Editorial

For a very long time, people in general and doctors in particular have considered microorganisms such as bacteria a potential infectious agent and something they should avoid contact with or get rid of. As bacteria, viruses and yeast were being identified, measures were developed for effective ways to protect oneself from these by vaccines or antibiotics. The average human being harbors 10 times more bacterial cells than their own cell numbers. These microbes colonize the skin, nasal and oral cavity, urogenital and gastrointestinal tract (GIT). Among all sites, the GIT is the most densely populated area with the colon alone harboring over 10^{10} – 10^{12} colony-forming units per gram of feces, or 70% of all microbes in the human body.

The term ‘microbiome’ was coined by Joshua Lederberg, who argued that microorganisms inhabiting the human body should be included as part of the human genome, because of their influence on human physiology. As microbiome we consider the collective genomes of the microorganisms that reside in an environmental niche. The human microbiome (formerly known as human microbiota) is the aggregate of microorganisms that resides on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the GIT. They include bacteria, fungi, and archaea. Human-associated bacterial species comprise the vast majority of the human microbiome in terms of microbial DNA content and cell count. In fact, in one recent study, more than 99% of mapped DNA sequencing reads in healthy adults were bacterial sequences.

The idea that a large part of our lives can be controlled by our intestinal bacteria is quite frightening! To realize that such things as our mother’s weight, the way we are born, and what we are fed can determine the degree of bacterial diversity that we will have early in life, which in turn will affect our immune system, metabolism, etc., adds more reasons to pay particular attention to what happens in the first 1,000 days of existence. This subject has developed its own terminology, which at times makes it difficult to follow. However, the topic is so fascinating and the ramifications of such relevance that I encourage you to make an effort and read and re-read it until the concepts are understood. In multi-authored publications, there is always the risk of repetition. And I acknowledge that there is some repetition among the four excellent contributions that make this issue of the supplement of *Annals of Nutrition and Metabolism*. Dr. W. Allan Walker, Conrad Taff Professor of Nutrition at Harvard Medical School, Boston, Mass., USA, discusses the establishment of the intestinal microbiota. Dr. Walker explains how the newborn, full-term, vaginally-delivered infant initially colonizes its GIT and how, with full colonization, a symbiotic relationship develops between colonizing bacteria and the underlying epithelial and lymphoid tissues. This relationship results in both nonspecific and immunologic (innate and adaptive immune responses) defenses which collectively comprise the intestinal mucosal barrier to pathogens and noxious antigens. An important component of mature intestinal immune homeostasis is the development of oral tolerance

to benign commensal bacteria and noxious antigens. Disruption of these events results in inadequate colonization which leads to dysbiosis, an undesirable alteration of the microbiota resulting in an imbalance between protective and harmful bacteria, and increased expression of immune-mediated and allergic disease states.

Dysbiosis has been implicated in many human disease conditions including local gastrointestinal and systemic diseases. The second paper by Dr. Deanna Gibson and colleagues from British Columbia, Canada, discusses the fact that dietary patterns alter the intestinal microbiota ecologically and functionally, which results in physiological consequences to the host. Changes to the community structure of the intestinal microbiota are not without consequence, considering the wide effects that the microbes have on both local and systemic immunity. A complex tripartite relationship between diet, microbes and the gut epithelium is the basis for health or certain diseases. This is followed by a summary of clinical evidence of diet-induced dysbiosis as a contributing factor in the development of gastrointestinal diseases like inflammatory bowel disease, irritable bowel syndrome and colorectal cancer, as well as systemic diseases like obesity, diabetes, atherosclerosis and nonalcoholic fatty liver disease. Finally, the current dietary and microbial interventions to promote a healthy microbial profile are reviewed. This article presents a table where papers describing clinical effects of different probiotics are listed.

The paper by Dr. Erika Isolauri's group in Turku, Finland, addresses the issue of how reshaping the gut microbiota at an early age may have a functional impact on obesity risk. Recent scientific advances point to an aberrant compositional development of the gut microbiota and low-grade inflammation as contributing factors, in conjunction with excessive energy intake. A high-fat/energy diet alters the gut microbiota composition, which reciprocally engenders excessive energy harvesting and storage. Further, microbial imbalance increases gut permeability, leading to metabolic endotoxemia, inflammation and insulin resistance. Local intestinal immunologic homeostasis is achieved by tolerogenic immune responses to microbial antigens. In the context of amelioration of insulin sensitivity and decreased adiposity, the potential of gut microbiota modulation with specific probiotics

and prebiotics lies in the normalization of aberrant microbiota, improved gut barrier function and the creation of an anti-inflammatory milieu.

In 2001, the Food and Agriculture Organization and the World Health Organization adopted a definition of the term 'probiotic' as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host'. In the last contribution to this issue, Dr. James Versalovic of Houston, Tex., USA, addresses the fact that the relative abundance of probiotic genera and species in the healthy human microbiome is a relevant consideration and discusses whether microbial deficiencies in individual species could be readily corrected by administration of probiotics to children. Alternatively, do probiotics simply enhance the ability of other bacterial genera to proliferate and reduce the numbers of potentially harmful bacteria? Research related to the mechanisms of probiosis during the 1990s and the rapid coalescence of the human microbiome research community globally since 2005 have provided the basis for the current era in metagenomics (the genomic analysis of microorganisms by direct extraction and cloning of DNA from an assemblage of microorganisms). We intentionally chose a more basic science approach to this topic dealing with what we know today about the mechanisms by which probiotics act, rather than offering a more practical review of which probiotic has proven to be good for what.

At a recent meeting at the National Institute of Health, the microbiome research over the last 7 years was reviewed in a 3-day symposium. Individual presentations can be seen at their website (<http://www.genome.gov/27554404>).

We hope that this issue will trigger your curiosity, modify the way that you think about bacteria, provide you with scientific evidence to try to convince pregnant women to have natural births whenever feasible, breastfeed at least as long as recommended, avoid arbitrary use of non-milk supplements under the age of at least 4 months, and avoid unnecessary antibiotics, in order to allow for a healthy development and preservation of your patients' intestinal microbiota. Groom your intestinal microbiota from the start!

Carlos Lifschitz