Ten parts bacteria, one part human

What does it mean to be human? Philosophers have pondered that particular riddle for centuries. It turns out the answer may be: a whole lot of nasty little bugs.

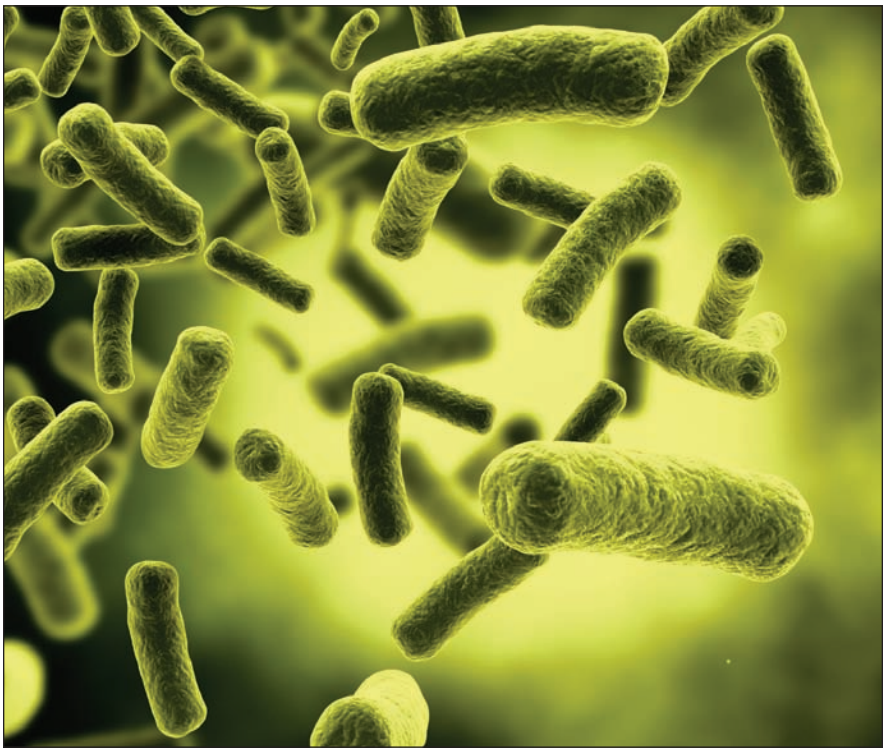
By cell count alone, just a tiny fraction of what makes up any one human being is actually human, by most ontological definitions of the term. And most of those nonhuman parts are, to borrow a philosophic concept, a necessary condition of life or survival.

Or as Dr. Martin J. Blaser, chairman of the Department of Medicine and professor of microbiology at the New York University School of Medicine, puts it: "ten parts microbe and one part human. But that's only counting microbial cells as the unit. If we look at unique genes, then the difference is a factor of 100. We are only 1% human in terms of unique genes."

But the nuances of modern life, as well as widespread and indiscriminate use of antibiotics, are having drastic effects on this hidden microbial majority, the consequences of which, Blaser says, are not just the creation and explosive growth of drug-resistant bacteria, or so-called superbugs, like methicillin-resistant *Staphylococcus aureus*. They also include the increasing incidence of "postmodern diseases, such as obesity, as well as allergies, inflammatory bowel disease, asthma, type 1 diabetes and gastroesophageal reflux, which have more than doubled in many populations," he asserts.

"The microbes in the human body are not accidental, but have coevolved with humans over eons. But things have changed in the last century, our ancient microbes are disappearing and that is what is fueling many of our modern diseases," Blaser adds.

To fully understand that development, and the processes by which human beings are being transformed, the United States National Institutes of Health has shelled out US$160 million for a creature called the Human Microbiome Project, which aims to map out and characterize our changing microbiota landscape (http://commonfund.nih.gov/Hmp/).



The obliteration of bacteria that have lived in the human gut for thousands of years may be a simplistic approach to fighting disease and could actually endanger the health of the human race.

Its central premise is that the human body is sort of a farm, growing both beneficial and harmful bacteria. It's a notion that has been dubbed the "microbiome" and is prompting a paradigm shift away from the traditional germ theory of disease.

"The microbiome is the name given to the aggregate microorganisms that reside on the skin, in the saliva and oral mucosa, and in the urogenital and gastrointestinal tracts," explains Dr. Maria Y. Giovanni, assistant director for microbial genomics and advanced technology at the National Institute of Allergy and Infectious Disease, and the Division of Microbiology and Infectious Diseases at the National Institutes of Health.

Since the time of Louis Pasteur and his experiments during the 1860s, modern medicine has essentially been practised on the somewhat dogmatic proposition that the only good bacteria is dead bacteria. Bacteria make us sick; ergo, they must be eliminated.

No better example of this was the 1982 discovery by scientists Barry Marshall and Robin Warrant that *Helicobacter pylori* is the cause of peptic ulcers. Prior to their momentous discovery, for which they shared a Nobel Prize in 2005, it had commonly been held that stress was the major cause of peptic ulcers.

This represented such a change in thinking for medicine that it's now altogether common for physicians to express the opinion, in corridor chatter, that the solution is to eradicate *H. pylori* once and for all. "We are taught that *Helicobacter* is simply bad for us. So the idea was — we need to rid our bodies of this harmful pathogen,"

Blaser says. Perhaps. Therein lies the paradigm shift.

As Blaser notes, "we don't live in a germ-free world." Given the validity of that proposition, "a more ecological approach is required."

While the identification and elimination of *H. pylori* has saved thousands of lives, obliteration of the bacteria may be a simplistic response to the problem that could actually endanger the health of human race, he explains.

"We're talking about a bug that's been in the human gut for at least 100 000 years if not longer," he notes. "This did not happen by chance."

"It is striking that this organism that has been with us for such a long time is disappearing," he adds. "We are already measuring the consequences of this, such as decreased ulcers and rates of stomach cancer. But we are also seeing increased rates of esophageal diseases, and increased incidence of adenocarcinoma of the esophagus, which is the fastest growing cancer in North America."

"There are specific circumstances under which *Helicobacter* can cause harm," he says. "But without it we are going to be in real trouble."

There appears to be evidence in support of the notion. In 2007, after analyzing samples from more than 7500 adults, Blaser and colleague Yu Chen concluded that people who don't have *H. pylori* in their gastrointestinal tracts are far more likely to have had asthma as children (*Arch Intern Med* 2007; 167:821-7). This was confirmed by a study in Switzerland in which investigators infected a cohort of mice with *H. pylor*i, then exposed the mice to allergens known to induce cellular inflammation (the hallmark of asthma). In every case, mice without the bacterium became ill, while those with it were protected from developing asthma (*J Clin Invest* 2011;121:3088-93).

There is equally compelling evidence that eradicating *H. pylori* could affect metabolism in ways that increase the risk of obesity. Several research groups, including Blaser's, have found a strong relationship between *H. pylori* and levels of ghrelin — a hormone that is known to increase appetite. Eradication of the bacteria led to significant weight gain (*BMC Gastroenterol* 2011; 11:37).

Blaser believes that children are most at risk. "The average child is receiving between 10 and 12 courses of antibiotics during childhood. A generation of kids are growing up without *H. pylori* regulating their levels of ghrelin," he says. "We are deranging our microbiota and as a result, the message to stop eating never makes it to the brain. If those hormones aren't controlled, it becomes far more difficult to control one's weight."

Earlier this year, Blaser's team found that mice fed antibiotics in doses similar to those given children with ear infections gained considerable more weight (*Nature* 2012; 488:621-6). That's entirely consistent with findings that low-dose antibiotics prompt growth and weight gain in animals (*Appl Environ Microbiol* 1987;53:331-6).

While for years the mechanism remained somewhat of a mystery, these new data suggest to Blaser that "low-dose antibiotics change the animals' intestine microbiota which in turn alters the way the animals process and metabolize nutrients. The same process may be occurring in humans."

From that perspective, Blaser says the microbiome project will help to resolve some of the mechanisms and processes that are at play in the survival of humans.

Until those issues are resolved, clinicians would be ill-advised to abandon antibiotics, Blaser adds. But they should also disavail themselves of the notion that antibiotics are "biologically free."

Current medical and agricultural practices are causing a "global warming of the stomach," he quips. "In many ways, we are doing the same to our micro-ecology as we are to our macro-ecology."

Giovanni hopes that the project will capture the imagination of the public. "While we're in the early stages, the data collected from the microbiome project are foundational and completely open for all members of the public to study. It is the beginning of something big. … Characterizing and understanding the microbes within us will undoubtedly give us pieces to the puzzle of many complex diseases. It's exciting." — Paul Kudlow MD, Toronto, Ont.

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