FEATURE ARTICLE

Microbes in your Body!

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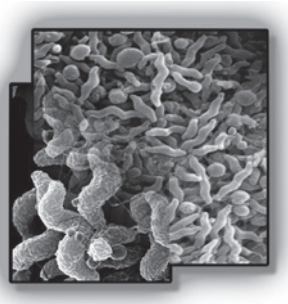

Do we each have distinct microbial signatures at birth, or do they evolve as we age? And how much do they matter?

WITHIN the body of a healthy adult, microbial cells are estimated to outnumber human cells by a factor of ten to one. These communities, however, remain largely unstudied, leaving almost entirely unknown their influence upon human development, psychology, physiology, immunity, and nutrition. To take advantage of the recent technological advances and to develop new ones, the National Institutes of Health, Bethesda, USA has initiated a research initiative termed as the Human Microbiome Project (HMP). Its mission is to generate resources enabling comprehensive characterization of the human microbiota and analysis of its role in human health and disease.

Traditional microbiology has focused on the study of individual species as isolated units. However many, if not most, have never been successfully isolated as viable specimens for analysis, presumably because their growth is dependent upon a specific microenvironment that has not been, or cannot be, reproduced experimentally. Among those species that have been isolated, analyses of genetic makeup, gene expression patterns, and metabolic physiologies have rarely extended to inter-species interactions or microbe-host interactions.

Advances in DNA sequencing technologies have created a new field of research, called metagenomics, allowing comprehensive examination of microbial communities, even those comprised of uncultivable organisms. Instead of examining the genome of an individual bacterial strain that has been grown in a laboratory, the metagenomic approach allows analysis of genetic material derived from complete microbial communities harvested from natural environments. In the HMP, this method will complement genetic analyses of known isolated strains, providing unprecedented information about the complexity of human microbial communities.

By leveraging both the metagenomic and traditional approach to genomic DNA sequencing, the Human Microbiome Project will lay the foundation for further studies of human-associated microbial communities. Broadly, the project has set the following goals:

- Determining whether individuals share a core human microbiome
- Understanding whether changes in the human microbiome can be correlated with changes in human health
- Developing the new technological and bioinformatic tools needed to support these goals, and
- Addressing the ethical, legal and social implications raised by human microbiome research.

Notably, however, the utility of the techniques and technologies pioneered by the HMP will not be limited to studies of human health but will be applicable to the study of microbes in a wide range of biological processes. Microbes profoundly shape this planet and all life on it, and yet the test tube of the laboratory is rarely reflective of how they actually exist in the environment. The ability to study native microbial communities represents a fundamental shift in microbiology and is one whose implications can only be imagined.

The Gut Microbiome

The human gut is sterile at birth. Immediately after birth, it is colonized by numerous types of microorganisms. Some of these microorganisms enter the body through air that is breathed in, some through water, food and still others through contact with persons around and objects surrounding the person at different stages of life. In the first weeks of life, tremendous temporal and inter-individual variation is evident in the infant's microbial populations (microbiome). By 1 year of age, while babies retain their unique bacterial profiles, these converge toward a profile characteristic of the adult individual gastrointestinal tract (Palmer et al., 2007).

While significant changes may occur during disease, infections, stress, and depending on the diet in the intestinal microbiome, this tends to revert to that which was established in infancy if the external factors change. Traditional methods that rely on the isolation of microbes in culture, although invaluable to clinical microbiology, cannot address ecological questions because of the complexity of intestinal microbial communities. Indeed, by far the majority of these microbes are not readily cultured and are generally referred to as 'unculturable.'

Recent advances in molecular-based technologies, however, now permit genetic analysis of complex microbial populations without the need for cultivation. As a result, gut microbiota have now been estimated to consist of at least 1800 genera and up to 40,000 species of bacteria based on the analysis of 16S ribosomal RNA. They have an estimated mass of 1–2 kg, number 100 trillion (Frank and Pace, 2008) and together possess 100 times the number of genes in the human genome (Kurokawa et al., 2007). Now that the human and many animal genomes have been unraveled, a significant worldwide effort is being invested in the characterization of the human microbiome ([Kinross et al., 2008] and [Turnbaugh et al., 2007]).

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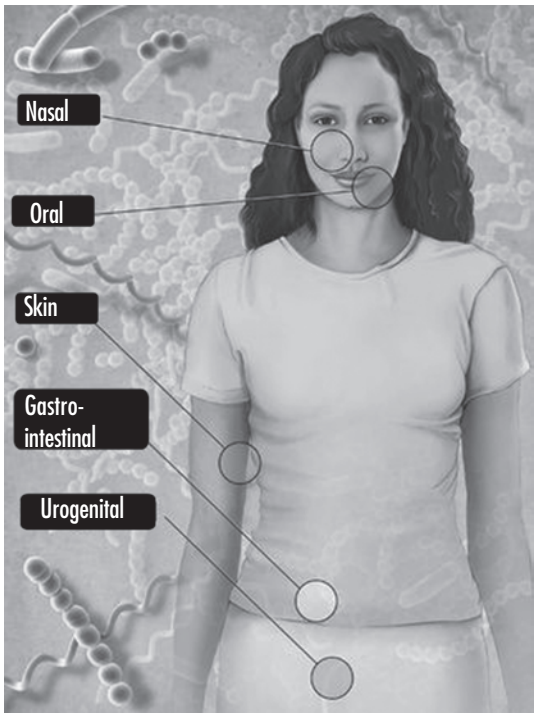
While a limited number of metagenomic analyses of the human gut microbiome have been published already, much still needs to be done before we can compare individual analyses, or better still, look for abnormal patterns in disease. It should also be emphasized that almost all the work done so far in this area comes from analysis of fecal (and therefore largely colonic) samples, and very little information exists on the microbial content of the small intestine where considerable microbe-host biological interaction occurs.

Microbiota and Animal Behaviour

The idea that the composition of bacteria present in the intestines of a person may affect mood and behaviour is supported by a series of several published scientific studies. For example, *Campylobacter jejuni* infection increases anxiety-like behaviour in the holeboard: It has been shown that orally administered *Campylobacter jejuni*, in subclinical doses too low to elicit overt immune activation, result in anxiety-like behaviour in mice. It is also reported that areas of brainstem activation, such as the nucleus tractus solitarius and lateral parabrachial nucleus, participate, presumably via the vaug nerve pathway; in neural information processing that ultimately lead to autonomic, neuroendocrine and behavioural responses. These types of experiments all support the suggestion that the gut microbiome may be intimately involved in the modulation not only of the peripheral but also aspects of the central nervous system including behaviour.

The intestinal microbial balance may also be temporarily changed by an alteration in diet and the effects of the latter upon cognition and behaviour are well recognized. A recent study showed that a specific dietary manipulation positively affected memory and reduced anxiety-like behaviour. These changes were associated with significant increases in diversity of the microbiome as analyzed by the most up-to-date molecular methodology—pyrosequencing.

The human host and its microbial flora constitute a complex ecosystem whose equilibrium serves as a remarkable example of reciprocal adaptation. Intestinal bacteria play an important role in the development of the immune system. The normal intestinal flora is responsible for resistance to colonization by exogenous pathogenic microorganisms. Nevertheless, it also constitutes a reservoir of potentially pathogenic bacteria in close contact with the host. These bacteria are responsible for opportunistic infections in immunocompromised hosts. The equilibrium of the flora can be upset by antibiotics, leading to infections as a result of proliferation of antibiotic-resistant pathogenic bacteria.



There is a greater diversity of bacteria living on the human forearm than on any other part of the body, according to a new study. On average, 44 different types of bacteria reside on the forearm, compared with 19 species living behind the ear, says the study by the National Human Genome Research Institute in the US. Reporting the results of the study, *ScienceNow*, a science journal, said: "Microbes that live *in* and *on* our bodies outnumber our own cells ten to one." Intriguingly, these microscopic passengers were found to be evenly distributed around the body.

In broad terms, research has revealed that a far wider variety of bacteria live on our skin than was previously believed. It also showed that dry and moist skin had a broader variety of microbes than oily skin. Scientists have developed an atlas of the bacteria that live in different regions of the human body.

Some of the microbes help keep us healthy by playing a key role in physiological functions. The University of Colorado at Boulder team found unexpectedly wide variations in bacterial communities from person to person. Researchers hope their work, published in *Science Express*, will eventually aid clinical research. They say that it might one day be possible to identify sites on the human body where transplants of specific microbes could benefit health.

This study was based on an intensive analysis of the bacteria found at 27 separate sites on the bodies of nine healthy volunteers. Not only did the bacterial communities vary from person to person, they also varied considerably from one site on the body to another, and from test to test – but some patterns did emerge. They used the latest gene sequencing and computer techniques to draw up a profile of the microbes found at each specific site. Most sites showed big variations in the bacteria they harboured from test to test even within the same individual. However, there was less variation in the bacteria found in the armpits and soles of the feet – possibly because they provide a dark, moist environment.

The least variation of all was found in the mouth cavity. Skin sites in the head area, including the forehead, nose, ear and hair, were dominated by one specific type of bacterium. Sites on the trunk and legs were dominated by a different group.

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