



ALLERGIES, METABOLIC DISEASES, NERVOUS SYSTEM: the immense fields of possibilities opened by our intestinal bacteria

Paris, 1st and 2nd December 2011.

One year after the success of the first 'Microbes for Health' international symposium, Danone Research, Inra and Institut Pasteur co-organized the second edition which was held in the heart of Paris on the Institut Pasteur campus on 1st and 2nd December 2011.

The objective of the symposium: sharing within the scientific community the most recent discoveries in the field of microbiota (formerly called intestinal flora) and, in particular, the role of those bacteria with respect to human health. This field of research is currently undergoing a formidable acceleration providing the grounds for hoping that, in the near future, there will be numerous application possibilities in the fields of health and nutrition.

This year again, the program brought together internationally reputed researchers from all over the world to present their most recent results on the microbiota itself or on its influence on the immune system (allergies, asthma), metabolism (obesity, heart disease, inflammation) on the nervous system, and in aging.

Among the numerous lessons learned, it is to be noted that:

- 1.** there are not infinite combinations but only a few types of microbiota or enterotypes, rather like blood groups;
 - 2.** in our excessively hygienic countries, certain bacteria and even parasitic worms may be beneficial for our immune system;
 - 3.** as of very early life, our microbiota may predispose to obesity and then, throughout life, play a role in the emergence of metabolic diseases and heart disease;
 - 4.** lastly, the bacteria hosted in our gut may have an effect on anxiety and even be involved in potential behavioral modifications or the emergence of neurodegenerative disease.
- Among the ranks of those attending in order to share these discoveries were researchers from the academic world and industry specialized in the fields of microbiology and immunology, and, in particular, those interested in 'translational'* approaches.

Lastly, for the second year running, the event benefited from live Twitter feeds enabling direct information of the scientific community online and incorporation of feedback in the discussion. Researchers and scientists attending the conference posted tweets, immediate echoes of the discoveries, results and conclusions presented, as the speakers' presentations progressed.



The content of those exchanges is available at

http://www.netvibes.com/metahit#MFH_2011

28,065 people reached via 1,233 tweets

(Europe 33%, US 20%, France 6%)

Event website:

<http://www.microbes-for-health.com/>

* The translational medicine concept is based on two notions: The rapid transition from research to practice, meaning tests on animals and humans, with ongoing alternations between the two, thus deepening or validating hypotheses; and transversal expertise, based on joint, multidisciplinary work (biological sciences, computer sciences, humanities, etc.) for more efficiency and to achieve measurement and monitoring of the impact on public health.



On the 1st and 2nd December, Institut Pasteur, Danone Research and, for the new edition, the National Institute for Agricultural Research (INRA) jointly held the second edition of the international 'Microbes for Health' symposium at Institut Pasteur, Paris. The organizers' objectives consisted in: bringing together eminent members of the scientific community to discuss the most recent discoveries relating to the microbiota¹ (formerly called intestinal flora); reviewing the most recent results with regard to the influence on our health of the bacteria living in our intestinal lumen; interconnecting the work of teams addressing immunity, others focusing on obesity, and still others elucidating the relationships between the microbiota and nervous system.

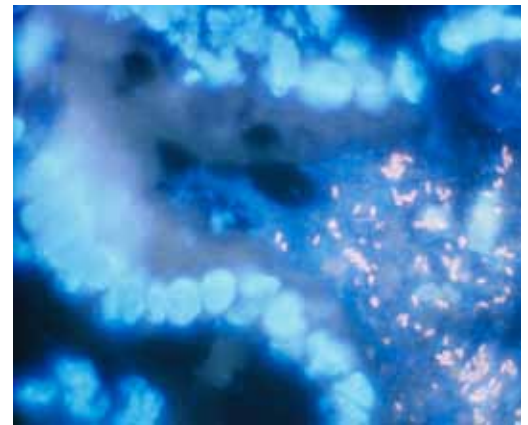
Over the two days, international experts, leaders in the fields of host-bacteria interactions at intestinal level and their impact on human health, succeeded each other. This was the opportunity for the 400 researchers attending the symposium to conduct a searching review of current knowledge and stress the progress research has made in just one year since the first edition of 'Microbes for Health'.

THE MAIN LESSONS OF THE SYMPOSIUM

Microbial ecology reveals its secrets

As Willem M. de Vos (University of Wageningen, the Netherlands, and University of Helsinki, Finland) was to remind us in his introduction to the symposium session devoted to microbial ecology, 'since early life, intestinal microbes dominate our body and outnumber our own cells by one or more orders of magnitude'. The collective genome of those microbes, known as the microbiome, greatly contributes to the functions of our body. 'However, unlike our own genome, the microbiome² is not strictly vertically inherited and, moreover, this personalized organ can be modified by diet, lifestyle and antimicrobials.'

In order to further elucidate the functions of the microbiota, a qualitative and quantitative description of the major members of the microbial community is necessary. 'Moreover, as the intestinal



Intestinal flora and colonic epithelial cells

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microbes have developed intimate relations with the host, their dynamics and interactions should be analyzed', continued Prof. Willem de Vos. Among the major advances of 2011, that reported by Dusko Ehrlich (INRA, Jouy-en-Josas, France), head of the European research program, MetaHIT³ >> See, Session 01: 'We have detected three gut enterotypes to which humans belong characterized by different bacterial communities. This basic feature of human biology remains to be elucidated but the enterotypes will be crucial to stratify individuals and assess the microbial communities associated with health and disease.' In other words, there are microbiota types rather than blood groups.

1 - All the bacteria that naturally live in the human intestine such as *Lactobacillus*, *Bacteroides*, *Enterobacter*, *Streptococcus*, *Clostridium*, etc.

2 - Sum of the microbial genes of the microbiota considered together.

3 - Metagenomics of the Human Intestinal Tract (MetaHIT) is a European project coordinated by Inra whose objectives are to characterize the genes and bacterial functions of the intestinal microbiota and study the effects of the genome in terms of diet and health.



The results presented by Paul O'Toole (Alimentary Pharmabiotic Centre, Cork, Ireland) who studied the microbiota of 191 older subjects (>65 years) whose food consumption and clinical measures were recorded, supported distinct microbiota lineages: *'Correlation analysis showed clear linkages between dietary intake and microbiota profile; associations between microbiota and indices of health in older persons are still being investigated.'*

How the microbiota acts on our immune system



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Technological platform in the Human Immunology Center

'Throughout our lives, humans continuously encounter microorganisms that range from those essential for health to those causing death, explained Sarkis Mazmanian (California Institute of Technology, USA). Consequently, our immune system is charged with the critical task of distinguishing between beneficial and pathogenic microbes.' Thus, for example, the bacterium, *Bacteroides fragilis*, frequent in our digestive system, uses a symbiosis factor, a sort of key which deactivates the immune response that would otherwise have eliminated it.

As Brett Finlay (University of British Columbia, Canada) pointed out, *'In the developed countries, we have gone to great length to minimize our exposure to microbes, both pathogenic and harmless. The hygiene hypothesis suggests that perhaps we have gone too far as hominids have evolved in*

a sea of microbes and actually need exposure early in life to microbes to minimize allergic diseases.' >> See, [Session 02](#). This seems to be confirmed by the work on mice of Marc Daëron's team (Inserm and Institut Pasteur, France) using the bacteria *Lactobacillus casei* which protects against allergies and autoimmune diseases: *'Probiotics⁴ may play a role in the effector phase⁵ of adaptive immunity in allergic and autoimmune diseases. They might therefore prevent inflammation in patients who have already synthesized specific IgE or autoantibodies.'* We will also remember the results reported by David Elliott (University of Iowa, Carver College of Medicine, USA) who improved the health of mice by increasing the regulation of their immune response via the introduction of a parasitic worm into their digestive systems. All the results provide grounds for hope in the combat against the current marked expansion of inflammatory and autoimmune disease in man.

How the microbiota plays a role in heart disease, hypertension, obesity and inflammatory diseases

The human body and the incredible number of bacteria it harbors in the



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Microbiota study using PCR technics

digestive system have reached a finely regulated symbiosis. *'Recent data suggest that if this symbiosis is disrupted, we are exposed to an increased risk of developing common diseases such*

4 - Live microorganisms which when administered in adequate amounts confer a health benefit on the host (FAO-WHO)

5 - The acquired immune reaction consists of three phases: induction (recognition phase), amplification (multiplication of immune cells, production of messengers, etc.) and the effector phase which leads to neutralization.



as inflammatory bowel disease and obesity' summarized Fredrik Bäckhed (Sahlgrenska Center for Cardiovascular and Metabolic Research, University of Göteborg, Sweden) >> See, Session 03. The strength of the influence of the microbiota is also illustrated by studies showing how the intrauterine environment and that of the first days of extrauterine life leave a strong metabolic imprint which may last years and may predispose premature or low birth weight infants to metabolic syndrome⁶. This point was stressed by Martin Blaser (New York University Langone Medical Center, USA) who considers that the influence of the microbiome begins in early life and 'shapes the developmental pathway' influencing the emergence of overweight or even obesity.

Cardiovascular disease

'Recent research indicates that, in both germ-free and antibiotic models of microbial depletion, the bile acid profiles of several tissues, including those of the liver, kidney and heart, are significantly different from conventional animals, containing a substantially higher percentage of tauro-conjugated bile acid species indicating that the presence of microbiota influences the global metabolism of the host and may impact on the development of heart disease and metabolic disorders', explained Prof. Elaine Holmes (Imperial College, London, UK). In her presentation on all the potential metabolic influences of the microbiota, she was also to highlight the fact that 'several of the strongest candidate biomarkers of hypertension were of microbial origin.'

Obesity and inflammation

'Studies in both animal models and humans have shown that obese and lean individuals carry a different gut microbial composition', explained Prof. Holmes. 'Bariatric surgery induces a marked

change in the composition of both fecal metagenome and the metabolome. Post-surgical diet also impacts on the development and stability of the microbial-host metabolic profile.' Nathalie Delzenne (Catholic University of Louvain, Belgium) reported that 'interventional studies in obese and diabetic patients are in progress to estimate the relevance of microbial changes occurring on prebiotics⁷ but also targeted probiotic approaches on the potential improvement of the inflammation and glucose homeostasis associated with obesity.'

How intestinal bacteria act on our nerves and brain

As we have seen, the microbiota is able to influence mammalian physiology, both at immune system level and at metabolic or endocrine system level. More surprising is the recent discovery that the central nervous system and brain are also potential targets. This area of research constitutes, in addition, one of the great novelties presented during the second edition of the symposium. 'Gut microbiota may control barrier function across the body which we think is potentially relevant for brain development and function' explained Sven Petterson (Department of Tumor Biology and Microbiology, Karolinska Institute, Stockholm, Sweden). To such an extent that the Swedish team feels that potential behavioral changes are under the influence of intestinal bacteria and that there are implications in terms of neurodegenerative diseases. How can such an influence be possible? Michel Neunlist (UMR Inserm U913, Institut of Digestive Diseases, University of Nantes, France) sketched a response: 'The enteric nervous system (ENS) located within the gut is the second largest nervous system of the body besides the brain. The constituents of the ENS are key regulators of gastrointestinal functions such as motility, barrier functions and immune responses.'

6 - Coexistence of several metabolic disorders (hyperglycemia, abdominal obesity, hypertension, hypertriglyceridemia, hypo-HDL cholesterolemia) in a given subject.

7 - Non-digestible food ingredients that stimulate the growth and/or activity of specific bacteria in the intestinal microbiota



The ENS lies in close proximity only separated by the intestinal barrier from the microflora. Bacteria or key bacterial metabolites can induce major neuroplastic changes in the ENS and mediate thereby microbiota effects upon gut functions.'

John Bienenstock (McMaster Brain-Body Institute, St. Joseph's Healthcare, Hamilton, Canada) pursued: 'We have shown that certain bifidobacteria and lactobacilli exhibit strain-specific and dose-dependent effects on gut motility and visceral pain perception after ingestion.' Even more surprisingly, the action of the bacteria is even felt in the brain where they have been shown to induce an anxiolytic effect in the mouse. In other words, the bacteria reduce anxiety. This change in behavior

is associated with a change in GABA receptors (a well known target of anti-anxiety medication) in the dedicated areas of our brain >> See, Session 04 given that the link between the brain and intestine is ensured by the vagus nerve according to a recent publication in the highly reputed journal *PNAS*⁸.

Joël Doré (Inra, Jouy-en-Josas, France) formulated a conclusion: 'We are still quite far from delivering causal inter-relations between features of the microbiota and host physiopathology but current observations converge towards a general model with physiopathological relevance.'

8 - Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in the mouse via the vagus nerve. *Proc Natl Acad Sci U S A*. 2011 Sep 20;108(38):16050-5.

9 - Results of a search for 'gut microbiota' at www.ncbi.nlm.nih.gov/pubmed

10 - Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR et al. Enterotypes of the human gut microbiome. *Nature*. 2011 May 12;473(7346):174-80.

11 - Hansen EE, Lozupone CA, Rey FE, Wu M, Guruge JL, Narra A, Goodfellow J, Zaneveld JR, McDonald DT, Goodrich JA, Heath AC, Knight R, Gordon JI. Pan-genome of the dominant human gut-associated archaeon, *Methanobrevibacter smithii*, studied in twins. *Proc Natl Acad Sci U S A*. 2011 Mar 15;108 Suppl 1:4599-606

12 - Goodman AL, Kallstrom G, Faith JJ, Reyes A, Moore A, Dantas G, Gordon JI. Extensive personal human gut microbiota culture collections characterized and manipulated in gnotobiotic mice. *Proc Natl Acad Sci U S A*. 2011 Apr 12;108(15):6252-7.

13 - Muegge BD, Kuczynski J, Knights D, Clemente JC, González A, Fontana L, Henrissat B, Knight R, Gordon JI. Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science*. 2011 May 20;332(6032):970-4.

14 - Faith JJ, McNulty NP, Rey FE, Gordon JI. Predicting a human gut microbiota's response to diet in gnotobiotic mice. *Science*. 2011 Jul 1;333(6038):101-4.

15 - Elinav E, Strowig T, Kau AL, Henao-Mejia J, Thaiss CA, Booth CJ, Peaper DR, Bertin J, Eisenbarth SC, Gordon JI, Flavell RA. NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. *Cell*. 2011 May 27;145(5):745-57.

2011, the year of the microbiota

Following the symposium, one can only conclude that the science of the intestinal microbiota is progressing quickly, very quickly in fact. The scientific community has shown great interest in the innovative subject: out of the 1600 publications on the intestinal microbiota listed by PubMed since 1977⁹, over 500 were published in 2011 alone.

The same year was also characterized by several major publications for the scientific community working on the microbiota: like that published in the prestigious journal *Nature*¹⁰ in which the team of the MetaHIT european research consortium announced the discovery of three specific combinations of microbial community (christened 'enterotypes') rather like blood groups.

The dynamism has also been illustrated by certain researchers such as Prof. Gordon, precursor of a revolutionary look at the intestinal microbiota and its role in human health. In 2011, among other papers, the scientist co-authored two research articles in the journal *PNAS*^{11/12} (US scientific journal publishing the proceedings of the National Academy of Sciences and second most cited journal after *Nature*), two other research articles in *Science*^{13/14} and a publication in the equally prestigious journal *Cell*¹⁵. In July 2011, Prof. Gordon was recompensed by his peers, who awarded him the Danone International Prize for Nutrition, considered the equivalent of a Nobel Prize in the field of nutrition.



ABOUT DANONE RESEARCH

Danone was born of the conviction that is now a central tenet of the group's mission: 'Bringing health through food to as many people as possible.' The ambition is great and largely based on the mobilization and skills of the group's R&D teams. The R&D skills are concentrated in Danone Research, a worldwide organization present in some fifteen countries, employing about 1,200 people, maintaining a network of almost 200 scientific collaborations worldwide, and contributing to the generation of scientific knowledge in specific fields (pre- and probiotics, breast milk, immunology, metabolic fingerprinting, etc.). Danone operates in four fields, namely: fresh dairy products (No. 1 worldwide), water (No. 2 worldwide for bottled water), infantile nutrition (No. 2 worldwide) and medical nutrition.

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ABOUT INRA

INRA (French National Institute for Agricultural Research) is a mission-oriented public research institute under the supervision of the French Ministries for Research and Agriculture, and carries out research in the fields of agriculture, food and the environment. As the leading agricultural research institute in Europe, and the second largest in the world for the number of its publications, INRA aims at ensuring healthy and high-quality food, competitive and sustainable agriculture and an environment that is preserved and developed, in the context of global climate change and a projected world population of 9 billion by 2050. INRA maintains scientific partnerships with major scientific research institutes worldwide, universities, agronomy and veterinary schools, and is committed to take part in building the European Research Area.

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ABOUT INSTITUT PASTEUR

Louis Pasteur created the Institut Pasteur in 1887 as a private non-profit foundation that rapidly became world-renowned for its biomedical research. The main aim of the Institut Pasteur is understanding and preventing diseases throughout the world through excellent scientific and public health research, teaching and other activities. Together with its major contribution to a deeper understanding of fundamental aspects of life, the Institut Pasteur continues to devote a large part of its efforts to infectious diseases, inherited disorders, neurodegenerative diseases and certain cancers. Close to 2,600 people work on its main campus in Paris, which is at the heart of an international network of 32 research institutes on 5 continents. Over the years, 10 Institut Pasteur researchers have received the Nobel Prize.

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Intestinal microbial ecology

Zoom on Dusko Ehrlich's presentation

Enterotypes: microbial equivalents of blood groups?

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Just as there are blood groups, there are three 'enterotypes' or intestinal bacterial signatures that have been identified by the researchers of the European MetaHIT research consortium coordinated by INRA. Thus, individuals are divided into three distinct groups on the basis of the microbial content of their gut *'independently of their geographic origin, state of health - overweight or inflammatory bowel disease - gender or age'* observed Dusko Ehrlich. Because this classification, like the blood group classification, is specific to individuals the researchers created the 'enterotype' concept.

A result validated on three continents

In order to demonstrate the unexpected and fundamental characteristic with respect to human biology, the researchers analyzed the metagenome of bacteria derived from intestinal samples from 39 subjects on three continents: French, Danish, Italians, Spaniards, Americans and Japanese subjects. Subsequently, they extended the analysis to 85 samples from the Danish population and then 154 from the American population in order to determine whether the classification was valid beyond the 39 initial sequences. *'The results show that all the subjects may be classified in three distinct groups depending on the nature of the bacteria in their digestive tract and the functions they code'* summarized the researcher.

Contributing to the diagnosis of Crohn's disease and obesity or predicting the effect of treatment

Using certain bacterial genes as biomarkers¹⁶, the scientists also showed that there is a correlation between the function markers and characteristics such as age, gender, geographic origin or body weight. *'This proves the concept that analysis of the intestinal microbiota may contribute to diagnosis of diseases such as obesity or Crohn's disease'* states Dusko Ehrlich.

The scientist also added: *'This study opens the way for research on the differences between the bacterial composition of the intestinal microbiota in healthy subjects and disease sufferers. Awareness of the classification of individuals will now enable constitution of homogeneous groups with a view to comparative analyses addressing, in particular, the factors that promote obesity, diabetes, etc.'*

In the field of personalized medicine, this classification will help develop diagnostic tools enabling detection of cases for whom a given treatment will not be effective and treatment adaptation in consequence. Lastly, the classification will enhance nutritional studies aiming to determine the effect of a given food on human health.

¹⁶ - Biomarker: a molecule which reflects a normal or abnormal biological process or the presence of a disorder or disease.

Microbiota and immunity

Zoom on Brett Finlay's presentation

Asthma and infectious diarrhea: the microbiota to the rescue of our hyper-hygiene?

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DR

In developed countries, we have gone to great length to minimize our exposure to microbes, both pathogenic and harmless'. But this is perhaps not such a good idea. 'The hygiene hypothesis suggests that perhaps we have gone too far as hominids have evolved in a sea of microbes' explained Brett Finlay. In order to further elucidate the links between the microbiota and immune system, his research laboratory is working, in particular, on the central role of the microbiota in the occurrence of infectious diarrhea.

What happens to the microbiota in infectious diarrhea?

More precisely, B. Finlay's teams are working on a murine model in which an infection of the large intestine is caused by a natural pathogenic bacterium, *Citrobacter rodentium*. 'This model is interesting in that it closely mimics the E. coli-related diarrhea observed in man, which is also correlated with marked changes in the microbiota,' indicated the researcher. Thus, when a mouse is infected with *Citrobacter rodentium*, the pathogen undergoes a classic developmental cycle: it begins by multiplying for a week; the next week, *Citrobacter rodentium* population peaks and the mouse shows symptoms; subsequently, the number of *Citrobacter rodentium* decreases and the symptoms resolve. 'Further study has shown that the development of the pathogen is accompanied by a drastic fall in the colonic population together with a redistribution of the bacterial forces present: the Firmicutes population falls, then that of Bacteroidetes, before they both return to normal levels.' The change is caused by the host's inflammatory response to the presence of the pathogen which creates an environment conducive to the multiplication of *Citrobacter* and related species. However, once the host's acquired immunity has been activated, the pathogen is eliminated and the composition of the microbiota normalizes.

When transfer of flora is sufficient to transfer resistance or sensitivity to infection

But B. Finlay's team's work to determine which out of the host, pathogen and flora is responsible for the effects observed goes further. The fecal flora from mice resistant to infections was transferred to non-resistant mice. With the new microbiota, the non-resistant mice became resistant and no longer suffered from the infection. In contrast, mice that were resistant and which received flora from non-resistant mice fell sick when exposed to the pathogen. Microbiota transfer thus seems sufficient to transfer resistance or sensitivity to infection. Brett Finlay concludes: 'A given mouse confronted with the same pathogen responsible for diarrhea will fall sick or not depending on the microbiota hosted.'

What are the underlying mechanisms? One possible explanation is based on interleukin-22 (IL 22), a sort of communication agent synthesized by immune system cells which acts remotely on other cells to regulate their activity and function. IL-22 is up-regulated in resistant mice and also in non-resistant mice to which resistant mouse microbiota have been transferred. In contrast, transfer of flora from a sensitive mouse to a resistant mouse induces a fall in IL-22 expression.

In the future: reducing inflammatory diseases and asthma

Through B. Finlay's team's work, a concept is emerging: in reality we may need early exposure to microbes in order to minimize allergic diseases, including asthma. The researchers' enhanced understanding of the mechanisms and forces involved provides hope for prevention via the microbiota.

Microbiota, metabolism and disease

Zoom on Fredrik Bäckhed's presentation The role of microbiota in inflammation and atherosclerosis



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The human gut is home to an inconceivable amount of bacteria that has co-evolved with us and established a fine tuned symbiosis. Recent data suggest that if this symbiosis is disrupted, we are exposed to an increased risk of developing common diseases such as inflammatory bowel disease and obesity.

Increased energy yield

The majority of our bacteria live in the colon where they are essential for fermentation of dietary polysaccharides that our own enzymatic repertoire is not able to degrade. *'Increased energy harvest and altered lipid portioning contribute to increased adiposity of colonized mice compared with their germ-free counterparts,'* reports Fredrik Bäckhed.

Bacteria responsible for inflammation

However, there is also a downside: the gut microbiota is also a source of pro-inflammatory molecules, lipopolysaccharides (LPS). LPS are toxic complexes constitutionally present in the outer membrane of certain bacteria in our gut. Bacterial wall LPS can enter the host's blood stream and thus increase inflammatory tone and increase the accumulation of crown-like structures (CLS) consisting of an adipocyte surrounded by a crown of macrophages, in adipose tissue. It is to be remembered that while the cells are rare in subjects of normal weight, a large number of macrophages infiltrates adipose tissue in obese subjects interfering with the biological functions of the tissue and, particularly, secretory function.

In studies, *'Monocolonization of germ-free mice with Escherichia coli but not an isogenic mutant deficient in LPS biosynthesis increased adipose inflammation and CLS formation identifying a direct link between LPS in the gut and adipose inflammation.'*

From inflammation to atherosclerosis

Since impaired lipid metabolism and inflammation are characteristic of atherosclerosis and bacterial infections have been known to be associated with atherosclerosis for decades, Fredrik Bäckhed's team investigated how the oral and intestinal bacterial communities are correlated with the process. A positive correlation between leukocytes and the quantity of bacterial DNA present in atheromatous plaque was observed (in other words, the more bacterial DNA there is in the plaque, the more immune cells [leukocytes] are present). The same bacterial species were present in the plaque and in the mouth or intestine. *'Our data thus suggest that bacteria derived from the human mouth or gut may promote inflammation in the plaque'* concluded the researcher.

Toward enhanced management of metabolic diseases

Accordingly, the gut microbiota may contribute to metabolic disease by regulating energy acquisition, entero-endocrine function and inflammatory tone. These findings provide the grounds for hoping for innovative treatments for inflammatory diseases such as atherosclerosis and obesity in the future.

Microbiota and neurosciences

Zoom on John Bienenstock's presentation

Bacteria to reduce anxiety

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DR

As we have seen, the gut microbiome¹⁷ exerts major influence on mammalian physiology by, for example, modulating the metabolic, endocrine and immune systems. However, the fourth and last session of the 2011 'Microbes for Health' congress also revealed a very new field of research addressing the relationship between the microbiota and nervous system as John Bienenstock was to confirm. *'Recent attention has started to focus on components of the systems which can influence the brain and behavior and this has been referred to as the gut-brain axis.'*

Bacteria that affect intestinal motility and pain

Under John Bienenstock's team's microscope: rodents with a microbiota or rodents without a microbiota (sterile digestive tract). *'We have been examining the effects of different commensals and symbionts on the enteric and central nervous system in several different experimental conditions: in vitro [cultured cells], in vivo [live animals] and ex vivo [sampled cells]'* explained the Canadian scientist. The results? Certain bifidobacteria and lactobacilli exhibit an effect on gut motility and visceral pain perception after ingestion and this is specific to the bacterial strain and dependent on the bacterial dose. This is accompanied by specific ion-channel inhibition in a subset of neurons in the myenteric plexus¹⁸ and the dorsal root ganglia¹⁹. These effects were reproduced within minutes in an *ex vivo* model of luminal perfusion.

From the intestine to the brain

Mechanically, how does it work? *'These types of effects are also conducted from the gut to the brain via vagal²⁰ and spinal²¹ afferents'* continued the scientist. *'Central nervous system effects of feeding single organisms for 28 days to normal mice include changes toward anxiolytic behavior and alterations in GABA receptors²² in specific areas of the brain associated with such behavioral change.'* In contrast, the effects were not observed in animals having undergone prior subdiaphragmatic vagotomy. *'At least in this model, the intact vagus nerve is an essential pathway in this example of gut to brain communication.'*

The prospects

'Taken together, these types of data confirm the complexity and significance of the gut microbiome in the development and function of the nervous system as a whole' summarized John Bienenstock. While these studies may only constitute the first paces in a new field of totally innovative research they afford multiple and exciting prospects for the treatment of nervous system diseases.

17 - Sum of the microbial genes of the microbiota considered together.

18 - Nerve fibers constituting part of the enteric nervous system and controlling, in particular, motility.

19 - Dorsal root ganglion (also called the spinal ganglion) which contains the cell bodies of sensory neurons, particularly for pain.

20 - Tenth cranial nerve.

21 - Nerves emerging from the spine.

22 - Synaptic receptors of the nervous system targeted by anxiolytic medications such as benzodiazepines.