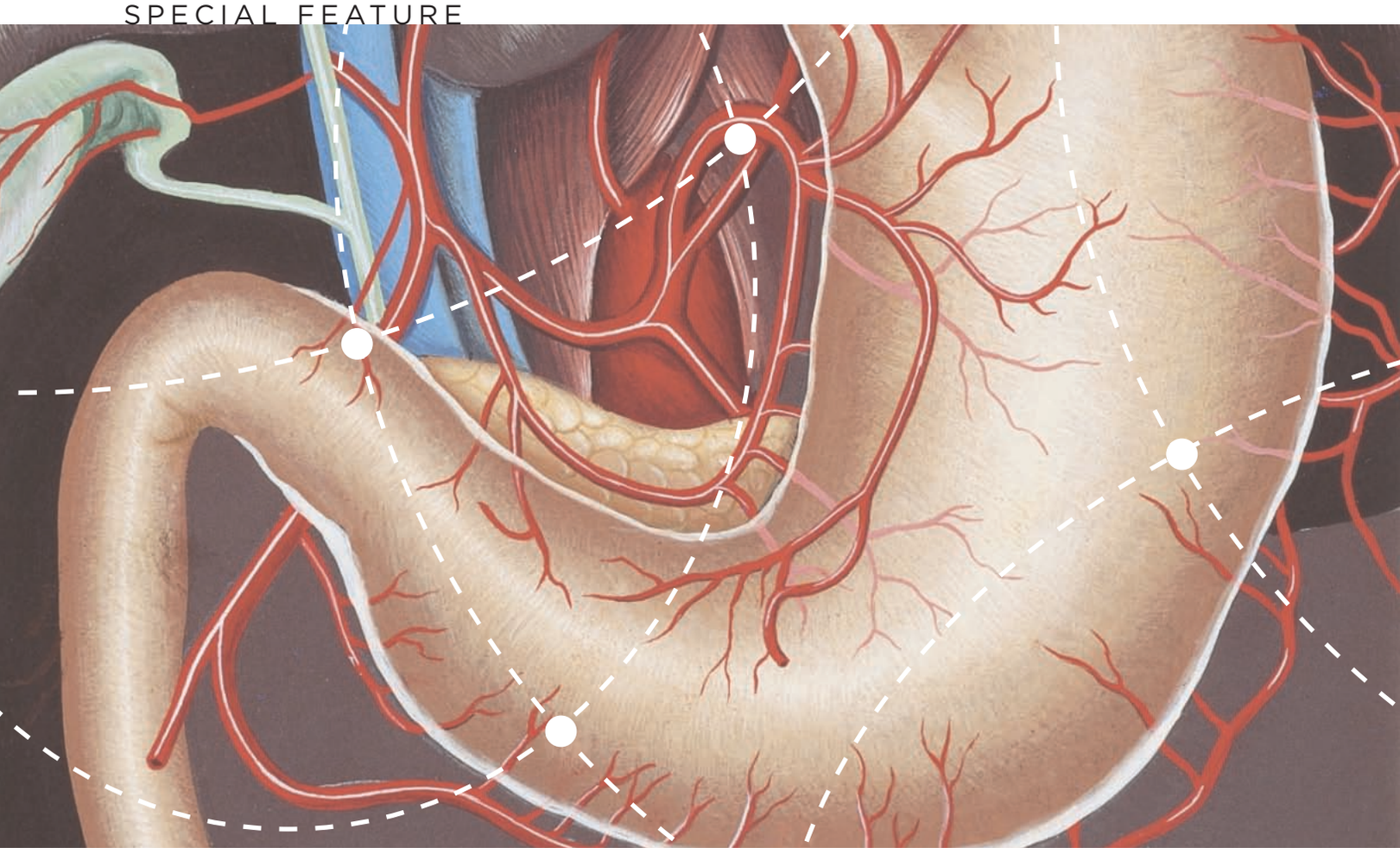

Mapping Bacterial Worlds, from Sea to Stomach

The study of an ecosystem within our bodies may redefine how physicians approach infectious diseases

By Rob Mitchum

Humans are a minority in their own bodies. For every human cell, there are at least 10 times as many bacterial cells living inside and outside of the body. Millions of individual cells from thousands of species inhabit the digestive system, body cavities and the surface of the skin. Yet, until recently, we have only understood a mere fraction of these ecosystems within our bodies, how they sustain us in health and how they harm us in disease.

The collective genomes of these microbial worlds are known as the human microbiome. Scientists are just beginning to discover the role that a faulty microbiome plays in acute and chronic disease, creating a new kind of science that applies the methods of ecology to the biomedical domain.

"Everything we eat, the things we are exposed to, our lifestyles — all of that changes our microbiome," said Eugene B. Chang, MD, the Martin Boyer Professor of Medicine. "Its potential in terms of drug and reagent discovery is the equivalent of an Amazon rain forest. There exists enormous untapped biological opportunity for discovery."

While microbiologists were classically limited to studying only bacterial species they could get to grow in a laboratory dish, the new method of metagenomics has allowed ecologists to discover thousands of new species in a single scoop of soil or teaspoon of seawater. Now that technology is being applied by University of Chicago Medical Center researchers, in collaboration with Argonne National Laboratory, to the ecosystem of the human gut.

New Insights into Microbial Diseases

Before a baby is born, its gut is sterile, entirely free of bacteria. During delivery, the baby's first bacterial colonies are seeded by bacteria from the mother, and early exposure to the environment and diet fill in the rest of the ecosystem. But in some babies born prematurely and underweight, the construction of the microbial community is defective, leading to a potentially fatal bowel disease called neonatal necrotizing enterocolitis.

ABOVE An artist's rendering of a human stomach. *DEA Picture Library*

New genetic techniques have given a group led by Erika Claud, MD, associate professor of pediatrics, deeper insight into how a premature microbiome can cause the disease. A 2009 study used sequencing techniques on fecal samples from premature infants with and without the disease, and it identified that afflicted infants tended to have fewer bacterial species in their gut.

"It wasn't one bacterium causing this disease," Claud said. "It seemed to be the overall community structure that was favorable or unfavorable in these patients."

Claud's study also reinforced the remarkable individuality of the microbiome. Even in premature infants only weeks old, the bacterial population in the gut of each infant was already distinct and unique — even in genetically identical twins. The fact that microbiomes are as different as fingerprints may present a short-term challenge to researchers studying the systems, but it could have long-term benefits for personalized medicine.

"If we knew exactly what bacteria each individual has, we could be more selective in terms of the treatments that we give that person," Claud said. "I think it would be very beneficial."

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Steps toward Disease Prevention

In adults, the microbiome has accumulated complexity thanks to diet, lifestyle, antibiotic use and other lifetime influences. Most of the time the microbial colonials live in happy equilibrium, but when the structure breaks down in a process called dysbiosis, inflammatory bowel diseases are a potential result.

Chang's research group is looking for warning signs of impending dysbiosis in a group of ulcerative colitis patients at risk for recurrent disease. These patients have had their colons surgically removed and a section of the small intestine reconstructed to serve as a pseudorectum called the ileal pouch. Many of these patients, within one year of surgery, develop a new inflammatory condition of the ileal pouch called "pouchitis."

Interestingly, patients with other diseases who undergo the same procedure rarely develop this complication, indicating that the condition is inherent to ulcerative colitis. Moreover, most patients can be treated with antibiotics, indicating this condition is likely caused by inhabitants of the gut. In collaboration with Argonne and other institutions, Chang is following these patients before recurrence to gain rare insight into the microbiome before the disease manifests itself.

"We have one of the very, very few studies that actually prospectively follows the patients," Chang said. "If we identify a dysbiotic profile, that becomes a diagnostic tool for us to predict who's going to get ulcerative colitis, and we can hopefully do something to prevent that dysbiosis, so we can prevent the onset of disease."

The latter goal, however, may be further down the road. Though some "probiotic" bacteria have been tested for treatment of bowel diseases, the complex nature of the microbiome suggests that merely adding or killing off one species is too simplistic.

"We'd love to think we'll be able to pull all the levers to make a microbial community do what we want it to do," said Dionysios Antonopoulos, PhD, assistant professor of medicine at the Medical Center and assistant biologist at Argonne. "But at this stage, it's pretty much like we're riding a tricycle, and the controls of that system are like flying a 747."

A Change in Strategy

The tranquility of the microbiome may also be destroyed when its human home becomes less hospitable. After intense surgery, a minority of patients contract serious infections. Traditionally, these infections were thought to be the result of contamination during the surgical procedure. But over a century of improved sterile techniques has yet to completely eradicate postsurgical infections, causing some researchers to look at the bacteria within the patient.

John Alverdy, MD, professor of surgery, has been studying one such microbial resident, called *Pseudomonas aeruginosa*. Normally docile, *P. aeruginosa* can be transformed after surgery by the patient's overstressed immune system into what Alverdy calls a "trigger-happy killer." He and his collaborators have identified the immune and metabolic signals that trigger the alarm system of *P. aeruginosa*, research that may define a new type of protection against infection. Rather than indiscriminately slaughtering gut bacteria through prolonged use of antibiotics, maintaining a healthy system that interrupts these alarm signals might convince bacteria that their home remains stable.

"It's sustaining the ecosystem therapy," Alverdy said. "It's a new way of thinking about infection, because we're already doing everything we can — washing our hands, sterilizing the site, giving our patients antibiotics — and some of the infections seem to be getting worse. There's got to be a strategy change, and I think we're at the forefront of understanding that."

The work merges with new ecological data about the bacterial ecosystems in the world around us. The Earth Microbiome Project, an international collaboration co-directed by Jack Gilbert, PhD, assistant professor of ecology and evolution at the University of Chicago and environmental microbiologist at Argonne, has the ambitious goal of systematically characterizing all microbial life on Earth. Researchers with the project are repeatedly sampling soil, seawater, animals and many other sources to find out what bacteria live there and how populations change over time.

By measuring water from the English Channel over six years, Gilbert discovered that the roster of players in a bacterial ecosystem does not change, but the environment selects which species will be abundant at different times of the year. This "everything is everywhere" principle might also have implications for medicine, Gilbert said, where the fight against infectious diseases has traditionally focused on external invaders.

"We don't have to try and find out where that pathogen came from," Gilbert said. "That pathogen might have already been there, and the environment would have selected for it to suddenly bloom and therefore attack its host. If that's true, then we can change the way we do medicine." ■