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NUTRITION AND RESISTANCE TO DISEASE

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EPIDEMIC OF CHRONIC AND DRUG-RELATED DISEASES

My decision to become a surgeon was made in the early fifties. At that time pharmaceutical medicine had made some remarkable progress and created a great enthusiasm for the future of therapy with pharmaceutical drugs, an enthusiasm similar to the expectations for the future of gene therapy often met today. There were those, who forecasted that within a few years most diseases, if not all, would successfully be controlled by pharmaceuticals. It is a fact, that I was so affected by this that I felt a real hesitance to choose surgery as my profession, fearing that within few years this form of therapy would be redundant. I would at that time have had difficulties to accept suggestions that as we enter a new century and a new millennium, surgery would be the leading therapy for organ failures such as those of the liver, lung, heart, kidney, intestine but also for diabetes, arteriosclerosis and obesity.

Pharmaceutical medicine, particularly that based on synthetic drugs, has in general failed to meet the high expectancies from 50 years ago, sometimes to the extent that many, especially in the US, seriously question its importance for human health and some turn back to herbal medicine. It is obvious that the Western world as we enter a new millennium suffer more than ever of an epidemic of chronic (Table 1) and of drug-induced (Table 2) diseases. Adverse drug reactions (ADR), e.g. side effects, which occur despite taking the drugs in dosage as prescribed, has become a serious problem as drugs be-

Table 1: Chronic diseases frequent in the Western world, of which most are increasing in incidence (after: *Carper*, 1997)

- One million get cancer each year – in lifetime 40 % of the population
- 60 millions suffer from Hypertension
- 40 millions suffer from Arthritis
- 23 millions suffer from Migraine

Increasing in incidence are:
- Asthma and other allergies
- Chronic fatigue
- Coronary Heart Disease
- Congenital malformations
- Diabetes
- Immune deficiency
- HIV
- Neurodegenerative diseases
- Obesity
- Overwhelming infections

Table 2: Negative consequences of use of pharmaceutical drugs
(after: *Johnson* and *Bootman*, 1995; *Bates* et al., 1997; and *Carper*, 1997)

Each year do:
- about two millions get adverse effects to drugs and
- 106,000 die in adverse drug effects (compare accidents 91,000)
- 61,000 get drug-induced Parkinsonism
- 16,000 are involved in automobile accidents due to drugs
- 163,000 get drug-reduced memory
- 32,000 get hip fractures caused by drug-induced falls
- 6 millions abuse prescription drugs and
- more than 100,000 die in overdose of drugs
- 97,000 die in "medical accidents"

comes increasingly stronger, and it is reported that about seven percent of hospital patients suffer ADR. Each year do only in the US 106000 persons die in ADR, which is more than in accidents (91000) (*Lazarou* and *Pomeranz*, 1998). It has been calculated that the total costs for treatment of ADR only in the US is equal to or eventually exceeds the total costs for care of diabetes and cardiovascular disease, when added together (*Bates* et al., 1997; *Johnson* and *Bootman*, 1995). Also the use of antibiotics is becoming increasingly controversial and there are those who suggest that we are in the process of leaving the antibiotic era (*Roszkowski* et al, 1988). Restricted use of antibiotics is increasingly recommended not only because antibiotics induce antibiotic resistance of some pathogens, but also because they reduce the preventive commensal flora and also temporarily reduce or eliminate macrophage activity (*Henderson* et al, 1996).

ARE ALL DISEASES INFECTIOUS?

We are increasingly aware that health is much depending on interactions between micro-organisms and the human body but also depending on a harmonic balance between microbes and resistance to disease. Robert Koch was in 1876 the first to prove that a disease was caused by a particular micro-organism (anthrax) (*Stanier* et al., 1963). Since the introduction of modern techniques such as polymerase chain reaction (PCR) the establishment of an association of a specific infectious agent and a disease have been made possible without the fulfilment of the so called Koch postulates. This has lead to a revolution in the understanding of disease, showing that infectious agents can be the causes of, precipitating factor for, or risk factors for various diseases that not previously were considered to be caused by transmissible agents. Consequently it has been suggested that eventually all diseases are infectious (*Lorber*, 1996). Not only are there strong indications that diseases such as peptic ulcer disease (*Helicobacter pylori*; *Cover* and *Blaser*, 1995) and arteriosclerosis/cardiovascular disease (*Chlamydia pneumoniae*; *Leinonen* and *Saikku*, 2000) but it is also suggested that various forms of cancers, psychiatric (mental depression), inflammatory, and degenerative diseases are suggested to be infectious.

It is not easy to define health and

well-being, but it is likely to occur as the result of a dynamic interplay between factors that in the body control numerous important processes such as growth, cell proliferation, repair systems, apoptosis, stress response, appetite, energy balance, metabolic rate and numerous other important processes (*Frame* et al., 1998). It is suggested that health and well-being is depending on harmonious interaction in the body of more than two 2 million different chemical molecules. Only of fats have more than 250 thousand been identified in the human body. It is suggested that our Palaeolithic forefathers on annual basis consumed between four and five hundred various plants, a consumption, which modern man to a large extent has reduced to a few such as potato, rice, corn and wheat. In addition do we cook, fry, freeze and dry our food, which is known to destroys numerous important food ingredients (*Schroeder*, 1971), including lactic acid bacteria, but also induce production of mutagenic substances (*Lankaputhra* and *Shah*, 1998). It is against the background of this information the importance of unipharmacy and of synthetic drugs are increasingly questioned, and suggested that "polypharmacy" in the form of proper nutrition and in the form of various herbs and spices should be important to human health and well-being. Many of the numerous health-promoting nutrients such as short chain fatty acids (SCFAs), amino acids and polyamines, vitamins and antioxidants etc. are released in the large intestine by bacterial enzymes (for further information see: *Bengmark*, 2000a).

PARADOXICAL MALNUTRITION COMMON IN WESTERN COUNTRIES

There are those who suggest that all Westerners are malnourished in the sense that they do not receive the large variety of molecules with the food as our ancestors did. Two rather recent studies, one performed in the UK (*McWhirter* and *Pennington*, 1994) and the other in the US (*Gallagher-Allred* et al., 1996) suggest that about half the population are either severe malnourished or at the border of malnourishment. These persons are not malnourished in the traditional sense (as seen in starvation); they show instead signs of overfeeding as they are often obese (paradoxical malnutrition). Clearly it is in this group that we see a significantly increased morbidity and mortality. These individuals show clear signs of metabolic dysfunction and of disease clustering. When subject to surgical operations they often develop complications such as sepsis, thrombosis and also severe adhesion formation. They do often suffer hypertension, arthritis, dyslipdaemia, glucose intolerance and insulin resistance, a condition given the name of metabolic syndrome X (MSX), and suggested to occur in about 20% of the population in Western countries, in about 50% of hospital patients and in almost every patient suffering from severe complications to surgery. Overconsumption/abuse of diary products and red meat (C12-C16 saturated fatty acids and trans fatty acids) and of refined sugar, plus an obvious underconsumption of fresh fruits and vegetables, is suggested to be the cause. Among the food ingredients, which have been suggested to reduce or prevent MSX are various fibres, polyunsaturated fatty acids, phytosterols (rich in soya and in rye), garlic, and fermented products containing LAB.

LESS SATURATED FAT, MORE FIBRE AND LACTIC ACID BACTERIA

It was suggested in 1985 that our genes, which during millions of years of human life on earth are adapted to the pre-agricultural lifestyle do badly tolerate the dramatic change in lifestyle, including eating habits, which has occurred in more recent years (*Eaton* and *Konner*, 1985). It is an interesting hypothesis that this should be the reason why humans are increasingly sensitive to disease and should eventually explain why we suffer an epidemic of chronic diseases. A study of a population uninfluenced by Western dietary habits gives support to such an assumption (*Lindeberg*, 1994). At the island of Kitava in New Guinea do the inhabitants not eat diary products, margarine, lard, oils, refined sugar, alcohol and cereals, which constitutes more than 70% of the Western diet. Such diseases as sudden cardiac death, stroke, retrosternal angina are here virtually absent despite the fact that the majority of the population on this island often smoke and saturated fat from the coconut is a frequent staple food (*Lindeberg*, 1994; *Lindeberg* et al., 1994, 1997, 2000). Here no signs of metabolic syndrome X, which is a serious infliction to about 20% of Westerners, were found. On examination this population is characterised by leanness, low diastolic blood pressure, low values of plasminogen activator inhibitor-1 (PAI-1) (*Lindeberg* et al., 1997) and low serum insulin (*Lindeberg* et al., 2000).

PALAEOLITHIC FOREFATHERS CONSUMED LARGE AMOUNTS OF LACTIC ACID BACTERIA

Our Palaeolithic forefathers ate much less saturated fat, protein, and sodium salt. Instead they consumed up to ten times more of fruit and vegetable fibre, ten times or more of vitamins and other antioxidant, about fifty times of more of omega-3 fatty acids and most interestingly billions of times more of non-pathogenic bacteria, mainly lactic acid bacteria (LAB) such as *Lactobacillus plantarum, Lactobacillus pentoceus, and Lactobacillus paracasei*. Their foods were often stored in the soil, where it became naturally fermented. Furthermore, the food consumed by our palaeolithic forefathers was mainly raw and uncooked. Instead it was often fermented and rich in lactic acid bacteria (LAB).

The food eaten in Western countries has during the last hundred years become increasingly sterilised/pasteurised. The last traces of naturally fermented food (sauerkraut) disappeared from the daily diet in most Western countries during the last fifty years. But, the ability of fermentation to preserve nutrients is much superior to “modern” technologies for processing and storing foods such as drying, freezing, cooking and canning, as it preserves important but sensitive food ingredients much better (examples: various vitamins, antioxidants such as glutathion, and amino acids such as glutamine), ingredients which most often are destroyed by Western methods for handling and treatment of the food.

FIBRE-FERMENTING LACTIC ACID BACTERIA ARE IMPORTANT

Fibre-fermenting bacteria such as *Lactobacillus plantarum* are still dominating among the LAB colonising the intestine of rural Asians, Africans and most likely also South Americans. *Lactobacillus plantarum* is the dominating species in fermented foods such as sour dough, sauerkraut, natural wines and beers and in most third world staple foods such as African *ogi*, *kenkey* and *wara* (*Olasupo* et al., 1995). Although several of these fibre-fermenting LAB do no longer colonise the gut of Westerners, they are still often found in vegetarians. A study performed in the USA showed that about 65% of vegetarians to be colonised with *Lactobacillus plantarum* compared to only 25% of the omnivorous (*Finegold* et al., 1983). A recent study performed in Sweden suggest the largest LAB taxa found on rectal mucosa in healthy humans are *Lactobacillus plantarum, Lactobacillus rhamnosus,* and *Lactobacillus paracasei* ssp. *paracasei* isolated in 52%, 26% and 17% respectively (*Ahrné* et al., 1998). Commonly milk-born LAB such as *Lactobacillus casei, Lactobacillus reuteri* and *Lactobacillus acidophilus* was found on the colonic mucosa only in a minority of individuals, 2%, 2% and 0%. It is reported that cosmonauts on return to earth from space flights have lost most of their commensal flora: *Lactobacillus plantarum* to 100%, *Lactobacillus casei* to almost 100%, *Lactobacillus fermentum* to appr. 50%, only to mention a few (*Lencner* et al., 1984), but also increased their flora of potentially pathogenic micro-organisms, changes attributed to the poor food eaten in the space and to stress. It is suggested that many Westerners also on Earth have an "astronaut-like" lifestyle, which could explain their, compared to our forefathers and to rural Africans and Asians, deranged intestinal flora.

NOT ALL LACTIC ACID BACTERIA SURVIVE GASTRO-INTESTINAL PASSAGE

It is important to remember that there is a great variety among the LAB in their ability to survive passage through the gastro-intestinal tract and to influence the immune system. A recent study compared in a gastro-intestinal model four different LAB: *Lactobacillus plantarum* (E98), *Lactobacillus paracasei* (E510), *Lactobacillus rhamnosus* (E522) and *Bifidobacter* animalis (E508), all administered in a dosis of 10^8 (*Miettinen* et al., 1998a). All strains were reduced in number, but the survival was much better for *Lactobacillus plantarum* (remaining 10^7) than for *Lactobacillus rhamnosus* (remaining 10^2). Most strains showed after the passage a weak ability to induce cytokine, but *Lactobacillus plantarum* demonstrated despite its reduction in numbers, an increased ability to induce production of cytokines such as TNF-α and IL-6, suggesting that this particular LAB is activated during the passage through the gastro-intestinal tract.

TWO PRINCIPALLY DIFFERENT DIGESTION SYSTEMS

Digestion is depending on two different digestion system, one based on digestive enzymes produced by eukaryotic cells and secreted as saliva, gastric, pancreatic and intestinal secretions, the other based on microbial enzymes produced mainly in the large intestine. It is obvious that the microbial system is much more complex and much richer in various enzymes. An indication of this is that the microbial genome is calculated to contain about four to five times as many genes as the human genome (about 300,000 versus 60,000). It is in the large intestine that complex carbohydrates and proteins are broken down and hundreds of thousands if not millions of nutrients set free and absorbed. Among these are short chain fatty acids, amino acids, polyamines, various other fatty acids, vitamins, antioxidants, growth factors and coagulation factors, and messenger molecules such as cytokines and nitric oxide produced.

It is increasingly recognised that an important part of the food should be of a type which reaches the large intestine more or less untouched, e.g. to large extent fruits, vegetables, pulses, tubers, a type of food often referred to as colonic food. Health authorities in various countries do also recommend that about 70% of the food eaten should be of the type destined for the colon. While the importance for health of daily supply of prebiotics/plant fibres is well documented in the literature, there is not yet enough evidence in the literature to support the necessity of daily consumption of probiotics. It seems often difficult to understand that a few grams of daily consumption of LAB can have a significant influence on human health when the large intestine in a normal and healthy individual contains one kilogram or more of live bacteria. However, it cannot be excluded that daily intake of LAB is of the greatest importance for the upper gastro-intestinal tract, the stomach and the small intestine, which are poorly colonised by LAB (*Lencner* et al., 1984).

MICROBIAL DYSBALANCE AND REDUCED RESISTANCE TO DISEASE

The microbial content of the colon of Westerners is quantitatively and qualitatively much different from that of rural Africans and, most likely, also from that of our Palaeolithic forefathers. There are good reasons to suggest that all Westerners have a dysbalance of the commensal flora, and that this could be associated with the observed reduced resistance to disease. Not only is the flora larger in rural Africans (about 2 kg versus about 1 kg in Westerners), it is also much richer.

Among the pathogenic bacteria associated with MSX are *Helicobacter pylori* and C*hlamydia* pneumoniae (*Laurila* et al., 1997, 1999). There are good reasons to speculate that the main reason why these microbes cause morbidity is a reduced resistance to disease, parallel to a microbial dysbalance, which leads to abnormal short-term (acute phase) and long-term (chronic phase) responses (*Bengmark*, 2000a). It appears in this connection to be of the greatest interest that LAB are shown to inhibit not only the growth of *H pylori in vitro* but also to exhibit strong antagonistic activity against *H. pylori in vivo* (*Kabir* et al., 1997; *Coconnier* et al., 1998).

Gastric production of NO is suggested to be crucial for control of the

Table 3: Content of arginine (mg/100 g) in some arginine-rich foods, compared to common Western foods such as hamburgers and French fries

Gelatine		6,000
Pumpkin seeds		4,030
Soya protein		3,760
Pea nuts		3,600
Sesame seeds		3,330
Soya beans		2,730
Almonds		2,500
Sunflower seeds		2,400
Brazil nuts		2,390
Peas, lentils		2,050
Shrimps		2,000
Baker's yeast		2,000
Parmesan cheese		1,560
Meat, fish		1,500
HAMBURGERS		950
Cereals	appr.	500
FRENCH FRIES		140
KETCHUP		125
Vegetables	appr.	100
Pulses	appr.	100
Fruits	appr.	50

pathogenic flora in the stomach, and acidified nitrite is shown to be effectively eliminate *Candida albicans, Escherichia coli, Shigella, Salmonella, H. pylori* but also conditions such as amoebic dysentery and chronic intestinal parasitism (*Duncan* et al., 1995). Adding 1 mM of nitrite *in vitro* of to an acidic solution (pH 2) will within 30 minutes produce a complete kill of *H. pylori*, which is not seen when acid alone is administered ($p<0.001$) (*Dykhuizen* et al., 1998). Gastric NO production does not occur in germfree animals, or when some pharmaceutical drugs influencing gastric secretion, especially H_2-blocking agents or proton inhibitors, are administered. It is also significantly less when antibiotics are supplied.

It is suggested that in the oral cavity species such as *Actinomyces* spp. and *Veillonella* spp., but not the most frequent species *Streptococcus* spp., exhibit a strong capacity to reduce nitrate and to produce NO (*Smith* et al., 1999). This process is both in the oral cavity and in the stomach influenced by the level of the pH in the oral cavity and a sucrose rinse results in a significant decrease in intra-oral generation of NO.

A link between endogenous nitric oxide production, MSX and occurrence of arteriosclerosis and thrombosis has been suggested (*Petrie* et al., 1996; *Pollard*, 1997), and dietary supply of the NO donor molecule L-arginine has been shown to reduce oxidative stress and preserve endothelial function in hypercholesterolaemic rabbits (*Böger* et al., 1998). NO-donating molecules such as arginine (Table 3) and nitrate/nitrite (Table 4) are rich in some foods such as some vegetables and fruits (*Andersson*, 1985). It is likely that also NO produced by bacterial action is important not only to the control of microbial overgrowth, but also to regulation of mucosal and

Table 4: Content of nitrate (mg/kg) in some nitrate-rich vegetables (after: *Andersson*, 1985)

Fennel	3,200
Lettuce	2,900
Celery	2,700
Mangold	2,600
Dill	2,400
Spinach	1,900
Beetroot	1,700
Nettle	1,600
Radish	1,300
Chinese cabbage	1,100
Savoy cabbage	1,100
Leek	700
Rhubarb	700
Chives	670
White cabbage	620
Squash	580
Broccoli	490
Horse radish	390

splanchnic (digestive tract) blood flow and to stimulation of gastro-intestinal motility (*Bengmark*, 2000b).

Rhubarb is rich in nitrate and when tried as a rhubarb decoction in experimental pancreatitis a significant reduction in the rate of microbial translocation to mesenteric lymph nodes and to pancreatic tissue (treated 25% vs. controls 100%), in mortality (1/8 vs. 5/8 animals) and in serum endotoxin levels (treated: 5.41±3.6 pg/L vs. controls: 61.36±28.3 pg/L, $p<0.001$) was observed (*Chen* and *Ran*, 1996). The authors did also observe that the gut motility otherwise seriously inhibited in pancreatitis was "significantly improved by administration of rhubarb."

HOMEOSTASIS/EQUILIBRIUM IN BODY SYSTEMS ARE IMPORTANT

Equilibrium in various body systems was regarded as extremely important to health by ancient medicine both in the East and the West. The French physiologist Claude Bernard introduced in the 19th century the concept of homeostasis to describe the importance of balance in the body of water and electrolytes. Today this concept has received a much broader meaning. Much support as a matter of fact that health is depending on numerous cellular systems and bodily processes in equilibrium: eukaryotic and prokaryotic cells, growth/regeneration and apoptosis, omega 3 and omega 6 fatty acids, pro-inflammatory and anti-inflammatory cytokines, just to mention a few.

It has in recent years often been suggested that a balance between Th1-lymphocytes, primarily associated with cellular immunity, and Th2-lymphocytes, mainly associated with humoral immunity is essential to health and well-being. Reduced microbial stimulation during early infancy and childhood, especially in developed countries, has been associated with the increasing

prevalence of allergy in children and young adults (*Björksten*, 1994). Reduced microbial stimulation is associated with slower postnatal maturation of the immune system, a delayed development and lack of balance between Th1 and Th2 immunity (*Lucey* et al., 1996).

Swedish infants have been reported to have a different gut flora than both Pakistani (*Adlerberth* et al., 1991) and Estonian children (*Sepp* et al., 1997). Some *Lactobacillus* species promotes Th1-type response and inhibits Th2-type immune response through stimulation of IFN-γ and IL-12 production (see below), hereby inhibiting allergic reactions (*Murosaki* et al., 1998). Stimulation of human peripheral blood mononuclear cells (PBMC) with various *Lactobacillus rhamnosus* and *Lactobacillus bulgaricus* strains leads to induction of Th1 type cytokines IL-12, IL-18, and IFN-γ (*Miettinen* et al., 1998b); and supply of *Lactobacillus casei* (*Shida* et al., 1998) and *Lacobacillus plantarum* (*Murosaki* et al., 1998) respectively to a total inhibition of antigen-induced IgE secretion both in ovalbumin- and casein-primed mice, an effect not observed when *Lactobacillus johnsonii* is tried.

SOME LACTIC ACID BACTERIA PROMOTE APOPTOSIS

Programmed cell death, apoptosis, is an important process, which leads to control of diseases such as cancer but also infections, especially those of viral origin. Some foods, such as diary products, rich in fat and in insulin-like growth factor 1 (IGF-1) and other tropic hormones and often also xeno-estrogens (from pesticides) are known to delay apoptosis (*Outwater* et al., 1997; *Westin* and *Richter*, 1990). On the other hand foods rich in fibres such as oat, wheat, rye, and chicory (inulin) will significantly increase apoptosis and prevent diseases such as cancer (*Hong* et al., 1997). It has been observed in experimental animals that feeding beans increases the production of short chain fatty acids (SCFAs) sevenfold (*Key* and *Mathers*, 1995), and that feeding fibres such as oligofructans (inulin) inhibits induction of colonic preneoplastic lesions (*Reddy* et al., 1997). As LAB produce SCFAs and SCFAs are known to promote apoptosis (*Heerdt* et al., 1994; *Marchetti* et al., 1997) and inhibit neoplasm, it should be reasonable to assume that LAB have an important role in cancer prevention.

SOME LACTIC ACID BACTERIA ACTIVATE MACROPHAGES

Saturated fat is known to inhibit the important process of phagocytosis e.g. the ability to engulf, kill and eliminate invading micro-organisms and/or defective cells, but also to eliminate toxins, mutagens and other poisonous substances. Also many chemicals including drugs and antibiotics do significantly inhibit apoptosis, effects, which has not been investigated and considered, as they should. Phagocytosis is known to be significantly enhanced by low molecular weight peptides obtained from species of the indigenous gastro-intestinal tract microflora such as such as *Bacteroides sp.*, *Clostridium sp.*, *Propionibacterium sp.* and from *Lactobacillus sp*. (*Pulverer* et al., 1990; *Kilkullen* et al., 1998), as well as of live bacteria including LAB, although not

all. As an example it has been observed that *Lactobacillus fermentum* is unable to increase macrophage activation (Kato et al., 1988).

CYTOKINE RELEASE INFLUENCED BY LACTIC ACID BACTERIA

The explosion in cytokine research in recent years and the availability of commercial kits to study cytokine reactions has lead to a flood of studies where reactions in various cytokines are observed in trauma and disease, but also after supplementation of LAB. There seems to be support for the assumption that the cytokine profile observed after oral administration of LAB reflects the direction and efficacy of the humoral response, and that different LAB, when supplied, influences this effect in different ways. Most of the attention is so far given to the cytokine production by monocytic cells such as macrophages, but mononuclear eukaryotic cells are also important sources of cytokines. It has become increasingly evident that tissues such as intestinal mucosal cells (*Eckmann* et al., 1995) and prokaryotic cells such as commensal flora and/or supplemented probiotic bacteria (*Ogle* et al., 1997; *Henderson* et al., 1997) secretes a spectrum of chemo-attractants and cytokines or cytokine-like molecules, often called bacteriokines.

Supplementation with some LAB seems to significantly influence the expression of cytokines by the cells, but the cytokine response is very different depending on the strain of LAB, which is supplied. It is regrettable that research has concentrated on the effects of milk-born LAB, but there is today a growing interest specifically in LAB with ability to ferment plant fibres, which are expected to have much stronger immunological effects. Among such LAB are bacteria such *Lactobacillus plantarum, Lactobacillus paracasei* ssp. *paracasei, Lactobacillus pentoceus* but also various *Lactococcus, Pediococcus* and eventually also *Enterococcus* species.

STRAIN-RELATED RESPONSE TO LACTIC ACID BACTERIA

St. thermophilus stimulates macrophage and T-cell cytokine production to a greater extent than *Lactobacillus bulgaricus, Bifidobacterium adolescentis* and *Bifidobacterium bifidum*, but a significant variability in effect has been observed between four different strains of *S. thermophilus* tried (*Marin* et al., 1998). Heat-killed *Lactobacillus acidophilus* (LA 1) has *in vitro* been shown to increase the production by mouse macrophages of IL1-α (appr. 300%) and TNF-α (appr. 1000%), an effect said to be of considerably greater magnitude than that produced by other tried *Lactobacillus* and *Bifidobacteria* (*Rangavajhyala* et al., 1997). The activity of 2´-5´synthetase, an expression of interferon-gamma (IFN-γ), in blood mononuclear cells of healthy subjects is 24 hours after a LAB-containing meal shown to be significantly increased (appr. 250%) (*Solis-Pereyra* et al., 1997). Significant increases in cytokine activity compared to controls are also observed when human mononuclear cells are incubated in the presence of the yoghurt bacteria; *L. bulgaricus (BUL),* and *S. thermophilus (Ther),* alone or in combination (Yog); INF-γ*: Bul* 775 %,

Ther 2100%, Yog 570 %, TNF-α: *Bul* 1020%, *Ther* 3180 % Yog 970%, and in IL-1β: *Bul* 2120 %, *Ther* 1540%, Yog 1920 %, all indicating a significant immuno-activation after supply of LAB.

Lactobacillus casei, when administered intrapleurally in tumour-bearing mice induces significant production of cytokines such as IFN-γ, IL1-β, TNF-α, paralleled by inhibited tumour growth and increased animal survival (*Matsuzaki* et al., 1997). Supply of this LAB to diabetes-prone and alloxan-treated animals delays also the onset of diabetes (*Matsuzaki*, 1998). It is of interest to observe that in experimental animals nitric oxide (NO)-donating molecules such as L-arginine and sodium nitroprussid when supplied will restore antioxidant status to almost normal and to prevent alloxan-induced beta-cell damage (*Mohan* and *Das*, 1998).

LACTIC ACID BACTERIA INDUCE GUT Ig-A PRODUCTION

Adaptive immunity at mucosal surfaces provides an immunological barrier to foreign matter, particularly pathogenic micro-organisms, allergenic food proteins and carcinogens. Immunoglobulin A (IgA) and to some extent immunoglobulin M (IgM) are dominant among the intestinal secretion immunoglobulins. Selective IgA deficiency is the most common immunodeficiency in Westerners. Decreased IgA levels are often compensated for by increased production of IgM, which is why clinical abnormalities often are difficult to recognise. IgA does not participate in the pro-inflammatory and cytotoxic responses that are readily activated by other immunoglobulins such as complement activation, nor in antibody-directed cytotoxic responses (*Kagnoff*, 1993).

Large quantities especially of IgA are transferred each day from the lamina propria to the lumen of the gut. It has been calculated that about 80% of all the body's Ig-producing immunocytes are localised in the gut (*Brandtzaeg* et al., 1989). The synthesis of IgA is highly dependent on T-cells and several cytokines produced by activated lymphocytes, which influence different steps in the IgA differentiation pathway (*Kiyono* and *McGhee*, 1994). Changes in nutrition, physical activity, sleep, mood, age, gender, circadian rhythm, drug use, medical illness and other innate changes are known to influence lymphocyte function and the Ig-production and hereby also resistance to disease. It has as an example been observed in liver transplantation patients that deficiency in IgA, but not in IgG and IgM, is associated with significantly increased morbidity and mortality in sepsis by opportunistic infections after major surgery, but also with increased rejection after liver transplantation (*van Thiel* et al., 1992).

LAB may during fermentation release components that possess immunomodulatory activity. However not all LAB may possess that ability. As an example, only 3/120 *Bifidobacteria* strains isolated from human faeces - two *Bifidobacterium breve* and one *B. longum* - had when studied in tissue culture the ability to induce production by Peyer´s patches of large quantities of IgA (*Yasui* et al., 1992). Supply of LAB such as *Lactobacillus* GG in Crohn´s disease is reported to significantly increase the IgA immune response (*Malin* et al., 1996). LAB are also reported to enhance the IgA response to rotavirus (*Kaila* et al., 1992). Intake of *Lactobacillus acidophilus* will

Table 5: Results of treatment with *Lactobacillus plantarum 299* after liver transplantation in man* (after *Rayes* et al., 1999)

Patient group	Treatment	30-day infection rate
Group 1	Selective bowel decontamination (tobramycine, cefalaxine and metronidazole) for 4 weeks. 2 litre enteral nutrition without fibre from the second postoperative day.	6/15 (40%)
Group 2	2 litre enteral nutrition with inulin fibre and heatkilled Lactobacillus plantarum from the second postoperative day.	4/15 (27%)
Group 3	2 litre enteral nutrition with inulin fibre and live *Lactobacillus plantarum* 299 from the 2nd day.	2/15 (13%)

*Enteral nutrition via naso-jejunal tube from day 2, peri-operative antibiotics (tobramycine, cefalaxine, and metronidazole) to all patients, prophylaxis against HSV (acyclovir), PcP (co-trimoxazole, cyclosporine or tacrolimus).

a >4 fold increase in IgA response, when challenged by *S. typhi* (*Solis-Pereyra* et al., 1997), and supplementation of *L. reuteri* (R2LC) or *L. plantarum* (299 V, DSM 9843) to rats with methotrexate colitis to significantly increase small and large intestinal IgA secretion to elevate the numbers of both CD4 and CD8 T-cells (*Mao* et al., 1997).

STRONG CLINICAL EFFECTS OF LACTIC ACID BACTERIA IN VARIOUS DISEASES

Numerous studies have proved the efficacy of LAB in various induced diseases in rats such as acetic acid colitis, methotrexate colitis, intra-abdominal infections, pancreatitis, acute liver injury etc. – for review see *Bengmark*, 1998a,b,c, 1999, 2000a,b,c,d; *Bengmark* et al., 2000. A recent study in rats documented efficiency of *L. plantarum* to preserve the gut mucosal barrier and to prevent colitis in Interleukin-10 knockout mice (*Kennedy* et al., 2000). Another recent published study demonstrated improved healing of colonic anastomoses after administration of *L. plantarum* to rats (*Colucci* et al., 2000).

So far only few controlled clinical studies with LAB and fibres have been performed but several studies are on the way. However, a most interesting study in liver transplantation patients was recently published (Table 5) (*Rayes* et al., 1999). The one-month sepsis rates were with selective decontamination 40%, enteral supply with inulin and oat fibres plus heat-killed Lactobacillus plantarum 299 27% and the same fibres + live *Lactobacillus plantarum 299* 13%. *Lactobacillus plantarum 299* was also in recent study found to significantly improve natural immunity, nutritional status and to improve growth in children with congenital HIV (*Cunningham-Rundles* et al., 2000).

IMMUNOLOGICAL EFFECTS MORE IMPORTANT THAN NUTRITIONAL

Two recent studies compared short-term enteral and parenteral supply to patients after larger operations (liver resection: *Shirabe* et al., 1997) and acute severe disease (pancreatitis: *Windsor* et al., 1998). They found no difference when measuring nutritional parameters but very significant differences when measuring immune-related parameters, paralleled by significant reduction in sepsis and sepsis-related complications in the enterally nourished groups. From these studies and others it has become increasingly evident that the immunological effects of nutrition is far more important than those obtained by measuring traditional nutritional parameters such as energy and nitrogen balance. Much support that immunological effect of nutrition is an important key to the understanding and control also of chronic diseases. As we enter a new millennium there seem to be a fast increasing interest in the role of nutrition to control disease within the medical professions as well as among the consumers. Government and other health authorities are also increasingly involved and publish dietary guide recommending dramatic life-style changes. It is my believe that the recommended alternative life-style and food habits should not only consist in a significantly increased consumption of fibre- and antioxidant rich fruits and vegetables, but also an increased consumption of especially fibre-fermenting lactic acid bacteria.

There is in modern medicine a tendency that the sickest patients, those in intensive care, will get the poorest foods, often only provided as semi-synthetic powders. This must immediately be changed and the sickest patients also receive fresh juices of fruits and vegetables but also of lactic acid bacteria.

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