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SYNBIOTIC TREATMENT IN CLINICAL PRAXIS

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"Health and well-being is more than merely absence of disease"
Mark Twain

INTRODUCTION

Health and well-being seems depending on availability of some more than two million different molecules, all available in the body in rather exact amounts. Most of the molecules are supplied by foods and made available in the large intestine by fermentative actions. It is a considerable problem that the variability in the food supplied both to domestic animals and humans has dramatically decreased in the modern society. Our Palaeolithic forefathers are said to each year have consumed food from some four to five hundred plants. Modern man has reduced this to a few dozens, and furthermore, many important molecules in foods are destroyed by modern methods to store and prepare the food. The nutritional content of key farming products such as meat and milk has with modern farming methods changed dramatically. As an example, due to the limited variation of diet to domestic cows is the content of omega-3 fatty acids only about 2% in beef and milk, compared to about 30% in free-living, grass-eating and fresh-plant eating cows. It is also known that treatment of foods with high temperature not only destroys important nutrients, particularly antioxidants, but also adds to the food cancer-promoting chemicals, mutagens.

Several observations suggest that health and well-being is the result of a dynamic interplay and balance - homeostasis – between numerous processes that control energy balance, appetite, cell proliferation, repair systems, apoptosis, metabolic rate, stress response, immune response and numerous other processes on which we are depending for our well-being (*Frame* et al., 1998). The attention increasingly given to the homeostasis between omega-3 and omega-6, to the balance between pro- and anti-inflammatory cytokines, and balance in Th1 and Th2 immune response serves as examples.

FERMENTED FOOD HAS OUTSTANDING QUALITY

Our Palaeolithic forefathers used fermentation as their main method to prepare and store food. This method, unfortunately today abandoned in developed countries, but still in use in most developing countries is superior to modern technologies as it not only maintains the content of important nutrients, especially antioxidants, but also sometimes increases it. Microbial enzymes are known to release numerous nutrients from fruit and vegetable fibres

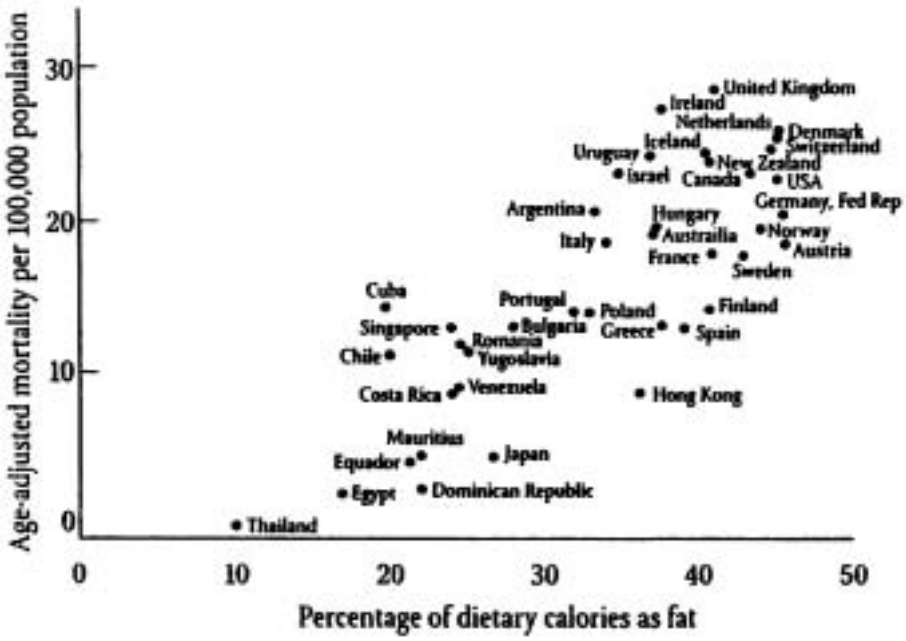

Figure 1: Correlation between percentage of calories as fat in various countries and age-adjusted mortality in breast cancer. (Reproduced with permission from: *Carroll*, 1994).

and make them accessible to the metabolism of the body. As a matter of fact the majority of the more than two million molecules constituting our body are products of microbial digestion in the lower GI tract. The complexity of functions by the flora is illustrated by the fact the intestinal microbes together contain more than 300,000 different genes, compared to the about 65,000 in the rest of the human body.

The Palaeolithic food, the food to which are genes have been adjusted during several millions of years, is said to have contained only half as much of proteins, 1/4 as much of saturated fat and 1/10 of sodium salts. Instead it contained at least 4-5 times as much of plant fibres, 10 times as much of antioxidants, fifty times as much of omega-3 fatty acids, and billion times or more of microbes. It is reasonable to assume that the human genes, adapted during million of years to the lifestyle and food habits of our prehistoric ancestors, badly tolerate the dramatic changes, especially in food habits, which have occurred, during the recent few hundred years (*Eaton* and *Konner*, 1985), and that this could be an explanation to the epidemic in chronic diseases, which has occurred during the last few decades – see further *Bengmark* (2001).

It is clear that people, who live in rural areas of developing countries, and consume large amounts of fruits, vegetables and live microbes – but also much less of animal fat have a much richer GI flora, a better immune response, a compared to Westerners reduced ability to form blood clots, and a significantly better resistance to disease. They also rarely suffer the endemic diseases so frequently observed in Western countries as demonstrated for breast cancer in Figure 1, similar associations being demonstrated for several forms of cancer such as colonic cancer and prostatic cancer, prostatic hyperplasia, diabetes, coronary heart disease, neuro-

Table 1: Probiotics-claimed molecular effects

General:	Produces nutrients and antioxidants
	Produces growth and coagulation factors
	Activates the MALT system
	Modulates Th1/Th2 response
	Promotes antioxidant actions
	Controls potentially pathogenic microorganisms (PPMs)
	Reduces production of endotoxins
	Reduces mutagenicity
Humoral:	Stimulates IgA production
	Inhibits IgE production
	Stimulates NO production
	Modulates cytokine response
Cellular:	Stimulates macrophage function
	Stimulates NK cell activity
	Promotes growth and regeneration
	Promotes apoptosis

degenerative diseases and other endemic diseases. It is not unrealistic to suggest that the numerous compounds released by microbial fermentation and absorbed by the mucosa are important contributing factors.

FLORA BOOSTS THE IMMUNE SYSTEM OF THE HOST

It is increasingly observed that the GI tract is a key organ in our immune defence. Here up to 80% of the immune cells are to be found, and here up 80% of the immunoglobulins are produced (*Brandzaeg* et al., 1989). Commensal flora, some powerful supplemented lactic acid bacteria (LAB), often referred to as probiotics, and bioactive fibres from fruit and vegetables, often called prebiotics, as well as their fermented products, synbiotics, are known to have immuno-modulatory, anti-infectious, anti-inflammatory and antioxidant effects. Table 1 summarises some the effects on the immune system described in the literature. But not all LAB and all fibres are equally effective. The LAB in various yoghurts are chosen for their palatability and have most often rather weak immuno-modulatory effects. LAB do not constitute an authentic genus, it is said that there are greater genetic differences between on LAB and another than between a fish and a human being. LAB with the strongest ability to ferment fibre are found on fruits and vegetable fibres, often semi-resistant to fermentation/digestion by microbial enzymes and found in ethnic foods such as sauerkraut and sourdough. As an example, oligofructans such as inulin and phleins, fibres rich in several fruit and vegetables, but claimed to have strong biological effects, are difficult to ferment and only a few LAB are able to do so (*Müller* and *Lier*, 1994). Only 16 of studied 712 LAB were able to ferment phlein-type fibre and only 8/712 inulin type fibre. *Lactobacillus plantarum* was clearly the most effective and only three other LAB species, *Lactobacillus paracasei* subsp. p*aracasei*, *Lactobacillus brevis* and *Pediococcus pentosaceus*

demonstrated ability to ferment these relatively resistant fibres. *Kruszewska* et al. (2002) did in a recent study isolate no less than 180 microbial strains from growing rye. Several of these demonstrated strong bioactivity including strong adhesion to human mucus, induction of pro- and anti-inflammatory cytokines and antioxidant activity. As some of the isolated LAB showed superior bioactivity did they choose to specifically study the effects of *Leuconostoc mesenteroides* 77:1, *Lactobacillus plantarum* 2592, and Pediococcus *pentosaceus* 16:1 – one from each genus of the family of *Lactobacillus* – plus *Lactobacillus paracasei* subsp. *paracasei* 19, chosen among 355 human strains. Interestingly all the strains were able to transcribe NF-κB, to induce pro-inflammatory cytokines (IL-1β and IL-8) and anti-inflammatory (IL-10) and to produce antioxidants. In all these processes did *Lactobacillus plantarum* 2592 show superior ability compared to the others. These four LAB are together bioactive fibres (inulin, beta-glucan, resistant starch and pectin) chosen to constitute a new symbiotic composition – Synbiotic 2000 – which presently is under clinical evaluation (see further below).

PREBIOTIC FIBRES ARE ESSENTIAL

The human digestive tract is for its growth and functions much depending on supply of prebiotics. In contrast to cows milk is breast milk very rich in fibres. Apart from elephant milk, no other mammalian milk analysed till today contains as much of fibre as breast milk (*Gnoth* et al., 2000). The complex fucosylated oligosaccharides in human milk, with structural similarities to immunomodulating cell surface glycoconjugates, are supposed to protect breast-fed infants against inflammations and infections (*Gnoth* et al., 2000). In addition, these fibres are likely to function as prebiotics and stimulate growth of the non-pathogenic gut microflora in the breast-fed infants.

Fruit and vegetable fibres are known to also have strong influence on intestinal growth in most mammalians. As an example, six weeks of supply of fermentable fibres (beet pulp and oligofructose) to experimental animals increases the GI surface area by 28%, the mucosal mass by 37%, the mucosal weight by 35% and the capacity for carrier-mediated glucose uptake by 95% (*Buddington* et al., 1999). Another important function of fibre is to block receptors and prevent colonisation by potentially pathogenic microbes. For example mixing 2.5% of D-mannose into drinking water reduces significantly colonisation of newborn chicken with *Salmonella* (*Oyofo* et al., 1989).

Up to 25% of the adult population in Western countries suffer today of metabolic syndrome, a condition in which insulin resistance is a significant characteristics. However, increased intake of dietary fibre (celluloses, hemicelluloses, pectins and starches), the main substrate of SCFA production, increases insulin sensitivity in humans (*Randle* et al., 1963). Malhotra, an Indian physician, observed already in 1968, that men living in North India (Udaipur), and consuming large quantities of cellulose and vegetable fibres + live lactobacilli had a longer mean clotting time, and soft jelly-like clots compared to men in urban Madras. It has also been shown that supplement of the fibre konjac-glucomannan to baboons living on Western diet significantly lowers the plasma level of fibrinogen and of factor X (*Vorster* et al., 1985)

and that plasma viscosity and fibrinogen levels decrease significantly in diabetic children on supplementation with the fibre guar gum (*Koepp* and *Hegewisch*, 1981). It is also reported in the literature not only that the incidence of post-operative thrombosis is significantly reduced in patients on a high fibre diet (*Frohn*, 1976; *Latto*, 1976), and that supply of fibre (glucans) will significantly reduce the mortality rate in hospital infections in patients with severe trauma (*DeFillipe* et al., 1993).

Another group of fibres, fructo-oligosacharides (FOS), are known both to increase the numbers of certain lactic acid bacteria, particularly *Bifidobacteria*, but also to significantly decrease the number of *Enterobacteriaceae* in healthy humans. Mixing 10% of FOS in the diet to experimental animals had both protective and therapeutic effects against sodium sulphate-induced colitis (*Umemoto* et al., 1998). It is observed that supplementing patients with IBD with 30 g fructo-oligosaccharides (FOS) per day increases significantly the amount of luminal SCFAs (*Umemoto* et al., 1998). But also other fibres such as *Psyllium husk* (*Hallert* et al., 1991) and *Platago ovata* seeds (pectins) (*Fernandez-Banares* et al., 1999) are reported to have similar effects. A most recent study is of considerable interest. Germinated barley, the aleurone and scutellum fraction, of the grain is known to be rich both in hemicellulose fibres and in glutamin-rich proteins. When supplied to experimental animals did it result in dramatic improvement of induced colitis, an effect further attenuated by combining with LAB (*Fukuda* et al., 2002). Also antibiotics (vancomycin, metronidazole) did in this study significantly attenuate clinical and pathological scores – but in contrast to treatment with pre- and probiotics did treatment with antibiotics result in a significant decrease in caecal buturate levels.

Pectins are one of the several fibre groups known for their many strong bioactivities. It is a superior mucosa protectant, strong antioxidant, vehicle for transport of LAB through the GI tract and a superior substrate for bacterial fermentation. The unripe banana (green sweet banana as well as plantain) is rich in both pectin and resistant starch. 250 g/l of green banana (equivalent to two fruits) or 2 g pectin/kg food was recently tried as a supplement to rice diet in children in Bangladesh suffering from persistent diarrhoea. The amounts of and frequency of stools, the duration of diarrhoea, numbers of vomiting, and use of oral rehydration or amounts i.v. fluid solutions given were all significantly reduced in the two treatment groups (*Rabbani* et al., 2002). Recovery on third day was seen in 59% in the green banana group, in 55% in the pectin group compared to 15% in the only rice group.

PROBIOTICS IN DIARRHOEA IN CHILDREN

A larger European multi-centre trial in children one month to three years of age was undertaken: One-hundred-and-forty children were randomly allocated to oral rehydration and placebo, another 147 children to oral rehydration and daily supply of 10^{10} CFU of *Lactobacillus* GG (*Gualdalini* et al., 2000). Clinical signs of diarrhoea lasted 58.3±27.6 hours in the LAB-treated group to be compared to 71.9±35.8 hours (p=0.03) in the placebo group. Diarrhoea lasted in rotavirus-positive children treated with LAB 56.2±16.9 hours compared to 76.6±41.6 in the control group (p=0.008).

Lactobacillus GG was also tried in order to prevent diarrhoea in a placebo-controlled trial performed in 204 undernourished Peruvian children, age 6 to 24 months (*Oberhelman* et al., 1999). The treatment was given to all children during a period of 15 months. The lactobacillus-treated children had fewer episodes if diarrhoea (5.21 episodes/child and year compared to 6.02 in the placebo group, p=0.028). The therapeutic gain, as pointed out by *du Pont* (1999) and others, must be regarded as modest. Most likely use of other and more potent LAB, or combinations of LAB, should lead to a more significant therapeutic success.

One thousand three-hundred-thirty-six new-born Columbian children with risk of developing severe diarrhoea received prophylactically during one week (or until they were discharged) a daily supply 250 million live *Lactobacillus acidophilus* and 250 million live *Bifidobacterium infantis* and the outcome compared to outcome for similar children treated during the year before (*Hoyos*, 1999): The incidence of narcotising enterocolitis was reduced by two third (18 vs. 47, p<0.0005), and by half (19 vs. 38, p<0.03) in the patients transferred from other hospitals – patients which most likely were sicker and came late under treatment. No complications could be attributed to the use of probiotics, even when given to very sick new-born children with an average weight of 2600 g (range <1000 to >4000 g), and often suffering from severe conditions such as sepsis, pneumonia or meningitis. Incidentally it was observed that the LAB-treated children suffered significantly less diaper dermatitis.

Lactobacillus GG (LGG) was also tried in order to prevent diarrhoea in a series of 202 antibiotic-treated children. Twenty-five of the placebo placebo-treated (26%) and only 7 of the LGG-treated children developed diarrhoea (*Vanderhof* et al., 1999). The mean duration of diarrhoea was 4.7 days in the LGG group vs. 5.88 days in the placebo group. Again, the efficacy of the treatment is not impressive, and as pointed out by *Saavendra* (1999), "the reduction of 1 day of two liquid stools over a 10 day period in a child might be questioned".

PROBIOTICS – AND PREBIOTICS - IN INFLAMMATORY BOWEL DISEASE (IBD)

We observed in the early nineties that humans with inflammatory bowel disease have a reduced LAB flora, but also that induced colitis in experimental animals could be significantly reduced by supply of a combination of pre- and probiotics – synbiotics (*Fabia* et al., 1993a, 1993b). Subsequently it has been convincingly demonstrated that the concentrations of endogenous *Lactobacillus* and *Bifidobacteria* are significantly reduced in patients with active Crohn´s disease, ulcerative colitis, pouchitis as well as in experimental colitis (*Favier* et al., 1997; *Sartor*, 1999). Another recent study found both quantitative and qualitative changes in the LAB flora, when studying colonic biopsies from patents with ulcerative colitis (UC) (*Pathmakanthan* et al., 1999). A significant quantitative decrease in growth of *Lactobacillus* spp. in colitis biopsies was observed, but also a reduction in total aerobic speciation: 18 subspecies being found in UC patients compared to 32 in controls. Furthermore, anaerobic speciation revealed in average 4.7 subspecies in UC patients compared to 6.7 in controls. Incidentally it was observed that *Bacteroides*

thetaiotaomicron occurred more often in UC patients: 8/10 biopsies vs. 4/10 in controls - an observations, which significance remains to be explored.

A LAB cocktail called VSL#3 consisting in four *Lactobacillus* strains, three *Bifidobacterium* strains plus *Streptococcus salivarius* ssp. *thermophilus* ($5x10^{11}$ cells/g) is presently tried quite extensively around the world. This composition is most probably chosen at random without any further documentation of the molecular/immunological effects for each of the LAB, nor any evidence of synergistic effects. When three gram a day was given during one year did 15/20 patients remain in remission, one lost to follow up and 4/20 showed signs of relapse (*Venturi* et al., 1999). VSL#3 was also tried in a small controlled study in patients with pouchitis. Only 3/20 patients had relapse of the disease when supplied with VSL#3 compared 20/20 control patients (*Gionchetti* et al., 2000). These results are most likely better than what presently can be achieved by any conventional treatment, an assumption supported by a recent systematic review of the literature suggesting that " metronidazole is an effective treatment for active chronic disease" (odds ratio 12.34) but "oral probiotic therapy with VSL#3 for maintaining remission" (odds ratio 15.33) (*Sandborn*, 1999).

Although the scientific basis for treatment of IBD seems reasonable and attractive, it must be emphasised that it is far too soon to recommend routine use of probiotics in IBD. Further studied are much warranted. The good results obtained in the two small studies cited above seem to suggest that combination of several LAB might have strong clinical effects in IBD, eventually stronger than the use of single-bacteria treatments. It is tempting to anticipate that a cocktail consisting in LAB, where each of the bacteria has been chosen with the regard to their documented metabolic and immunological effects, should eventually be even more successful. It also tempting to suggest that combination with strong bioactive fibres (prebiotics) might even more improve the efficacy of treatment. The ideal treatment remedy will probably be complex, and much remains before the most suitable prebiotics, and the most effective probiotics have been identified.

A most recent study is of considerable interest (*Swidsinsky*, 2002). These authors studied the flora in 305 IBD patients and 40 controls using the most modern techniques: Quantitative PCR, cloning, sequencing fluorescence *in situ* hybridisation and electron microscopy. They observed a high density of mucosal bacteria in sick patients, but also that the microbial "close to mucosa"-density of microbes increased progressively with increasing severity of disease. Patients with > 10,000 CFU/μl showed a pronounced "band" of bacteria attached to mucosa, and patients with >50,000 CFU/μl had also signs of inclusions of polymorphic bacteria within solitary enterocytes next to lamina propria. The authors speculate that healthy mucosa is sterile - capable of holding back faecal bacteria and prevent a close contact of the microflora to the epithelial surface. It is likely that this function can be supported by treatment with a combination of pre- and probiotics (synbiotics).

PROBIOTICS IN *HELICOBACTER PYLORI* INFECTIONS

It is now almost fifteen years since it was demonstrated that lactic acid produced by *Lactobacillus acidophilus* has the capacity to inhibit *Helicobacter pylori* (*Bhatia* et al., 1989). The antibacterial activity of seventeen strains of lac-

tobacilli against ten different strains of *H. pylori* was recently studied (*Lorca* et al., 2001). All *Lactobacillus* strains were able to inhibit *H. pylori*, but the effect was lost if pH was adjusted to 6.0. However, the effect of *Lactobacillus acidophilus* CRL 639 remained even after pH was adjusted. The effect seemed less related to pH and more to release of a proteinaceous compound, with autolysin effects.

One-hundred-and-twenty *H. pylori* patients were randomised to, in addition to a 7-day triple therapy (Rabeprozole, Chlarithromycin, Amoxicillin), receive either placebo or a lyophilised and inactivated culture of *Lactobacillus acidophilus*. The eradication rate was significantly improved by supplementation of the LAB: 52/59 patients (88%) vs. 42/58 patients (72%) (p=0.03) (*Canducci* et al., 2000). The effects of live *Lactobacillus* GG was also investigated but with less success: although the study reports improved tolerability (reduced antibiotic-induced bloating, diarrhoea and taste disturbances), no improvement in the rate of eradication was when live *Lactobacillus* GG was used (*Armuzzi*, 2001a, 2001b).

Daily oral consumption of 4x50 ml of the supernatant from a whey-based *Lactobacillus acidophilus* (La1) culture, combined with either omeprazole or placebo, was reported to show a significant reduction in breath test both with and without supply of omeprazole, immediately as well as six weeks after the treatment episode (*Michetti* et al., 1999). It should be remembered that whey is extraordinarily rich in immunologically active and anti-infectious substances such as lactoferrin, lysozym and many other antimicrobial peptides. It is thus, this far not clear whether the observed effects are due to the *Lactobacillus* used, to the whey or a combination of both.

A recent study (*Sakamoto* et al., 2001) reports considerable improvement, both in urea breath test and serum pepsinogen in 31 patients with *Helicobacter pylori infections* treated during eight weeks with *Lactobacillus Gasseri OLL 2716*.

SYNBIOTICS IN ICU PATIENTS

There are good reasons to believe that pre-, pro-, and synbiotics could dramatically change the outcome for critically ill patients, and be a good alternative to the use of antibiotics in ICU patients. It is regrettable that this far only a handful of studies have been performed in critically ill and postoperative patients, and, furthermore, and most of these studies are under publication.

Severe acute pancreatitis

Contamination of the pancreatic tissue occurs frequently in severe pancreatitis, being reported to be 24% during the first week and amounting to 72% during the third week (*Beger* et al., 1986). Pancreatic sepsis seems to be a strong determinant for complication such as multiple organ failure (MOF) and of death. It has rather recently been shown that infection of the pancreatic tissue is almost always preceded by about one week of colonisation the large intestine with non-coli Gram-negatives: *Pseudomonas*, *Klebsiella*, *Citrobacter*, *Enterobacter*, *Acinetobacter*, *Morganella*, *Serratia* or *Proteus* (*Luiten* et al., 1998). Prevention of such a colonisation could be expected to have a dramatic influence on outcome.

A prospective double-blind randomised study, comparing the influence of *Lactobacillus plantarum* 299 and oat fi-

bre with heat-killed Lactobacillus plantarum 299 and oat fibre (control) was recently performed in severe pancreatitis (*Oláh* et al., 2002). The study was designed to be concluded when repeat statistical analysis demonstrated statistically significant differences between the two study groups. This occurred after all together 45 patients had entered the study. At that time 22 patients had during seven days received treatment with live LAB and 23 with heat-killed LAB during seven days. Infected necrosis and abscesses occurred in 1/22 patients (4.5%) in the live LAB group and in 7/23 patients (30%) with heat-killed LAB. Abscesses occurred in 1/22 (4.5%) in the treatment group vs. 7/23 (30%) ($p=0.023$) in the control group. Although the length of stay was 13.7 days in the treatment group vs. 21.4 days in the control group, the differences had not reached statistical significance at the time when the study was interrupted. The only patient who developed sepsis in the treatment group did that after fifteen days, e.g. eight days after the treatment has been discontinued. This seems to suggest that treatment should be provided for a minimum of 14 days and most likely as long as the patients are on antibiotics or have signs of GI colonisation.

Abdominal surgery patients

A prospective randomised study compares the effect of live *Lactobacillus plantarum* 299 in a dosis of 10^9 with heat-killed *Lactobacillus plantarum* 299 in the same dose and parenteral nutrition in 3x30 patients undergoing abdominal operations such as liver resection, pancreas resection, gastric resection, colon resection and intestinal by-pass (*Rayes* et al., 2002a). The groups treated with either live or heat-killed LAB suffered less infections (3/30 in each group, e.g. 10%) compared to 9/30 (30%) in the parenteral group ($p>0.001$). An even larger difference was observed when the subgroup of gastric and pancreatic surgery patients was separately analysed: None of eight patients receiving live LAB group, one of eight patients (12%) receiving heat-killed LAB group and 3/6 (50%) conventionally treated with parenteral nutrition suffered infections.

Liver transplantation patients

A separate study was performed in human liver transplants by the same group of clinicians in a study with a similarly sized material of patients. Comparison was made between selective bowel decontamination (SBD) + a standard enteral formula, live *Lactobacillus plantarum* 299 + oat and inulin fibres, and heat-killed *Lactobacillus plantarum* 299 + oat and inulin fibres (*Rayes* et al., 2002b). The total amount of fibres in the two last groups was about 11 gram. The LAB were supplemented during the first five days. The sepsis rate was 48% in the selective bowel decontamination group, 34% in the group treated with heat-inactivated LAB and 13% in the group receiving live LAB. Also the mean duration of antibiotic therapy, the mean total hospital stay and the stay on ICU were shorter compared to the groups with inactivated lactobacilli and fibre or with SBD. However, the size of the patient material did not allow statistical significance to be reached.

FLORA IMPORTANT ON ALL BODY SURFACES

Not only the gastro-intestinal tract, but also all body surfaces are coated by a protective flora, essential for prevention of infection and inflammation. Second to the GI tract with its one to two kg of flora is the skin, calculated in the

adult human to be inhabited by approximately 200 gram of bacteria. Other important sites are the mouth and pharynx, the respiratory tract and the vagina, each supposed to be inhabited by approximately 20 gram of flora. Too much washing and cleaning will impair this defence and open the door for opportunistic infections. Animals have the instinct to lick their wounds and hereby provide both protective flora and growth factors, produced by the salivary glands. To apply topically lactic acid bacteria on the skin and around all penetrations of the skin by foreign materials such as tubes, drains, tracheostomies etc is receiving an increasing interest. Such a treatment could also be of potential interest for treatment of burns.

It has been observed that infants treated with probiotics suffer much less diaper dermatitis (*Hoyos*, 1999). Two recent reports suggest that consumption of LAB-containing drinks prevents formation of biofilm and removes both yeast and bacteria from silicon rubber voice prostheses (*Free* et al., 2000; *van der Mei* et al., 2000). The flora is invariably reduced at all these sites in sick and hospitalised patients due to special hygienic requirements and large supply of antibiotics and other drugs. An overflow of probiotic bacteria from the GI tract to all the other sites seems normally to occur, a function, which most likely is severely reduced in the sick. It is not unlikely that in the future a dietary supply of pre- and probiotics be complemented by spraying or applying gels of LAB on sensitive body surfaces, especially around the skin penetrations, but also by using LAB-containing aerosols to promote flora of the respiratory tract, where such a protection layer is much needed.

GUT ECOLOGY AND HEALTH – FUTURE ASPECTS

Gut ecology is of the greatest importance for maintenance of health and prevention of diseases, increasingly seen in Western countries and increasingly linked with deranged gut flora and mucosal lesions. Not only has it been observed that diseases such as rheumatoid arthritis (*Midtvedt*, 1987; *Zhang* et al., 2000; *Nieuwenhuis* et al., 2000) and atopic diseases (*Satomi*, 1966; *Rock*, 1998; *Wold*, 1998) are associated with gut flora derangements but also diseases such as autism (*Sandler* et al., 2000; *Wakefield* et al., 2000; *Furlano* et al., 2001; *Lindsey*, 2001; *Torrente* et al., 2002), graft-versus-host disease (*van Bekkum* et al., 1974; *Porrata* et al., 2001) and formation of serosal adhesion (*Bothin* et al., 2001) are intimately associated with gut flora and mucosa.

Some observations suggest that both pre- and probiotics can modify basic bodily functions such as appetite, sleep, mood and circadian rhythm, most likely through signal molecules but also through metabolites produced by microbial fermentation in the gut, known to influence lymphocyte function, production of immunoglobulins and resistance to disease - see further *Bengmark* (2002a,b).

There are also indications in the literature that intestinal microflora stimulates myo-electric activity in the intestine and hereby controls gastrointestinal motility and transit of food under digestion (*Husebye* et al., 1994). Recent studies performed in germfree animals do also suggest (*Hooper* et al., 2001) that some commensal bacteria modulates the genes involved in whole series of important intestinal functions such as nutrient absorption, mucosal barrier fortification, xenobiotic metabolism,

angiogenesis and postnatal intestinal maturation.

The dramatic change in recent years in our knowledge and understanding of the complex functions of the lower GI tract and its function has without question contributed considerably to our understanding of health and disease. During my lifetime the view on the large intestine and its functions has radically changed from being an organ mainly for re-absorption of electrolytes and water to a complex organs, which holds important keys to health and well-being. Further exploration of the large intestine and its interaction with flora has the prospect of helping us to understand and prevent a whole series of diseases including the endemic diseases so much plaguing the Western, and increasingly also the Eastern world.

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