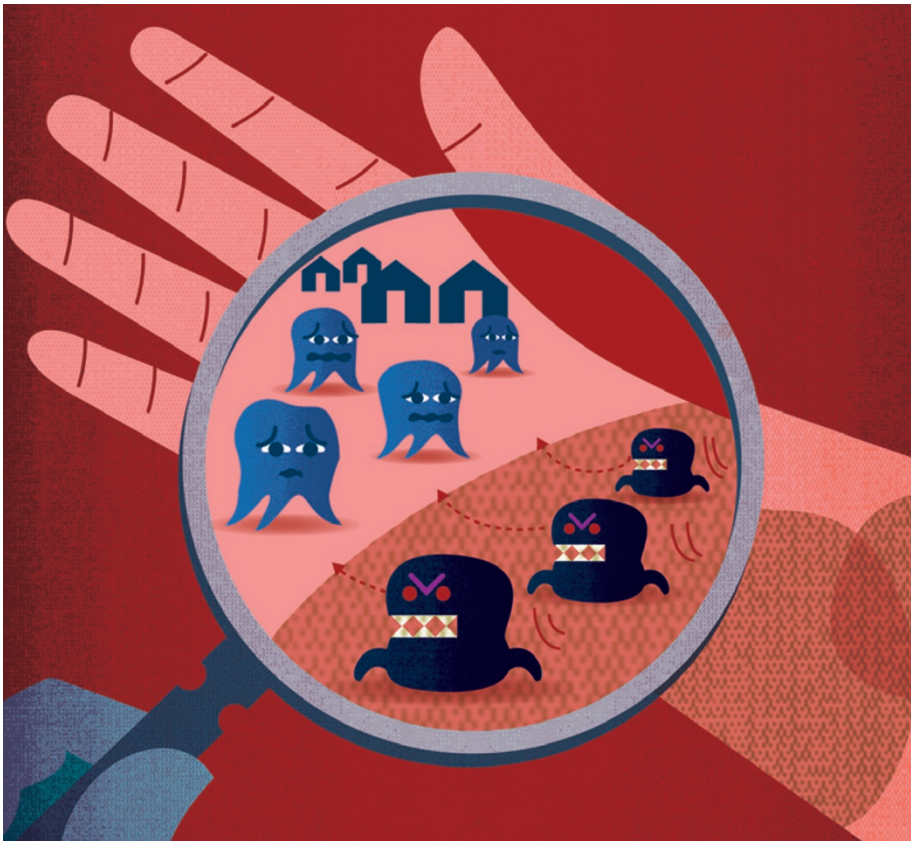


ANDREW BAKER

MICROBIOME

The surface brigade

Our skin is home to thousands of species of bacteria — and when these microscopic societies are disrupted, skin infections can arise.

BY BIJAL TRIVEDI

Each one of us is home to some 100 trillion bacteria. This mass of microbes — accounting for 1–3% of our body weight — resides in our mouth, nose, genitals and intestines, as well as on our skin. Although we are only just beginning to discover what these microscopic hitchhikers do, it is already obvious they are not freeloaders — many play an important role in maintaining human health. There is even preliminary evidence[1] suggesting that when we eradicate certain species of bacteria or alter their relative populations, we inadvertently contribute to the development of diseases ranging from obesity to asthma.

Determining the identity and roles of these microorganisms is the goal of the Human Microbiome Project. In June 2009, scientists from the project released a survey[2] of microbes dwelling at 20 locations on the skin of the human body. This census, based on 10 healthy volunteers, produced two significant results, says Julie Segre, a leader of the skin microbiota sequencing efforts at the National Human Genome Research Institute in Bethesda, Maryland. First, it revealed the diversity of microbes that reside on healthy skin. Second, it showed that the organisms varied depending on whether the area was oily like the chest; moist, as in the armpit; or dry, like the forearm (see 'Microbiome map').

Just as the microbes in the gut provide nutritional benefits, those on the skin also earn their keep. Some have evolved to eat dead skin, some transform the oils that skin cells produce into a natural moisturizer, and others are thought to keep harmful bacteria and viruses from invading. And in the past few years investigators, including Segre, have started to explore whether an imbalance in microbes contributes to skin diseases such as psoriasis and eczema.

SKIN SURVEY

Martin Blaser, a microbiologist at New York University's Langone Medical Center, became interested in psoriasis almost a decade ago after personally developing a mild case. As a physician specializing in infectious diseases, Blaser was well aware of the skin's contingent of normal flora, and wondered whether a change in these microbes had triggered his disease. He investigated this question and in 2007 published one of the earliest surveys of microbes living on the human forearm. Following the launch of the Human Microbiome Project in December 2007, he received a grant from the US National Institutes of Health to further explore the link between microbes and psoriasis along with his then colleague, dermatologist Bruce Strober.

Psoriasis, which typically causes red, raised, scaly, itchy plaques, affects about 2–3% of the world's population (see 'Psoriasis uncovered', page S50). Although Blaser's case was mild, the disease can be debilitating. Those most severely affected "can be among the most miserable patients on Earth", says Strober, now at the University of Connecticut in Farmington. Blaser's team in New York examined the microbes inhabiting the lesions of psoriasis patients. Using a damp cotton applicator, Strober swabbed the plaques for a bacterial sample. Then he took another sample from the patient's healthy skin. He also collected microbes from patients with no signs of the disease.

Blaser discovered[3] that the cast of microbes inhabiting the plaque is much more diverse than on healthy skin from either psoriatic or unaffected individuals. He also found that the major phyla of bacteria were present on both psoriatic and healthy skin, but in different ratios. Most notably, there was a striking trend in bacteria from the *Proprionibacterium* genus: healthy skin had most, unaffected skin from psoriasis patients had moderate levels, and psoriatic lesions contained least.

This was a small study, says Strober, and it's far from clear whether these differences are a "cause, effect or correlation". Although he admits that "this issue is in its infancy", he is convinced there is a microbial component to psoriasis. One clue, Strober says, comes from identical twins: in 70% of cases, both suffer from the disease. "That's proof that the environment plays a part and it's not all genetic," he explains. What's more, he says, the unexpected flare-ups that characterize the disease might be set off by environmental triggers that alter the composition of the skin's microbe population.

Blaser, meanwhile, has expanded the study and will submit results for publication at the end of 2012. The data suggest there is no single

organism that is present in the psoriatic lesions but not on healthy skin, so there is unlikely to be an obvious microbial villain to exterminate. "It's going to be more complicated," he says.

The link between microbes and psoriasis is still unproven. "It's early days," says Frank Nestle, a skin immunologist and dermatologist at King's College London. Nestle is taking an active role in exploring this association as leader of the UK arm of a US$6.5-million international consortium to probe the skin microbiome. The project, Microbes in Allergy and Autoimmunity Related to the Skin (MAARS), aims to identify the microorganisms that protect against allergy and autoimmune diseases, as well as the pathogenic bacteria that trigger them. MAARS will focus on the two most prevalent chronic inflammatory skin diseases: eczema and psoriasis.

SURFACE ISSUES

Research on the skin microbiome lags behind that of the gut microbiome. Nevertheless, there are signs that skin microbes play a crucial role in overall health. In 2012, Yasmine Belkaid, an immunologist at the US National Institute of Allergy and Infectious Diseases in Bethesda, described[4] a link between the microbes on the skin and the body's ability to mount a robust immune response. Belkaid discovered that mice raised in sterile chambers, lacking bacteria on the skin, in the gut and elsewhere, were unable to fight off the parasite *Leishmania major*. However, if the germ-free mice were inoculated with *Staphylococcus epidermidis* — a common skin microbe on mice and humans — at the same time as the *L. major* infection, they were able to defeat the parasite.

Belkaid discovered that *S. epidermidis* interacts with T cells in the skin to produce inflammatory molecules that are central to the immune response. "It's possible that other bacteria on the skin can also rescue this immune response," says Belkaid, "but the point is that there is a link between the community of microorganisms on the skin and the animals' ability to protect against harmful microbes." If a lack of microbes on the skin cripples the immune system, she adds, then it's not unreasonable to think that disrupting the skin's microbial communities might leave it vulnerable to disease.

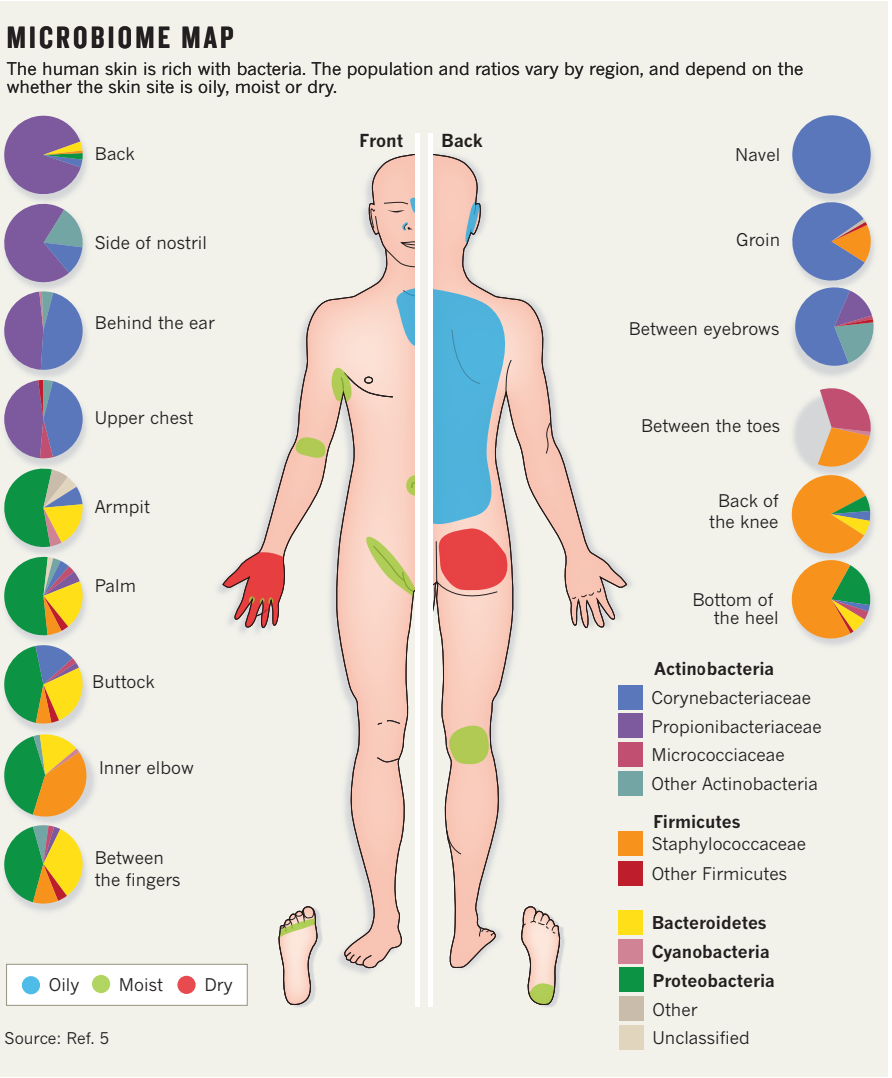
The evidence linking the microbiota and eczema, which affects more than 15% of children and 2% of adults in the United States, is more solid than for psoriasis. The number of children suffering from eczema has tripled in industrialized nations in the past 30 years, suggesting an environmental trigger. Research has shown[5] that more than 90% of eczema patients have colonies of *Staphylococcus aureus* on both their affected and unaffected skin. In contrast, the microbe is rarely present on healthy people. Segre adds that, in contrast to psoriatic lesions, eczema sores tend to have a much lower diversity of bacteria than healthy skin. What's more, as the condition worsens, *S. aureus* will often overwhelm the whole microbial community.

Proven treatments for eczema include topical antibiotics, steroids and mild bleach baths. But there are no effective antimicrobial treatments for psoriasis. That might seem like a strike against the link between microbes and psoriasis. But, says Blaser, history teaches us not to be so quick to dismiss such an idea. Early efforts to treat gastritis with antibiotics failed, arguing against a bacterial cause. It wasn't until Barry Marshall and Robin Warren discovered *Helicobacter pylori* in the stomachs of patients suffering from inflammation and ulcers that it became possible to develop a targeted regimen — two or three antibiotics plus an acid suppressant — that eradicated the specific bacterium and cured patients.

In a parallel with Blaser's hypothesis about psoriasis, Segre says it is unlikely that *S. aureus* alone leads to eczema. "We have to move away from the idea that one bacterium causes one disease," she says. "It's going to be much more subtle." Blaser and Segre suspect that diseases such as eczema and psoriasis might instead be related to a shift in the balance of microscopic skin-dwellers. "The challenge is to find out whether there's a causal link between a disturbance in the microbiome and a particular disease," says Blaser.

Future psoriasis therapies, Blaser suggests, might include ointments and creams spiked with particular bacteria that block the growth of other harmful bacteria, or that interact with the immune system to boost its ability to heal skin lesions and maintain skin health.

Whatever eventual treatments come from this work, it is increasingly apparent that our skin is not the first line of defence against the external world: that role falls instead to the army of microbes that live there. Keeping them happy could be the key to keeping our skin soft, supple and healthy. ■



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