Invited Review

Prebiotics and Synbiotics in Clinical Medicine

Stig Bengmark, MD, PhD*; and Robert Martindale, MD, PhD†

*Departments of Hepatology and Surgery, University College London (UCL), London, United Kingdom; and
†Department of Surgery, Medical College of Georgia, Augusta, Georgia

ABSTRACT: Pharmaceutical medicine has thus far been unable to stop the increasing global morbidity and mortality both in acute and chronic diseases. Typically, medical practice has focused on reducing the aggressor with treatments such as antibiotics; little interest has been given to efforts to increase the individual's resistance to disease. The increased morbidity has occurred in parallel to a deviation from a large consumption of fresh fruits, vegetables, and tubers rich in live lactic acid bacteria (LAB), plant fibers, and natural antioxidants to an industry-produced diet rich in fat and refined sugar but containing little fiber, antioxidants, and LAB. Plant fiber/prebiotics, plant-derived antioxidants, and LAB/probiotics are known to have the potential to reinforce the immune system of the body and increase resistance to disease. However, this depends on the type of fiber, antioxidant, and strain or combination of strain used. At this stage, only about 10% of the LAB studied have proven strong immunosupportive effects. Similarly, only a few plants contain what has been called superantioxidants, antioxidants 10 or more times stronger than vitamin C and E. Increasing evidence suggests that combining several probiotic bacteria into multistrain probiotics will achieve stronger effects than single-strain probiotics. And combining probiotics and prebiotics into "synbiotics" will further enhance the immunosupportive effects. There is little evidence that a single-strain-based "superprobiotic"/magic LAB will ever be found. Instead, combining several specific and defined probiotics and several key plant fibers into multistrain/multifiber synbiotics appears to be the most promising alternative. Some edge-cutting effects from using multistrain and multifiber compositions are reported both from animal and controlled clinical studies.

The human body meets the outside world by a surface area of approximately 400 m^2. The skin makes up only a miniscule portion, at 2 m^2; the largest contact is through the gastrointestinal (GI) mucosa and respiratory surface epithelium. All human exterior surfaces, with the exception of the most distal part of the respiratory tract, are colonized with a microbial flora, microbes living in symbiosis with their host. These flora are often referred to as the commensal flora (Table 1).

Microbes and plants have developed sophisticated protection systems, in many respects superior to those of man. Most of the food we eat derives from plants, either directly or indirectly *via* animals. Furthermore, natural foods (fresh fruits and vegetables) are a rich source of microbes and, in many cases, are fermented by microbial enzymes before they are consumed.

Fermented foods have been an important food ingredient during man's evolution, and in many cultures, fermented foods remain as a key component of the diet. Our ancestors often stored their food for weeks and months in the soil, and the food, when eaten, contributed large amounts of bacteria to the human digestive tract. It is estimated that our Paleolithic forefathers consumed billions more microbes than are presently consumed in a Western diet. As a consequence, our forefathers had much more diversified and rich microbial flora than we have today. A similar difference is found today when the gut flora of people consuming "Western" diets are compared with those living under more primitive conditions, eating a large variety of fresh raw plants. Paleolithic foods and today's "primitive" foods eaten by various ethnic groups are based on raw plants and consequently contain large amounts of plant fibers, important food ingredients for both man and flora.[1] The present global epidemic of chronic diseases is strongly associated with reduced intake of plants and plant products, fruits, and vegetables. This association is clearly noted for diseases such as arteriosclerosis/coronary heart disease, cancer, and type 2 diabetes. Other diseases not commonly associated with nutrition changes, such as Alzheimer's to polycystic ovary disease, have some links with reduced intakes of plants. Table 2 summarizes the estimated fiber intake for different groups of people and another primate, the chimpanzee, and its association with a parameter of good health, serum cholesterol.

Correspondence: Stig Bengmark, MD, PhD, Departments of Hepatology and Surgery, University College of London (UCL), London Medical School, 69-75 Chenies Mews, London, WC1E 6HX United Kingdom. Electronic mail may be sent to s.bengmark@ucl.ac.uk.

0884-5336/05/2002-0244$03.00/0
Nutrition in Clinical Practice 20:244–261, April 2005

Table 1
The microbe organ: normal flora, gram bacteria, wet weight at various human body surfaces

Gram bacteria, wet weight	
Eyes	1
Nose	10
Mouth	20
Lungs	20
Vagina	20
Skin	200
Intestines	1000–2000

Table 3 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, all foods that are no longer eaten in the quantities they deserve. A common recommendation of minimum daily fiber intake is in the range of 30–35 g per day,[2] which roughly corresponds to about 0.5 kg of fruits and vegetables, or, as often expressed, 5–8 servings of fresh fruits and vegetables per day. The recommendations for children above the age of 2 years are usually expressed as age + 5 g/day.[3] Currently, no precise recommendation exists addressing fiber intake under conditions of disease. Most nutrition "experts" agree that the daily intake of dietary fiber is unsatisfactory in all Western countries, especially among people in lower socioeconomic groups. In the United States, the estimated daily intake of fiber is approximately 14–15 g/day, or about 50% of what is recommended,[4] and far below the 60 to 80 g/d of substrate required to maintain a large bowel flora of 10^{14} microorganisms, known to be typical for an 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. The most common lactic acid bacteria (LAB) in the intestine of rural Asians and Africans consuming large quantities of fresh plant-based foods is *Lactobacillus plantarum.* Western lifestyle and diet disfavors colonization with this and other LABs; *L plantarum* was indentified 20 years ago in about two-thirds of vegetarian North American Seventh-Day Adventists, and only in approximately one-fourth of omnivorous North Americans.[5] A more recent study in a north European population found *L plantarum*, *L rhamnosus*, and *L paracasei* ssp *paracasei* on the rectal mucosa of healthy humans in 52%, 26%, and 17% respectively.[6] The colonization rate with other commonly milk-born probiotic bacteria, such *L casei*, *L reuteri*, and *L acidophilus* was in the same study only 2%, 2%, and 0% respectively.

Table 2
Consumption of fiber in various civilizations and its correlation to a "health parameter" such as cholesterol in serum

	Daily fiber consumption	Cholesterol/s	
		mg/dL	mM/L
Recommended	>30 g/d	<200	<5.18
Actual intake	<20 g/d		
Rural Chinese	80 g/d	127 ± 15	3.3 ± 0.4
Paleolithic ancestors	>100 g/d		
Native Americans > 100 years ago	>100 g/d		
Rural Africans	120 g/d		
Hunters/gathers	123 ± 7	3.2 ± 2.2	
Chimpanzee	>200 g/d	90–135	2.3–3.5

See reference 1 for further information. This table is to a large extent based on information in Eaton SB, Konner M. Paleolithic nutrition: a consideration of its nature and current implications. *N Engl J Med* 1985;312:283–289.

Table 3
Constituents of dietary fiber according to the classification of American Association of Cereal Chemists

- Nonstarch polysaccharides and resistant oligosaccharides
  - Cellulose
  - Hemicellulose
    - Arabinoxylans
    - Arabinogalactans
  - Polyfructoses
    - Inulin
    - Oligofructans
  - Galactooligosaccharides
  - Gums
  - Mucilages
  - Pectins
- Analogous carbohydrates
  - Indigestible dextrins
    - Resistant maltodextrins (from maize and other sources)
    - Resistant potato dextrins
  - Synthesized carbohydrate compounds
    - Polydextrose
    - Methylcellulose
    - Hydroxypropylmethyl cellulose
  - Indigestable ("resistant") starches
    - Lignin
- Substances associated with nonstarch polysaccharide and lignin complexes in plants
  - Waxes
  - Phytate
  - Cutin
  - Saponins
  - Suberin
    - Tannin

See also reference 12.

Commonly consumed cooked root and other starchy vegetables, grains consumed as bread, cereals, and porridge, but also most fruits consumed in Western countries, contain relatively little fiber, usually no more than 1–3 g/serving.[7] The largest amount of consumed plant fiber is provided by resistant starch (raw potato, unripe green banana, cooked but thereafter cooled potato, and whole-grain bread). However, the daily consumption of this type of fiber varies with several hundred percent from one individual to another (approximately 8–40 g/d).[8] The second-largest source of fiber is nonstarch polysaccharides (approximately 8–18 g/d). A third group of fibers is oligosaccharides (onions, artichoke, banana, chicory), which, although important to health, are currently consumed in relatively small amounts (approximately 2–8 g/d).[8]

A Dual Digestive System

Plants are the main provider of literally thousands of beneficial nutritional components other than calories, including antioxidants to short-chain fatty acids (SCFAs). Raw plants are mainly digested in the lower digestive tract, where their nutrients are absorbed. Highly refined plant foods and cooked plant foods, if eaten hot, are preferably digested and absorbed in the upper digestive tract. This is especially true for potato and other root vegetables rich in starch, which have a high glycemic index and contribute to postprandial hyperglycemia. However, when cooked root vegetables are allowed to cool down before eating, the starch will recrystallize, returning a portion to become fiber again. Dried fiber-rich foods such as seeds, nuts, beans, and peas seems to maintain their high fiber content and other nutrient-rich ingredients.

The digestive process of foods in the upper GI tract is driven and controlled by secretory digestive enzymes from mucosa and pancreas. The digestion in the lower digestive tract, however, is almost entirely based on microbial enzymes. This process is of importance for nutrition of both microbes and the host. When the nutrition supply and environment is optimal for the microbial flora, it will grow in size and improve its function. The host will benefit from this as more antioxidants and nutrients are made available by the microbes for the host to absorb. Fibers with ability to increase the flora are called prebiotics. When the concept of prebiotics was introduced, it was thought that only a few fibers, mainly oligosaccharides such as inulin, had the ability to increase gut flora. However, more recent research has demonstrated that several fibers, including resistant starches, β-glucans, and pectins, also possess this ability.

Colonic Foods

The nutrition for the microbial flora comes from 3 main sources: consumed plants, sloughed GI epithelia, and GI secretions. The flora constitute an important link in nitrogen sparing. About 400 g of sloughed cells and several liters of GI secretions, including various proteins, lipids, and mucins, are digested daily by luminal flora. This "recycling" system serves as an important protein and nutrient source for the host. It is an important observation that the colonic mucosa has limited ability to nourish itself from the blood; instead, it depends on specific nutrients, especially SCFAs and particularly butyrate, produced as a product of microbial metabolism. Plants are rich in a wide variety of antioxidants and nutrients, of great importance for human health, but also for maintenance of a rich and healthy flora. It has been estimated that our Paleolithic forefathers received their nutrition from more than 500 different plants. Modern Western diet is based on nutrients received from only a small number of plants; 80% of the nutrients come from 17 plants and 50% of the calories from 8 grains.[9] Furthermore, a significant portion of Western foods are extensively processed, which further reduces the nutritional value of the food. Examples of nutrients and antioxidants that do not survive heating and drying are the conditionally essential amino acid glutamine and the body's main endogenous antioxidant, glutathione. In addition, manipulation and "processing" of foods, especially heating, increases the content of unwanted byproducts of oxidized fatty acids, *trans*-fatty acids, and mutagens. Furthermore, processing reduces or even eliminates the viability of probiotic microbes, normally rich on plants and naturally supplied by eating raw plants. It is known that the degree of milling of grains and the degree of mastication strongly influence the proportion of food reaching the colon. Large particles have been shown to travel more rapidly through the gut, which is why reduced degree of milling and less mastication will reduce the degree of digestibility and increase the amount of food left for fermentation in the colon.

Dietary Fibers, Medical Fibers: Function and Definition

The term *dietary fiber* was coined about 50 years ago and was suggested to include cellulose, hemicellulose, and lignin,[10] all indigestible constituents of the cellular walls of plants. The concept was defined about 20 years later as "plant fibers and lignin, which are resistant to hydrolysis by the digestive enzymes of man."[11] A recent definition by 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 fiber includes polysaccharides, oligosaccharides, lignin, and associated plant substances. Dietary fibers promote beneficial physiologic effects including laxation, blood cholesterol attenuation, and blood glucose attenuation."[12] Table 3 summarizes the what AACC regards as dietary fibers. According to this definition, some noncarbohydrates like waxes, phytate cutin, saponins, suberin, and tannins are also included in the concept. These substances are sometimes referred to as those associated with nonstarch polysaccharide and lignin complex in plants. Of the many substances shown on the list, only a few are presently used for clinical purposes (eg, as medical fibers).

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

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

Consumption of medical fibers is always a surrogate for inadequate consumption of 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 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 always be remembered, however, 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. Juicing machines can be important nutrition tools for nutrition of the very sick patients, those in the intensive care units (ICUs) being no exception. Supply of fresh juices from various raw fruits and raw vegetables could be considered for critically ill patients, even those who are requiring tube feeding. The goal always is to supply each individual with the recommended daily 5–8 servings of fresh fruits and vegetables.

Health Benefits From Eating Fiber

Evidence-based information on beneficial effects from consumption of plant fibers/prebiotics exists especially for 2 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. Sugars "entrapped" in plant cells are 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; see, for example, the difference between raw and different types of cooked potato (Table 4). Studies suggest that the most pronounced effects of fibers on glycemic index are obtained by water-soluble fibers. Guar-gum, by far the most-tried fiber, reduces blood glucose about 44% according to 15 different studies.[13] It is too early to determine if long-term consumption of fiber prevents development of diabetes mellitus. However, fiber, when regularly supplied to patients with diabetes mellitus, significantly reduces the level of blood glucose and the need for insulin.

Lipid Control/Prevention of Coronary Heart Disease

Soluble fibers such as pectin, guar gum, and β glucans (oat) have repeatedly been shown to reduce blood cholesterol both in hypercholesterolemic and normocholesterolemic individuals, effects not found when insoluble fibers such as cellulose and wheat bran were used. All water-soluble fibers are gel-forming. It has also been suggested that the gel formed in the GI tract could inhibit cholesterol absorption and affect bile acid absorption and metabolism. Soluble fibers are excellent substrates for production of SCFAs in the large intestine, which might also influence the levels of cholesterol(s). Studies both in animals and in humans suggest that it is especially propionic acid that is hypocholesterolemic.[14] The effect of fiber intake on the risk of coronary heart disease was recently the object of a meta-analysis.[15] This review identified 17 studies, of which 16 reported protective effects, which were statistically significant in 14. The general observation was the effect of whole-grain cereals and cereal-derived fibers was stronger than that of fruit and vegetable fibers. Again, the mechanism for effects is not clear. However, fiber consumption, in addition to its cholesterol-reducing effects, also reduces clotting

Table 4
Content of fiber in various plant-derived foods, g fiber per 100 g food

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

and increases fibrinolysis, which are also very important for prevention of both the building of plaques in the arterial walls and thrombosis formation.

Some Commonly Used Fibers

Amino acids such as arginine, glutamine, histidine, taurine, various sulfur-containing and -related amino acids, polyamines, and ω-fatty acids and numerous vitamins and antioxidants are delivered to the body from plants. One cannot expect any specific nutrient or antioxidant to be delivered at the level of colon, if not existing in the foods eaten. It is thus important that the fibers be chosen with knowledge and care. It is also always important to remember that key nutrients such as ω-3 fatty acids, glutamine, glutathione, and several other nutrients do not tolerate either processing or storage. Dried fiber cannot be expected to contain any larger amounts of these key nutrients because they are mainly derived from unprocessed foods. It is therefore highly desirable that, whenever possible, the supply of commercial nutrition formulas be complemented by a supply of fresh fruit and vegetable juices, locally produced at the wards or in ICUs.

It is highly desirable that several types of fiber be supplied in parallel and that both soluble and nonsoluble fibers be used. Oat fiber is mainly metabolized in the proximal colon, whereas wheat fiber is known to be effective in the distal part of the colon (eg, the part of colon where most cancers are localized). Oat has mainly shown sepsis-reducing effects, whereas wheat has mainly been effective in cancer prevention. Table 5 summarizes sources rich in some important amino acids. In general, seeds, nuts, beans, and peas are rich sources of these and most other amino acids. Soy especially seems to be a reliable source, leading one to contemplate using soy as a staple food. Table 6 summarizes the content of some antioxidants and minerals in some plant-derived foods. Again seeds, nuts, beans, peas, fresh fruits, and vegetables are rich in antioxidants and minerals, whereas common Western foods, fast foods, and dairy products are relatively poor sources not only of antioxidants but also minerals.

Medical Fibers

Here follows a description of some interesting commonly used so-called medical fibers.

Algal Fibers

Most of the algal fibers are resistant to hydrolysis by human endogenous digestive enzymes but are, to various degrees, fermented by colonic flora. The soluble fibers consist in lamarans (a sort of β-glucan associated with mannitol residues), fucans (sulfated polymers associated with xylose, galactose, and glucuronic acid), and alginates (mannuronic and guluronic acid polymers). The insoluble algal polymers exist mainly in cellulose. It is still questionable whether fucans are fermentable, but fermentation of alginates yields high levels of acetate (80%), and lamirans yield preferably butyrate (16%). The physiologic effects of various algal fibers have just begun to be investigated, and it is most likely that these fibers within a few years will be routinely used in clinical enteral nutrition (EN) formulas.

Fructans

Fructans serve in the plantlike starch and sucrose as reserve carbohydrates. They are also produced by some bacteria and fungi. Fructans are said to enhance tolerance to stress such as cold and draft and make it possible for plants to survive under harsh conditions. The most well-known fructans are inulin (rich in chicory, artichoke, onions, banana) and phleins (rich in various grasses). It is mainly inulin that has been evaluated in human nutrition. Various oligosaccharides are especially known for their ability to encourage growth of beneficial *Lactobacilli* and *Bifidobacteria* in the large intestine, thereby reducing the amount of potentially pathogenic microorganisms in the intestine. Increase in the *Bifidobacteria* flora is regarded as especially favorable because *Bifidobacteria* are generally believed to produce and deliver important vitamins, including thiamine, folic acid, nicotinic acid, pyridoxine, and vitamin B_{12}. Recently, another fructan called neokestose (found in onion) has shown even better ability than inulin to promote growth of LAB.[16] Supplementation of fructans reduces serum concentrations of insulin, cholesterol, triacylglycerol, and phospholipids. It also promotes resorption of calcium and other minerals, which might be useful in prevention of osteoporosis. Other oligosaccharides might possess health-promoting effects. Among these are those extracted from peas and beans like the soya bean oligosaccharide (raffinose and stachyose) and pyrodextrin, produced by pyrolysis of maize and potato starch. Oligosaccharides are increasingly used by the food and pharmaceutical industries.

Glycomannans

Glycomannan, a glucose/mannose polymer derived from a plant called *Amorphophallus konjak*, has several English names, including devil tongue, elephant yam, and umbrella arum. It has unique hydroscopic abilities and will, on contact with water, swell and form a viscous gel, which like other gels 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 mainly been used in Japan and other Asian countries to treat diabetes, hypertension, and hypercholesterolemia. Dietary supply of konjak mannans has been shown in experimental animals to alter the

Table 5
Content of some amino acids, mg per 100 g food, in some amino acid–rich food compared to typical Western foods such as hamburgers, French fries and ketchup

Alanine		**Arginine**		**Cysteine**		**Glycine**	
Gelatin	8570	Gelatin	6000	Wheat germs	750	Sesame seeds	1900
Dry yeast	2250	Pumpkin seeds	4030	Gelatine	670	Peanuts	1850
Soya beans	1530	Soya protein	3760	Lamb	600	Soya beans	1420
Sesame seeds	1410	Peanuts	3600	Sesame seeds	520	Chicken	1410
Beef	1340	Sesame seeds	3330	Wheat bran	440	Almonds	1240
Chicken	1270	Soya beans	3330	Oat flakes	390	Beef	1130
Fish	1200	Almonds	2500	Almonds	360	Turkey	1110
Peanuts	1180	Sunflower seeds	2400	Walnuts	350	Fish	1000
Pumpkin seeds	1160	Brazil nuts	2390	Peanuts	340	Lentils	990
Sunflower seeds	1120	Peas and lentils	2050	Beans	315	Pig meat	910
Wheat germs	1080	Shrimps	2000	Soya beans	310	**HAMBURGERS**	900
Lentils	1030	Baker's yeast	2000	Chicken and turkey	290	Salmon	880
HAMBURGERS	990	Parmesan cheese	1560	Parmesan cheese	270	Peas	860
Almonds	940	Meat and fish	1500	Peas and lentils	240	Beans	820
Peas	900	**HAMBURGERS**	950	**HAMBURGERS**	110	Walnuts	760
Cheeses	900	Cereals	500	Cheeses	100	Cheeses	650
Walnuts	690	**FRENCH FRIES**	140	Banana	60	Banana	190
Banana	220	**KETCHUP**	125	Figs	60	**FRENCH FRIES**	100
FRENCH FRIES	125	Vegetables	100	**FRENCH FRIES**	28	**KETCHUP**	29
KETCHUP	40	Fruits	50	**KETCHUP**	5		

Glutamic acid		**Histidine**		**Leucine**		**Methionine**	
Parmesan cheese	9750	Soya protein	2500	Soya beans	2460	Brazil nuts	1010
Gelatine	9150	Parmesan cheese	1630	Pumpkin seeds	2150	Sesame seeds	900
Low-fat cheese	6490	Tuna fish	1220	Sesame seeds	2150	Cheeses	900
Soya beans	6440	Sardines	950	Peanuts	1930	Gelatin	670
Peanuts	6350	Pheasant	940	Lentils	1710	Fish	600
Almonds	5930	Cheese, low fat	940	Almonds	1550	Chicken	570
Sunflower seeds	5580	Soya beans	930	Beans	1650	Beef	560
Sesame seeds	4940	Eel	880	Walnuts	990	Pumpkin seeds	550
Lentils	3900	Dry yeast	770	Peas	620	Dry yeast	520
High-fat cheese	3770	Beef	770	**FRENCH FRIES**	190	Sunflower seeds	490
Peas	3490	Peanuts	750	Banana	170	**HAMBURGERS**	360
Oat flakes	3000	Pumpkin seeds	680	**KETCHUP**	50	Beans	325
Beans	2840	Sesame seeds	680			Peanuts	280
Cereals	2500	Lentils	650			Peas	260
HAMBURGERS	2060	**HAMBURGERS**	590			Cereals	200
Meat and fish	2000	Gelatin	580			**FRENCH FRIES**	48
KETCHUP	600	**FRENCH FRIES**	60			**KETCHUP**	11
FRENCH FRIES	460						
Vegetables	100						
Fruits	50						

Proline		**Serine**		**Tryptophan**		**Tyrosine**	
Gelatin	13100	Parmesan cheese	2410	Parmesan cheese	570	Parmesan cheese	2340
Parmesan cheese	4880	Soya beans	1910	Sesame seeds	470	Cheeses	1550
Cheeses	3500	Wheat germs	1550	Dry yeast	430	Peanuts	1260
Soya beans	1580	Peanuts	1500	Pumpkin seeds	430	Soya beans	1200
Sesame seeds	1360	Beans	1350	Cheese, low fat	400	Sesame seeds	1130
Peanuts	1300	Cheeses	1400	Wheat germs	330	Pumpkin seeds	1120
Almonds	1230	Sesame seeds	1310	Peanuts	310	Sunflower seeds	930
Sunflower seeds	1180	Lentils	1250	Tuna fish	270	Peas	860
Chicken	1170	Peas	1000	Turkey and chicken	250	Lentils and beans	750
Lentils and beans	1030	Almonds	900	Feta cheese	240	Beef	740
Beef	930	Fish	900	Hazelnuts	220	Fish	700
Fish	850	Beef	880	Fish	200	Almonds	710
Peas and beans	810	Walnuts	780	**HAMBURGERS**	165	**HAMBURGERS**	570
HAMBURGERS	670	Chicken	760	Soya beans	135	Chicken	550
Walnuts	550	**HAMBURGERS**	640	Peas	110	Milk	130
Banana	230	Cereals	500	Tofu	95	**FRENCH FRIES**	70
FRENCH FRIES	60	Pasta	500	**FRENCH FRIES**	55	**KETCHUP**	15
KETCHUP	30	Milk	190	**KETCHUP**	35		
		FRENCH FRIES	120				
		KETCHUP	40				

Table 6
Content of some vitamins and minerals in some vitamin-mineral-rich foods compared to typical Western foods such as dairy products and hamburgers, French fries and ketchup

Vitamin C mg/100 g		**Vitamin E mg/100 g**		**β Carotene mg/100 g**		**Folic acid μg/100 g**	
Rose hip dried	270	Wheat germ oil	149.0	Carrot	9800	Yeast	1000
Black currents	210	Sunflower oil	59.0	Rosehip, dry	7000	Black eye beans	635
Guava	184	Grapeseed oil	29.0	Pumpkin seeds	6500	Chicken peas	560
Persil	180	Sunflower seeds	28.0	Squash seeds	6500	Beans	425
Nettles	175	Pumpkin seeds	28.0	Kale	5350	Lentils	425
Yellow pepper	170	Squash seeds	26.0	Apricots	4350	Soya beans	425
Horseradish	152	Almonds	24.0	Chives	3400	Wheat germs	330
Kale	120	Rapeseed oil	23.0	Watercress	2800	Wheat bran	260
Fennel	100	Hazelnuts	21.0	Nettles	2400	Spinach	195
Brussels sprouts	85	Olive oil	12.0	Mango	2350	Peanuts	105
Broccoli	83	Wheat germs	11.0	Red pepper	1790	Orange	30
Cauliflower	73	Caviar	10.0	Lettuce	1600	Banana	20
Strawberries	65	Eel	8.0	Peach	1290	**CHEESE 28%**	18
Kiwi	65	Green pepper	3.1	Papaya	1200	**FRENCH FRIES**	17
Orange	53	Spinach	2.9	Prunes	1190	Fish	15
Lemon	53	Walnuts	2.6	**KETCHUP**	**1150**	Potato	13
Grapefruit	39	Black currants	2.1	Broccoli	920	Pasta	10
KETCHUP	15	**FRENCH FRIES**	2.0	Dill	600	Rice	10
Potato	11	**KETCHUP**	1.5	Brussels sprouts	530	**HAMBURGERS**	7
FRENCH FRIES	4	**CREAM 40%**	1.0	Beans	400	**KETCHUP**	5
Milk	0	**CHEESE 28%**	0.5	**CREAM 28%**	144	**Milk**	5
CREAM 40%	0	**HAMBURGERS**	0.3	**CHEESE 28%**	100	**CREAM 40%**	4
HAMBURGERS	0	Milk	0	**HAMBURGERS**	8	Sausage	4
CHEESE 28%	0			Milk	4		
				FRENCH FRIES	0		

Glutathione Nmol/g		**Zinc mg/100 g**		**Magnesium mg/100 g**		**Calcium mg/100 g**	
Broccoli (flower)	440	Sesame seeds	10.2	Pumpkin seeds	540	Baking powder	11300
Parsley (leaf)	400	Flax seed	7.8	Squash seeds	540	Parmesan cheese	1380
Spinach	400	Pumpkin seeds	7.5	Wheat bran	480	Sesame seeds	980
Yellow squash (fresh)	320	Squash seeds	7.5	Brazil nuts	355	**CHEESE 28%**	750
Yellow squash (frozen)	70	Pecan nuts	5.5	Sesame seeds	350	Agar	600
Potato (raw)	230	Sunflower seeds	5.1	Wheat germs	290	Nettles	490
Potato (boiled 15 min)	110	Beef	4.4	Almonds	280	Persil	340
Tomato	170	Soy protein	4.4	Soya beans	265	Dill	343
Green pepper	170	Brazil nuts	4.2	Cashew nuts	260	Peas	300
Tangerine	140	**CHEESE 28%**	4.1	Rosehip, dry	240	Beans	300
Broccoli (stem)	140	**HAMBURGERS**	3.9	Oat bran	235	Almonds	265
Cauliflower	130	Peas	3.8	Peanuts	235	Sunflower seeds	265
Orange	130	Lentils	3.1	Beans	190	Flax seeds	198
Cornmeal	130	Peanuts	3.1	Peas	150	Sardines	190
Peas	90	Bacon	3.0	Cocos flakes	90	Brazil nuts	180
Carrot	70	Walnut	3.0	Lentils	80	**CREAM 40%**	135
Pear	40	Beans	2.8	Cheese 28%	35	**MILK**	120
Banana	20	Dill	1.8	**FRENCH FRIES**	35	Fish	100
Apple	20	**FRENCH FRIES**	0.4	**HAMBURGERS**	20	Bread	48
Rye bread	20	Milk	0.4	**KETCHUP**	18	Butter	18
Green beans	15	**CREAM 40%**	0.3	**MILK**	15	**HAMBURGERS**	10
Oatmeal	<1	**KETCHUP**	0.2	**CREAM 40%**	14	**FRENCH FRIES**	9
Corn flakes	<1			Butter	3	**KETCHUP**	7

flora and reduce tumorigenesis. It is also effective to control diarrhea in EN, especially in elderly patients known to have a reduced *Bifidobacteria* flora.

Oat Gum

Oat contains a series of interesting compounds, which is the reason why an increasing part of the world production of oat goes to the pharmaceutical and cosmetic industries. The amino acid pattern of oat is rather 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. Oat was extensively used before synthetic antioxidants were available 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 known to enhance natural killer cell activity and to suppress tumor growth.[17] Oat is also rich in polyunsaturated fats/polar lipids such as phosphatidylcholine, known for its protective effects of mucosal surfaces.

Pectin

Pectin also is an interesting fiber, extensively used by pharmaceutical and food industry. It has a unique ability to form gels and is commonly used as a carrier of pharmacologically active substances and is common in infant foods. A recent and important finding is that pectin is a very strong antioxidant against the 3 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. Pectins have shown strong protective and healing effects on gastric but also on intestinal mucosa in experimental studies, not inferior to what is observed with H_2-blockers, proton inhibitors, and surface-protection agents.[18,19] Pectin appears ideal for perioperative use and facilitates maintenance of gastric acidity, which is important for prevention of colonization of the stomach with pathogens. Furthermore, pectin is an excellent substrate for microbial fermentation. The only problem with pectin is that it has a tendency to clog feeding tubes, therefore requiring special attention.

Fermentation of Fibers by LAB

Not all fibers are easily fermented in the gut. Among the more fermentation-resistant fibers are wheat fibers that usually are not digested until they reach the descending colon. In addition, oligofructans (inulin or phleins) are difficult to ferment, and only a small minority of LABs are able to do so. When the ability of 712 different LABs to ferment oligofructans was studied, only 16 of 712 were able to ferment the phleins; and 8 of 712, inulin.[20] Apart from *L plantarum*, only 3 other LAB species, *L paracasei* subsp. p*aracasei*, *L brevis*, and *Pediococcus pentosaceus*, were able to ferment these relatively resistant fibers. A more recent study investigated the ability of 28 LABs to ferment pure fructooligosaccharides (FOS). All *L plantarum*, *L casei*, and *L acidophilus* strains studied and most *Bifidobacteria* used FOS, in contrast to yogurt bacteria such as *L bulgaricus* and *Streptococcus thermophilus* and also *L strain* GG,[21] which were all unable to ferment these fibers.

Potential Negative Effects of Dietary Fibers

Few negative effects of fiber consumption are reported in the literature. However, consumption of dietary fiber may partly be responsible for the lower bioavailability of carotenoids both from food and from purified supplements. The effects of different kinds of dietary fiber on the absorption of carotenoids and α-tocopherol was investigated in healthy young women, who were supplemented an antioxidant mixture consisting of β-carotene, lycopene, lutein, canthaxanthin, and α-tocopherol, together with a standard meal.[22] The meal, which did not contain any additional dietary fiber, was enriched with 0.15 g/kg body weight of pectin, guar gum, alginate, cellulose, or wheat bran. The increases in plasma carotenoid and α-tocopherol concentrations were followed over 24 hours. The uptake of β-carotene was significantly ($p < .05$) reduced by the water-soluble fibers pectin, guar gum, and alginate (mean decrease 33%–43%) but not by cellulose and wheat bran. All tested fibers significantly reduced the uptake of lycopene and lutein by 40%–74% ($p < .05$). Also, the uptake of canthaxanthin was reduced by dietary fiber ($p = .059$). No effect was observed on the uptake of α-tocopherol.

Clinical Experience With Supplemented Prebiotics

Prebiotics 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 has been suggested that reduced fiber intake could play a role in its pathogenesis. In a case-control study, a randomized sample of 291 children with idiopathic chronic constipation was compared with 1602 healthy controls.[23] Nutrition data were obtained by dietary history complemented with 3-day dietary records. Constipation was clearly negatively correlated with low intake of cellulose and pentose fibers ($p < .001$). Constipated children also demonstrated a lower caloric and nutrient intake ($p < .001$), lower body weight/height ($p < .001$), and higher prevalence of anorexia ($p < .001$) than controls.

FOS may also have potential benefits in constipation because they exhibit many soluble dietary fiber-like properties. In a recent study, a total of 56 healthy infants aged 16–46 weeks (mean age 32 weeks) were randomly assigned to receive either 0.75 g FOS or placebo added to a serving of cereal for 28 days.[24] Consumption of FOS led to regular and softer stools, without diarrhea, and to less-reported frequency of symptoms associated with constipation, hard stools, or skipped days without stool. 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 ($p = .02$). There were no differences between the groups for crying, spitting up, or colic.

Prebiotics to Prevent and Treat Diarrhea

In a large randomized study, in acutely ill medical and surgical patients who required EN for a minimum of 5 days, supplementation of hydrolyzed guar gum was compared with fiber-free EN. The incidence of diarrhea was 9% with fiber supplementation compared with 32% with fiber-free nutrition ($p > .05$).[25] One of the effects of certain fibers, especially oligosaccharides, is to increase the bioavailability and absorption of zinc. Zinc supplementation was evaluated in a randomized study in 3- to 59-month-old children in Bangladesh. Zinc supplementation lowered both the incidence of diarrhea and the duration of diarrhea.[26] In another study in Bangladesh, 250 g/L of green (unripe) banana (equivalent to 2 fruits) or 2 g pectin/kg food was supplemented to rice for children with persistent diarrhea.[27] The amount and frequency of stools, the duration of diarrhea, number of vomiting episodes, use of oral rehydration, and volume of infused IV fluid solutions given were all significantly reduced in the children supplemented with green banana and pure pectin. Recovery on the third day was seen in 59% in the green-banana group, in 55% in the pectin group compared with 15% in the rice-only control group.

Prebiotics in Inflammatory Bowel Disease (IBD)

Although IBD is a typical Western disease, there is presently no evidence that lack of fiber in the diet plays any role in the pathogenesis of either ulcerative colitis (UC) or Crohn's disease. Despite that, attempts have been made to treat these diseases with various plant-derived fibers. The ability of maintaining remission in UC patients of a daily supply of 10 g of *Plantago ovata* seeds (also called psyllium or ispaghula husk) was compared with daily treatment of 500 mg of mesalamine and a combination of the 2.[28] Twelve months of treatment led to no statistical difference in clinical benefits between the 3 groups. Germinated barley foodstuff, a by-product from breweries, rich in hemicellulose and glutamine, was evaluated in 39 patients with mild to moderate active UC.[29] Daily supply of 30 g reduced significantly disease activity, increased concentration of SCFAs, and increased the numbers of *Bifidobacterium* and *Eubacterium* in stool. A controlled study was recently reported in 22 patients plus 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%) and also improvement in abdominal pain and symptoms of reflux. All the treated patients tolerated large doses of fiber, and none showed any sign of relapse of the colitis.[30] Butyrate has recently been shown in patients with ulcerative colitis to inhibit NFκB activation of lamina propria macrophages and reduce the number of neutrophils in crypts and surface epithelia and the density of lamina propria lymphocytes/plasma cells, all findings that correlate well with the observed decreased disease activity.

Prebiotics in Irritable Bowel Syndrome (IBS)

The etiology of IBS remains obscure. It has been observed, however, that feces of IBS patients contain lower concentrations of total SCFA, acetate, and propionate but higher concentration and percentage of *n*-butyrate than that of individuals with healthy intestines. Fecal flora from IBS patients also produce significantly less SCFA in an *in vitro* fermentation system when incubated with various carbohydrates and fibers. It has been observed that consumption of fiber can trigger pain or bloating in IBS patients. It is also observed that mast cells, eventually activated by nonfermented fibers, might perturb nerve endings in the colonic mucosa. A recent study showed that 34 of 44 IBS patients (77%) had an increased area of mucosa occupied by mast cells ($p < .001$) compared with controls. The number of degranulating mast cells increased 150% ($p = .026$) in the IBS patients.[31] Furthermore, mast cells of IBS patients also spontaneously released more tryptase ($p = .015$) and histamine ($p = .015$). Mast cells located within 5 μm of nerve fibers were observed to be increased by approximately 300% in IBS patients ($p < .001$). Interestingly, a significant correlation was observed between density of mast cells close to nerves and severity ($p < .001$) and frequency of abdominal pain/discomfort ($p = .003$). Although probiotics still may be useful in IBS, prebiotics seems to offer little benefit.

Prebiotics 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; minerals such as phosphorus, potassium, magnesium; and 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 also in elderly subjects, both women and men.[32,33] Good results are also reported from studies of Chinese women consuming soy products. Of pure fibers available, the effects of oligosaccharides have been studied most widely. Calcium absorption, bone calcium content, bone mineral density, bone balance, and bone formation/bone absorption index were reported to significantly increase in rats after 3 weeks of supplementation with a mixture of inulin and FOS.[34]

Prebiotics to Control Weight

No major effects on body weight by supplementation of only prebiotic fiber 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. One hundred eight of 135 members completed the trial: 23 controls, 45 ingesting ispaghula granulates, and 40 ingesting bran sachets.[35] 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 ($p > .05$ for both groups). Although supply of dietary fiber immediately before meals reduced the feeling of hunger, it did not provide any additional benefits to the weight reduction. In a recent crossover-designed study, supplementation with 27 ± 0.6 g/d of fermentable fibers (pectin, β glucan) was given *vs* supplementation of similar amounts of nonfermentable fiber (methylcellulose). Parameters under evaluation included the ability to decrease *ad libitum* energy intake, hunger, and to increase satiety and cause spontaneous body weight and fat losses.[36] The daily satiety level was significantly higher with nonfermentable than with fermentable fibers ($p = .01$), but no differences in reported energy intake, body weight, or loss of body fat could be observed.

Prebiotics in Clinical Nutrition Solutions

Practicing physicians, dietitians, nutritionists, and nurses are increasingly aware of the necessity of providing substrate for the flora, colonic food, also to very sick patients. Industry has also been quick to provide suitable fiber-rich formulas for EN. It is not long since the need for fiber in the nutrition of the very sick was totally ignored. Today, it is possible to supply the daily recommended intake of 30 g and even more. Most of the companies provide formulas containing about 15 g of fiber per liter (see Table 7). Most of the nutrition solutions are based on 3 different sources of fibers. Novartis (Nyon, Switzerland) provides formulations with 20 g/L in Europe but not yet in the United States. Also, Fresenius (Bad Hamburg, Germany) has in Europe a series of products containing 20 g, called Fresubin, mainly based on inulin but with added oat fiber and resistant starch. Ross (Columbus, Ohio) manages to provide even more than 20 g/L mainly by mixing 5 different fibers into the solutions. Nutricia (Amsterdam, The Netherlands) provides formulations with 6 fibers but in smaller amounts. Almost all solutions contain soy fiber, some guar gum, or gum arabic; a few solutions contain oat, FOS, or cellulose; 2, either acacia or fruits and vegetables; and only 1 has either pectin or resistant starch. The solutions are this far dominated by insoluble fibers (soy polysaccharides and cellulose), the percentage varying from 100% (Advera and Jevity 1.0; Ross Products) to 48% (Isosource 1.5, Isosource VHN, Novasource Pulmonary; Novartis). Fibersource Std and Fibersource HN (Novartis) contain 75% insoluble fibers. On the other hand, Diasip and Diason (Nutricia) contain as much as 80% soluble fiber.

Table 7
Fiber content of selected enteral formulas

Product	Manufacturer	Fiber (g/L)
Jevity 1.2, Jevity 1.5	Ross	22
Glucerna Select	Ross	21.1
Glucerna, Promote with fiber	Ross	15.6
Glytrol, Replete with fiber	Nestle Nutrition (Glendale, CA)	15
Replete with fiber	Nestle Nutrition	15
Jevity 1.0	Ross	15
Nepro	Ross	14.4
Choice DM	Novartis	14
Ultracal	Novartis	14
Cubison, Diason, Nutrison Multifibre	Nutricia	14
Resource Diabetic	Novartis	12.8
Fibersource, Fibersource HN, Isosource VHN, Ultracal Plus HN	Novartis	10
Probalance	Nestle Nutrition	10
Equalyte	Ross	10

Some food supplements on the market today contain as much as 25 g fiber per liter. Soon, there will be available nutrition solutions containing 30 g or more per liter. It should be possible to increase especially the amount of soluble fibers. Some excellent fibers such as pectin are clearly underused, probably as they create problems with clogging of tubes. However, this excellent fiber should be much more commonly used because tube clogging can be overcome both by choice of type of pectin and by microgranulation of the fiber. In addition, FOS of various types are presently underrepresented in existing formulations. Other interesting fibers to look at in the future are various alginates, chitosans, and glycomannans. It is likely that fiber solutions will contain 10 or more different natural fibers. The trend to use fruits and vegetables will also increase. In the future, formulas may contain live LAB.

Prebiotics Supplemented to EN Solutions

Prebiotics Supplemented to Control Diarrhea in Patients Receiving Parenteral Nutrition (PN)

Tube feeding may be discontinued because of GI side effects, particularly diarrhea. Although the causes of diarrhea are diverse, the EN solution *per se* is frequently suspected of playing a leading role in causing diarrhea. One hundred patients receiving EN with a standard nutrition solution were randomly chosen to either receive supplementation with 20 g of soluble fiber (containing partially hydrolyzed guar gum) per 1000 mL.[37] Seventy patients received the supplementation and 30 patients served as controls. The patients receiving supplementation with soluble fiber had decreased incidence of diarrhea but increased flatulence. EN was not discontinued because of GI side effects in any of the 70 patients receiving fiber supplementation. In the 30 patients receiving standard nutrition without fiber supplementation, the EN was discontinued in 4 patients ($p < .05$). A similar study was undertaken in patients with severe sepsis and septic shock.[38] All patients were mechanically ventilated and treated with catecholamines and antibiotics. Enteral feeding was provided through a nasogastric tube for a minimum of 6 days. The patients were consecutively enrolled and randomly assigned to receive either an enteral formula supplemented with 22 g/L partially hydrolyzed guar or an isocaloric, isonitrogenous control feeding without fiber. Twenty-five patients fulfilled the criteria for data analysis. Soluble fiber was supplemented to 13 patients. The mean frequency of days with diarrhea was significantly lower in patients receiving fiber than in those receiving standard alimentation ($8.8 \pm 10.0\%$ *vs* $32.0 \pm 15.3\%$; $p = .001$). The whole group of fiber-fed patients experienced fewer days with diarrhea per total feeding days compared with controls (16/148 days [10.8%] *vs* 46/146 days [31.5%]; $p < .001$) and also a lower mean diarrhea score (4.8 ± 6.4 *vs* 9.4 ± 10.2; $p < .001$).

Prebiotics to Control Infections

Unfortunately, too few studies evaluating effects of supply of various plant fibers in surgical and ICU patients are available in the medical literature. In addition, most of the studies in the literature are based on supplementation of not only fiber but a combination of several nutrition supplements. An example is a recent study designed to evaluate the effects of a high-protein formula enriched with arginine, fiber, and antioxidants compared with a standard high-protein formula for early EN in critically ill patients.[39] Two hundred twenty patients were enrolled in a prospective, multicenter, single-blind, randomized trial in 15 ICUs. The supplemented group had, in comparison with nonsupplemented controls, a lower incidence of catheter-related sepsis (0.4 episodes/1000 ICU days) than the control group (5.5 episodes/1000 ICU days) ($p < .001$). No differences were observed between the groups in incidence of ventilator-associated pneumonia, surgical infection, bacteremia, or urinary tract infections. Nor were any significant differences observed in ICU mortality, in-hospital mortality, or long-term survival. This study and others demonstrate clearly the relatively small advantage of attempts to improve outcome in critically ill patients with the use of so-called immunonutrition formulas. This should make trials with the use eco-immunonutrition (supplementation of both probiotic bacteria and fibers) highly interesting.

Prebiotics + Probiotics = Synbiotics

Natural foods supplies both LAB and fiber. Unfortunately, few studies have looked at the synergistic effects of simultaneous supply of the 2 in synbiotics. Most studies published in the literature have tried either pro- or prebiotics. Most of the studies published this far have involved the following 2 compositions:

1. A 1-LAB 1-fiber composition, produced by fermentation of oatmeal with *L plantarum* strain 299, containing 10^9 of LAB and approximately 10 g oat fiber (Probi AB, Lund, Sweden).[40] In a few studies, a commercial fruit juice containing 10^7 of a related *L plantarum* strain called 299V (PRO VIVA; Skånemejerier, Malmö, Sweden) was evaluated.
2. A 4-LAB 4-fiber composition, called Synbiotic 2000 (Medipharm AB, Kågeröd, Sweden; and Des Moines, IA) consisting in a mixture of 10^{10} (and more recently a Synbiotic FORTE with 10^{11}) of each of 4 LABs: *Pediacoccus pentosaceus* 5 to 33:3, *Leuconostoc mesenteroides* 32 to 77:1, *L paracasei* subsp paracasei 19, and *L plantarum* 2362 and 2.5 g of each of the 4 fermentable fibers (prebiotics): β glucan, inulin, pectin, and resistant starch.[41,42]

Most of the LABs used by food industry have no or limited ability to ferment strong bioactive fibers such as inulin or phlein, no ability to adhere to human mucus, low antioxidant capacity, and most importantly, do not survive the acidity of stomach and bile acid content. Strong bioactivity can often not be expected from LAB such as yogurt bacteria, chosen mainly for their palatability. Most of the LABs presently used in sick patients were originally identified in plants. The LABs used in the synbiotic studies have been selected because of their bioactivity.[43]

Clinical Experience With Synbiotics in Chronic Conditions

There are good reasons to expect beneficial effects of synbiotic treatment in chronic conditions such as cancer, chronic kidney disease, chronic lung disease, etc, but systematic studies are this far limited to arteriosclerosis, Crohn's disease, and chronic liver disease.

Synbiotics in Arteriosclerosis

An impressive and statistically significant reduction in serum fibrinogen and low density lipoprotein cholesterol was observed when the rose-hip drink PRO VIVA (Probi AB), containing oat fiber and *L plantarum* 299V (LP299V) in rather dilute concentrations (LP299V 5×10^7) was supplied in a 6-week, controlled study of 30 middle-aged men with moderately elevated serum cholesterol levels.[43] In a second controlled, randomized, double-blind trial by the same group, the effects of LP299V and oat fiber on lipid profiles, inflammatory markers, and monocyte function in heavy smokers were studied.[44] Over a 6-week period, 36 healthy volunteers (18 women and 18 men) aged 35 to 45 years drank 400 mL/day a product with bacteria (5×10^7) or without bacteria. Significant decreases in systolic blood pressure ($p < .001$), serum leptin levels ($p < .001$), and serum fibrinogen levels ($p < .001$) were recorded in the treated group, but no such changes observed in the control group. Decreases in serum levels of F(2)-isoprostanes (37%) and interleukin 6 (IL-6; 42%) were also observed in the group supplied the LAB-supplemented drink. Monocytes isolated from the treated subjects showed significantly reduced adhesion ($p < .001$) to native and stimulated human umbilical-vein endothelial cells. It was concluded that administration of *L plantarum* and fiber leads to a reduction in cardiovascular disease risk factors and should be useful as a protective agent in the primary prevention of atherosclerosis in smokers.

Synbiotics in Crohn's Disease

Sixty-three patients with active Crohn's disease received induction treatment with 5 mg/kg IV infliximab and were randomized to subsequent treatment with 1 daily sachet of Synbiotic 2000 ($n = 32$) or to placebo ($n = 31$).[45] The patients were followed every 4 weeks until clinical relapse occurred or up to 6 months. Median time to relapse was 9.79 (interquartile ratio [IQR] 6.04–13.07) weeks in the synbiotic-treated group compared with 10.14 (IQR 5.93–13.43) weeks in the placebo group (unpaired *t* test, $p = .51$). The median interval between infliximab infusions before inclusion was 11.68 weeks (IQR 9.45–17.91) in the synbiotic group and was decreased by 2.83 weeks (median) during synbiotic therapy. The median interval between infusions before inclusion was 9.23 (IQR 6.92–12.39) in the placebo group and increased by 1.24 weeks (median) during therapy (NS). Twenty-five patients (13 in the treated group and 12 in the placebo group) prematurely discontinued treatment because of intolerance. It was concluded that in the patients who completed the study, there were no differences between the groups in response to treatment.

Synbiotics in Chronic Liver Disease

Activation of macrophages by endotoxin is assumed responsible for increased circulating tumor necrosis factor α (TNF-α) and soluble TNF receptor (sTNFR) levels in patients with cirrhosis. Relevant to this is expression of toll-like receptor (TLR) 4 and TLR2, which are critically involved in production of TNF-α in response to endotoxin and gram-positive microbial stimuli, respectively. Circulating endotoxin, TNF-α, and sTNFR levels, peripheral blood mononuclear cell (PBMC) expression of TLR4 and TLR2, and *in vitro* TNF-α production by PBMCs stimulated with endotoxin or *Staphylococcus aureus* enterotoxin B were measured in 36 cirrhotic patients and 32 controls.[46] PBMC expression of TLR2, circulating TNF-α levels, and *in vitro* TNF-α production were reassessed after supplementation with Synbiotic 2000. Supplementation with the synbiotic regimen resulted in significant up-regulation of PBMC expression of TLR2. Serum TNF-α levels were further increased, and *in vitro* TNF-α production was further reduced in most patients. It was concluded that up-regulation of PBMC expression of TLR2 but not TLR4 occurs in cirrhosis, which, contrary to previous assumptions, implies an important stimulatory role for gram-positive microbial components but not endotoxin.

A subsequent study by the same group was undertaken in patients with liver cirrhosis and minimal encephalopathy. Minimal hepatic encephalopathy (MHE) is an important disorder that may seriously impair daily functioning and quality of life in patients with cirrhosis. Treatment with lactulose is known to be beneficial. Fifty-five patients with documented MHE were randomized to receive Synbiotic 2000 ($n = 20$), the fiber in Synbiotic 2000 alone ($n = 20$), or placebo ($n = 15$) for 30 days.[47] The patients with cirrhosis and MHE were found to have substantial derangements in the gut microecology, with significant fecal overgrowth of potentially pathogenic *Escherichia coli* and staphylococcal species. Synbiotic treatment significantly increased the fecal content of non–urease-producing *Lactobacillus* species at the expense of these other bacterial species. Such modulation of the gut flora was associated with a significant reduction in blood ammonia levels and reversal of MHE in 50% of patients. Synbiotic treatment was also associated with a significant reduction in endotoxemia. The Child-Turcotte-Pugh functional class improved in nearly 50% of cases. Treatment with fermentable fiber alone was also of benefit in a substantial proportion of patients. It was concluded that treatment with synbiotics or fermentable fiber is an alternative to lactulose in the management of MHE in patients with cirrhosis.

Intervention aimed at reducing intestinal levels of endotoxin-containing gram-negative bacteria is reported to improve systemic hemodynamic disturbance in cirrhosis; however, beneficial effect on hepatic blood flow is unknown. A study in 15 cirrhotic patients (hepatitis C virus, $n = 7$; alcohol, $n = 6$; primary biliary cirrhosis, $n = 1$; idiopathic, $n = 1$; Child-Pugh grade A, $n = 6$; B, $n = 5$; C, $n = 4$) and 11 patients with chronic hepatitis (hepatitis C, $n = 9$; hepatitis B, $n = 1$; nonalcoholic steatohepatitis, $n = 1$) evaluated indocyanine green retention at 15 minutes (ICG_{R15}) measured at baseline and following oral supplementation for 7 days with Synbiotic 2000.[48] ICG_{R15} was significantly higher in cirrhotic patients (median, 38.3; range, 5%–60%) than those with chronic hepatitis (median, 5.3; range, 1.8%–9.7%) ($p < .0005$). Supplementation with the synbiotic formulation was associated with a significant reduction in ICG_{R15} in the cirrhotic group ($p = .003$). ICG_{R15} was reduced by a median 17.5% (range, 1.4%–65%) of baseline values in 14 of 15 (93%) such patients and increased by 4.1% in 1 patient. The treatment led to no significant change in ICG_{R15} in patients with chronic hepatitis ($p = .65$). It was concluded that the synbiotic preparation significantly improved ICG clearance in cirrhotic patients, presumably by reversing a disturbance in gut flora occurring in cirrhosis but not chronic hepatitis.

Clinical Experience With Synbiotics in Acute Conditions

Synbiotics in Acute Pancreatitis

Microbial infection of the pancreatic tissue in patients with severe acute pancreatitis increases considerably morbidity and mortality. Colonization of the lower GI tract and oropharynx with gram-negative, but sometimes also gram-positive, bacteria precedes contamination of the pancreas. Patients with acute pancreatitis were randomized into 2 double-blind groups.[49] The treatment group received a freeze-dried preparation containing live *L plantarum* 299 in a dose of 10_9 organisms, together with a substrate of oat fiber, for 1 week administered by nasojejunal tube. The control group received a similar preparation, but the *Lactobacillus* was inactivated by heat. A total of 45 patients completed the study; 22 patients were treated with live and 23 with heat-killed *L plantarum* 299. Infected pancreatic necrosis and abscesses occurred in 1 of 22 patients (4.5%) in the treatment group, compared with 7 of 23 in the control group (30%, $p = .023$). The only patient in the live LAB group who developed infection had signs of urinary infection on the 15th day (eg, at a time when he had not received symbiotic treatment during the last 8 days). When comparing treated *vs* control groups, positive growth was observed in pancreatic tissue in 1 *vs* 7 patients, in pancreatic necroses in 1 *vs* 4 patients, and in blood cultures in 1 *vs* 3 patients. Reoperations were performed on 1 treated *vs* 7 control patients. No significant differences in numbers of chest infections, systemic inflammatory response syndrome, multiorgan failure, or mortality were observed. The length of stay was considerably shorter in the live LAB group (13.7 days *vs* 21.4 days), but the limited sample size did not allow statistical significance to be reached. It was concluded that synbiotic treatment is a good tool to prevent colonization of pancreas and to reduce morbidity in severe acute pancreatitis.

Synbiotics in Abdominal Surgery

Early EN with probiotics and fiber has in experimental studies proven effective to prevent bacterial translocation and subsequent infection. In a prospective randomized trial in 172 patients undergoing major abdominal surgery or liver transplantation, the incidence of bacterial infections was compared in patients receiving either conventional PN or EN, EN with *L plantarum* 299 and fiber, or EN with heat-inactivated lactobacilli and fiber (control).[50] Routine laboratory parameters, nutritional parameters, and the cellular immune status were measured preoperatively and on postoperative days 1, 5, and 10. The incidence of bacterial infections after liver, gastric, or pancreas resection was 31% in the conventionally treated group compared with only 4% in the synbiotic-treated group and 13% in the control group. Cholangitis and pneumonia were the most frequent infections and enterococci the most frequently isolated bacteria. Fiber and lactobacilli were well tolerated. The beneficial effects of synbiotic treatment seemed to be most pronounced in gastric and pancreatic resections, with a sepsis rate of 7% with live LAB, 17% with heat-inactivated LAB, and 50% with standard EN. The live-LAB-treated patients received significantly less antibiotics ($p = .04$); the mean length of antibiotic treatment was 4 ± 3.7 days with live LAB, 7 ± 5.2 days with heat-killed LAB, and 8 ± 6.5 days with only standard EN. The incidence of noninfectious complications was EN 30% (9/30), heat-inactivated LAB 17% (5/30), and live LAB 13% (4/30). No differences were observed in length of hospital stay. No significant changes were observed in levels of hemoglobin, leukocytes, C-reactive protein, blood urea nitrogen, bilirubin, albumin, total lymphocyte count; in CD45 RA, CD45 RO, CD4, CD8, or in NK cells; or in CD4:CD8 ratio. A recent not-yet-published study in abdominal-cancer surgical patients reports postoperative infections were 6.7% when treated with Synbiotic 2000, 20% when treated with only the fibers in the composition of Synbiotic 2000, and 47% with standard EN (Han Chun Mao et al, personal written communication, March 1, 2004). Significant improvements in serum concentrations of prealbumin, C-reactive protein, cholesterol, and endotoxin and white cell blood count were also observed.

Synbiotics in Liver Transplantation

Liver transplant patients are extremely susceptible to infections, and infection rates of 50%–85% have recently been reported.[51,52] It is generally agreed that microbial overgrowth in the intestine is a major source of infection, but efforts to reduce the infection rate by aggressive antibiotic policies have generally failed. In a prospective, randomized, placebo-controlled trial consisting of 95 patients, the incidence of postoperative infections and other complications after liver transplantation was studied in 3 groups of patients.[53] All groups were supplied with early EN with a standard formula; 1 group underwent selective digestive tract decontamination (SDD), another group received live *L plantarum* 299 and fiber, and a third group received heat-killed *L plantarum* 299 and fiber.[53] The patients who received living lactobacilli plus fiber developed significantly fewer bacterial infections (13%) than the patients with SDD (48%). The incidence of infections in the group with inactivated lactobacilli and fiber (HLP) was 34%. The numbers of postoperative infections were SDD 23, HLP 17 and LLP 4. Signs of infections occurred in SDD 47% (15/32), in HLP 34% (11/32) and in LLP 13% (4/31), $p = .017$, respectively. The most dominating infections were cholangitis, occurring in SDD 10, HLP 8, and LLP 2 patients, respectively, and pneumonia, in SDD 6, in HLP 4, and LLP 1 patient respectively. The most often isolated microbes were *Enterococci* (SDD 8, HLP 8, and LLP 1 patient) and *Staphylococci* (SDD 6, HLP 3, and LLP 1 patient, respectively). No *E. coli* or *Klebsiella* infections were seen in the LLP group. The numbers of patients requiring hemodialysis were SDD 8, HLP 4, and LLP 2 and the number of reoperations, SDD 6, HLP 2, and LLP 4, respectively. The CD4/CD8 ratio was higher in the LLP group compared with the other 2 groups ($p = .06$), and the ICU stay, hospital stay, and length on antibiotic therapy also shorter, none of them reaching statistical significance. In the LLP group, the mean duration of antibiotic therapy, the mean total hospital stay, and the stay on the intensive care unit were shorter than in the other 2 groups. However, these differences did not reach statistical significance. It was concluded that in early EN, the synbiotic solution is not only well tolerated, it decreases markedly the rate of postoperative infections both in comparison with heat-inactivated *Lactobacillus* and fiber and most significantly in comparison with SDD. It was suggested that further studies should evaluate whether this treatment should be instigated immediately in patients on waiting lists for transplantation.

The same investigators continued their efforts to try to further reduce the morbidity in connection with liver transplantation, this time with the combination of 4 LAB and 4 fibers and also a 40-times-larger dose of LAB. A prospective randomized double-blind trial was undertaken in 66 liver-transplantation patients; 33 patients were supplied Synbiotic 2000, and the other 33 patients received the 4 fibers only, which are ingredients in the synbiotic formulation Synbiotic 2000.[54] All patients received EN beginning immediately after the operation. The incidence of postoperative bacterial infections was significantly reduced: 48% with fibers only and 3% with live LAB and fibers. No difference was observed in length of hospital stay, but the duration of antibiotic therapy was significantly shorter in the group receiving live LAB and fibers. It was concluded that supply of a formulation consisting in live LAB fiber (Synbiotic 2000) is a most effective new tool to control infections in human liver transplantation and has the potential to dramatically reduce hospital costs in connection with liver transplantation and other advanced medical and surgical treatments.

Synbiotics in ICU Patients

ICU patients have a 5- to 10-fold increased risk of contracting infection when compared with patients elsewhere in the hospital. Although there are a number of studies now under way using synbiotics in this setting, the only pilot data available thus far involve a comparison between treatment with live lactobacilli plus oat fiber and heat-treated lactobacilli with oat fiber as a control.[55] There were 19 patients in each group, and mortality was 26% in the active synbiotic group *vs* 42% in the controls. Although this is too small a study to allow statistical significance, the same unit is currently undertaking a large-scale trial, and over 300 patients have thus far been recruited (Gomersall CH, personal written communication, January 1, 2005).

A recent, not-yet-published study in acute trauma patients reports a dramatic decrease in the number of respiratory infections when patients were given tube feeding plus Synbiotic 2000 compared with tube feeding plus only fiber, peptide, or glutamine. Infection rates were Synbiotic 2000: 1 of 14 patients (7%); only fiber: 11 of 28 patients (39%); peptide: 10 of 21 patients (48%); glutamine: 12 of 37 patients (32%). Equally, the total number of infections was decreased: Synbiotic 2000: 2 of 14 patients (14%); only fiber: 16 of 28 patients (57%); peptide C: 11 of 21 patients (52%); glutamine: 19 of 37 patients (51%). Both glutamine and Synbiotic 2000 were observed to down-regulate IL-6 but not IL-8 and TN-α (Kompan L, personal written communication, June 1, 2004).

Synbiotics in UC

Most studies in ulcerative colitis have evaluated only probiotics and no additional fiber. A small study is, however, reported, where the synbiotic composition, Synbiotic 2000, was applied rectally to patients with so-called distal colitis during 2 weeks. The patients were monitored for 3 weeks and symptom scores registered for 3 weeks. During this observation time, stool urgency decreased from 1.9 to 1.0, episodes of diarrhea from 2.4 to 0.8 stools per 24 hours, nightly diarrhea from 0.5 to 0 stools per night, visible blood on stool from 2.2 to 0.8 stools per 24 hours, and consistency of stool from 1.1 to 0.8.[56]

Choice of Synbiotic Composition

It is important to recognize that no conclusions about bioactivities can be drawn from one LAB to another as they all are different in function and genetically unrelated. Producers of probiotic products often claim health benefits from their product, which in most cases are unsubstantiated and not true. The truth is that only a small minority of LABs have the health potentials needed for use in clinical medicine. Most of the probiotic bacteria sold on the market do not survive the acidity of the stomach or in the small intestine with its high bile acid content, nor do they adhere to colonic mucosa or even temporarily colonize the stomach or intestine. Recently, it has become increasingly common that milk-fermenting LABs, such as yogurt bacteria and, for example, *L acidophilus*, are used also in clinical medicine. Yogurt bacteria have, like most other LABs, a low survival in an environment with acidity and bile acids like the upper GI tract and do generally exhibit only limited or no biologic influences, nor provide any clinical benefits. The great differences between the ability of some LABs to survive and to influence cytokine production after passage through the stomach and small intestine were well demonstrated in a study comparing 4 different LAB species: *L plantarum*, *L paracasei*, *L rhamnosus*, and *Bifidobacter animalis*[57]: 10^8 cells/mL of each LAB was administered; only between 10^7 (*L plantarum*) and 10^2 (*L rhamnosus*) bacterial cells remained after the passage through the stomach and small intestine. After passage through the small intestine, most of the strains tested had a significantly reduced or weak (especially *L rhamnosus*) ability to influence, for example, cytokine production. If some other LABs, such as yogurt bacteria, had been chosen for the study, most likely an even smaller survival of bacteria would have been observed.[58,59]

The absence of clinical efficacy of bacteria, commonly used by dairy industry, applied in severely sick patients was recently demonstrated. A standard commercial product, TREVIS (Chr Hansen Biosystem, Denmark), containing *L acidophilus* LA5, *Bifidobacterium lactis* BP12, *Streptococcus thermophilus*, and *L bulgaricus* was mixed with 7.5 g oligofructose and administered in 2 separate controlled studies. In a group of surgical patients, 72 patients were randomized to receive TREVIS and 65 to receive placebo. The patients in the TREVIS group received a 2-week preoperative course of the composition, whereas patients in the placebo group received placebo capsules with sucrose powder.[58] At surgery, a nasogastric aspirate, mesenteric lymph node, and scrapings of the terminal ileum were harvested for microbiological analysis. Serum was collected preoperatively and on postoperative days 1 and 7 for measurement of C-reactive protein, interleukin 6, and antiendotoxin antibodies. Septic morbidity and mortality were recorded; there were no significant differences observed between the synbiotic and control groups in bacterial translocation (12.1% *vs* 10.7%; $p = .808$), gastric colonization (41% v 44%; $p = .719$), systemic inflammation, or in septic complications (32% v 31%; $p = .882$). The authors rightly concluded that no measurable effect could be observed on gut-barrier function in elective surgical patients.

Another study was undertaken in 90 patients admitted to an ICU; half of them received TREVIS and the other half, placebo.[59] The gut-barrier function was assessed by measurement of intestinal permeability (lactulose/rhamnose test) and culture of nasogastric aspirates on days 1 and 8. After 1 week of therapy, patients in the TREVIS group had lower incidence of potentially pathogenic bacteria (43% *vs* 75%, $p = .05$) and multiple organisms (39% *vs* 75%, $p = .01$) in their nasogastric aspirates than the controls, but there were no differences between the groups in terms of intestinal permeability, septic complications, or mortality. The authors also concluded that, although the treatment favored the microbial composition of the upper GI tract, it did not influence intestinal permeability, nor was it associated with measurable clinical benefits.

One of us (SB) was invited by the editors of *Clinical Nutrition* to provide a commentary to the last paper.[60] It was suggested that any of several of the following factors might explain the poor results:

- The time point when instituted: Animal studies suggest that there is a therapeutic window for modulation of superinflammation of approximately 24–36 hours. Clearly, ICU patients have passed that time and might be resistant to therapy.
- The type of disease and stage of disease: patients in the ICU had a large variety of diseases.
- The type of strains of LAB and fiber used for the treatment: The present formulation was based on yogurt bacteria. Such bacteria are known to have a limited capacity for immunomodulation. It should also be remembered that most probiotic bacteria do not survive acidity of the stomach and bile acid content of the intestine. This is certainly so for most bacteria used by the dairy industry.
- The amount of LAB and fiber supplied: The study provided 3 daily doses of probiotics totaling 10^9 bacteria. However, the dose of each of the 4 LABs used was obviously much less and eventually no additive effects could be expected by the use of 4 different strains.
- The method of administration: The LABs were supplied in enterocapsules. It is not known how much this will influence the results, but it is known that probiotics and synbiotics are considerably activated when rehydrated and left in room temperature for 1–2 hours.

The fact that negative effects were also obtained with TREVIS in postoperative patients, a group of patients in which other studies with different LAB formulations have proven effective, supports the conclusion that the choice of probiotics is the main reason for failure. However, ICU patients are most likely a disadvantageous group to treat because the treatment is installed after the peak of acute-phase response and trauma- or disease-induced cytokine storm. But again, other studies, using other formulations report significant benefits from the treatment, as discussed earlier.

The LABs used in most of the synbiotic studies above were selected after extensive studies of >350

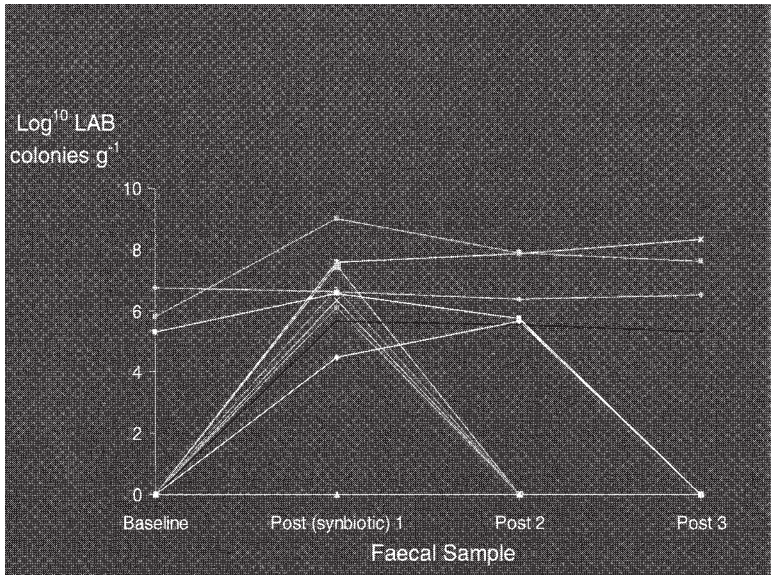

Figure 1. Counts of lactic acid bacteria in 10 at random ICU patients. Seven patients had no remaining LAB flora. Supply of Synbiotic 2000 FORTE did normalize the counts. Figure provided by Keith Girling and David Knight in Nottingham UK. See also Knight et al.[61]

human fecal bacteria and >180 bacteria harvested from fresh growing rye.[41,42] They were chosen because of unique and superior abilities to survive in the low pH of the stomach and in the high-bile-acid content of the small intestine; to attach to colonic mucosa and to temporary colonize the large intestine; to ferment various types of plant fibers, including rather fermentation-resistant fibers such as inulin; and because of a balanced production of both pro- and antiinflammatory molecules such as cytokines; strong ability to produce several bioactive molecules, especially heat-shock proteins; and production of significant amounts of antioxidants. Similarly, the added fibers were chosen because of their documented bioactivities. Simultaneous fibers added a significantly to further improvements in the above-described functions.

Future Aspects

Undoubtedly, the sickest patients receive the worst food. Clinical nutrition provided to patients in the ICU and to patients after advanced medical and surgical procedures is still very primitive. Many support that proper nutrition to the sickest patients is not so important from the perspective of supplying nutrients and calories as it is for maximizing the immune response and modulation of inflammation. The key organ is the large intestine and its flora. The intestinal mucosa can only nourish itself satisfactorily from the lumen, which makes constant presence of food in the colon to be of extreme importance. Furthermore, the food aimed for the colon is mainly vegetables and fruits, and it is mainly microbial enzymes in the colon that have the capacity to release all the antioxidants and nutrients needed for health and recovery from serious disease. Normal food, as our forefathers ate, is said to contain approximately 2 million different substances. The nutrition formulas with fiber as provided today contains most likely <10% of such substances. All these are based on a few fibers, all are based on dry fibers, and all are provided in relatively small quantities. Many important ingredients of food such as glutamine and glutathione do not tolerate processing. It is thus mandatory that, whenever possible, supply of nutrition formulas be complemented by supply of fresh fruits and vegetables. For such supply, juicing machines and production of local nutrition solutions based on fresh fruits and vegetables are of greatest importance.

We are also increasingly aware of the fact that the flora, and the conditions for colonic fermentation and production of nutrients, are severely impaired in ICU patients. It is more often an exception than the rule to find a patient in the ICU with an intact, protecting flora (Fig. 1). Usually the stress, the supply of drugs, and antibiotics contribute to elimination of the protective flora and to overgrowth of and increased virulence of the potentially pathogenic flora. The nutrition of the sickest in the 21st century will most likely be based on synbiotics–simultaneous supply of pre- and probiotics. The results from studies thus concluded seem to show that dramatic improvements can be obtained by such simple and inexpensive treatment. However, it must be remembered that only a minority of LABs have been shown to have the abilities needed for control of inflammation and infection.

Thus far, most attempts to give synbiotic treatment have been through oral supply. Preliminary studies suggest that excellent results can also be obtained by topical application on skin and wounds, on burned surfaces, and around tube, line, and drain penetrations through the skin. When applied around tracheostomies and entrances of tubes and lines, biofilm is dissolved and removed and protection offered against infections.

There is a lot to gain from bringing the management of critically ill patients in line with modern bioecological and evidence-based principles.

References

1. Eaton SB, Eaton SB 3rd, Konner MJ, Shostak M. An evolutionary perspective enhances understanding of human nutritional requirements. *J Nutr.* 1996;126:1732–1740.
2. Gustafsson BE. *Germfree Research.* New York, NY: Alan R Liss Inc; 1985:17–23.
3. Williams CL, Bollella M, Wynder EL. A new recommendation for dietary fiber intake in childhood. *Pediatrics.* 1995;96(suppl):985–988.
4. Pilch S. *Physiological Effects and Health Consequences of Dietary Fiber.* Bethesda, MD: Life Science Research Office, Federation of American Societies for Experimental Biology; 1987.
5. Finegold SM, Sutter VL, Mathisen GE. Normal indigenous intestinal flora. In: Hentges DJ, ed. *Human Intestinal Microflora in Health and Disease.* London: Academic Press; 1983:3–31.
6. Ahrné S, Nobaek S, Jeppsson B, Adlerberth I, Wold AE, Molin G. The normal *Lactobacillus* flora in healthy human rectal and oral mucosa. *J Appl Microbiol.* 1998;85:88–94.
7. Slavin JL. Dietary fiber: classifications, chemical analyses and food sources. *J Am Diet Assoc.* 1987;87:1164–1171.
8. Topping DL, Fukushima M, Bird AR. Resistant starch as a prebiotic and synbiotic: state of the art. *Proc Nutr Soc.* 2003;62:171–176.
9. Cordain L. Cereal grains: humanity's double-edged sword. *World Rev Nutr Diet.* 1999;84:19–73.
10. Hipsley H. Dietary fibre and pregnancy toxaemia. *BMJ.* 1953;ii:420–422.
11. Trowell H, Southgate DA, Wolever TM, Leeds AR, Gassull MA, Jenkins DJ. Dietary fibre redefined. Letter. *Lancet.* 1976;i:967.
12. AACC Dietary Fiber Technical Committee. The definition of dietary fiber. *Cereal Foods World*. 2001;46:112–129.
13. Wolever TMS, Jenkins DJA. Effect of dietary fiber and foods on carbohydrate metabolism. In: Spiller GA, ed. *Handbook of Dietary Fiber in Human Nutrition.* Boca Raton, FL: CRC Press; 1993:111–152.
14. Todesco T, Rao AV, Bosello O, Jenkins DJ. Propionate lowers blood glucose and alters lipid metabolism in healthy subjects. *Am J Clin Nutr.* 1991;54:860–865.
15. Anderson JW. Whole grain protect against atherosclerotic cardiovascular disease. *Proc Nutr Soc.* 2003;62:135–142.
16. Killan S, Kritzinger S, Rycroft G, Gibson GR, Du Preez J. The effects of the novel bifidogenic trisaccharide, neokestose, on the human colon microbionta. *World J Microbiol Biotechnol.* 2002;18:637–644.
17. Baten A, Ullah A, Tomazic VJ, Shamsuddin AM. Inositol-phosphate-induced enhancement of natural killer cell activity correlates with tumor suppression. *Carcinogenesis.* 1989;10:1595–1598.
18. Dunjic BS, Svensson I, Axelsson J, et al. Is resistance to phospholipase important to gastric mucosal protective capacity of exogenous phosphatidylcholine? *Eur J Gastroenterol Hepatol.* 1994;6:593–598.
19. Dunjic BS, Svensson I, Axelsson J, Ar'Rajab A, Larsson K, Bengmark S. Green banana protection of gastric mucosa against experimentally induced injuries in rats: a multicomponent mechanism? *Scand J Gastroenterol.* 1993;28:894–898.
20. Müller M, Lier D. Fermentation of fructans by epiphytic lactic acid bacteria. *J Appl Bacteriol.* 1994;76:406–411.
21. Kaplan H, Hutkins RW. Fermentation of fructooligosaccharides by lactic acid bacteria and bifidobacteria. *Appl Environ Microbiol.* 2000;66:2682–2684.
22. Riedl J, Linseisen J, Hoffmann J, Wolfram G. Some dietary fibers reduce the absorption of carotenoids in women. *J Nutr.* 1999;129:2170–2176.
23. Roma E, Adamidis D, Constantopoulos A, Messaritakis J. Diet and chronic constipation in children: the role of fiber. *J Pediatr Gastroenterol Nutr.* 1999;28:169–174.
24. Moore N, Chao C, Yang LP, Storm H, Oliva-Hemker M, Saavedra JM. Effects of fructo-oligosaccahride-supplemented infant cereal: a double-blind randomized trial. *Br J Nutr.* 2003;90:581–587.
25. Spapen H, Diltoer M, Van Malderen C, Opdenacker G, Suys E, Huyghens L. Soluble fiber reduces the incidence of diarrhea in septic patients receiving total enteral nutrition: a prospective, double-blind, randomized, and controlled trial. *Clin Nutr.* 2001;20:301–305.
26. Baqui AH, Black RE, El Arifeen S, et al. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial [abstract]. *BMJ.* 2002;325:1059.
27. Rabbani GH, Teka T, Zaman B, et al. Clinical studies in persistent diarrhea: dietary management with green banana or pectin in Bangladesh children. *Gastroenterology.* 2001;121:554–560.
28. Fernadez-Banares F, Hinojosa J, Sanchez-Lombrana JL, et al. Randomized clinical trial of *Plantago ovata* seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. *Am J Gastroenterol.* 1999;94:427–433.
29. Kanauchi O, Iwanaga T, Mitsuyama K. Germinated barley foodstuff feeding: a novel neutraceutical strategy for ulcerative colitis. *Digestion.* 2001;63(suppl 1):S60–S67.
30. Hallert C, Björck I, Nyman M, et al. Increasing fecal butyrate in ulcerative colitis patients by diet: controlled pilot study. *Inflamm Bowel Dis.* 2003;9:116–121.
31. Stanghellini BG, De Giorgio R, Cremon C, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology.* 2004;126:693–702.
32. Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PWF, Kiel DP. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *Am J Clin Nutr.* 1999;69:727–736.
33. Tucker KL, Chen H, Hannan MT, et al. Bone mineral density and dietary patterns in older adults: the Framington Osteoporosis Study. *Am J Clin Nutr.* 2002;76:245–252.
34. Zafar TA, Weaver CM, Zhao Y, Martin BR, Wastney ME. Nondigestible oligosaccharides increase calcium absorption and suppress bone resorption in ovariectomized rats. *J Nutr.* 2004;134:399–402.
35. Hylander B, Rössner S. Effects of dietary fiber intake before meals on weight loss and hunger in a weight-reducing club. *Acta Med Scand.* 1983;213:217–220.
36. Howarth NC, Saltzman E, McCrory MA, et al. Fermentable and nonfermentable fiber supplements did not alter hunger, satiety or body weight in a pilot study in men and women consuming self-selected diet. *J Nutr.* 2003;133:3141–3144.
37. Homann HH, Kemen M, Fuessenich C, Senkal M, Zumtobel V. Reduction in diarrhea incidence by soluble fiber in patients receiving total or supplemental enteral nutrition. *JPEN J Parenter Enteral Nutr.* 1994;18:486–490.
38. Spapen H, Diltoer M, Van Malderen C, et al. Soluble fiber reduces the incidence of diarrhea in septic patients receiving total enteral nutrition: a prospective, double-blind, randomized, and controlled trial. *Clin Nutr.* 2001;20:301–305.
39. Caparros T, Lopez J, Grau T. Early enteral nutrition in critically ill patients with a high-protein diet enriched with arginine, fiber, and antioxidants compared with a standard high-protein diet: the effect on nosocomial infections and outcome. *JPEN J Parenter Enteral Nutr.* 2001;25:299–308.
40. Johansson ML, Molin G, Jeppsson B, et al. Administration of different *Lactobacillus* strains in fermented oatmeal soup: *in vivo* colonization of human intestinal mucosa and effect on the indigenous flora. *Appl EnvironMicrobiol.* 1993;59:15–20.
41. Kruszewska K, Lan J, Lorca G, et al. Selection of lactic acid bacteria as probiotic strains by in vitro tests. *Microecol Ther.*

2002;29:37–51. The proceedings of the XVI International Congress on Microbial Ecology and Disease held at Noordwijkerhout, The Netherlands, October 2001.
42. Ljungh Å, Lan J-G, Yamagisawa N. Isolation, selection and characteristics of *Lactobacillus paracasei* ssp *paracasei* isolate F19. *Microb Ecol Health Dis.* 2002;suppl 3:4–6.
43. Bukowska H, Pieczul-Mroz J, Jastrzebska M, Chelstowski K, Naruszewicz M. Decrease in fibrinogen and LDL-cholesterol levels upon supplementation of diet with *Lactobacillus plantarum* in subjects with moderately elevated cholesterol. *Atherosclerosis.* 1998;137:437–438.
44. Naruszewicz M, Johansson ML, Zapolska-Downar D, Bukowska H. Effect of *Lactobacillus plantarum 299v* on cardiovascular disease risk factors in smokers. *Am J Clin Nutr.* 2002;76:1249–1255.
45. Rutgeerts P, D'Haens G, Baert F, et al. Randomized placebo controlled trial of pro-and prebiotics (synbiotics cocktail) for maintenance of infliximab induced remission of luminal Crohn's disease (CD) [abstract]. *Gastroenterology*. 2004;126:A-467 (T130).
46. Liu Q, Duan ZP, Ha da K, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. *Hepatology.* 2004;39:1441–1449.
47. Riordan SM, Skinner N, Nagree A, et al. Peripheral blood mononuclear cell expression of toll-like receptors and relation to cytokine levels in cirrhosis. *Hepatology.* 2003;37:1154–1164.
48. Kurtovic J, Ruettimann U, Adamson H, et al. Improvement in indocyanine green clearance following synbiotic treatment in cirrhosis [abstract]. *Gut.* 2003;52(suppl):A3.
49. Oláh A, Belágyi T, Issekutz Á, Gamal ME, Bengmark S. Early enteral nutrition with specific lactobacillus and fibre reduces sepsis in severe acute pancreatitis. *Br J Surg.* 2002;89:1103–1107.
50. Rayes N, Hansen S, Boucsein K, et al. Early enteral supply of fibre and lactobacilli vs parenteral nutrition: a controlled trial in major abdominal surgery patients. *Nutrition.* 2002;18:609–615.
51. Wade JJ, Rolando N, Hayller K. Bacterial and fungal infections after liver transplantation: an analysis of 284 patients. *Hepatology.* 1995;21:1326–1336.
52. Zwaveling JH, Maring JK, Klompmaker IJ, et al. Selective decontamination of the digestive tract to prevent postoperative infection: a randomized placebo-controlled trial in liver transplant patients. *Crit Care Med.* 2002;30:1204–1209.
53. Rayes N, Hansen S, Seehofer D, et al. Early enteral supply of *Lactobacillus* and fibre vs selective bowel decontamination (SBD): a controlled trial in liver transplant recipients. *Transplantation.* 2002;74:123–127.
54. Rayes N, Seehofer D, Theruvath T. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation: a randomised, double-blind trial. *Am J Transplant.* 2005;5:123–130.
55. Gomersall CM. *Does the Administration of Lactobacillus to Critically Ill Patients Decrease the Severity of Multi-Organ Dysfunction and Failure? A Pilot Study*. London: Roehampton Institute, School of Life Sciences; 1998.
56. Pathmakanthan S, Walsh M. Bengmark S, et al. Efficacy and tolerability treating acute distal ulcerative colitis with synbiotic enemas: a pilot trial [abstract]. *Gut.* 2002;51(suppl):A307.
57. Miettinen M, Alander M, von Wright A, et al. The survival of and cytokine induction by lactic acid bacteria after passage through a GI model. *Microb Ecol Health Dis.* 1998;10:141–147.
58. Anderson AD, McNaught CE, Jain PK, MacFie J. Randomised clinical trial of synbiotic therapy in elective surgical patients. *Gut.* 2004;53:241–245.
59. Jain PK, McNaught CE, Anderson ADG, MacFie S, Mitchell CJ. Influence of synbiotic containing *Lactobacillus acidophilus LA5*, *Bifidobacterium lactis BP12*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and oligofructose on gut barrier function and sepsis in critically ill patients: a randomized controlled trial. *Clin Nutr.* 2004;23:467–475.
60. Bengmark S. Synbiotics to strengthen gut barrier function and reduce morbidity in critically ill patients. *Clin Nutr.* 2004;23:441–445.
61. Knight DJW, Ala'Aldeen D, Bengmark S, Girling KJ. The effect of synbiotics on gastrointestinal flora in the critically ill [abstract]. *Br J Anaesth.* 2004;92:307P–308P.