BILL BRANSON, NIH

Up Close With

Elizabeth Grice

GENETICIST

"I didn't know what I wanted to do until relatively recently. I just stuck to what I enjoy doing."

FIRST JOB

Detasseling corn

FAVORITE FOOD

Chocolate

PETS

Two adopted shelter cats, Dolce and Gabbana

FAVORITE CITY

Athens, Greece

HIDDEN TALENT

Baking creative desserts

The Clone Zone

Body Bacteria

Exploring the Skin's Microbial Metropolis

BY ALLISON MACLACHLAN

Imagine a landscape with peaks and valleys, folds and niches, cool, dry zones and hot, wet ones. Every inch is swarming with diverse communities, but there are no cities, no buildings, no fields and no forests.

You've probably thought little about the inhabitants, but you see their environment every day. It's your largest organ—your skin.

"The skin is like our shell. That's what people see of us first," says Elizabeth Grice, who just finished a postdoctoral fellowship in genetics at the National Institutes of Health (NIH) in Bethesda, Maryland. "It's a defining feature, but it's also an important organ for human health."

Our skin is home to about a trillion microscopic organisms like bacteria and fungi. Together, these creatures and their genetic material—their genomes—make up the microbiome of human skin.

Grice studies the skin microbiome to learn how and why bacteria colonize particular places on the body. Already, she's found that the bacterial communities on healthy skin are different from those on diseased skin.

She hopes her work will point to ways of treating certain skin diseases, especially chronic wounds.

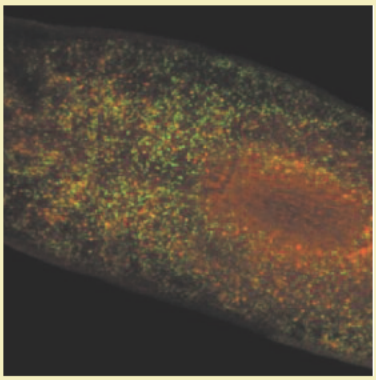
"I like to think that I am making discoveries that will impact the way medicine is practiced," she says.

Entering the Field

Growing up in Wisconsin and Iowa, Grice was exposed to biology at a young age—but in a field, not a laboratory.

"My first job was detasseling corn," she remembers. Pulling the tassel, or pollen-producing flowers, off the tops of corn plants is a way to breed high-yield hybrid corn with specific traits.

BILL BRANSON, NIH



PHILLIP NEWMARK

At less than an inch in length, a flatworm called a planarian can regrow its entire body from just a section of tissue. In this image from under a microscope, fluorescent dyes show which cells in the worm have copied their DNA and are ready to split in two.

Making Heads or Tails of Regeneration

A small flatworm called a planarian possesses an extraordinary ability: It can regenerate its entire body from a tiny slice of tissue. Scientists in Massachusetts have discovered how the worm makes heads or tails of what body part to regrow from a wound site.

The process involves a gene called notum and a genetic pathway called Wnt. Researchers led by Peter Reddien at the Whitehead Institute for Biomedical Research in Cambridge discovered that Wnt stops a wounded planarian from sprouting a head. But with Wnt around, how do heads ever form?

The scientists found that, if a wound is near the top half of the worm, Wnt activates notum. The notum gene appears to keep Wnt in check, dialing down the pathway's activity so a head can form.

In back-end wounds, the researchers noted that notum is less active, allowing tails to grow.

Both notum and Wnt are found in organisms ranging from fruit flies to humans. Could it play a role in repairing—or even regrowing—tissue in these other animals? Only science can tell.

—Allison MacLachlan

Bacteria aren't all bad.

Summer days in the fields were hot and taxing. "That was when I realized I didn't want to do manual labor," Grice laughs.

When Grice was in middle school, her mother went back to college for a bachelor's degree in biology. Reading off flashcards to help her mom study sparked Grice's own interest in science.

In high school, Grice trained to become a certified nursing assistant and worked in a nursing home. Then she enrolled at Luther College in Decorah, Iowa for a bachelor's degree in biology, with dreams of being a doctor.

When biology professor Marian Kaehler announced a summer research opportunity for seasoned students, Grice—a freshman with no lab experience—knocked on Kaehler's door 10 minutes later and asked for the job.

"She was determined, enthusiastic and confident, and we decided to try it," Kaehler remembers. "It worked out extraordinarily well."

Grice studied plant genetics in Kaehler's lab throughout college. She found the environment, with its experiments and challenges, a more comfortable fit than a career focused on seeing patients—or summers breeding corn.

Several research internships later, Grice earned a Ph.D. in human genetics and molecular biology from the Johns Hopkins School of Medicine before coming to NIH to tackle bacterial genomics.

The Good, the Bad and the Acne

When you use antibacterial hand soap or take antibiotics, it's easy to think of bacteria as bad guys. After all, *Salmonella* and *E. coli* can give you food poisoning, and *Staphylococcus aureus (S. aureus)* can cause pneumonia, meningitis or serious wound infections.

But bacteria aren't all bad. Many are harmless, and some are actually very helpful. On the skin, *Staphylococcus epidermidis* protects us by taking up

The bacterium that causes acne protects our skin by crowding out other, more dangerous bacteria.

Some are actually very helpful.

space that the harmful *S. aureus* would otherwise colonize.

The common skin bacterium that causes acne works the same way. "It's occupying a niche so that other, more potentially harmful bacteria don't invade," Grice explains.

It might sound unhealthy or even dangerous to have skin that's teeming with bacterial colonies. But as Grice points out, it's completely ordinary.

Your skin was sterile only once in your life—when you were in the womb. Minutes after you were born, bacteria began to colonize it. Your body relies on some of these bacteria as part of its first line of defense.

Many bacteria on the skin defend themselves by secreting antimicrobial peptides, or small proteins that kill harmful invaders. In protecting themselves, they also protect us.

Diverse Settlements

Like plants, bacteria don't all fare well in the same environment. Some are better suited to moist, humid folds like the armpit or navel. Others colonize dry expanses like the forearm or oily nooks like the side of the nostril.

Grice has surveyed the microbial landscape of human skin like a topographer charts a territory and an anthropologist studies its populations.

From a study of 20 different skin sites on a group of healthy people's bodies, Grice and her colleagues identified three types of environments: moist, dry and sebaceous (oily). Then they investigated which types of bacteria colonize what sites.

Scientists have traditionally studied skin bacteria by smearing a sample of them onto a layer of nutrient-rich gel in a Petri dish.

But 99 percent of the microbes won't grow on laboratory plates, because they need to interact with other members of the skin's bacterial community to survive. It's also tough to replicate the exact nutrients and environment the skin provides.

Grice calls this "the great plate count anomaly"—bacteria that grow well in the lab aren't necessarily major players on the skin.

Grice employed a newer technique that uses a gene called 16S rRNA.

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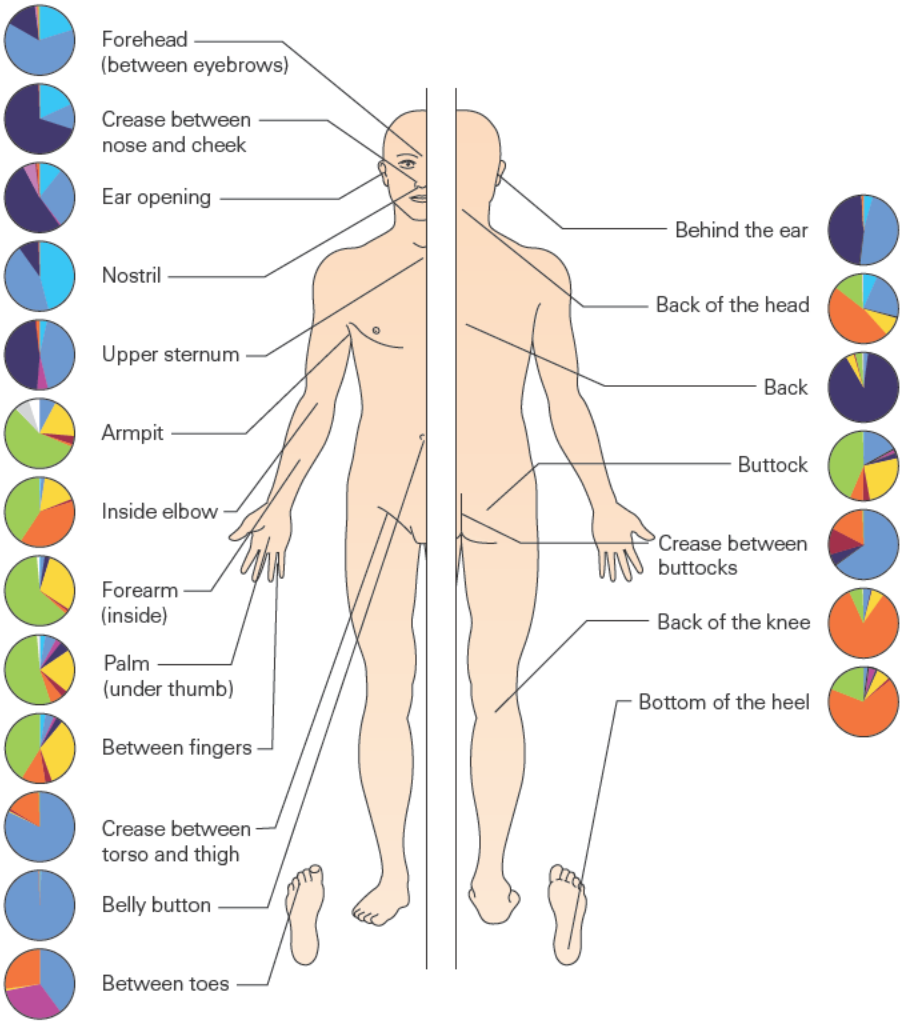

Types of Bacteria

Actinobacteria
- Corynebacteriaceae
- Propionibacteriaceae
- Micrococciaceae
- Other Actinobacteria

Bacteroidetes

Cyanobacteria

Firmicutes
- Staphylococcaceae
- Other Firmicutes

Proteobacteria

Bacterial types contributing <1%

Unclassified

Our bodies are teeming with bacteria. Some bacterial families colonize in warm, moist places like between the toes, while others prefer dry, open spaces like the buttocks.

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Bacterial diversity is probably a good thing,

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This gene provides the code for part of a bacterial ribosome, the essential machinery needed to make proteins.

The 16S rRNA gene is present in every known bacterium, but in each one, it has a slightly different DNA sequence. Scientists can use the sequence of this gene to classify the bacteria.

The Petri dish method has uncovered 10 different types of skin bacteria. The method Grice used revealed more than a thousand. Her study was the first to use the technique for such a large survey of human skin.

She found that moist areas tend to host similar bacterial communities in all of her volunteers. The same holds for dry and sebaceous areas. Each skin environment determines its bacterial inhabitants just as an outdoor environment determines its plant life—rainforests support leafy trees, while deserts have cacti.

Even with these patterns, the skin still has a surprising amount of variation from person to person.

Skin microbiomes are like snowflakes: No two are exactly alike. Your unique pattern depends on things like your age, sex, sun exposure, diet, hygiene and even where you live and work.

Microbes in Medicine

By getting a sense of bacteria on healthy skin, Grice hopes to figure out what's different about the microbes on diseased skin—and maybe even find a way to fix the problem.

She's most excited about applying her work to the chronic wounds that are common in people who have diabetes or spend most of their time in beds or wheelchairs.

People with diabetes can lose some of the sensation in their limbs, making it harder for them to feel pain and easier for any of their injuries to fester.

On top of that, they may have poor blood flow, which makes healing tough.

As Grice explains, your body needs blood to deliver oxygen, immune cells and important proteins to the site of an injury to help cells regenerate.

A Problem Afoot

Almost 10 percent of the United States population has diabetes, and up to a quarter of these 24 million people will get a painful wound known as a diabetic foot ulcer.

These ulcers are very difficult and expensive to treat. And the problem is increasing: As obesity rates rise, diabetes—and diabetic foot ulcers—are becoming more common.

"It's such a far-reaching problem that it's clearly an area of need," says Grice. "That's what really drives me the most."

Grice suspects that bacteria make chronic wounds worse because they spur the human immune system to trigger inflammation. Although designed to kill infected cells, inflammation also prevents skin cells from regenerating after an injury.

The immune system acts slightly differently in each of us, thanks to our genetics. Grice's work takes a micro-level look at interactions among human genes, the immune system and the skin's bacterial communities.

Defense Mechanisms

To investigate what role bacteria play in diabetic wounds, Grice used a group of laboratory mice bred to display common features of diabetes—like wounds that don't heal well.

Grice and her colleagues took skin swabs from both diabetic and healthy mice, and then compared the two. Using the 16S rRNA technique, they found that diabetic mice had about 40 times more bacteria on their skin, but it was concentrated into few species. A more diverse array of bacteria colonized the skin of healthy mice.

THE JACKSON LABORATORY

especially in wounds…

"People with diabetes have high blood sugar, which is known to change the skin's structure," says Grice. "These changes likely encourage a specific subset of bacteria to grow."

The researchers then gave each mouse a small wound and spent 28 days swabbing the sites to collect bacteria and observing how the skin healed.

They found that wounds on diabetic mice started to increase in size at the same time as wounds on healthy mice began to heal.

In about 2 weeks, most healthy mice looked as good as new. But most diabetic mouse wounds had barely healed even after a month.

Interestingly, bacterial communities in the wounds became more diverse in both groups of mice as they healed—although the wounds on diabetic mice still had less diversity than the ones on healthy mice.

"Bacterial diversity is probably a good thing, especially in wounds," says Grice. "Often, potentially infectious bacteria are found on normal skin and are kept in check by the diversity of bacteria surrounding them."

Then Grice and her colleagues examined differences between healthy and diabetic mice at the genetic level. They focused on the genes that control aspects of the immune system in the skin.

They found distinctly different patterns of gene activity between the two groups of mice. As a result, the diabetic mice put out a longer-lasting immune response, including inflamed skin. Scientists believe prolonged inflammation might slow the healing process.

Grice's team suspects that one of the main types of bacteria found on diabetic wounds, *Staphylococcus*,

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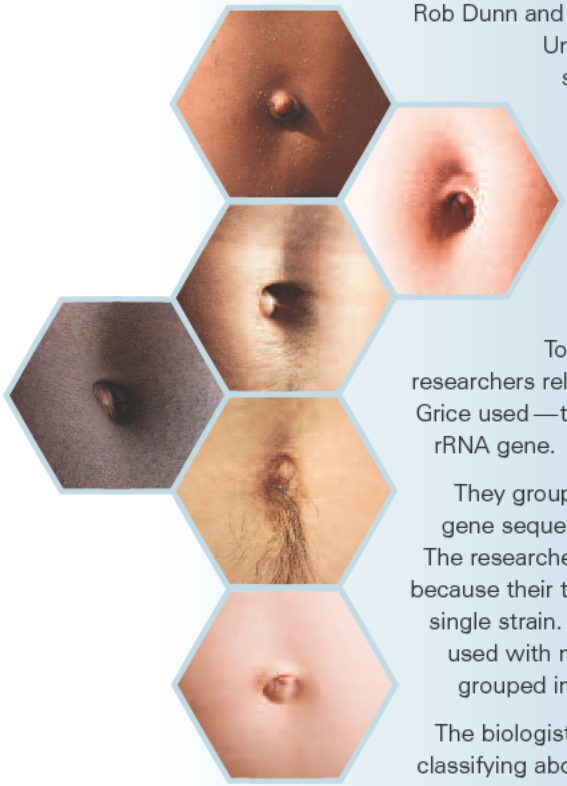
Belly Button Bacteria

Your belly button is way more exciting than you probably ever imagined. To bacteria, that is.

The belly button is a good place to look for bacteria because its warm, moist environment is protected, for the most part, from soap and scrubbing.

Some surprising results are coming out of the Belly Button Biodiversity project (http://www.yourwildlife.org/bellybutton-biodiversity/). This effort, which focuses on identifying bacteria in the human navel, is part of a broader survey of the life around us called Your Wild Life.



The belly button diversity research team was led by Rob Dunn and Jiri Hulcr at North Carolina State University in Raleigh. They found that swab samples from about a hundred volunteers' belly buttons contained an unexpected 1,400 different strains of bacteria! And that's in a part of the body that Grice found to have the *least* bacterial diversity! (See "Body Bacteria: Exploring the Skin's Microbial Metropolis," page 2.)

To identify the different strains, researchers relied on the same basic technique that Grice used—they looked for variations in the 16S rRNA gene.

They grouped together any bacteria whose 16S gene sequences differed by 3 percent or less. The researchers know 1,400 is an underestimate, because their technique doesn't separate every single strain. For instance, if the technique were used with mammals, dogs and cats would be grouped in the same category.

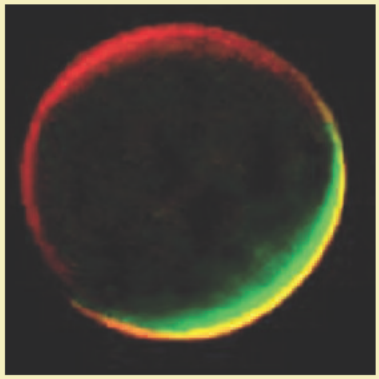
The biologists were stumped when it came to classifying about half of the strains, because there are no categories for them yet.

In other words, researchers say, these bacterial strains are about as new to science as African rhinos and elephants were to early European explorers.

Interestingly, 80 percent of the crowd is made up of about 40 main bacterial players.

So, the scientists wonder, are these main players protecting us from other, harmful members of the crowd? Or are they just better suited to survive in a moist environment?

We'll have to wait and see what else the Belly Button Biodiversity project uncovers. Until then, you've got a good excuse to go navel gazing. —*A.M.*



NEHA KAMAT, UNIVERSITY OF PENNSYLVANIA

The stressed region of this polymersome is evident (in green) before the membrane ruptures.

Microscopic Mood Rings

Scientists have designed tiny, glowing capsules that shine in stressful situations—literally. A team led by Daniel Hammer and Ivan Dmochowski at the University of Pennsylvania in Philadelphia engineered polymersomes, membrane-encased spheres only a few microns in diameter. The polymersomes act as miniscule mood rings, changing color in response to stresses like heat, membrane-disrupting chemicals and the mechanical stress of being sucked into a glass tube.

Here's how it works: The polymersomes are studded with natural light-emitting pigments called porphyrins that change shape when exposed to environmental stress. For porphyrins, a shape change means a change in the wavelengths of light they emit—their color. The new color reveals when and where the membrane is stressed.

The scientists suggest lots of potential applications. Polymersomes could be injected into the bloodstream to provide clues about nearby stresses, such as arterial blockages. They might carry a medicine into the body and reveal its release over time. They could even be used in body-scanning technology that would rely on light rather than radiation. —*A.M.*

Skin isn't the only place in the

continued from page 7

makes one of the inflammation-causing genes more active.

Now that they know more about the bacteria that thrive on diabetic wounds, Grice and her colleagues are a step closer to looking at whether they could reorganize these colonies to help the wounds heal.

More Than Skin Deep

Skin isn't the only place in the body that's crawling with bacteria.

Grice also spends time studying bacteria that live in the intestines. There too, microbes can be helpful.

Certain strains of *E. coli* in our digestive tracts help keep dangerous bacteria at bay and produce K- and B-complex vitamins, which our bodies can't make enough of on their own.

Grice is involved with a study of Hirschsprung disease, a genetic disorder that leaves parts of the digestive tract without enough nerve endings to push wastes out.

Some children born with the disease get enterocolitis, a painful inflammation in the gut, and others don't. Together with geneticist Bill Pavan, who also works at NIH, Grice is looking at gut bacteria to see if their distribution differs between the two groups.

If the researchers find a pattern, it might help predict which patients will need surgery to reduce inflammation. Grice and Pavan also think that redistributing some of the bacteria in inflamed intestines might help.

Pavan admires Grice's confidence and dedication to her science, and he also says that working with her is a lot of fun.

"She is driven to get high-quality research done, but she's still extremely friendly and interactive on a personal level," he says. "She has an infectious laugh."

Pavan said Grice is well known for whipping up impressive treats like miniature chocolate mice, which are very popular in the lab. And whenever a lab-mate has a birthday, Grice brings in a custom-baked cake with whatever flavor and frosting the person wants.

"Most people wouldn't suspect that I'm very domestic," says Grice, who lists cooking as one of her hobbies. "You get to a point where you're comfortable experimenting with recipes and seeing what works."

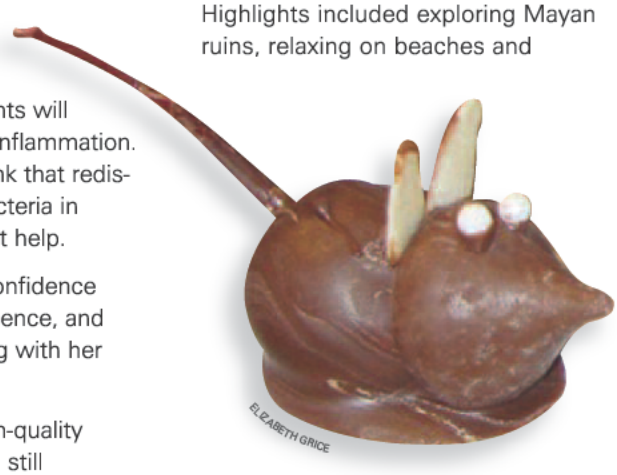
Grice likes getting creative with her experiments in the kitchen as well as in the lab. "My husband doesn't really eat vegetables, so it's always a challenge to work around that," she laughs.

Taking Exploration Global

For Grice, exploring diverse landscapes and populations goes far beyond skin samples. Outside of her work, she enjoys traveling to exotic locations to soak up the culture.

She and her husband were married in Belize, a country they chose for its natural beauty and its preserved culture. "It's one of those places that you feel isn't overrun by civilization," she says.

Highlights included exploring Mayan ruins, relaxing on beaches and



ELIZABETH GRICE

Grice enjoys cooking, baking and creating playful sweets like these chocolate mice.

body that's crawling with bacteria.

ELIZABETH GRICE

Grice loves to experience the natural beauty and local culture in countries like Belize, Greece and Costa Rica.

snorkeling in the striking coral reefs off the coast.

Grice also counts Greece among her favorite destinations because of its architecture and the laid-back Mediterranean attitude. "I love Athens and all the old ruins that are just integrated into the city," she says.

When she's home, Grice likes to explore other cultures and civilizations by reading. A self-professed bookworm, her favorite genre is historical fiction, including novels about the Tudor period in Britain.

Tying her hobbies to her career choice is easy for Grice. "I really like experiencing different cultures, and science is so multicultural—you get to interact with a diverse group of people," she says.

Charting New Ground

During the preparation of this article, Grice was considering job offers for a faculty position. She decided to join the University of Pennsylvania's dermatology department and will start working there in January 2012.

In her new job, she will continue her research on the wound microbiome and teach graduate and medical students.

She hopes that she, like her longtime mentor Marian Kaehler, will inspire and challenge her students.

"She was just so tough, and I really respected that," Grice says of Kaehler.

"Having a female mentor was also really important to me, because otherwise, how do you picture yourself in that role?"

Even now that she's landed that role, Grice's ambition isn't flagging. She aims to sustain a successful research program, improve the way chronic wounds are managed and keep time for personal goals like traveling to new continents.

Kaehler, for one, is confident that Grice will succeed. "She has a very strong sense of self, and there's nothing more important for people making career decisions than knowing where you're going to find a niche that makes you satisfied and challenged," she says.

Like the bacteria she studies, Grice knows where she thrives. ● ● ●

FIND MORE @

See a video of Grice explaining her research at http://www.scivee.tv/node/10037

To read about other geneticists, select "Genetics" in the "By Topic" search on http://publications.nigms.nih.gov/findings

For a story about another scientist who studies wound healing, go to http://publications.nigms.nih.gov/findings/sept07/healing.html