-anal anastomosis received 24 g of inulin daily for 2 weeks. Significant reduction in inflammation was observed with endoscopy and histology. In addition, significant increase in fecal concentrations of butyrate and reductions in fecal pH, fecal content of secondary bile acids, and growth of *Bacteroides fragilis* were observed.[49]

8.8.6 Plant Fiber in Irritable Bowel Disease

Dysmotility disorders are increasingly common in Western societies. Some evidence suggests that various dysmotility disorders, gastroesophageal reflux problems, infant colic, and constipation are all food-related features, and often due to intolerance to cow's milk proteins.[50] IBS is a clinical diagnosis based on the occurrence of abdominal distension, abdominal cramps, often increased transit time, more

frequent stools, and relief of pain on defecation. The prevalence of the syndrome varies between 7 and 22 percent, making IBS the most common functional GI disorder.[51] Unfortunately, no effective pharmaceutical treatment exists or when existing is unacceptably toxic.[52] This has resulted in a need for additional modalities for the treatment of IBS. In this perspective, pre- and probiotics appear as attractive alternatives (see recent reviews[53,54]). Data from human intervention studies and especially results from recent animal studies clearly indicate that prebiotics have an impact on the immune system: immune cells of the GALT including Peyer's patches are primarily responsive to the oral administration of prebiotics.[55] However, a consequence of feeding the currently favored prebiotics (inulin, FOS, trans-galacto-oligosides, and lactulose) is increased gas production in the gut, which might preclude prebiotic use in diarrhea-predominant IBS, or where bloating or gas are prominent symptoms, but might allow their mild laxative properties to be useful in constipation-predominant IBS.[53] A few small open trials have been performed, but thus far no larger and randomized trial has been reported. However, a recent small open label trial supplementing 15 g/day of a mixture of oligofructose (70 percent) and inulin (30 percent) reports significant reduction in disease activity (Harvey Bradshaw index fell from 9.8, SD 3.1 to 6.9 SD 3.4, $p = 0.01$) in parallel with a significant increase in fecal bifidobacteria concentration (from 8.8, SD 0.9 log10 to 9.4, SD 0.9 log10 cells/g dry feces $p = 0.001$). Also the interleukin 10 (IL-10) positive dendritic cells increased (from 30 to 53 percent, $p = 0.06$), and the percentage of dendritic cells expressing Toll-like receptor 2 (TLR2) and TLR4 increased from 1.7 to 36.8 percent, $p = 0.08$, and from 3.6 to 75.4 percent, $p = 0.001$),[56] respectively, which offers hope for the future.

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Other dietary fibers have also been tried in various groups of abdominal pain. A recent Cochrane review was unable to find any evidence that fiber supplements, lactose-free diets, or *Lactobacillus* supplementation is effective in the management of children with recurrent abdominal pain.[57] However, a study in adult patients reports significant success with fibers other than the classical prebiotics. In one study, 188 adult patients with IBS were classified as having diarrhea-predominant, constipation-predominant, or changeable bowel habit type IBS and randomly assigned to groups receiving 30 g/day of wheat bran) or 5 g/day of guar gum (PHGG).[58] After 4 weeks, patients were allowed to switch group, depending on their subjective evaluation of their symptoms. Both fiber and PHGG were effective in improving pain and bowel habits. Significantly more patients switched from fiber to PHGG (49.9 percent) than from PHGG to fiber (10.9 percent) at 4 weeks. Intention-to-treat analysis showed a significantly greater success in the PHGG group (60 percent) than in the fiber group (40 percent). In addition, significantly more patients in the PHGG group reported a greater subjective improvement than those in the fiber group. It was concluded that improvements in core IBS symptoms were observed with both bran and PHGG, but the latter was better tolerated and preferred by patients.[58]

The capsaicin (chili pepper) receptor (TRPV1) is known to play an important role in visceral pain and hypersensitivity states. It is of special interest that the numbers of TRPV1-immunoreactive fibers was found to be increased by 3.5 times in biopsies from patients with IBS compared with controls ($p < 0.0001$).[59] Substance

P-immunoreactive fibers ($p = 0.01$), total nerve fibers (PGP 9.5) ($p = 0.002$), mast cells (c-kit) ($p = 0.02$), and lymphocytes (CD3) ($p = 0.03$) were also all significantly increased in the IBS group. However, in multivariate regression analysis, only TRPV1-immunoreactive fibers ($p = 0.005$) and mast cells ($p = 0.008$) were significantly related to the abdominal pain score. The information of increased TRPV1 nerve fibers in IBS, in addition to the observed low-grade inflammatory response, makes TRPV1 nerve fibers an interesting new therapeutic target.[59]

8.8.7 Plant Fiber to Control Infections

In an effort to prevent nosocomial pneumonia and sepsis, patients with severe multiple trauma were treated with beta-1-3 polyglucose (glucan)—a component of cell walls of plants and microbes.[60] Pneumonia occurred in 2 of 21 glucan-treated and in 11 of 20 patients in the control group ($p < 0.01$). Infectious complications (pneumonia and/or general sepsis) occurred in 14 percent of the glucan-supplemented patients versus 65 percent in the control group ($p < 0.001$). Another study compared the effects of a high-protein formula enriched with fiber but also arginine and antioxidants with a standard high-protein formula in early enteral nutrition in critically ill patients.[61] The supplemented group had, in comparison to nonsupplemented controls, a lower incidence of catheter-related sepsis (0.4 episodes/1,000 intensive care unit, ICU, days) than the control group (5.5 episodes/1000 ICU days) ($p < 0.001$), but no differences were observed between the groups in incidence of ventilator-associated pneumonia, surgical infection, bacteremia, urinary tract infections, mortality, and in long-term survival.[61]

8.9 PLANT FIBERS RICH IN ANTIOXIDANTS

LAB produce themselves and/or release from consumed plants a whole range of important vitamins and antioxidants. One important example is the essential B vitamin, folate, known to have a strong effect in reducing homocysteine and an ability to prevent some chronic diseases. Folate is synthesized by LABs such as *Lactococcus lactis* and *Lactobacillus plantarum*. Other LABs, however, such as *L. gasseri,* are net comsumers of folate. A recent publication describes successful transfer of five genes essential for folate biosynthesis from *Lactococcus lactis* to *Lactobacillus gasseri,* turning *L. gasseri* into a net producer of folate.[62] Anemia, iron deficiency, and folate deficiency are common among patients with both acute and chronic diseases such as IBD.[63,64]

In a pediatric study of 43 patients and 46 controls, plasma total homocysteine (tHcy) concentrations were shown to be significantly higher in children with IBD than in control subjects ($p < 0.05$). Furthermore, the level of plasma tHcy levels correlated well with observed reductions in plasma 5-methyltetrahydrofolate ($p < 0.0005$).[65] A similar study in 108 adult patients with IBD and 74 adult healthy controls found significantly lower levels of folate ($p < 0.05$) in patients with both UC and Crohn's disease (CD).[66] Also in this study, the serum concentration of tHcy was

significantly higher in both groups: UC 15.9 ± 10.3 mmol/l and CD 13.6 ± 6.5 compared to controls 9.6 ± 3.4 ($p < 0.05$).

The choice of fibers for medical use has probably not considered the content of vitamins and antioxidants as it should. Pectin has demonstrated high antioxidant ability, but most of the fibers generally used are not particularly rich in antioxidants. Numerous other plant fibers exist that should be considered as medical fibers and used either as replacement for or complements to other fibers in various enteral nutrition solutions. Plants with documented ability to boost resistance and decrease vulnerability to disease, often referred to as chemopreventive agents, are usually easily available, inexpensive to produce, rich in fibers, and have no or limited toxicity. Among the numerous agents with chemopreventive abilities are a whole series of phenolic and other compounds suggested to reduce the speed of aging and often documented to prevent degenerative malfunctions of organs: isothiocyanates in cruciferous vegetables, epigallocatechin-3-gallate (EGCG) in green tea, caffeic acid in coffee, capsaicin in hot chili peppers, chalcones in apples, euginol in cloves, gallic acid in rhubarb, hisperitin in citrus fruits, naringenin in citrus fruits, kaempferol in white cabbage, myricetin in berries, quercetin in apples and onions, resveratrol and other procyanidin dimers in red wine, and various curcumenoids found in turmeric curry foods, in addition to thousands of hitherto less explored or unexplored substances. Turmeric, dried and powdered roots of the plant *Curcuma longa*, is rich in natural antioxidants, and has proved to be a strong inhibitor of proinflammatory messengers such as NF-κB, cyclooxygenase-2 (COX-2), matrix mettaloproteinase-9 (MMP-9), inducible nitric oxide synthase (iNOS), TNF, IL-8, eotaxin, cell surface adhesion molecules, and antiapoptotic proteins.[67] See further a recent review.[68]

Chili pepper, a herb with high content of flavonoids (>100 mg/100 g), has recently caught attention, especially since a specific receptor for its active substance, capsaicin, has been demonstrated and cloned.[69] The cloning of the vanilloid receptor 1 (TBRV1) has opened a floodgate for discoveries regarding the function of this complex molecule[70] and provided explanation for earlier observed clinical effects of intake of chili peppers. This receptor is associated with nociceptive afferent nerve fibers and broadly expressed, especially in brain, epidermis, and visceral cells. Old observations as well as recent studies suggest a great potential of antioxidant-rich chili fibers for control the immune cells, both innate and acquired,[71] of chronic diseases especially diabetes, both type 1 and 2,[72,73] hypertension,[74] and cancer,[75] as well as chronic pain conditions[76] and obesity.[77]

8.10 DIVERSITY IN MICROBIOTA FOR BARRIER FUNCTION

The gut mucosa and microbiota are intimately joined in the maintenance of a well-functioning barrier between the host and the external environment—see further two excellent reviews.[78,79] The barrier is suggested to be composed of three barriers in one: the physical barrier, the innate immune barrier, and the adaptive immune barrier. Emphasis has in the past focused mainly on the physical barrier, but tends

in more recent years to switch to the importance of the innate immune mechanisms, particularly the role of antimicrobial peptides such as defensins and more recently angiogenins.[80]

Several plant fibers (prebiotics) and a few LABs (probiotics) have documented significant effects in improving both the function of the innate immune system and the physical barrier and in increasing resistance to disease. The hope is that combined supply of these components will have synergistic, that is, more than additive, effects in boosting the immune system and enforcing the barrier functions. Products that combine pre- and probiotics are called synbiotics and treatment using the combination is termed synbiotic treatment.

The term "defense by diversity" was coined in 1999,[81] and seems applicable to synbiotic treatment. Natural foods supply both LAB and a great variety of plant fibers. A recent study concludes that combining several fibers has more than additive effects on the microbial ecosystem and immune responses,[82] and a recent review suggest that multispecies probiotics are superior to single-species probiotics to enhance growth, reduce antibiotic-associated diarrhea, prevent infections (*S. typhimurium*) and reduce pathogenic colonization (*Escherichia coli*).[83] The choice of pre- and probiotics must be based on scientific evidence—see further below. This is especially important in the selection of LABs, as the majority of LABs have no or much limited effects on immune functions and outcome. It is important to remember in constructing synbiotic formulations that most of the LABs used by the food industry have no or limited ability to ferment bioactive fibers such as inulin or phlein, no ability to adhere to human mucus, low antioxidant capacity, and most important do not survive the acidity of the stomach and bile acid content. Stronger bioactivities cannot be expected from LABs such as yogurt bacteria, chosen mainly for their palatability. The LAB used in the synbiotic studies must be selected according to their bioactivity. Unfortunately, few studies have looked at the synergistic effects of simultaneous supply of LAB and fibers—synbiotics.

Although some studies have used various synbiotic compositions, only two such compositions have been produced after extensive preclinical studies:

1. *A one LAB/one fiber composition,* produced (Probi AB, Lund Sweden) by fermentation of oat meal with *L. plantarum* strain 299, containing 10^9 of LAB and approximately 10 g oat fiber.[84] In a few studies a commercial fruit juice, PRO VIVA™ containing 10^7 of a related *L. plantarum* strain called 299V (Skånemejerier, Malmö, Sweden), has also been tried.
2. *A four LAB/four fiber composition,* called Synbiotic 2000™, consisting in a mixture of 10^{10} (more recently also a Synbiotic Forte™ with 10^{11}) of each of four LAB: *Pediacoccus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* subsp. *paracasei* 19, and *L. plantarum* 2362 and 2.5 g of each of the four fermentable fibers (prebiotics): betaglucan, inulin, pectin, and resistant starch (Medipharm AB, Kågeröd, Sweden and Des Moines, Iowa).

Lund University microbiologists Åsa Ljungh and Torkel Wadström developed this multistrain/multifiber synbiotic formula, which in recent years has been extensively used in clinical trials. The choice of LAB for the formulation was done after

extensive studies of more than 350 human[85] and more than 180 plant microbial strains[86] and was based especially on the ability of the LAB to produce bioactive proteins, transcribe NF-κB, produce pro- and anti-inflammatory cytokines, produce antioxidants, and most important to functionally complement each other. In recent studies both the Synbiotic 2000 Forte and a Probiotic 2000 Forte™ (no fiber added), containing 10^{11} of each of the four LABs, that is, 400 billion LAB per dose, have been tried. The effects of Synbiotic 2000 have thus far been investigated in a series of conditions.

8.10.1 Synbiotics in Acute Pancreatitis

In one study, 62 patients with severe acute pancreatitis (SAP) (Apache II scores: Synbiotic 2000-treated 11.7 ± 1.9, controls 10.4 ± 1.5) were given either two sachets/day of Synbiotic 2000 (2 × 40 billion LAB/day and a total 20 g fibers) or the same amount of fibers (20 g) as in Synbiotic 2000 during the first 14 days after arrival to the hospital. [87] Of 33 patients, 9 (27 percent) in the Synbiotic 2000-treated group and 15 of 29 patients (52 percent) in the only fiber-treated group developed subsequent infections. Of 33 Synbiotic 2000-treated patients, 8 (24 percent) and 14 of 29 (48 percent) of the only fiber-treated patients developed SIRS, MOF, or both ($p < 0.005$).[88] A total of 7 pathogenic microorganisms were cultivated in the synbiotic-treated group compared to 17 in the fiber-only group.

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8.10.2 Synbiotics in Polytrauma

In patients with polytrauma two prospective randomized trials with Synbiotic 2000 and Synbiotic 2000 FORTE have been concluded. The first study compared the following treatments in patients with acute extensive trauma: (1) Synbiotic 2000 (40 billion LAB/day) with (2) a soluble fiber, (3) a peptide diet (Nutricomp, Braun Inc Germany), and (4) supplementation of glutamine. Treatment with Synbiotic 2000 led to a highly significant decrease in number of chest infections (4/26 patients, 15 percent), compared to peptide diet (11/26 patients, 42 percent, $p < 0.04$), glutamine (11/32 patients, 34 percent, $p < 0.03$), and fiber only (12/29 patients, 41 percent, $p < 0.002$).[89] The total number of infections was also significantly decreased: Synbiotic 2000 5/26 patients (19 percent); fiber only 17/29 patients (59 percent); peptide 13/26 patients (50 percent); and glutamine16/32 patients (50 percent).

In the second study 65 patients with polytrauma were randomized to receive Synbiotic 2000 Forte (400 billion LAB + 10 g fiber, see above) once daily for 15 days or maltodextrine as placebo. Significant reductions were observed in number of deaths (5/35 vs. 9/30, $p < 0.02$), severe sepsis (6/35 vs. 13/30, $p < 0.02$), chest infections (19/35 vs. 24/30, $p < 0.03$), central line infections (13/32 vs. 20/30, $p < 0.02$), and ventilation days (average 15 vs. 26 days).[90] A total of 54 pathogenic microorganisms were cultivated in the symbiotic-treated group compared to 103 in the fiber-only group.

8.10.3 Synbiotics in Abdominal Surgery

In a randomized controlled study, 45 patients undergoing major surgery for abdominal cancer were divided into three treatment groups: (1) enteral nutrition (EN) + Synbiotic 2000 (LEN), (2) EN + only the fibers in the same amounts (20 g) as in Synbiotic 2000 (FEN), and (3) standard parenteral nutrition (PN). All treatments lasted for 2 preoperative and 7 days postoperative days. The incidence of postoperative bacterial infections was 47 percent with PN, 20 percent with FEN, and 6.7 percent with LEN ($p < 0.05$).[91] A total of 34 pathogenic microorganisms were cultivated in the symbiotic-treated group compared to 54 in the fiber-only group. Significant improvements were also documented in prealbumin (LEN, FEN), C-reactive protein (LEN, FEN), serum cholesterol (LEN, FEN), white cell blood count (LEN) , serum endotoxin (LEN, FEN), and IgA (LEN).

In another prospective randomized, double-blind trial, 80 patients subjected to pylorus-preserving pancreatoduodenectomy (PPPD) received twice daily either Synbiotic 2000 (2 × 40 billion LAB) or only the fibers in composition from the day before surgery and during the first 7 postoperative days.[92] A highly significant difference in infection rate ($p = 0.005$) was observed as only 5 of 40 patients (12.5 percent) in the Synbiotic 2000-treated group suffered infections (4 wound and 1 urinary tract infection) versus 16 of 40 (40 percent) in the fiber-only group (6 wound infections, 5 peritonitis, 4 chest infections, 2 sepsis, and 1 of each of urinary tract infection, cholangitis, and empyema). The infecting microorganisms in the symbiotic-treated group were *Klebsiella pneumoniae* (2 patients), *Enterobacter cloacae* (2 patients), *Proteus mirabilis* (1 patient), and *Enterococcus faecalis/faecium* (1 patient); in the fiber-only group *Enterobacter cloacae* (8 patients), *Enterococcus faecalis/faecium* (7 patients), *Escherichia coli* (7 patients), *K. pneumoniae* (2 patients), *Staphylococcus aureus* (2 patients), and *Proteus mirabilis* (1 patient); see Table 5. Statistically significant differences between the groups were also observed in use of antibiotics (mean: Synbiotic 2000; 2 ± 5 days, fiber-only; 10 ± 14 days).

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8.10.4 Synbiotics in Chronic Liver Disease and Liver Transplantation

In a study, 58 patients with liver cirrhosis suffering minimal encephalopathy were randomized into three treatment groups: Group 1 (20 patients) received Synbiotic 2000 (40 billion LAB); group 2 (20 patients) received the same amount of the fibers in Synbiotic 2000; and group 3 (15 patients) received placebo (nonfermentable, nonabsorbable fiber—crystalline cellulose).[93] A significant increase in intestinal LAB flora was observed after 1 month of supplementation in the synbiotic-treated group, but not in the other two groups. Intestinal pH was significantly reduced in both treatment groups but not in the placebo-treated group. Significant decreases in fecal counts of *Escherichia coli, Staphylococcus* and *Fusobacterium,* but not in *Pseudomonas* and *Enterococcus,* and significant decreases in ammonias, endotoxins, ALTs, and bilirubins (original level 252 ± 182) were observed in the Synbiotic 2000-treated group (84 ± 65, $p < 0.01$) and in the fiber-only-treated group (110 ± 86,

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$p < 0.05$) while it remained unchanged in the placebo group. The improvements in liver function were accompanied by significant improvements in psychometric tests and in degree of encephalopathy.

In a follow-up study by the same group of investigators 30 patients with liver cirrhosis were randomized to receive either Synbiotic 2000 or placebo (crystalline cellulose) for 7 days.[94] Viable fecal counts of *Lactobacillus* species, Child-Pugh class, plasma retention rate of indocyanine green (ICG_{R15}), whole blood TNF-α mRNA, IL-6 mRNA, serum TNF-α, soluble TNF receptor (sTNFR)I, sTNFRII and IL-6, and plasma endotoxin levels were measured pre- and posttreatment: Synbiotic treatment was associated with significantly increased fecal lactobacilli counts and significant improvements in plasma retention rate of ICG_{R15} and stage of liver disease (Child-Pugh classification). No significant changes in any study parameter followed placebo treatment, but significant increases in whole blood TNF-α mRNA and IL-6 mRNA, along with serum levels of soluble TNF receptors sTNFRI and sTNFRII, were observed in the Synbiotic 2000-treated patients. TNF-α and IL-6 levels correlated significantly, both at baseline and after synbiotic treatment. Synbiotic-related improvement in ICG_{R15} was significantly associated with changes in IL-6, both at mRNA and protein levels, and unrelated to plasma endotoxin values. It was concluded that even short-term synbiotic treatment can significantly modulate gut flora and improve liver function in patients with cirrhosis. The observed benefits seemed unrelated to reduction in endotoxemia, but could be mediated, at least in part, by treatment-related induction of IL-6 synthesis by TNF-α. These results offer great hope that synbiotic treatment of patients on the waiting list for liver transplantation might prevent septic episodes, improve liver function, and promote successful outcome of surgery.

In another study, 66 patients were randomized to either receive Synbiotic 2000 or only the fibers in Synbiotic 2000 in connection with human orthotopic liver transplantation. The treatment started on the day before surgery and continued for 14 days after surgery. During the first postoperative month only 1 patient in the Synbiotic 2000-treated group (3 percent) showed signs of infection (urinary infection) compared to 17 of 33 (51 percent) in the patients supplemented with only the four fibers.[95] The infecting organisms in the synbiotic-treated group were *Enterococcus faecalis* in 1 patient and in the only fiber-treated group *E. faecalis/faecium* in 11 patients, *Escherichia coli* in 3 patients, *Enterobacter cloacae* in 2 patients, *Pseudomonas aeruginosa* in two patients, and *Staphylococcus aureus* in 1 patient; see further table 6. The use of antibiotics was on average 0.1 ± 0.1 days in the synbiotic-treated patients and 3.8 ± 0.9 days in the fiber-only group.

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8.10.5 Synbiotics in Inflammatory Bowel Disease

Daily rectal instillations with Synbiotic 2000 reconstituted in saline were given to 10 patients with distal colitis for 2 weeks. One patient withdrew after 1 week; the remaining patients showed dramatic improvements in various disease scores during the 3 weeks of observation: episodes of diarrhea (decreased from 2.4 to 0.8), visible blood in stool (2.2 to 0.8), nightly diarrhea (0.5 to 0), urgency (1.9 to 1.0), and consistency of stool (1.1 to 0.8).[96] In the study, 2 patients reported significant

bloating and wind but no other adverse or side effects were reported. In another study, 8 patients with active ulcerative colitis (UC) received a synbiotic composed of 4×10^{11} freeze-dried *Bifidobacterium longum* and 6 g of a prebiotic FOS/inulin mix called Synergy daily for 4 weeks. These patients were compared to 8 similar patients receiving placebo.[97] Levels of intestinal bifidobacteria at the end of the study were increased 42-fold compared to 4.6-fold in the placebo group. The sigmoidoscopy score decreased on average by 1.3 compared to an increase of 0.58 in the placebo ($P = 0.06$). The mean histology score was decreased in the synbiotic group and increased in the placebo group. However, due to the small size of the patient group, these changes were not statistically significant. The bowel habit index scores decreased by 20.4 percent in the synbiotic group and the scores increased by 70.4 percent in the placebo group. Human beta-defensin (hBD) (2, 3, and 4), TNF-α, and IL-1 were all decreased after synbiotic treatment but remained unchanged in the placebo group ($P = 0.05$). These observations are most interesting and promising for future therapies. I fully agree with the statement of the reviewer: "Slowly, the links of diet to the intestinal environment and the association of the intestinal environment to IBD are becoming evident. The prebiotic and probiotic trials reveal the importance of the intestinal environment as a potent regulator of IBD activity."[98]

8.10.6 Synbiotics in Short Bowel Syndrome

Seven malnourished patients aged 2.5 to 24 years with short bowel syndrome and refractory enterocolitis received a synbiotic composition consisting ~1 billion *Bifidobacterium breve* and *Lactobacillus casei* and ~3 g galacto-oligosaccharides three times daily for 15 to 55 months.[99] Improvement of the flora as a whole (general increase in anaerobic bacteria and suppression of pathogenic flora) and an increase in fecal content of SCFAs (from an average of 27.8 to 65.09 ~mol/g wet feces) resulted. Six of seven patients increased their body weight between 1.0 and 4.2 kg/year. Prealbumin was increased in all treated patients ($p = 0.05$). These results in a small study offer hope that other eventually more potent probiotics in combination with other fibers and antioxidants will significantly contribute to the quality of life for patients with short bowel syndrome.

8.10.7 Synbiotics in Irritable Bowel Syndrome

The effects of twice-daily consumption of a probiotic fruit drink ProViva (Skånemejerier, Malmo, Sweden) containing *L. plantarum* 299v (6×10^7 cfu/drink) or placebo for 4 weeks were studied in a controlled study including 40 patients.[100] The vast majority (95 percent of LAB-treated vs. 15 percent of the placebo-treated patients) of individuals in the probiotic consumption group reported general improvement. A total of 20 of 20 patients in the LAB-supplemented group and 11 of 20 patients in the placebo group ($p = 0.0012$) reported resolution of abdominal pain. A similar study, using the same formula, was performed in patients who received the treatment for 4 weeks. A significant enhancement of LAB composition in probiotics-supplemented patients was described. Flatulence was rapidly and significantly reduced in the LAB-

treated group, but no difference in bloating was reported between the groups.[101] The same formula was applied in a cross-over trial of 4 weeks duration in 12 patients. A significant reduction in breath hydrogen was registered after 2 hours of ingestion, without a change in total hydrogen production or any symptomatic improvement.[103] A total of 68 patients with IBS were treated for 12 weeks with a vitamin- and plant fiber-enriched diet containing either live or heat-inactivated LAB including 10^9 each of *L. acidophilus*, *L. helveticus,* and *Bifidobacterium* spp.[104] Of the patients, 80 and 40 percent, respectively, reported significant improvements in pain, bloating, constipation, and bowel habits ($p < 0.01$).

8.10.8 Synbiotics in *Helicobacter pylori* Infections

A clinical trial was carried out in a school in a low socioeconomic area of Santiago. *Helicobacter pylori* (Hp) positive children were randomly distributed into four groups: (1) antibiotic treatment (lanzoprazole, clarythromycin, and amoxicillin) (Ab) daily for 8 days; (2) 250 mg *Saccharomyces boulardii* plus 5 g inulin (SbI) daily for 8 weeks; (3) 1 billion *L. acidophilus* LB (LB) daily; or (4) no treatment.[105] A ^{13}C-urea breath test (^{13}C-UBT) was performed before and after the study and the differences in $^{13}CO_2$ over baseline were calculated (DDOB). Hp was eradicated in 66, 12, and 6.5 percent of the children from the Ab, SbI, and LB groups, respectively, while no spontaneous clearance was observed in the children without treatment. A moderate but significant difference in DDOB was detected in children receiving living SbI (76.31; 95 percent CI: 711.84 to 70.79), but not in those receiving LB (+0.70; 95 percent CI: 75.84 to +7.24). Although more studies are needed to confirm the effects and elucidate the mechanisms, it is clearly an interesting observation that Hp infection was eradicated in 12 percent of synbiotic-treated and 6.5 percent of probiotic-treated Hp-infected children. It is likely that other LAB and larger doses of both LAB and prebiotics might achieve much stronger effects.

8.10.9 Synbiotics in Allergy

A synbiotic combination of *L. casei* subsp. *casei* + dextran prevented cedar-pollen induced nasal and ocular symptoms, increased cedar pollen-specific IgE, and increased the number of eosinophils.[106]

In another recent randomized study children > 2 years with atopic dermatitis received either potato starch and *L. rhamnosus*-based synbiotics or the prebiotic alone three times a day for 3 months. The disease score decreased with synbiotic treatment from 39.1 to >20.7 ($P < 0.0001$), and with prebiotic treatment from 39.3 to 24.0 ($P < 0.0001$). No difference was observed after 3 months of treatment ($P = 0.535$).[107]

8.10.10 Synbiotics in Prevention of Cancer

A synbiotic preparation consisting of oligofructose-enriched inulin (12 g) (SYN1), *L. rhamnosus* GG (LGG), and *B. lactis* Bb12 (BB12) (10^{10} cfu), was recently administered in a 12-week randomized, double-blind, placebo-controlled

trial including 37 patients with colon cancer and 43 polypectomized patients.[108] The intervention resulted in significant changes in the fecal microbiota, including elevations of *Bifidobacterium* spp. and *Lactobacillus* spp. and reductions of *Clostridium perfringens*. The intervention reduced colorectal proliferation, the capacity of fecal water to induce necrosis in colonic cells, and improved epithelial barrier function in polypectomized patients. Genotoxicity assays of colonic biopsy samples at the end of the intervention period indicated a decreased exposure to genotoxins in the polypectomized patients. Synbiotic consumption prevented an increased secretion of IL-2 by peripheral blood mononuclear cells in the polypectomized patients and increased the production of interferon-gamma (IFN-γ) in the patients with colon cancer. It was concluded that several colorectal cancer biomarkers may be favorably altered by synbiotic intervention.

8.11 TREATMENT-RESISTANT CONDITIONS

Treatment with synbiotics has failed in two types of patients: those with CD and general intensive care patients.

8.11.1 Crohn's Disease

Attempts in the past to affect CD by probiotic interventions have generally failed. Daily oral administration of 10^{10} of the probiotic LA1, even when instituted early after ileo-cecal resection, failed to exert any protective effect on early endoscopic recurrence in patients with CD. The histological score, the serum inflammatory parameters, and the clinical relapse rate were similar to those of the controls.[109] Two studies with Synbiotic 2000 have also ended with negative outcome. In one study, after an initial treatment with infliximab 63 patients were randomized to daily receive either Synbiotic 2000 or crystalline cellulose as placebo.[110] Median time to relapse was 9.8 and 10.1 months, respectively. In a second study patients following surgery were supplemented with either Synbiotic 2000 or crystalline cellulose as placebo. In the synbiotic-treated group, 7 patients completed the scheduled 24-month treatment, as did and 2 patients in the placebo group.[111] No differences were observed between the two groups either in endoscopic findings or rate of clinical relapse. After 3 months of treatment, the Rutgeerts disease scores were 0.6 ± 0.8 in the synbiotic-treated group and 0.8 ± 1 in the placebo group (NS).

8.11.2 General Intensive Care Patients

Two large studies have been performed in a general intensive care population; one with Synbiotic 2000 and one with Synbiotic 2000 Forte. Synbiotic 2000 (40 billion LAB) was given to 162 patients and only the fibers in the synbiotic composition to 168 patients. No difference was observed in mortality or in multiorgan dysfunction.[112] In the other study Synbiotic 2000 Forte was supplemented to 130 patients twice a day throughout the whole intensive care unit stay (2×400 billion LAB) and

compared to 129 patients supplemented with a cellulose-based placebo. No statistical difference was demonstrated between the groups in the incidence of ventilator-associated pneumonia (VAP) (9 and 13 percent, $P = 0.31$), the rate of VAP per 1,000 ventilator days (13 and 14.6, $p = 0.73$), and hospital mortality (27 and 33 percent, $p = 0.32$).[113]

8.12 CHOICE OF LACTIC ACID BACTERIA AS PROBIOTICS

Only a few probiotic strains have thus far shown ability to eliminate or reduce unwanted proinflammatory molecules such as AGE, ALE, glutenoids, and heterocyclic amines from food. Furthermore, only a minority of several hundred tested probiotic strains have demonstrated ability to suppress inflammation in the body, when supplemented. Especially desirable strains are those that improve immune function by increasing the number of IgA-producing plasma cells, improve phagocytosis, and the proportion of Th1 cells and NK cells.[114] The genetic differences between different LAB are large, said by some to be larger than those between fish and humans. The choice of probiotics for clinical use is critical, especially as strains which carry the same name have often different and sometimes opposite effects. A recent study selected 46 strains of *Lactococcus lactis* from about 2,600 LAB and compared their ability to induce production of cytokines.[115] Even if the different strains carry the same name, their ability to produce pro- and anti-inflammatory cytokines varies widely, which seems to underline the importance of a meticulous choice for clinical studies and use. Some strains, however, are more likely to have strong clinical effects; among them are such strains as *Lactobacillus paracasei* subsp *paracasei, L. plantarum,* and *Pediococcus pentosaceus.* Especially *L. paracasei* has a solid record. It has been shown to induce cellular immunity and stimulate production of suppressive cytokines such as transforming growth factor beta (TGF-β) and Il-10 and to suppress Th2 activity and CD4 T cells,[116,117] to suppress splenocyte proliferation,[118] and to decrease antigen-specific IgE and IgG_1.[119] *Lactobacillus paracasei* was also shown to be the strongest inducer of Th1 and repressor of Th2 cytokines when more than 100 were compared.[120] A recent study in rats compared the ability of four different strains: *L. paracasei*, *L. johnsonii*, *B. longum*, or *B. lactis* to control *Trichinella spiralis*-induced infection; only *L. paracasei* but not the other LAB was able to reduce the infection-associated Th2 response, muscle levels of TGF-β, COX-2, and PGE2, and attenuate infection-induced muscle hypercontractility.[121] An even more recent study compared three probiotic strains—*B. lactis* NCC362, *L. johnsonii* NCC533, and *L. paracasei* NCC2461—and their effects on stress-induced changes in gut permeability and on sensitivity to colorectal distension. Again, only *L. paracasei* but not the other LAB significantly prevented visceral hyperalgesia, reduced visceral pain, and restored normal gut permeability.[122] However, *L. plantarum* also has an excellent record. When the ability of 50 different LAB to control 23 different *Clostridium difficile* strains was studied, only *L. paracasei* and *L. plantarum* were effective in eliminating all *C. difficile* strains; more than half of the tried LAB strains were totally ineffective, and some only against a few.[123] Some LAB can be AU: clarify?

potentiated by simultaneous supply of prebiotic fibers (probiotics + prebiotics = synbiotics) but there are great differences in their ability to utilize semifermentable fibers such as oligofructans. When 712 different LAB strains were tested, only a handful demonstrated ability to ferment inulin and phlein, namely, *L. plantarum* (several), *L. paracasei* subsp. *paracasei, L. brevis,* and *Pediococcus pentosaceus*.[124]

8.13 FINAL WORDS

Aging and various chronic diseases are all associated with an increasingly deranged function of the neuroendocrine axis resulting in an increased status of systemic inflammation.[125–128] This affects the intestinal microbiota, which become reduced both in diversity and numbers. Continuous supplementation of pro- and synbiotics, as well as plant fibers and antioxidants, provides a promising alternative to suppress systemic inflammation, reduce the risk of developing other chronic diseases or complications to disease, and to considerably improve quality of life. Treatment with lactic specific LAB and plant fibers (Synbiotic 2000) has shown a unique ability to suppress inflammation in animal models—neutrophil accumulation in tissues, release of markers of inflammation: myeloperoxidase, malondialdehyde, nitric oxide—and to prevent destruction of tissues.[129] This offers great hope for the future.

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