





# Interior Life

BY DAN GORDON

MICROBIOME PHOTOGRAPHY BY DR. MARTIN OEGGERLI • PORTRAITS BY ANN JOHANSSON

Exploring the brave new world of microbiota — the microorganisms that flourish within our bodies — may one day lead to the development of better ways to manage infections, create new antibiotics and address such pressing health issues as obesity, heart disease and cancer.

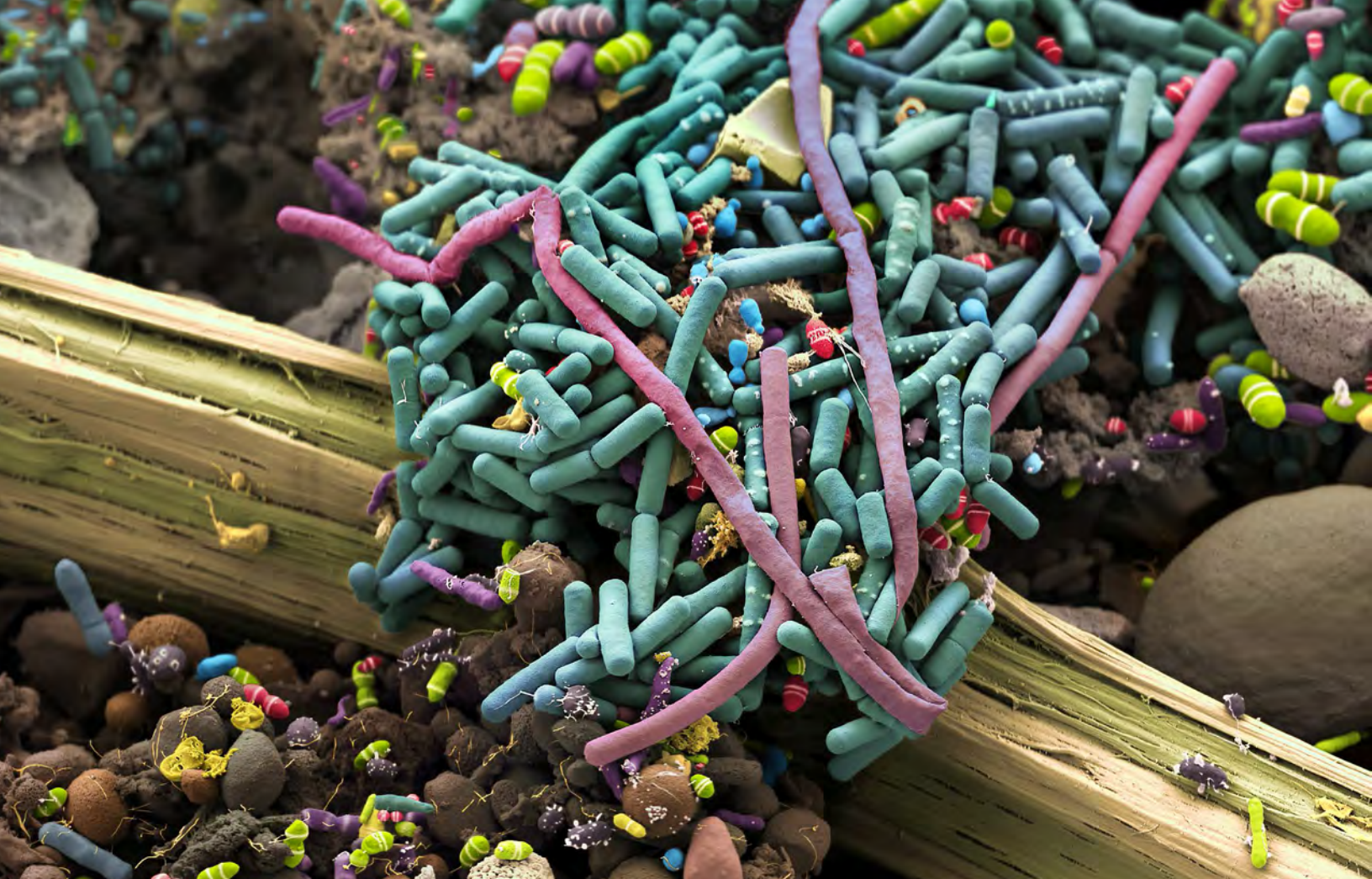
**T**his may strike many readers as distasteful, but human stool now is used as a medical therapy against at least one dangerous infection. It is happening at UCLA and at a small number of other major medical centers, where processed stool from healthy donors is being introduced into the gastrointestinal tracts of patients with *Clostridium difficile*, or *C. diff*. The infection is most commonly acquired in the hospital, causing diarrhea, intestinal pain and cramps, fever and potentially worse — 14,000 people die from *C. diff* in the U.S. each year.

While the cure may sound worse than the disease, the therapy, known as fecal microbial transplant (FMT), has been shown to be highly effective; by infusing the patient via colonoscopy with normal gut bacteria, the spectrum of intestinal microbes is dramatically altered, essentially overwhelming and suppressing the pathogen. In 2013, the *New England Journal of Medicine* published results from a randomized controlled trial comparing FMT with vancomycin, the standard treatment for patients with recurrent *C. diff*. The study was halted after an interim analysis found FMT to be substantially more beneficial.

Only now are scientists beginning to appreciate the extent to which the 100-trillion (give or take) bacteria and other microbes that reside within our bodies keep us healthy, contribute to disease or, as in the case of FMT, can potentially be manipulated to cure what ails us. At UCLA alone, recent findings in this nascent field of study suggest a role for the microbiota beyond what anyone might have imagined a decade ago. To name just a few discoveries: a product derived from gut bacteria found to be a risk factor for heart disease on par with high cholesterol, hypertension and tobacco use; the first evidence in humans that beneficial bacteria ingested in food — so-called probiotics, in this case through regular consumption of yogurt — can positively affect brain function; and perhaps most tantalizing of all, studies by Elaine Hsiao, PhD, at Caltech, showing that manipulating the microbiota can ameliorate behavioral abnormalities in a mouse model for autism.

Amid an explosion of research into how this universe of invisible cohabitants affects our lives, it has become apparent that microbiota — the collection of microorganisms that populate the intestine, skin, lungs, urinary tract and many other body sites — exerts considerable influence on our health. Some scientists have been led to muse that the human body is merely a vehicle for microbes to pursue their own interests. Heart disease and cancer, diabetes and metabolic disease, obesity and nutrition issues, inflammatory bowel disease, autoimmune disorders, allergies and neurologic disorders ranging from autism to Alzheimer's — all may be associated in some way with microbes gone awry. A 2013 article in *Science* dubbed microbiomics (the study of the collection of genes represented by the microbiota) “The Germ Theory of Everything.”

“For many years, the thinking was that these organisms were living within us, but they probably didn’t do much,”



**Top:** It is estimated the microbiota that resides within our bodies comprises some 100-trillion bacteria and other microbes. This image shows *Streptococci sp.*, *Staphylococci sp.*, *Enterococci sp.*, *Enterobacteria sp.*, *Mycobacteria sp.*, *Spirochetes sp.*, *Corynebacteria sp.*, *Clostridia sp.* and *Lactobacilli sp.*

**Right:** Dr. Jeffery F. Miller: "We're realizing that from the moment of conception, we develop in a soup of microbial products. We are affected by microbes in profound ways, and we're at the very beginning of being able to understand what that means for health."

**Previous Page:** *Helicobacter pylori*.

says Eric Esrailian, MD (FEL '06), MPH, co-chief of the Division of Digestive Diseases at the David Geffen School of Medicine at UCLA. "Now there's an awareness of their significant role in everything from infection to inflammatory diseases and potentially even malignancy. This is a new frontier that is fundamentally altering the direction of research in our field."

Observes Jeffery F. Miller, PhD, former chair of the Department of Microbiology, Immunology and Molecular Genetics and current director of UCLA's California NanoSystems Institute, "We're realizing that from the moment of conception, we develop in a soup of microbial products. We are affected by microbes in profound ways, and we're at the very beginning of being able to understand what that means for health."

UCLA is substantially ramping up efforts to better grasp these effects — including actively recruiting leading researchers in the field and



taking the first steps toward establishing a center for the study of microbiota, with bench scientists working alongside clinicians to not only learn how microbes affect human health, but also to use that information to explore new therapeutic strategies. “It’s an exciting time at UCLA and other medical centers,” says Dr. Miller, one of the leaders of the effort. “These disease areas that once seemed so separate now appear to be connected by the profound realization that we are a superorganism — an organism of organisms.”

**THEY ARE THE ORIGINAL INHABITANTS OF THE PLANET**, evolving over the course of some 3.8-billion years and predating humans by several eons. Throughout human history, they have lived in symbiosis with us, both sides getting what they need through an elaborate exchange of signaling molecules. But it’s only within the last decade, thanks to the power of modern research and computational tools, that scientists have begun to acquaint themselves with microbiota in a systematic fashion — and to understand how it can tip the balance between health and disease.

In the past, the study of microbiota was dependent on the ability to grow the organisms in the laboratory, and for the vast majority of bacteria, scientists lacked the know-how to cultivate them. Thus, these culture techniques opened a window just a tiny crack onto a small minority of the microbe community — typically infectious organisms. It’s also difficult, if not impossible, to replicate in the laboratory the complex environment of, for example, the human gut. As a result, “We had a skewed view of what was there, because we’d see only a subset — and with artificial criteria,” Dr. Miller says.

That changed with the advent of modern gene-sequencing technology. “This was a delightful and unexpected outcome of the Human Genome Project,” says Jonathan Braun, MD, PhD, chair of the Department of Pathology and Laboratory Medicine. “The Human Genome Project drove a revolution in DNA sequencing and the computational techniques to understand that genome data.

Those tools were then used by researchers to analyze the composition of organisms and metabolic pathways in ways that were never before possible.”

A seminal study published by researchers at Washington University in St. Louis in 2006 showed fundamental differences in the gut microbiomes of lean and obese mice — and found that transplanting the microbial communities of obese and lean mice into germ-free adult mice resulted in the recipients taking on the weight characteristics of their donors. The study triggered a surge of new interest, as the relationship between the microbiome and fundamental aspects of health, such as metabolism, became more apparent.

In 2007, the Human Microbiome Project was launched by the National Institutes of Health to characterize the microbial communities of various body sites, determine the extent to which we share a common microbiome and explore how changes in the human microbiome are related to diseases. The study of 242 healthy individuals, tracked over a two-year period, was eye-opening even to those who had long immersed themselves in the study of human bacteria. Among the conclusions: Our intestinal tract alone hosts an estimated 100-trillion microbes — outnumbering human cells 10-to-1. For every human gene, there are at least 100 microbial genes. But beyond the numbers, the explosion of information resulting from the use of modern techniques to study the microbiome revealed a remarkable level of diversity — at least 2,000 types of bacteria in the gut, along with tens of thousands of types of viruses — and substantial differences in the microbiota from one healthy individual to the next.

“We were aware that there were organisms that colonized different parts of the body, but until a few years ago, we didn’t realize how enormous this population was,” Dr. Braun says. “Now we know that we can think of ourselves as a composite organism with not only human cells, but also these other categories of cells that live with us throughout our lives and shape our biology.”

“This is like a hidden organ, larger than any other in the body in terms of cell numbers,” adds Emeran Mayer, MD, professor of medicine and physiology. “Now we’re seeing the ability to transplant entire phenotypes from one mouse to another, suggesting



**Top:** Dr. A. “Jake” Lusis: “The idea that one of the major risk factors for heart disease is produced by gut bacteria is very important. Now we should be able to learn why levels of this molecule vary in the population, as well as how to control it.”

**Bottom:** Dr. Zhaoping Li: “We now know it’s not as simple as how many calories come in minus what we burn. The cluster of bacteria is different in obese vs. lean people.”



**Top:** Dr. Daniel Uslan: “The antibiotics people take to treat an infection kill healthy bacteria in addition to the unhealthy bacteria, creating space for *C. difficile* to come in.”

**Bottom:** Dr. Jeffrey H. Miller: “The field is now at the stage where it’s very easy to collect the data, but a lot of it is descriptive. The challenge now is to do studies that, beyond simply characterizing the microbiome, are fruitful in advancing health.”

**Opposite Page:** Dr. Jonathan Braun (left): “We know that we can think of ourselves as a composite organism with not only human cells, but also these other categories of cells that live with us throughout our lives and shape our biology.”

Dr. Eric Esraillian (right): “For many years, the thinking was that these organisms were living within us, but they probably didn’t do much. Now there’s an awareness of their significant role in everything from infection to inflammatory diseases and potentially even malignancy.”

**Opposite Page:** *Escherichia coli*.

that something very profound is going on with what these microbes produce that can affect the host in complex ways — even changing entire behavior patterns. We’re still just scratching at the surface, but the field is moving extremely fast.”

**FOR THE MOST PART, EFFORTS TO BETTER UNDERSTAND THE MICROBIOTA** have thus far been focused in the laboratory, with few clinical applications. The most prominent exception is the use of FMT. *C. diff*, which affects as many as half-a-million people each year, is more likely to take hold after broad-spectrum antibiotics have disrupted protective gut microbes. “The antibiotics people take to treat an infection kill healthy bacteria in addition to the unhealthy bacteria, creating space for *C. difficile* to come in,” says Daniel Uslan, MD, an infectious-disease specialist who performs FMT at UCLA as part of a partnership between the Division of Infectious Diseases and Division of Digestive Diseases. The problem, Dr. Uslan notes, is that many of the antibiotic drugs used to treat *C. diff* continue to kill healthy bacteria; thus, studies have shown that at least 20 percent of patients experience one or more relapses after treatment — in some cases leading to severe complications.

Rather than perpetuating the vicious circle by continuing to administer antibiotics in patients who aren’t cured by the conventional treatment, FMT takes stool from a healthy, pre-screened donor, prepares it in the laboratory and then transplants it into the afflicted patient. “Instead of giving more antibiotics, this is repopulating the gut with healthy microorganisms,” Dr. Uslan explains. Although the method may sound crude, the science is strong. “Patients who have been suffering with this infection for weeks or months will typically experience relief within 24 hours and are back to normal within two days,” Dr. Uslan says. “It’s pretty remarkable.”

Although FMT has been proven to work only for *C. diff* patients, Dr. Esraillian notes that researchers are exploring its use for other indications, including irritable bowel syndrome and inflammatory bowel disease. Dr. Uslan also expects that as it becomes clearer which bacteria are needed to restore healthy gut function, the procedure will evolve to the point where laboratory-grown bacteria, rather than stool, can be used for the treatment.

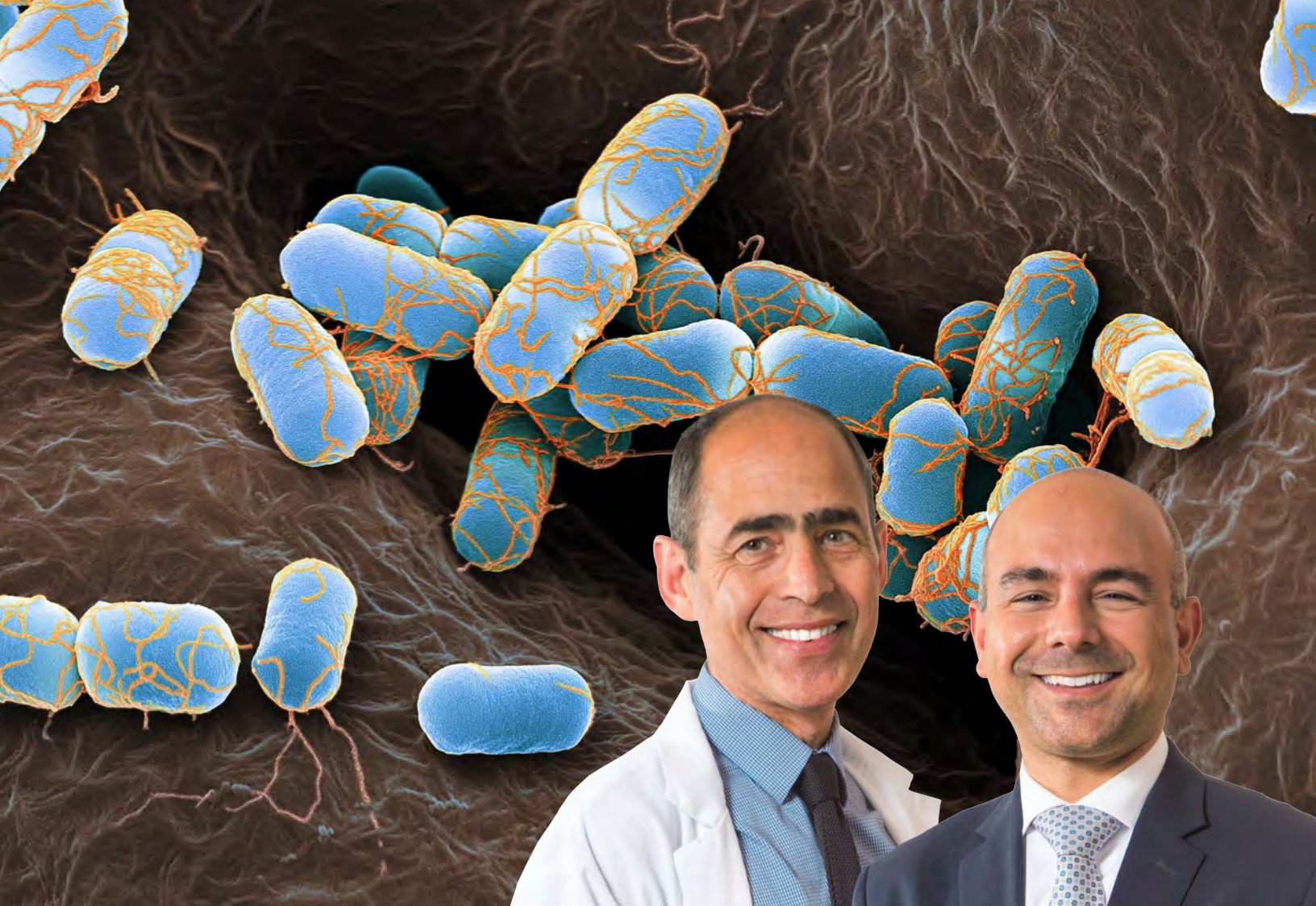
As researchers gain a better grasp of the microbiome’s impact, other clinical applications are likely to follow. Dr. Braun notes that for inflammatory diseases of the skin, lung and intestine, it appears likely that microorganisms interact with genetics and environmental triggers to determine susceptibility. His group has made key discoveries showing the link between genes and the microbiome when it comes to inflammatory bowel disease. “Your genetics determines how well you handle the undesirable products of your microbiome,” Dr. Braun says. “People with the disease typically have a distinct set of bacteria that is making these annoying products, and if their genetics interferes with the ability of their intestinal epithelial cells or immune system to cope with the annoying bacteria, it leads to a destructive inflammatory response.”

With more than 200 molecules identified as potential culprits, Dr. Braun’s group is focused on studies to determine which are the most important in driving inflammatory bowel disease and targeting those products for treatment.

Meanwhile, a growing body of evidence suggests a pivotal role for microbiota in obesity — including the possibility that an unhealthy diet can conspire with one’s genetic predisposition and lifestyle to create an imbalance of the microbiota in the gut, setting off a cascade that leads to inflammation, weight gain, insulin resistance and other conditions characteristic of the metabolic syndrome that increase the risk of diabetes, heart disease, stroke and certain cancers. “The transplant experiments in animals suggest that the microbiota may have a causative role in the development of obesity,” Dr. Mayer says. “The question is when we see differences in the microbiota of obese and lean humans, is that secondary to the dietary differences or is it playing a causative role? It’s much easier to test that in animals than in humans, but based on the animal studies, you almost have to assume there’s a causative role.”

The makeup of the microbiota in the intestine, researchers believe, goes a long way in determining how much energy is extracted and the profile of the nutrients as a result of the food we consume — suggesting an important connection between our gut bacteria and malnutrition as well as obesity. “We now know it’s not as simple as how many





calories come in minus what we burn,” says Zhaoping Li, MD (FEL ’94), PhD, director of the UCLA Center for Human Nutrition. “The cluster of bacteria is different in obese vs. lean people.” Studies by her group and others are beginning to identify specific dietary strategies with the potential to alter the microbiota in ways that improve metabolism for obese individuals.

A UCLA group headed by A. “Jake” Lusis, PhD, professor of microbiology, immunology and molecular genetics and vice chair of human genetics, has been exploring how host genetics contributes to gut-microbiota composition. In collaboration with researchers at the Cleveland Clinic, he recently identified a molecular substance that appears to be almost as strongly associated with heart disease as are cholesterol levels. Dr. Lusis and colleagues found that the molecule, trimethylamine N-oxide, is derived entirely through the interaction of gut microbiota and dietary





Dr. Emeran Mayer (left, with gut-brain research collaborator Dr. Kirsten Tillisch): "It's not yet clear to what degree [our research] will ultimately translate into novel treatments, but I think it will definitely contribute to a better understanding of the importance of the gut microbiota in the developing brain, as well as new insights into autism, Alzheimer's disease and Parkinson's disease, among others."

*Escherichia coli*

products that include choline and carnitine — major components of egg yolk and red meat, respectively. By transplanting the microbiota of a mouse with high levels of the substance to one with low levels, the researchers showed that the composition of the gut bacteria is critical in determining the response to these dietary factors. "The idea that one of the major risk factors for heart disease is produced by gut bacteria is very important," Dr. Lusis says. "Now we should be able to learn why levels of this molecule vary in the population, as well as how to control it."

Then there is the intriguing evidence that changes in the microbiota could have an impact on the brain. In a study published in 2013, Dr. Hsiao and her Caltech colleagues and mentors, the late Paul H. Patterson, PhD, and Sarkis Mazmanian,



PhD '02, produced autism-like behavior in the offspring of mice that they treated with a viral mimic during pregnancy. These offspring, which were found to have altered gut bacteria, showed reduced autism-like behaviors when treated with a health-promoting bacterium. Inspired by this work, Dr. Hsiao, who is joining the faculty of UCLA's Department of Integrative Biology and Physiology in the fall, has continued to examine molecular mechanisms underlying how the gut microbiota interacts with the nervous system. In a study published this year, Dr. Hsiao's laboratory discovered that particular bacteria from human-gut microbiota stimulate host biosynthesis of the hormone and neurotransmitter serotonin. At UCLA, her lab will continue to investigate microbiota-nervous system interactions and their effects on health and disease.

Other research, also in mice, has found that if the mother is injected with a stress hormone during pregnancy, it changes the composition of her vaginal microbiota to the extent that it affects the microbiome of the infant as it goes through the birth canal, ultimately influencing brain development. "It almost sounds like science fiction," Dr. Mayer says. "Ten years ago, nobody would have believed these kinds of studies, and now they're coming out of some of the best investigative groups in the country."

Dr. Mayer, a leader in research showing the relationship between the gut and the brain, contributed in a major way to the intrigue through the 2013 publication of one of the first studies showing that changing the bacteria environment of the gut can affect human brain function. His study with Kirsten Tillisch, MD '97 (RES '99, FEL '04), associate professor in the Division of Digestive Diseases, found that healthy women who regularly consumed beneficial bacteria, known as probiotics, through yogurt, showed positive altered brain function, both while in a resting state and in response to an emotion-recognition task. Since that key discovery, Dr. Mayer's group has conducted follow-up studies demonstrating a relationship between changes in the gut microbiota and either brain function or structure.

"It's not yet clear to what degree this will ultimately translate into novel treatments," Dr. Mayer says, "but I think it will definitely contribute to a better

understanding of the importance of the gut microbiota in the developing brain, as well as new insights into autism, Alzheimer's disease "and Parkinson's disease, among others."

#### IT STILL IS EARLY IN THE SCIENCE, AND THE ENORMOUS POTENTIAL

in mining the microbiome is for the most part just that — potential. One of the major challenges for researchers in the field is how to ascribe causality given that the microbiota is so diverse and dynamic. Across a group of healthy people, for example, there can be substantial differences in the collection of microorganisms in the gut, both in terms of the mixture and the relative numbers. And even when altered bacteria can be captured and associated with a disease, the question is if the changes caused the disease or resulted from it. "The field is now at the stage where it's very easy to collect the data, but a lot is descriptive," says Jeffrey H. Miller, professor of microbiology, immunology & molecular genetics, who organizes a biennial international meeting on microbial genomics, much of which is devoted to advances in microbiome studies. "The challenge now is to do studies that, beyond simply characterizing the microbiome, are fruitful in advancing health."

But he and others are optimistic that as methods for studying microbiota continue to advance, revolutionary discoveries are inevitable. "There was a lot of excitement that the Human Genome Project was going to change medicine fundamentally, and it turned out to be just the beginning of a long process," Dr. Mayer concludes. "But learning about these microbes goes way beyond the human genome. This has the potential to completely transform our understanding of human disease."

**Dan Gordon** is a regular contributor to U Magazine.

**Martin Oeggerli, PhD**, is an award-winning Swiss science photographer, whose images have been published in *Nature*, *Cell* and *National Geographic*. Dr. Oeggerli's photographs illustrating this article were created using a scanning electron microscope at magnifications ranging from 1,000 to 50,000 times. His work can be found online at [micronaut.ch](http://micronaut.ch).



Gerald and Gail Oppenheimer

Photo: Alex J. Berliner/BEImages

## WHY WE GIVE

Gail and Gerald Oppenheimer are dedicated UCLA supporters. Through the Gerald Oppenheimer Family Foundation, they have made long-term commitments to the university — in particular to UCLA's Division of Digestive Diseases. Gerald is a member of the David Geffen School of Medicine at UCLA Board of Visitors and sits on several other boards. The Oppenheims endowed the Gail and Gerald Oppenheimer Family Center for the Neurobiology of Stress.

"Gail and I could not be more proud to support the UCLA investigators breaking new ground in science and developing holistic treatments at the leading edge of human microbiome research. It is incredibly exciting."

— Gerald Oppenheimer