From England to Germany via France and the US: Microbiologist Ruth Ley has not only worked on a diverse array of bacteria over the course of her career, she has also encountered a cultural difference or two between various countries.

Exploring the **Microbial Cosmos**

The human body is home to countless microbes. The intestinal tract, in particular, is colonized by innumerable bacteria. As a young environmental microbiologist, **Ruth Ley** never imagined that she would one day find herself interested in the human gut and the microbiota that reside in it. Today she conducts research at the **Max Planck Institute for Developmental Biology** in Tübingen, investigating the role the countless intestinal bacteria play in our health.

TEXT **CORNELIA STOLZE**

The different stages of her career read like a travel agency's top exclusive nature and adventure destinations: A semester on Mo'orea, a small tropical island in the South Pacific near Tahiti; several weeks on Guadeloupe in the Caribbean; three years out and about in Hawaii's national parks. Next, a longer stay in Boulder, Colorado with regular high-alpine skiing and trekking in the Rocky Mountains. Then on to an excursion to Mexico's salt flats thanks to a NASA Fellowship and – as the icing on the cake – a several-week Antarctic expedition.

Ruth Ley, who has been a Director at the Max Planck Institute for Developmental Biology since mid-2016, has seen a good bit of the world. Her passion for travel, however, has nothing to do with a jet-set lifestyle or a fondness for extreme sports. "To be honest, I should have been the last person to go, for instance, on these tours of the Rocky Mountains. I'm an awful skier," says Ley, and laughs. It was her scientific interest in ecology that led her to remote corners of the globe.

She has studied the biology of the reef at Mo'orea, where the University of California, Berkeley maintains a research station, caught lizards for a project on Guadeloupe, investigated Hawaii's ecosystem ecology and analyzed the microbial diversity of Mexico's salt flats. "At that time I would have gone anywhere for an interesting project – what I cared about most was working with people I could learn from," says Ley. Little things like heat or cold have never put her off doing her research. English by birth, she learned to adapt to new challenges at an early age and not to be easily deterred by obstacles.

She became a backcountry skier, for instance, when her job as a biologist required such skills. While working on her PhD at the University of Colorado, she often had to don leather mountain boots and Telemark skis and trudge across snowy, windswept slopes at subzero temperatures to reach altitudes of up to 3,700 meters before heading off back home across country. "And all that effort just to collect samples of sand and gravel up there for our research," adds Ley with a grin.

An unusual project indeed. Especially for a biologist whose focus, after studying at the University of California, Berkeley, had turned to the interactions of living organisms with their environment and to the investigation of microbes and their complex communities. According to many scientists at the time, the ground in which Ley took measurements and samples in summer and winter alike was lifeless at extreme altitudes like those above the tree line in the Rocky Mountains. It was widely believed that neither bacteria nor oth-

Bacteria have colonized nearly every habitat on Earth. Ruth Ley visited some of them on her research expeditions.

Above The scientist in one of Antarctica's Dry Valleys.

Right A piece of a bacterial mat from Mexico.

er microbes could survive the inhospitable conditions of frosty winters in sand or gravel under as much as 10 meters of snow.

Ley's research soon showed that this was incorrect. She discovered that such regions did indeed present signs of life. Measurements showed that, somewhere between the ground and the snow, ammonia was being oxidized to form nitrate. Her previous scientific investigations of Hawaiian soils had taught her that such a thing was possible only if certain microbes were present. That's why Ley went to the trouble of setting up her measuring equipment between the sand and snow high up in the mountains. Back in the laboratory, she searched her soil samples for traces of bacteria and other kinds of life.

Success wasn't long in coming. Thanks to her treks through snow and ice, Ley was able to prove that high-alpine soils aren't lifeless at all; rather, they are the permanent habitat of numerous species of bacteria. For her doctoral thesis, she identified microbes

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» The decision to conduct research at a medical faculty was one of the best I ever made in my career.

that, protected from cold by the thick snow cover, are also active in winter – thus contradicting some of the theories held by geologists.

RAISED WITH CULTURAL DIFFERENCES

Ley's courage in challenging old certainties and exploring new territory isn't surprising. At the age of six. she moved with her parents and two sisters from Surrey in the UK to Paris. Her father was an engineer and had been offered an attractive post there. That left the daughters little choice but to rapidly adapt to the new environment and learn the unfamiliar language as quickly as possible.

Seven years later came the next change. Ley, now 13 years old, had grown to feel very much at home in her new country, and spoke only French with her friends and sisters. Once again, the move was due to her father's job. This time it was to another continent – from Europe to Palo Alto in California's Silicon Valley. Again she discovered that both school and everyday life followed completely different rules than before.

"It was difficult adjusting," Ley recalls. "France and the US are culturally very different." Once more, she and her sisters had to learn new daily "codes" of behavior. Things that were normal and common in one country, Ley discovered, were considered snobby and elitist in another – and vice versa. Ley's British accent, which to the ears of her American schoolmates initially made her sound pretentious, was the first thing that made her stand out (she had continued to speak English with her parents through the years). She was also confronted with differing status symbols and eating habits. A small example? Ruth Ley thinks for a moment. "Baguette and Camembert would be one. In Paris that's a simple lunch for normal working people. In California it has the aura – who knows why – of a high-society lunch."

She made similar observations at school. In France you addressed your teachers quite naturally using the polite *vous* form, or as *monsieur* or *madame*. In the US, students and teachers, so it appeared at first glance, were suddenly on the same level. Everyone used the egalitarian English "you," and teachers were simply "Bob" or "Jane." But Ley quickly realized that appearances could be deceptive. Despite the seemingly more relaxed rules, American kids had, to her amazement, much more respect for authority in school. "In Paris, kids made off with anything that wasn't nailed down. I never experienced that in California."

Without doubt, such radical and opposing cultural habits take some getting used to. But experiencing early on in life that it's worth being open to new ideas and examining things carefully stands you in good stead for a life pioneering a completely new scientific discipline. Ruth Ley is now in the vanguard of a field of research that has been expanding at a breathtaking pace over the last few years. Her aim is to decode the microbiome: the collection of microbes that, numbering in the millions, colonize the human body as permanent inhabitants of the skin and digestive tract. One thing we can already say for sure is that microbiome research is shedding new light on unexpected relationships that control our bodies.

UNKNOWN LODGERS

Together with other researchers, Ley was able to show for the first time that the human microbiome is much more than just a collection of stowaways that help break down food into usable components. In fact, the myriad microorganisms in the intestines play a crucial role in our health and contribute, for instance, to obesity, diabetes and chronic autoimmune disorders. Medications, in turn, can have deleterious effects on the microbiome.

The individual intestinal microbiota each of us possesses depends on where we have been in life, as we don't pick up microbes until we are born. Before then, our intestines are thought to be sterile. The first bacterial species to populate the intestines come from a newborn's immediate environment and are composed of maternal vaginal, gut and skin bacteria. Little by little, other species of bacteria from the environment are added. The microbiome's community composition at any given time depends primarily on our diet, but also on many other factors. This means the microbiome of each individual, each family and each human population can have a distinct composition.

In Tübingen, Ruth Ley aims to investigate how genes, the immune system and environmental factors affect the human microbiome. The intestinal bacterium *Escherichia coli* (right) is an infrequent member of this bacterial community. Most strains are harmless, but some can also trigger infectious diseases.

Medical care also plays an important role in our intestinal microbiota. After only one week of antibiotics, for example, the composition and activity of the microorganisms alters dramatically. Dozens of species may disappear and others take their place. Measurements show that many of the approximately 2,000 chemical metabolic products commonly found in feces – a sort of fingerprint for bacterial activity – change temporarily in concentration following antibiotic ingestion.

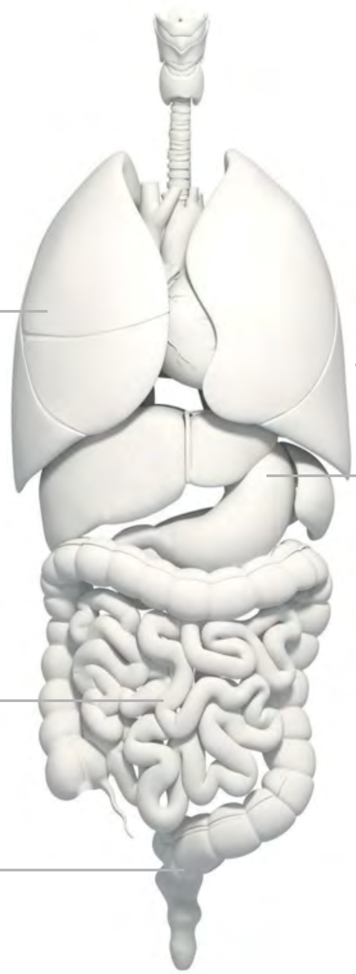
"Essentially, we've known for a long time that certain bacteria in the human intestinal tract are very important for the body," explains Ley. "Despite this, we knew very little about most of them until the early 2000s." The reason was that most of these microscopically small organisms couldn't be investigated in the lab, as we weren't yet able to grow them in culture dishes using artificial nutrient media.

"But microbiome research has exploded since 2004," says Ley. Several advances have been critical. First, the composition of the intestinal microbiome can now be determined using molecular biology methods, eliminating the need to culture the bacteria in the laboratory. In addition, modern sequencing techniques now enable us to rapidly decode the genetic composition of microbes, and computer analysis of data has accelerated tremendously.

USING MICE WITH NO INTESTINAL FLORA AS A MODEL

In the early 2000s, researchers from Washington University in St. Louis (USA) working with clinician Jeffrey Gordon investigated the link between obesity and gut bacteria using germ-free mice. Raised from birth in a bacteria-free environment, these animals have no intestinal microbiota of their own. This makes them an ideal model for elucidating the influence of specific members of the microbiome on health. With microbiota-free mice, scientists are able not only to precisely control the type of food they are given, but also to administer selected intesti-

Photo: Jörg Abendroth/derphotograph.de (top), Jürgen Berger/MPI for Developmental Biology



Humans offer microorganisms a home in a variety of organs, including the respiratory tract, the skin and the gastrointestinal tract.

nal bacteria to test the effects of the microbes and of differing diets on individual functions of the body.

Just when Gordon's team started to sequence the genome of gut bacteria, Ley joined the team. It was a decision that proved fortuitous for a number of people. Ley had already met a research colleague who would go on to become her life partner. Lars Angenent, a successful Dutch bioprocess engineer, had been working at the same university as Ley in Boulder. Soon afterwards, however, he was offered a position as an assistant professor at Washington University in St. Louis, while Ley stayed on at the University of Colorado. The couple traveled back and forth between the two cities for several years – and for much of that time with no prospects of ever being able to live in the same place.

Then they had a sudden stroke of fortune. Ley discovered that Gordon's team in the medical faculty of Washington University offered the perfect working environment for somebody with precisely her expertise. Not only was Gordon's laboratory large and successful; he and his colleagues were in the process of applying techniques from Ley's specialty field – environmental microbiology – to research into the microbes of the human digestive tract. Ley therefore left him a message one day asking if he needed a microbial ecologist. After visiting and interviewing with Gordon and his group, she joined as a postdoc in fall 2004.

MICROBIOME MIXTURE AFFECTS BODY WEIGHT

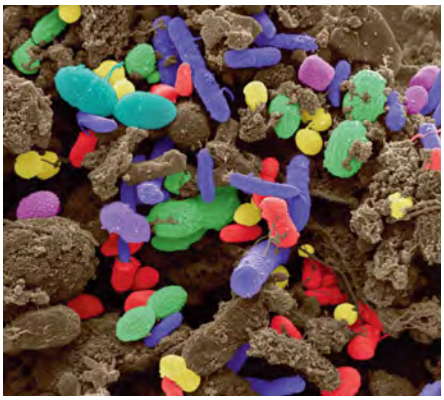
A short time later, Gordon's team published a groundbreaking paper. For the first time in medical history, the scientists were able to show that – contrary to long-held belief – our body weight is by no means solely dependent on how much we eat and how much energy we expend through exercise. A third factor, the microbial composition of our intestines, is involved.

The researchers employed an elegant trick to prove this. They transferred the intestinal microbiome of conventionally raised laboratory mice to germ-free mice. Despite having unlimited access to food, the animals that are kept in sterile conditions and that possess no intestinal bacteria of their own normally have extremely little body fat. That changed abruptly when they were colonized by gut microbiota. Even though the mice ate no more food than before, their fat stores grew.

Shortly afterwards, Ley was able to demonstrate another connection between microbes and body weight in a clinical weight-loss study involving 12 obese individuals. The results showed that, similar to mice, obese and normal-weight people can have different mixtures of bacteria in their intestinal tract. The most marked difference was in the proportion of the two most common representatives of intestinal bacteria, the *Firmicutes* and *Bacteroidetes* phyla. Obese individuals enrolled in this study, Ley found, had significantly more *Firmicutes* and fewer *Bacteroidetes* than normal-weight people, and their microbiomes came to resemble those of the lean controls more as they lost weight.

Gordon's team then went one step further. This time they transferred intestinal microbiomes from normal-weight and from genetically obese laboratory mice into germ-free mice. The

Graphic: Science Photo Library



Left Bacteria are essential for effective digestion: More than half of human feces consists of excreted intestinal bacteria.

Above The composition of the bacterial community also affects body weight: Obese mice have more *Firmicutes* bacteria than *Bacteroidetes*; this relationship is reversed in animals with a normal body weight.

results were clear: mice that had been germ-free and had been given a microbiome from obese rodents became fatter than those that received microbiomes from lean donors.

The result electrified the whole team. For the first time, researchers had been able to demonstrate that a propensity for obesity could be transferred from one animal to another – simply by manipulating the mixture of the microbiome in their gut. "It was one of those 'Oh my God!' moments. We were absolutely elated," Gordon told a reporter. Ley, too, found her time in Gordon's team to be a particularly inspiring experience: "I never thought I would be applying for a job at a medical faculty, but that decision was one of the best I ever made in my career."

FAMILY AND CAREER

Among other things, the large number of groundbreaking papers she has published in the last few years testifies to this. She discovered, for instance, that the intestinal microbiota changes drastically during pregnancy, which impacts the mother's metabolism and thus ensures the optimal provision of nutrients to the fetus. Just as significantly, Ley worked on identifying human genetic determinants of the microbiome – in other words, how much of the variation in the microbiome is due to our genes.

Last but not least, Ley's crossover to biomedical research had another fruitful outcome for her and Angenent, who is now her husband. Since their time in St. Louis, the two researchers have not only started a family – their son is now 10 years old – Ley and Angenent have since also succeeded in planning their career moves from post to post together. In 2008, Ley moved with her husband and son to Ithaca, New York, where they continued their work at Cornell University. In 2013 she became an associate professor in the Department of Molecular Biology and Genetics.

At the Max Planck Institute in Tübingen, Ley plans to establish a new microbiome research program over the next few years. She is currently also expanding her laboratories as well as forming new joint research teams involving the Institute and the Faculty of Medicine at the University of Tübingen.

One special focus of her future research will be performing large-scale studies to sample microbes from the intestines of individuals from different backgrounds. Using these samples, she aims to investigate what effects genes, the immune system and environmental factors have on human intestinal microbiota. As Angenent has taken up a position as a Humboldt Professor in the Department of Geoscience at the University of Tübingen, their shared life as researchers can now continue. ◂

GLOSSARY

Microbiome: The totality of all microorganisms that inhabit a living organism. Humans, for instance, are home to 10 times more microbes than their bodies possess cells. It is estimated that each of us is inhabited by approximately 100 trillion bacteria. Most of these live in the intestines, but we also have lodgers on our skin, in the oral and nasal cavities, and on our sex organs. There is frequently a symbiosis between humans and microbes, benefiting both. Some bacteria, however, are only "table companions", neither harming nor helping.

Firmicutes/Bacteroidetes: Two phyla of bacteria, usually with differing cell wall structures. Firmicute bacteria convert fiber into short-chain fatty acids that the body can absorb. The *Bacteroidetes* phylum, in contrast, breaks down complex polysaccharides. Together they account for the majority of the intestinal microbiota.

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