



THE HOTEL ROYAL at Évian Resort where workshops of the 1st World Summit on Gut Microbiota for Health were held.

Exploring the new organ

Interview with Professor Fernando Azpiroz (Autonomous University of Barcelona, Spain)

Prof. Azpiroz, it is only recently that the Gut Microbiota & Health Section was founded as part of the European Society of Neurogastroenterology and Motility (ESNM). What were the motives?



PROF. FERNANDO AZPIROZ,
Chairman of ESNM's Gut Microbiota & Health Section

Prof. Fernando Azpiroz: Within our society, we have for a long time been concerned with the interaction between the gut and the brain but it was not until a few years ago that it became apparent that there was a third player to be taken into account: the gut microbiota. We integrated this "new organ" in our framework, so that we now speak of the microbiome-gut-brain axis, which is bidirectional in terms of cause and effect. Due to the medical importance of these findings, we felt the need to create a sec-

Continued on page 3 →

There's life in inner space

Gut microbiota can be regarded as a "new organ"

A fascinating yet previously unknown diversity of life forms has been discovered, not in outer space but inside our bodies. Myriads of bacteria symbiotically living within the human gut form a biological society that profoundly influences our health. The 1st World Summit on Gut Microbiota for Health (26–28 March 2012, Évian/France) provided physicians, nutritionists and specialist journalists with new insights into a most promising field of cutting-edge research.

For three days the charming town of Évian, located at Lake Geneva, provided the venue for a conference on the latest developments in the field of gut microbiota research. Round tables, lectures and workshops organised by the Gut Microbiota & Health Section of the European Society of Neurogastroenterology and Motility (ESNM) and held by internationally distinguished experts attracted clinicians, general practitioners and nutritionists alike. They learned that the intestinal microbiota (formerly called "gut flora") can rightly be regarded as a whole organ in itself, including the incredible amount of at least 10^{14} bacteria weighing between 1.5 and 2kg.

EIGHT MILLION GENES

As Prof. James Versalovic (Baylor College of Medicine, Houston, USA) pointed out, this abundant variety of life forms comprises more than 1,000 bacterial species

Continued on page 2 →

CONTENT

Truly interactive: in Évian, old-fashioned lecturing was abandoned	3
Birth shapes gut microbiota: mode of delivery can make a difference	4
Intricate interplay: immune system and gut microbiota are intertwined	5
Rich harvest: gut bacteria help getting the most out of food	6
Diet – the driving force:	
unhealthy food triggers nutritional diseases via gut microbiota	7
The potential of probiotics: promising outlook but many open questions	8

and consists of 10 times more cells than there are human cells in the body. So far 8 million genes of bacteria living in human intestines have been catalogued. Thus, the gut microbiota's metagenome – the so-called "microbiome" – turns out to be much more diverse than the human genome with its 23,000 genes and does in fact form a "second genome" harboured by the human gut.



PROF. JAMES VERSALOVIC,
Baylor College of Medicine, Houston, USA

Unlike human genes, however, the gut microbiome is not inherited genetically as we are all sterile at birth. The composition of the microbiota and its equilibrium is strongly influenced by conditions of birth, diet or intake of antibiotic drugs. But recent studies show that, in spite of all individual differences, the world's human population can be divided into not more than three "enterotypes" – classes which are defined by the domination of certain species within the individual's intestinal bacterial population. These enterotypes are not related to nationality, age or gender.

REMARKABLE SCIENTIFIC PROGRESS

The remarkable scientific progress that has been made during the past years regarding the gut microbiota is largely due to innovative research techniques. These allow to investigate in detail large numbers of samples of microbial DNA as



LA GRANGE AU LAC,
the venue for the summit's plenary sessions

well as individuals' interactions between host and microbes, as Prof. Joël Doré (INRA / French National Institute for Agricultural Research, France) pointed out. Until recently, microbiota bacteria could mostly be studied only under laboratory conditions, which meant considerable restrictions as around 60% of bacterial species will not grow in such an environment. Important insight is also gained by transferring bacteria of healthy and diseased individuals into the colons of animals which are germ-free (i.e. without gut microbiota) in order to observe the effects on the animals' health. By considerably accelerating the technological capacity and extending the state-of-the-art knowledge during the past decade, microbiota research has become one of the most exciting fields of cutting-edge science within gastroenterology. The current dynamics of scientific activity are reflected in the fact that nearly one third of the 1,600 publications on the intestinal microbiota listed by PubMed since 1977 appeared in 2011.

HUGE IMPACT ON HEALTH

All this has a huge bearing on our health as the microbial activities are strongly linked with the whole human body. Both

Prof. Versalovic and Prof. Doré presented the audience with a variety of recent studies showing the tight interplay between the gut microbiota and a broad variety of malfunctions. Nutrition-related disorders, inflammatory bowel diseases and certain allergies can often be linked to varying compositions of the intestinal microbiome. A better understanding of the gut microbiota will therefore provide information essential for improving diets and efficiently dealing with diseases such as obesity, metabolic syndrome, food intolerance, ulcerative colitis or IBS.



PROF. JOËL DORÉ,
INRA, Jouy-en-Josas, France

Analysing the microbiota might also allow to predict an individual's risk to develop gut diseases.

As mental processes are also affected through communication paths between intestine and central nervous system, even the treatment of certain mental disorders is likely to benefit from the ongoing research. Though, in order to make use of this huge diagnostic and therapeutic potential, much basic and clinical research remains to be done. But Prof. Versalovic and Prof. Doré left no doubt that the answers to the still open questions will soon improve the prevention, diagnosis and treatment of a broad range of gastrointestinal diseases in many ways.

"The gut microbiota is extremely complex and diet influences the microbiota composition. We have lots of evidence that the microbiota composition is associated with health."



Colin HILL [Speaker] - Ireland



THE SUMMIT'S PARTICIPANTS could use the "SpotMe" device to communicate with the speakers

Truly interactive

In Évian, old-fashioned lecturing was abandoned

At the 1st World Summit on Gut Microbiota for Health, gastroenterologists met with biologists, nutritionists and experts from various other fields. Together they shared the experience of three days filled with inspiring information exchange, thought-provoking discussions and open-minded interdisciplinarity. This outcome was made possible to a large extent through the interactive character of the event's formats.

The summit's attendees already became aware at the registration desk that this was going to be a truly interactive event: everyone was handed a "SpotMe" device. The small black box, which provided the names, photos and some basic professional features of all participants at the touch of a few buttons, accompanied the attendees all through the conference: it enabled them to locate colleagues, send messages, exchange information and arrange meetings. In addition, a particularly useful function allowed speakers and audience to communicate during the talks and presentations.

The organisers of the event had abandoned the old-fashioned lecture with the audience just passively listening to the expert. Due to the fact that microbiota research is a newly emerging area with "stakeholders" from very different backgrounds and with diverse expectations, they relied on formats which stimulated discussions and the exchange of

different points of view. At the beginning of the conference, round tables featuring experts from the various fields served to make the audience familiar with the current state of research while ample time was allotted to questions and comments. This input from the participants, coming via SpotMe as well as Twitter, provided the speakers with valuable information on the background knowledge and the demands of their audience. That in turn helped them design the workshops – taking place on day two of the conference – according to the needs of the attendees. These workshops, being the second main format of the summit, allowed focusing on certain selected aspects. Here, the emphasis on interactivity was even stronger as discussions and working groups held centre stage. Once again, SpotMe came in handy: it allowed the workshop leaders to direct standardised questions to all participants concerning their opinions and experiences – useful input to build the presentations on.

Interview continued from page 1

tion which deals specifically with this issue and which is open to everybody working in the field.

What are the goals of the section?

Prof. Fernando Azpiroz: Our main activities comprise education, information dissemination and, of course, healthcare as we want to translate scientific knowledge into clinical application for the patients' benefit.

How did the idea of the 1st World Summit come into being?

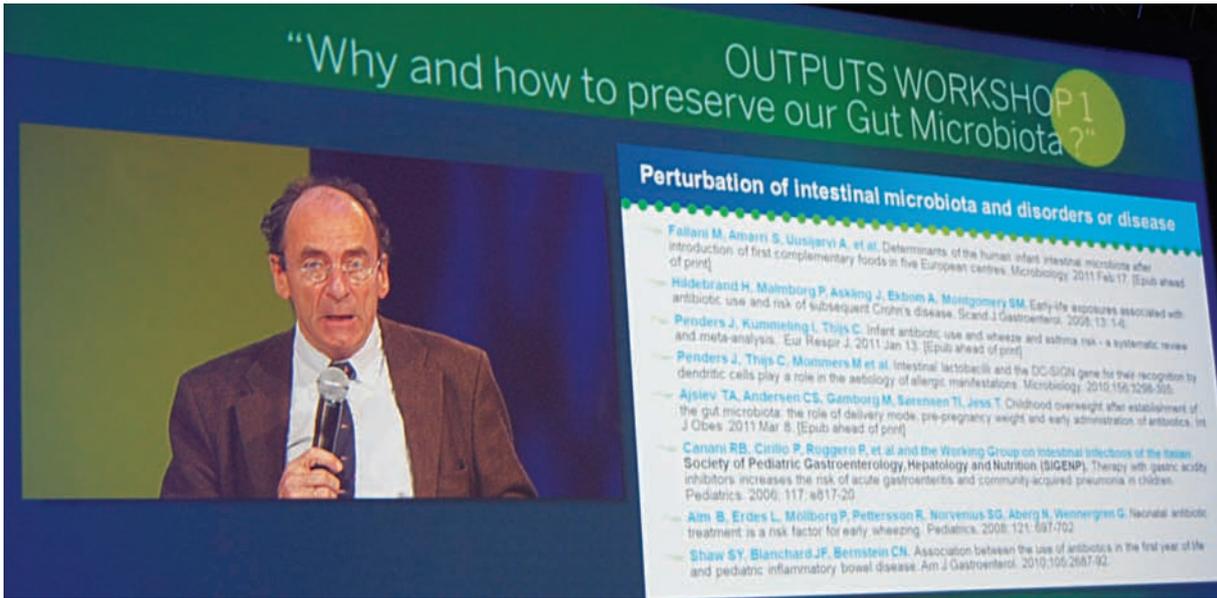
Prof. Fernando Azpiroz: This meeting was the first major action that was taken by our section and it was prepared within a very short period of time. With so many exciting developments being under way right now, we felt the urge to react and provide a platform for high-quality information and exchange.

Have your expectations been fulfilled?

Prof. Fernando Azpiroz: Absolutely. Particularly well received was the format of this meeting, which was quite unique insofar as we placed strong emphasis on the overall interaction between participants and speakers. Another particularity of the event was that the excellence of the speakers was matched by that of the attendees. The success of this event encouraged us to prepare a 2nd summit for spring 2013, to be held in Spain.



"This summit was really an exchange of the opinion leaders of the world. That must be useful for the planning and direction of research in this important field in the future."



PROF. OLIVIER GOULET, Necker Hospital for Sick Children, Paris, France, at the Gut Microbiota for Health summit

Birth shapes gut microbiota

Mode of delivery can make an important difference

Whether a baby is delivered vaginally or by caesarean section, whether it is breast- or formula-fed has great impact on the colonisation of the gut. The consequences for the individual's well-being may be far-reaching, even in adulthood.

In most cases the bacterial colonisation of the gut starts with the baby's passage through the birth canal. However, with children who are delivered by caesarean section the situation is somewhat different. Their intestines are initially colonised by environmental microbes from their mother, the air, and the nursing staff. According to Prof. Olivier Goulet (Necker Hospital for Sick Children, Paris, France), these differing birth conditions have important consequences: vaginally-delivered infants receive more of the beneficial bacteria which provide shelter against diseases, help extracting nutrients and support the maturation of the intestinal mucosa. Most prominent among these is *Bifidobacteria*, a species that helps to produce certain vitamins as well as to protect against immune and nutritional disorders.

At the same time, the guts of caesarean-delivered babies contain a higher amount of less beneficial or even potentially harmful bacteria, one example being *Clostridium perfringens*, a type that might cause infections. In a similar way, breastfeeding offers better condi-

tions for a balanced and healthy microbiota than formula feeding.

BIRTH CONDITIONS AND DISEASES

How important these starting conditions may be is shown by studies which statistically link caesarean delivery and formula feeding as well as antibiotic treatment in early childhood to an increased risk for IBD, digestive disorders and allergies. The precise causal relations, however, remain to be clarified. Prof. Goulet points out that parents of caesarean-delivered or formula-fed children need not be alarmed, though, as the deficits of these microbial populations are often levelled out after around six months. Nevertheless, caution and awareness are advisable as the colonisation of the infant's gut already gives shape to the composition of the microbiota in later years. At around one year of age, the child's intestinal microbiota already starts to resemble that of a young adult. "A well-balanced gut microbiota is key in preserving one's well-being," says Prof. Goulet. "The foundations for this are laid very early."

Apart from birth conditions, another factor in putting a healthy composition of the gut microbiota at risk has emerged during the past decades. According to Prof. Goulet, the highly improved hygiene in western countries, which has decreased the number of infectious diseases, also has its down side: as the exposure to microorganisms during infancy has been significantly diminished, the immune functions, which depend heavily on the intestinal microbiota, develop inappropriately in a growing number of individuals. The result has been an increase in immune disorders such as IBD, asthma or type 1 diabetes.



"What the summit did best was to summarise a broad range of topics. I did not know as much about the paediatric side of things, about the initiation of the microbiome and things that might influence that."

Intricate interplay

Immune system and gut microbiota are tightly intertwined

The immune system and the gut microbiota interact to protect the body against hostile intruders. However, when immune functions fail, it may lead to inflammatory conditions such as ulcerative colitis or Crohn's disease. Growing insight into the interplay between immune cells and bacteria will help to establish therapies which are based on supporting the beneficial species of the gut microbiota and on correcting defective immune signalling pathways.

Why do we not all develop inflammation as we all harbour such a huge amount of bacteria, including potentially harmful ones, inside our intestine?" Prof. Balfour Sartor (University of North Carolina, USA) took this question as a starting point to outline the complex interactions between gut microbiota and immune system. Normally the gut serves as an efficient barrier against bacteria and their products as it consists of several layers of defence. These include the mucus, the epithelial wall and the intestinal immune system, which functions through complex interactions of cellular signalling pathways that stimulate the immune response. As much as 70% of our immune cells are located in the gut.

By no means all bacterial species are harmful to the host, as Prof. Sartor pointed out. Some are neutral or even protective. These beneficial functions include the direct inhibition of pathogen growth, the depletion of pathogens' nu-

PROF. BALFOUR SARTOR,
University of North Carolina, USA



trients or the stimulation of immune responses. The gut immune system and gut microbiota work closely together as the intestinal cells' immune responses control and shape gut bacteria into communities that help defend the body against disease-causing invaders.

INFLAMMATORY CONDITIONS – A PRODUCT OF INTERACTION

However, when gut barrier functions fail, it may lead to inflammatory conditions. In certain cases of Crohn's disease, a mal-



Senne STARCKX- Belgium

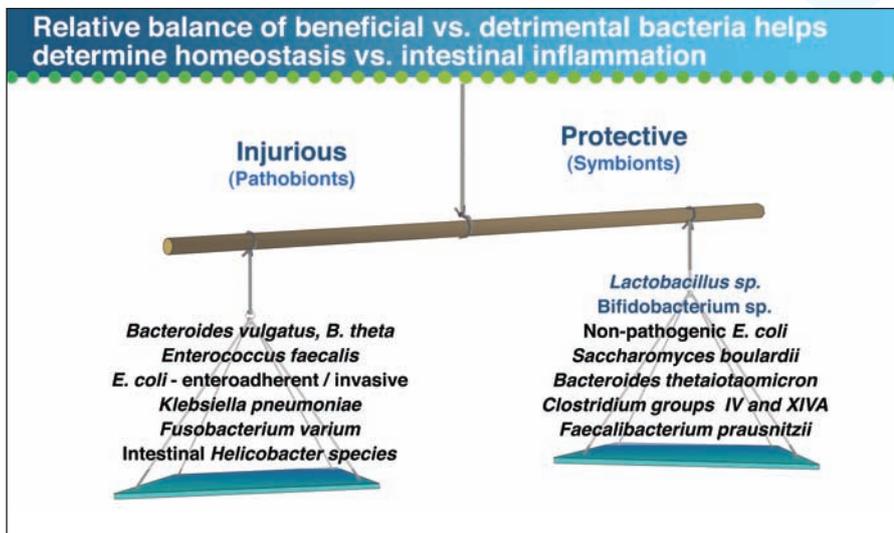
"My first impression of the summit is it's quite high level. There are many experts here from different fields. I learned that the gut microbiota is some kind of ecosystem because it's quite on its own. And the more diverse it is, the more stable it is."

function of the NOD2 gene induces an overreaction of the immune system against several bacterial components. "We believe that Crohn's disease is a product of interaction between genetic susceptibility, environmental factors such as diet or antibiotic treatment and certain bacteria that provide antigens which drive an immune response that in the end leads to the disease," says Prof. Sartor.

In the healthy individual, the composition of the microbiota is very diverse, including a high level of protective and a low amount of potentially harmful species. In patients with ulcerative colitis and Crohn's disease, the general diversity is lower and the proportion of beneficial and pathogenic bacteria is reversed.

BETTER UNDERSTANDING – IMPROVED TREATMENT

According to Prof. Sartor, translating the better understanding of the gut microbiota interaction into better and less aggressive treatments will include the selective elimination of detrimental bacteria while at the same time preserving or enhancing the protective bacterial species as well as correcting defective immune signalling pathways.



A WELL-BALANCED MICROBIAL COMPOSITION is key in preserving gut health.



DAILY FOOD – gut bacteria help to make the most of it

Rich harvest

Gut bacteria help getting the most out of food

About 20,000 single functions have been attributed to intestinal microbes. A great many of them are linked to digestion. Without the gut microbiota, many components of our food would be wasted. The intestinal bacteria are capable to extract and store energy from food that body cells cannot process efficiently. Recent findings show that diet, gut microbiota and health are mutually intertwined as diet, health status and microbial compositions often correspond.

The gut microbiota is a powerful helper in making efficient use of the consumed food and providing the body with the energy gained from it. This has been demonstrated quite vividly by trials with germ-free mice, as Prof. Francisco Guarner (University of Barcelona, Spain) pointed out: the germ-free animals needed to eat more while at the same time accumulating a lower amount of fat and growing less than normal animals. What makes the gut bacteria so efficient is their ability to extract, use and store energy that the body cells cannot extract from the food and that would otherwise be lost as waste. Several gut bacteria species can, for example, metabolise certain carbohydrates the gut cells cannot break down in order to make use of them. Bacteria of the gut microbiota are also able to produce amino-acids, vitamins and minerals.

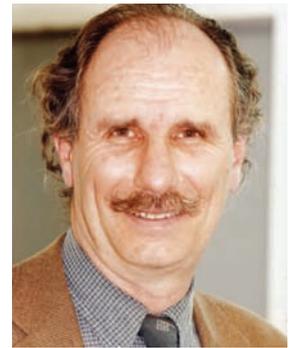
"Most of the bacterial action takes place in the proximal colon with rapid

bacterial growth while in the distal colon most of the substrates the bacteria are working on have disappeared and bacteria grow considerably slower," says Prof. Francisco Guarner. According to him, probably from very early on in evolution, animals have been living in symbiosis with gut microbes which provided their hosts with essential compounds and which obtained energy from different

sources. "The gut microbiota's collective metabolic activity makes it equal to a virtual organ within the gastrointestinal lumen," says Prof. Guarner.

NO ONE-WAY ROAD

A total of about 20,000 single functions linked with the intestinal microbes have been identified so far. 6,000 out of these are core functions that are present in the



PROF. FRANCISCO GUARNER,
University of Barcelona, Spain

guts of all individuals. Apart from maintaining the immune system or promoting the growth and development of the intestine's nervous system, the efficient harvesting of nutritional energy is one of the main tasks the gut microbiota has to fulfill.

However, the relation between gut microbiota and diet is not a one-way road: not only does the composition of the microbiota influence digestive processes, but the food one eats contributes to shaping the gut microbiota. This applies above all to diet patterns that remain stable over long periods. Other important factors can be diseases, medications or changes of the location as with travelling. Diet, microbiota and health are mutually intertwined as it has become quite clear through recent studies that a balanced diet corresponds with a well-composed microbial community.

"This summit really left a very good impression because a multidisciplinary approach is needed to understand what the gut microbiota is doing for the human organism."

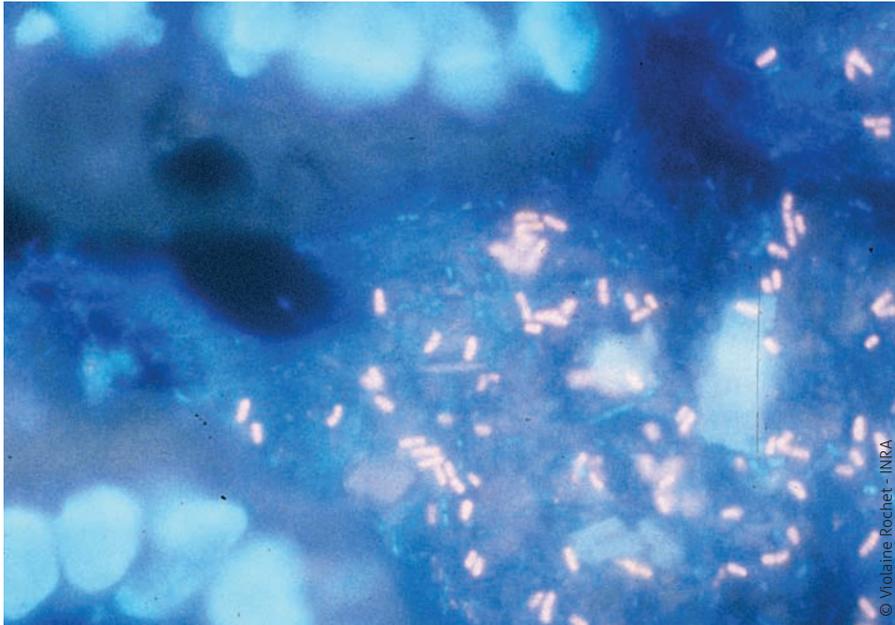


Heinz HAMMER - Austria

Diet – the driving force

Unhealthy food triggers nutritional diseases via gut microbiota

Metabolic disorders such as obesity or diabetes are triggered by several factors among which the interaction of diet with the digestive functions of the gut microbiota plays a key role. Healthy and diverse food intake significantly influences the gut microbial composition and thus the health status.



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LINKS BETWEEN GUT BACTERIA AND HEALTH provide a promising field for research.

Prof. Colin Hill (University College Cork, Ireland) and Prof. Jan Tack (University of Leuven, Belgium) presented the audience with a number of studies which reveal that obese and lean individuals carry a clearly distinct gut microbial composition. In obese individuals, the efficiency of energy harvest is particularly high while mechanisms essential for controlling food intake are disturbed. Two main groups of gut bacteria are known to be responsible: *Firmicutes*, which are capable of extracting and storing

energy from otherwise indigestible alimentary components, and *Bacteroidetes*, the function of which is somehow opposed as they encapsulate carbohydrates which are then being excreted. In healthy individuals, the occurrence of both species is more or less balanced, while in those suffering from obesity, the *Firmicutes* outnumber the *Bacteroidetes*, thus causing a considerable gain of weight and fat mass through an over-efficient energy extraction. How tightly changes in diet, body weight and gut microbiota composition are linked has been shown by utilising mice which were fed a high-fat diet. Within a short period of time, the food intake increased the relative abundance of *Firmicutes* at the expense of *Bacteroidetes*. But after shifting back to the original diet, the changes in the microbial composition were reversed. Similar results have been gained through experiments with microbiotas from lean and obese mice being transplanted into the colons of germ-free mice.



PROF. COLIN HILL,
University College Cork, Ireland



Nigel KLEIN - UK

"This very exciting area is in its infancy. I think we're just at the beginning of understanding the importance of the gut microbiota and its relevance to human disease."

LOSS OF DIVERSITY CAUSES DISEASES

While it is beyond doubt that gut microbial composition, diet and health status are associated, the causal direction between them is still a matter of discussion and further research. According to Prof. Tack and Prof. Hill, the current state of research seems to point to diet as the main driver in changing health conditions while the gut microbiota has an amplifying effect. Evidence is being provided, among other findings, by an ongoing investigation of food intake and other life style factors of elderly people in relation to their gut microbial composition and health status. "The results that have been gained so far support the claim that as the food gets less healthy and less diverse, the gut microbial composition follows," said Prof. Hill. This loss of diversity can not only trigger digestive disorders such as obesity and diabetes but probably inflammatory bowel diseases, allergies and mental disorders too.



PROF. JAN TACK,
University of Leuven, Belgium



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PROBIOTICS are often included in dairy products.

The potential of probiotics

Promising outlook but many open questions

Probiotics can help in the treatment of a number of GI conditions such as gas-related disorders, diarrhoea or IBS. However, in many cases the precise effects as well as the most efficient modes of clinical application remain to be clarified. This also affects the question which kind of evidence is needed to establish a public health claim for food containing probiotics.

Probiotics have attracted public attention for quite a long time. Although their principally beneficial role is undisputed, there are still many aspects under scientific discussion. These regard the precise effects of probiotics considering various conditions as well as how to employ probiotics most efficiently for prevention and treatment.

"The most compelling evidence for the impact of probiotics in patients with bowel function disorders is their effect on gas-related symptoms such as bloating and flatulence," said Prof. Magnus Simrén (University of Gothenburg, Sweden). Another promising field for appli-

cation is abdominal pain: patients with a high degree of pain were shown to have a low proportion of Bifidobacteria, one of the most prominent bacterial strains used as probiotics, and vice versa. Probiotics have similar beneficial effects on diarrhoea associated with antibiotics: studies show that this condition can be prevented to a large extent through probiotic products. With regard to acute diarrhoea in children, the results are somewhat mixed: although certain probiotic preparations reduced the duration of the disease and improved the stool consistency, they had no effect on fever and vomiting.



PROF. MAGNUS SIMRÉN,
University of Gothenburg, Sweden

HELPFUL AGAINST IBS

An extensively researched area is the impact of probiotics on IBS. As Prof. Simrén pointed out, probiotics can affect different factors that are responsible for IBS including the intestinal barrier, neuromotor functions, gut-brain functions and visceral hypersensitivity. "Many clinical trials show some kind of effect. But there is still insufficient evidence as to which probiotic should be given to which pa-

tient," says Prof. Simrén. With regard to inflammatory bowel diseases, according to him, so far probiotics have not proven very successful compared to other treatment options.



DR MARY ELLEN SANDERS,
Davis, USA

The various research issues which are awaiting further investigation raise the question of what kind of evidence is needed to establish a health benefit for probiotics. Dr Mary Ellen Sanders (Davis, USA) tackled this question with regard to probiotics that are not administered as drugs but included in food. She pointed out that companies wishing to communicate health claims on the labels of their probiotic products have to meet rather strict regulations as the EU requires evidence based on scientific assessment of the highest possible standard. The result is that the great majority of health claims is rejected. One possible solution might be to accept different grades of evidence while at the same time informing the consumer which of these standards is met by the respective products.



Nathalie JOBIN - Canada

"The main message is that everything concerning probiotics is very promising."

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