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The Influence of Soil on Immune Health

Recent work in humans and mice highlights how exposure to environmental microbes helps protect against allergies and other inflammatory diseases.

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People living along the border between Finland and Russia are yielding valuable data that could shed light on people's relationship with nature—particularly when it comes to the link between environmental exposure and immune health. During the Second World War, Finland ceded a large swath of territory to the Soviet Union. In the second half of the 20th century, the Finnish side became modernized, while people on the Soviet side maintained a traditional lifestyle. And by the 21st century, according to a study carried out by researchers at the University of Helsinki, the prevalence of allergies on Finland's side of the border region known as Karelia was significantly higher than that of people living on the Russian side.

Immunologist Nanna Fyhrquist, who joined the University of Helsinki team in 2011 and helped carry out the research, wanted to know why. The group suspected that the differences in allergy incidence between the two sides of the Finnish-Russian border might have something to do with exposure to environmental microbes. The late ecologist Ilkka Hanski of the University of Helsinki along with Helsinki University Central Hospital researchers Tari Haahtela and Leena von Hertzen had recently formalized the biodiversity hypothesis, arguing that the total biodiversity—and correspondingly, microbial diversity—of people's living environments influences human health via changes to the composition of the microbiome. A global loss of biodiversity, they reasoned, was to blame for the dysregulation of the human immune system and thus the increase in allergic and inflammatory diseases observed in developed nations around the world.

The idea is an extension of the decades-old hygiene hypothesis, developed in the late 1980s and '90s as researchers came to realize that living in a modernized world where bacterial exposure is limited was linked with hay fever and other disorders characterized by immune dysfunction. Later, University College London microbiologist and immunologist Graham Rook took a similar view with his "old friends" hypothesis, which posits that

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—Martin Breed, Flinders University

humans—and specifically their immune systems—have become dependent on the microbes they coevolved with for tens of thousands of years or more. “The immune system [is] a learning system,” Rook tells *The Scientist*. “Unless you put the data in, it can’t function correctly.”

The team in Finland has since been exploring mechanisms by which environmental microbes might influence the human immune system. One way could be through the shaping of humans’ resident microbiota, which has been linked to the development of allergies. The idea is already somewhat supported by data from the Karelia study. In the Finnish skin swab samples, “we saw children living in the countryside surround by forest and green area were much less allergic [than Finnish children in more-urban environments], and they also had a much richer skin microbiota,” says Fyhrquist.

Specifically, the country kids had more, and more-diverse, bacteria on their skin, with a particularly high abundance of *Acinetobacter*—a genus of microbes in the *Proteobacteria* phylum that are commonly found on plants. The researchers further found that children with more *Acinetobacter* on their skin had more leukocytes in their bloodstream and that these cells were much more capable of producing the anti-inflammatory cytokine IL-10 compared with the leukocytes of urban kids. “This led us to think that this particular group of microbes derived from nature might be able to somehow contribute training or calibration of the immune system,” says Fyhrquist. Samples from the less-developed Russian side of the border supported that idea, containing a higher abundance of *Acinetobacter* than the samples from the Finnish side regardless of the specific living environment. “The Russian lifestyle being so profoundly different from the Finnish, it appears to override possible effects of rural versus urban living environments,” she says.

A sampling site in Pitkäranta (Russian Karelia)
TARI HAAHTELA

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But to know if exposure to soil microbes was causing the microbiome differences linked to the Russian population's relatively low rates of allergies, the team needed to do an experiment. Last year, Fyhrquist, now at the Karolinska Institute in Sweden, and her collaborators used a mouse model of asthma, a disease triggered by the same type 2 helper T cell (Th2) immune response that underlies allergic reactions. They housed some female animals on clean bedding while their sisters' cages were sprinkled with potting soil and kept in a stable that housed other animals such as sheep.

After six weeks, mice that had lived on clean bedding were more susceptible to developing lung inflammation in response to an asthma-triggering allergen than were the mice in contact with soil. The team also found that, in agreement with some previous research, the guts of soil-exposed mice contained more bacteria in the *Bacteroidetes* phylum than in the *Firmicutes* phylum—the opposite of the microbial signature usually associated with asthma and inflammation in general in both mice and humans. Soil-exposed animals also had higher levels of anti-inflammatory proteins that keep the immune system in check, including an enzyme called A20 that has previously been shown to be protective in mouse models of asthma. "It was quite amazing to see so many different levels of modification and induction of tolerance in the mice," says Fyhrquist.

The Finnish team's mice were in prolonged physical contact with microbe-filled soil, but other work suggests that even trace amounts of airborne soil—along the lines of what a person might experience by spending time in nature—could have effects on mouse health. In work published this month, restoration ecologist Martin Breed of Flinders University in Adelaide, Australia, and his colleagues placed small amounts of soil with varying levels of biodiversity in a tray outside a mouse cage, and ran a fan over it for two hours a day to create "a very light wafting" towards the animals, Breed describes. The soil load amounted to a 100 to 1,000 times lower dose than that used in other studies, he says.

Nevertheless, after seven weeks of this sort of exposure to soil with high microbial diversity, the animals showed changes in their microbiomes, and scored lower on standard stress tests. "By the end of the experiment, the feces of the mice in the high biodiversity enclosures were more like the high diversity soils than they were at the start," Breed says. "There was direct colonization into the gut . . . from the soil. . . . I was floored by the fact that we could pick up mouse poo differences based on such tiny levels of exposure."

The field is using results such as these to begin making the case that exposure to diverse bacteria in the environment is one mechanism underlying the wide-ranging health benefits of spending time in nature. "I think there is more and more evidence to back up this statement that there is a direct contribution of

the soil to human health," says Sophie Zechmeister-Boltenstern, head of the Institute of Soil Research at the University of Natural Resources and Life Sciences Vienna (BOKU). "If there is more biodiversity," she adds, "then there is more resilience and resistance against pathogens."

See "Time Spent in Nature Is Good for You"

But this conclusion comes with a problem: biodiversity in the world's soils is dwindling, says Zechmeister-Boltenstern, meaning that even people who do spend time in nature are getting exposed to fewer types of bugs now than they were in the past. She and her colleagues recently reported that the diversity of the human gut microbiome is decreasing right alongside this loss of biodiversity in the environment.

"People are not so much aware of this immense biodiversity which is harbored in the soil," says Zechmeister-Boltenstern, "but soil is actually the most diverse habitat on Earth."

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This story is part of a series by *The Scientist* on how natural environments affect human health.

Click through to find out more about some of the other proposed mechanisms linking spending time in nature to physical and mental health benefits.

Correction (January 9): The original version of this story referred to Finland as a Scandinavian country. The Scientist *regrets the error.*

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