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Aliens Inside Us: A (Mostly Friendly) Bacterial Nation

By JAMES GORMAN

In the movie "Alien," the creature of the title grows toothy and impatient inside John Hurt, finally bursting through his stomach in a fit of extreme and bloody pique, looking something like an albino salamander with fangs. It promptly scuttles off to become even more obnoxious.

Leave it to the movies to exploit, with an unabashed lack of subtlety and taste, the nagging fear that there is something awful inside us. The fear is not without foundation. Peach trees and watermelon vines will not grow there, but parasites, worms and cysts will do fine. The list of potential co-inhabitants is long and gruesome. Any medical student knows that there is no need to fret about what lurks under the bed when you can lose sleep thinking about what lies within.

On a deep level, it is not really the odd parasite that worries us. The unsettling fact is that each of us, sick and healthy, could start speaking in the first person plural, not with the editorial, but the biological "we." We may not all have multiple personalities, but it is fair to say that the self some of us try so relentlessly to improve is really community property.

There is a world within each of us, a living, evolving ecological system of 500 to 1,000 species of microbes, a "bacterial nation" in the words of Dr. Jeffrey I. Gordon, a microbiologist at Washington University in St. Louis. In fact, by numbers of cells, a human being has 10 times as many bacteria as human cells. The bacterial cells are much smaller, which is why we do not look like an overgrown petri dish.

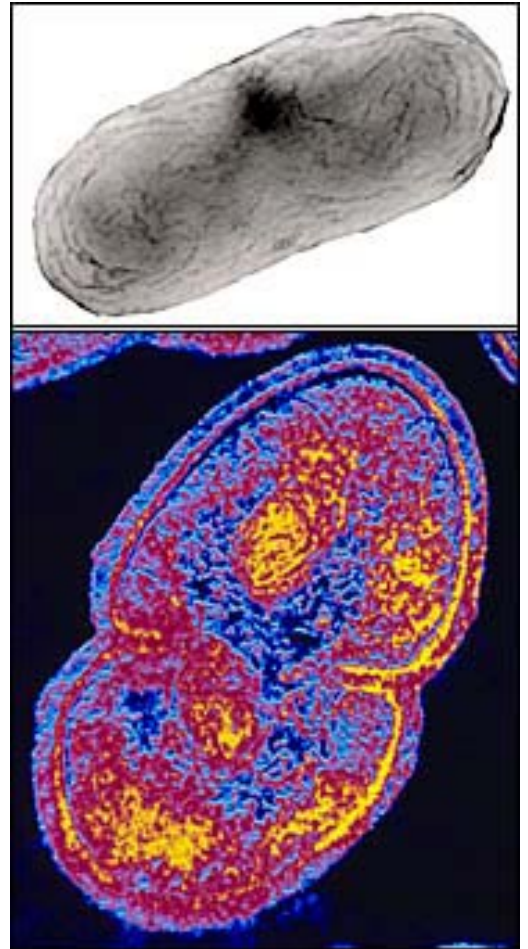
Nor are we simply hosts to a random collection of bugs. The bugs appear to be organized. The good news is that they are on our side most of them, most of the time. They function, Dr. Gordon would say, as an organ, or, as they are commonly called, the gastrointestinal consortium, a parliament of the bowels.

"I think of it," Dr. Gordon said, "as a life form within us exquisitely tuned to our biology."

Our internal bacteria help us digest food that otherwise would simply pass through us. They fend off unfriendly bacteria and even regulate the development and metabolic processes of the host.

The presence of these bugs in the gut is well known, but the nature of these microbes what they do, what species they belong to is still poorly understood. Nobody even knows how many species inhabit us, partly because they have not been easy to grow outside of their home environment.

But now, as two papers and a commentary in the current issue of the journal *Science* suggest, the powerful techniques of genomic research are providing new ways to investigate the lives of these bacterial cells. In separate reports, scientists describe the genomes of two different, common bacteria. One is *Bacteroides*



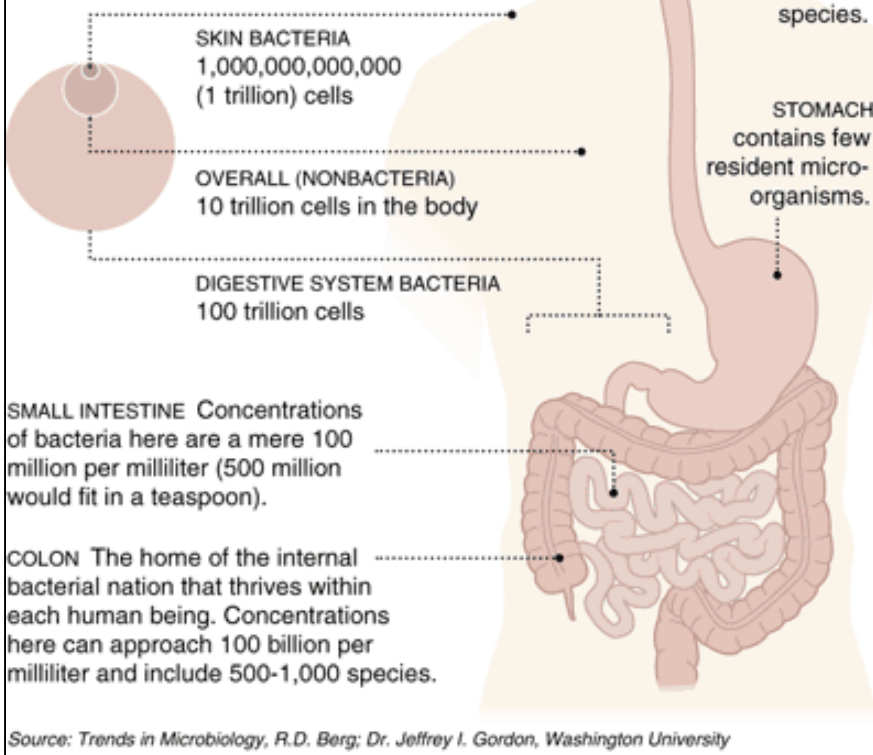
Lisa Roberts/Washington University School of Medicine (top)

Intestinal bacteria include *Enterococcus faecalis*, bottom (Alfred Pasteka/Photo Researchers Inc.), which can be drug-resistant, and the digestion aid, *Bacteroides thetaiotaomicron* (top).

The World Within

The human gut is home to a consortium of bacteria — an entire microbial world so tuned to human biology that it functions much like an organ.

CELL NUMBERS (approx.)



thetaiotaomicron, a friendly symbiont; the other is a traitorous drug-resistant variant of *Enterococcus faecalis*, an otherwise mild-mannered garden-variety citizen of the gastrointestinal consortium.

In the new research report, Dr. Gordon, Dr. Jian Xu and six colleagues, all at Washington University, describe sequencing the genome of *Bacteroides thetaiotaomicron*. That particular bug is ubiquitous in humans and many other creatures.

"We are not alone in developing co-conspiracies with bacteria," Dr. Gordon said. He and his co-workers have conducted much of their work in the mouse gut, because they can rear mice in a germ-free environment and introduce one germ at a time.

In past work, the researchers have found that without the presence of bacteria, blood flow to the intestine does not develop correctly. The growth of a capillary network is apparently initiated by the presence of bacteria, either *Bacteroides thetaiotaomicron* alone or a sampling of the full consortium. Without bacteria, digestion and proper development are impaired.

By sequencing the genome, Dr. Gordon and his colleagues found many genes devoted to processing carbohydrates that humans cannot digest. They also discovered genes devoted to processing some materials produced by the human cells like mucin. These bacteria graze in the mucous lining of the intestine. Apparently they do not damage their range-land.

"There's grazing and then there's destruction," Dr. Gordon said. "And these are good grazers."

Not all is cooperation and mutual back-scratching in biology, however. Good bugs go wrong. Ancient biological alliances break down. In another paper in *Science*, Dr. Ian T. Paulsen of the Institute for Genomic Research in Rockville, Md., and 31 other researchers report on the sequencing of a turncoat genome. The bug in question, *Enterococcus faecalis*, is normally a commensal bacteria. In other words, it lives within us, and we both seem happy enough about the arrangement, although whether it helps us is unknown.

But some variants of *Enterococcus* are dangerous and drug resistant. They cause infections, particularly in hospital patients. Dr. Paulsen and colleagues sequenced the first strain of *E. faecalis* in the United States that was found to be resistant to vancomycin, an antibiotic that is often a drug of last resort.

The sequencing suggests how the bacteria went wrong. Nearly a third of its genome consists of mobile elements of DNA on its chromosomes and in self-contained packets called plasmids. The toxic effects and drug resistance are a result of this mobile DNA.

Dr. Paulsen said that the greatest significance of the sequencing was in "finding how much genetic exchange has gone on in the evolution of this pathogen." It is, he said, "easy to transfer resistance genes among enterococcus bacteria and to other things like staphylococcus."

Drug-resistant staphylococcus is a major problem for hospitals and, Dr. Paulsen said, one or two strains had "virtually certainly gained resistance genes from an enterococcus."

In a commentary on the two papers, Dr. Michael S. Gilmore and Dr. Joseph J. Ferretti at the University of Oklahoma at Oklahoma City, wrote that the two studies illuminated the way the consortium worked and what the members were doing. For instance, Dr. Gilmore said, with *B. faecalis*, the research showed "that it devotes a lot of its genetic material to enzymes that occur on the surface of the cell." That suggests it is breaking down material for some other organism, perhaps aiding certain sorts of bacterial neighbors.

"I'd bet a thousand dollars that those neighbors are cultivating something that *Bacteroides* can take advantage of," Dr. Gilmore said in an interview. It is that kind of cross talk between bacteria that may be elucidated in further genomic studies, he said.

The work on *Enterococcus* suggests what is going on when strains of bacteria leave the colon, say, and go to another location where they are damaging to the host. He said *Enterococcus* had 130 new genes from other organisms in its mobile DNA.

"What can you do with 130 new genes?" Dr. Gilmore asked. "Be more aggressive in the relationship with the host."

Enterococcus might be gaining the ability to move closer to the small intestine or the urinary tract, that is, to colonize new areas. To the host, that would mean an infection.

The possibilities of genomic research into the bacteria of the gut are almost unlimited. Dr. Gordon suggested that one could think of the collected genomes of the bacterial species as a single unit, a microbiome. It would be similar in size to the human genome on the basis of the amount of raw DNA. But it would be much larger, 100 times as large, in terms of actual genes DNA sequences that code for proteins.

In the future, Dr. Gordon said, scientists may "discover novel components of our biology that are modulated by bacteria." Perhaps obesity or susceptibility to heart disease may depend on the nature of an individual's internal bioreactor.

There is no escaping it. Our skin supports a veritable zoo of small creatures; our gut is home to an alien nation, except that in reality it is not at all alien. We may or may not be what we eat, but we certainly are what lives within us.

"It is important," Dr. Gordon said, "to think of our bodies as a summation of the metabolic capabilities provided by our own genome and the microbiome."

Because of the union of those abilities, he said, "we become a more complete and capable life form."

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