THE PICASSO OF DNA

George Church is learning to redraw the genetic code. Medicine may soon look totally different —and so could *Homo sapiens.*

Here is how to get an appointment with George M. Church, professor of genetics at Harvard Medical School, director of four organizations devoted to genomics, cofounder of four biotech firms within the past four years, scientific adviser to 17 ultralow-cost genome sequencing companies, and founder of the Personal Genome Project:

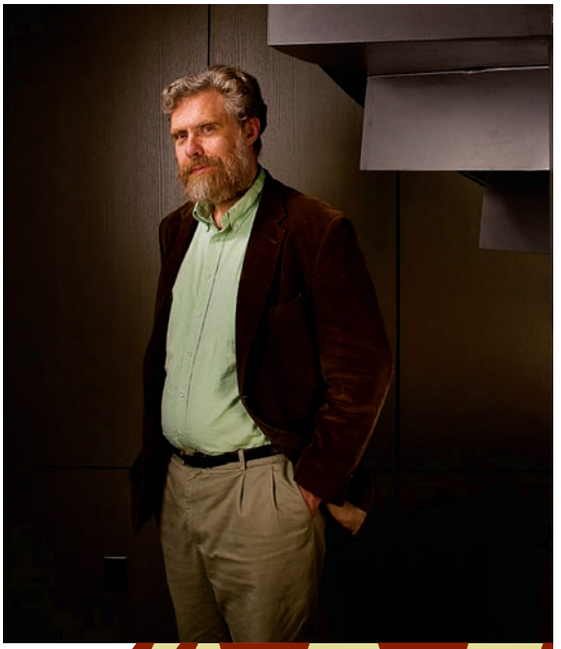
First, you send him an e-mail requesting a meeting. He will reply with the URL for a Web site that lists his current schedule. This, when printed out, proves to be a 10-page, single-spaced document in very small type that starts with "January 1, 2009: Holiday, New Year's Day" and ends with "September 17, 2010: International Steven Hoogendijk Award 2010 for G. Church, Rotterdam, Netherlands." Searching through hundreds of entries—as many as nine falling on a single day—you try to find an uncommitted hour. If successful, you contact either of Church's two administrative assistants to propose a date, time, and place. Then you hope for the best.

When the magical day arrives, the first question I ask Church is how he can possibly direct, create, advise, and mastermind so many projects (as well as teach classes and supervise Ph.D. dissertations) without going crazy. "Well, I think it's an assumption that I'm not crazy," he says. "They all seem pretty much the same to me. They're all integrated, and I guess what we try to do is—we try to do integration."

If Church's career has a single integrating theme, it is finding ways to apply the machinery of automation to the molecular basis of life, the genome. His infatuation with computers goes back to grammar school in Clearwater, Florida, when, at age 9, he built an electronic computer for a science fair. Genetics entered the picture in the spring of 1974. Then an undergraduate at Duke, Church typed into a computer all the transfer RNA sequences that were available at the time and folded each one into a three-dimensional structure, as RNA molecules were known to do. "I became obsessed with sequencing," he says. The obsession never faded. Today his myriad projects all emerge from his impulse to know, unravel, depict, use, and—better yet—tinker with and even create the RNA and DNA codes that constitute the software of living systems.

That ambition has resulted in a raft of Church-inspired technological innovations. His automated genome-sequencing machine is driving the price of mapping a person's entire genetic

TEXT BY **ED REGIS** PHOTO ILLUSTRATIONS BY **ANN ELLIOTT CUTTING**



> "WHEN SCIENTISTS GOT SERIOUS ABOUT DECODING THE HUMAN GENOME, CHURCH HELPED START THE PROJECT."

code down toward $1,000, almost unbelievably cheap considering that, less than a decade ago, the government-funded Human Genome Project spent roughly $3 billion to sequence a single genome. Low-cost sequencing has allowed Church to embark on a second venture, the Personal Genome Project (PGP), which aims to sequence the genomes of 100,000 volunteers for free. The project would provide the first extensive genome database that matches DNA to a wide range of traits—not merely physical attributes like height or eye color but also disease histories and personalities. The idea is to help inaugurate the field of personalized medicine, in which each individual would receive preventions and treatments tailored to his or her specific genetic makeup, along with predictions of future health issues.

The third major item on the Church agenda is to develop the ability to rewrite life's software, giving us the power to reprogram organisms to do things that are radically different from what they do normally. Such wholesale reprogramming would be prohibitively expensive with what he calls the "laborious and outdated" techniques of conventional genetic engineering, which make one alteration at a time to the DNA of organisms. Church therefore went out and invented new techniques. His latest creation is a set of tools and methods that he calls multiplex automated genome engineering, or MAGE. It introduces many modifications to a genome simultaneously, opening up the possibility of designing novel genomes—in essence, creating new forms of life. One of Church's most promising projects is to engineer bacteria that can produce jet fuel or gasoline from wood pulp or cornstalks. Another would tweak the DNA of microorganisms so that they metabolize carbon dioxide, turning it into a beneficial substance.

That is only the beginning of what MAGE could do. Ultimately Church's tools of synthetic genomics could lead to significant, even portentous, changes to plant, animal, or human genomes. They could turn back the clock of evolution: Church has proposed a way of altering the elephant genome until it is identical to a woolly mammoth's, or turning a human's DNA into a Neanderthal's. These tools could also be used to make people resistant to viruses, lengthen life span, and increase human intelligence. They could advance evolution—our evolution—to places it has never gone before.

George Church is a large specimen of a man, with a full beard and somewhat untamed hair. Now in his mid-fifties, he is rather easy to get to know because of his "Unauthorized Autobiography and Infrequently Asked Questions," which appears on his Harvard-hosted Web site. Here you will find, among other things, his online medical records, dietary notes, baby picture, signature, and random interests (which include waterskiing, rock climbing, and turtle breeding), as well as the exact latitude and longitude of his home and a map of his neighborhood.

For a man of such unusual talents and attainments, Church had a relatively conventional life until he entered college. He graduated magna cum laude from Duke University in two years, then proceeded to flunk out of graduate school. The reason, he says, is that he neglected "boring" course work in favor of lab research, which resulted in five papers published in peer-reviewed journals. That got him accepted to a doctoral program at Harvard, where he studied with molecular biologist Walter Gilbert. In 1980 Gilbert won a Nobel Prize for his work sequencing DNA.

Church thrived in Gilbert's lab. In 1977 he developed a way of automating a key step of Gilbert's DNA sequencing method. DNA strands are made up of combinations of four bases, molecules that are denoted by the letters A, T, C, and G. Sequencing DNA—reading out all the letters along the double helix—was a laborious process in which lab technicians used pipettes to deposit DNA samples onto the surface of a gel. The samples were labeled with radioactive isotopes, which meant that each individual base (the A, T, C, or G) produced a visual signature on film. It was up to the experimenter to read and record the sequences in the proper order. Church, who always wants to do things quickly, preferably by automation, figured out how to make a computer read the sequences. He did not yet have his Ph.D., but he was already making a major contribution to genetics.

He kept going. During the early 1980s he decided that he could speed the process further by "multiplexing" the DNA strands, sequencing small segments of them simultaneously. In the sort of lightning-bolt realization that often heralds a breakthrough, Church saw an analogy between biochemistry and electronic communications. Engineers can transmit many messages at once through an optical fiber by tagging each one with a number and sorting things out at the receiving end. In the same way, Church figured out how to break a long strand of DNA into pieces and tag each piece with an enzyme. That way, he could sequence all the pieces at once, getting the job done quickly, and reassemble the original DNA at the end.

It was another groundbreaking achievement, and it made Church a leading figure in genomics research. In 1984, when scientists began to get serious about starting the Human Genome Project, Church was the only scientist who attended all three of the early meetings that laid the project's foundation. "George has been perhaps the most creative single scientist in pioneering next-generation DNA sequencing," says Leroy Hood, founder of the Institute for Systems Biology in Seattle.

Despite these advances, DNA sequencing remained so slow and expensive that the notion of decoding even a single

SHAWN G. HENRY

human genome seemed monumentally difficult. In 1994 the Genome Therapeutics Corp., one of three sequencing centers that Church helped establish, produced the first genome sequence sold commercially: The company decoded the DNA of *Helicobacter pylori,* the bacterium that causes peptic ulcers (for the full story on this bacterium, see the DISCOVER Interview on page 66). The Swedish drug company Astra AB, which wanted to use the DNA sequence to design new antimicrobial agents, bought the rights to that single genome for $22 million. At that price, sequencing was hardly ready for the masses.

One reason sequencing was slow was that it was difficult to identify all the individual nucleotides, or structural components, within a single DNA molecule. Doing so reliably required making millions of copies of the same DNA strand by cloning it in a bacterium, sort of like printing out many versions of a document and then comparing them all to make sure there are no typos.

The technique for making copies was the polymerase chain reaction (PCR), which was used to replicate DNA for genetic studies or forensic analysis. At the time, PCR was normally done by lab bench–size machines using a complicated process. First the DNA molecules were heated to break them apart into their two separate strands. Then DNA polymerase, an enzyme, was added to make copies that were complementary to each of the original DNA strands. Finally the whole process was repeated several times. In 1999 Church and a graduate student at MIT, Robi Mitra, developed a streamlined version of this technique. Using clever chemistry, they performed millions of PCR operations simultaneously on a single glass microscope slide. The end result were "polonies," entire colonies of DNA molecules that had been amplified via PCR.

This was the breakthrough that led Church to create the Polonator, a high-speed, relatively inexpensive automated sequencer. (The name of its latest incarnation, the Polonator G007, is a reference not only to James Bond but also to the year of its release, 2007.) The Polonator was a landmark machine both for its low cost—$170,000, one-third the cost of anything else on the market—and for the fact that the machine is fully open to the user, who may reconfigure it at will. "Usually manufacturers make all these threats about voiding warranties, intellectual property, this and that," Church says, "whereas we actually want people to feel that they are enabled to improve the machine if they want to. Users can change the software, the hardware, the chemicals."

> "WHY NOT ASSEMBLE A DATABASE OF GENES CORRELATED WITH PEOPLE'S TRAITS? OTHERS COULD USE IT TO MAKE SMARTER LIFE CHOICES."

The Polonator became one of the basic technologies behind Church's Personal Genome Project, unveiled in October 2008. Initially the idea had been that every person would want to have his or her genome sequenced, if only for predictive reasons. Medical analysis of your genome could tell you what diseases you were genetically predisposed to; in some cases that knowledge would be actionable, meaning that you could take steps against contracting those diseases. For instance, if you knew as a teenager that you were genetically disposed to adult-onset diabetes, you might alter your dietary regimen many years beforehand. "We already have 1,530 highly actionable, highly predictive genetic associations," Church says. (You can review them on the Web at genetests.org.) Later, another rationale emerged for having one's genome sequenced: personalized medicine. The idea is that your doctor would be able to browse your genome in the examining room and select treatments, medications, and preventive strategies suited to your individual biology.

Soon Church had another far-reaching thought. Why not assemble a wide database of personal genomes and genes that were correlated with people's traits? Other people with the same genetic quirks could use those correlations to make smarter life choices. If, say, talented musicians tended to have the same set of genes, and if your child happened to have those genes too, music lessons might be a good idea. In addition to sequencing DNA, Church decided to ask participants about their life experiences and add that information to the database. "We shouldn't let genetics be destiny," he says. "But if your genome tells you, 'Hey, here's a hit; you might be really good at this thing,' it might encourage you to try really hard on something that you otherwise would have missed."

The fly in the ointment, Church thought, was that in order for the information to be useful, all of it would have to be publicly available. That meant test subjects would have to expose everything—their genes and traits, their strengths, foibles, and personal idiosyncrasies—on the Web for all to see. Revealing this information would make it impossible to keep the identities of the participants secret. Church worried about how he could preserve their privacy. The solution to this conundrum, he says, "struck me like cutting the Gordian knot." His idea: Recruit people who, like Church himself, were not shy about divulging details of their lives. "Instead of falsely promising privacy, which was where we were headed, let's promise them that their data *won't* be kept private and make sure they know what they're getting into." Participants would have to read and sign a consent form and, to make sure they had understood it, would be required to pass an online test.

The first 10 volunteers of the Personal Genome Project, known as the PGP-10, included Church himself, technology oracle Esther Dyson, and Harvard psychologist Steven Pinker. All of the volunteers' personal information—vital signs, allergies, medications, medical history, ethnicity, ancestry, traits, facial photographs, and yes, their genomic data sets—can be viewed, downloaded, and used without restriction at personalgenomes.org.

The Personal Genome Project was officially cleared to expand beyond the original 10 participants on DNA Day—April 25, 2009, the 56th anniversary of Watson and Crick's letter to the journal *Nature* on the double-helix structure of DNA. Any U.S. resident who is 21 or older and is willing to share genetic, medical, and life experience information may apply. If you are accepted, your genome will be sequenced for free. Financing has come in part from Google and other corporate sponsors, as well as from Church and various private donors. "In 10 years the personal genome could be one of the most important data sets for each individual patient," Hood says.

Before the Personal Genome Project had gotten off the ground, Church was already off and running on the next big


dna: Deoxyribonucleic acid
bases: Adenine
Thymine
Guanine
Cytosine
structure: Double Helix
22-26 Angstroms
ACGT
DNA
ATGCC TAATT

thing. Beyond his corner office in Harvard Medical School's New Research Building, with its floor-to-ceiling windows and imperial view down the Avenue Louis Pasteur, Church and his colleagues were busily developing MAGE, his shotgun approach to genetic modification.

The idea behind MAGE is to use the same kind of multiplexing technique that Church developed for sequencing (that is, breaking up a genome and tagging its constituent parts with enzymes) but then to add additional steps to insert, delete, and substitute passages of DNA. Instead of just copying existing sequences of DNA, MAGE could write new ones.

Church and his colleagues demonstrated the technique, in work published in *Nature* last July, by modifying the common bacterium *E. coli* to produce lycopene, an antioxidant found in tomatoes, watermelons, and red peppers. Scientists had previously used conventional genetic engineering techniques on *E. coli* to make it produce insulin and other substances, but they had typically targeted only one gene at a time. MAGE allowed Church to simultaneously target 24 genes, each playing a role in the production of lycopene.

Church started by producing thousands of variations of the target genes, concentrating on those passages of DNA that regulate how the genes interact with ribosomes, the parts of the cell that take information from the genes and use it to make proteins. With MAGE, he inserted these variations into the genomes of a large batch of *E. coli* cells. He began by using an electric current to open holes in the bacteria's cell walls. Then he sent the new gene variants into the cell, where the bacteria's own machinery for self-assembling DNA took over and incorporated the genes into the genome. In 24 hours Church was able to produce 4 billion different *E. coli* genomes. From there it was a relatively simple matter to select the variants that produced lycopene most prolifically.

This proof-of-concept experiment opens up staggering possibilities. Soon it may be possible to produce entire novel genomes or to make numerous changes in existing ones. In the lycopene experiment, Church did not know which modifications to make in the *E. coli* genes to get the result he wanted, but the technique could just as easily be used to introduce specific sets of changes into a genome, inserting and deleting hundreds or thousands of genes

> "ONCE YOU PUT A FRESHLY MINTED NEANDERTHAL GENOME IN A CELL, ALL YOU NEED TO DO IS IMPLANT THAT CELL INTO THE UTERUS OF A CHIMP."

at once. This capability would allow scientists to give an organism's DNA an extreme makeover, rather than just tinker with it.

A genetic sculptor could then alter physical traits or disease vulnerabilities that are not assigned to merely one or two stretches of DNA. For instance, a common lab mouse lives 2.5 years, on average, but a naked mole rat lives 25. That difference in life span might be governed by thousands of genomic variations, but soon we could have access to all of them. Once researchers identify the genes that contribute to the naked mole rat's longevity, they could make analogous changes in the genome of human adult stem cells. Over the generations, it should be possible to progressively increase the human life span.

Church thinks MAGE may also open the door to the ultimate antiviral strategy. In order to replicate and do their damage, viruses hijack the genetic machinery of their host organisms. To thwart the invaders, you could make certain alterations in the genetic code of the host's cells. If you could figure out which modifications work, and if you could also find some gene-therapy technique for delivering those changes to the host cells, you could in principle make a person (or livestock, or any other creature) inherently resistant not to just one virus but to all viruses, even those that have not been discovered.

MAGE could also be used to reverse-engineer the genome of a species, transforming it into the genome of another. On February 12, 2009 (the 200th anniversary of Charles Darwin's birth), paleogeneticist Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Germany announced that he and a team of researchers had sequenced about 63 percent of the Neanderthal genome. Afterward, Church told *The New York Times* that "a Neanderthal could be brought to life with present technology for about $30 million."

Church would start by breaking up the human genome into 30,000 or so separate chunks, each about 100,000 base pairs long. Once Pääbo's team had fully sequenced the Neanderthal genome, Church would use a computer to compare that genome, chunk by chunk, to the modern human genome to see where and how the two differed. Where the Neanderthal had gene variants for a larger skull, for instance, Church would use MAGE to modify the nucleotide sequences that constituted those genes in one or more of the chunks of human DNA. He would keep doing the same with the genes underlying every trait that made Neanderthals different from humans. Finally, he would put all the separate, reworked genetic chunks back into a human stem cell. Each would find its own way, via the cell's natural ability to assemble DNA, to the proper location. The result would be a freshly minted Neanderthal genome in a living cell. From there, creating a living, breathing Neanderthal would merely require implanting the cell into the uterus of a chimpanzee, or perhaps into an adventurous human female.

The implications are so mind-blowing that I have to ask, "You don't see anything sacrilegious about this?"

"I wouldn't say sacrilegious," Church responds. "Humans have been manipulating humans in many ways for many years."

Despite juggling all of these projects, Church does not feel rushed. On the contrary, he feels that he has had a great deal of time to think through the implications of his work. "I'd like to see us have basic enabling technologies that improve our quality of life, so we can safely analyze and engineer biological systems, make biofuels, and have personalized medicine. And have deeper self-knowledge," he says.

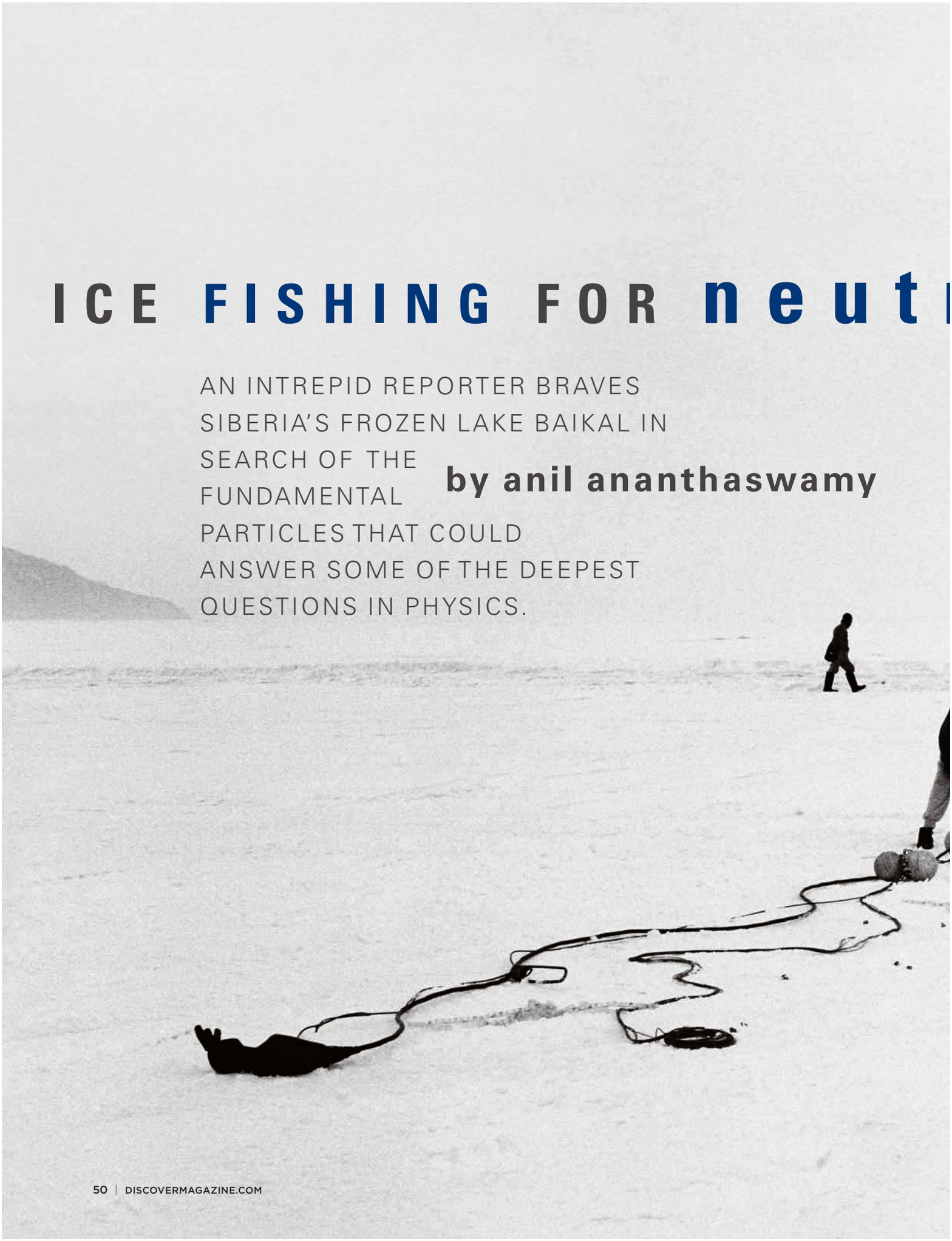
Resurrecting a Neanderthal strikes Church as a constructive project, not a lark. "You could argue that it would give us an inkling into an alien intelligence possibly greater than our own, one that could save our species someday or keep us out of intellectual ruts," he says. "Or Neanderthals might be resistant to some key diseases like AIDS, smallpox, tuberculosis, or the next pandemic. You might even be able to converse with them at length."

The Neanderthal, though, would first have to contact one of Church's two secretaries.

ICE FISHING FOR neut

AN INTREPID REPORTER BRAVES SIBERIA'S FROZEN LAKE BAIKAL IN SEARCH OF THE FUNDAMENTAL PARTICLES THAT COULD ANSWER SOME OF THE DEEPEST QUESTIONS IN PHYSICS.

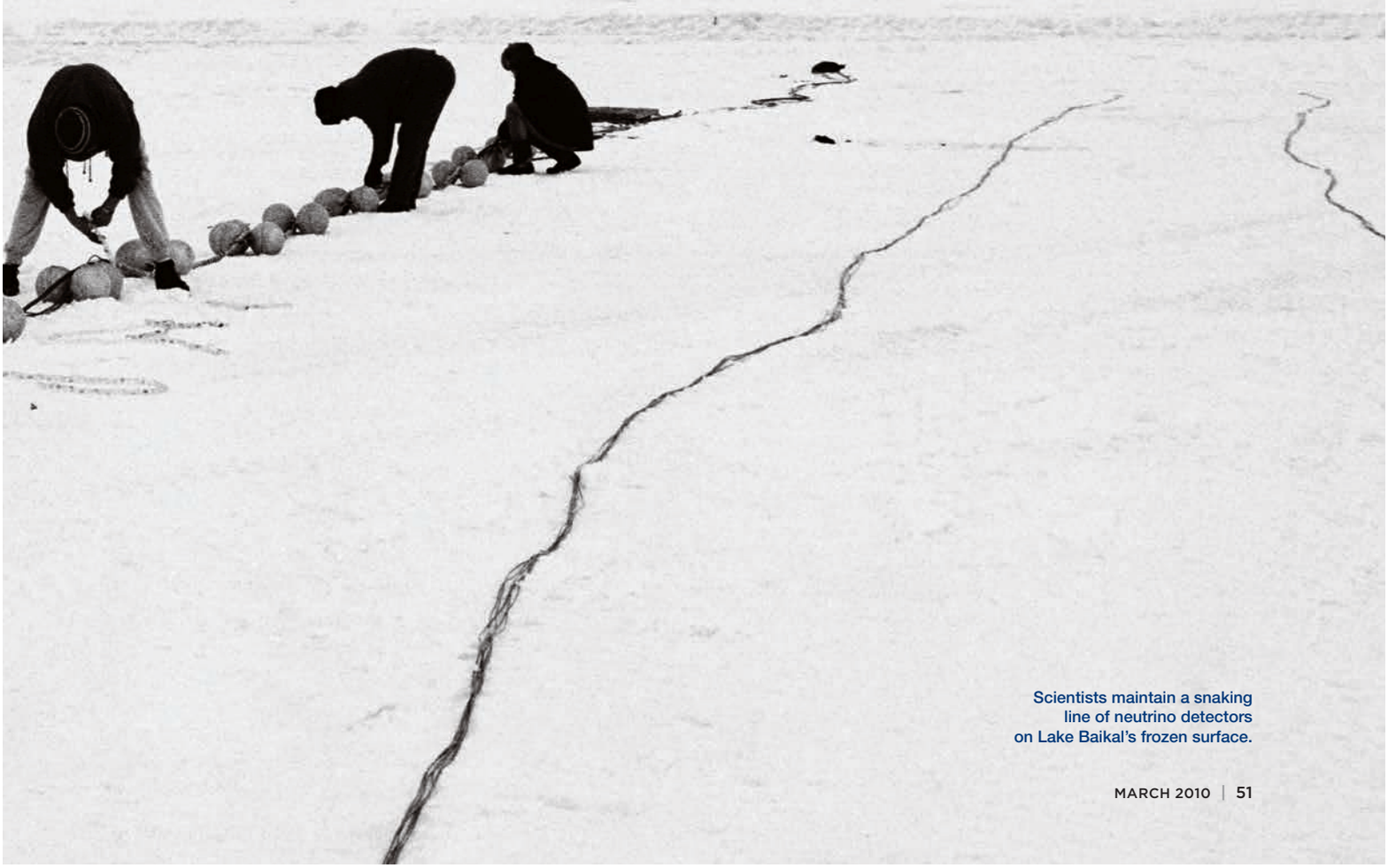
by anil ananthaswamy



rinos

about 25 million years ago, Earth parted in the southeast corner of Siberia. Since then, countless rivers have converged on the gaping continental rift, creating the vast body of water known as Lake Baikal. Surrounded by mountains, this 400-mile-long inland sea has remained isolated from other lakes and oceans, leading to the evolution of unusual flora and fauna, more than three-quarters of which are found nowhere else on the planet. Russians regard it as their own Galápagos. The lake contains 20 percent of the world's unfrozen freshwater—or just a little less during the severe Siberian winter when, despite its enormous size and depth, Baikal freezes over.

On one such winter's day, I found myself on the lake near the town of Listvyanka, which is nestled in a crook of the shoreline. I was in an old van that was



Scientists maintain a snaking line of neutrino detectors on Lake Baikal's frozen surface.

trying to head west, not along a coastal road—for there was none—but over the ice. The path, however, was blocked by a ridge. It looked like a tectonic fault: Two sections of the lake's solid surface had slammed together and splintered, throwing up jagged chunks of ice. The driver, a Russian with a weather-beaten face, peered from underneath his peaked cap, looking for a break in the ridge. When he spied a few feet of smooth ice, he got out and prodded it with a metal rod, only to shake his head as it crumbled: not thick enough to support the van. We kept driving south, farther and farther from shore, in what I was convinced was the wrong direction. The van shuddered and lurched, its tires crunching on patches of fresh snow and occasionally slithering on ice. The ridge continued as far as the eye could see. Suddenly we stopped. In front of us was a dangerous-looking expanse littered with enormous pieces of ice that rose from the lake's frozen surface like giant shards of broken glass.

The driver seemed to be contemplating going around them to look for thick ice that would let us reach our destination, an underwater observatory operating in one of the deepest parts of the lake. But if he did that, we'd get even farther from the shore, and it would take just one punctured tire to strand us. The sun was little more than an hour from setting, and the temperature was falling. I couldn't ask the driver if he had a radio or a phone to call for help, since he did not speak a word of English and the only Russian phrase I knew was *do svidaniya*. The last thing I wanted to say to him at this point was "Good-bye."

Thankfully, he decided to turn around. We drove along until we came upon vehicle tracks that went over some ice covering the ridge. The driver swung the van westward and cleared the ridge, and soon we were racing across the lake at a speed that turned every frozen lump into a speed bump. The van's front rose and fell sickeningly, rattling the tools strewn around on the front seat. I worried that the ice would give way and we would plunge into the frigid waters below. But it remained solid, and the van, despite its appearance, was in fine mechanical fettle, its shock absorbers holding firm. In the distance I spied a dark spot on the otherwise white expanse. As we approached, the spot grew to its full size, revealing itself as a three-foot-high Christmas tree. We still had 20 miles to cover, and the sun would soon disappear below the icy horizon. But now that we had found the Christmas tree, I knew we were fine.

I had first seen the tree two days earlier, with Nikolai (Kolja) Budnev, a physicist from Irkutsk State University, and Bertram Heinze, a German geologist. We were headed to the site of the Lake Baikal neutrino observatory, which lay deep beneath the ice. We had just driven onto the lake from the shore near Listvyanka when Heinze asked, "When does the ice start breaking?"

"Sometime in early March," Budnev answered. My heart skipped a beat. It was already *late* March, and we were on the ice in an old, olive-green military jeep. "Sorry, sometime in early April," Budnev corrected himself. Phew.

For more than two decades now, Russian and German physicists have camped on the frozen surface of Lake Baikal from February to April, installing and maintaining instruments to search for the elusive subatomic particles called neutrinos. Artificial eyes deep below the

ALL PHOTOS: CHRISTIAN THIEL/IMAGES.DE

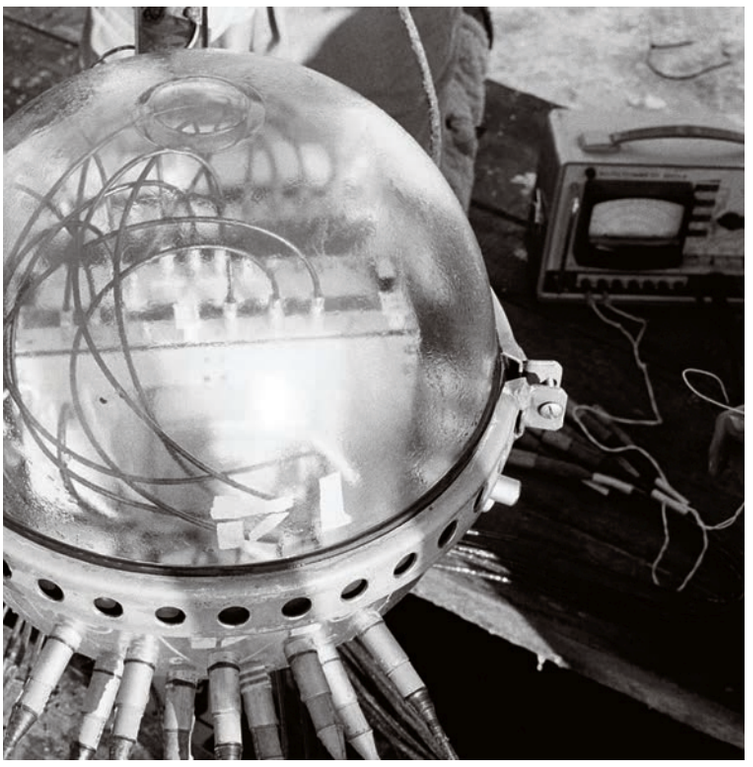
Above: A frigid, rustic campsite is home to the scientists who maintain the Baikal Neutrino Telescope. Right: One of the telescope's 228 detectors, which pick up flashes of light triggered by passing neutrinos.

EACH YEAR THEY SET UP **an ice camp, racing against time to** FINISH THEIR WORK BEFORE **the lake's frozen surface** STARTS TO CRACK.

surface of the lake look for dim flashes of blue light caused by a rare collision between a neutrino and a molecule of water. I was told that human eyes would be able to see these flashes too—if our eyes were the size of watermelons. Indeed, each artificial eye is more than a foot in diameter, and the Baikal neutrino telescope, the first instrument of its kind in the world, has 228 eyes patiently watching for these messengers from outer space.

The telescope, which is located a few miles offshore, operates underwater all year round. Cables run from it to a shore station where data are collected and analyzed. It is a project on a shoestring budget. Without the luxury of expensive ships and remote-controlled submersibles, scientists wait for the winter ice to provide a stable platform for their cranes and winches. Each year they set up an ice camp, haul the telescope up from a depth of 0.7 mile, carry out routine maintenance, and lower it back into the water. And each year they race against time to complete their work before the sprigs of spring begin to brush away the Siberian winter and the lake's frozen surface starts to crack.

What is it about the neutrino that makes scientists brave such conditions? Neutrinos—some of them dating back to right after the Big Bang—go through matter, traveling unscathed from the time they are created and carrying information in a way no other particle can. The universe is opaque to ultraenergetic photons, or gamma rays, which are absorbed by the matter and radiation that lie between their source and Earth. But neutrinos, produced by the same astrophysical processes that generate high-energy photons, barely interact with anything along the way. For instance, neutrinos stream out from the center of the sun as soon as they are produced, whereas a photon needs thousands of years to work its way out from the core to the sun's brilliant surface.

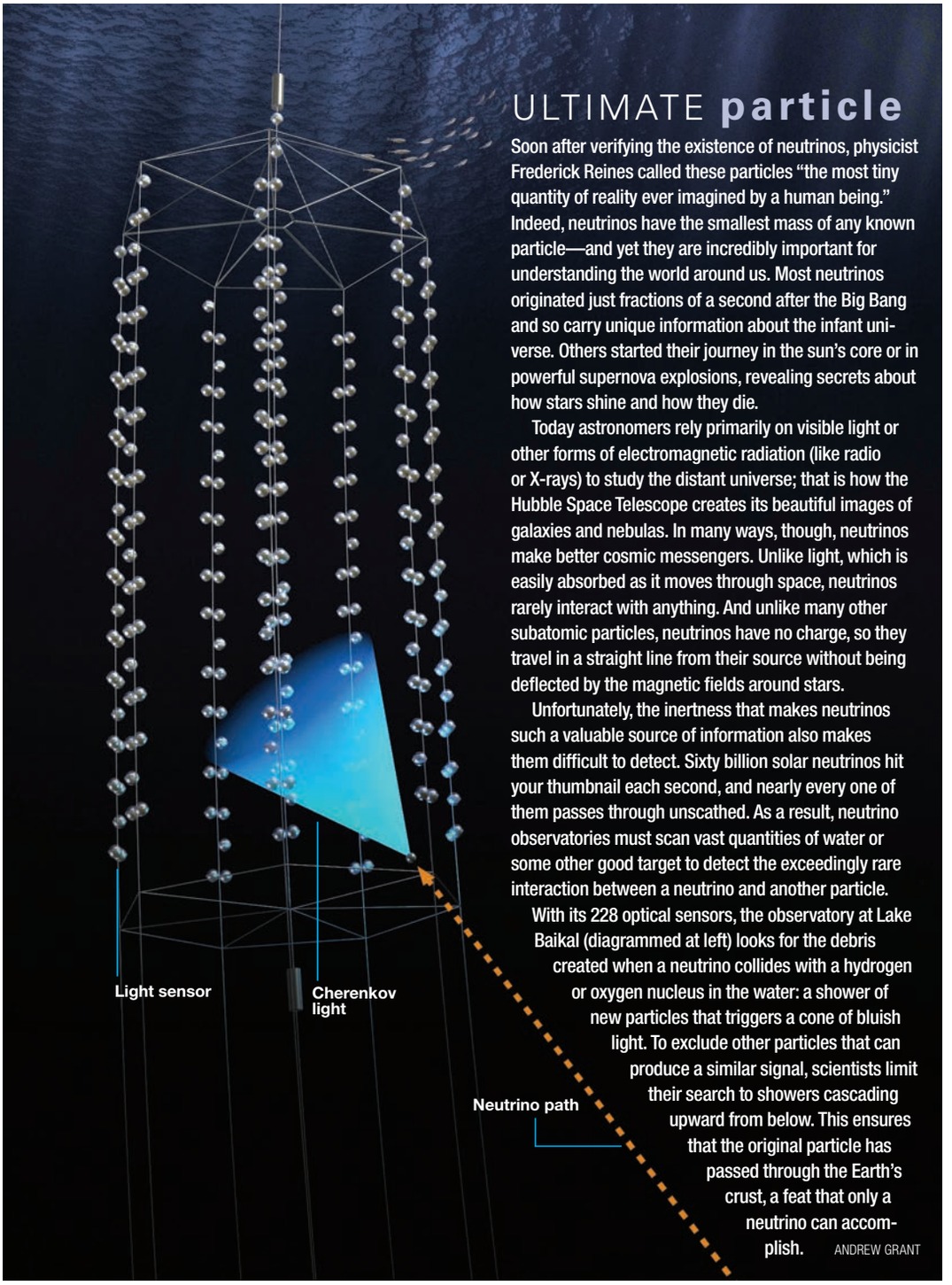


Neutrinos therefore represent a unique window into an otherwise invisible universe, even offering clues about the missing mass called dark matter, whose presence can be inferred only by its gravitational influence on stars and galaxies. Theory suggests that over time the gravity wells created by Earth, the sun, and the Milky Way would have sucked in an enormous number of dark-matter particles. Wherever they gather in great concentrations, these particles should collide with one another, spewing out (among other things) neutrinos. It is as if a giant particle accelerator at our galaxy's center were smashing dark-matter particles together, generating neutrinos and beaming them outward, some toward us.

t h a t neutrinos play such a key role in advancing physics would have surprised scientists of a few generations ago. For them the neutrino was a figment of imagination, a theoretical necessity, but one that seemed impossible to detect because of its ethereal nature—a ghost of a particle. The story of the neutrino begins in the late 1920s. Physicists had been puzzling over something called radioactive beta decay, in which one kind of atom changes into another. For instance, carbon-14 has eight neutrons and six protons. During beta decay, one of these neutrons decays into a proton and emits an electron. The new nucleus, now with seven protons and seven neutrons, is transformed into nitrogen-14. But during this process, some energy seemed to go missing. It was the Austrian-born physicist and Nobel laureate Wolfgang Pauli who theorized that beta decay must emit an as yet undiscovered neutral particle. A few years later, the physicist Enrico Fermi jokingly named the particle a neutrino, Italian for "little neutral one," and the name stuck.

For decades the neutrino remained a theoretical construct, a useful particle that helped physicists save their theories from embarrassment. Nobody had seen one. Nobody even knew how to find one—until Frederick Reines, a researcher working at Los Alamos during the 1950s, realized that a nuclear bomb would be a significant source of neutrinos. Reines and his colleague Clyde L. Cowan Jr. thought a nuclear power plant would also be a source. They calculated that a detector near a nuclear reactor would encounter nearly 10^{13} neutrinos per square centimeter per second. There was just one small problem: Since neutrinos are electrically neutral, they could be detected only if they directly hit the nucleus of an atom. Reines and Cowan would have to look for the signature of such a collision. And they found it.

By the 1960s, physicists following up on Reines's work had started building neutrino detectors inside mines, using the ground as a natural shield from cosmic rays, which can swamp the signal from neutrinos. (Neutrinos can pass through the thick walls of the mines, but cosmic rays cannot.) In 1968 Raymond Davis and his colleagues from Brookhaven National Laboratory completed an experiment inside the Homestake Gold Mine in Lead, South Dakota. They used a tank containing 100,000 gallons of tetrachloroethylene, a common dry-cleaning agent. When a neutrino smashed into an atom of



ULTIMATE **particle**

Soon after verifying the existence of neutrinos, physicist Frederick Reines called these particles "the most tiny quantity of reality ever imagined by a human being." Indeed, neutrinos have the smallest mass of any known particle—and yet they are incredibly important for understanding the world around us. Most neutrinos originated just fractions of a second after the Big Bang and so carry unique information about the infant universe. Others started their journey in the sun's core or in powerful supernova explosions, revealing secrets about how stars shine and how they die.

Today astronomers rely primarily on visible light or other forms of electromagnetic radiation (like radio or X-rays) to study the distant universe; that is how the Hubble Space Telescope creates its beautiful images of galaxies and nebulas. In many ways, though, neutrinos make better cosmic messengers. Unlike light, which is easily absorbed as it moves through space, neutrinos rarely interact with anything. And unlike many other subatomic particles, neutrinos have no charge, so they travel in a straight line from their source without being deflected by the magnetic fields around stars.

Unfortunately, the inertness that makes neutrinos such a valuable source of information also makes them difficult to detect. Sixty billion solar neutrinos hit your thumbnail each second, and nearly every one of them passes through unscathed. As a result, neutrino observatories must scan vast quantities of water or some other good target to detect the exceedingly rare interaction between a neutrino and another particle.

With its 228 optical sensors, the observatory at Lake Baikal (diagrammed at left) looks for the debris created when a neutrino collides with a hydrogen or oxygen nucleus in the water: a shower of new particles that triggers a cone of bluish light. To exclude other particles that can produce a similar signal, scientists limit their search to showers cascading upward from below. This ensures that the original particle has passed through the Earth's crust, a feat that only a neutrino can accomplish. ANDREW GRANT

chlorine, the atom was transformed into one of radioactive argon. By counting the number of argon atoms that were produced, the physicists could calculate the flux of neutrinos coming from the sun. Then in the early 1980s, researchers around the world built detectors using thousands of tons of water in underground tanks lined with photomultiplier tubes (PMTs). The PMTs look for light emitted when a neutrino smashes into water. Normally the neutrino will pass right through water without any interaction. But on the rare occasions when one does hit a nucleus of hydrogen or oxygen, the collision can spit out another subatomic particle, a muon. The charged muon interacts with the water electromagnetically, and because it is moving faster than the speed of light in water, it leaves in its wake a cone of blue light. This is called a Cherenkov cone, after the Russian physicist who first described the phenomenon. It is analogous to the sonic boom caused by an aircraft traveling faster than the speed of sound.

It was another Russian researcher, Moisey Alexandrovich Markov, a "poet" of astroparticle physics, who suggested using natural bodies of water as neutrino detectors. Instead of building tanks of water inside mines, why not use lakes or even oceans? Just submerge long strings of photomultiplier tubes into the water and watch for the Cherenkov light left behind by neutrino-generated muons. The idea was enticing, but there were huge practical difficulties. For one thing, without rock above to protect it, a detector would be exposed to cosmic rays that could drown out signals from neutrinos. More to the point, sunlight (not a problem inside mines) would blot out the Cherenkov emission.

The solution was to go deep, where the sun's rays could not reach. The physicists realized that they could use the Earth itself as a shield. While many muons can make it through a mile of water, a similar stretch of rock will stop them cold. So a neutrino detector can sit deep underwater, near the lake bed, looking downward for muons created by neutrinos that come from below. None of the muons created by cosmic rays in the atmosphere on the other side of the Earth can penetrate the planet. Neutrinos, however, zip right through, and occasionally one will hit a nucleus in the water or in the lake bed itself. Such a collision generates a muon, which then shoots up toward the surface. Catch an upward-moving muon and you have essentially detected a neutrino that came from the other side of the Earth. All that was needed was a suitable body of water. By the mid-1980s, the Russians realized that they had a massive tank of pure water in their own backyard: Lake Baikal.

On my first morning in Siberia, we drove across the lake toward the telescope. The frozen white lake spread for miles around us in every direction except to the northwest, where we were relatively close to shore. When we stopped to rest, men milled around the vehicles. The subzero temperature seemed to affect everyone differently. Some stood bareheaded; others had woolen caps rolled down to the tips of their ears. And then there was Ralf Wischnewski, in his enormous Russian fur cap that looked like a fluffed-up rabbit. A German neutrino physicist who had been working with the Russians at Lake Baikal for 20 years, Wischnewski was the reason I was here. I had met this ruddy-faced man six months earlier in London, outside

ILLUSTRATION BY JOHN MACNEILL

the Tate Modern museum on the south bank of the Thames. We walked over to a Greek pub and discussed the Baikal expedition over chilled lager. It was he who had alerted me to the tradition of bringing spirits to share with the Russians during the winter evenings.

And here we were, except that it was still morning. The Russians had planned a welcome drink for Heinze. Kolja Budnev bounded out of our jeep with a bottle of vodka. Someone sliced a sausage into circular pieces. Bright yellow, blue, and red plastic cups were set up on the jeep's expansive hood, and soon everyone had a vodka-filled cup in hand. Budnev dipped a finger into his and flicked a few drops onto the ice—an offering to the great spirit of Lake Baikal.

BUDNEV FLICKED A FEW **drops of vodka onto the ice—** AN OFFERING TO THE GREAT SPIRIT OF LAKE BAIKAL.

Soon we got back into our vehicles and headed toward the neutrino telescope, a contraption made of 11 strings of photomultiplier tubes, each with a large buoy at the top and a counterweight at the bottom. Smaller buoys attached to the strings float about 30 feet below the surface. All year round, a total of 228 PMTs watch for the Cherenkov cones. Each winter the team has to locate the telescope, the upper part of which drifts slightly over the course of the year. The team has two months to carry out any routine maintenance, put the strings back in the water, and get out before the ice cracks.

The term "experimental physics" took on new meaning in this biting cold, which at times dropped to –4 degrees Fahrenheit. Most of the physicists lived in 10-by-20-foot cabins, two to a cabin. Others slept in bunk beds at the shore station, amid workbenches cluttered with computers, electronics, wires, and cables. They worked long hours, from early in the morning to sometimes well past midnight. There was no running water, which meant no showers for two months. Toilets were wooden cabins with pits in the ground. The extreme cold helped control the stench, but it still wafted up when warm urine hit the pit. There was one luxury: the *banya,* a traditional Russian sauna. Naked men sat in an outbuilding, chucked water on hot stones to raise steam, and beat one another with leafy twigs and branches of birch.

A wicked wind kicked up one evening. It was time for everyone to leave the open ice and head back to the shore station. Once there, I gratefully sat down for a cup of tea, and a can of sweet, syrupy condensed milk materialized. One scientist looked at the can wistfully. Condensed milk had been his dream as a child growing up in the Siberian city of Tomsk. "They had this in Moscow," he said, "but not in Tomsk."

Later that evening, I had to head back out and traverse part of the icy lake to reach the canteen for dinner. It wasn't going to be

easy. I had turned up on a frozen lake in the depths of a Siberian winter in "European summer shoes," as Wischnewski put it, disbelief in his voice. On the lake I found walking nearly impossible, my smooth-soled shoes slipping the entire way. After a few days, I learned to find fresh snow for my shoes to grip, but that night, fear nearly paralyzed me. Fortunately, a jeep pulled up beside me, and Wischnewski, having noticed my plight, asked the driver—Igor Belolaptikov, a tall, mustached physicist from the Joint Institute of Nuclear Research in Dubna, near Moscow—to take me to the canteen. I sat with Belolaptikov at dinner and happily accepted a ride back to his small cabin for a chat about neutrinos.

"My business is the reconstruction of muons and neutrinos," Belolaptikov said, laughing with a childlike joy as he made this disclosure. That reconstruction is tricky business. Hundreds of photomultiplier tubes watch for the flashes of Cherenkov light at the bottom of Lake Baikal. As a neutrino-induced muon races through the water, the light from its Cherenkov cone reaches different tubes at slightly different times. The skill lies in collecting all the information and sifting through it to reconstruct the path of the upward-moving muon. This can then be used to calculate the path of the original neutrino. It is this ability to figure out where a neutrino comes from that differentiates a neutrino telescope from a mere neutrino detector. A telescope must identify the source of neutrinos in the sky, and the Lake Baikal instrument can do so with an angular resolution of about 2.5 degrees, meaning that it can distinguish neutrinos coming from points in the sky separated by a distance of five full moons. So far the Baikal telescope has seen only atmospheric neutrinos, secondary particles created by cosmic rays crashing into atoms in the air. Everyone here is waiting for the day when a high-energy neutrino from outer space makes its presence felt in their little corner of the lake.

Scientists retrieve light detectors for maintenance above the Siberian ice before returning them to the depths of Lake Baikal.

Belolaptikov recalled his first neutrino—indeed, the Baikal detector's first—from 1993. "It was great," he said. "Here, you can see." He leaned over his bunk bed and removed a piece of paper pinned to the wall above. It was a printout of the path of an upward muon, reconstructed from the detection of its Cherenkov cone: the first-ever neutrino seen by humans using a natural body of water as a detector. Belolaptikov and colleagues had done the reconstruction and put the Lake Baikal detector on the map.

The next two days slid by, but even in this short time a rhythm was established. A trip down to the lake in the mornings to get a bucketful of drinking water from a hole in the ice. Then back to the cabin for coffee with condensed milk and honey, making sure to plug the hole in the can of milk with paper to prevent "little animals" (as Wischnewski calls insects) from getting in. From my cabin I could see clear across the lake, and I had to remind myself that it had more water than America's five Great Lakes put together and a surface area larger than Belgium. Eighty percent of Russia's freshwater was here. Even at great depths, the lake is well oxygenated, making it one of the most hospitable waters for life. Because of the voracious crustaceans that live at all depths, nothing dead or dying lasts more than a few days in this lake. If fishermen leave their catch in the nets too long, the crustaceans invade the fish through their mouths and gills, eating them from the inside out. These critters keep the lake free of dead matter, leaving it unimaginably clear, especially deep down. Murky waters would make watching for muons nearly impossible. "It is a very, very kind water," Budnev said.

when the Russians turned on the Lake Baikal telescope in 1993, it was the only game in town. That has since changed. European physicists have started building similar detectors in the Mediterranean. And an American-European team went to the South Pole in the mid-1990s to construct the Antarctic Muon and Neutrino Detector Array (AMANDA) while laying the groundwork for IceCube,

the largest-ever neutrino detector. Several German physicists who had worked at Lake Baikal joined the South Pole team. For a few years Wischnewski, too, split his time between Antarctica and Baikal before committing fully to Baikal. The South Pole detectors are looking for Cherenkov light emitted when muons hit the ice, and IceCube will be watching a cubic kilometer of ice for these ephemeral flashes.

The innovations at Baikal—including Belolaptikov's work on reconstructing muons—inspired the early efforts in Antarctica. Although Antarctic ice is clearer than the waters of Lake Baikal, for now the water has a unique advantage. Light can travel more than 10 times as far in the lake as it can in the ice before it is scattered. Catch the photons before they scatter and you can tell exactly where they are coming from. Catch them after they have been scattered a few times and it gets hard to work out their original direction. This means that more PMTs are needed in the Antarctic ice to achieve the same end.

Grigory Domogatsky, spokesman for the Baikal project, made this point emphatically one evening while we were sitting at a table in his cabin next to a roaring fire. Despite a rasping smoker's cough that could stop him in midsentence, he passionately argued that the world's biggest neutrino detector should be built right here in Lake Baikal. The Americans and their European partners were spending $270 million on IceCube, and Domogatsky thought that a tenth of that would be enough to build a comparable detector in Siberia. Besides the advantage of needing far fewer photomultiplier tubes to detect high-energy neutrinos, Domogatsky pointed out that only a detector in the Northern Hemisphere could see neutrinos from the center of our galaxy.

"But you can see the center of the Milky Way from the South Pole," I said, somewhat puzzled.

"Yes, but not neutrinos," Domogatsky replied, with the gentle yet triumphant note of a teacher who has just made a telling point. Of course: Neutrino detectors that use natural bodies of water or ice can see only those neutrinos that come through the Earth, so they have to look upside down—and from that vantage, the center of the Milky Way never comes into view at the South Pole. Domogatsky further argued that Lake Baikal was the best body of water in which to build such a detector, for there are no deepwater currents, as there are in the Mediterranean. "Lake Baikal is like an aquarium," he said. Besides, scientists in the Mediterranean need ships to lower their strings into the sea and remote-controlled submersibles to wire them up, making the operation expensive. Here, winter ice makes retrieving and working on the detectors comparatively simple. But, Domogatsky sighed, convincing people to work in Siberia during the winter, when the alternative was the sun-soaked Mediterranean, was going to be hard.

Domogatsky's heavily furrowed face showed the effects of 40 years of physics, many of them spent in this hostile place. Now he was looking to pass the baton. His team had just figured out that the telescope they had built so far could form a cell of a much, much larger telescope. Put next to each other, such cells could cover a cubic kilometer of water. All he needed was about $25 million, an order of magnitude less than the money being spent on the Mediterranean neutrino projects or at the South Pole.

The fire died. Outdoors the sun was setting. "I hope to help start this project," Domogatsky said. "But the work should be performed by younger physicists." We stepped outside. I took a picture of this grand old man of contemporary Russian physics against the backdrop of his beloved lake, then started walking back to the shore station. There was just one thing left to do. Wischnewski had suggested that my visit would be incomplete without my spending a night in one of the cabins at the ice camp. I had agreed. But then he casually mentioned that the ice heaves. Despite the lake's thickly frozen surface, the water beneath is alive and kicking. Sometimes the entire sheet of ice below the camp can jerk and lurch. That night we drove to the ice camp and a graduate student named Alexey Kochanov ushered me into his cabin. He told me not to worry; he found the sound of ice creaking beneath him relaxing. Obviously he had been here way too long—but then he explained. The creaking means that the ice cover is solid. It is the sound of ice moving in response to the motion of the water beneath. It is only when you don't hear the creaking that you should worry. That's when the cracks are so big that there is plenty of give in the ice and you should not be on the lake.

Suddenly the ice's protestations were music to my ears. All night it groaned. When sounds came from far away, they were like muffled gunshots; when they were close, more like the crack of a whip. At five in the morning, the ice heaved. It was the only significant movement I had felt all night. I couldn't go back to sleep, so I went outside. It was still dark. The ice did not open to swallow me. Thin cracks crisscrossed the surface. You could tell that the new fissures had formed in the night because they had not yet been covered by snow. Scorpio's tail was visible next to the moon, and overhead was Ursa Minor. On the far shore, embers of a forest fire glowed on the slopes of the Khamar-Daban range.

Somewhere deep below, a cone of bluish light raced upward through the cold water. A neutrino had traveled from some distant part of the universe, escaped collision with every bit of matter across trillions of miles, and gone through the center of the Earth, only to collide with a molecule of water in Lake Baikal and disappear in a flash of light.

NEUTRINO SPOTTING

Lake Baikal is not the only place where physicists are using elaborate detectors to study the most evasive particles in the universe. Here are other sites around the globe where the work goes on:

ICECUBE, ANTARCTICA The latest and greatest neutrino observatory can be found in one of the most inhospitable locales on Earth. Scientists have buried beads of optical sensors under almost a mile of ice, where it is dark and clear enough to detect the blue light of a neutrino-induced particle shower even from hundreds of feet away.

SUPER-KAMIOKANDE, JAPAN Within a mine more than half a mile underground, 13,000 detectors probe 50,000 tons of purified water for the blue-flash signature of neutrinos. In 1998 scientists at Super-Kamiokande found the first evidence that neutrinos have mass.

SUDBURY NEUTRINO OBSERVATORY (SNO), CANADA An engineering marvel, SNO is a transparent spherical chamber filled with liquid, ringed with sensitive light detectors and submerged in a water-filled mine. To improve sensitivity, researchers removed the heavy water that initially filled the chamber so that a petroleum-like liquid could be injected instead.

MAIN INJECTOR NEUTRINO OSCILLATION SEARCH (MINOS), U.S. This underground observatory in Minnesota detects neutrinos beamed from Fermilab, 450 miles away near Chicago. Scientists at MINOS hope to learn more about the three neutrino "flavors": electron, muon, and tau.

OSCILLATION PROJECT WITH EMULSION-TRACKING APPARATUS (OPERA), ITALY Here, a man-made beam of neutrinos (created near Geneva) hits 150,000 lead bricks separated by photosensitive plastic. A. G.

Where the WILD THINGS ARE

A prehistoric park challenges our most cherished ideas about the true state of nature.

BY **ANDREW CURRY**

On the train headed north from Amsterdam's Central Station, be sure to sit to the left. Just past the town of Almere, as you round a right-hand bend, you will find a sight unseen in Europe for centuries, if not millennia: hundreds of red deer, plodding groups of long-horned wild cattle, and skittish herds of low-slung brown horses, all moving through the open landscape like something out of a cave painting. This place goes by the name of Oostvaardersplassen. It is a nature reserve, yes, but it is also a far-reaching experiment. Biologists worldwide are increasingly talking about using large herbivores like the ones sharp-eyed passengers can spot from the train to re-create prehistoric, and sometimes even prehuman, ecosystems.

When keystone species—from ancient mammoths, woolly rhinos, and giant bears to more prosaic grazers like bison, horses, and deer—are wiped out, ecosystems that had sustained themselves in perpetuity collapse. The result is a severe loss of biodiversity. By reintroducing approximations of extinct animals to modern habitats, rewilding advocates want to reestablish dynamic systems that have not existed since the rise of human settlement in Europe. This reserve is the first place where they have done more than talk. Just a short train ride from downtown Amsterdam, nearly 3,000 wild

Konik stallions fight for mares during breeding season on the wetland reserve of Oostvaardersplassen in the Netherlands.

horses, deer, and descendants of prehistoric cattle roam a landscape that is being dramatically shaped by their presence.

The brainchild of a pugnacious Dutch ecologist named Frans Vera, Oostvaardersplassen is challenging some of our most basic assumptions about wildness. Today thick, dense forests are considered synonymous with unspoiled nature. "The current idea is that when you have an area and you do nothing with it, it turns into a forest," Vera says. Ecologists call this one-way process "succession"

and say it rules the unfolding of ecosystems much as natural selection rules evolution. The theory has dominated conservation for centuries, virtually unchallenged.

Until now. Vera says his experiment in rewilding has revealed succession as a human artifact: an unnatural, unbalanced outcome created when people killed off the woolly mammoth and corralled wild horses and cattle. Without free-roaming herds of grazing animals to hold them back, closed-canopy forests took over the land wherever humans did not intervene. The result is a crippled collection of ecosystems that need constant human help to limp along. But Oostvaardersplassen, some 25 years in the making, stands as a test case of what the wild animals that once roamed Europe might create when left to their own devices.

The existence of a prehistoric wilderness in the middle of one of the most densely populated countries in Europe is remarkable in its own right, but Oostvaardersplassen is much more. By forcing ecologists to rethink traditional ideas of hands-on conservation, which focus on micromanaging and preserving species, it heralds the birth of a new model, one in which natural systems work best when they are left alone.

Calling Oostvaardersplassen a "restored" landscape would be totally wrong. Half a century ago, the fields we are chugging across were underneath a vast inland sea. As part of an engineering project to reduce the risk of floods and reclaim land, Dutch authorities essentially created a new province from nothing. Though the engineering challenges are substantial, the principle is simple: Build a dike to wall off the sea, pump out the water to drain the land behind it, let the soil settle, and build. The reclaimed land, called a polder, was once a shipping route in and out of Amsterdam; *Oostvaardersplassen* means "lakes of the ones who sail east." When it was drained in 1968, this area was slated to be an industrial park.

By a stroke of luck, the Dutch economy in the early 1970s was in the doldrums. The chemical plants planned for the new land never materialized. Instead the drained area sprouted reeds and willows—and attracted birds by the tens of thousands, including endangered species rarely seen in the Netherlands. A coalition of Dutch bird-watchers and nature groups pushed, successfully, to set the area aside as a bird refuge.

Wildlife experts worried that without regular mowing and management, the reed beds, meadows, and marshes supporting such a rich collection of migrating birds would soon give way to bushes and willows. Wait long enough, they predicted, and that growth would in turn give way to dense stands of ash and birch, with the occasional oak managing to push its way through the canopy.

Nature had a surprise in store. In 1978 a few thousand greylag geese landed at Oostvaardersplassen for molting season, the vulnerable spring month when they grow new feathers. The grassy, flat polder was perfect for geese. It had marshy areas for feeding located near open meadows that let geese look out for predators. Within a few years, government experts determined there were an astonishing 60,000 geese molting and breeding at Oostvaardersplassen. They devoured a pound of vegetation a day and stayed for four to six weeks at a time. Everything, from the grass to willow seedlings and reeds, was shorn nearly to the dirt by the ravenous birds.

MOSAIC OF GRASSLANDS, marshes, and stands of trees in Oostvaardersplassen probably resembles the landscape of prehuman Europe.

SIEBE SWART/PHOTOSHELTER. PREVIOUS PAGES: TERRY WHITTAKER/AGE FOTOSTOCK

Vera, then a young biologist working for the forest service, read about the winged invasion and began to wonder if the succession model might have a key weakness. In all the traditional models of unmanaged wilderness, the variable was humans; animals

In Vera's vision, the Europe of the past looked more like a city park than an impenetrable thicket of trees.

were an afterthought. Take people out, the thinking went, and forests will follow. And since dense forests cannot support many large herbivores, large herbivores could never have been very numerous.

The more Vera considered that model, the less sense it made. If prehistoric Europe was densely forested, how had meadow-loving geese evolved in the first place, without people mowing to keep their habitat open? How had grazing animals thrived in shadowy, thick woods, let alone evolved to prefer grass? "People argue that animals follow succession; they don't influence it," Vera says. "But Oostvaardersplassen shows animals steering the succession."

Vera saw the reserve as an opportunity to test his theory. If geese alone could shape the landscape, what would happen if the animals that inhabited Europe before humans arrived were introduced to the reserve and allowed to graze freely? From within the forest service, he began a campaign to expand the reserve and reroute a planned train track, which would have cut the reserve in half. He won the battle. ("I was committing the two biggest sins in the civil service," he says now. "I didn't obey my superiors, and I turned out to be right.")

The railroad was diverted in 1982, effectively carving out a 15,000-acre wildlife reserve less than 20 miles from Amsterdam. Vera set out to find stand-ins for extinct European grazers like aurochs (ancestral to today's cows) and wild horses. A year later he introduced 32 Heck cattle, bred by Germans in the 1930s, to approximate the aurochs; a year after that, 20 konik ponies, a Polish-bred version of the wild horses painted on Paleolithic caves, were set free. Forty-four red deer followed in 1992.

Since then the animal populations have exploded. There are now close to 3,000 deer, cattle, and horses living wild in the reserve, which is one of Europe's largest. The free-roaming herds are not given extra food or shelter during the Dutch winters, which can be cold and long. There are no big predators at the reserve, so more than 20 percent of the large herbivores starve during the winter, numbers that mirror annual deaths at African game reserves.

The decision to let nature take its course initially drew fire from Dutch animal rights activists, who complained that letting horses and cows starve to death was cruel. In a concession to those concerns, rangers now stalk the reserve with high-powered rifles, finishing off animals clearly too weak to survive another week. The carcasses are quickly stripped to the bone by foxes and carrion birds, including the first breeding pair of white-tailed eagles seen in the Netherlands since the Middle Ages.

For Vera it is evidence of a system in balance. The herds have been about the same size for five years, swelling with new calves, foals, and fawns in the spring and shrinking again by winter's end. When I visit in early May, Hans Breeveld, a wry park ranger with a ruddy beard, takes me for a ride across the polder. The open fields, which are closed to the public, are so closely grazed they remind me of a putting green. "They haven't been mowed in 12 years," Breeveld tells me.

As we bounce across the polder, there is constant motion. Flotillas of geese shepherding unruly goslings launch themselves into ponds as we approach. Dozens of cattle stare, then turn and hurry away from the car. The deer are the strangest sight. I've seen large groups of cattle before (though usually in stockyards) and small herds of horses at pasture. But I am used to deer as nearly solitary creatures, flitting through the woods in groups of two or three at most. Conventional wisdom holds that three deer per a couple of hundred acres is pushing a forest's capacity. Oostvaardersplassen's fields support more than 16 times that many, creating what could be a scene from an old *Wild Kingdom* special on Africa's Serengeti: hundreds of red deer bounding in tight herds across the open landscape, turning and running away from Breeveld's battered green Suzuki 4×4 in unison.

As we drive I borrow Breeveld's binoculars and stare. Three hours ago I was in central Amsterdam, and now I'm in what looks like a chilly, gray savanna. I ask Breeveld if such huge herds of deer are normal. He looks at me with a slightly mocking smile, as if he is wondering whether I've been paying attention for the last few hours. "What is 'normal'? What's your reference point? We've never let them be in an area this open and large before," he says.

Oostvaardersplassen is the world's largest and most advanced exercise in rewilding, but others could soon follow. North America offers some prime settings for another test. Today it is very different from what it was like when humans first arrived some 14,000 years ago. Within a few millennia, the continent lost 59 species weighing more than 100 pounds—from mammoths and horses to lions, saber-toothed tigers, and giant bears.

After decades of focusing on climate as the prime mover in shaping the North American landscape, scientists are increasingly recognizing that animals may have played a major role in shaping their own habitats. Jacquelyn Gill, a University of Wisconsin at Madison paleoecologist, recently used pollen records from an Indiana lake to prove that the disappearance of mammoths and other large herbivores had a major impact on the types of trees that flourished in the region more than 15,000 years ago. Another change: Major wildfires began only after the mammoths were gone, suggesting that the herbivores may have eaten up all of the fire-prone biomass. "We lose so many of our large herbivores, it's intuitive that the landscape would notice, but the ecological consequences have been largely ignored," Gill says. "It's a big question mark as to how much animals were creating and maintaining that habitat."

Cornell biologist Josh Donlan has proposed running experiments on private land or within nature reserves in the United States to answer that question, using "analogue species" for what he calls Pleistocene rewilding. Elephants from zoos would stand in for mammoths and mastodons, and herds of buffalo and wild horses are already on hand to step back into their Pleistocene places. Donlan has proposed creating protected enclaves similar to Oostvaardersplassen, areas where the impact of large herbivore analogues could be studied. He notes that private game-hunting reserves stocked with everything from gazelles to cheetahs already exist in the American West. So far, though, no one has been willing to let him try. "We pointed to Oostvaardersplassen as a model," he says. "If Vera can do it in the Netherlands, we can certainly do it in the United States."

At a remote Siberian research station 100 miles south of the Arctic Ocean, Russian biologist Sergey Zimov is already running a

PAGES 64-65, CLOCKWISE FROM LEFT: RUBEN SMIT (2); TERRY WHITTAKER/AGE FOTOSTOCK

similar experiment. He has been monitoring small herds of moose, horses, and reindeer at what he calls Pleistocene Park for the past 20 years. In 2005 Zimov argued in *Science* that establishing herds of large herbivores in Siberia might one day change the region's scrubby, swampy tundra back to the grasslands that once stretched from one side of Eurasia to the other. So far, Zimov is seeing landscape changes similar to what is going on at Oostvaardersplassen.

It may take quite a few of those demonstrations to establish the idea that closed-canopy forests, which most people regard as the normal state of nature, may actually be man-made. In fact, those forests are forbidding places for migrating birds. The forest floor is too barren to support large numbers of grazers, and the canopy is too dense to let light-hungry trees like oaks sprout and grow. They are leafy deserts. Yet traditional forest management usually winds up culling deer and bison—not to mention beavers and boar—when their behavior starts to affect trees. "The tragedy is that biodiversity is sacrificed on the altar of the closed-canopy forest," Vera says. "There's this crazy idea that no animals should damage trees, as if trees are made by God not to be eaten."

Vera, Donlan, and Zimov all say that large animals are the keystones of entire ecosystems. Take them out and things begin to fall apart. Setting the system in motion again, whether with the original species or with modern equivalents, is a boon for biodiversity. Many species flourish on the edges between forests and fields. Ironically, suburban America—landscaped with small stands of trees and wide-open lawns—creates a rough approximation of Vera's mosaic of forest and field. No wonder there is a plague of deer in America's backyards.

The day after Breeveld takes me on a tour of the reserve, Vera drives over from his home near Utrecht to explain the science behind Oostvaardersplassen. In the cluttered break room of the ranger station, he pours a cup of coffee and pulls out a map to illustrate his plan to expand the reserve via a corridor to a forest 10 miles away, roughly doubling the area the animals will have access to and opening up forested space.

In 2000 Vera's doctoral thesis was translated and published in English as *Grazing Ecology and Forest History*. The book made an immediate splash, dividing the ordinarily sedate field of forest ecology into Vera supporters and everyone else. "It's the nearest I've come to being involved in one of those great Victorian debates," says Keith Kirby, a forestry expert at Natural England, England's conservation authority. "Vera is really the first person to develop a coherent alternative to the closed-forest idea."

ABOVE: A red stag deer with a herd on the open grass plains of Oostvaardersplassen. TOP RIGHT: A close-up of a red fox. BOTTOM: A horse stripping bark from a willow for a meal.

Grazing Ecology is not your typical biology text. Vera draws on everything from pollen analysis and ecology to medieval woodcuts, etymology, and Latin grammar to prove that we have let shifting perceptions blur what "wild" really means and that, as a result, we are working to conserve an artificial, dysfunctional landscape. In Vera's vision, the Europe of the past looked more like a city park than an impenetrable thicket of trees. Before humans altered the landscape, it was a mosaic of grasslands and marshes dotted with stands of trees and the occasional isolated oak or lime tree, two species that need ample light to grow.

Presumably, herds of everything from mammoths to deer would have roamed this European savanna, keeping it open by grazing and eating all but the luckiest saplings. Once herds of bison, deer, wild horses, and cattle were wiped out or domesticated, land that was not farmed or managed rapidly turned into thick forest. Over time the dark, menacing woods of fairy tales and Renaissance paintings came to define everything we see as uncivilized and wild.

Vera's multidisciplinary approach was not well received. One reviewer sniffed at his attempt "to demonstrate not only his ecological competence but also his linguistic interests." His sharpest critics say that he cherry-picked and misinterpreted his pollen data. Prehistoric pollen taken from the bottom of lakes and peat bogs is considered the best evidence we have for what primeval Europe really looked like, and Vera points out that hazel and oak predominate in the pollen record. Both trees need ample light to regenerate—a strong indicator that the past landscape looked very different.

In one of the few studies to directly

address Vera's claims, paleoecologist Fraser Mitchell of Trinity College in Dublin compared Irish pollen records to those from mainland Europe from around the same time. Even though there is no evidence that large herbivores ever grazed in isolated Ireland, the Irish pollen profile from oak and hazel is essentially the same as the rest of Europe's. "Ireland is full of both hazel and oak but no large grazing animals," Mitchell says. "The implication is that grazing animals are not the cause." Others have chipped away at the edges of Vera's argument, quibbling with his take on the data or his interpretation of historical documents. And others have conceded that Vera may have some good points, while noting that allowing herds of wild animals to roam free across Europe is impractical.

But no one has directly confronted the heart of his argument: that we have wildly underestimated the impact that animals, especially large ones, had on the environment. Even Vera's critics say they appreciate the debate he has stirred up, if only because it has made them reexamine their convictions. "It's paradigm shifting; it challenges everything we used to think," says Peter Szabo, a Czech Academy of Sciences ecologist who took on Vera's analysis of medieval records in a recent article. "Most people kind of welcome the idea."

The hardest part of Vera's argument to accept is that individual species may come and go, as long as the system stays stable. Oostvaardersplassen suggests that ecosystems are complete only when they need no human help. "Frans has taken more than his fair share of criticism because it is so at odds with some of the conservation philosophy in Europe," says Kathy Willis, a professor of long-term ecology at Oxford University. "It's in people's psychology that they want to manage, and this is very hands-off."

Rewilding cuts against just about everything conservationists have been taught. Over and over, people intervene to help species in jeopardy, altering the environment piece by piece without looking at the big picture. Vera is willing to let individual species suffer if it means restoring the balanced dynamics of an entire system. That often means going against a host of special-interest groups. "Here in the Netherlands, we still have biological apartheid: There are bird-watchers, tree-watchers, insect-watchers, butterfly-watchers," he says. "There is no tradition of looking at a site from the point of view of a system."

Take spoonbills, which thrived in ponds and ditches at Oostvaardersplassen until a dry season a few years ago eliminated their habitat. Old-school conservation might have called for flooding the area temporarily, something bird-watchers did in fact insist on when the spoonbill population crashed. Vera just shrugs. "Most nature conservationists don't deal well with dynamics," he says. "New species come when the old ones go. People say you should keep them both, but that's impossible." (Some concessions have been made. Vera would very much like to see wild boar at the reserve, but so far, fears that boar would eat the spoonbills have kept them out.)

The larger issue may be that we like our forests dark and leafy—that our image of wild nature is hard to change, even if it is wrong. "Because we have modified the landscape and been the dominant force for so long, the wildlife patterns we value depend on human practices," Natural England's Kirby says. "If we want to maintain those particular ones, then we have to maintain these practices." In other words, the "wilderness" we imagine and crave requires constant, costly maintenance, from fire suppression and deer hunting to protect trees to annual mowing to keep meadows open for birds. When Vera was first maneuvering to establish Oostvaardersplassen, critics told him the idea of such a large reserve was impractical. "They said you can never have such a large nature reserve in the Netherlands because you can't manage it," he recalls. "That's the absurd consequence of the old system."

After we talk, Vera offers to drive me back to the train station in Lelystad, a city of 70,000 just north of the reserve. On the way we drive along the dike that separates Oostvaardersplassen from the sea. It is a reminder that this re-creation of primeval Europe is taking place on land that has no past. Oostvaardersplassen is several meters below sea level. A massive pumping station works constantly to keep it from flooding. If it were to stop, the reserve's 15,000 acres would be underwater again within a year.

It may be impossible to settle the debate over what kind of landscape our ancestors encountered when they first walked across prehistoric Europe. But Oostvaardersplassen is proving that, given a little time and autonomy, nature can take care of itself. "If you want openness, you can cut and mow," Vera says. "Or you can say, 'If this is a system that worked for hundreds of thousands of years, why not reinstall it?'"

In other words, reboot. Reintroduce large herbivores. Rewild.

THE DISCOVER INTERVIEW

BARRY MARSHALL

The medical elite thought they knew what caused ulcers and stomach cancer. But they were wrong—and did not want to hear the answer that was right.

BY **PAMELA WEINTRAUB** PHOTOGRAPHY BY **IAN REGNARD**

For years an obscure doctor hailing from Australia's hardscrabble west coast watched in horror as ulcer patients fell so ill that many had their stomach removed or bled until they died. That physician, an internist named Barry Marshall, was tormented because he knew there was a simple treatment for ulcers, which at that time afflicted 10 percent of all adults. In 1981 Marshall began working with Robin Warren, the Royal Perth Hospital pathologist who, two years earlier, discovered the gut could be overrun by hardy, corkscrew-shaped bacteria called *Helicobacter pylori.* Biopsying ulcer patients and culturing the organisms in the lab, Marshall traced not just ulcers but also stomach cancer to this gut infection. The cure, he realized, was readily available: antibiotics. But mainstream gastroenterologists were dismissive, holding on to the old idea that ulcers were caused by stress.

Unable to make his case in studies with lab mice (because *H. pylori* affects only primates) and prohibited from experimenting on people, Marshall grew desperate. Finally he ran an experiment on the only human patient he could ethically recruit: himself. He took some *H. pylori* from the gut of an ailing patient, stirred it into a broth, and drank it. As the days passed, he developed gastritis, the precursor to an ulcer: He started vomiting, his breath began to stink, and he felt sick and exhausted. Back in the lab, he biopsied his own gut, culturing *H. pylori* and proving unequivocally that bacteria were the underlying cause of ulcers.

Marshall recently sat down with DISCOVER senior editor Pam Weintraub in a Chicago hotel, wearing blue jeans and drinking bottled water without a trace of *Helicobacter*. The man *The Star* once called "the guinea-pig doctor" can now talk about his work with the humor and passion of an outsider who has been vindicated. For their work on *H. pylori*, Marshall and Warren shared a 2005 Nobel Prize. Today the standard of care for an ulcer is treatment with an antibiotic. And stomach cancer—once one of the most common forms of malignancy—is almost gone from the Western world.

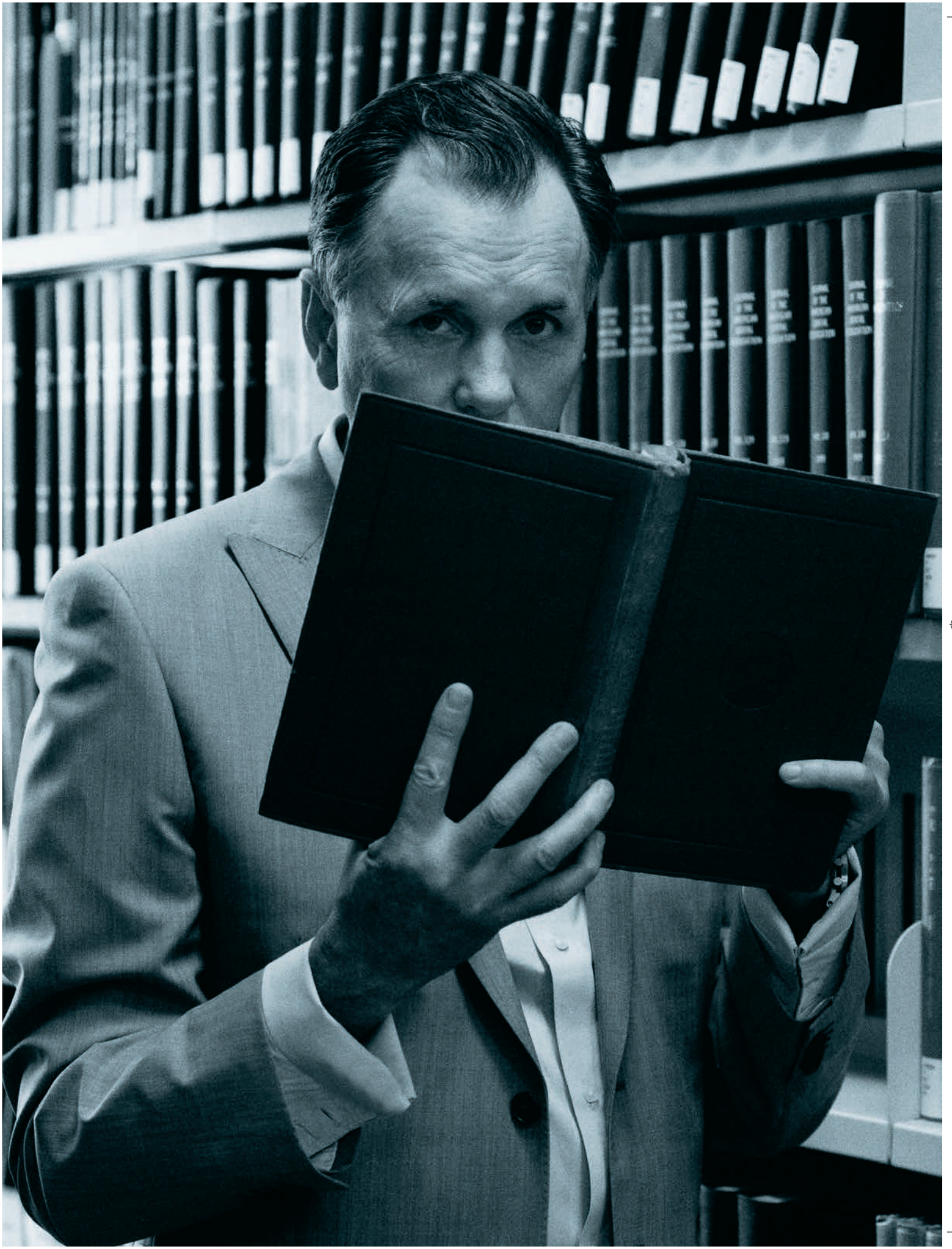
Having rid much of the globe of two dread diseases, Marshall is now turning his old enemy into an ally. As a clinical professor of microbiology at the University of Western Australia, he is working on flu vaccines delivered by brews of weakened *Helicobacter*. And in an age when many doctors dismiss unexplained conditions as "all in the head," Marshall's story serves as both an inspiration and an antidote to hubris in the face of the unknown.

You grew up far from big-city life. What was it like?

I was born in Kalgoorlie, a gold mining town about 400 miles east of Perth. My father was a fitter and turner, fixing steam engines and trains. My mother was a nurse. All the miners owed a lot of money and drank a lot of beer, so Mom said, "We've got to get out of here before we go the way of everybody else." In 1951 we headed for Rum Jungle, where a uranium boom was on, but halfway there we stopped in Kaniva, another boomtown, with a whaling station and high-paying jobs. Then my father started managing chicken factories in Perth. We never wanted for anything. It was like the TV show *Happy Days*.

What sparked your interest in science?

My mother had nursing books around. I had three brothers, and we always had electronics and gunpowder and explosions and welding. All I can say is that some things you get from your parents through osmosis. In high school I had Bs and Cs, not too many As, but I must have done well on that medical school test and I must have



had some charisma in the interview, so I ended up in medicine. Being a general practitioner was all I aspired to. I was good with patients and very interested in why things happened. Eventually I developed a more mature approach: I realized that at least 50 percent of patients were undiagnosable.

You found yourself confronting unexplainable diseases?
In medical school it's quite possible to get taught that you can diagnose everybody and treat everything. But then you get out in the real world and find that for most patients walking through your door, you have no idea what's causing their symptoms. You could slice up that person into a trillion molecules and study every one and they'd all be completely normal. I was never satisfied with saying that by ruling out all these diseases, a person must have a fake disease, so I accepted the fact that lots of times I couldn't reach a fundamental diagnosis, and I kept an open mind.

Is that how you came to rethink the cause of ulcers?
Before the 20th century, the ulcer was not a respectable disease. Doctors would say, "You're under a lot of stress." Nineteenth-century Europe and America had all these crazy health spas and quack treatments. By the 1880s doctors had developed surgery for ulcers, in which they cut off the bottom of the stomach and reconnected the intestine. We're pretty certain now that by the start of the 20th century, 100 percent of mankind was infected with *Helicobacter pylori,* but you can go through your whole life and never have any symptoms.

What was the worst-case scenario for ulcer patients?
An ulcer with a hole in it, called a duodenal ulcer, is acutely painful due to stomach acid. When you eat a meal, the food washes the acid away temporarily. When the meal is digested, the acid comes back and covers the raw base of the ulcer, causing pain to start up again. These problems were so common that the Mayo Clinic was built on gastric surgery. After that surgery, half the people would feel better. But about 25 percent of these cured patients became so-called gastric cripples, lacking appetite and never regaining complete health.

With so much physical evidence of a real condition, why were ulcers routinely classified as psychosomatic?
Eventually doctors realized they could see the ulcers with X-ray machines, but, of course, those machines were in big cites like New York and London—so doctors in those cities started identifying ulcers in urban businessmen who probably smoked a lot of cigarettes and had a high-pressure lifestyle. Later, scientists induced ulcers in rats by putting them in straitjackets and dropping them in ice water. Then they found they could protect the rats from these stress-based ulcers by giving them antacids. They made the connection between ulcers, stress, and acid without any proper double-blind studies, but it fit in with what everybody thought.

How did you come to challenge this prevailing theory?
I was in the third year of my internal medicine training, in 1981, and I had to take on a project. Robin Warren, the hospital pathologist, said he had been seeing these bacteria on biopsies of ulcer and stomach cancer patients for two years, and they were all identical.

What was distinctive about these infections?
The microorganisms all had an S-shaped or helical form, and the infections coated the stomach. Warren had found them in about 20 patients who had been sent to him because doctors thought they might have cancer. Instead of cancer, he had found these bacteria. So he gave me the list and said, "Why don't you look at their case records and see if they've got anything wrong with them." It turned out that one of them, a woman in her forties, had been my patient. She had come in feeling nauseated, with chronic stomach pain. We put her through the usual tests, but nothing showed up. So of course she got sent to a psychiatrist, who put her on an antidepressant. When I saw her on the list, I thought, "This is pretty interesting."

Then another patient turned up, an old Russian guy who had severe pains. Doctors gave him a diagnosis of angina, pain that occurs when blood to the heart can't pass through a narrowed artery. It's rare, but you can theoretically get that in your gut, too. There was no treatment for an 80-year-old man in those days, so we put him on tetracycline and sent him home. He goes off, and two weeks later he comes back. He's got a spring in his step, he's practically doing somersaults into the consulting room. He's healed. Clearing out the infection had cured him. I had one more year to go, so I did the paperwork to set up a proper clinical trial with 100 patients to look for the bacteria causing the gut infection; that started in April of 1982.

But at first nothing was turning up, right?
Yes—not until patients 34 and 35, on Easter Tuesday, when I got this excited call from the microbiologist. So I go down there and he shows me two cultures, the grand slam, under the microscope. The lab techs had been throwing the cultures out after two days because with strep, on the first day we may see something, but by the second

day it's covered with contamination and you might as well throw it in the bin. That was the mentality of the lab: Anything that didn't grow in two days didn't exist. But *Helicobacter* is slow-growing, we discovered. After that we let the cultures grow longer and found we had 13 patients with duodenal ulcer, and all of them had the bacteria.

When did you realize *H. pylori* caused stomach cancer, too?
We observed that everybody who got stomach cancer developed it on a background of gastritis, an irritation or inflammation of the stomach lining. Whenever we found a person without *Helicobacter,* we couldn't find gastritis, either. So as far as we knew, the only important cause of gastritis was *Helicobacter.* Therefore, it had to be the most important cause of stomach cancer as well.

People were totally skeptical. To gastroenterologists, the concept of a germ causing ulcers was like saying that the Earth is flat. The idea was too weird.

How did you get the word out about your discovery?
I presented that work at the annual meeting of the Royal Australasian College of Physicians in Perth. That was my first experience of people being totally skeptical. To gastroenterologists, the concept of a germ causing ulcers was like saying that the Earth is flat. After that I realized my paper was going to have difficulty being accepted. You think, "It's science; it's got to be accepted." But it's not an absolute given. The idea was too weird.

Then you and Robin Warren wrote letters to *The Lancet*.
Robin's letter described the bacteria and the fact that they were quite common in people. My letter described the history of these bacteria over the past 100 years. We both knew that we were standing at the edge of a fantastic discovery. At the bottom of my letter I said the bacteria were candidates for the cause of ulcers and stomach cancer.

That letter must have provoked an uproar.
It didn't. In fact, our letters were so weird that they almost didn't get published. By then I was working at a hospital in Fremantle, biopsying every patient who came through the door. I was getting all these patients and couldn't keep tabs on them, so I tapped all the drug companies to request research funding for a computer. They all wrote back saying how difficult times were and they didn't have any research money. But they were making a billion dollars a year for the antacid drug Zantac and another billion for Tagamet. You could make a patient feel better by removing the acid. Treated, most patients didn't die from their ulcer and didn't need surgery, so it was worth $100 a month per patient, a hell of a lot of money in those days. In America in the 1980s, 2 to 4 percent of the population had Tagamet tablets in their pocket. There was no incentive to find a cure.

But one drug company did provide useful information, right?
I got an interesting letter from a company that made an ulcer product called Denel, which contained bismuth—much like Pepto-Bismol in the United States. The company had shown that it healed ulcers just as quickly as Tagamet, even though the acid remained. The weird thing was that if they treated 100 patients with this drug, 30 of them never got their ulcer back, whereas if you stopped Tagamet, 100 percent would get their ulcer back in the next 12 months. So the company said: "This must heal ulcers better than just removing the acid. It must do something to the underlying problem, whatever that is." They sent me their brochure with "before" and "after" photographs. On the "before" photograph they had *Helicobacter* in the picture, and in the "after" picture there was none. So I put their drug on *Helicobacter* and it killed them like you wouldn't believe. They helped me present at an international microbiology conference in Brussels.

The microbiologists in Brussels loved it, and by March of 1983 I was incredibly confident. During that year Robin and I wrote the full paper. But everything was rejected. Whenever we presented our stuff to gastroenterologists, we got the same campaign of negativism. I had this discovery that could undermine a $3 billion industry, not just the drugs but the entire field of endoscopy. Every gastroenterologist was doing 20 or 30 patients a week who might have ulcers, and 25 percent of them would. Because it was a recurring disease that you could never cure, the patients kept coming back. And here I was handing it on a platter to the infectious-disease guys.

Didn't infectious-disease researchers support you, at least?
They said: "This is important. This is great. We are going to be the new ulcer doctors." There were lots of people doing the microbiology part. But those papers were diluted by the hundreds of papers on ulcers and acid. It used to drive me crazy.

To move forward you needed solid experimental proof. What obstacles did you encounter?
We had been trying to infect animals to see if they would develop ulcers. It all failed; we could not infect pigs or mice or rats. Until we could do these experiments, we would be open to criticism. So I had a plan to do the experiments in humans. It was desperate: I saw people who were almost dying from bleeding ulcers, and I knew all they needed was some antibiotics, but they weren't my patients. So a patient would sit there bleeding away, taking the acid blockers, and the next morning the bed would be empty. I would ask, "Where did he go?" He's in the surgical ward; he's had his stomach removed.

What led up to your most famous and most dangerous experiment, testing your theory on yourself?
I had a patient with gastritis. I got the bacteria and cultured them, then worked out which antibiotics could kill his infection in the lab—in this case, bismuth plus metronidazole. I treated the patient and did an endoscopy to make sure his infection was gone. After that I swizzled the organisms around in a cloudy broth and drank it the next morning. My stomach gurgled, and after five days I started waking up in the morning saying, "Oh, I don't feel good," and I'd run in the bathroom and vomit. Once I got it off my stomach, I would be good enough to go to work, although I was feeling tired and not sleeping so well. After 10 days I had an endoscopy that showed the bacteria were everywhere. There was all this inflammation, and gastritis had developed. That's when I told my wife.

How did she react?
I should have recorded it, but the meaning was that I had to stop the experiment and take some antibiotics. She was paranoid that

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she would catch it and the kids would catch it and chaos—we'd all have ulcers and cancer. So I said, "Just give me till the weekend," and she said, "Fair enough."

Your personal experience convinced you that *Helicobacter* infection starts in childhood. Can you explain?
At first I thought it must have been a silent infection, but after I had it, I said, "No, it's actually an infection that causes vomiting." And when do you catch such infections? When you're toddling around, eating dirty things and playing with your dirty little brothers and sisters. The reason you didn't remember catching *Helicobacter* is that you caught it before you could talk.

You published a synthesis of this work in *The Medical Journal of Australia* in 1985. Then did people change their thinking?
No, it sat there as a hypothesis for another 10 years. Some patients heard about it, but gastroenterologists still would not treat them with antibiotics. Instead, they would focus on the possible complications of antibiotics. By 1985 I could cure just about everybody, and patients were coming to me in secret—for instance, airline pilots who didn't want to let anyone know that they had an ulcer.

So how did you finally convince the medical community?
I didn't understand it at the time, but Procter & Gamble [the maker of Pepto-Bismol] was the largest client of Hill & Knowlton, the public relations company. After I came to work in the States, publicity would come out. Stories had titles like "Guinea-Pig Doctor Experiments on Self and Cures Ulcer," and *Reader's Digest* and the *National Enquirer* covered it. Our credibility might have dropped a bit, but interest in our work built. Whenever someone said, "Oh, Dr. Marshall, it's not proven," I'd say: "Well, there's a lot at stake here. People are dying from peptic ulcers. We need to accelerate the process." And ultimately, the NIH and FDA did that. They fast-tracked a lot of this knowledge into the United States and said to the journals: "We can't wait for you guys to conduct these wonderful, perfect studies. We're going to move forward and get the news out." That happened quite quickly in the end. Between 1993 and 1996, the whole country changed color.

You have since devised tests for *H. pylori*. How do they work?
The first diagnostic test, done after a biopsy, detected *Helicobacter* that broke down urea to form ammonia. More recently I developed a breath test for *Helicobacter* based on the same principle. That test was bought by Kimberly-Clark, and they sell it all over the world. That one little discovery set me up for the rest of my career.

Is it possible to create a vaccine against *Helicobacter*?
After 20 years and a lot of hard work by companies spending millions, we have still been unable to make a vaccine. The reason is that once it's in you, *Helicobacter* has control of your immune system. Once I realized this, I said, well, if it's too difficult to make a vaccine against *H. pylori*, what about loading a vaccine against something else onto the *Helicobacter* and using it as a delivery system? So that is my vaccine project, and it is my life at the moment. I'm making a vaccine against influenza. We'll find a strain of *Helicobacter* that doesn't cause any symptoms. Then we'll take the influenza surface protein and clone that into *Helicobacter* and figure out how to put it in a little yogurt-type product. You just take one sip and three days later the whole surface of your stomach is covered with the modified *Helicobacter*. Over a few weeks, your immune system starts reacting against it and also sees the influenza proteins stuck on the surface, so it starts creating antibodies against influenza as well.

How would this be better than current flu vaccines?
Right now it takes a year to make 50 million doses of flu vaccine, so you only get vaccinated against last year's flu. Whereas we are building swine flu vaccine as we speak. We know the sequence of the swine flu virus. You can make the DNA. You can put it in *Helicobacter*—with a home brew kit, I can make 100,000 doses in my bathtub. Using the same method, a *Helicobacter* vaccine against malaria would be dirt cheap. You could make 100 million doses in the middle of Africa without a refrigerator. You could distribute it at the airport through something like a Coke machine.

Based on this experience, should we be taking a fresh look at other diseases that do not have well-understood causes?
Helicobacter made us realize that we can't confidently rule out infectious causes for most diseases that are still unexplained. By the 1980s, infectious disease was considered a has-been specialty, and experts were saying everyone with an infectious disease could be cured by antibiotics. But what about when your kids were 2 years old? Every week they'd come home with a different virus. You didn't know what the infections were. The kids had a fever for two days, they didn't sleep, they were irritable, and then it was over. Well, you think it is over. It might be gone, but it has put a scar on their immune system. And when they grow up, they've developed colitis or Crohn's disease or maybe eczema. There are hundreds of diseases like this, and no one knows the cause. It might be a germ, just one you can't find.

How can we track down these mystery pathogens?
What we would like to do, hopefully with funding from NIH, is launch big, long-term programs. You would enter your baby into a trial the day he is born. We would have his genome decoded. We'd survey your microbiome [all the microorganisms in the body and their DNA] and maybe your husband's microbiome, and all that would go in a database. Then we would come along and take a feces culture from your baby each month. And if ever he got a fever, we would swab his cheek and save that. We would do 10,000 kids like this. Then, in 20 years' time, we would find that 30 of them developed colitis, and we would go back. If we could get all of that material out of the deep freeze and run it through the sequencing machine, we would find the answer. In the last 20 years, people have been so focused on linking disease with environmental factors like chemicals and pollution. But the environmental factor could be an infectious agent that you had in your body at some time in your life. Just because somebody ruled out an infectious cause in the 1980s or '90s doesn't mean this was correct. Technology has moved forward a long way.

Even now, though, isn't it hard for new ideas to be heard when medical journals are gatekeepers of the status quo?
It's true, but they have their ears pricked up now because every time a paper comes to them, they say: "Hang on a minute, I had better make sure that this is not a Barry Marshall paper. I don't want to have my name on that rejection letter he shows in his lectures." Now they might say, "It's so off-the-wall.... Is it true?"