Probiotics are live microorganisms, which, when administered in adequate amounts confer a health benefit on the host. In the U.S., they are present in conventional foods and dietary supplements, but not in human drugs. They represent a rapidly expanding field, both scientifically and commercially. In 2005, there were 40 probiotic products on the market in the U.S. By 2007, there were 300. Over the past 20 years, this field has progressed from one characterized by unsubstantiated hypotheses and largely untested products to one that has gained the attention of top-notch scientists and clinical researchers publishing in the world’s best scientific journals. But the field still has far to go.

In June, 2010, academic and industry scientists and government regulators gathered in New York City for the symposium Probiotics: From Bench To Market, jointly presented by The New York Academy of Sciences and The Dannon Company, Inc., to highlight progress in identifying mechanisms and measuring the extent of probiotic functionality in the gastrointestinal, nervous, and immune systems. Presentations by industry scientists described novel ways that commercial probiotic products are being studied in order to determine their health effects. Academic scientists addressed challenges in the conduct of probiotic clinical research, and U.S. regulators described appropriate approaches to conducting probiotic research.

The science behind probiotics and their impact on human health is still emerging. But the science may be the easy part. Current U.S. regulations do not allow probiotic foods to be marketed for the multitude of health benefits suggested by emerging science because regulators argue that the legal definition of “food” excludes its use in preventing, curing, treating or mitigating acute disease or providing dietary support to help people cope with adverse health conditions. Your doctor may tell you to “eat yogurt” when prescribing an antibiotic, but such a suggestion would make that yogurt an illegal drug in the eyes of regulators if made in advertising or labeling.

During this symposium, the probiotic research, industry and regulatory communities engaged in an open conversation about challenges affecting the interface of research, product marketing and regulatory oversight. Figuring out a path to encourage strong probiotic research and responsible product marketing while satisfying regulators that food law is upheld and that consumers are protected is a high priority. I hope our discussions in New York provide the necessary impetus for changes in the path of probiotics from the bench to market.

Sincerely,

Mary Ellen Sanders, PhD
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Probiotics: From Bench To Market
The New York Academy of Sciences
New York, NY | June 11, 2010

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Most people are well aware of the fact that the central nervous system (CNS) and the gut are intimately connected. Many common neurophysiological states, including stress, pain, and depression, can have intense effects on gastrointestinal (GI) function. For example, the churning stomach and diarrhea associated with stress or fear, or the loss of appetite that stems from grief or depression. The reverse is also true: physiological state of the gut can have effects on mood, behavior, and perception of pain. Recent studies have elucidated the role of the gut microbiota in this important ongoing conversation between gut and brain, known as the gut-brain axis (GBA). Please see Figure 1 for some examples of interactions along the GBA.

Stress has multiple effects on the gut, including increased gastric acid production and increased GI motility, which would affect the gut environment and thus the growth and physiology of bacteria living there. Stress has also been shown to cause changes in the composition of gut microbiota in studies of infant rats and monkeys subjected to premature separation from their mothers. Certain probiotics have been shown to reverse these changes and to normalize altered stress responses found in animals subjected to stress such as early life stress. Stress also causes changes in neurotransmitter levels, which could affect not only the gut itself but also the bacteria therein. It has long been known that certain neurotransmitters can have direct effects on bacterial physiology. The neurotransmitter norepinephrine, for example, has been shown to promote virulence in highly pathogenic strains of Escherichia coli and in another intestinal pathogen Campylobacter jejuni.

Studies have also implicated the gut microbiota in modulating the sensation of pain. Treatment with antibiotics can lead to pain hypersensitivity (hyperalgesia) in the intestine, and it has been shown that this hypersensitivity can be reduced with the use of probiotics.

Certain probiotics have also been shown to reduce pain sensitivity in animal models of pain such as acute inflammatory hyperalgesia. It is hypothesized that this antihippocampal effect of probiotics is related to the engagement of endogenous opioid systems. At the same time, however, studies in germ-free mice have shown that the presence of the gut microbiota is necessary for the development of a hyperalgesic state, perhaps because in the normal gut, the presence of bacteria stimulates the production of interleukin-10, a cytokine involved in suppressing the inflammatory response. Further research will be needed to reconcile these somewhat contradictory results.

A number of other research lines suggest that intestinal microbes have important effects on psychological states. Animal studies provide evidence that the state of the gut can affect both mood and behavior. In rats, initial intestinal infection with Toxoplasma gondii, followed by localization to the brain, has been reported to have direct effects on performance in behavioral tests. A recent study of the neurobiological and immunomodulatory effects of a probiotic strain of Bifidobacterium infantis in rats suggests that this probiotic could have antidepressant effects in this model. In mice, infection with the bacterium Citrobacter rodentium has been shown to induce anxiety-like behavior.

In humans, epidemiologic studies show that negative emotions are often associated with the development of acute GI infections, and conversely, chronic GI inflammation has multiple effects on mood, including symptoms of depression and fatigue. Risk factors for the development of irritable bowel syndrome include adverse life events, depression, and neuroticism.

These multiple lines of evidence illustrate the intimate nature of the connections between gut, brain, and gut microbiota, and suggest that the use of probiotics might someday go beyond maintenance of intestinal health alone. Further investigation in both animals and humans will allow greater delineation of these connections, perhaps one day allowing the use of probiotics as clinical agents to treat or assist in the management of serious psychological conditions such as depression or post-traumatic stress disorder.

Dr. Mayer has a long-standing interest in clinical and neurobiological aspects of brain-gut interactions. He has made seminal contributions to the characterization of physiologic alterations in patients with functional disorders, particularly in the areas of visceral pain, stress-induced visceral hyperalgesia and altered brain responses.
Understanding and Altering the Intestinal Microbiota

Justin L. Sonnenburg, PhD
Assistant Professor, Microbiology & Immunology
Stanford University

One of the difficulties with attempting to manipulate the gut microbiota is the current scarcity of knowledge regarding exactly how they function. In order to manipulate the gut microbiota for clinical purposes, it will be important to understand, in a systemic way, how these microbes adjust to changes in host diet, and how they adapt to the introduction of new species or to the loss of species, and what role host genetics play in the ecosystem's composition and function. The Human Microbiome Project (http://commonfund.nih.gov/hmp) has generated large amounts of important sequence data that identifies the many bacterial species and genes involved; however, knowledge of how this complex ecosystem actually functions has lagged significantly.

The development of simplified model systems of the gut microbiota can potentially allow such questions to be addressed more readily, and these models could facilitate investigation of the multifaceted roles microbiota occupy. One particularly important function of the gut microbiota is metabolism of carbohydrates, which serve as one of the primary nutrient sources for this community. Due to the density of microbes within the complex intestinal ecosystem, numerous bacterial species compete to break down and utilize the carbohydrates that we ingest, particularly the more complex plant carbohydrates that we are poorly equipped to metabolize on our own.

In recent studies in Dr. Sonnenburg's laboratory, germ-free mice were colonized with simplified microbial communities to investigate how the genetics of both host and microbes affect metabolic function. Although 10 bacterial divisions and thousands of species are represented in the human and mouse gut microbiota, more than 90% of the microorganisms belong to the Bacteroidetes and Firmicutes divisions of bacteria, so one way to reduce complexity is by working just with representatives of these two groups.

Initial experiments looked at the genetics and metabolism of a single species in this model system, Bacteroides thetaiotaomicron (B. theta). This organism is a prominent member of the human microbiota that has the advantage of being easily cultivated outside the body. The genome of B. theta, largely geared toward carbohydrate metabolism, includes at least 64 enzymes that are devoted specifically to the digestion of plant polysaccharides that humans cannot digest and over 260 carbohydrate-degrading enzymes in total, out of a total genome of 4779 genes. When compared to the many carbohydrate-degrading enzymes in total, out of a total genome of 25,000 genes, this microbial resident of the human body evidently possesses many novel and important metabolic capabilities.

Functional genomics techniques were used to examine how the expression of these carbohydrate-degrading genes changes when different foods are introduced into the mouse host's diet. Addition of another species, Bifidobacterium longum, to the system, allowed study of this organism's gene expression, as well, providing valuable information on how these two species compete for and adapt to the ecological niches that are available under different conditions.

Studies are also examining the effects of inulin, a dietary polysaccharide from the fructan family that is found in many plants. Inulin is present in many processed foods and is widely used as a prebiotic—a non-digestible food ingredient that stimulates the growth and/or activity of bacteria in the digestive system that are beneficial to the health of the body. Inulin has been shown to alter the composition of the human gut microbiota, in some cases by expanding the population of Bifidobacterium species. In Bacteroides, inulin induces the expression of a series of enzymes that are needed for inulin's metabolism. It may be possible to use the gene sequences that encode these enzymes as biomarkers to detect specific diet-induced changes in microbiota composition in humans as well.

These studies will help to elucidate the mechanisms of pre- and probiotics, and to identify whether changes in gut microbiota are the cause or the result of a given disease state. The insights gained should someday allow more precise manipulation of the human gut microbiota, which will be particularly important once a better understanding of the microbial ecosystem's optimal content has been achieved.

Figure 2. B. thetaiotaomicron (B. theta) and B. longum bacteria, when occupying the same cecal space (co-colonized), show differential expression of glycoside hydrolase and polysaccharide lyase genes. Results indicate B. theta expands expression of glycoside hydrolases in co-colonization with B. longum—a greater variety of genes associated with digestion of dietary plant or host mucus polysaccharides show increased expression in co-colonization compared to mono-association. (Figure adapted from Sonnenburg JL et al, PLoS Biology, 2006)
As in many areas of clinical research, probiotics studies will progress more quickly and cost-effectively with the development of in vitro model systems that can be used to test new ideas before they are tried in animals or humans. Such models can be particularly challenging to develop for pre- and probiotics because the gut and the gut microbiota are such highly complex systems.

Multiple research groups have taken on the challenge of developing such models, ranging from fairly simple, single-vessel fermentation setups to complicated, multi-stage fermentation systems that are intended to replicate the sequence of digestive compartments formed by all or part of the human gut. In a single-vessel batch fermentor, pH and nutrient concentrations are controlled to allow relatively simple studies of the growth and physiology of mixed fecal cultures or other inocula. Micro-fermentors that use very small volumes have also been developed, which are particularly useful when it is necessary to conserve study materials.

In more complex, multi-compartmental fermentation systems, computers are used to control conditions at each stage so that each acts as a representation of a specific digestive compartment, forming a complex model of all or part of the gut lumen. These more complex systems are useful for studying both the effects of pre- and probiotics and particularly how they persist with time. Such systems make it easier to model complex interactions between gut compartments and their resident microbiota, and they can also be used to study the effects of experimental compounds that are in development as clinical therapies.

One such system consists of a series of culture vessels whose contents replicate the sequence of volumes and pHs found in different areas of the human large intestine. The properties of each vessel in this continuous system were validated against the gut contents of victims of sudden death to provide a more accurate model system. The system is inoculated with mixed fecal bacteria from human volunteers and allowed to run continuously to set up an in vitro model of this area of the gut. Pre- or probiotics are then added to the system to study their effects and their persistence in an environment that is very similar to the human gut.

This system has been used to investigate the functions of a prebiotic known as GOS, a mixture of galactooligosaccharides. GOS intake has been shown to reduce symptoms in patients with irritable bowel syndrome and travelers’ diarrhea and to modulate levels of pro- and anti-inflammatory cytokines in elderly individuals. Addition of GOS to the model system has a considerable effect on the distribution of bacterial species, including a large increase in Bifidobacterium species. This increase has also been observed in healthy human volunteers and in individuals with irritable bowel syndrome who ingest GOS. The in vitro system thus appears to replicate the human system adequately. These experiments will help to elucidate both the mechanisms by which GOS raises Bifidobacterium content and how such an increase might alleviate irritable bowel symptoms.

Ultimately, studies of pre- and probiotics must be done in humans before it will be possible to make health- or disease-related claims for these agents, but the information provided by in vitro models will provide valuable guidance on what might or might not be fruitful when tried in humans. In addition, these models will allow the elucidation of the mechanisms of pre- and probiotics, important information that can be difficult to gain with studies using animals and humans.
Depending on their intended uses, probiotics are subject to a wide range of potential types of regulation. Factors that may influence how a probiotic product is regulated include formulation (pills or capsules), route of administration (oral for foods and supplements), targeted consumers, and food safety considerations if new dietary ingredients are involved. Because of their many forms and uses, probiotics may be regulated as conventional foods, as dietary supplements, or as drugs, and are subject to different labeling and marketing restrictions based on the uses claimed by their manufacturers. Companies producing probiotics are understandably eager to communicate the health benefits of their products to consumers but must be careful to follow these regulations if they are to avoid penalties from the U.S. Food and Drug Administration (FDA).

Claims for probiotics could potentially range from structure/function claims (e.g., “helps support the immune system”) to health claims (i.e., that the product reduces the risk of a specific disease). A probiotic that is intended for use in diagnosing, curing, mitigating, treating, or preventing a human disease is considered a drug. Clinical trials to evaluate probiotics for medical uses require an Investigational New Drug application (IND) to be submitted to the FDA.

Health claims must be based on the FDA’s review and approval of a health claim petition or notification of an authoritative statement from a scientific body of the U.S. government or the National Academy of Sciences, or the claims must be qualified if the science has not yet reached the level of significant scientific agreement. FDA guidance published in 2008 describes what is needed to substantiate structure/function claims for foods, including dietary supplements. Currently there are no FDA-recognized health claims for probiotics.

Structure/function claims, which focus on the maintenance or support of body structures or functions in healthy individuals rather than disease prevention or treatment, are not subject to FDA approval, but statements made in product labeling must be truthful and not misleading. Frye shared the examples that the claims: “Helps maintain healthy intestinal flora” or “Helps support immune function” are considered structure/function claims, not disease claims, whereas “Helps individuals using antibiotics to maintain normal intestinal flora” or “Protective against the development of diarrhea” would be viewed as unauthorized health claims or drug claims. In all cases, the burden of proof for product labeling rests with the manufacturer to have accurate substantiation supported by competent and reliable scientific evidence.

Probiotics manufacturers face substantial challenges in navigating these regulatory requirements. They must have a good working knowledge of the regulations involved and word their package labeling so that the claims align with available evidence. Often manufacturers themselves will need to develop, by performing or funding clinical studies, the necessary scientific evidence for claims they wish to make. Novel types of claims may also require manufacturers to seek expert counsel or to ask the FDA to provide specific guidance on how to substantiate them. These rules and regulations are sometimes difficult to follow but provide needed protection for the consumer.

Ms. Frye represents member companies on product safety, food labeling and standards of identity, ingredient technologies, and nutrition and health issues. She is responsible for the technical development and regulatory oversight of nutritional marketing programs and processor materials that incorporate breaking medical and nutritional research. Furthermore, Ms. Frye chairs the International Dairy Federation Standing Committee on Food Labeling and Terminology.
Many researchers are interested in studying probiotics in foods because of the potential for a higher impact than when they are ingested alone as supplements. Such studies are necessary because probiotics that are successful as supplements do not necessarily work in the form of a yogurt, cheese or cereal. Probiotics occupy an unusual position in the FDA approval process because in many cases they are components of foods that have been consumed for centuries without apparent ill effects. Some researchers would argue that testing these substances for safety slows down the approval process unnecessarily and wastes money.

After conducting a number of randomized trials of probiotics in healthy children, NIH funding was obtained for a study on whether consuming probiotics, in the form of yogurt, reduces diarrhea in children who are taking antibiotics. Because this study would investigate the ability to cure or mitigate a disease condition, the NIH center that funded the project, the National Center for Complementary and Alternative Medicine (NCCAM), required that the Center for Biologics Evaluation and Research (CBER) at the FDA be asked if an IND (Investigational New Drug) application was required. Probiotics fall under the definition of biologics, and as such are regulated by CBER rather than by the Center for Drug Evaluation and Research (CDER), which is responsible for evaluating drug compounds.

Previous studies of probiotics in healthy children did not require INDs (Investigational New Drug applications) because, according to the stated aims of the studies, they were intended to support only structure/function claims. Outcomes that were assessed in these studies included the prevention of daycare absences and reduction of parental reports of loose stools. For comparison, another study currently in preparation will compare amoxicillin, prednisolone, and neti-pots for the treatment of sinusitis. This planning grant is supported by the National Institute of Allergy and Infectious Diseases (NIAID), which also required contact with the FDA to inquire about a potential IND. CDER, under the auspices of an investigator-initiated IND, exempted the study from an IND process because of the long-standing uses of the therapies involved.

Submitted in October 2006 and approved in June 2007, the grant application for funding the proposed diarrhea clinical trial was then required to undergo an IND review process. After multiple rounds of communication, the IND was approved in November 2008. NCCAM issued the grant award in August 2009, more than two years after indicating its intent to award the grant. As part of the process, the FDA required, and NIH funded, an initial safety study of the yogurt with probiotics in healthy adults, even though the product was equivalent to one currently on the market as a food and had been ingested by many people. This requirement is in keeping with current FDA general recommendations that drugs should be tested in adults before they can be tested for pediatric uses.

There are several steps that the FDA and NIH could take to reduce the difficulties associated with testing probiotics for drug indications. CBER currently does not grant investigator-initiated INDs as does CDER. Since many probiotics, especially those found in foods, have been consumed widely, it seems that probiotics studies would be likely to gain exemptions if CBER were able to give them. In addition, it will be important for the NIH to fund more patient-oriented clinical trials in this area, in addition to the Phase 1 safety studies and basic science studies of the microbiome and probiotic mechanisms that are currently funded. Such studies would produce more immediate public health benefits by providing evidence of the health effects of probiotics in individuals with disease conditions. The U.S. could fall behind considerably in probiotics studies if such changes are not made in the near future.

Dr. Merenstein’s research interests include complementary and alternative medicine, sinusitis and probiotics. He approaches all of these interests with primary care in mind. In the last 3 years he has been the principle investigator on 5 different probiotic pediatric trials that have enrolled over 1,300 participants.
In recent years, there has been a trend towards more probiotics trials outside the U.S. and more in healthy individuals. Studies in the database are primarily intended to provide evidence for the treatment or prevention of diarrhea and other GI conditions, but they also include studies on allergies, respiratory diseases, and conditions related to premature birth. Studies are occurring in all age groups, from children, including neonates, to the elderly.

Unfortunately, in the past many studies of probiotics have been of poor quality, including many with problems concerning the underlying biologic rationale, experimental design, safety, and measurement of appropriate clinical outcomes. The Cochrane Review, which conducts rigorous analyses of clinical evidence, has raised questions about the quality of clinical trials in most areas where probiotics have been tested. One difficulty in gauging the quality of the evidence is that the Cochrane Review's analyses aggregated studies on many disparate types of probiotics, most likely of necessity since clinical trials are still quite uncommon. It is likely that the effects of probiotics are species and even strain specific.

Dr. Hibberd’s group recently prepared two investigator-initiated INDs (Investigational New Drug applications) for two NIH-supported trials on the use of probiotics to prevent infection. One IND eventually had to be withdrawn due to a number of issues, including minimal assistance from a prior manufacturer. The resubmitted IND had strong support from the new manufacturers but was placed on clinical hold when the FDA requested a Phase I study in healthy adults before the original, NIH-funded adult and pediatric study could proceed. In July 2009, after revisions to the research design to accommodate the FDA’s request, the hold was lifted and the Phase I study in healthy adults was able to proceed. Some of these difficulties could have been avoided by requesting a pre-IND meeting with the FDA to find out what was likely to be required in the IND and by obtaining assurances from the manufacturer of the products that they would cooperate before embarking on the IND process.

As a key funder of clinical studies of probiotics, NC- CAM (the National Center for Complementary and Alternative Medicine) at the National Institutes of Health (NIH) plays a major role in guiding the research agenda and in encouraging collaboration with other organizations to improve the quality and value of the research. Collaborations of importance include those with investigators funded by the NIH-funded Human Microbiome Project and the U.S. Department of Agriculture. These collaborating investigators have cutting-edge technology that is being used to study the mechanisms of action of probiotics. However, the multiple layers of review and regulatory oversight at the NIH and the FDA have resulted in considerable delays (stretching to several years) before any part of the funded research can proceed. There is also a disconnect between the FDAs need for the Phase I safety studies to be conducted prior to probiotics studies in patients and the process of peer review at NIH. Peer reviewers are looking for cutting-edge science of public health importance, and Phase I safety studies do not usually meet those requirements, by definition. It is also difficult for reviewers and many others to understand why Phase I safety studies are needed when there are extremely long histories of probiotics use without reported safety concerns. However, the FDA assesses the quality of the manufactured probiotic and the safety and quality of the clinical trials being conducted with the probiotic in the IND process.

Since many probiotics studies are plagued by poor design, it is thought that completion of an IND will lead to a higher quality study, since such an application requires interactions with and advice from experts at the FDA. However, while completing an IND does confer benefits, among them, assistance with product quality issues and other valuable guidance, it also creates substantial challenges, including the time involved and the need to reconcile FDA requirements, it is thought that completion of an IND will lead to a higher quality study, since such an application requires interactions with and advice from experts at the FDA. However, while completing an IND does confer benefits, among them, assistance with product quality issues and other valuable guidance, it also creates substantial challenges, including the time involved and the need to reconcile FDA requirements. In addition, it remains to be seen whether completing an IND improves the credibility of clinical trials of probiotics with health care professionals or the general public. In the end, the quality of a given study remains the responsibility of the investigator, and the quality of the probiotic product remains the responsibility of the manufacturer, whether or not an IND is filed. High quality research in humans remains the goal, and research quality will ultimately determine whether probiotics are accepted in the mainstream to improve human health and treat diseases.

Dr. Hibberd’s research is focused on Global Health, the prevention and treatment of childhood pneumonia and diarrhea, mechanisms of action of probiotics, and their effects on prevention and treatment of infections. This research involves clinical/translational research methods and the conduction of Phase I/II clinical trials under investigator-initiated INDs.
In Brief: Innovations in Probiotics Research

Ongoing research projects are probing the mechanisms of pre- and probiotics in order to facilitate the transition of these agents from benchtop to marketplace.

Probiotics Inhibit Behavioral Signs of Depression After a Myocardial Infarction in a Rat Model
Guy Rousseau, PhD
Department of Pharmacology
Université de Montréal (Québec), Canada

- Over 20% of patients who suffer a myocardial infarction (MI) develop major depression, which is associated with a 3- to 4-fold increase in subsequent mortality.
- This phenomenon is thought to be related to the release of pro-inflammatory substances and increased cell death, or apoptosis, in specific areas of the brain.
- Prophylactic intake of a combination of the probiotics, Lactobacillus helveticus R0052 and Bifidobacterium longum R0175, was found to reduce post-MI apoptosis in rats with experimentally induced MIs, to reduce levels of the inflammatory cytokine interleukin-1β and signs of depression, and to restore intestinal barrier function.

Lactobacillus rhamnosus GG Attenuates Interferon-γ and Tumor Necrosis Factor-α-Induced Epithelial Dysfunction
Kevin A. Donato, HonBSc
Hospital for Sick Children, Toronto, Canada

- Pathogenic bacteria like E. coli strain O157:H7 can break down tight junctions between epithelial cells in the mucosal layer of gut, causing watery diarrhea and dangerous fluid loss.
- The bacterium Lactobacillus rhamnosus GG (LGG) prevents the colonization of pathogenic bacteria and influences immune responses in the human gut.
- Testing in intestinal cell tissue culture shows that LGG attenuates barrier dysfunction, apparently by reducing the attachment of pathogenic bacteria and modulating pro-inflammatory epithelial cell signaling.

Study of the Interplay Between Gut Microbiota and Ingested Beneficial Bacteria in Irritable Bowel Syndrome Subjects with Predominant Constipation
Patrick Veiga, PhD
Danone Research, France

- Genetic analyses were used to monitor changes in the gut microbiota of individuals with irritable bowel syndrome with constipation. These individuals were monitored after they consumed yogurt containing the probiotic Bifidobacterium lactis DN-173 010.
- Instead of large global shifts in microbial species, results showed only a few species changed a great deal with ingestion of the probiotic product.
- Survival of the ingested probiotic strain, as monitored in fecal samples, varied from person to person, which may be related to whether or not individuals with irritable bowel experience relief from symptoms with probiotic ingestion.

Exacerbation of Dextran Sulfate Sodium (DSS)-Induced Colitis by Localized Delivery of Interferon-β Secreted by Lactobacillus acidophilus
Howard A. Young, PhD
National Cancer Institute

- Probiotic strains have the potential to be used as delivery systems for therapeutic compounds, including immunomodulatory peptides such as interferons.
- Previous studies suggested that treatment with interferon β-1a might benefit patients with ulcerative colitis, while others suggested that the peptide causes ulcerative colitis when used to treat patients with multiple sclerosis or hepatitis.
- In accordance with the latter results, mice inoculated with a probiotic Lactobacillus acidophilus strain expressing interferon β-1a were rendered more susceptible to experimentally-induced colitis.

Administration of Probiotic Bifidobacterium lactis 420 Reverses Diabetic Status in Mice Under High-Fat Diet
Arthur Ouwehand, PhD
Danisco Health and Nutrition, Finland

- Probiotics are under investigation as therapies for metabolic syndrome, which is thought to be related to the high levels of systemic inflammation promoted by a high-fat diet.
- One proposed mechanism of this inflammation is that increased fat in the gut breaks down its barrier function, allowing highly inflammatory lipopolysaccharides (LPS), produced by Gram negative bacteria in the gut, to enter the blood and tissues.
- The probiotic Bifidobacterium lactis 420 reverses diabetic changes and reduces fat mass in mice fed a high-fat diet while reducing blood levels of LPS and markers of inflammation and counteracting changes in the gut microbiota.

Development of Bifidobacterium longum infantis 35624 for a Probiotic Supplement
Duane Charbonneau, PhD
Procter and Gamble Company

- Bifidobacterium longum subsp. infantis 35624 is in development as a probiotic for use in treating infection and irritable bowel syndrome.
- B. longum dramatically reduces Salmonella colonization in mice.
- Ongoing studies in humans with irritable bowel syndrome have been hampered by difficulties with the formulation of this probiotic, which have made results troublesome to interpret.
Suggested Reading


Resources

International Scientific Association for Probiotics and Prebiotics
www.isapp.net
This association is a non-profit collaboration of scientists dedicated to advancing the science of probiotics and prebiotics.

Group Danone
www.danone.com
Group Danone is a health and nutrition company that produces dairy products, bottled waters, and baby and medical nutrition products.

WGO Practice Guideline - Probiotics and Prebiotics
www.worldgastroenterology.org/probiotics-prebiotics.html
A set of clinical practice guidelines for the use of probiotics and prebiotics from the World Gastroenterology Organisation

Human Microbiome Project
nihroadmap.nih.gov/hmp
The Human Microbiome Project is a research program initiated by the NIH Roadmap intended to generate resources leading to a comprehensive characterization of the human microbiota and their role in human health and disease.

An Introduction to Probiotics
ncam.nih.gov/health/probiotics
The National Center for Complementary and Alternative Medicine has developed an informational page on probiotics.

Dietary supplements:

Industry Information and Regulations
www.fda.gov/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/ucm107201.htm
This page provides FDA guidance on dietary supplement labeling, new dietary ingredients, and other areas of interest to probiotic manufacturers.

FDA Guidance for Industry:
Evidence-Based Review System for the Scientific Evaluation of Health Claims
www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm073332.htm
This page provides recent FDA guidance on the use of health claims in food product labeling.

Frequently Asked Questions

Are health claims currently allowed for probiotics in the U.S.?
No. Today only structure-function claims are currently allowed for probiotics in the U.S.

Are probiotics currently under clinical investigation for the treatment or prevention of disorders other than gastrointestinal conditions?
Yes. Because of their putative effects on immune function, probiotics are under clinical investigation for the treatment of infections and allergies, and in a number of other clinical settings as well.

Are studies of probiotics in humans subject to FDA oversight through the Investigational New Drug (IND) application process?
It depends. Trials in healthy individuals in which the stated aims are to evaluate structure/function claims would not ordinarily require an IND. However, an IND is likely to be required if the trial is investigating the effects of a probiotic on a disease condition, which would bring the research into the realm of drug investigation.

Is there any scientific evidence to suggest that probiotics may be useful against psychological conditions such as stress and depression, or neurophysiological states such as chronic pain?
Considerable preclinical and basic science evidence suggests intimate connections between neurophysiological states, such as mood and pain, and the gastrointestinal tract. Several lines of evidence also suggest that these states are affected by the composition of the gut microbiota, which may in turn be affected by the introduction of probiotics.

What is known about the optimal composition and the functions of the human gut microbiota?
There is currently no definitive answer to this question. Although substantial data have been gathered on the microbial species present in the gut, the complexity of the gut microbiota has required the development of a number of model systems to investigate how these species interact with each other and the human host and to study the exact roles played by the microbiota in health and disease. Considerable research is still needed to answer these questions and to determine how probiotics might affect these interactions.

Podcast
More Than Yogurt
www.nyas.org/morethanyogurt
Delve into the world of prebiotic and probiotic science and learn why keeping the good microbes in our bodies happy means a lot for health.

eBriefing
To watch speaker presentations and slideshows from this Symposium, please visit www.nyas.org/probiotics-eB.

Webcasts
www.usprobiotics.org/webcast.asp
Probiotics: Applications in Gastrointestinal Health & Disease
(October 2007)

http://nutrition.med.harvard.edu/webcast.html
The Health Impact of Active Cultures: Probiotics
(September 2006)

Probiotics and the Hygiene Hypothesis: A Case for Protective Nutrients
(April 2006)

Probiotics and Intestinal Health in Children
(October 2005)

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