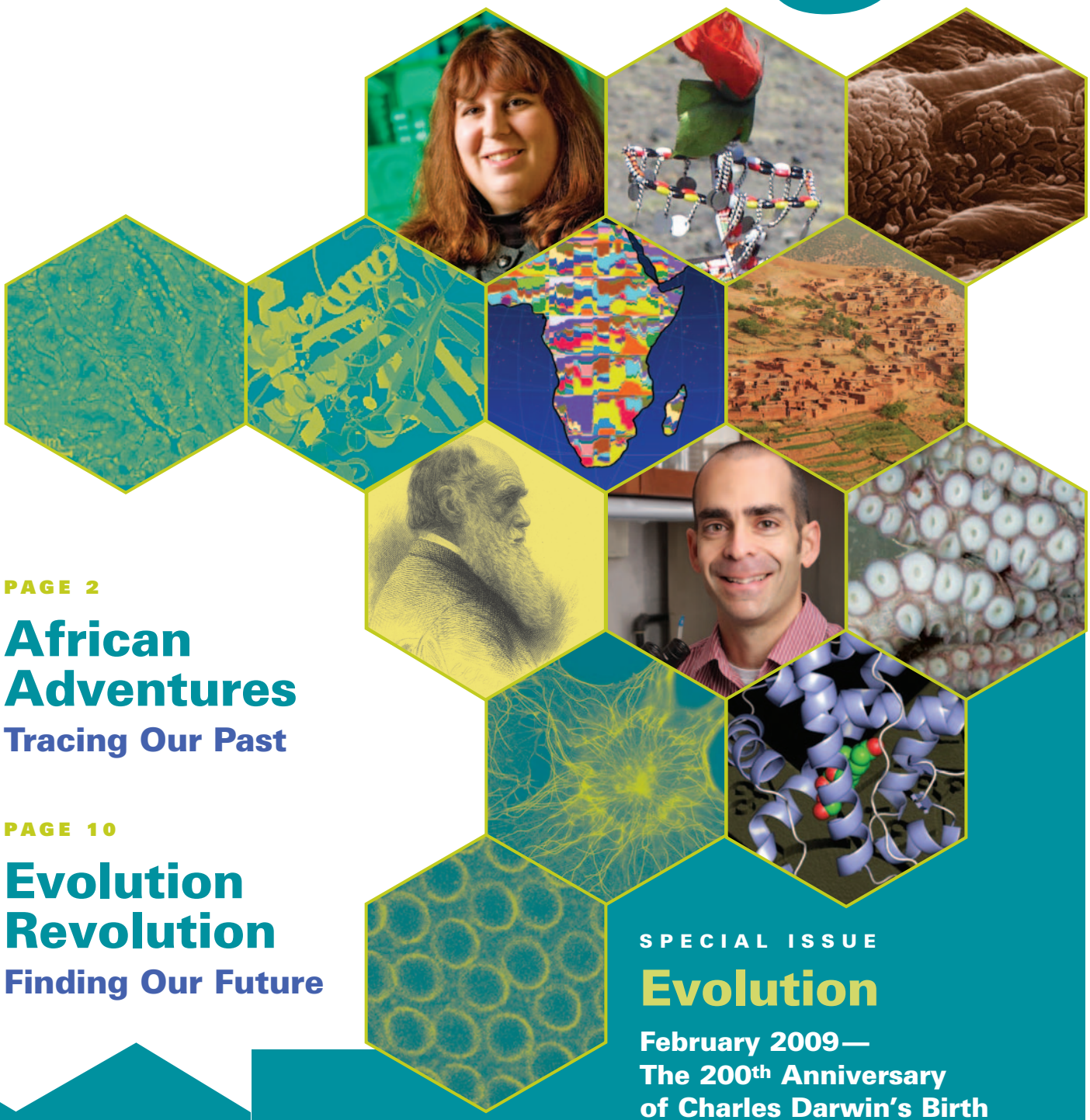
Findings

FEBRUARY 2009



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SPECIAL ISSUE

Evolution

**February 2009—
The 200th Anniversary
of Charles Darwin's Birth**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of General Medical Sciences

Inside Science: Life in the Lab

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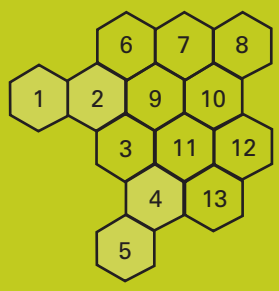

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TOMMY LEONARDI

Up Close With

Sarah Tishkoff

EVOLUTIONARY GENETICIST

"In some contexts, I'm a geneticist. In others I'm an anthropologist. And other times I'm an evolutionary biologist. I wear many hats."

FAVORITE AFRICAN ANIMAL

Warthogs… or giraffes

INTERESTING FACT

Speaks Kiswahili

MUSICAL TALENT

Plays Beethoven on the piano

MISSES MOST WHILE IN AFRICA

A hot shower

TOMMY LEONARDI

Genetic Footprints

BY ERIN FULTS

Where did I come from?

What makes me unique?

What makes a human…a human?

These simple questions are not so easy to answer. We still do not know what makes you "you," your mother "her" and your brother "him." Nor do we know, precisely, why we do not look or act just like chimps.

Evolutionary geneticist Sarah Tishkoff doesn't know the answers either. But these are the questions she asks every day as part of her job running a lab at the University of Pennsylvania in Philadelphia.

You might say Tishkoff has a long commute—traveling more than 8,000 miles to do her fieldwork in Africa. There, she collects data to help her understand evolution and its role in shaping human history and human health.

JIBRIL HIRBO

Sarah Tishkoff's research gives her the opportunity to learn about African culture.

Working alongside African researchers, Tishkoff looks at DNA to trace the paths of human evolution. Her training in anthropology—the broad study of humanity itself—gives Tishkoff a unique perspective on genetic research, the study of heredity.

Tishkoff says that in many ways, genetics can begin to answer the questions of where we came from and what makes us unique—as individuals and as a species.

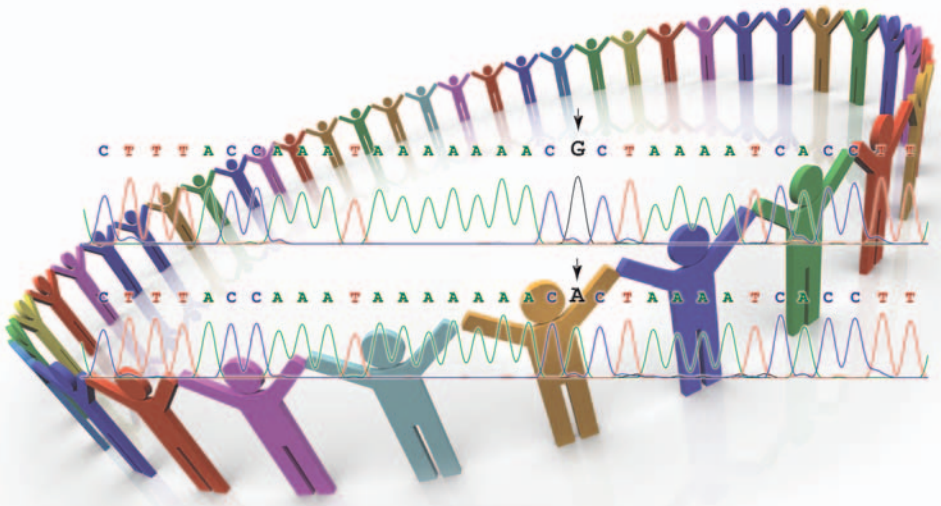
"What drove me to this work was being able to ask the questions philosophers ask," says Tishkoff.

Every new answer brings with it a new question. And that means a lot of changing and adapting. With each project she meets new people and finds new diseases. The work is not always easy, Tishkoff says.

"Not easy" means setting up a lab in the middle of nowhere. It means using a car battery to power equipment, riding in a Land Rover® and colliding head-on with a bus, and sleeping in tents where zebras come to visit.

It also means: She'd hardly give it up.

What drove me to this work was being able to ask



These two DNA sequence readouts show genetic variation, with either a G or A nucleotide at the same position in the DNA of two different people.

Little Letters, Big Dig

A genome is all of the genetic information in an organism, stored in the form of DNA. This DNA is Tishkoff's archaeological "dig site."

Often called the code of life, DNA carries the genes you got from your parents.

To an extent, genes are what give you your mother's eyes or your grandfather's hair. Genes also affect your health—if heart disease runs in your family, you may be at risk for getting it yourself.

Of course, genes aren't the whole story. Where and how you live, what you eat and whether you exercise, drink alcohol or smoke are all hugely important in your health and your appearance.

DNA has four different nucleotide "letters" that string together into gene "words." Our bodies use genes as the templates to make RNA and proteins, which are the main workers in cells.

While the genome is mostly the same in all people, slight differences exist. This genetic variation makes up about one-tenth of a percent of each person's DNA. These spelling differences, spread across many genes, are what make you unique.

This genetic variation is enough to distinguish you from your next-door neighbor, the president of the United States and millions of other people all over the world.

Genetic variation is inherited, so the more closely related two people are, the more similar their DNA is likely to be.

Individuals within a population have DNA that is more similar to each other's than it is to that of people in other populations, because they share an ancestry that is at least partly captured in DNA variation. So people whose ancestors have lived for generations in Sweden will have DNA more similar to other Swedish people than to modern-day Koreans whose families settled long ago in Korea.

Medical researchers are interested in genetic variation because it helps them understand disease risk. For example, some people are naturally resistant to getting AIDS after becoming infected with HIV because they have a specific change, or variant, in their DNA. The variant is extremely rare, but examining the genetics of how it happens could lead to ways to prevent or treat this killer disease.

Scientists like Tishkoff who study genetic variation are actually studying evolution. Over time, changes occur in DNA, affecting the readout of the genetic message. If the changes are helpful to the organism, they have a greater chance of being passed on to future generations because they provide a survival advantage.

Of course, it takes many, many generations for these changes to catch on.

Into Africa

Tishkoff first got hooked on tracking evolution in the early 1990s while in graduate school at Yale University in New Haven, Conn. She had the chance to scan one of the largest collections of DNA samples from populations all over the globe.

One of Tishkoff's first observations was that Africa was represented by genetic information from only two ethnic groups. That's hardly enough to cover this vast continent, she thought.

At the time, Tishkoff explains, researchers hadn't yet realized what

FIND MORE @

Hear a native Xhosa click-speaker at
http://www.youtube.com/watch?v=gytCi5a7AJg&feature=related

the questions philosophers ask.

they were missing. "People had no idea how much genetic diversity there was in Africa. They thought, 'well, any African population will do,'" she recalls.

Tishkoff made her first trip to South Africa in 1997. Working with a researcher in Johannesburg, she analyzed DNA samples and was amazed at what she saw. Tishkoff discovered that the hundreds of different African tribes who speak around 2,000 different languages also had a tremendous amount of genetic variation.

One thing Tishkoff didn't fully appreciate until she arrived in South Africa was that she couldn't take safety for granted. At the time, the University of the Witwatersrand in Johannesburg where she was working was in a dangerous part of town, and Tishkoff had to stay within the university's walls. That meant a permanent curfew.

"I could work day and night," says Tishkoff. "It kind of forced me to."

Since she couldn't experience the bustling city herself, Tishkoff learned about it from television. She watched interviews with people from different African tribes and started to pick up on cultural differences.

JIBRIL HIRBO

After work hours, a truck battery-powered television entertains Sarah Tishkoff and her research team in Africa.

Tishkoff became interested in the phenomenon of click-speaking, tonal languages in which the same sequence of consonants and vowels can have different meanings depending how you say them. One of the most distinctive features of a tonal language is its many click consonants. For example, the !Xóõ language, with roughly 4,000 speakers in the South African nation of Botswana, has 83 click sounds—the largest number of consonants in any known language.

Because using clicks as a form of communication is very unusual, you might assume that click speakers are closely related. But they're not as related as you might think.

Tishkoff looked for an explanation in their DNA and uncovered only a very distant relation between Tanzanian click-speaking tribes, but a common ancestry between some click speakers and a non-click tribe called the Pygmies.

Studying the click tribes and tracing tribal relationships is one example of a new science called molecular anthropology (see "The Big Family Tree," page 6).

Molecular anthropology uses information from DNA and proteins to determine evolutionary links between populations. In this way, scientists like Tishkoff are molecular navigators who can investigate long-ago worlds.

Decoding Disease

Tishkoff, like other medical researchers, is very interested in how what happened long ago shapes genes that affect our health. This evolutionary information may translate into ways to understand, treat and prevent human diseases.

In Africa, Tishkoff lived in areas with high rates of malaria, an infectious

story continues on page 6

Chimp DNA may hold clues for improving human health.

Chimp Changes

You may be surprised at how little human DNA differs from that of the great apes. Chimps, our closest living relatives, share perfect identity with 96 percent of our genome.

But chimps are unlike us in many ways besides being furry and really loving bananas: They do not get AIDS, many cancers or deadly malaria.

Can evolution explain the differences and help us combat killer diseases?

Yes, says evolutionary biologist **Ajit Varki** of the University of California, San Diego. He discovered that chimps—but not people—produce the natural glycan molecule "Gc." Glycans are essential body sugar molecules that can also attract disease-causing microbes.

But Varki also found that many people have Gc in their bodies and anti-Gc antibodies in their blood. He thinks that people are exposed to Gc by consuming red meat and milk, two rich sources of the glycan.

An evolutionary change that dropped a Gc-producing enzyme from human DNA may now put us at risk, Varki guesses. He is investigating whether the human immune reaction against Gc may spur some cancers and infectious diseases. —*Alison Davis*

The Big Family Tree

Where was your grandmother from? Your great-grandmother? Now how about your great-great-great-great-grandmother?

No doubt your family tree gets fuzzy the further back you go. But as humans, we can all trace our roots back to a common ancestor. Evolution and the migration of ancient peoples made humans a large and diverse population today.

But how do we find our ancestors? How do we learn where we came from and how we got here? The answer is molecular anthropology.

NOAH ROSENBERG, MARTIN SOAVE

This field of science uses a blend of methods to determine evolutionary links between ancient and modern people. It can also be used to reveal our connections to closely related species, like chimps and gorillas.

To connect the dots using molecular anthropology, scientists look at DNA. They look for differences and similarities in the sequences of nucleotides—the "letters" that make up the genetic material.

As different as people look, our DNA is actually amazingly alike. And, get ready for this: Your DNA is about 96 percent the same as a chimp and 85 percent the same as a mouse!

Molecular anthropology is important for understanding human origins and human evolution. Knowing our DNA roots can also help us learn more about diseases and genetic changes that our ancestors developed and passed on to us. This knowledge may be the key to finding new treatments and vaccines. —*E.F.*

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disease spread by parasite-infested mosquitoes. Despite the fact that effective prevention methods exist—including bed nets and medicines like chloroquine—malaria is an enormous worldwide health menace. In Africa, where access to prevention and treatment is scarce in many regions, the disease kills a child every 30 seconds.

Yet some people inherit protection against malaria. Variations in a gene called G6PD are common in people who live in areas of Africa with widespread malaria. But although this variant of a particular gene guards against malaria, it also has a dark side, causing anemia and sometimes death.

Another example of a double-edged genetic variation is sickle cell disease, a lifelong problem in which the body makes misshapen red blood cells that don't move easily through blood vessels. They're stiff, gummy and tend to form clumps that get stuck, causing intense pain, serious infections and organ damage.

By any standard, sickle cell disease is not a good thing to have, except for the fact that people who have a sickle cell gene variant—along with one normal gene—have protection against malaria. As with the G6PD genetic variant, evolution tolerates the sickle cell gene variant and it gets passed on to future generations of people because it gives them a survival advantage.

But the story gets even more complicated. Just as the human genome adapts, so too does that of the parasite living inside the mosquito that transmits malaria. For this reason, Tishkoff laments, we will probably never be fully protected from the disease.

"We're in an arms race with the parasite that causes malaria," Tishkoff says.

what makes everybody unique.

However, all is not lost. Tishkoff thinks that by finding the genetic variants that contribute to parasites' resistance to our drugs, scientists may be able to develop more durable malaria treatments and vaccines.

Got Milk?®

Tishkoff explains that the evolutionary race between the malaria parasite and human defense mechanisms is an example of co-evolution, where two species adapt and evolve in response to one another.

Other interactions occur, such as genetic adaptation to a cultural change. Take the case of humans who can drink milk and eat dairy products without getting sick.

Believe it or not, the inability to drink milk, called lactose intolerance, is very common in adults around the world. Most have a burned-out version of the enzyme lactase that digests milk and dairy products.

That's in contrast to baby mammals, who need milk to survive and can easily digest it because their lactase enzyme is working fine.

Most adults who trace their ancestry to Asia or Africa cannot digest milk. However, some people from these African tribes are pastoralists, meaning that they keep domesticated cows. These people can drink milk long into adulthood.

Tishkoff wondered: Could there be a connection between raising cows and being able to drink milk as an adult?

She collected blood samples from different tribes in Africa and analyzed their DNA. Her hunch was correct: African populations with recent ancestors who were pastoralists had a genetic change in the gene that produces lactase, allowing them to digest milk.

SARAH TISHKOFF

African populations that domesticated cattle acquired a genetic variation enabling them to digest milk, an advantage passed on to future generations.

Tishkoff also found a link between genetic and archaeological evidence. The genetic variant for lactose tolerance became common in East Africa between 3,000 and 7,000 years ago. Archaeological data suggest that cattle were domesticated in parts of Eastern Africa at the same time.

"To me, this was the ultimate find," says Tishkoff. "It was everything I had been trying to do since college—tying together history, anthropology and genetics."

So, a genetic change—the lactase gene variation—and a cultural change—the domestication of cattle—occurred at the same time and created a selective advantage. People with the genetic change could drink milk, become stronger and have more children, thus passing on the beneficial trait to more individuals and extending the benefit to future generations.

But which came first?

Did African farmers gradually gain the ability to digest milk after domesticating cattle, or did they seek cattle as a source of milk for protein?

Tishkoff is quick to point out that it's not so clear. Right now, no one knows for sure.

Out of Africa

Tishkoff has recently turned her evolutionary focus toward height, weight, taste perception and metabolism. She has lots to do, since very basic traits like these are often the most complex at the genetic level. Height alone, she says, is thought to be controlled by around 100 genes.

story continues on page 8

FIND MORE @

Watch an interview with Sarah Tishkoff at
http://publications.nigms.nih.gov/multimedia/captions/tishkoff-captions.html

JAMES GATHANY, CDC

Parasite-infected mosquitoes can transmit malaria when they bite people.

Mystery Malaria

Malaria, caused by infection with parasite-infected mosquitoes, is rampant in Africa.

The disease also devastates populations in Latin America and Asia, but the parasite culprit in these other regions, called *P. vivax*, differs from the African parasite in many ways.

Although *P. vivax* rarely kills, it does cause severe illness. And because it can lie dormant in the body for many years, those infected could get malaria again—months or years later.

Until now, researchers knew very little about *P. vivax* because they could not get it to grow in the lab. Now, parasitologist **Jane Carlton** of the New York University Langone Medical Center and an international research team have broken new ground by cracking the parasite's genetic code.

Carlton and her team also compared the *P. vivax* genome with that of other malaria parasites and learned that *P. vivax* is unusual in many ways. She hopes that its evolutionary secrets will point to effective ways to control malaria or to eradicate the parasite in affected regions.—*A.D.*

Every answer brings with it a new question.

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Studying genetic variation and metabolism may have important health benefits. In modern humans, the ability to store fat and quickly increase blood sugar can lead to obesity and diabetes—widespread health conditions associated with many other diseases.

Tishkoff explains that in the not-too-distant past, these traits may have been adaptive. In times of food scarcity, the ability to store fat was an evolutionary plus. Now, with abundant food available in countries like the United States, obesity has become common.

Using molecular anthropology, Tishkoff will try to figure out how metabolism-related genetic variants evolved. In this way, she will effectively retrace the paths of many of today's "civilization" diseases like obesity, high blood pressure and type 2 diabetes.

Aside from the obvious health implications, Tishkoff is also driven by the same curiosity we all have.

"I want to know what makes everybody unique," she says.

Now 42, Tishkoff has visited more than 40 countries. She has made more than 10 trips to Africa, sometimes staying for months at a time. Her international travels have inspired a taste for exotic and ethnic foods and a rich appreciation for world culture.

It seems like forever since her first trips abroad, Tishkoff says, adding that she didn't know what to expect that first time in Africa.

"I didn't know where I was going to sleep. I didn't know how I was going to do my labwork. I had no idea if anything was going to work at all," she recalls.

"It was trial and error, and it was miraculous that everything worked so well."

Now, with two young children, Tishkoff can't just pack up and head to Africa as frequently as she used to.

"I miss it terribly," she says. But it hasn't stopped her research there, and Tishkoff still works with African researchers and looks forward to taking her children with her one day.

But for now, her graduate students are the ones peeking through the tent flaps, wondering just what that savanna sound was. ●●●

SARAH TISHKOFF

Sarah Tishkoff wants to know how genetic variation contributes to differences in inherited traits like height and weight.

JACK LIU

Up Close With

Joe Thornton

EVOLUTIONARY BIOLOGIST

"To understand ourselves, we need to understand where we came from."

JOB TITLES

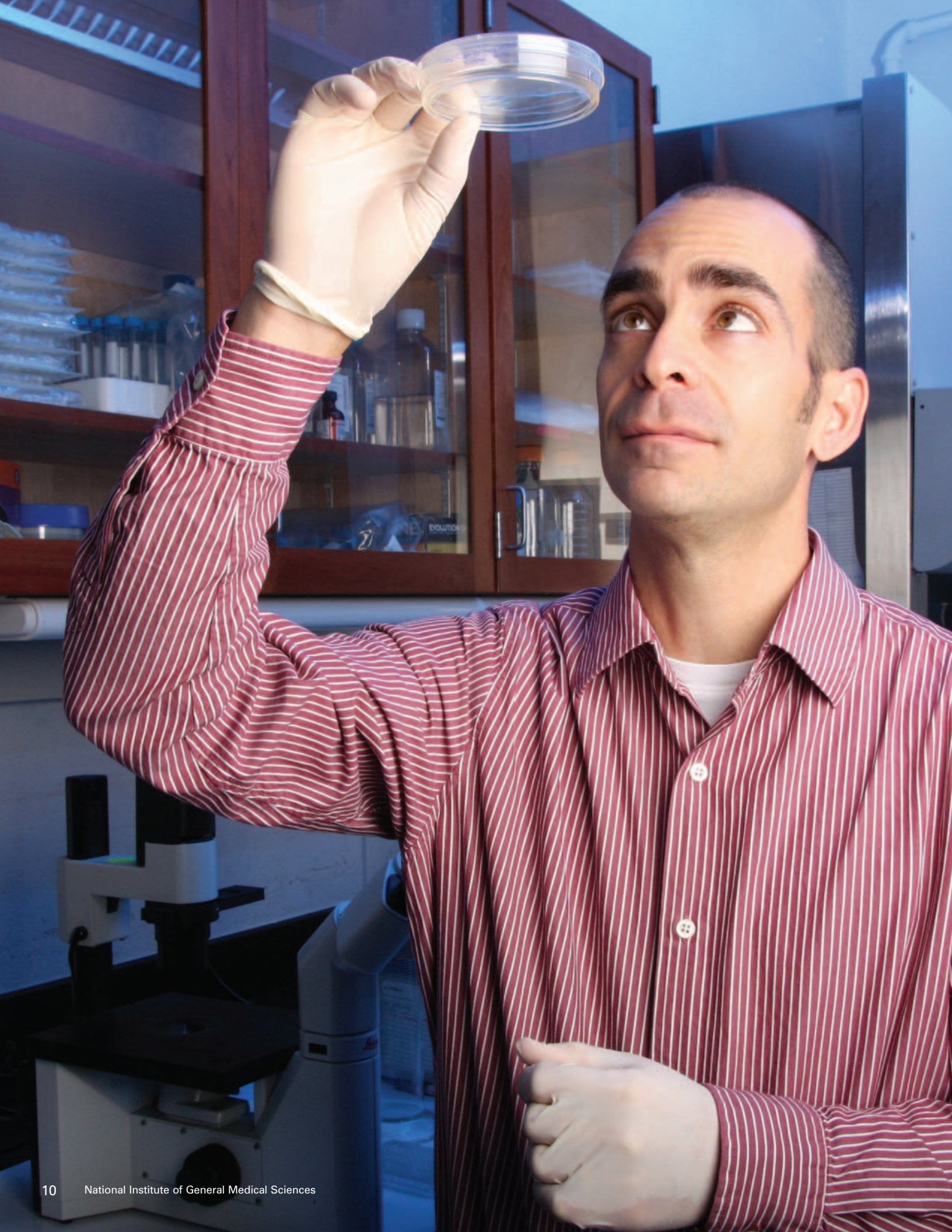
Evolutionary biologist, political activist, writer

PAST CAREER OPTIONS

Rock bassist, English professor

HOW HE SPENDS HIS SPARE TIME

Hiking and skiing Oregon's mountains, playing music with his family, shooting ice-hockey pucks



JACK LIU

Past to Present

BY EMILY CARLSON

Evolutionary biologist Joe Thornton rolls up his sleeve and reaches into a blue and white plastic cooler, just like the one you might take to a soccer game or the beach.

But you won't find cold sodas or turkey sandwiches in this one, and its contents might be among the grossest things you've ever seen.

Inside, sand-colored, snakelike hagfish writhe like hoses bursting with water. They lunge against the side of the cooler and squirm under Thornton's grip as he reaches in with his arm. When he pulls out his hand, it drips with wads of clear, snotty goo.

"A few of these hagfish can fill a 5-gallon bucket with slime in a few minutes," Thornton says. "It's amazing."

Hagfish are slimy, slithery creatures that offer a clue to our deep past. By studying the DNA of hagfish and other unusual animals, Thornton has been able to resurrect 450-million-year-old genes and use them to make equally ancient proteins. This archaic biology, he says, can help us better understand who we are today.

"Science isn't just about shining a bright light on nature and seeing the truth," says Thornton. "It's a way to reflect on the human condition and to see our place in the world."

Thornton's research focuses on our endocrine system, a complex network of glands and hormones found in most animals with well-developed nervous and circulatory systems. Glands like the thyroid, adrenal and ovary make hormones, which travel through the bloodstream as chemical signals that trigger our bodies to do all the things we need to survive.

Thornton studies a specific group of hormones called steroids. Examples include estrogen and testosterone. While known mostly for their role in reproduction, these hormones are also key players in bone and cardiovascular health, our stress response and diseases like cancer.

To do their jobs, all hormones must latch onto specific proteins called receptors on or inside cells. Think of them as part of a lock-and-key system. When you have a match,

JOE THORNTON

Steroid hormone receptors are ancient molecules that are widespread throughout the animal kingdom, including this octopus.

One of the most important aspects of doing science well is

the door opens—triggering a cascade of biochemical changes within the cell.

"Virtually everything a living cell does is controlled by specific interactions between molecules, like hormones and their receptors," explains Thornton. "But despite their importance, we know very little about how these kinds of specific interactions evolved."

Origin of a Scientist

Thornton wasn't always interested in studying steroid hormones. Before graduating from college with a degree in English, Thornton says he wanted to "connect with reality" and began working for Greenpeace, an international organization that educates the public on global environmental problems and solutions for a greener future.

For about 10 years, Thornton traveled to communities with major sources of chemical pollution. Part of his job involved reading about scientific studies and translating the results for local residents.

JOE THORNTON

Evolutionary biologists can learn a lot from jawless, slime-producing hagfish.

Thornton wrote dozens of reports and articles describing the health hazards posed by chemical pollution and arguing for specific solutions. He explained these ideas to the press and testified before Congress.

"I became a specialist in helping communities understand the scientific literature to protect themselves and the environment," says Thornton.

The experience sparked his interest in endocrine disruptors, synthetic chemicals that mimic our natural hormones. They enter the air, water or food supply as byproducts of many chemical, manufacturing and agricultural practices.

Because they are so widespread, everyone is exposed to them. Endocrine disruptors have been linked to reproductive problems, impaired immune function and various cancers.

Endocrine disruptors affect animals, too. Scientists suspect they're responsible for a decline in Florida's alligator population, the feminization of male marine organisms, and damage to fish and bird populations.

Alarmed by these potential threats to our environment and our bodies, Thornton started asking questions of his own.

Why do these chemicals have such a big effect on biology? How did hormones and their receptors evolve? Can we predict which chemicals are likely to cause endocrine disruption if we have a better basic understanding of receptors?

"When it came time for me to move on [from Greenpeace], I was so fascinated with the science that I wanted to pursue it directly," says Thornton.

So he went back to school and took his first biology class at age 30. Now 43 and running his own lab at the University of Oregon in Eugene, Thornton is finding the answers to the questions that drove him to science and environmental activism.

Molecular Time Machine

Like a historian studying the past to make sense of current events or an anthropologist examining ancient cultures to understand today's customs, Thornton goes back in time to piece together the evolution of hormones and their receptors. His main objective: to unravel the history of our endocrine system. The findings could help other researchers understand the origins of hundreds of diseases related to the endocrine system and identify new ways to treat or prevent them.

Thornton starts by studying hormone receptors in living animals. On any given day, Thornton's lab might have a cooler full of undulating octopi, jawless lampreys, predatory worms, sea slugs or the slimy hagfish. These organisms, he says, occupy critical spots on the evolutionary tree of animal life for understanding the evolution of the endocrine system. Each species shares an ancient common ancestor with humans and split off the evolutionary tree around the time that certain receptors first evolved.

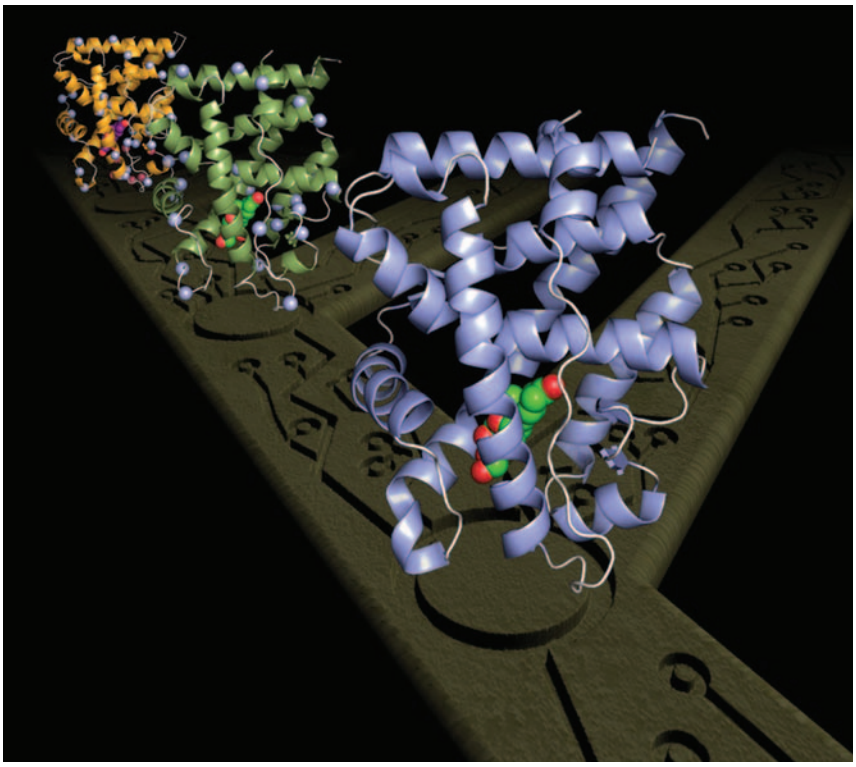
"My kids like coming in and seeing us dissect these fantastic creatures," says Thornton, whose children are 8 and 11.

FIND MORE @

Watch hagfish dance and make slime!

http://www.uoregon.edu/~joet/hagfish.html

being able to communicate your findings.



JOE THORNTON

Colored spheres show which pieces of an ancestral receptor evolved over time (back to front). Joe Thornton resurrected an ancient version of the receptor in his lab.

"I think that exposure to what I'm doing gives them an appreciation for how old and diverse life on Earth is," he adds. (And it makes their dad seem forever young.)

Thornton extracts genetic material and hormone-containing serum from the hagfish and other organisms. Then, he examines the DNA to find ancestral receptor genes.

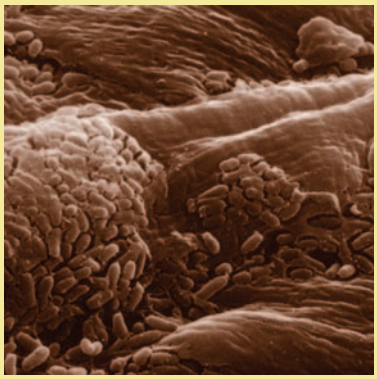
He does this with the help of computers and other molecular biology tools. Thornton looks in huge databases of DNA sequences to search for similarities between the gene sequences from his living creatures and those of hundreds of other receptors cataloged in the database. Software programs can turn this information into phylogenies—family trees that show varying degrees of relatedness.

For centuries, these "trees" were based mainly on visible traits, such as bone structure, wings or the presence of fur. But as more tools for studying DNA have become available, evolutionary trees have expanded to include genetic information.

Thornton then uses biochemistry techniques to actually synthesize the DNA for ancient genes and molecular biology methods to find out how they functioned. The search has taken him back 450 million years to the time of the last common ancestor of you…and a hagfish.

Back then, the only vertebrates around were fish without jaws. The climate, which had been quite warm, cooled. Water temperatures dropped to about what they are today, making

story continues on page 14



DARLYNE MURAWSKI, NATIONAL GEOGRAPHIC SOCIETY

This microscopic image shows bacteria living underneath a human toenail.

Bugs On Us

Believe it or not, bacteria are not so bad—they actually play key roles in our health. Bacteria help us digest food, provide vitamins we can't make ourselves, and act as part of our immune defense.

To understand more about the role of bacteria on human skin, scientists need to know which ones are there and whether they differ much between people. Geneticist **Elizabeth Grice** of the NIH in Bethesda, Md., took an inventory of skin bacteria from several healthy people.

Grice collected bacteria by swabbing, scraping or cutting out a tiny piece of inner elbow skin. After analyzing the genetic material in all the samples, Grice found a common subset of elbow skin microbes in all the people tested. But the bacteria were very different from those in the intestines and other skin areas of the same people, revealing an extraordinary diversity of life in and on our bodies.

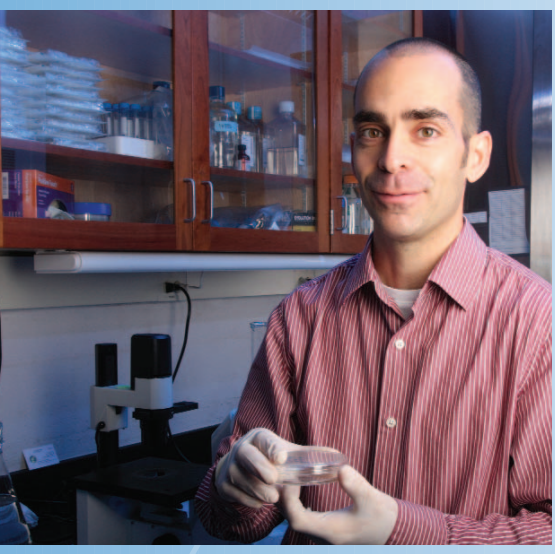
The evolutionary question of how and why bacteria share our bodies is likely to be important for modern-day health. Altering the balance of skin bacteria, for example, may promote health and fight disease.—*A.D.*

Joe the Scientist

I became a scientist for two reasons. I wanted to use knowledge to help protect the environment and human health. And I wanted to contribute to culture—our shared understanding of ourselves and our world—the same way writers and artists do.

Think of an interesting or controversial issue, and science probably has something important to offer on it. For some issues, like global warming or high breast cancer rates, science's role is obvious. But science has a lot to say about less technical questions, too, including some that go right to the core of our self-understanding.

Consider the biggest one of all: What does it mean to be human? Writers and philosophers have been wrestling with this one for centuries. But scientific discoveries have radically reshaped the answers we can give today.



JACK LIU

We have learned that we share many behaviors—and even more aspects of the nervous and endocrine systems that produce them—with chimpanzees, zebrafish and even sea slugs. In my lab, we are discovering precisely when and how some of these features first evolved.

Big cultural issues will never be answered by science alone, because they also involve values, ethics and spirituality. But our biology is a significant part of who we are, and science is the best way to generate knowledge about nature.

When a scientific discovery changes the lens through which we see ourselves and the world, we can appreciate it the same way we do a van Gogh painting or a Shakespeare play.

My job is to go to the lab each day and try to continue that tradition.

How cool is that?—*Joe Thornton*

By doing science

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the sea a more hospitable environment. That was a good thing, because the ocean offered just about the only real estate.

It might seem nearly impossible to imagine we'd share anything in common with the ocean dwellers that lived hundreds of millions of years ago. But Thornton has a fridge of tiny test tubes and incubators with petri dishes to prove that we do.

Each tube contains millions of copies of resurrected receptor genes. Cells living on the plastic plates in the incubator produce the receptor proteins encoded by these ancient genes. Thornton and others can use these proteins to see how they respond to different hormones. By changing the ancient DNA, they can retrace the process by which evolution tweaked the receptors' sensitivity to various hormones.

With the help of a technique called structural biology, they can also see how the receptor proteins' shapes changed over time. Under certain conditions, proteins form crystals that can be bombarded with high-energy X-rays to determine their shape. By using these methods, Thornton has determined the precise atomic structure of several ancient receptors and has shown how that structure changed as the receptors evolved to bind new hormones in a lock-and-key fashion (see image, page 13).

Evolution Explained

Often called the father of evolution, biologist Charles Darwin thought of evolution as a tree where all species branched from a common ancestor. As nature selected for certain advantageous traits, he reasoned, organisms with helpful genetic changes survived to pass those genes to offspring.

we're contributing to culture.

Repeated over long periods of time, populations would adapt to their environments. Isolated populations that evolve independently would diverge, eventually forming new species.

Can this explanation of such gradual adaptation apply to the evolution of systems in which the function of the whole requires all the parts to be present? If a hormone needs a receptor and a receptor needs a hormone, then how do you explain the evolution of one without the other?

Or, for that matter, how do you explain the evolution of any complex system with many parts?

The explanation is beautifully simple, Thornton says.

"These systems were assembled by evolution in a piece-by-piece fashion from molecules that once did other jobs." And his research tells the whole story, from beginning to end.

Here's what Thornton has learned. In distant times, there was a single ancient hormone receptor that worked in partnership with a single ancient hormone. That receptor was only as specific as it needed to be at that time. Other hormones with slightly different shapes could have activated it, but only one of these was actually available.

Then, about 450 million years ago, the gene for the ancient receptor got duplicated. Over millions of years, the two copies gradually amassed different sets of genetic changes, leading to two different receptors present in most vertebrates living today.

One of these duplicate receptors retained the ancestral shape and continued to partner with the ancient hormone and other similarly

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Over time, genetic changes create new species on the evolutionary "tree of life."

shaped hormones that emerged later in evolution. Today, this receptor interacts with aldosterone, the hormone that regulates salt and water balance in humans and four-legged animals.

As for the other duplicated copy, Thornton has tracked the changes in its DNA over time. He showed that two mutations altered the receptor's shape in a way that changed its lock-and-key fit. As a result, the receptor lost its ability to interact with the ancestral hormone but gained an ability to partner with cortisol, a hormone that today controls our response to long-term stress.

Thornton explains that the specific hormone-receptor pairs we have in our bodies today came about by subtle modifications of hormones and receptors that already existed for different purposes. He calls this idea "molecular exploitation."

"It's taking old parts and reusing them for new purposes by bringing them into newly built systems," he says.

Because of modern scientific tools and technologies like ancestral gene resurrection, Thornton says evolutionary biologists can now study evolutionary changes and the processes driving them in a much more detailed and decisive way than has ever been possible.

Citizen Scientist

But understanding evolution can also help us to understand the present and future, Thornton says. The concept of molecular exploitation, for example, helps him explore endocrine disruption and try to make sense of it.

The discovery that hormone receptors are only as specific as they need to be at any one time in evolution, he says, explains why they are susceptible to disruption by pollutants.

"The chemical industry has produced tens of thousands of chemicals in the last 60 years, but our receptors evolved hundreds of millions of years ago and have not had a chance to evolve resistance against them," he says.

Could our bodies evolve to shut out endocrine disruptors? That process could take thousands of generations, "and I'm not willing to wait for evolution to solve the problem for us," Thornton says.

So Thornton does what he can for the environment. After his time with Greenpeace, Thornton wrote a 600-page book, *Pandora's Poison*, outlining the health dangers of chemical pollution. It was printed on chlorine-free paper.

On a more personal level, Thornton and his family try to leave a small environmental footprint. When he and his wife built their house, they avoided using materials containing

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Some African tribes live in mountainous regions, while others are nomadic or live in cities.

Lifestyle Effects

In many ways, our DNA is like a fossil record, accumulating genetic changes due to lifestyle, climate and other shifts.

Geneticist **Greg Gibson** of North Carolina State University in Raleigh wanted to know more about how the environment we live in shapes our DNA.

He sampled blood from subgroups of Moroccan Amazighs in Northwest Africa and then measured the activity of several hundred genes. The Amazighs, while genetically similar as an ethnic group, live very different lives as subgroups. Some wander as nomads, while others have settled in the mountains or in coastal cities.

Gibson discovered that the activity of about one-third of the Amazigh white blood cell genes varied among the three subgroups, suggesting that environmental triggers cause genes to be read differently according to region.

Tracking the interplay between genes and the environment will be key to understanding how modern-day diseases gain a foothold, Gibson thinks. And intercepting these interactions may help researchers find new ways to steer clear of disease. —*A.D.*

How did hormones and their receptors evolve?

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polyvinyl chloride (PVC, a type of vinyl). The Thorntons buy organic food and leave the car at home as often as they can.

"We try to be as low-impact as possible," Thornton says, but admits, "We're not perfect. Very few families are."

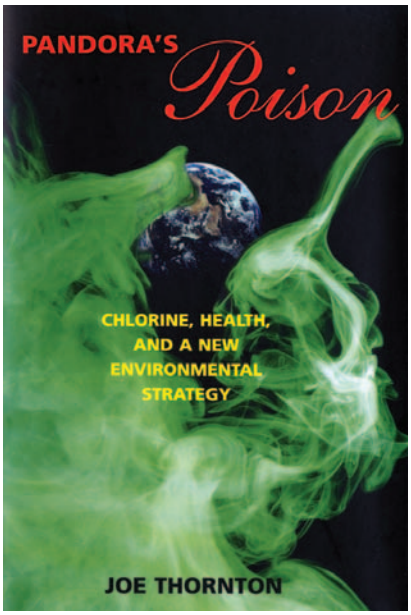
He assists environmental groups, and he uses his knowledge about the evolution of hormones to teach a course that inspires students to explore the intersections of science and policy.

"I take every opportunity I can to discuss how research can affect our understanding of the effects of chemicals on health and what we can do about it," says Thornton.

He considers sharing his work and its implications with the public and the broader research community to be among the most crucial—and rewarding—jobs of a scientist.

"One of the most important aspects of doing science well is being able to communicate your findings, to tell their story," he says. "A great experiment won't contribute anything if you can't make other people understand it and appreciate why it's important."

Thornton says this perspective didn't come from working in the lab. It came from reading literature, writing a book and simply talking to people.



JOE THORNTON

Joe Thornton's concern about chemical pollution led him to write the book *Pandora's Poison*.

These activities also prepared him well for thinking about science and doing experiments, he says.

Thornton believes that scientists leave an important mark on society.

"By doing science, we're contributing to culture in the same way novelists and philosophers and historians and artists are," Thornton says.

"Science allows us to reflect on our condition and our place in the world, and what it means to be who we are."

FIND MORE @

Listen to Joe Thornton talk about his research at http://publications.nigms.nih.gov/multimedia/thornton.html

EXPLORE IT **PUZZLE IT** FIND IT

What is the process by which advantageous traits are passed to offspring?

What are the building blocks of DNA?

How many genes are thought to control height?

What do hormones latch onto to do their jobs?

Who are our closest living animal relatives?

Who is called the father of evolution?

What field of science is the broad study of humanity itself?

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