

ASTROPHYSICS
Antimatter-Sparked
SUPERNOVAE

NEUROSCIENCE
Building a
MACHINE BRAIN

PHYSICS
The Rough Road to
FUSION ENERGY

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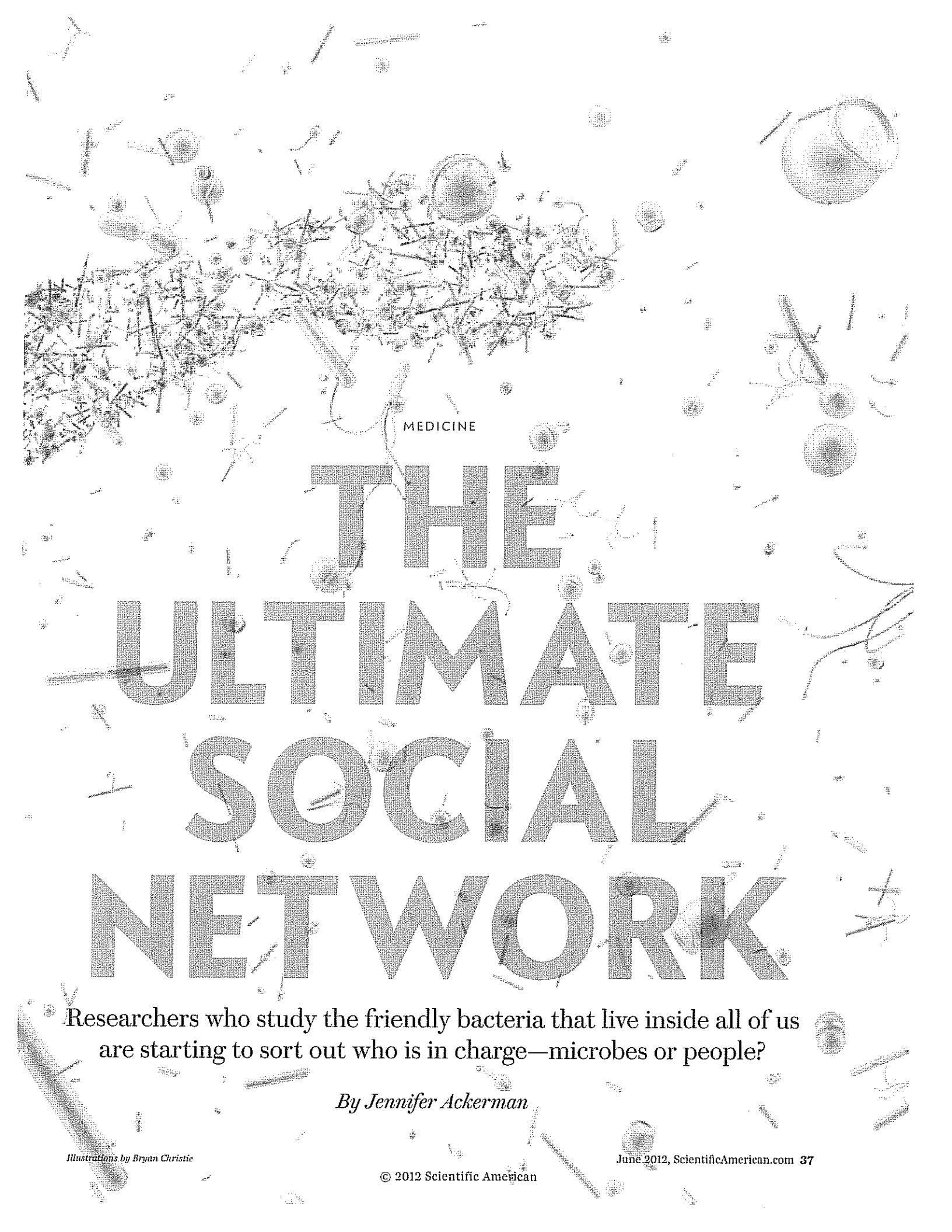
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Your Inner Ecosystem

**In your body, bacteria outnumber
your own cells 10 to 1.**

Who's in control?

A detailed black and white illustration of various microorganisms, including spherical bacteria, elongated bacilli, and complex viral-like structures, scattered across the page. The word "MEDICINE" is printed in a small, sans-serif font above the main title.

MEDICINE

THE ULTIMATE SOCIAL NETWORK

Researchers who study the friendly bacteria that live inside all of us are starting to sort out who is in charge—microbes or people?

By Jennifer Ackerman

Illustrations by Bryan Christie

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BIOLOGISTS ONCE THOUGHT THAT HUMAN BEINGS WERE physiological islands, entirely capable of regulating their own internal workings. Our bodies made all the enzymes needed for breaking down food and using its nutrients to power and repair our tissues and organs. Signals from our own tissues dictated body states such as hunger or satiety. The specialized cells of our immune system taught themselves how to recognize and attack dangerous microbes—pathogens—while at the same time sparing our own tissues.

Over the past 10 years or so, however, researchers have demonstrated that the human body is not such a neatly self-sufficient island after all. It is more like a complex ecosystem—a social network—containing trillions of bacteria and other microorganisms that inhabit our skin, genital areas, mouth and especially intestines. In fact, most of the cells in the human body are not human at all. Bacterial cells in the human body outnumber human cells 10 to one. Moreover, this mixed community of microbial cells and the genes they contain, collectively known as the microbiome, does not threaten us but offers vital help with basic physiological processes—from digestion to growth to self-defense.

So much for human autonomy.

Biologists have made good progress characterizing the most prevalent species of microbes in the body. More recently, they have begun to identify the specific effects of these residents. In so doing, they are gaining a new view of how our bodies function and why certain modern diseases, such as obesity and autoimmune disorders, are on the rise.

OUT OF MANY, ONE

WHEN PEOPLE THINK of microbes in the body, they usually think of pathogens. Indeed, for a long time researchers focused solely on these harmful bugs and ignored the possible importance of more benign ones. The reason, argues biologist Sarkis K. Mazmanian of the California Institute of Technology, is our skewed view of

the world. “Our narcissism held us back; we tended to think we had all the functions required for our health,” he says. “But just because microbes are foreign, just because we acquire them throughout life, doesn’t mean they’re any less a fundamental part of us.”

Indeed, all humans have a microbiome from very early in life, even though they do not start out with one. Each individual acquires his or her own community of commensals (from the Latin for “sharing a table”) from the surrounding environment. Because the womb does not normally contain bacteria, newborns begin life as sterile, singular beings. But as they pass through the birth canal, they pick up some of Mom’s commensal cells, which then begin to multiply. Breast-feeding and handling by proud parents, grandparents, siblings, and friends—not to mention ordinary contact with bedsheets, blankets, and even pets—quickly contribute to an expanding ark of microbes. By late infancy our bodies support one of the most complex microbial ecosystems on the planet.

For the past five years or so scientists have been working to characterize the nature of this ecosystem. The task has been devilishly difficult. The bacterial cells in the intestines, for example, have evolved to grow in the crowded, oxygen-free environment of the gut, so many species do not survive well in the lonely expanse of a petri dish. Researchers have gotten around this problem, however, by studying the genetic instructions, the strands of DNA and RNA, found within a microbe rather than the whole cell itself. Because DNA and RNA can be manipulated in a normal, oxygenated laboratory environment, investigators can take microbial samples from the body, extract the genomic material and analyze the results.

Each species of commensal bacteria has a signature, it turns out—its own unique version of a gene (known as the 16S ribo-

IN BRIEF

Bacterial cells in the body outnumber human cells by a factor of 10 to 1. Yet only recently have researchers begun to elucidate the beneficial roles these microbes play in fostering health.

Some of these bacteria possess genes that encode for beneficial compounds that the body cannot make on its own. Other bacteria seem to train the body not to overreact to outside threats.

Advances in computing and gene sequencing are allowing investigators to create a detailed catalogue of all the bacterial genes that make up this so-called microbiome.

Unfortunately, the inadvertent destruction of beneficial microbes by the use of antibiotics, among other things, may be leading to an increase in autoimmune disorders and obesity.

SOURCE: JENNIFER ACKERMAN

somal RNA gene) that codes for a particular RNA molecule found in the ribosomes, the protein-making machinery of cells. By determining the sequence of this gene, scientists are creating a catalogue of the entire human microbiome. In this way, they can glean which species exist in our bodies and how the precise combination of species may differ from one person to another.

The next step is to analyze other genes found in the microbial community to determine which ones are active in people and what functions they perform. Again, that chore is a tall order because of the great number of species and because their genes get mixed together in the extraction process. Determining whether a specific bacterial gene is active (or expressed) in the body is relatively straightforward; figuring out to which species that particular gene belongs is not. Fortunately, the development of ever more powerful computers and ultrafast gene sequencers in the first decade of the 21st century has turned what would once have been an impossible task of sorting and analysis into merely a very complicated one.

Two separate groups of scientists, one in the U.S. and the other in Europe, have harnessed this new technology to enumerate the bacterial genes within the human body. In early 2010 the European group published its census of microbial genes in the human digestive system—3.3 million genes (from more than 1,000 species)—about 150 times the 20,000 to 25,000 genes in the human genome.

Research into the nature of the human microbiome has yielded many surprises: no two people share the same microbial makeup, for instance—even identical twins. This finding may help unravel a mystery presented by the Human Genome Project, which confirmed that the human DNA of all people the world over is 99.9 percent alike. Our individual fates, health and perhaps even some of our actions may have much more to do with the variation in the genes found in our microbiome than in our own genes. And although the microbiomes of different people vary markedly in the relative number and types of species they contain, most people share a core complement of helpful bacterial genes, which may derive from different species. Even the most beneficial bacteria can cause serious illness, however, if they wind up somewhere they are not supposed to be—for example, in the blood (causing sepsis) or in the web of tissue between the abdominal organs (causing peritonitis).

FRIENDS WITH BENEFITS

THE FIRST INKLING that beneficial bugs might do us good came decades ago during research on digestion and the production of vitamins in the guts of animals. By the 1980s investigators had learned that human tissue needs vitamin B₁₂ for, among other things, cellular energy production, DNA synthesis and the manufacture of fatty acids and had determined that only bacteria synthesize the enzymes needed to make the vitamin from scratch. Similarly, scientists have known for years that

gut bacteria break down certain components of food that would otherwise be indigestible and would pass out of the body unused. Only in the past few years, however, have they learned the juicy details: two commensal species in particular play major roles in both digestion and the regulation of appetite.

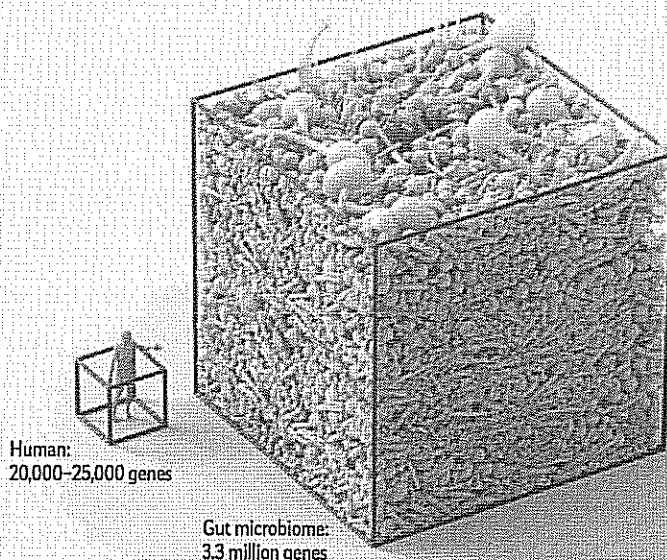
Perhaps the prime example of a helpful bug sounds like it was named after a Greek sorority or fraternity. *Bacteroides thetaiotaomicron* is a champion carbohydrate chomper, capable of breaking down the large, complex carbohydrates found in many plant foods into glucose and other small, simple, easily digestible sugars. The human genome lacks most of the genes required to make the enzymes that degrade these complex carbohydrates. *B. thetaiotaomicron*, on the other hand, has genes that code for more than 260 enzymes capable of digesting plant matter, thus providing humans with a way to efficiently extract nutrients from oranges, apples, potatoes and wheat germ, among other foods.

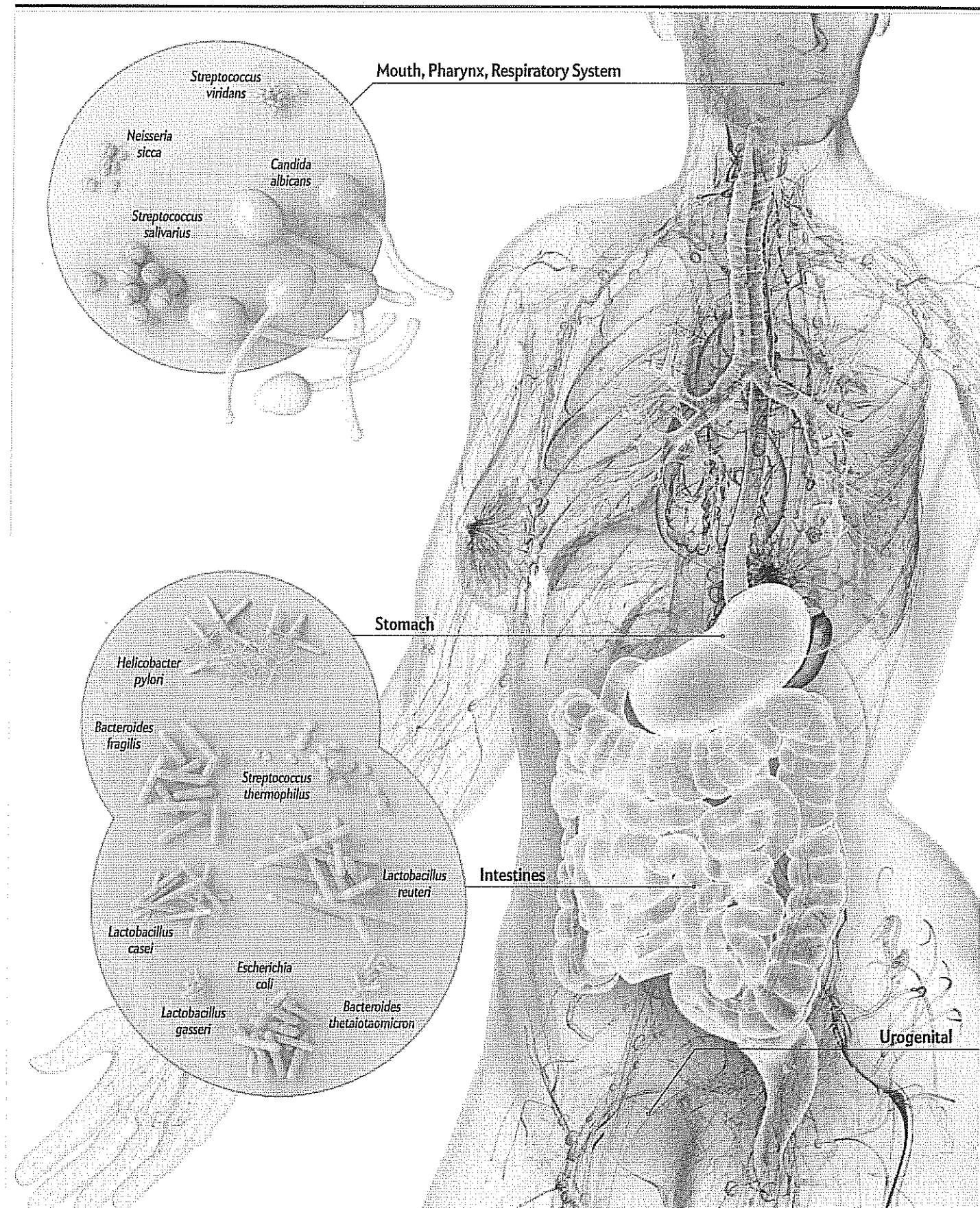
Fascinating details about how *B. thetaiotaomicron* interacts with, and provides sustenance to, its hosts come from studies of mice raised in a completely sterile environment (so they had no microbiome) and then exposed only to this particular strain of microbes. In 2005 researchers at Washington University in St. Louis reported that *B. thetaiotaomicron* survives by consuming complex carbohydrates known as polysaccharides. The bacteria ferment these substances, generating short-chain fatty acids (essentially their feces) that the mice can use as fuel. In this way, bacteria salvage calories from normally indigestible forms of carbohydrate, such as the dietary fiber in oat bran. (Indeed, rodents that are completely devoid of bacteria have to eat 30 per-

MORE THAN HUMAN

Buddy, Can You Spare a Gene?

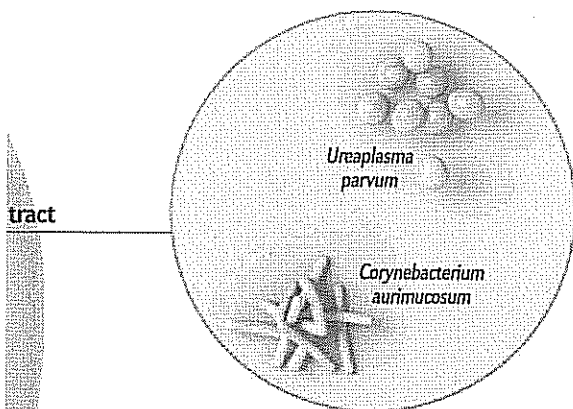
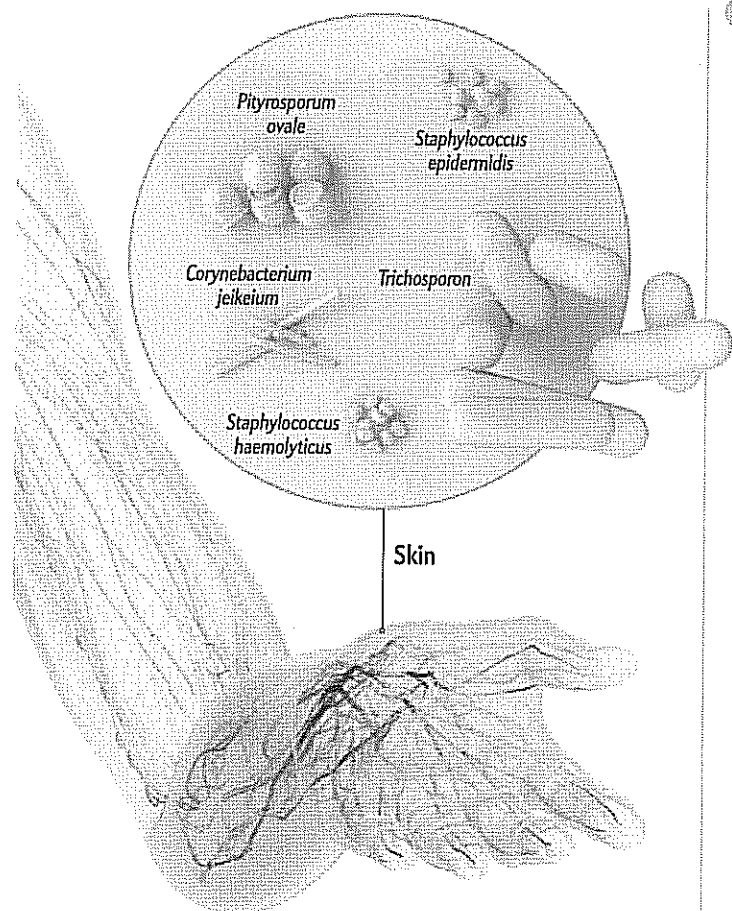
Helping hands: The number of genes distributed among the friendly bacteria that live inside people's bodies and on their skin far outnumbers the number of genes we inherit from our parents. Researchers are figuring out in greater detail which of these microbial genes benefit their human hosts and how.



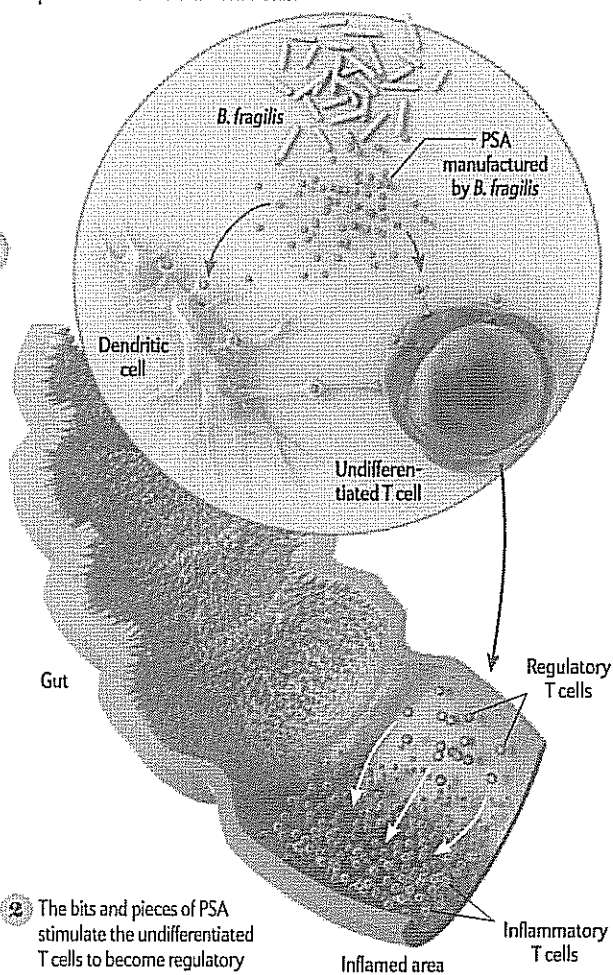


Different Species for Different Reasons

Various types of microbes congregate everywhere in and on the human body. Their presence maintains their host's health in part by making it hard for disease-causing germs to gain access to the body. Several species, such as *Bacteroides fragilis*, also perform specific useful functions, including aiding in the development and regulation of the immune system (below, right).



- 1 Immune cells called dendritic cells pick up a molecule called polysaccharide A (PSA) from the *B. fragilis* cells and present it to undifferentiated T cells.



- 2 The bits and pieces of PSA stimulate the undifferentiated T cells to become regulatory T cells, which in turn produce substances that tamp down the aggressive efforts of inflammatory T cells.

Case Study: How One Bacterial Species Helps

Studies on mice raised in sterile conditions reveal that *B. fragilis* bacteria are crucial to maintaining the health of the intestines. In one experiment, germ-free mice that were given a strain of *B. fragilis* bacteria that produced the complex carbohydrate polysaccharide A did not develop inflammation of the intestine (colitis), whereas mice that were given a strain of *B. fragilis* bacteria that did not make PSA developed chronic inflammation of the gut. Investigators showed that the presence of PSA stimulated the development of regulatory T cells that in turn switched off the inflammatory T cells, thereby restoring health.

SOURCE: "INSIDE THE MICROBIAL AND IMMUNE Labyrinth: CUT ANGIOGENESIS, FRIENDS OR FENESTRA? BY WARREN STROBER, IN NATURE MEDICINE, VOL. 16, 2010 (B. fragilis case study)