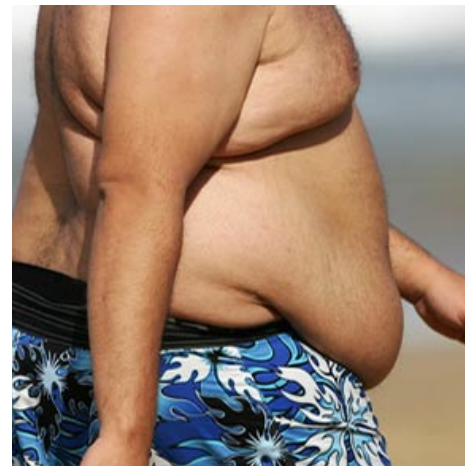


# Getting down to the core of the problem: Microbiota and diseases of the modern world

Author: Dr. Kristen Kerksiek | January 17, 2010

Its depths are teeming with life, an ancient and complex ecosystem that we don't fully know or understand. Over thousands of years, this community has evolved to ward off pathogenic microorganisms, participate in digestion, synthesize essential nutrients and train the immune system. However, it seems that a fragile balance has been damaged, and it's probably affecting our health. The depths in question are in our own bodies, and the life is the microbiota – resident microorganisms - that colonize our mucosal and cutaneous surfaces. Although it has long been appreciated that these microorganisms (primarily bacteria) are beneficial, recent research indicates that they may also be crucial for the development and regulation of the immune system; by altering the composition of this community, the stage may have been set for many health problems that have emerged in the modern world.



Do our gut microbes share some blame for the rise in obesity?  
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## Habitat *Homo sapiens*

The human body must make a good home: we are accompanied by 10-fold more bacteria than we have eukaryotic cells, and the genes of our microbiota outnumber our own by more than 100-fold. Although the existence – and importance – of our microbiota is nothing new, advances in molecular biology are enabling scientists to get a much better look at our live-in guests. Many – if not most - microorganisms can't be cultured using traditional methods, so much of the microbial world has remained unknown to us. However, with improvements in sequencing technology and decreasing costs for the service, microbiology has entered a new era. The era of metagenomics.

**Metagenomics** is the sequencing of genomic DNA from environmental (uncultured) samples. Metagenomic studies not only reveal the composition of complex microbial communities (including the relative abundance of different organisms), they can also be used to determine potential metabolic activity of the population.

In the **Human Microbiome Project**, a National Institutes of Health (NIH)-funded project launched in 2007, researchers are combining metagenomics and extensive whole-genome sequencing to determine whether a “core” (standard) human microbiome exists and to understand how our microbiome is associated with health.

For more information see <http://nihroadmap.nih.gov/hmp/>

In an initial metagenomic analysis of the gastrointestinal tract, Paul Eckburg and colleagues (*Science*, 2005) found that the diversity of our microbiota is much greater than we had known: 80% of the sequences were from species that had not been cultured, and 62% were novel. Subsequent studies have confirmed the rich diversity of species and strains in the human microbiota (although 99% of the bacteria fall into just 4 phyla). At the level of bacterial gene families, there appears to be a core gut microbiome (Turnbaugh *et al.*, 2009), but each individual has a unique composition, something like a microbial “fingerprint”.

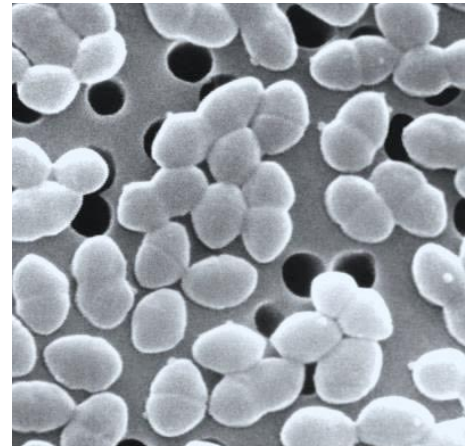
Humans are, after all, diverse, and we have lived with – and co-evolved with – our microbiota throughout human existence. Some of them help us selflessly (commensals), while others get something from the deal, too (symbionts). A few of them can turn pathogenic if they have the chance (pathobionts). But they’re part of us, and it’s clear that we benefit from their presence. Just how much do we depend on them?

### An ecosystem in chaos?

Sanitation, cleaner water, vaccination, antibiotics...these and other changes in human lifestyle are bound to have affected our microbial flora. Detailed study of our inner diversity is really just beginning, but increasing attention is being paid to the notion that alterations in exposure to microbes *inside* us (rather than outside us, *i.e.* Hygiene Hypothesis) may be an important factor in the rapid rise of certain health problems in the developed world.

Is there any proof that species within our microbiota are deserting their posts? For at least one species, the answer may be “yes”: *Helicobacter pylori*. The notorious Gram-negative bacterium linked to gastric ulcers and stomach cancer was once present in nearly 80% of the population, but with antibiotic treatment and reduced transmission, frequencies are in the single digits for children in some Western populations. Good riddance? Well, perhaps not for everyone.

It turns out that *H. pylori* affects the regulation of gastric hormones in its host, and acid production decreases with extended colonization. As *H. pylori* infection rates have decreased, there has been a corresponding rise in the incidence of gastric (acid) reflux and associated diseases (Barrett’s esophagus, esophageal adenocarcinoma). Some researchers believe the disappearance of the gastric menace could also have a contributing role in the increase of chronic metabolic and allergic diseases (see Blaser and Falkow review).

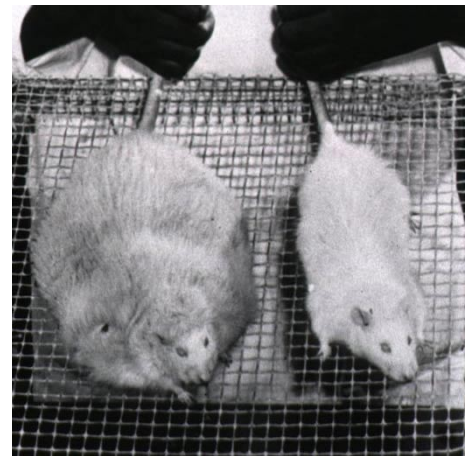


Some members of our microbiota, such as these Gram-positive *Enterococcus sp.*, can become pathogenic if their host is immunosuppressed. © CDC Janice Carr



*H. pylori* causes inflammation of the stomach lining (chronic gastritis), but most infected individuals never experience symptoms. © Yutaka Tsutsumi, Fujita Health University School of Medicine

Microbial flora, pathogen or both? The jury is still out, but at least the ongoing research on *H. pylori* can take full advantage of our knowledge about the bacterium and the multiple tools for identifying it. Our examination of the role between other – many still unidentified – members of our microbiota and human diseases is more difficult. That's where metagenomics comes in. Take, for example, obesity, which was formally recognized as an epidemic by the World Health Organization (WHO) in 1997. Obesity and its associated diseases (*e.g.* type II diabetes mellitus, atherosclerotic cardiovascular disease) are predicted to replace infectious diseases and malnutrition as the most important cause of poor health worldwide. There is certainly an important behavioral (lifestyle) component to the rise in obesity. However, in 2006 Turnbaugh et al. demonstrated that the gut microflora in obese mice can extract more energy (calories) from food, and transfer of the microbiota to non-obese mice resulted in a significant increase in body fat. In a study published in 2009, the same group from the laboratory of Jeffrey Gordon used metagenomics to examine the microflora in lean and obese humans (54 sets of twins and their mothers) and found alterations in bacterial diversity and the use of bacterial genes/metabolic pathways.



Obese *ob/ob* mice consume more food than lean mice, but their intestinal microbiota are also more efficient at extracting energy from it.  
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Obesity is only one of many health problems of the modern world that has been linked to changes in intestinal microbiota: studies in animal models and humans have indicated that our inner microbial ecosystem may also influence, for example, diabetes, allergies and inflammatory bowel disease. Metagenomics is still in its infancy, but there is great hope that this rapidly growing field, supported by the Human Microbiome Project and other efforts, will advance medical science to a new level.

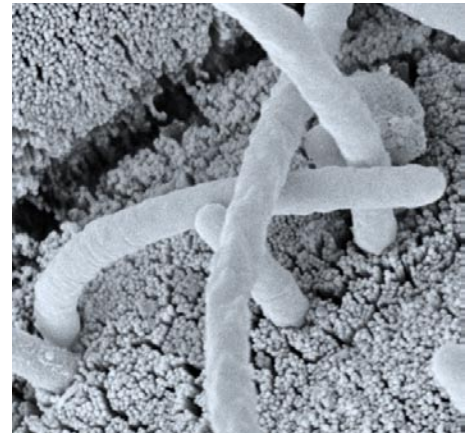
### The power of one

How much influence can a single bacterial species have within the complex ecosystem of our microbiota? Evidently a lot. In October 2009 two independent groups demonstrated that segmented filamentous bacteria (SFB) control CD4<sup>+</sup> T cell responses in the gut.

Ivanov et al. (*Cell*) showed that SFB are sufficient to induce CD4<sup>+</sup> Th17 cells in mice; Th17 cells secrete IL17 and IL22, serve to defend against bacterial and fungal pathogens at mucosal surfaces and are also important mediators of autoimmune diseases. Gaboriau-Routhiau, V. et al. (*Immunity*) showed that SFB control the maturation of Th1, Th17 and regulatory T cell responses in the gut.

## A reason to hope

Although we've lived with our microbiota forever (in human terms), we may be just starting to really appreciate them. New technologies have enabled us to recognize the complexity and diversity of our microflora, strengthened the evidence for their importance and given hints as to what might happen when our internal microbial balance is disturbed. However, we are at the beginning of our voyage of understanding, and the questions still greatly outnumber the answers: Are alternations of the microbiota in diseased individuals the cause – or an effect – of the illness? What environmental variables affect our microbiota and to what degree? How much does “normal” flora today differ from that of our ancestors? The hope for the future is, of course, that if we find what is “broken” then it can be fixed. It is important, however, to start doing something today: when we think of human health – and health care – we must keep our microbial co-inhabitants in mind. We are not alone.



Nonculturable, *Clostridia*-related segmented filamentous bacterium (SFB) exhibits remarkable control over CD4<sup>+</sup> T cells in the gut. © Mark Jepson, University of Bristol

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