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Bring Us Your Genes

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MAY/JUNE 2015 Science Connected **NAUTIL.US**

The Genetics Gold Rush

IT'S ONE OF THE NEATER COINCIDENCES in scientific history that an ancestor of James Watson, co-discoverer of the structure of DNA, participated in the California Gold Rush of 1848. Referring to this fact, Watson remarked that "DNA was my only gold rush."

The analogy might be offhand, but it is appropriate. Where California had nuggets of gold strewn about streams and rivers, the genetic age has hidden mutations and markers strewn about the billions of base pairs that make up human DNA. In both cases, finding them can make you rich. And they are there for the taking.

On page 20 of this issue, Adam Piore tells us the story of one company chasing genetic gold in one of the best places on Earth to do so: Iceland. Besides its landscape, Iceland is remarkable for the genetic homogeneity of its population, which makes the mutations that influence disease easier to isolate.

Using a combination of full and partial sequences, the company, called Decode, could infer the genetic mutations in virtually the entire Icelandic population—mutations that increase the risk for conditions like Alzheimer's, gallstones, and liver disease.

There's a rush to data in the United States, too. In February of this year, the Food and Drug Administration permitted the personal genomics company 23andMe to market its first health-related test, for Bloom syndrome, which it developed with the aid of the 900,000 or so sequences it had collected. In April, a startup called Color Genomics accelerated its own plans for data collection with a $249 screen for the *BRCA* gene, implicated in breast and ovarian cancer—about a tenth of the price of other tests on the market.

Where are 23andMe and Color Genomics headquartered? In California, of course.

These same ideas also make up the genome of this edition of *Nautilus*: rushing and slowness, unforeseen consequences, and mutations and error. Welcome to the May/June print edition.

—Michael Segal
Editor in Chief


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—Helen Fisher, p. 42

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"Words, sights, sounds, feelings, and even smells can influence our understanding of objects and direct our behavior toward them."

—Richard E. Nisbett, p. 94

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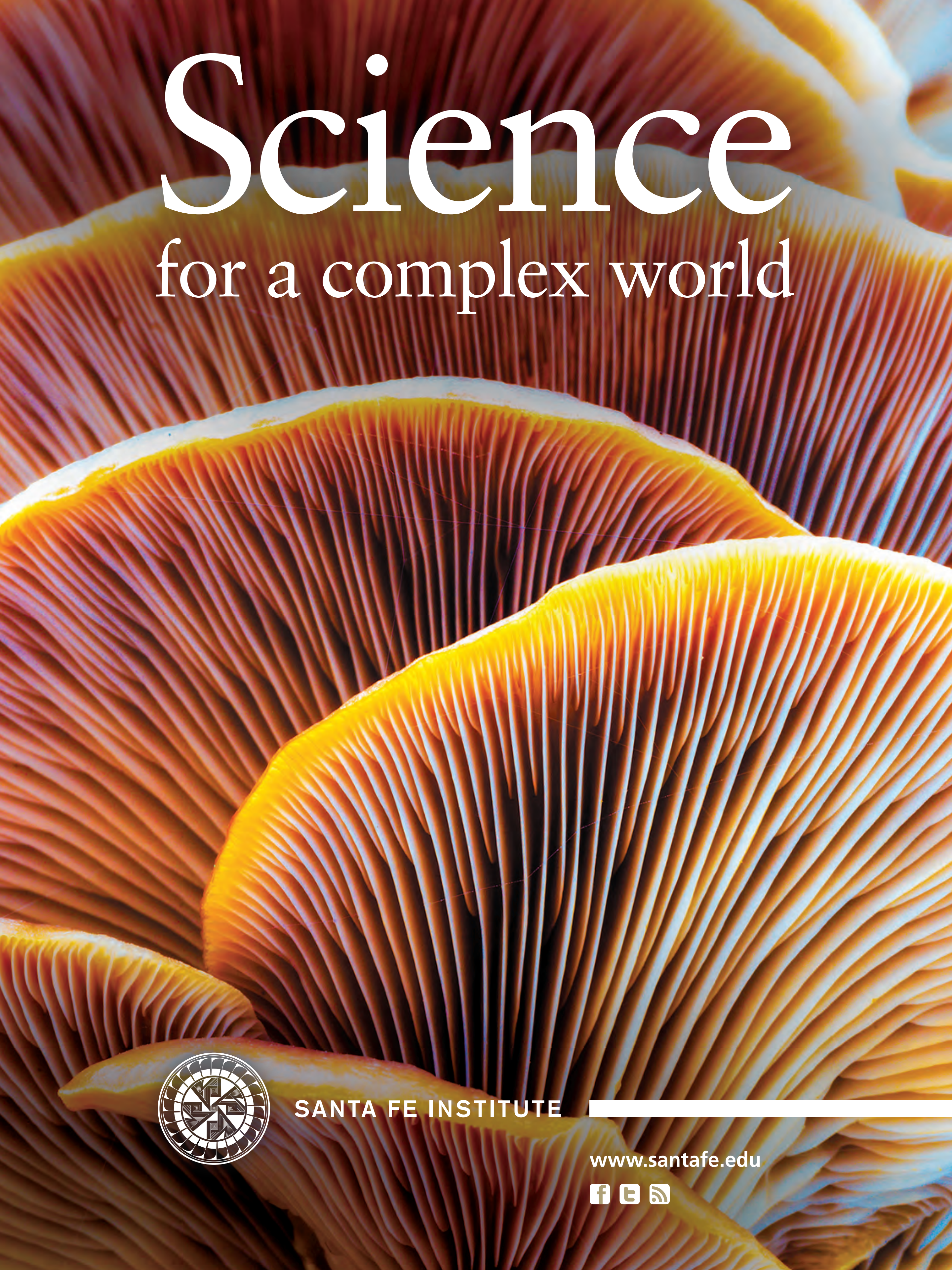
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FIFTEEN
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EIGHT
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THREE
3
WEEKS OLD

Preludes

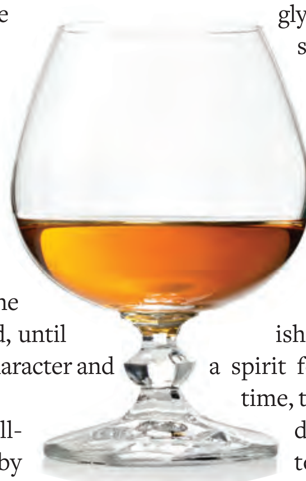
CHEMISTRY

Whiskey Can't Hide Its Age Either

Anxious distillers are trying to make bourbon old before its time

IN CASE YOU HAVEN'T HEARD, doomsday is coming—more droughts, floods, famine, class warfare, and, brace yourself: a bourbon shortage! Yes, traditional Kentucky distillers didn't predict or prepare for this *Mad Men*-inspired mixology epoch. And if it continues on this trajectory, thousands of years from now archaeologists will identify the bourbon-free era in the absence of fancy rectangular bottles in the remains of fallen civilizations.

That is, unless scientists can build a whiskey time machine, a way to cheat the slow aging process that offers bourbon its rich oaky tones and sweet and smooth finish. Enter entrepreneurs with start-up spirits and a potential solution.



STEPHEN ROBERTSON/SHUTTERSTOCK

Whiskey aging traditionally starts when an oak barrel is charred, breaking down the lignin in the wood into organic compounds called aldehydes. Add alcohol to the barrel and oxidation transforms the aldehydes into acids. Changes in heat and pressure push and pull the alcohol in and out of the wood. There is a back-and-forth between aldehyde and acid, until the acids accumulate and turn into esters, adding complex character and deep flavors.

One entrepreneur trying to cheat Father Time is Tuthilltown Spirits in Gardiner, New York, makers of Hudson Baby Bourbon. When it opened in 2003, Tuthilltown started accelerating the maturation of single malt, rye, and bourbon whiskeys by letting the alcohol settle in 2- to 5-gallon oak barrels, instead of the industry-standard 53- to 55-gallon oak casks, increasing the alcohol-to-barrel-surface ratio. The company has been able to get its whiskey to market in about four months, and its brewers like the vanilla flavor they are getting by using small barrels.

Terressentia, near Charleston, South Carolina, uses increased oxidation to mimic aging and take impurities out of young whiskeys. Its brewers start with undrinkable 4- to 6-month-old whiskey because they want its whiskey to be brown—something you can't get without time in an oak barrel. They filter it in plastic tanks with a technology that expedites the aldehyde and acid dance, creating drinkable esters in just eight hours. The process has the added benefit of turning some of the fatty acids from the original fermented grains into glycerides, which act as a smoothing agent, taking the bite out of the final product.

Most bourbon experts are not sold on fast whiskey. They say it has a "raw taste" with a "shorter finish." "When you're aging a spirit for a short amount of time, the aldehydes and acids don't have time to come together," says Scott Spolverino, an industry consultant from Scotland with a degree in distilling science. The raw, edgy flavors in fast-tracked whiskeys often come from an overabundance of aldehydes.

According to Liza Weisstuch, who writes regularly for *Whisky Magazine*, "time in the barrel is like sandpaper, smoothing out the rough edges."

—Tasha Eichenseher

ILLUSTRATION BY DANIEL ZALKUS

CELLULAR BIOLOGY

The Executioner We Can't Live Without

You're dead meat without special molecules that kill rotten proteins

AARON CIECHANOVER WON a Nobel Prize in Chemistry in 2004 for helping to identify one of biology's most remarkable processes, how a molecular Pac-Man called a ubiquitin races through our bodies and devours damaged proteins. He talked us through how it works.

I'm no different than a piece of meat that I left on a table. But I have a way to take these rotten proteins and replace them.

You define proteins as little machines that run our lives. Yet there's a wrench in the works.

Proteins have a problem. They're very sensitive to all kinds of effects. They're sensitive to temperature. Take a piece of meat. You go to the butcher. You buy a steak and you forget to put it in the refrigerator. Within a few hours, it's gone. It becomes brownish-greenish, stinking. What happened to it? The proteins in meat were affected by the temperature and got what we call denatured, misfolded, inactivated. Bring the metaphor a little further. The same meat is here in my thigh, in my forearm, in my calf. Why is it that in my body, within a few hours, this meat doesn't get spoiled and on the table it does? I, as a living organism, take the spoiled proteins, the brownish-greenish proteins, trash them and renew and replace them with new ones all the time. That's the difference between being dead and being alive.

How does your body know when to take out the trash?

Let's say that one day you get the flu. You make antibodies to defeat your flu virus. Then the virus is defeated. Now you don't need the antibodies anymore. There's no virus. So you turn off the antibody faucet in your body by shredding the faucet itself. This is control. The fact that we are living means that we have a very sophisticated shredder. It shreds only proteins that should be garbage, but it keeps proteins that should be alive.

How do protein shredders do their dirty work?

Think about being in Texas and you raped a woman or you robbed and murdered the owner of a gas station. You're being brought to a court and the court finds you guilty and sentences you to death. You are put on death row in Huntsville Prison. To identify you on death row, they put you in an orange gown. In order for the shredder to identify proteins, we first have to mark them. So we put the molecule ubiquitin on the doomed protein. Ubiquitin is the orange coat for the executioner to come and execute.

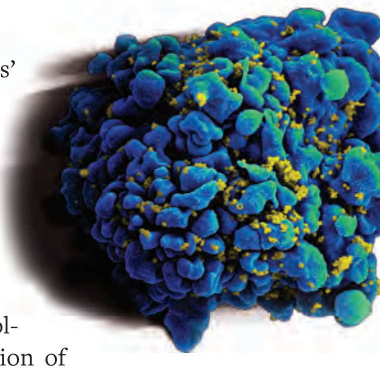
—*Pamela Weintraub*

ILLUSTRATION BY FRANCESCO IZZO

GENETICS

The Tiny, Random Errors That Can Kill

Even small mutations can wreak havoc on a cellular level



Viruses, to the chagrin of the hosts they infect, have the highest mutation rates around.

IT'S EASY TO THINK of our cells' inner workings as parts in a well-oiled machine—like tiny crankshafts and gears they chug along in their endless task of transcribing information from DNA, manufacturing proteins, and sending them off to transact the business of living.

Much popular writing about cell biology emphasizes the exquisite precision of this process, and not unfairly—these minute workings can seem far more exact than humans who stub toes and struggle to assemble IKEA furniture. The fact that cells have proofreaders, proteins that skim along freshly made DNA checking for and removing errors, only adds to the impression of fierce efficiency.

But, despite the proofreaders, errors creep in during DNA replication, and the resulting mutations can cause diseases like cancer. Yet messiness can sometimes be helpful for species in the long run, and likely contributed to the shape of life today.

Viruses, to the chagrin of the hosts they infect, have the highest mutation rates around. They don't have cells—just protein shells packed with genetic material and little else—and it's debatable whether they're even alive, yet they use similar machinery to propagate. And they make mistakes constantly when fabricating new copies of their genetic material for their daughter viruses, with mutation rates up to 20 million times higher than in humans. These mistakes doom a certain portion of them but also allow for extremely fast evolution: When the piled-up mistakes change the virus enough so that it becomes invisible to a host's immune system, it can hack its way into our cells and reproduce in enormous numbers. This fast evolution is why you need a fresh flu shot every year, and why we don't have a cure for the common cold. It's why you can't predict whether an individual will progress from HIV to AIDS, even when they are teeming with viruses. A 2014 study in the *Proceedings of the National Academy of Sciences* suggests that individuals with identical genetic backgrounds can have vastly different disease outcomes—developing AIDS or not—because of random, chance mutations in the virus. Even having good genes can't always save you: It's a messy, uncertain world on the cellular level. Randomness is at work.

—*Veronique Greenwood*

SEX

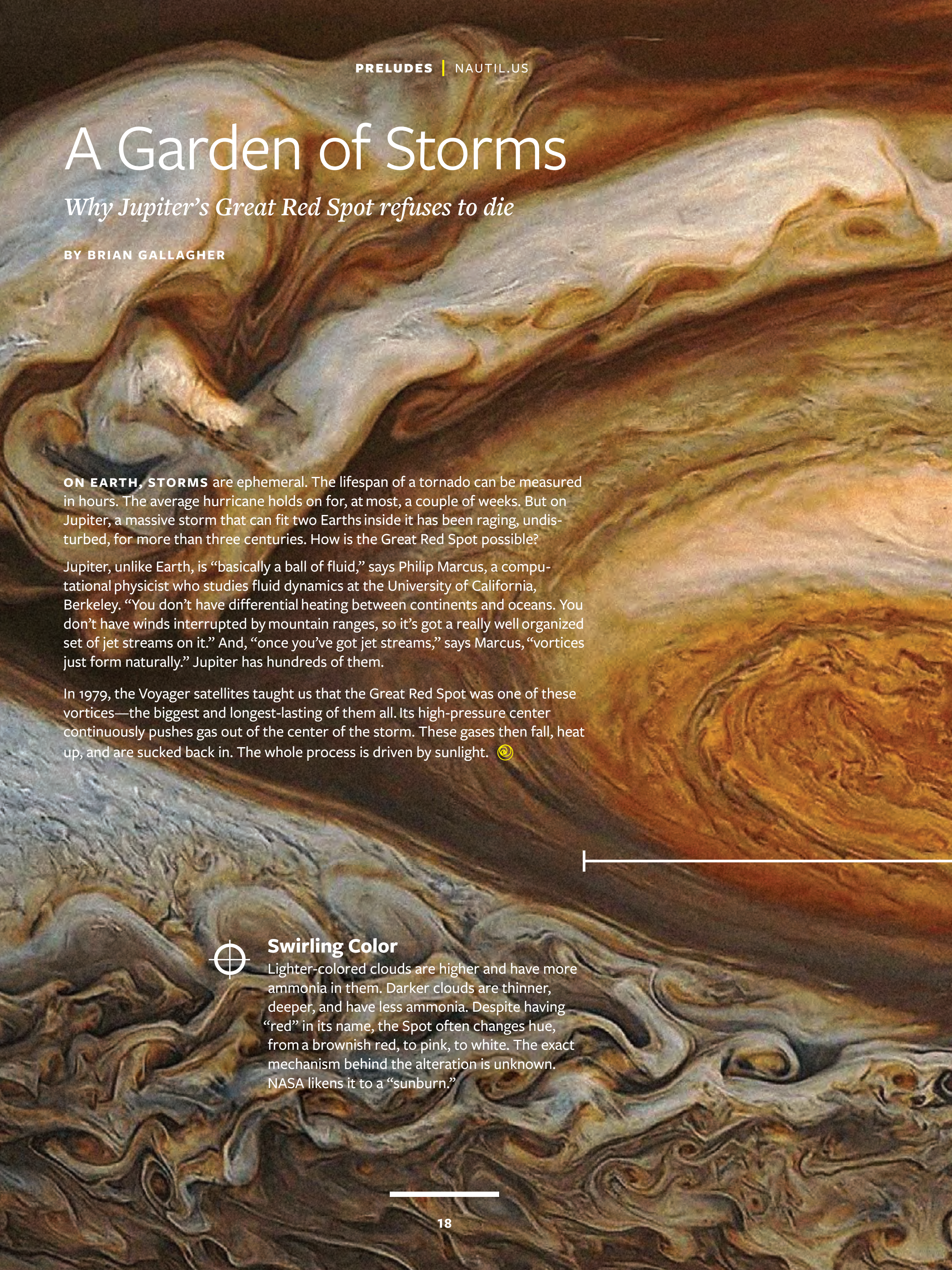
One Question for Helen Fisher

What are the benefits of casual sex?

YOU LEARN A GREAT DEAL about a human being between the sheets. You learn how flexible they are, whether they can be attentive to you, whether they're eager to please you, whether they can listen. So an awful lot of people have casual sex to get to know somebody as rapidly as they can before they become too attached. Sex is dangerous. You trigger brain circuitry for romantic love and feelings of attachment and suddenly you're off to the races with the wrong girl or boy. It's dangerous because you could fall in love.

—*Helen Fisher is a biological anthropologist and Senior Research Fellow at the Kinsey Institute.*

HELEN FISHER ILLUSTRATION BY LEN SMALL
IMAGE OF HIV PARTICLES INFECTING A HUMAN T CELL: NIAID



A Garden of Storms

Why Jupiter's Great Red Spot refuses to die

BY BRIAN GALLAGHER

ON EARTH, STORMS are ephemeral. The lifespan of a tornado can be measured in hours. The average hurricane holds on for, at most, a couple of weeks. But on Jupiter, a massive storm that can fit two Earths inside it has been raging, undisturbed, for more than three centuries. How is the Great Red Spot possible?

Jupiter, unlike Earth, is "basically a ball of fluid," says Philip Marcus, a computational physicist who studies fluid dynamics at the University of California, Berkeley. "You don't have differential heating between continents and oceans. You don't have winds interrupted by mountain ranges, so it's got a really well organized set of jet streams on it." And, "once you've got jet streams," says Marcus, "vortices just form naturally." Jupiter has hundreds of them.

In 1979, the Voyager satellites taught us that the Great Red Spot was one of these vortices—the biggest and longest-lasting of them all. Its high-pressure center continuously pushes gas out of the center of the storm. These gases then fall, heat up, and are sucked back in. The whole process is driven by sunlight.

Swirling Color

Lighter-colored clouds are higher and have more ammonia in them. Darker clouds are thinner, deeper, and have less ammonia. Despite having "red" in its name, the Spot often changes hue, from a brownish red, to pink, to white. The exact mechanism behind the alteration is unknown. NASA likens it to a "sunburn."

Rotation Station

As an anticyclone, the Spot spins opposite to the planet's rotation, just like 90 percent of Jupiter's storms that measure at least 1,250 miles in diameter. The Spot makes a full rotation every six Earth days.

Jet Stream Power

The horizontal wind speeds on either side of the Spot peak at around 270 miles per hour. The speeds inside the vortex are about the same. While the vertical winds are much slower, clocking inches per hour, Marcus says they're nevertheless essential to the survival of the Spot.

Pancaked

Although it is 25,000 miles wide, the Spot is only about 37 miles thick.

Wide Load

A century ago, the Spot had a diameter of around 25,000 miles. Now it's around 15,000 miles, still large enough to fit two Earths inside. It's unknown whether the Spot will continue to shrink.

Bring Us Your Genes

A Viking scientist's quest to conquer disease

BY ADAM PIORE

IN THE NINTH CENTURY there was a Norwegian Viking named Kveldulf, so big and strong that no man could defeat him. He sailed the seas in a longship and raided and plundered towns and homesteads of distant lands for many years. He settled down to farm, a very wealthy man.

Kveldulf had two sons who grew up to become mighty warriors. One joined the service of King Harald Tangle Hair. But in time the King grew fearful of the son's growing power and had him murdered. Kveldulf vowed revenge. With his surviving son and allies, Kveldulf caught up with the killers, and wielding a double-bladed ax, slew 50 men. He sent the paltriest survivors back to the king to recount his deed and fled toward the newly settled realm of Iceland. Kveldulf died on the journey. But his remaining son Skallagrim landed on Iceland's west coast, prospered, and had children.

Skallagrim's children had children. Those children had children. And the blood and genes of Kveldulf the Viking and Skallagrim his son were passed down the ages. Then, in 1949, in the capital of Reykjavik, a descendent named Kari Stefansson was born.

Like Kveldulf, Stefansson would grow to be a giant, 6'5", with piercing eyes and a beard. As a young man, he set out for the distant lands of the universities of Chicago and Harvard in search of intellectual bounty. But at the dawn of modern genetics in the 1990s, Stefansson, a neurologist, was lured back to his homeland by an unlikely enticement—the very genes that he and his 300,000-plus countrymen had inherited from Kveldulf and the tiny band of settlers who gave birth to Iceland.

Stefansson had a bold vision. He would create a library of DNA from every single living descendent of his nation's early inhabitants. This library, coupled with Iceland's rich trove of genealogical data and meticulous medical records, would constitute an unparalleled resource that could reveal the causes—and point to cures—for human diseases.

In 1996, Stefansson founded a company called Decode, and thrust his tiny island nation into the center of the burgeoning field of gene hunting. "Our genetic heritage is a natural resource," Stefansson declared after returning to Iceland. "Like fish and hot pools."

Stefansson set sail on an epic journey. He and his crew collected DNA from 150,000 of their fellow countrymen (half the population) and constructed a genealogical chart that accounts for the family tree of virtually every member of the small island nation. Next they succeeded in reading the entire 3-billion nucleotide

ILLUSTRATIONS BY JOHN HENDRIX

genetic sequences of more than 11,000 Icelanders. They could now infer the individual genomes of the entire Icelandic population. Then they embarked on a massive treasure hunt for individual Icelanders with missing segments of DNA carried by the rest the population. They matched these "knocked out" genes with their impact on the individuals carrying them. That quest has only just begun. But already it has resulted in a rich bounty.

In 2015, Stefansson and his team reported they had found rare mutations that increase the risk of Alzheimer's disease, gallstones, atrial fibrillation, and thyroid disease. If researchers can find the chemical pathways the mutations affect, they will have unprecedented insights into the causes—and possible cures—of some of humanity's worst diseases.

In the Middle Ages, scribes set down the legendary deeds of Kveldulf the Viking and the nation's legendary explorers and families in the Sagas of the Icelanders. In the depth of winter not long ago, I ventured to Iceland to write my saga of the Icelander who would conquer the genetic code.

ICELAND IN DECEMBER IS A COLD and forbidding place. The sun doesn't rise until 11 a.m. By 4, it's gone. The wind whips down glacier-capped mountains, across barren, volcanic plains. On the dark morning I set out from my waterfront hotel to meet Stefansson, a bitter chill was in the air.

Decode's well-lit, modern headquarters, with its cheerful potted plants and hardwood floors, is perched on the outskirts of Reykjavik like a warm medieval castle on the edge of a forest. But as I approached, I was apprehensive. Famed for a mercurial temperament, Stefansson has been known to get up and leave when irritated by an interviewer—or simply drop his forehead to the edge of his desk and loudly sigh. Due to a misunderstanding, I was half an hour late.

Outside Stefansson's office, Decode's press handler sat next to me seething. He warned that his mercurial boss's reaction was impossible to predict. Would he still meet with me at all? "We'll see," he muttered.

Finally, Stefansson emerged. Trim, tall, with a beard, a shock of white hair, wearing sneakers and a white striped hoodie, he extended his hand. I apologized.

"Americans have a tendency to be arrogant, devious, and stupid," Stefansson replied, smiling. Then he led me into his office.

Stefansson often adopts a subversive, Viking-like defiance, and enjoys playing the provocateur. The son of a famous Icelandic radio journalist, Stefansson insists he remains an artist at heart, who grew up "absolutely determined" to become a writer and a poet—a path that seemed very likely until fate intervened. One night just as Stefansson was completing high school, he got drunk with a classmate, and stayed out wandering around after the bars closed.

"In the morning, when we were somewhere between drunk and hungover, we decided to walk to the university and apply for medical school," Stefansson said. "I had no interest in it. He wanted to go to medical school. And then, all of a sudden, I was in medical school.

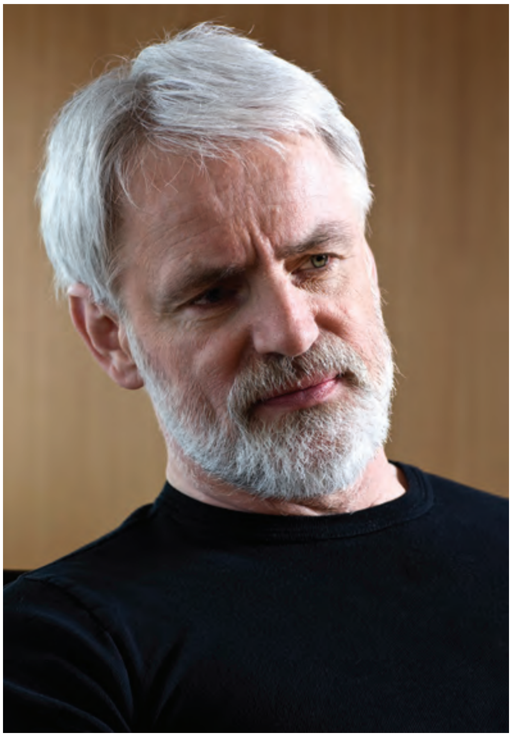
"I found medical school extraordinarily boring," Stefansson added. "I don't know why I stayed."

There was at least one reason to stay. By the time Stefansson left home, he had developed a personal understanding of the ravages of unchecked diseases. Stefansson's beloved older brother—a gifted athlete, who had "forced good literature on me" and "was my hero growing up"—had a psychotic break. Stefansson was struck by the power of his brother's delusions—at one point, he called up Stefansson and apologized for attacking him with an ax, an incident that never occurred—and the devastating impact the little-understood disease wrought on his family.

"He was completely off the wall," Stefansson said. "Schizophrenia is a disease of thoughts and emotions. And what defines you as an individual are your thoughts and emotions. So once you are hit by a disease like that, you are changed. You become a different creature to those who interact with you."

Stefansson dove into the psychiatric literature of the time searching for answers, and for a time flirted with the possibility of devoting his life to psychiatry. But he found psychiatrists to be "poorly educated" with "an uninteresting approach to the problem." Instead he focused on the biological study of diseases of the nervous system, neurology, and pathology.

In 1977, he landed at the University of Chicago as a postdoc and, eventually, a member of the faculty. It was there that he fell in love with science and



THE ICELANDER COMETH In the 1990s, Kari Stefansson, founder and CEO of Decode, set sail on an epic journey to sequence the DNA of every living Icelander. His quest followed an unsatisfying position at Harvard. "It was a boring place," he said.

DECODE GENETICS/CHRIS LUND

surrendered to his true calling. In Chicago, Stefansson distinguished himself for his work on multiple sclerosis (MS), the crippling disease where the body's own immune system attacks the lipid brain coatings, known as myelin sheaths, crucial to the transmission of the electrical impulses that run the nervous system.

As a young professor and researcher in the 1980s, Stefansson and a graduate student named Jeffrey Gulcher spent months hunting for individual proteins expressed in the brain that might be causing the body to attack the sheaths. If they could identify them, they reasoned, perhaps drugs could neutralize them. But the approach was frustrating. Even when they succeeded in isolating a protein that appeared to be associated with the onset of an immune attack, there was no way to know for sure it was actually the cause of the disease, and not part of the body's response to it.

Stefansson recognized genetics might provide a far better solution. Every one of us carries somewhere in the neighborhood of about 20,000 different genes in our cells, each compromised of anywhere from 27,000 to 2.4 million pairs of DNA's core building blocks, nitrogen compounds known as nucleotides that contain one of four bases, cytosine, guanine, adenine, and thymine. The sequences of these bases, referred to by their first letters—"A," "C," "G," and "T"— encode the molecular level instructions for every single protein our bodies produce. Those proteins in turn determine everything from our hair color to our temperament to the shape of our toes.

But sometimes our genomes contain typos—mistakes in the sequence of base pairs that can cause the body's instructions to go awry. It is the combination of lifestyle and these mutations in the DNA sequence that lies at the root of most human diseases, most scientists believe.

It seemed obvious to Stefansson that if you could find differences in the genes coding for proteins unique to individuals afflicted with MS, there was a high likelihood that protein played a role in causing the disease and would serve as a promising drug target.

IN THE 1980S, IDENTIFYING GENETIC differences was a Herculean chore. During their initial exploration of proteins involved in MS, Stefansson and Gulcher sequenced a single 7,500-unit strand of DNA that coded for a specific protein using the best tools science had to offer. It took three years.

By the early 1990s, Stefansson had become convinced that things were about to change. Scientists had launched the Human Genome Project, a $3 billion international effort to identify all the genes in human DNA, and determine the sequence of the estimated 3 billion chemical bases thought to comprise those genes. In 1993, Stefansson and Gulcher were recruited by Harvard Medical School, and the new technology would be just what they needed to study MS.

At Harvard, Stefansson had a breakthrough idea. He would conduct his MS study in Iceland. In diverse populations like the United States, disease-causing genes are difficult to distinguish from other variations

WOLFGANG KAEHLER/GETTY IMAGES

GENE NATION Famous for its volcanoes, fjords, and Bjork, Iceland is now a world capital of genetics. "Decode has assembled an astonishing collection of genetic data—the deepest genetic characterization of any national population," said Daniel MacArthur, a geneticist at Massachusetts General Hospital.

because there are a dizzying number of individual variations to sort through. Any given American might be carrying DNA reflecting mutations unique to Africa, Eastern Europe, Brazil, Russia, and the North Pole. Finding which one of those mutations accounts for a given disease is a little like searching for a typo by comparing a book in German to its counterpart in French.

But Icelanders had been living in geographic isolation since the days of Skallagrim and his fellow settlers, incubating an unusually homogenous gene pool of blonde-haired, blue-eyed virtual cousins. The insular population would make it far easier to spot errant disease-causing mutations, and gain new insights into the causes of a wide array of human ailments. Stefansson asked an Icelandic neurologist to recruit MS patients and instruct them to bring along a close, healthy relative for comparison. Many arrived instead trailing large entourages of extended family, all eager to help.

Gulcher and Stefansson returned to Boston with DNA from 200 MS patients, just 15 siblings, but hundreds of more distant kin. Most geneticists relied on sibling pairs for studies. But Stefansson had the insight that his distant relatives would prove even more useful. Distant relatives inherit far fewer common genes than two individuals who have the same parent (who share roughly 50 percent of the same DNA). While that made it harder to find two distant relatives who carried the same disease-causing mutation—once you located them, there would be fewer additional commonalities to eliminate as the cause of the disease.

A confident Stefansson decided to expand his lab and hunt for shared DNA sequences that would narrow the location of the gene or genes related to MS. When the pair applied to the U.S. National Institutes for Health for funding, however, they received a bitter dose of reality. The reviewers were unimpressed by his sample of Icelandic relatives. Why, they asked, weren't there more sibling pairs? Siblings were the accepted protocol for genetics studies, they reminded Stefansson and Gulcher, because they share DNA—entirely overlooking the fact that distant relatives carry shared DNA as well.

Gulcher was furious. But Stefansson was undeterred. Even if they had received the grant, he did not believe it would have been sufficient to finance the vision he had begun to develop since returning from Iceland. Over morning breaks with Gulcher at a Starbucks down the street from his Harvard lab, Stefansson argued for something far larger in scope. Iceland had an obsession with genealogy, a tradition of centralized medical record keeping, and an altruistic populace. The nation had a massive tissue bank that had been preserving samples from autopsies since 1915, and had recorded every single case of cancer diagnosed since 1952.

If Stefansson and Gulcher could open an institute, or sell venture capital firms on a private company, they could be the ones to harness Iceland's vast genetic resources to glean insights, not just about MS—but about all human diseases. If they could raise the money, import big biotechnology to Iceland, reverse the brain drain—bring back all those Harvard and Stanford Ph.D.s who'd gone abroad for want of local opportunity—they could rely on widespread support. There was no telling what they might be able to do.

The pair began approaching venture capital firms. Within a couple of months, Stefansson raised $12 million. He was headed back to Iceland to set up shop.

As for his coveted job at America's most famous college? "Harvard is a lousy university," Stefansson said. "It's a loose confederacy of independent institutions and I was eager to get away from there. It was a boring place."

> "Americans have a tendency to be arrogant, devious, and stupid," said Decode CEO Kari Stefansson, smiling. Then he led me into his office.

ONE OF THE FIRST THINGS Stefansson did after launching Decode in 1996 was gain access to Iceland's largest genealogy database, created by a computer programmer on his off time for family-tree enthusiasts. It contained 400,000 records, dating to the settlement of Iceland, including calfskin manuscripts, church records, and the census of 1703, allowing virtually all Icelanders to gain at least some insights into their family origins. But the database was not as comprehensive as it could have been, and so Stefansson sent teams to comb through parish records and subsequent censuses to beef it up.

Icelandic political leaders were hungry to build a strong biotech sector. In 1998, Stefansson began lobbying for a vast, new database that would include the national health insurance records of all living Icelanders, and could be cross-referenced with genealogy and DNA samples. Though much of the data had already been computerized, it was spaced out in hospitals and doctor's offices across the country, in a wide array of disparate systems that would have to be standardized and unified.

The government unveiled a bill to grant Decode the exclusive right to build the database and market it abroad to researchers. The legislation created a firestorm. It contained a provision that assumed Icelanders granted Decode universal consent to use their information, kept anonymous, unless they submitted forms opting out. Critics labeled it an Orwellian power grab. Harvard molecular biologist Richard Lewontin compared Stefansson unfavorably to his Viking ancestors—"at least they made no pretense that their raids were in the public interest"—and suggested a scientific boycott of Iceland. A Dutch Data Protection Commissioner warned Iceland risked conviction by a European Court. After months of vitriol, the legislation passed Parliament. But it was so freighted with privacy

BANK ON IT Decode, which houses blood samples from thousands of Icelanders, has constructed a genealogical chart that accounts for virtually every member of the small island nation.

protections—including a requirement that Decode fund a watchdog—that Stefansson abandoned the effort to partner with the government to create a national database. "It would have driven us into bankruptcy overnight," he said.

It proved a minor setback. Decode continued to collect medical records and DNA from volunteers—along with the permission to reuse them for future studies approved by government bioethics and privacy committees. Each volunteer filled out detailed questionnaires on characteristics ranging from hair color to cholesterol levels to smoking habits, adding up to 2,500 traits. By 2001, Decode reported it discovered or localized genes with small but significant links to preeclampsia, osteoporosis, schizophrenia, Alzheimer's, stroke, and heart attack. Its database was seen as an information goldmine.

That year, Decode launched an initial public offering on NASDAQ and was valued north of $1 billion. By the mid 2000s, Stefansson headed a huge enterprise with hundreds of scientists, geneticists, computer engineers, investor relations personnel—even anthropologists. They were housed in a gleaming new headquarters with an airy atrium lunchroom ringed by several floors of glass-walled offices and laboratories, and topped with a polished glass ceiling that bathed the blond wood floors and paneled walls in sunlight almost 24 hours a day during Iceland's luxurious summers.

In 2000, the Human Genome Project unveiled a draft sequence, revealing that 99.9 percent of the 3 billion bases carried by each individual are identical. Many geneticists argued that meant the causes of common diseases were likely to lie in the remaining 0.1 percent, and most variations were in single bases attached to nucleotides, called "single nucleotide polymorphisms" (SNPs).

Scientists discovered that most genetic material is passed from each parent to child in a remarkably structured architecture that consists of a predictable number of genes chunked together and kept largely unchanged, in a grouping called a haplotype. These haplotypes were believed to have developed very early in human evolution, which meant there were only a small number of common flavors possibly carried by every single person.

In 2002, an international consortium of geneticists set out to find and catalogue individual mutations that were thought to be distinct to every single known individual haplotype, in order to build such a reference guide. By the fall of 2005, scientists had catalogued almost 1.5 million points of DNA, or SNPs, associated with specific haplotypes—which could be quickly identified in blood samples using ingenious chips, called SNP chips. These SNPs could then serve as genetic "signatures" for specific haplotypes, or regions of haplotypes. If you could find SNPs unique to individuals with a disease, it was thought, you could home in on that area of the haplotype and find the mutation that caused that disease.

When the first SNP chips arrived in Decode headquarters in 2006, Stefansson met with his lieutenants

DECODE GENETICS
OPPOSITE PAGE: LINDSAY BLATT

SPLENDID ISOLATION Icelanders had been living in geographic isolation since the days of Vikings, incubating an unusually homogenous gene pool of blonde-haired, blue-eyed virtual cousins. The insular population makes it relatively easy for geneticists to spot errant disease-causing mutations.

to strategize. One day, his computer and statistician whiz, Danial Gudbjardsson, an MIT-trained electrical engineer, burst into Stefansson's office "absolutely fuming with enthusiasm," Stefansson recalled. Earlier that day Decode had received word from the Icelandic Government's Data Protection Commission and Ethics committee granting it permission to do a study on atrial fibrillation (AF), the most common form of irregular heartbeat. Now Gudbjardsson had arrived to report that his team had homed in on the locations of two genetic variants that conferred about a 70 and 40 percent increase in the likelihood of developing AF. Those with two copies of the more powerful variant—one from each parent—had a significant increase in the likelihood of developing the disease. AF was a big fish—it can cause palpitations, congestive heart failure, and increases the risk of stroke four to six times. And they had already done a study on strokes. All they'd had to do was pull out the DNA they already had in their genetic library and run a SNP chip searching for the genetic mutations they found that were associated with AF.

Finding genetic links to the disease using the new methods had taken three hours. In the following months, Decode found common variants of genes associated with glaucoma, sleep disorder, breast cancer, heart attack, osteoporosis, obesity. "After the SNP chips, we had almost a factory of discoveries," Stefansson said. "We left the rest of the world behind in the dust."

EVEN SO, WITHIN JUST a couple of years, skepticism about the power of the new techniques began to grow.

David Goldstein, director of the Institute for Genomic Medicine at Columbia University, had collaborated with Decode on at least two studies. But after a 2007 study coordinated by a research institute of the University of Oxford, he emerged as a critic. The two-year study, which drew on data from 50 research groups, screening the genes of 17,000 people, was described as the biggest study of common disease every completed. It linked 24 genes to seven of the most common diseases, including heart disease, Type 1 and 2 diabetes, bipolar disorder, and Crohn's disease.

But Goldstein was struck by the fact that the study had found only one gene in the case of bipolar disorder—a disease known to be influenced by inherited genes—and the number of bipolar cases correlated with the gene was "barely significant." In fact, the sum of all the genes associated with the various diseases in the study—even if you added in Decode's findings on some of those diseases—didn't seem to come close to accounting for all of the cases one would have expected based on how often these diseases ran in families.

"There were many individuals in the study, so the sample size was reasonable, there should have been more there if common variation was the cause," he said. "There just wasn't much there." Scientists began to refer to this confounding outcome as the "mystery of missing heritability." Perhaps, Goldstein and others argued, most diseases weren't as influenced by common variants as many had assumed, but rather were more influenced by a wide variety of rare mutations—too rare to assume they could be reliably found on haplotypes.

Stefansson continued to argue that even if common variants only explained part of the story, they could still be useful for treating diseases. If they revealed insights into the underlying chemical pathways involved in diseases, those could be used to develop drugs.

But he had bigger problems. By January of 2009, Decode had just $3.7 million left. The credit markets were frozen, and the Icelandic government could do nothing to help—the nation itself was teetering on the verge of insolvency. In November, Decode declared bankruptcy.

Stefansson was not yet willing to concede defeat, and he was pretty certain he knew at least a couple financiers who might be willing to help buy his company out of bankruptcy. When Decode had first gone public in 2000, two venture capital funds—Arch Venture Partners, in Seattle, and Massachusetts-based Polaris Venture Partners—had both cashed out to the tune of about a 700 percent return on investment. A persuasive Stefansson talked the two venture capital companies back into the fray; for significant shares in Decode, they ponied up a total of $40 million. "It seemed to me the company was hitting its stride," said Terry McGuire, a partner at Polaris.

Indeed, just as Decode emerged from bankruptcy in January 2010, a new innovation was hitting the market that would prove more transformative than SNP chips—techniques for sequencing an entire human genome faster and cheaper than ever. If you could sequence an entire human genome cheaply and compare it with others, you didn't need to look at common haplotype markers. You could compare the genetic code at every spot and theoretically, with enough computing power, pick out those rare mutations. The Human Genome Project unveiled a draft of the first fully sequenced genetic code in 2000 for about $500,000. For that same amount of money in 2010, Decode could acquire a revolutionary new machine created by the biotechnology company Illumina that was capable of fully sequencing three DNA samples simultaneously every 10 days. One of the first things Stefansson did was strike a deal to acquire four of the machines.

The invention and commercialization of whole-genome sequencing machines was a breakthrough. Previously, scientists had assumed the answer to understanding disease lay in finding common mutations passed down from long ago and identifiable using SNP chips. But this approach had what many would come to see as a major limitation. Common haplotypes were old. If a mutation caused a disease wouldn't it reduce an individual's chance of survival? Wouldn't that then reduce that individual's chances of passing on his DNA to his offspring? Wouldn't natural selection weed out the mutation?

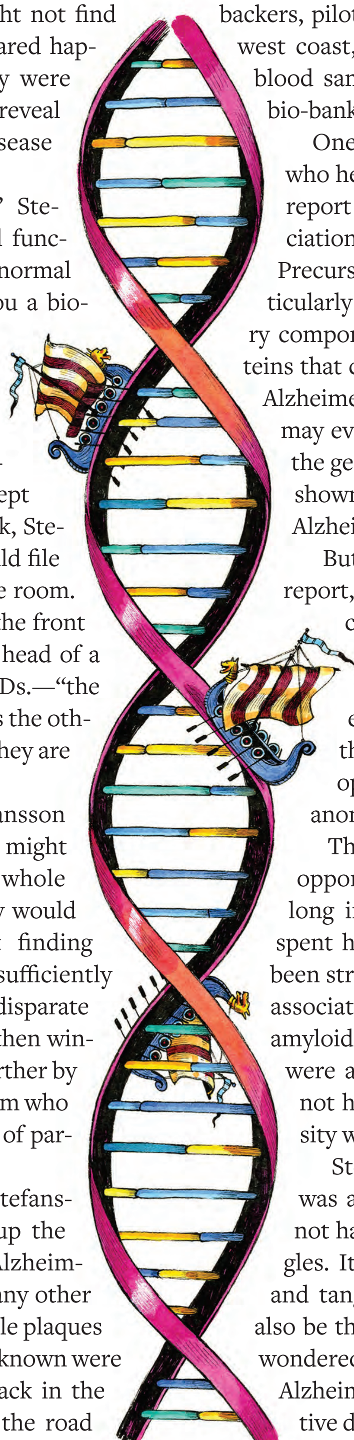
Now, with whole genome sequencing, it became possible to look for extremely rare, relatively new mutations—mutations so powerful they were likely to be quickly weeded out of the population by natural selection. They were so deadly, in other words, they reduced the likelihood a person would live to pass on the mutation to offspring. You might not find these mutations on the ancient, shared haplotypes. But precisely because they were so deadly, they were more likely to reveal something significant about a disease pathway.

These "disasters of evolution," Stefansson said, "disrupt physiological function rather than placing you on a normal distribution curve. But they give you a biochemical pathway—they give you clear indication as to what biochemistry and what biology is being perturbed to cause the disease."

As Decode emerged from bankruptcy in 2010, a new excitement crept into the offices. Several times a week, Stefansson and his top lieutenants would file into a small, glass-walled conference room. Stefansson would emerge, stroll to the front of the room, and take a seat at the head of a big table, facing his brain trust of Ph.Ds.—"the kids"—arrayed in front of him across the other side "so that I can see them, and they are very nice to me."

Sitting around that table, Stefansson and his team discussed how they might most effectively use their new whole genome sequencing machines. They would do so by "double-dipping"—first finding a large group of Icelanders with sufficiently variant family trees to capture the disparate genomes present in every branch—then winnowing down those samples even further by selecting individuals from within them who also happened to have rare diseases of particular interest.

As a young neuropathologist, Stefansson had spent many days slicing up the brain tissue from patients with Alzheimer's disease, contemplating as so many other researchers had before him the telltale plaques and tangles that scientists have long known were associated with the disease. Way back in the winter of 1997, Stefansson had hit the road with his wife and one of his venture capitalist backers, piloting a car through Iceland's picturesque west coast, visiting nursing homes and collecting blood samples which still remain in a basement bio-bank available for sequencing.



One afternoon in 2011, Thorlakur Jonsson, who headed the Alzheimer's project, scanned a report and noticed that it tagged a strong association on a gene known to code for Amyloid Precursor Protein (APP). The finding wasn't particularly surprising. APP was known to be a primary component of amyloid plaques, misfolded proteins that clogged the brains of those stricken with Alzheimer's disease, plaques that many believed may even cause the disease itself. Mutations in the genes coding for APP had long before been shown to increase the likelihood of developing Alzheimer's disease.

But when Jonsson looked closer at the report, he spotted something unexpected—the computer's algorithms had flagged the APP mutation not because it was associated with patients who had the disease. It had flagged the mutation because those who had it were less likely to develop Alzheimer's disease. Could this be an anomaly?

The finding presented Stefansson with an opportunity to explore a question that had long intrigued him. In the many hours he'd spent hunched over a microscope, he'd always been struck by the fact that many of the features associated with Alzheimer's—most notably its amyloid plaques and the neurofibrillary tangles—were also present in elderly patients who did not have the disease. It was just that the density was much higher.

Stefansson knew that cognitive decline was associated with aging. Young people did not have cognitive decline, or plaques and tangles. It seemed likely to him that the plaques and tangles associated with Alzheimer's might also be the cause of cognitive decline. Stefansson wondered if the mutation that protected against Alzheimer's also protected against regular cognitive decline. Proving that point would "give an extraordinarily strong argument in support of the notion that Alzheimer's is just an accelerated form of aging in the brain," he said.

To test the hypothesis, the Decode team sequenced the genes of a control group—a focused population of elderly patients of similar age and living under similar circumstances. When they compared the sequences from elderly patients with and without cognitive decline, they proved this point—the elderly patients they sequenced who had the mutation did not exhibit signs of cognitive decline. Those without the mutation—even those without Alzheimer's—often exhibited cognitive decline.

When Decode published its paper on the new gene, it made worldwide headlines. If drug makers could find a way to replicate the gene, they would have a blockbuster drug that might cure Alzheimer's disease and other forms of senility long associated with aging.

The company was on a new roll. In 2012, Augustine Kong, the company's vice president of statistics, had begun to dig into the numbers associated with the fully sequenced schizophrenic and autistic samples, paying special attention to what are called "de novo" mutations—spontaneous mutations appearing in a child that were not present in either of the parents. After identifying de novo mutations in the schizophrenic, autistic, and other samples by comparing the DNA of individuals with the DNA of their parents, Kong began to look for any common characteristic in the parents that appeared to be associated with the mutations.

One variable in particular stuck out—in well over 90 percent of the cases, the increased number of mutations appeared to be associated with the age of the father. Stefansson was astounded. He and Kong went back through Decode's genealogy database, browsing hundreds of years into the past, and analyzing how the ages of new fathers had changed over the years. To their surprise, the mean age of fathers at conception of a child was far higher in the 19th century, then much of the 20th century. Then in the 1980s, the mean age of the father at the time of conception rose again—which, when you analyzed the correlations, appeared to go hand-in-hand with the rate of autism.

In a paper published in a 2012 issue of *Nature*, Stefansson, Kong, and collaborators presented evidence from 219 samples culled from 78 trios of two parents and a child with autism or schizophrenia. In addition, they sequenced the genomes of high-risk families of schizophrenia and autism to see if they could find any inherited genes that might predispose individuals to the disease. The finding gibed with others coming out at the time that had found a link between older fathers and higher rates of schizophrenia and autism. Decode's paper generated worldwide headlines. In fact, Stefansson argued, the finding showed not only what might be the cause of schizophrenia and autism, but it explains nearly all the difference in the rate of new mutations introduced into populations around the world. The older the age of the fathers at the time of conception—the more variation you are likely to see in the population.

> A Harvard biologist compared Stefansson unfavorably to his Viking ancestors—"at least they made no pretense that their raids were in the public interest."

Itsik Pe'er, an associate professor of computer science at Columbia University who studies computational genetics, said the link between paternal age and mutation rate is now widely accepted, as is the idea that such mutations increase the likelihood of autism and schizophrenia. However, he noted, "mutations occur in nature in all the time. So there are mutations that occur before the father is older, and these mutations are not affected by age."

IN 2012, AS STEFANSSON and his company were unveiling their new studies, Stefansson learned Decode had an admirer in Amgen, the world's largest biotechnology company. Two of the most promising drugs in the Amgen pipeline had grown out of the discovery of rare, but powerful mutations of exactly the sort Decode was now unearthing. Within a month, Amgen struck a deal to acquire Decode for $415 million. The acquisition revived the criticism among a vocal group of Icelanders that Decode was profiting on the DNA and medical records of Iceland's citizens, who saw little in return. One writer and blogger mocked Decode for giving citizens a T-shirt when they signed the consent forms.

In 2015, Stefansson told me Amgen "has left us completely alone," and insisted that he is dedicated to his country's citizenry. "The people have been so generous in contributing to our research," he said. "What is our obligation or duty toward them?" His answer is to work out rules with the nation's health care and ethics authorities to inform Icelanders when they are carriers of "dangerous mutations," like the gene associated with breast cancer. "I think it is basically criminal not to do it, and not in keeping with the general philosophy in our society," he said. "We should help those who are at serious risk and the current minister of health is very enthusiastic about finding ways to take advantage of this."

Decode published four papers in *Nature* in March of 2015. It announced it had sequenced 2,635 Icelanders, a number that allowed it to infer (using family tree data and what it knew about the mutation rate) the genomes of more than 100,000 Icelanders whose genomes have not yet been fully sequenced. It has now sequenced 11,000 full genomes. Using the same statistical methods, Decode could infer the likely presence of mutations in virtually the entire Icelandic population, as they know the mutation rate, how most of the population is related, and how much DNA everyone shares.

In the trove of data, Decode found rare mutations that dramatically increase the risk for Alzheimer's, gallstones, atrial fibrillation, and liver and thyroid diseases—mutations that appear to be the result of "knocked out" or missing pieces of DNA. Perhaps most intriguing is the detective work that lies ahead. All told, Decode identified 1,171 knocked out genes, present in nearly 8 percent of the 104,000 people studied. The next step is to work backward—in the opposite direction one normally goes in genetics research—and cross-reference these knockouts with medical records and phenotypical data and try to determine the impact of these mistakes in nature.

Daniel MacArthur, a geneticist at Massachusetts General Hospital, and assistant professor at Harvard Medical School, who was not involved in the Decode study, called its reach astonishing. "It's a pretty amazing set of results," he said. "Decode over the last decade has assembled an astonishing collection of genetic data—without question the deepest genetic characterization of any national population in the world." He pointed out, however, that in a "bottleneck" population like Iceland's, "you can only find a relatively small subset of [knockout] genes." Decode can identify mutations that cause disease in Iceland, but it will be up to other groups studying other populations elsewhere to identify the vast mutations that remain in the human genome.

In Stefansson's office on that winter day, the Viking scientist concluded our interview with a nod toward his brother, his hero, who ingrained a love of literature in him. "When I think about what I have been doing in science, I am convinced that this all has to do with a story," he said. "If you cannot tell a story with your science, your science isn't worth a shit. I'm 63 and I think back on what is important in my life. I wish I would be a better man. I wish I had been a better husband and a better citizen. But I have told a certain story with my life, and, probably the most interesting aspect of that story are the discoveries that I've made in the science lab—the contribution I have made to the understanding of how man is put together.

"If you think about what is most important when it comes to life on this planet, it is this information that lies in DNA. If you take Walt Whitman and a leaf of grass, the difference between the two lies in the difference in the sequence of their A's, C's, G's, and T's. DNA is the holy grail of life."

Adam Piore is a freelance writer based in New York.

22

SLOW IS GOOD. That's the message of more than a dozen modern slowness movements, from slow fashion to slow food to slow church, most of which have sprung up in the last 20 years, and most of which point a steady finger at modernity. "We do say yes to the accelerated science of the early 21st century," reads the Slow Science manifesto. "However, we maintain that this cannot be all." The World Institute of Slowness puts it more poetically: "Slowness is the forgotten dimension of time."

And this section is indeed full of people chasing slow. The very idea of slow has a hold on us. In fact, we like it so much that we sometimes rush to get it. Are you a woman who wants to have kids late in life? You might want to freeze your eggs, today. Want to give yourself the chance to know your future partner before committing? The one-night stand can help you start.

Slow, it turns out, is nothing without its opposite, and one leads to the other. Which raises the question, is it really an inherent good? We'll let you judge for yourself—take your time.

Welcome to "Slow."

—MS

"We now insist that Web pages load in a quarter of a second, when we had no problem with two seconds in 2009 and four seconds in 2006."

CHELSEA WALD
"Why Your Brain Hates Slowpokes" p. 56

Slow

ANOTHER TIME

Why Egg Freezing Is an Impossible Choice

I don't want to surrender to a lottery. But will I regret not playing?

BY ABBY RABINOWITZ

LAST FALL, I WENT to an egg freezing cocktail hour. The downstairs bar of the glossy SoHo hotel was thronged with women in heels and sleek business attire. Club music thumped, cameras flashed, and I narrowly missed being hit by a videographer angling a tripod over the crowd. The evening was hosted by Eggbanxx, a startup that sells financing for egg freezing, framed as fertility insurance for the forward-thinking urban professional woman.

At the bar, where they were serving up free "Banxxtini" cocktails, I spoke with a 27-year-old who was "95 percent sure" she would freeze her eggs and a 36-year-old data scientist who claimed to be "skeptical." Together, we filed into a screening room adjoining the bar, where three New York-area endocrinologists lectured us on a new technique that, they claimed, could freeze our reproductive chances in time. Female fertility declines sharply at 37, due to a decline in the quantity and quality of eggs. But when women use fresh eggs from a young donor in an in vitro fertilization (IVF) cycle—a process in which fresh eggs are harvested from the donor, fertilized, and transferred to the uterus—live birth rates rise across ages to 56 percent.[1] Now, thanks to a new freezing technology, women could become their own future egg donors, rather than relying on the fresh eggs of another, younger donor. "It's good to be empowered as a woman," beamed Janelle Luk, a doctor at Neway Fertility.

Nicole Noyes of the New York University Fertility Center, lean and intense, spoke energetically about egg freezing, a field in which she was an early leader. She began with a reassuring screenshot of her recent study finding no higher risk of birth defects among 900 children born from frozen eggs.[2] Her clinic's results seemed incredible: If a woman freezes her eggs at 35, Noyes told us, and uses them at, say, 43, she has a 50 percent chance at a live birth from one IVF cycle. Compare that to her unaided chances of conception (using IVF or naturally) at age 43: 5 percent each cycle. If she freezes her eggs later, at 38, her success rate for one IVF cycle dips to 37 percent. According to Noyes, success is determined by the age at which you froze the eggs. "Thirty-one is as long as I'd wait," she told one questioner in a swarm of audience members, many still clutching purple cartons of popcorn, after the presentation. I had lost sight of the 27-year-old, but I spotted the data scientist hurrying up an aisle to sign up.

On the subway ride home, as I pawed through my gift bag containing, among other goodies, a single miniature Lindt white-chocolate egg, I felt anxious, convinced that if I didn't freeze my eggs, I'd be sorry when I was 40. Either I'd gotten a dose of reproductive straight-talk or I'd fallen for a pitch to which—naively—I'd thought myself immune.

Because I actually froze my eggs once before, seven years ago. When I was a 28-year-old graduate student, I learned I had endometriosis, which is often linked with infertility. As I had already lost one ovary, I met with a fertility preservation specialist, who advised me to freeze my eggs. I got 22 eggs, which are still stored in a cryobank, at a cost of $700 a year. At the time, the treatment was experimental: The odds of those eggs resulting in pregnancy are slim, about 4 percent each. But still, I have a stake in those eggs—I realized it back at the cocktail hour, when I learned how poorly their odds compare to eggs frozen with today's improved technology. Now, at 36, I can still have children and am still not ready to do so, because I don't want to raise kids alone. And so, to my surprise, I found myself considering egg freezing again, based on a biomedical marketing event dressed up as a girls' night out in *Sex and the City.*

I decided to look into the science of egg freezing myself, hoping that what I found could determine my choice. But it didn't. Not only were there competing statistics about the odds of conception with frozen eggs, there were also the odds of finding the right partner in time, and a calculation of our precise degree of regret if I make the wrong choice now. Elective egg freezing, I discovered, demands a decision, but does not admit any clear answers.

"I think this egg freezing business puts women in a hard position," I told one of the doctors I interviewed. He had no idea what I meant. "Any option is better

ILLUSTRATION BY OLIMPIA ZAGNOLI

than no option," he told me. By which he meant, any increased chance of getting pregnant later is better than no increased chance. But at this particular cultural moment, and for this generation of women, he was missing the point.

> I found myself considering egg freezing again, based on a biomedical marketing event dressed up as a girls' night out in *Sex and the City*.

SOMETIME AFTER THE EGGBANXX EVENT, I woke to another article in *The New York Times* by a woman who regretted not having children in time: "Freeze your eggs now!" she exhorts a 37-year-old protégée, and, by extension, the reader. By all accounts, more and more healthy women are choosing to freeze their eggs. While there are no official statistics, doctors from two major fertility centers say the number of patients seeking elective egg freezing has doubled annually since 2010, and the use of assisted reproductive technologies, chiefly IVF, has doubled in the past decade.

Egg freezing and IVF are arguably part of a vast demographic shift—a global trend toward delayed childbirth among the affluent.[3] According to the Centers for Disease Control and Prevention (CDC), American women 35 years and older had first children nine times as often in 2012 as they did 40 years earlier. This trend has made for big business: In *The Baby Business*, former Harvard economist and president of Barnard College Debora Spar estimates the United States fertility industry was worth about $3 billion in 2004, of which IVF and fertility drugs accounted for $2.4 billion.[4] Writing in 2006, Spar predicted one obvious way for the market to grow was by extending services from the infertile, about 15 percent of American women, to the perfectly fertile—women eager to "hedge" their fertility bets by freezing their eggs.

Just last October, NBC reported that Apple and Facebook would pay $20,000 for healthy female employees to freeze their eggs electively, for the purpose of delaying motherhood, prompting massive online debate. Supporters backed it as a bold new initiative to empower career-minded women, while critics derided it as a cynical ploy to get women to work longer hours courtesy of an expensive, risky (they claimed) procedure. With this move, the tech companies effectively endorsed the new fertility technology, adding to a widespread conviction that freezing your eggs as a childless, 30-something woman who can afford the out-of-pocket price tag ($10,000-$15,000 just for the drugs and egg retrieval process) is the obvious thing to do.

For many, egg freezing can seem to be just what the doctor ordered. But what is lost in the debate is that both the effectiveness and the risks of egg freezing are far from certain. The science of egg freezing is just too new.

Just 2,000 babies have been born from cryogenically frozen eggs *in the world*—and only 20, for instance, in all of Great Britain.[5] Early data suggests that egg freezing is a woman's best bet for having her own genetic children in her 40s, but framing egg freezing as reliable fertility insurance encourages women to rely too heavily on a technology that is still being refined in many of the clinics where it is being sold.

For decades, the technological barrier to freezing eggs was the difficulty of thawing them. "I had just hundreds of women clamoring after me for egg freezing technology," said Michael Tucker, a leading embryologist at Shady Grove Fertility and Donor EggBank USA. He was describing the flood of phone calls he received after the publication of a 1997 article about the old egg-freezing technology. At the time, embryologists were using the "slow-freeze method"—the one I'd used—which he and the rest of his field generally found unreliable. The egg, as the largest human cell, is

JOIN THE PARTY A stack of fliers advertising EggBanxx's "backup plan" is displayed during the EggBanxx Egg Freezing Party for women's fertility preservation using vitrification in Beverly Hills, California.

PATRICK T. FALLON FOR *THE WASHINGTON POST* VIA GETTY IMAGES

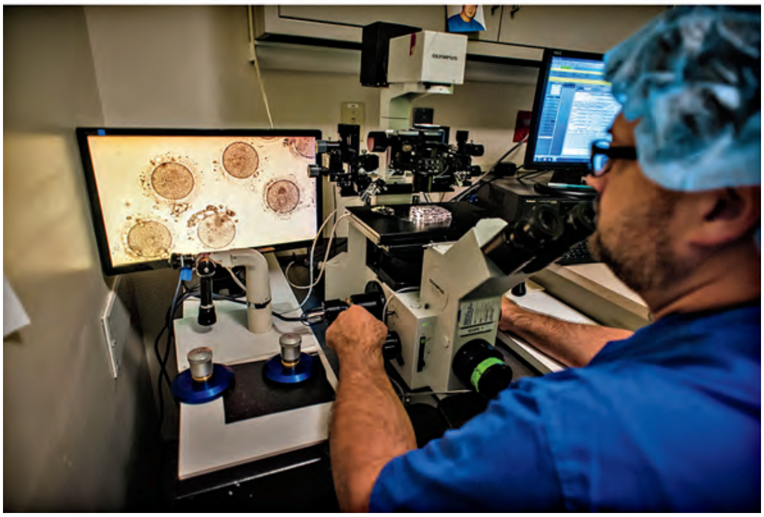
highly liquid; as it freezes, it forms ice crystals, which crack upon thawing.

In the late 1990s, scientists started developing the new vitrification process, in which the egg is dehydrated, treated with anti-freeze, and flash-frozen at a lower temperature, which prevents ice crystals from forming and increases chances of a successful thaw. Over the past 10 years, vitrification has largely supplanted slow-freezing. Using vitrification, Tucker was "much more supremely confident to say, yes, we can provide consistently good fertility outcomes."

That Shady Grove Fertility has seen 200 babies born from frozen eggs supports this claim, but Tucker—like other doctors I interviewed—insists that egg-freezing success varies widely by clinic. For one thing, vitrification is finicky. Tucker told me it requires deft coordination and visual judgment, adding, "We have 26 embryologists and I would trust vitrification to six of them. And warming to four." Tucker, who has led training programs across the country, says he believes that it will be at least four years until clinics across the board can offer similarly consistent results. "That smacks of self-promotion," he acknowledged, but Tucker is hardly alone in this cautious assessment.

The American Society of Reproductive Medicine (ASRM), the self-regulatory organization for U.S. fertility clinics, is not ready to endorse the commercialization of egg freezing. In 2012, the ASRM lifted egg freezing's "experimental" label, thanks to the success and apparent safety of the vitrification process. For a woman, the main risk of egg freezing is ovarian hyperstimulation syndrome (OHSS), caused by fertility drugs, which can cause everything from bloat to, in severe cases, urine stoppage and bleeding.[6] The ASRM has claimed that, without embryo transfer, the risk of OHSS is low, and that 0.4 percent to 2 percent of women taking fertility drugs experience severe OHSS.[7,8] It is more difficult to resolve the question of risks to children born from frozen eggs, as this technology is too new for long-term studies, but the ASRM cited good results from recent studies on infants, including Noyes'.

Still, while the ASRM approved egg freezing for medical purposes—largely for young women with cancer about to undergo sterilizing chemotherapy—the organization cautioned against its "widespread elective use to delay child bearing." After reviewing nearly 1,000 papers, the ASRM could find only four randomized control trials that compared fresh and frozen eggs, mostly from clinics with high pregnancy rates, using eggs from young donors. Not a wide pool of clinics, or 30-something patients. Therefore, the authors concluded, a woman should not put off having children in favor of



AT WORK Jim Graham, the director of Lab Services at Shady Grove Fertility, displays a sample of mature eggs on an HD monitor. Shady Grove, long known for IVF, is now offering egg freezing services for women with health issues or who would otherwise want to postpone childbirth.

ANDRE CHUNG FOR *THE WASHINGTON POST* VIA GETTY IMAGES

freezing her eggs, because "there are no data to support the safety, efficacy, ethics, emotional risks, and cost-effectiveness" of using egg freezing for this purpose.[9]

This is the Catch-22 of elective egg freezing: Its actual effectiveness will remain unknown until enough frontrunners join the experiment.

Of course, the ASRM's stance is far too cautious for some women eager to hedge their fertility bets, and for some ASRM-member fertility clinics, many of which have actively endorsed elective egg freezing for years. In 2010, 143 fertility clinics reported that they offered egg freezing, with 63 percent of the clinics offering elective egg freezing.[10] The technology is very promising, according to Pasquale Patrizio, the director of the Yale Fertility Center, which offers elective egg freezing (they do not partner with Eggbanxx). Patrizio repeated the same formulation I'd heard at the cocktail hour: If a woman freezes an egg, she freezes her chances of getting pregnant with that egg. "The data is starting to appear now," he said. He'd just seen some reassuring statistics presented at the annual ASRM convention in Hawaii, by Noyes.

In the weeks after the egg freezing cocktail hour, it was Noyes' ringing endorsement that lingered in my mind—and her data, which shows the powerful potential of elective egg freezing. When we connected by phone, Noyes told me that in Hawaii she'd presented statistics similar to those at the cocktail hour: Using frozen eggs, the NYU Fertility Center had achieved 62 births and ongoing pregnancies—a 44 percent success rate by cycle, which is impressive, considering that about a third of IVF cycles produce live births.[11] Thirty-one of those 62 births and pregnancies were with women using their own eggs. Those who had frozen their eggs between ages 25 and 34 had a 42 percent chance of a delivery or ongoing pregnancy per cycle; using eggs frozen between 35 and 40, a 37 percent chance per cycle; from 41 to 42, a 33 percent chance per cycle (though this oldest group was represented by a small sample size). Noyes would later tell me that she has revised her estimates to be slightly more conservative. To be on the safe side, Noyes recommends that a woman should freeze 20 eggs for one pregnancy, and, in her late 30s, should expect three freezing cycles to produce that many eggs—and to thaw and implant them. This, of course, translates to a huge investment of time and effort for women hoping to get pregnant. And, of course, money: At the NYU Fertility Center, one cycle of egg freezing, two years of storage, and three attempts to thaw and use those eggs currently costs, by my calculations, $39,410 to $46,560.

Tucker gave me unpublished data similar to Noyes':

Out of 98 pregnancy and thaw cycles in which women used their own frozen eggs at Shady Grove Fertility, 36 produced ongoing pregnancies and live births, with results similarly varying by age. This means that, on average, women had a 36.7 percent chance of having an ongoing pregnancy or live birth by IVF cycle using frozen eggs, comparable to her chances at NYU. These are the kind of optimistic statistics that writer Sarah Elizabeth Richards, who paid nearly $50,000 to freeze 70 eggs between the ages of 36 to 38, quoted in her essay in *The Wall Street Journal*, "Why I Froze my Eggs (And You Should Too)."

But the largest data set available, which looks at outcomes for individuals from a wide range of clinics, suggests that NYU Fertility Center and Shady Grove Fertility's success rates are exceptional. A 2013 meta-analysis in *Fertility and Sterility*, which considers pregnancy outcomes from 2,265 thaw and implantation cycles, performed for 1,805 patients, shows rates roughly *half* as successful as those described by Noyes.[12] For patients who transferred three embryos, success rates were, at 35 years old, 19.3 percent; at 38, 16.5 percent; and at 40, 14.8 percent per cycle. Egg freezing critics use this study to claim that egg freezing fails outrageously often.

To get a clearer picture of these competing statistics, I called Kutluk Oktay, a reproductive endocrinologist at the New York Medical College best known for his revolutionary work on ovarian tissue freezing, a fertility preservation technique mainly intended for cancer patients. He was also, full disclosure, my fertility preservation specialist. Oktay seemed a bit surprised to hear the 2013 meta-analysis was being used to argue against elective egg freezing. He sees it as a slightly conservative assessment, as it draws from data from infertile patients, who likely have poorer outcomes than healthy women freezing electively. Still, he frames it as the best predictive data available to patients, disagreeing that any clinic can provide a baseline success rate by age, as Noyes did at the Eggbanxx event, without documenting hundreds of pregnancies first.

"There is no study that looks at elective freezing and if doing that helps women preserve fertility," Oktay said. This, he told me—as did Patrizio—is because very few women, healthy or otherwise, who have frozen their eggs have actually come back to thaw their eggs. So while the data looks promising, doctors can't make any guarantees—yet.

> The more I knew about egg freezing, the less I felt empowered—largely because of the impossible psychological stance I was being asked to take.

The data is further complicated by the fact that there is currently no way to compare clinics' programs. That's because although the CDC and the ASRM collect IVF data, they do not yet track egg freezing. Both warn potential patients not to use their data to compare clinics, as some clinics turn older, infertile patients away, or end unpromising cycles. So when choosing a clinic, a woman is limited to word-of-mouth—and gossip. "You have to go to a third-party source," Gina Bartasi, the founder and CEO of Fertility Authority, EggBanxx's parent organization, told me, comparing the process to choosing a hotel, complete with reviews. While it's easy to see how Eggbanxx can help a woman compare costs, which can vary widely between clinics (NYU charges about $2,400 more per freezing cycle than neighboring Weill Cornell), it's a bit too early for anyone to predict a clinic's success rates.

The important thing, said Patrizio, is for patients to understand that egg freezing offers not fertility insurance, but "hope." Oktay tells patients, "An insurance policy guarantees to pay if your house burns down," so "egg freezing is not an insurance policy. It's a lottery." He tells patients not to delay childbirth on account of their frozen eggs. "Freeze your eggs, but pretend that you did not freeze your eggs."

IN VITRO FERTILIZATION is the new normal in my part of Brooklyn. With enough time, money, and effort, the thinking goes, anyone can become a parent. You just have to give it your all! The Eggbanxx event framed elective egg freezing as part of this narrative, empowering women to seize control of their reproductive fates. Richards told me women she knows who have frozen their eggs speak of its psychological benefits, in part because it takes the pressure off dating: "If you think they're going to work, you're living your life with more confidence." Egg freezing seems to offer women the chance to decide what kind of life they want to live, freed from their biological clocks. It seems to give women a choice.

But this version of empowerment really points to a deeper constraint. The fact is that women mainly freeze their eggs because they haven't found a partner yet, as Emma Rosenblum found while researching her 2014 *Bloomberg Businessweek* cover story, "Later, Baby: Will Egg Freezing Free Your Career?"[13] Similarly, Noyes' team, surveying 183 egg-freezing patients on why they were delaying childbirth, found that just 24 percent cited professional reasons, while 88 percent cited lack of a partner.[14] In spite of this newfound choice, women are still bound by deeply held cultural expectations about motherhood, starting with the idea that childless women suffer endless regret. The opportunity to freeze their eggs can deepen the power of this expectation.

In researching egg freezing, I have been struck not just by the technology's potential, but also by the impossible psychological stance I have been asked to assume: That is, to have enough trust in this new technology to freeze my eggs, but not enough trust to alter my life choices—to delay having a child, possibly on my own, or seriously prepare myself for other options, like adopting children or not raising children, at all. I am not sure how to do all that.

I *am* sure that I don't want to buy into the unfortunate societal norms reified by egg freezing: That women with money can reproduce how and when they want to, while poor people can't; that we should have a genetic connection with our children; that even though a third of couples who struggle to conceive do so based on male infertility (which also increases as men age) infertility is pretty much a woman's fault, and therefore a woman's problem to solve. "There's this sense that it's all on us," one friend told me, adding that, for her, egg freezing feels "lonely and stigmatizing and hopeless."

I am also sure that I don't want to surrender a relative fortune and a month of my beautiful, ordinary life for bloat-inducing hormone injections, pelvic ultrasounds, weight gain, and worry about the future.

Then again, if I don't freeze my eggs now, I will have ignored all fair warnings from Noyes, various *New York Times* writers, and dog park acquaintances—not to mention statistical accounts of female fertility's decline. I will have rejected the best technological solution on the market. And so, if I can't have a baby one day, I will probably blame myself. That is why, for me, egg freezing is not fertility insurance: It's the perfect regret machine.

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REFERENCES

1. The American Congress of Obstetricians and Gynecologists: Committee Opinion. Female Age-Related Fertility Decline (2014).

2. Noyes, N., Porcu, E., & Borini, A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. *Reproductive BioMedicine Online* **18**, 796-776 (2009).

3. The Centers for Disease Control and Prevention: NCHS Data Brief. First Births to Older Women Continue to Rise. (2014).

4. Spar, D. *The Baby Business: How Money, Science, and Politics Drive the Commerce of Conception*. Harvard Business Review Press, Boston, MA (2006).

5. Gafson, I. The facts don't lie: We haven't cracked egg freezing. Not even close. *The Telegraph* (2014).

6. Johnston, J. & Zoll, M. Is Freezing Your Eggs Dangerous? A Primer. *New Republic* (2014).

7. Gera, P.S., Tatpati, L.L., Allemand, M.C., Wentworth, M.A., & Coddington, C.C. Ovarian hyperstimulation syndrome: steps to maximize success and minimize effect for assisted reproductive outcome. *Fertility and Sterility* **94**, 173-178 (2010).

8. Ovarian Hyperstimulation Syndrome. American Society for Reproductive Medicine www.asrm.org (2015).

9. The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. *Fertility and Sterility* **99**, 37-43 (2013).

10. Rudick, B., Opper, N., Paulson, R., Bendikson, K., & Chung, K. The status of oocyte cryopreservation in the United States. *Fertility and Sterility* **94**, 2642-2646 (2010).

11. 2012 Assisted Reproductive Technology: Fertility Clinic Success Rates Report. The Centers for Disease Control and Prevention www.cdc.gov (2012).

12. Cil, A., Bang, H., & Otkay, K. Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. *Fertility and Sterility* **100**, 492-499 (2013).

13. Rosenblum, E. The Real Reason Women Freeze Their Eggs Isn't Career Growth. *Bloomberg Business* (2014).

14. Hodes-Wertz, B., Druckenmiller, S., Smith, M., & Noyes, N. What do reproductive-age women who undergo oocyte cryopreservation think about the process as a means to preserve fertility? *Fertility and Sterility* **100**, 1343-1349 (2013).

Casual Sex May Be Improving America's Marriages

One-night stands and friends with benefits are just what your brain ordered

BY HELEN FISHER
ILLUSTRATION BY FEDERICA BORDONI

A**N AMERICAN MAN** and a French woman meet on a train in Eastern Europe. They live on different continents. But before the sun comes up, they have spent the night together. What happens next?

You'd expect the answer to be, nothing. It's just a one-night stand in a faraway place. But in director Richard Linklater's trilogy, *Before Sunrise*, *Before Sunset*, and *Before Midnight*, their romance blooms into commitment and kids.

While some might dismiss this as Hollywood romanticism, it is actually a common experience. For the past five years, my colleagues at Match.com and I have conducted an annual national study called *Singles in America*, and in each year, a majority of survey respondents have reported having a one-night stand. And 27 percent of our 2014 respondents reported having had a one-night stand turn into a long-term, committed partnership.[1]

Romantic love is like a sleeping cat; it can be awakened at any time. Feelings of deep attachment, however, take time.

We humans are a romantic tribe. Over 54 percent of American singles (which make up over half of the adult population) believe in love at first sight; 56 percent believe laws should make it easier to wed; 89 percent believe you can stay married to the same person forever. And, remarkably, 33 percent of American singles believe it's ok to leave a "satisfactory marriage" if you are no longer passionately in love. In America, as in much of the post-industrial world, romantic love is in full bloom.

Yet between 43 and 50 percent of American marriages will fail, and some 67 percent of American cohabiting couples report that they are terrified of the social, legal, emotional, and economic consequences of divorce.[2] Divorce, men and women wanly joke, is in the drinking water.

So I have come to believe that—motivated by romance and afraid of what sociologist Andrew Cherlin calls the marriage-go-round—today's singles are ushering a long *pre-commitment stage* into the courtship process. Fast sex is part of the package. Couples want to get to know everything about a potential life partner before they tie the knot. Welcome to the age of slow love.

***SINGLES IN AMERICA* IS NOT** a poll of the Match.com population. Instead, it probes an annual representative sample of over 5,000 Americans, based on the U.S. census. To date we have queried over 25,000 men and women—to my knowledge, the largest national representative study of singles. And what we have found is an abundance of caution.

HOW IT STARTS A scene from *Before Sunrise*, in which Ethan Hawke and Julie Delpy play characters that meet on a train and have a one-night stand. In the final movie of the trilogy, they have been together for years and have twin girls.

HULTON ARCHIVE / HANDOUT

Take hooking-up—an uncommitted sexual encounter between two people who are not currently in a romantic relationship with one another. Hooking up appears reckless. Certainly those who engage in one-night stands are risking sexually transmitted infections, unwanted pregnancy, and emotional trauma. Nevertheless, in the 2014 *Singles in America* study, 66 percent of single men and 50 percent of single women reported that they had engaged in a one-night stand—and these numbers have varied little over the past five years. Why do we hop into the sack with someone we hardly know?

Perhaps because you learn a lot about a person between the sheets. You might even kick-start a real relationship: Any stimulation of the genitals promotes dopamine activity, which can potentially push you over the threshold into falling in love. At orgasm, oxytocin and vasopressin—neurochemicals linked with feelings of attachment—spike. With just one night of casual sex, risky as it is, you may win life's greatest prize: a devoted mating partner.

Nevertheless, few race to the altar after a night in bed together. Instead, many take the next cautious step, a friends with benefits relationship—commitment-lite. In this sexual arrangement, a pair has coitus when convenient, but they don't appear in public as a couple. In 2013, 58 percent of men and 50 percent of women in our *Singles in America* study reported that they'd had a friends with benefits relationship, including one in three people in their 70s. And 28 percent of our 2014 participants had had a friends with benefits relationship turn into a long-term partnership.

Next, many couples move in together—another cautious step toward permanent pairing, which first entered the public discourse with a famous 1966 article by anthropologist Margaret Mead. Mead suggested that a young couple with no immediate plans to reproduce should first make an "individual marriage," a legal tie that excluded bearing children, did not imply a lifelong commitment, and had no economic consequences should the couple part. A "parental marriage" could come later if they so decided.

"Living together," a version of the first step of this two-step marriage, emerged in the 1970s; and today what had been scandalous has become routine. In 2012, 58 percent of those in our *Singles in America* study reported that they have lived with one to five partners outside of wedlock. And as the Pew Research Center notes, some 64 percent of Americans believe this living arrangement is a step toward wedding.[3]

Sexual liberalism has aligned our courtship tactics with our primordial brain circuits for slow love.

But discretion still reigns after partners have agreed to marry. In 2014, 36 percent of singles in our *Singles in America* study said they wanted a pre-nuptial agreement.

Even marriage is becoming provisional. Civil partnerships in England, civil unions in the U.S., and de facto partnerships in Australia enable a couple to start and end a partnership relatively easily. France's *pacte civil de solidarité*, or PACS, is particularly intriguing. Enacted in 1999 primarily to enable gays and lesbians to obtain a legal means of attachment without conventional matrimony, it immediately became popular among heterosexuals. All you do is go to a federal office with your partner and sign some papers to initiate a legal relationship. If you want to end it? Send in a form.

ONE-NIGHT STANDS; hooking-up; friends with benefits; living together; pre-nups; civil unions. These all spell caution. But they also spell logic—because our brain is soft-wired to attach slowly to a partner.

The basic circuits for romantic love lie in primitive regions of the brain, near those that orchestrate thirst and hunger. Romantic love is a drive—one of three basic brain systems that evolved to direct our fundamental human mating and breeding strategy. The sex drive predisposes you to seek a range of mating partners; romantic love enables you to focus your mating energy on a single individual at a time; and feelings of attachment incline you to form a pair-bond at least through the infancy of a single child. Feelings of romantic love and deep attachment to a partner emerge in a pattern highly compatible with the spirit of the times—that is, with slow love.

I say this because my colleagues Lucy Brown, Art Aron, Bianca Acevedo, and I have put new lovers into a brain scanner (using functional Magnetic Resonance Imaging, or fMRI) to measure neural activity as these men and women gazed at a photo of their sweetheart. Those who had fallen madly in love within the past eight months showed activity in brain regions associated with energy, focus, motivation, craving, and intense romantic love. But those who had been passionately in love for eight to 17 months also showed activity in an additional brain region associated with feelings of attachment.[4]

Romantic love is like a sleeping cat; it can be awakened at any time. Feelings of deep attachment, however, take time, and they can endure. In another of our studies, led by Acevedo, we put 17 men and women in their 50s and early 60s into the brain scanner. These participants had been married an average of 21 years, and all maintained that they were still madly in love with their spouse. Their brains showed that they were: They were deeply attached as well.

We have even begun to map some of the brain circuitry responsible for this marital happiness. In our study of long-term lovers, those who scored higher on a marital satisfaction questionnaire showed more activity in a brain region linked with empathy, a trait they had most likely retained from their initial passion.[5] Moreover, when psychologist Mona Xu and her team used my original research design to collect similar brain data on 18 young men and women in China, she found that those who were in love long term showed activity in a brain region associated with the ability to suspend negative judgment and over-evaluate a partner,[6] what psychologists call "positive illusions."[7] Much like men and women who have just fallen madly in love, these long-term partners still swept aside what they didn't like about their mate and focused on what they adored.

Because feelings of attachment emerge with time, slow love is natural. In fact, rapidly committing to a new partner before the liquor of attachment has emerged may be more risky to long-term happiness than first getting to know a partner via casual sex, friends with benefits and living together. Sexual liberalism has aligned our courtship tactics with our primordial brain circuits for slow love.

I AM OPTIMISTIC about the emergence of slow love. During our long agrarian past, our forebears married to please God, the local community, and their extended family. Spouses were tied to the land and to one another. Where could you go with a ton of wheat? A host of associated beliefs about the sexes emerged, including strictly arranged marriages, virginity at marriage, till death do us part, and the credo that a woman's place was in the home. Unchained from the constraints of farm living, today's singles are turning inward, choosing partners for themselves—and taking time to wed. Where marriage was the beginning of a partnership in farming societies, today it is the finale.

Slow love appears to be working, too. In 2012, with Match.com, I surveyed 1,095 married Americans (not on the dating site, of course). Among our questions was: "Knowing what you now know about your spouse, would you marry the same person again?" Eighty-one percent said yes. Moreover, 76 percent of these men and 73 percent of these women said they were still "very much in love." And a 2013 survey of more than 12,000 adults in 15 countries established that 78 percent of married men and women were also "happy."[8]

The marriage revolution going on today may actually enable more happy partnerships. Slow love is, after all, in our DNA.

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REFERENCES

1. All statistics from the *Singles in America* survey are unpublished, and provided courtesy of Helen Fisher.

2. Miller, A.M., Sassler, S., & Kusi-Appouh, D. The specter of divorce: Views from working- and middle-class cohabitors. *Family Relations* **60**, 602-616 (2011).

3. Pew Research Center: Social and Demographic trends. The decline of Marriage and Rise of New Families. www.pewresearch.org (2010).

4. Aron, A., *et al.* Reward, motivation and emotion systems associated with early-stage intense romantic love. *Journal of Neurophysiology* **94**, 327-337 (2005).

5. Acevedo, B., Aron, A., Fisher, H.E., & Brown, L.L. Neural correlates of marital satisfaction and well-being: Reward, empathy, and affect. *Clinical Neuropsychiatry* **9**, 20-31 (2012).

6. Xu, X., *et al.* Reward and motivation systems: A brain mapping study of early-stage intense romantic love in Chinese participants. *Human Brain Mapping* **32**, 249-257 (2011).

7. Zentner, M.R. Ideal mate personality concepts and compatibility in close relationships: A longitudinal analysis. *Journal of Personality and Social Psychology* **89**, 242-256 (2005).

8. Ipsos. Valentine's Day: Correlations Between Relationship Status and Happiness, Financial Situation. www.ipsos-na.com (2014).

What a 9,000-Year-Old Spruce Tree Taught Me

How photographing the world's oldest living things pushed me outside the boundaries of science

BY RACHEL SUSSMAN

I **HAD LITTLE IDEA** of what I would discover when I set out to find and photograph the oldest living things in the world. I expected that researching, traveling, and photographing would stretch my perspective, and force me to learn a lot of science: biology, genetics, chemistry, geology, and so on. But what I didn't expect to learn was that sometimes the right person for a scientific endeavor is an artist.

The *Oldest Living Things* project was motivated not by a narrow interest or a traditional scientific question, but by the idea of something called deep time. Deep time is not a precise demarcation in the way that geologic eras and cosmological epochs are. Rather, it's a framework in which to consider timescales too long for our shallow, physical experience, and too big for our brains to process meaningfully. And why should they be able to? The earliest modern humans had a life expectancy of around 32 years. What evolutionary need would they have had to comprehend what 10,000 years felt like? What I wanted to do was to find or forge something relatable, something to help process and internalize deep time in a meaningful way: to feel expanses of time that we were not designed to feel.

When I first had my "light bulb" moment conceiving the *Oldest Living Things*—which I would eventually publish as a book in 2014—I thought I would find an evolutionary biologist to partner with me. After all, I was an artist with a background in photography whose highest science qualification was 11th-grade physics. It hadn't occurred to me that scientists might declare themselves unqualified for such a broad project.

After a meeting in September of 2006 with an

PHOTOGRAPHY BY THE AUTHOR

Antarctic Moss # 0212-7B33 (5,500 years old; Elephant Island, Antarctica)

Assistant Curator at the New York Botanical Garden in the Bronx, I realized that the *Oldest Living Things* was, in a sense, at odds with scientific specialization. A bryologist might spend his or her career studying one species of moss, or even a single feature or genetic mutation of that moss. In comparison, by the time I'd finished the project, I'd researched two domains, three kingdoms, 12 classes, 21 orders, 31 families, and 39 species of living things, studied by mycologists, bryologists, astrobiologists, marine biologists, dendrochronologists, and climatologists, to name but a few. And while there are many studies on cell aging and death, there is not an established area of study that looks at longevity across species per se. So instead of partnering with a scientific overseer, I was going to have to step into that role myself.

MY FIRST TASK WAS to begin to curate a collection of organisms to photograph, each a minimum of 2,000 years of age. However, aside from some helpful old-tree lists, there was no such compendium of ancient beings already in existence. This in itself spoke to the fact that I was wandering outside the lines of traditional scientific methodologies. A lot of creative Google searching ensued, as well as reading published scientific research papers and reaching out to authors. The list changed and grew over the years, with new organisms being added even as the book went to print. "New" old organisms were discovered during that time, such as the Siberian Actinobacteria, and others had their ages downgraded, as was the case when the 13,000-year-old box huckleberry in Pennsylvania lost about 5,000 years with the insight of updated glaciation data.

To qualify for inclusion, each organism must have gone through at least 2,000 years of continuous life as an individual. I selected 2,000 years as my minimum age specifically to draw attention to the gentleman's agreement of what "year zero" means. In other words, 2,000 years serves both as an all-too-human start date, as well as the baseline age of my subjects. The requirement of endurance on an individual level was an important consideration, because we all innately relate to the idea of self. This was a purposeful anthropomorphization that would further imbue the organisms with a reflective quality in which we could glimpse ourselves.

But once I started digging into the science, things were not so tidy. While unitary organisms such as a single tree are not hard to keep a handle on, things like "clonal colonies" are trickier. Sometimes referred to as "vegetative growth" or "self-propagating," these individuals are able to generate new clones of themselves, as opposed to reproducing sexually like flowering plants do. They create new shoots, stems, or roots without the introduction of new outside genetic material, so that the new growth is genetically identical to—and part of—the original organism. This process can continue indefinitely, or for as long as the environment allows. This is what is meant when it's said that clones are theoretically immortal.

If I were a scientist, grouping unitary and clonal organisms together under the umbrella of "continuously living" would likely raise eyebrows, as this is simply too wide a view to produce a clean outcome. But this idiosyncratic taxonomy is something that I chose to do as an artist, leading to an idiosyncratic taxonomy. Collectively, its members live in some of the world's harshest conditions, uniquely adapted to extreme temperatures, low moisture and nutrient availability, and high altitudes that would leave others bereft. Many, instead of exhibiting fast or robust growth, exhibit quite the opposite: slow and steady. They gracefully weather adversity, bear witness to long expanses of time, and make the most of difficult situations. As a result, we can't help but infuse this ancient crew with sought-after human traits like patience and wisdom.

Over the years I packed up my medium-format film camera again and again, eventually landing on every continent, as I went searching for 5,500-year-old moss in Antarctica, a 2,000-year-old brain coral in Tobago, an 80,000-year-old Aspen colony in Utah, a 2,000-year-old primitive Welwitschia in Namibia, and a 43,600-year-old shrub in Tasmania that's the last of its kind on the planet, to name but a few. Scientists were more than willing to support my cause. I was sometimes invited to join them on their fieldwork expeditions, such as hunting lichens in Greenland or scuba diving amidst the seagrass meadows stretching between two Spanish Mediterranean islands. Sometimes they agreed to meet me on site and guide me to their subjects: the Palmer's Oak in Riverside, California, the Baobab trees of South Africa, and the alien-looking llareta in Chile.

It hadn't occurred to me that scientists might declare themselves unqualified for such a broad project.

Medusa Kelp in Hercules Bay (South Georgia)

Welwitschia Mirabilis #0707-22411 (2,000 years old; Namib Naukluft Desert, Namibia)

Other times I was sent maps and directions and GPS coordinates and sent out on my own. Once I was handed a branch snapped off of a propagated sapling in a research garden by a conservation biologist, who instructed me to match the leaf shape with that of the clonal eucalyptus I was in search of. I set out from Perth and drove south a few hours in search of the more than 6,000-year-old Meelup Mallee, which had survived a road bulldozed through its center and nearly succumbed to a parking lot before its importance was discovered, just in the nick of time. Guided by roadside markers and the relocated parking area, I took out the branch and dodged through thorny underbrush in the unremitting midday sun in search of my tree. Eventually I found a match to the leaf shape and structure—the Meelup Mallee stood just where I was told to look for it.

Finally, there were times when there was no scientific connection to be made and I had to depend on cultural signposts. In Sicily, I learned of a legend describing how a queen got caught in a severe thunderstorm en route to Mount Etna. She and 100 of her knights—and, presumably, their horses—all took shelter under the expansive canopy of a certain chestnut tree sometime between 1035 and 1715. The so-called Chestnut of 100 Horses has pride of place in the community, and has long been protected by a fence after a gentleman attempted to grill sausages *inside* the tree and nearly burnt it down. I heard that story directly from the gatekeeper, Alfio, who allowed me entrance on my visits to the site in 2010 and 2012. Likewise, on Crete, Sicily's Mediterranean neighbor, an ancient olive keeps the town of Ano Vouves on the map. Branches are still culled from it to make wreathes to adorn the winning athletes at the Olympics. The tree is hollow, so it cannot be cored, but if the tree is, in fact, the 3,000-year-old it's claimed to be, it would have already been 200 years old at the time of the first Games in Greece, in 776 B.C.

Over the years, I discovered much that was beyond imagination. My favorite statistic in the whole project came from map lichens (*Rhizocarpon geographicum*) in Greenland that grow only one centimeter every 100 years—something both perfectly relatable and utterly foreign. Continents are drifting away from one another

Stromatolites #1211-0518 (2,000-3,000 years old; Carbla Station, Western Australia)

faster than that. Then there were the stromatolites in Western Australia, bound cyanobacteria combined with non-living sediments, allowing them to straddle biologic and geologic classification. Some were shaped into strangely bulbous forms, and others flat expanses of microbial mats. Some were above water, and others under it. They are understood to be among the earliest living organisms on Earth, and also just so happened to oxygenate our atmosphere, setting the stage for all life to come. It took 900 million years.

IN SOME RESPECTS, what I was doing was not far from science. I was exploring and recording the world, and relying on the help of scientists and their tools and data. But my goals were also not solely—or even primarily—scientific. The *Oldest Living Thing*s is an eccentric archive and time capsule, constructed across disciplines, and at its heart a conceptual art project.

I also financed it on my own. While curiosity and experimentation define the work of both artists and scientists, the money comes from different places. I have yet to encounter a wholly independent scientist, conducting research without institutional funding, whereas there are very few fully—or even partially—supported artists. As for me, I couldn't not do the work, despite the fact that it came at great personal expense. I racked up credit card debt and student loans from an ill-fated foray into a Ph.D. program, bartered artwork for foreign travel immunizations and dentistry, accepted help from family, and borrowed money from friends.

One of my primary goals with this work was to create a little jolt of recognition at the shallowness of human timekeeping and the blink that is a human lifespan. Does our understanding of time have to be tethered to our physiological experience of it? I don't think so. Deep time is like deep water: We are constantly brought back to the surface, pulled by the wants and needs of the moment. But like exercising any sort of muscle, the more we access deep time, the more easily accessible it becomes, and the more likely we are to engage in long-term thinking. The more we embrace long-term thinking, the more ethical our decision-making becomes. It is not the job of traditional science to interpret and translate its findings. Art, on the other hand, is a great mediator.

The dialogue with environmental conservation is a perfect example of the importance of blending art, science, and long-term thinking. Our eyes might glaze over at reading about CO_2 levels at 400+ parts per million, as vital as that statistic is, because it is so hard to relate to such an abstraction. But take, for example, the 9,550-year-old spruce tree on a high mountain plateau in Sweden. For the first 9,500 years of its life it lived as a shrubby mass of branches, close to the ground. But around 50 years ago, a tall and spindly center trunk shot up: a direct effect of a warming climate. It is, in essence,

Chestnut of 100 Horses with fresh lava #0412-1031
(3,000 years old; Sant'Alfio, Sicily)

a portrait of climate change. Perhaps by visualizing such impacts, by anthropomorphizing these ancient lives and activating the science that tells their stories through an artistic lens, we might engage more readily in the long-term thinking required to extend their lives, and by proxy, our own.

Engagement with the sciences is part of how I measure the impact of the *Oldest Living Things* as well. Recently, a scientist that I've never met sent me an email saying that after reading my book, he is now approaching his work with a different, more open mindset. To me, that indicates something has been set into motion. After all, meaning is not made of lone facts, lone people, or lone disciplines, nor is it found in the valuing of the objective over the subjective. Rather, meaning comes by way of knitting together a bigger picture, filled with color and texture, and meant to be felt and understood. We most fully understand what we can internalize—that which becomes part of us. The importance of specializing can't be discarded, but working only within one discipline and strictly adhering to its rules is likely only to generate one kind of work, one kind of result.

We very well might end up missing the forest for the trees.

RACHEL SUSSMAN is a contemporary artist and author of *The New York Times* bestseller *The Oldest Living Things in the World*. She is a Guggenheim, NYFA, and MacDowell Colony Fellow, TED speaker, and a member of Al Gore's Climate Reality Leadership Corps.

Portions of this text originally appeared in Rachel's book, *The Oldest Living Things in the World*.

"LIVE FAST, DIE YOUNG"
ILLUSTRATION BY **KEITH NEGLEY**

Why Your Brain Hates Slowpokes

The high speed of society has jammed your internal clock

BY CHELSEA WALD

NOT LONG AGO I diagnosed myself with the recently identified condition of sidewalk rage. It's most pronounced when it comes to a certain friend who is a slow walker. Last month, as we sashayed our way to dinner, I found myself biting my tongue, thinking, *I have to stop going places with her if I ever want to ... get there!*

You too can measure yourself on the "Pedestrian Aggressiveness Syndrome Scale," a tool developed by University of Hawaii psychologist Leon James. While walking in a crowd, do you find yourself "acting in a hostile manner (staring, presenting a mean face, moving closer or faster than expected)" and "enjoying thoughts of violence?"

Slowness rage is not confined to the sidewalk, of course. Slow drivers, slow Internet, slow grocery lines—they all drive us crazy. Even the opening of this article may be going on a little too long for you. So I'll get to the point. Slow things drive us crazy because the fast pace of society has warped our sense of timing. Things that our great-great-grandparents would have found miraculously efficient now drive us around the bend. Patience is a virtue that's been vanquished in the Twitter age.

Once upon a time, cognitive scientists tell us, patience and impatience had an evolutionary purpose. They constituted a yin and yang balance, a finely tuned internal timer that tells when we've waited too long for something and should move on. When that timer went buzz, it was time to stop foraging at an unproductive patch or abandon a failing hunt.

"Why are we impatient? It's a heritage from our evolution," says Marc Wittmann, a psychologist at the Institute for Frontier Areas of Psychology and Mental Health in Freiburg, Germany. Impatience made sure we didn't die from spending too long on a single unrewarding activity. It gave us the impulse to act.

But that good thing is gone. The fast pace of society has thrown our internal timer out of balance. It creates expectations that can't be rewarded fast enough—or rewarded at all. When things move more slowly than we expect, our internal timer even plays tricks on us, stretching out the wait, summoning anger out of proportion to the delay.

"The link between time and emotion is a complex one," says James Moore, a neuroscientist at Goldsmiths, University of London. "A lot is dependent on expectation—if we expect something to take time then we can accept it. Frustration is often a consequence of expectations being violated."

"Time stretches," Wittman says. "We get mad."

Make no mistake: Society continues to pick up speed

PHOTO BY PETER MARLOW/MAGNUM PHOTOS

Can we stave off the slowness rage and revive patience? We need to find a way to reset our internal timers and unwarp time.

like a racer on Bonneville Speedway. In his book, *Social Acceleration: A New Theory of Modernity*, Hartmut Rosa informs us that the speed of human movement from pre-modern times to now has increased by a factor of 100. The speed of communications has skyrocketed by a factor of 10 million in the 20th century, and data transmission has soared by a factor of around 10 billion.

A down-to-earth gauge was established by psychologist Robert Levine in the early 1990s, when he sent his students around the world to take the pulse of 31 large cities. They timed random people as they walked over a distance of 60 feet. In Vienna, Austria, where I live, pedestrians covered the ground in a respectable 14 seconds. But in my former home of New York, pedestrians zoomed by in 12 seconds. In the 2000s, psychologist Richard Wiseman found worldwide walking speeds had gone up by 10 percent.

The pace of our lives is linked to culture. Researchers have shown society's accelerating pace is shredding our patience. In tests, psychologists and economists have asked subjects if they would prefer a little bit of something now or a lot of it later; say, $10 today versus $100 in a year, or two pieces of food now versus six pieces in 10 seconds.

Subjects—both human and other animals—often go for the now, even when it's not optimal. One study showed that exposing people to "the ultimate symbols of impatience culture"—fast-food symbols like McDonald's golden arches—increases their reading speed and preference for time-saving products, and makes them more likely to opt for small rewards now over larger ones later.

Our rejection of slowness is especially apparent when it comes to technology. "Everything is so efficient nowadays," Wittmann says. "We're less and less able to wait patiently." We now practically insist that Web pages load in a quarter of a second, when we had no problem with two seconds in 2009 and four seconds in 2006. As of 2012, videos that didn't load in two seconds had little hope of going viral.

Of course, we're not going to die if a website doesn't load immediately. But in what is probably a hangover from our primate past—when we could starve if impatience didn't spur us to act—it sure can feel like it. "People expect the payoff to come at some kind of rate, and when it doesn't come, this creates annoyance," posits evolutionary anthropologist Alexandra Rosati, a primate expert, who is finishing a postdoc at Yale before joining the faculty at Harvard.

The result is a less-than-virtuous cycle. The accelerating pace of society resets our internal timers, which then go off more often in response to slow things, putting us in a constant state of rage and impulsiveness. Your mileage may vary, of course, but overall, "we are getting to be a more and more impulsive society," Wittmann says.

Recent research points to a possibility that could make this cycle worse. As my slow-walking friend and I strolled at a snail's pace down the street, I started to fear that we would be so late for our reservation that we would miss it. But when we got to the restaurant, we were no more than a couple minutes behind. My sense of time had warped.

Why? Rage may sabotage our internal timer. Our experience of time is subjective—it can fly by in a flash, or it can drag out seemingly forever. And strong emotions affect our sense of time most of all, explains Claudia Hammond in her 2012 book *Time Warped: Unlocking the Mysteries of Time Perception*. "Just as Einstein's theory of relativity tells us that there is no such thing as absolute time, neither is there an absolute mechanism for measuring time in the brain," she writes.

Time stretches when we are frightened or anxious, Hammond explains. An arachnophobe overestimates the time spent in a room with a spider; a fearful novice skydiver, the time spent hurtling to Earth. People in car accidents report watching events unfold in slow motion. But it's not because our brains speed up in those situations. Time warps because our experiences are so intense. Every moment when we are under threat seems new and vivid. That physiological survival mechanism amplifies our awareness and packs more memories than usual into a short time interval. Our brains are tricked into thinking more time has passed.

On top of that, our brains—in particular, the insular cortex, linked to motor skills and perception—may measure the passing of time in part by integrating many different signals from our bodies, like our heartbeats, the tickle of a breeze on our skin, and the burning heat of rage. In this model, the brain judges time by counting the number of signals it is getting from the body. So if the signals come faster, over a given interval the brain will count more signals, and so it will seem that the interval has taken longer than it actually has.

"We don't have a specific clock in the brain ticking away, but we have the constant and ongoing feeling of our body, which is refreshed every second, and we use this as information when we ask ourselves how much time in the range of seconds has passed," Wittman says. When we're frightened—as well as anxious or unhappy—our bodies send more of these signals to the brain, which counts more seconds than it should. Ten seconds feel like 15; an hour feels like three.

The rush of society may affect our sense of timing and emotions in another way. Neuroscientists like Moore have shown that time seems to pass faster when we have a direct connection to a subsequent event, when we feel we've caused a particular outcome. They call the experience "temporal binding." Conversely, says Moore, "When we have, or feel we have, no control over events, the opposite happens: The internal clock speeds up, meaning we experience intervals as longer."

Can we stave off the slowness rage and revive patience? It's possible. But we need to find a way to reset our internal timers and unwarp time. We can try willpower to push back our feelings, but that only goes so far. All you have to do is watch chimps in lab experiments. When waiting for delayed rewards, even by their own choice, Rosati says, "they do things like exhibit negative vocalizations. They scratch, which is a sign of stress for primates, and they maybe bang the wall, sort of a temper tantrum." Those chimps are your brain on waiting.

There's another downside to the willpower approach. Using our willpower for one thing seems to make us more susceptible to the next temptation, says Northeastern University psychologist David DeSteno, who admits to being "the guy that sighs in the Starbucks line." If he uses all of his self-control to stay silent in line, he might give in to a craving for a Double Chocolate Chunk Brownie when he gets to the front.

Research has shown meditation and mindfulness—a practice of focusing on the present—helps with impatience, although it's not entirely clear why. It could be meditators are better able to cope with the emotional fallout of impatience because they're more used to it.

People who meditate "make friends with uncomfortable space," says Ethan Nichtern, a New York City-based senior meditation teacher in the Shambhala Buddhist tradition, and author of the forthcoming *The Road Home: A Contemporary Exploration of the Buddhist Path*. Meditation provides "a technique for just meeting the present moment as it is, without trying to change the situation."

However, says DeSteno, regular meditation practice isn't something impatient people are likely to practice. He suggests fighting emotion with emotion. He has found that gratitude is a mental shortcut to more patience. In one study, he found that people who did a short writing exercise about something for which they were grateful were more willing to forego smaller rewards now for bigger rewards later. Counting your blessings—even if they have nothing to do with the delay at hand—may remind you of the value of being a member of a cooperative human society and the importance of "not being a jerk," DeSteno says.

That's something I can try. On a recent stroll with my slow-walking friend, I find gratitude is easy to muster. I think fondly of her charming sense of humor, our fun outings, her support during tough times. As we walk, languidly, to a restaurant, I feel momentarily free of my sidewalk rage. Could I really fix this maladapted mechanism so easily? Yet as this warm feeling passes over me in the restaurant, I begin quietly raging at the server, the kitchen, the return tram. I'm even raging at my rage; it feels like it's lasting forever.

Next time, I better just entertain at home.

CHELSEA WALD is a freelance science writer based in Vienna, Austria. Locals know her as the one "presenting a mean face."

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ONE DREARY TUESEDAY, Leó Szilárd decided to take a walk past the British Museum in London. He was irritated by Ernest Rutherford's recent speech dismissing the possibility of practical atomic energy. The day was gray and wet. He was annoyed by a slow traffic light.

But the traffic light changed, and, as the story goes, one thing led to another. Crossing the street, Szilárd realized that nuclear reactions could be maintained by the neutrons they themselves produced. A self-sustaining nuclear reactor became a reality nine years later, and the bomb in another three. Rutherford's opinion had sparked its own undoing, one chain reaction leading to another.

This issue, we watch dominoes fall in human lives, across the oceans and under cities. They even crash the stock market. The end result? It's hard to say—which is kind of the point.

Welcome to "Dominoes."

—MS

"The trouble with these public attacks against the use of computers was, of course, that the country desperately needed computers."

SLAVA GEROVITCH
"How the Computer Got Its Revenge on the Soviet Union" p. 84

Dominoes

ONE THING LEADS TO ANOTHER

Fear in the Cockpit

The tragic plane crash in Taipei was the result of mechanical and psychological failures

BY JEFF WISE

THE MORNING OF FEB. 4, 2015, was drearily normal in Taipei. With the sky blanketed in low clouds, pushed by a moderate breeze, the day was neither hot nor cold, neither stormy nor fair. For many of the passengers that filed aboard TransAsia Airways Flight 235 at Songshan Airport, the journey ahead promised to be similarly workaday: not a jaunt to some exotic clime, but an hour-long puddle-jump across the Taiwan Strait to the city of Kinmen, where many of the passengers had family and work obligations.

At the front of the plane, 42-year-old captain Liao Chien-tsung and 45-year-old first officer Liu Tzu-chung strapped themselves into their seats and ran through their pre-flight checklists. Shortly after 10.30 a.m. the last of the passengers settled into their seats and the cabin crew closed the doors. As the plane started to move, passenger Lin Ming-wei had a hunch that one of the engines sounded funny, and requested that he, his wife, and their 2-year-old son be seated on the right side of the aircraft.

With practiced efficiency, Liao guided the ATR 72-600 along the network of taxiways to Runway 10. After receiving permission to take off, he rolled forward and swung the plane over the centerline. Engine throttles full forward, the twin turboprop engines roared and shook as each machine's six blades chopped the air. Liao released the brakes, and the plane leapt forward. The airspeed indicator slid past 116 knots as the plane's nose, then main wheels, lifted from the runway.

This moment—when a plane transitions from ground vehicle to air vehicle—is the most critical in aviation. It is the part of each flight when a plane has the least altitude, is moving the slowest, and carries the heaviest mass of fuel. Given how much happens in a short span of time, it's also the most mentally demanding. As Liao felt the seat press into his back, his eyes flitted from the instrument panel to the runway and back. Simultaneously he had to keep the plane centered on the runway, monitor its speed and acceleration, pay attention to the radio, and keep alert for signs of malfunction.

Normally this critical phase is over within a few minutes. But every once in a while something goes wrong. For TransAsia 235, that day was today.

At 10:52 a.m., the plane soared past the end of the runway at an altitude of 350 feet, its wheels tucking up into the underbelly as it climbed steeply over the Keelung River. From this height, the pilots could take in the sprawl of Taipei, a dense metropolis ringed on all sides by mountains, with the Keelung's serpentine course wending its way through a valley to the east. Liao held the plane in a right-hand bank, curving from east to southeast toward the heart of the city. Then one of the engines started to emit a disconcerting

ILLUSTRATION BY LINCOLN AGNEW

high-pitched whine. Moments later, an alarm blared in the cockpit. The engine had failed.

For any pilot, losing engine power is a nerve-wracking experience. Engine failure in a plane like the ATR-72-600 is not in itself a catastrophe. It's an eventuality that the planes are designed for—it's why they have multiple engines—and pilots train for. But Liao had to take the right steps immediately. His heart pounding, he knew that he had to throttle back the stricken engine and turn it off to reduce the risk of fire. Once that was done, he'd have enough power from the remaining engine to maintain altitude and maneuver back to the airport for a safe landing.

The plane's black boxes recorded what happened next. Liao reached forward and pulled back on one of the engine throttle levers. But he pulled back on the left one—the one for the good engine. Now the plane was 1,000 feet over one of the most densely populated cities in the world, 25 tons of metal, fuel, and human flesh, with no engines to keep it in the air. A worrisome but manageable problem had suddenly become an imminent and severe one.

THE HUMAN BRAIN HAS been described as the most complicated thing in the universe. It is capable of breathtaking feats of intellectual prowess and stunning leaps of creativity. Yet it is also capable of utterly failing us when we need it most. In the throes of a life-or-death crisis, human beings have an innate tendency to panic. Instead of taking necessary action to save our lives, many of us do the wrong thing, or nothing at all. Why? How could evolution burden us with a faculty so evidently ill-suited to the business of survival? How could an expert pilot make a beginner's mistake?

For millions of years, when our ancestors faced danger, they relied on the fight-or-flight response, a suite of hormonal and behavioral adaptations mediated by a branch of the brain called the sympathetic nervous system. The fight-or-flight response was a kind of autonomic "go bag" that could quickly reconfigure the body's settings for vigorous action.

We've all felt the physical effects: racing heart rate, shallow breathing, trembling, and sweaty palms. The mental effects are just as profound. In a state of heightened arousal, we lay down memories with great intensity, become insensible to pain, and experience an apparent slowing down of time.

In this aroused state, we experience what's known as "cognitive tunneling." Our attention narrows as we focus on the danger at hand. An elevated heart rate and quickened breathing ensures that well-oxygenated blood reaches the muscles. The opening of the sweat ducts reduces the risk that exertion will lead to overheating. Cognitive tunneling means that all mental resources are focused on the main threat.

EDGE OF PANIC This remarkable dashboard-camera image captures a final moment of TransAsia Airways Flight 235. Pilot Liao Chien-tsung, pulling back too hard on the controls, put the left wing into a full aerodynamic stall. With only the right wing now providing lift, the plane rolled over into a 90-degree bank, clipped the highway, inverted, and crashed into the Keelung River in Taipei.

WIKIMEDIA

Yet there is also a flipside. With a narrowed focus it becomes hard to multitask, to think complex thoughts, to decipher instructions, or to generate novel solutions. Our judgment can be clouded, and experience thrown out the window. In extreme cases, we lose the ability to consciously control our behavior at all, and find ourselves willy-nilly engaging in ancient stereotypical behaviors like fighting, running, or playing dead.

Psychologists have identified an optimal level of sympathetic-nervous-system arousal for peak performance. In general, automatic or "mindless" behaviors peak at higher levels of arousal, while more intellectually demanding tasks peak at lower levels. A test-taker sitting down to the SAT will benefit from a small spurt of adrenaline to stay focused and energized; a jogger who suddenly finds himself chased by an angry dog will benefit from having every available physiological resource dumped into the mindless pumping of his legs.

Lilianne Mujica-Parodi, the director of the Laboratory for Computational Neurodiagnostics at Stony Brook University, who has studied the effects of intense fear on humans, points out that one of the reasons fear causes us problems in the modern world is that the response evolved in an environment in which life-and-death threats were pretty simple. "In an evolutionary setting, the threat is physically present," she says. In that context, cognitive tunneling is an asset: "If you're running away from a tiger, you can attend a problem like that directly. You don't need a lot of cognitive room for planning or rumination."

Like a line of dominoes, a relatively minor problem can generate a feedback loop that quickly explodes into full-blown panic.

The problem is that the dangers we face today are best handled at a lower level of fight-or-flight arousal. "The stresses we experience are often abstract, and the cognitive skills that we require are actually disassociated with the actual threat," Mujica-Parodi says. "So you're asking the brain to do something that in an evolutionary setting would be adaptive, but in your current setting is maladaptive."

In other words, when a pilot who's managing a complex modern airliner realizes that his plane is going to crash, he needs the mild fight-or-flight response appropriate for taking a multiple-choice test, but what he gets is a five-alarm response better suited for surviving an animal attack.

IN THE COCKPIT OF TRANSASIA 235, Liao's state of heightened sympathetic-nervous-system arousal had enabled him to take swift action to shut down a stricken engine, but it reduced his ability to think through what he was doing and recognize the context of his actions. We'll never know exactly what was going through his head, but one thing is clear: The engine he shut was down the wrong one.

As he guided the plane along its planned departure route, he apparently did not immediately take in the significance of what had happened, and continued to hold the plane's nose high in order to climb. But a plane with no engine power is not going to gain altitude for long. Bleeding speed, it lofted up to 1,350 feet, held there for a moment, then began, inevitably, to fall.

As the stall alarm blared, Liao and Liu seem to have finally realized what was happening. The plane was losing altitude fast. Instead of continuing toward the crowded city center, Liao banked to the left to follow the course of the Keelung River. He or Liu called the control tower: "Mayday, mayday, engine flameout!"

For people in the grip of a life-or-death emergency, fear has a tendency to spiral. In the 1950s, psychologist Hugh Kohn conducted studies on the effects of stress in which he threatened to give people electric shocks. The threats disrupted their perception and concentration on tasks, creating a "vicious circle" in which "the perception of a poor performance results in an emotional experience, which acts to further decrease the efficiency of performance." In other words, physiological and mental manifestations of the fear response are themselves unfamiliar and powerful, leading to further fear. Like a line of dominoes, a relatively minor problem can generate a feedback loop that quickly explodes into full-blown panic.

A common, deadly mistake of overwhelmed pilots is to put their plane into an aerodynamic stall. When a plane is flying slowly at low altitude, there's an instinctive human reaction to want to move away from the immediate danger and pull back on the controls to gain altitude. Doing so, however, can have exactly the opposite effect. Climbing causes an airplane to slow down, and if its airspeed falls below a critical velocity, the wing dramatically loses its ability to generate lift. Instead of gaining altitude, the plane suddenly drops, often with fatal results. From the very start of flight training, pilots are taught to be extra careful not to raise the nose when low and slow. But every year, pilots panic, forget their training, and die.

The panic spiral is not inevitable, though. When faced with intense danger, some pilots manage to keep their wits about them and fly exactly as they should.

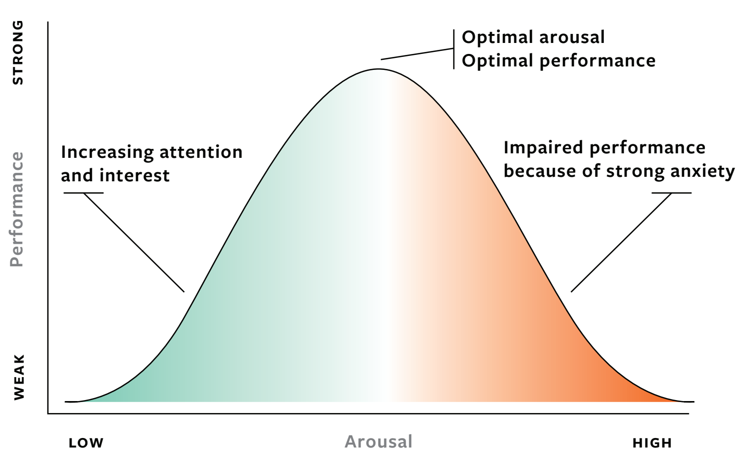
The most celebrated example in recent times is, of course, the "Miracle on the Hudson." On Jan. 15, 2009, Chesley "Sully" Sullenberger was at the controls of an Airbus A320 passenger plane with no engine power just minutes after taking off from LaGuardia Airport in New York City. He found himself gripped by terror. The moment he lost his engines, Sullenberger later wrote, "was the most sickening, pit-of-your stomach, falling-through-the-floor feeling I had ever experienced."

Sullenberger was able to stay mindful of what he needed to do. Keeping the nose low to maintain air-speed, he radioed air traffic control to discuss his options for an emergency landing. After weighing a turn-back to LaGuardia, and a straight-on approach to Teterboro Airport in New Jersey, Sullenberger managed to improvise a third option: to glide down over the top of the George Washington Bridge and ditch in the Hudson River. It was not an easy decision; no one had ever before pulled off such a ditching without fatalities. But Sullenberger had the presence of mind to identify the best among an array of bad choices and commit to it. In the minutes that followed he played his hand masterfully, controlling his speed so that at the moment of touchdown he was moving neither too slowly nor too fast. Not only did the plane remain intact, it stayed afloat long enough for all the passengers to disembark safely onto rescue boats.

What's the difference between Sullenberger, who was able to innovate solutions in the face of imminent death, and Liao, who apparently panicked and shut down the wrong engine? It's a question that researchers like Mujica-Parodi have puzzled over for decades and still haven't completely nailed down.

Physical fitness seems to play a role. Mujica-Parodi has conducted experiments that measure the stress of first-time skydivers. (They jump with electronic sensors on their bodies.) She found that subjects with a lower body mass index had lower stress-hormone levels and performed better on cognitive tasks. There may also be a genetic component: Polymorphisms in the gene for the mu-opioid receptor, located on neuron membranes, and related to hormone release and inhibition, seem to affect how individuals respond to stress. At this point, however, only one factor seems clear-cut, and that is training. We can prepare ourselves for specific dangers by practicing the necessary response to them over and over again.

"The trick is to take a task with a lot of moving parts and put it in muscle memory," Mujica-Parodi says. Once a skill is so well-learned that a person can



Charting Peak Performance

A psychological principle, the Yerkes-Dodson effect, holds that there is an optimal level of sympathetic arousal for peak performance. In general, as visualized in the graph to the left, automatic or athletic behavior like running or jumping (blue) peak with an increase in arousal, while more intellectually demanding tasks like flying a plane (orange) peak with a decrease in arousal.

perform it without conscious attention, it is no longer affected by cognitive tunneling and so is not degraded by increased stress.

Erin Bowen, the chair of the Behavioral and Safety Science Department at Embry-Riddle Aeronautical University, agrees about the importance of training, emphasizing that it has to be the right kind. She points to the work of K. Anders Ericsson at Florida State University, who has demonstrated that expert performance requires deliberate practice in which a person regularly and consciously seeks to identify and master specific skills. "If you engage in mindless practice, and disengage your brain so that you just go through the motions, you're not really focused on the task at hand," Bowen says. The key is to get your actions and awareness in perfect harmony through practice.

Sullenberger was superbly trained. Not only did he have nearly 20,000 hours of flight-time, he was also an experienced glider pilot and aviation safety expert. When it came time to act, he didn't have to think creatively or juggle multiple streams of thought. To him, what he had to do was simple.

TransAsia 235's crew may well have had Sullenberger's example in mind as they turned to follow the course of the Keelung River, but with just 5,000 hours of flight time, Liao may not have had basic aeronautical instincts wired into his system to the same extent. Holding the nose too high so that it remained just on the edge of a stall, Liao could see his altitude draining away. Unlike the Hudson River, the Keelung is narrow and winding. Just ahead of the plane's path, it took a sharp turn to the right, then followed a more-or-less straight course for about a mile—not an ideal ditching spot, but the best within sight. Liao and Liu struggled to restart their good engine as Liao put the plane into a broad right-hand turn to intersect the river's straight section. One final obstacle lay in their way: an elevated highway that ran along the right-hand riverbank. It must have seemed to Liao that if he could just milk a little bit more altitude, he might just clear it. It was a fatal temptation. Pulling back too hard on the controls, Liao put the left wing into a full aerodynamic stall. With only the right wing now providing lift, the plane rolled over into a 90-degree bank, clipped the highway, inverted, and crashed into the river upside-down.

TRANSCENDING FEAR The experienced Chesley "Sully" Sullenberger was able to remain mindful and keep panic at bay in his famous landing on the Hudson River. Recordings from air-traffic controllers reveal a man in control. When a controller asked which runway he would like at Teterboro Airport in New Jersey, he stated, "We're gonna be in the Hudson."

SETH WENIG-POOL/GETTY IMAGES

Of the 58 passengers and crew, only 15 survived. Among them were Lin Ming-Wei and his family, whose decision to move across the aisle proved prescient, as the right side of the plane was less severely damaged by the impact. Both Liao and Liu were killed. When rescuers reached Liao's body, they found his hands still clutching the controls.

We will never know Liao's precise mental state on the morning of February 4. Subjective human experience is not easily untangled by science. What air crash investigators can do, however, is establish the mistakes that pilots make, and try to change things like training syllabi, maintenance procedures, and cockpit layout to minimize the chance that they'll happen again.

At one level, the tragedy of TransAsia 235 is the story of one man's failure. But at another level, it's a reflection of the pitfalls of being a human in a complex and stressful environment. The panic spiral is a fundamental feature of our nervous system. Our saving grace is that while evolution has endowed us with a fatal flaw, it's also given us the smarts to work around it.

JEFF WISE, a science writer and private pilot, is the author of *Extreme Fear: The Science of Your Mind in Danger* and *The Plane That Wasn't There: Why We Haven't Found MH370.*

PTSD: The Wound That Never Heals

Coming back to life after losing my first child

BY LEELA CORMAN


I don't remember the EMTs carrying my daughter's body past me, though I was sitting right there by the door, where the police officer made me sit.
Where did that memory go? It's in there somewhere. It has to be.
But it's flaked away like enamel from an old plate.
The word "amygdala" sounds like a kind of jewel to me, and it sits in the brain like one, too.
...I'm sorry to have to tell you...
In a traumatic situation, it is the one doing the talking,
no matter what else you might be doing.
LIES MY AMYGDALA TOLD ME
I'm here to help you.
You shouldn't get too comfortable.
You never know when it all might collapse again.
Don't go to sleep.


The stress response is a tangled, complicated thing.
I hope a truck hits me today.
My eyes that can no longer see her.
A noisy conversation between your brain and the rest of you.
And really, the two aren't separate.
My womb that made her
My arms that can no longer hold her.
but which cannot forget holding her corpse for the last time.
My feet that itch and cry along with the rest of me.
PTSD symptoms include increased anxiety, avoidance behaviors, hypervigilance, despair,
and flashbacks, the star of the show, in the popular imagination.
You have to make them stop.
But that is just triage
You do that to stop the bleeding.
The wound never heals.


It is difficult to describe the black hole of hypervigilance to someone who isn't experiencing it.
Don't go to sleep.
I won't.
People won't understand.
$11.17, please.
That's the date of her death.
I know.
What?
Nothing.
They will think you're normal,
Because you will appear normal.
Hi.
Keep dancing!
Sure.


Dissociation is another often mentioned symptom.
"Some people will experience having limited ability to regulate their bodily functions and may feel like they are "going crazy" or are "out of my body" during dissociative events. Other people may lose control of their emotions or actions during a dissociative event and can do things that are otherwise quite uncharacteristic."
— National Alliance on Mental Illness (www.nami.org)
For me, it's not quite like that.
Left foot extended...
OWWW
I don't lose touch with consensual reality.
It's more like two movies are playing at once:
Where I am in time and space right now, and the moment of trauma.
Or moments, plural. I'll spare you the details.
Initial Trauma
The initial phase of the stress response seems to be the only predictable part of it.
The hypothalamus tells the pituitary gland to release adrenocorticotropic hormone (ACTH) into the adrenal glands, which then release...
CORTISOL
& NOREPINEPHRINE


After this, there are many different ways that trauma can manifest.
Depending on the person,
the experience,
on so many factors.
That is one reason PTSD is so isolating.
A person with PTSD is unable to unlearn the trauma state. In lab mice, this is called "impairment at extinction".
Of course. Who could "unlearn" losing her child?
She's FINE! You're going to wake her!
Phew...
zzz...
My PTSD mostly manifests now as terrible anxiety about her little sister.
When the brain is bombarded with stress hormones, as in a person with PTSD, cortisol levels can sometimes be too high, which causes hypersensitivity in the brain, and damages the way the brain and the body communicate. You become very sensitive to triggers.
The aftermath of a trigger reaction makes me feel like my insides are coated with something dark and disgusting.


So what can you do? There are many treatments, such as Exposure Therapy, in which the patient recounts the trauma in a controlled setting.
Eye Movement Desensitization and Reprocessing, or EMDR, in which the therapist uses eye movement and controlled talk therapy,
to reprogram emotional response.
And Cognitive Behavioral Therapy,
which seeks to alter harmful thought patterns and reactions in the patient.
Me, I needed to move.
But I made the mistake of treating my body as though nothing had changed,
and I pushed myself so hard that I eventually collapsed.
It turns out that trauma kicks your ass.
What were you thinking?!
Eventually, very gentle yoga, gentler than I'd ever given myself permission to do before, helped me get back to a base level of functioning.

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Yes, You Can Catch Insanity

A controversial disease revives the debate about the immune system and mental illness

BY ANDREW CURRY

O**NE DAY IN MARCH 2010**, Isak McCune started clearing his throat with a forceful, violent sound. The New Hampshire toddler was 3, with a Beatles mop of blonde hair and a cuddly, loving personality. His parents had no idea where the guttural tic came from. They figured it was springtime allergies.

Soon after, Isak began to scream as if in pain and grunt at his parents and peers. When he wasn't throwing hours-long tantrums, he stared vacantly into space. By the time he was 5, he was plagued by insistent, terrifying thoughts of death. "He would smash his head into windows and glass whenever the word 'dead' came into his head. He was trying to drown out the thoughts," says his mother, Robin McCune, a baker in Goffstown, a small town outside Manchester, New Hampshire's largest city.

Isak's parents took him to pediatricians, therapy appointments, and psychiatrists. He was diagnosed with a host of disorders: sensory processing disorder, oppositional defiance disorder, and obsessive-compulsive disorder (OCD). At 5, he spent a year on Prozac, "and seemed to get worse on it," says Robin McCune.

The McCunes tried to make peace with the idea that their son might never come back. In kindergarten, he grunted and screamed, frightening his teachers and classmates. "He started hearing voices, thought he saw things, he couldn't go to the bathroom alone," Robin McCune says. "His fear was immense and paralyzing."

As his behaviors worsened, both parents prepared themselves for the possibility that he'd have to be home-schooled or even institutionalized. Searching for some explanation, they came across a diagnosis called pediatric autoimmune neuropsychiatric disorders associated with streptococci, or PANDAS. First proposed in 1998, PANDAS linked the sudden onset of psychiatric symptoms like Isak's to strep infections.

They didn't give it much thought. Periodic strep tests on Isak had always come back negative. And his symptoms seemed too dramatic to be the result of a simple, common childhood infection.

ILLUSTRATION BY HADLEY HOOPER

But as Isak's illness dragged into its fourth year, they reconsidered the possibility. The year before the epic meltdowns began, his older brother had four strep infections; perhaps it was more than coincidence. In September 2013, three and a half years after his first tics appeared, a pediatric infectious-disease specialist in Boston put Isak on azithromycin, a common antibiotic used to treat food poisoning, severe ear infections, and particularly persistent cases of strep throat.

The results were dramatic. Isak's crippling fear vanished within days. Then he stopped grunting. Less than a week after starting his son on the antibiotic, Adam McCune saw Isak smile for the first time in nearly four years. After a few weeks, the tantrums that had held the family hostage for years faded away.

Today, Adam McCune, a writer, likens the experience to welcoming his son back from captivity. "It's like he was a POW for four years, and returned out of the blue one day," he says. "To have my son back within a week was incredible."

PANDAS REPRESENTS A STRIKING BRANCH of medical research that has been gaining acceptance in recent years, though not without controversy. In a field known as immunopsychiatry, researchers are exploring the possibility that inflammation, or an overactive immune system, is linked to mental disorders that include depression, schizophrenia, and Alzheimer's disease.

A host of recent genetic and epidemiological studies "have shown that when people are depressed or have psychotic episodes, inflammatory markers are found in their blood," says Golam Khandaker, a senior clinical research associate at the University of Cambridge, in England, who studies inflammation and the brain.

In the case of PANDAS, when the body reacts to strep infection, parts of the brain that help regulate motion and behavior wind up caught in the crossfire, mistaken for bacterial invaders by cells bent on destroying them. Eliminate the inflammation, some doctors say, and you signal the immune system to stand down, restoring normal brain function.

The emergence of immunopsychiatry is a story of rediscovery, reflecting the twists and turns of mental health treatment over the last century. In the 19th century, mental illness and infectious disease were closely linked. That connection came uncoupled in the 20th century and immunopsychiatry's argument that infection and inflammation can have a profound impact on the brain has struggled against psychiatric and neurological dogma. Yet emerging insights into mental illness unite the brain, body, and environment in ways that doctors and therapists are finally beginning to understand.

In the 1880s, German psychiatrist Emil Kraepelin argued that mental illness and insanity were biological or genetic conditions. Kraepelin put a wide range of conditions under the umbrella term dementia praecox, or "premature dementia." "He thought it was possibly linked with an infection somewhere in the body," says Khandaker. In the pre-Freud era, Kraepelin's classifications were tremendously influential.

At the time, nothing cemented the link between body and brain quite like syphilis, a sexually transmitted disease caused by the bacterium *Treponema pallidum*. Before antibiotics, a syphilis infection could be a slow-motion death sentence. In addition to ravaging the body, late-stage syphilis victims often escalated into what doctors at the time called neurosyphilis, a sort of manic, delusional state, before edging over into paralysis and death. It was a clear, common case of an infection causing psychosis.

Syphilis was so common it was called "the disease of the century." Most patients were middle-class men; according to one estimate, 10 percent of patients in turn-of-the-century asylums were there because of neurosyphilis. "Syphilis strengthened the idea that

Other kids afflicted with PANDAS hear voices or experience "Alice in Wonderland" syndrome—wildly distorted perceptions.

DAY TO NIGHT When Isak McCune was 2 (left), he was "carefree, pensive, smart, and funny," says his father, Adam McCune. At 4 (right), under the grip of a mysterious disorder, he had violent tics and terrifying visions. "His mood, his demeanor, his behavior—all total opposites of the happy boy we knew."

ADAM MCCUNE

infection and the immune system could be an important cause of mental illness," says Khandaker.

Some potential syphilis cures even seemed to leverage the immune system. In the 1920s, an Austrian psychiatrist named Julius Wagner-Jauregg employed an unconventional syphilis treatment that would be condemned as unethical today. He deliberately infected late-stage syphilitics with malaria, hypothesizing that the ensuing immune response, including high fevers, might somehow burn syphilis out of the system. The treatment killed some but seemed to cure others, a result striking enough to earn Wagner-Jauregg the 1927 Nobel Prize in Medicine, the first ever awarded to a psychiatrist.

In a dramatic turn of medical history, the discovery of penicillin the following year led to our modern age of antibiotics and pushed diseases like syphilis out of the medical mind before the mechanism of Wagner-Jauregg's cure was fully understood.

As antibiotics took hold in medicine, doctors increasingly treated the body and brain as separate entities. After WWII, Freud's influence pushed the search for the roots of mental illness away from infection and disease and toward early childhood, family influence, and society. Autism was blamed on emotionally unavailable "refrigerator mothers," OCD on overly strict toilet training, schizophrenia on harsh parenting styles. Depression was the result of childhood loss, or even an excess of parental love. Conversely, diseases we now know are infections—peptic ulcers, for example—were chalked up to stress and aggressive personalities. Most doctors and psychiatrists agreed that mental illness was all in the mind.

The growing influence of Freudian psychoanalysis coincided roughly with an understanding of the blood-brain barrier, a tightly woven net of tiny capillaries. The barrier acts as a fence between the circulatory system that supplies most of the body with blood and the brain's cerebrospinal fluid, allowing nutrients and oxygen through but keeping blood cells—including immune cells—out. Its existence was hypothesized in the early 20th century and confirmed with the advent of electron microscopy in the 1960s. The blood-brain barrier led physicians to discount the possibility that the immune system's antibodies might cause or contribute to mental illness. The brain was deemed "immunologically privileged."

But it turns out the "blood-brain barrier is not just not inviolate, it's incompletely protective," explains Mady Hornig, an epidemiologist specializing in neuropsychiatric disorders at Columbia University's Mailman School of Public Health. "Parts of the brain are not protected at all, like the hypothalamus. If you have something that opens up the blood-brain barrier, you're opening the gate. Antibodies are able to come into the brain and find their target."

Seen in a larger context, a behavioral response to physical ailments makes intuitive sense. When we're sick with the flu, we feel it, physically and emotionally. We're listless, down, lack appetite. High fevers, usually signs of extreme inflammation, can cloud thinking and induce hallucinations. "Behavior is the ultimate gauge of what's going on elsewhere," says Boris Sakic, a neurologist at Canada's McMaster University. "If you have the flu, your mood changes. You're not in the mood to light a cigarette, have chocolate, or make love to your partner."

Although it's ordinarily fenced off from the body's infection-fighting agents, the brain has a complementary system, called microglia, capable of clearing away damaged neurons and fending off infection. Specialized microglial cells make up 10 to 15 percent of the brain. When they go to work, you feel it. Active microglia interfere with neurotransmitters like serotonin, which activates the pleasure sensors in the brain. "That's why when we have a fever, we feel flat in our mood," Khandaker says.

Usually, so-called "sickness behavior" is just body and brain working together to fight an infection. Loss of appetite reduces the amount of nutrients available to invasive bacteria; low energy levels let the body route resources to the immune system. As soon as the flu clears up, our mood lifts too.

But when inflammation persists, putting the body and brain in a constant state of alarm, sickness behavior—depression, essentially—can become chronic. Over time, inflammation can do real damage to the brain, as the over-active microglia damage healthy brain cells. "The activation of microglia could be responsible for cognitive decline," Khandaker says.

Autoimmune diseases like Type 1 diabetes, lupus, arthritis, asthma, and celiac disease are a good model for understanding the link between inflammation, infection, and mental illness. They are some of the most pernicious chain reactions in the body: Immune cells, usually kept busy fighting infections, take aim at the body's tissues and organs instead, attacking and destroying them with often devastating consequences.

Epidemiological studies have begun to link autoimmune disease to mental illness, supporting the idea that misguided immune reactions can influence the brain. Schizophrenics often have celiac disease, an autoimmune condition of the gut. Lupus, an autoimmune condition that attacks the whole body, sometimes leads to psychotic episodes.

Sometimes the mechanism is even more direct. In her 2012 memoir *Brain on Fire*, journalist Susannah Cahalan described a precipitous descent into paranoia, psychosis, and violent seizures that landed her in the New York University Langone Medical Center epilepsy ward. She was finally diagnosed with anti-NMDA receptor encephalitis, a rare autoimmune condition that attacks the brain and was first described just seven years ago. After being prescribed steroids, which reduce inflammation, and an immune therapy that attacked the offending antibodies, Cahalan recovered her health.

IN 1994, SUSAN SWEDO, a researcher at the National Institute of Mental Health (NIMH) in Bethesda, Maryland, had a hunch that there might be an immunological explanation for obsessive-compulsive disorder. As a model, she was studying a phenomenon known as Sydenham's chorea, or St. Vitus' dance.

First described centuries ago, Sydenham's chorea is a rare manifestation of rheumatic fever that affects children almost exclusively. It is a disconcerting, unmistakable illness to witness. Children are overcome by rapid, uncontrollable jerking of the hands, feet, and face, contorting their bodies in a distorted, disturbing "dance."

Sydenham's chorea is caused by molecular mimicry gone wrong. Molecular mimicry generally works like a wolf in sheep's clothing. Streptococcus bacilli have thrived through the eons by cloaking themselves in proteins that resemble their host's own cells. Disguised, it evades the immune system just long enough to establish an infection.

But sometimes this tactic sets off an unfortunate chain of events. When the immune system mounts its counterattack, it wipes out the wolf and the sheepskin it's wearing. In classic rheumatic fever, the antibodies mistake the lining of the heart for strep bacilli. In Sydenham's chorea, the basal ganglia have a particularly fleece-y look. That, in turn, helps explain an afflicted child's odd motions. The basal ganglia are walnut-sized

> Nothing cemented the link between body and brain quite like syphilis. It was called "the disease of the century."

areas of the brain that serve as a sort of traffic light, signaling the muscles in the proper order to make voluntary movements.

When the basal ganglia are damaged or attacked, the disruption can be severe—as though the traffic light was permanently stuck on green. Parkinson's, cerebral palsy, and attention deficit hyperactivity disorder (ADHD) have been connected to damaged basal ganglia. "The basal ganglia are the gatekeeper between the brain stem and motor function and the upper brain. They say 'stop, go, stop, go,' " says Swedo. "When they don't work right, think of the gate as stuck open in certain areas—it's a failure to inhibit the motor impulse in blinking or twitching."

As Swedo collected case histories of children with OCD, she began to notice remarkable parallels with Sydenham's chorea. Most cases of OCD come on slowly, with tics accumulating and intensifying over months and years. But in about a quarter of the childhood-onset OCD cases Swedo looked at, the compulsive behavior came on like a light switch, going from normal to severe overnight. It was often accompanied by tics, like throat clearing and grunting; severe separation anxiety; bed-wetting; and changes in handwriting as fine motor control broke down.

Like rheumatic fever and Sydenham's chorea, Swedo found, children whose OCD, tics, separation anxiety, and other symptoms came on suddenly often had strep infections not long before their first symptoms appeared. If strep could cause Sydenham's chorea, she wondered, could it also be affecting kids' thoughts and behavior? In a 1998 paper, she proposed a link between strep, OCD, and the other symptoms she was seeing, calling the phenomenon "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections,"—PANDAS.

In classic autoimmune diseases like Type 1 diabetes or lupus, the immune system spontaneously mistakes cells in the body for invaders. In PANDAS and Sydenham's chorea, the attack is set off by an actual infection. As long as the immune system senses strep in the body, it produces antibodies tailored to fight the bacteria. In people with PANDAS, though, the antibodies slip through the blood-brain barrier to attack similar-looking proteins on the cells of the basal ganglia. "The antibodies are somewhat sloppy; they cross-react with other proteins and chemicals," says Hornig. "That can lead to changes in behavior or the brain."

When it comes to treatment, the presence of strep antibodies in the blood of children with OCD is a positive sign. Remove the infection, and the crippling behaviors often go away, too. Once their bodies stand down from the fight against strep, the "cross-reactive" attacks on the basal ganglia seem to stop as well.

Artificially dampening the immune system seems to work in a similar way. Tricia Lord, a California parent whose son Kirk was treated for PANDAS in 2011 with steroids, an immunosuppressant, says she saw improvement within hours. "He was back to what he was before all this happened," Lord says. "I couldn't believe it. He seemed better than 100 percent." (Kirk relapsed after a month, and doctors tried intravenous immunoglobulin, a procedure designed to regulate the immune system, that infuses patients with antibodies extracted from healthy donors. He's now off all medications and performing above his grade level.)

Much remains mysterious, Swedo says, about the symptoms of PANDAS. One of her early PANDAS cases was a 12-year-old girl convinced she caught rabies from an unopened hypodermic needle she found in her pediatrician's parking lot. At the age of 5, Kirk Lord developed severe separation anxiety almost overnight, and sunk into a listless state his parents dubbed "the Fog." Other kids afflicted with PANDAS hear voices or experience "Alice in Wonderland" syndrome, wildly distorted perceptions of size and distance some liken to waking nightmares. "Why is it rabies, or AIDS, or spearmint gum? Some are so random you scratch your head," Swedo says.

Just as puzzling are the kids who don't get PANDAS. Strep can be dangerous, but it's a common part of childhood. The average grade school student comes down with strep twice a year, according to the National Institutes of Health. Yet 1,999 out of 2,000 don't develop PANDAS. Swedo estimates PANDAS accounts for just 10 or 20 percent of all pediatric-onset OCD cases.

That's led to more than a decade of debate over whether PANDAS exists at all. When Swedo and her colleagues first published their PANDAS results, Harvey Singer, a professor of neurology and pediatrics at Johns Hopkins University, and Tourette's researchers questioned the idea that a common childhood illness caused tics and OCD. In a 2011 *Journal of Pediatrics* paper, Singer called the evidence that links strep to PANDAS "inconclusive."

Today Singer says that attempts in numerous studies to confirm the immune system as the "underlying mechanism in PANDAS have been equivocal." As a result, he and other doctors say the diagnosis isn't strong enough to justify giving kids powerful courses of antibiotics, let alone treatments like intravenous immunoglobulin, or plasmapheresis, a blood-filtering process typically used to treat severe autoimmune diseases like lupus. Treatments and medications for OCD and ADHD already exist, they say, and should be enough.

Swedo agrees that traditional treatments—cognitive behavioral therapy, for example—are part of the solution. "But if you culture for strep and treat early, you can abort the entire disease process," she says. "That's one of the reasons this controversy has been so painful."

Since Swedo's 1998 paper, researchers have used MRI scans to show inflamed basal ganglia in the brains of kids with PANDAS. They've swabbed slices of monkey brain with strep cultures taken from PANDAS patients, and observed immediate reactions in the equivalent of basal ganglia tissue. The immediate response to antibiotics and immune-suppressants underscored the connection between the compulsions and volatility of children with PANDAS and their strep infections.

Swedo and her colleagues realize that mental disorders caused directly by infection or autoimmune reaction are the exception rather than the rule. "Not everybody who gets strep ends up with this autoimmune response," says Hornig. "The majority of people are walking around with anti-brain antibodies, but are perfectly healthy. How can that be?"

The answer is that, as appealing as the "one bacteria, one reaction, one cure" model of mental illness may be, most cases can't be explained by looking at the immune system alone. Both advocates and critics of PANDAS agree that mental disorders like OCD, depression, or schizophrenia, in children and adults, should be looked at as a set of symptoms with a variety of possible causes. Genes, environment, and immunity all interact in ways doctors are just beginning to unravel.

As doctors and scientists return to an earlier, holistic understanding of the relationship between body and brain, they are potentially gaining new treatments for terrifying illnesses. Knowing that at least some mental disorders are caused by infection puts a new set of tools at doctors' disposal. Swedo, who today is chief of the Pediatrics and Developmental Neuroscience Branch at NIMH, says this new thinking offers tremendous hope. "The most important fact is just because we don't know what caused it doesn't mean it's not real, and it's not in the brain," she says.

ANDREW CURRY is a journalist in Berlin, Germany. He has written for a wide range of publications, including *Archaeology*, *Discover*, *National Geographic*, and *Wired*.

REFERENCES

1. Bernstein, G.A., Victor, A.M., Pipal, A.J., & Williams, K.A. Comparison of clinical characteristics of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and childhood obsessive-compulsive disorder. *Journal of Child and Adolescent Psychopharmacology* **20**, 333–340 (2010).

2. Garvey, M.A., Giedd, J., & Swedo, S.E. PANDAS: The search for environmental triggers of pediatric neuropsychiatric disorders. Lessons from rheumatic fever. *Journal of Child Neurology* **13**, 413-423 (1998).

3. Khandaker, G.M., *et al*. Inflammation and immunity in schizophrenia: Implications for pathophysiology and treatment. *The Lancet Psychiatry* **2**, 258–270 (2015).

4. Singer, H.S., Gilbert, D.L., Wolf, D.S., Mink, J.W., & Kurlan, R. Moving from PANDAS to CANS. *The Journal of Pediatrics* **160**, 725–731 (2011).

5. Swedo, S.W., *et al*. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. *American Journal of Psychiatry* **155**, 264-271 (1998).

6. Swedo, S.E., Leckman, J.F., & Rose, N.R. From research subgroup to clinical syndrome: Modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). *Pediatrics & Therapeutics* **2**, 1000113 (2012).

7. Tsay, C.J. Juius Wagner-Jauregg and the legacy of malarial therapy for the treatment of general paresis of the insane. *Yale Journal of Biology and Medicine* **86**, 245-254 (2013).

How the Computer Got Its Revenge on the Soviet Union

Condemned as a capitalist tool, the computer would help expose the USSR's weakness

BY SLAVA GEROVITCH

IN 1950, WITH THE COLD WAR in full swing, Soviet journalists were looking desperately for something to help them fill their anti-American propaganda quota. In January of that year, a *Time Magazine* cover appeared that seemed to provide just the thing. It showed an early electromechanical computer called the Harvard Mark III, and boasted the cover line, "Can Man Build a Superman?"

Here was a target that checked the ideological boxes. In May of 1950 Boris Agapov, the science editor of the Soviet *Literary Gazette*, penned a scornful critique of the American public's fascination with "thinking machines." He scoffed at the capitalist's "sweet dream" of replacing class-conscious workers and human soldiers—who could choose not to fight for the bourgeoisie—with obedient robots. He mocked the idea of using computers for processing economic information and lampooned American businessmen who "love information [like] American patients love patented pills." He poured contempt on the Western prophets of the information age, especially the most prominent of them—cybernetics creator Norbert Wiener, a mathematics professor at the Massachusetts Institute of Technology. Cybernetics, which was then just a couple of years old, declared that control and communication mechanisms in biology, technology, and society were fundamentally the same. Of course, Agapov did not actually read Wiener's famous book on the topic, called *Cybernetics*; the content of his article makes clear that all he knew about cybernetics was borrowed from the January 23 issue of *Time*, and possibly largely from its cover image.

In the paranoia-filled environment of the Soviet media, Agapov's article was perceived as a signal from above. The psychologist Mikhail Iaroshevskii took the hint and published two scathing attacks on cybernetics, one in the *Literary Gazette* and another in a 1951 collection of papers titled *Against the Philosophizing Henchmen of American and English Imperialism*. He accused Wiener of reducing human thought

ILLUSTRATION BY ROMAN MURADOV

to formal operations with signs, and labeled cybernetics a "modish pseudo-theory" fabricated by "philosophizing ignoramuses" and "utterly hostile to the people and to science." He went on to cite Wiener's well-known remark that the computer revolution was "bound to devalue the human brain" in the same way that the industrial revolution had devalued the human arm. While Wiener meant his comment to be a liberal critique of capitalism, and called on having "a society based on human values other than buying and selling," Iaroshevskii apparently interpreted it as a misanthropic escapade. "From this fantastic idea," he wrote, "semanticists-cannibals derive the conclusion that a larger part of humanity must be exterminated." Like Agapov, Iaroshevskii hadn't bothered to read any of Wiener's writing. Actually, it wouldn't have been easy: Wiener's *Cybernetics* was withdrawn from Soviet libraries after Agapov's attack. Instead, Iaroshevskii drew his arguments for his critique largely from Agapov's earlier article.

> The Soviet Union began to secretly pursue military computing while condemning the West for doing the same.

As one critic echoed another, repeating older accusations and making up new ones, an anti-cybernetics campaign coalesced. Critics didn't let their ignorance of the actual content of cybernetics stop them—in fact, it helped to unleash their imagination. Skillfully manipulating a handful of Wiener's quotations taken out of context, they stretched the clothing of cybernetics over an ideological straw man. Wiener's passing remark that "information is information, not matter or energy" was exaggerated to become the claim that information had "nothing to do with matter or consciousness," and the critics concluded that cybernetics was marching along a "straight road toward open idealism and religion" (both were, of course, pejorative terms in the Soviet Union).

Philosophers chimed in, bashing cybernetics for "clinging to the decrepit remnants of idealistic philosophy," as well as for being "mechanistic" in reducing the activity of the human brain to "mechanical connection and signaling." Cybernetics, they claimed, was doubly guilty. It deviated from dialectical materialism, the official Soviet philosophy of science, in two opposite directions—toward idealism and toward mechanicism—at the same time. The media portrayed it as both "idealistic" and "mechanistic," "utopian" and "dystopian," "technocratic" and "pessimistic," a "pseudo-science" and a dangerous weapon of Western military aggression. Soviet critics ignored, or possibly were unaware of, Wiener's openly pacifist stand, which he had taken after Hiroshima, and his refusal to participate in military research.

THE TROUBLE WITH THESE public attacks against the use of computers was, of course, that the country desperately needed computers. The military, in particular, recognized the value of the nascent technology, and the risks of being left behind.

So, in a classic example of "doublespeak," the Soviet Union began to secretly pursue military computing while condemning the West for doing the same. While the press ridiculed American "fantasies" of robots giving military orders, Sergei Sobolev, the chief mathematician of the Soviet nuclear weapons program, tirelessly promoted the development of new computers. These included the Soviet Union's first computer, the MESM, and its first small computer, the M-1.

The Soviets even launched a capitalist-style competition between two competing programs in January 1950, the same month that *Time Magazine* ran its famous cover. Each top-secret program was tasked with building large, high-speed electronic computers for military calculations. One, called the BESM, was developed by the Soviet Academy of Sciences; the other, *Strela*, by the Ministry of Machine-Building and Instrument Construction. Both agencies poured enormous resources into these flagship projects and in 1954, *Strela* was declared the winner. Seven copies of the gigantic, room-sized machine were produced and put to military service, helping with the design of the hydrogen bomb, nuclear strike efficiency simulations, missile defense system design, and various navy and

IULII GANF & N. SMOLIANINOV

air force projects. An improved version of the BESM became the fastest computer in Europe, and soon went into production as well. Computer specialists paid lip service to the anti-cybernetics campaign during their political education sessions, and then went to work developing new military control and communication systems based on cybernetic principles.

Working with computers required special care: One had to avoid using any suspicious cybernetic terms. Even the phrase "logical operations" was risky, because it might be interpreted as implying that machines could think. Instead of "computer memory," researchers used the more neutral, technical term, "storage." "Information" was replaced by "data," and "information theory" by the convoluted expression "the statistical theory of electrical signal transmission with noise." A joke about Stalin's henchman, Beria, who was responsible for the nuclear weapons program, became popular. Beria comes to his boss and asks permission to use the notorious field of cybernetics for military purposes. Stalin puffs on his pipe and says, "Okay, but just please make sure the other Politburo members don't find out."

BY 1953, SOVIET CYBERNETICS had spent three years in the doghouse. Its fortunes finally began to turn when, in March of that year, Stalin died, and when the Soviet Union tested its first thermonuclear device five months later (the United States had tested theirs two years before). Scientists and engineers, emboldened by the reputation they had earned for their military work, began to push back against ideologues and Party hacks, who had been supported by Stalin. Disciplines that had been suppressed under Stalin, such as genetics and mathematical economics, began to come back to universities and research labs. Scientists and computer specialists began arguing for a similar rehabilitation of cybernetics. In August 1955, the journal *Problems of Philosophy*, which had published scathing critiques of cybernetics, suddenly reversed

THE EVIL ROBOTS OF CAPITALISM This 1952 cartoon, published in a popular technology magazine, *Tekhnika–Molodezhi*, mocks the American cybernetic dystopia.

its position, like a weathervane sensing the winds of change. It published a landmark article in support of the discipline, called *The Main Features of Cybernetics*.

The article was signed by three heavyweights from the world of military computing, and dismissed all ideological accusations against cybernetics. Instead of trying to reconcile it with dialectical materialism, the authors simply stated that it works, and therefore it must be ideologically correct. Having read Wiener's work in the classified sections of military research libraries, they synthesized a Soviet version of cybernetics that drew its legitimacy from the practical value of computer technology.

The article spurred cybernetics enthusiasts to promote the introduction of computers into various sectors of the civilian economy—from transportation and industrial automation to weather forecasting and economic planning. Once again, the ideological clichés of the regime were brought to bear, but this time in support of the burgeoning field. Researchers began publishing an annual series called *Cybernetics in the Service of Communism*, stressing the bright prospect of computers helping to build a new society.

LARGER THAN LIFE The BESM computer, developed by the Soviets in the 1950s, could easily fill a room, and even an auditorium.

Big Brother, who wanted to see everything and know everything, became overwhelmed with information.

Party leaders were soon convinced, and the 1961 Communist Party Program singled out cybernetics as crucial to the construction of communism. The government issued a string of resolutions authorizing the construction of new computer factories, and the popular press began touting computers as the "machines of communism." The word "cybernetics" abandoned its spot on the blacklist and became a trendy moniker. Genetics was now "biological cybernetics," non-Pavlovian physiology "physiological cybernetics," and mathematical economics "economic cybernetics." Cybernetics was adopted as a new language for the organization of biological systems, and in physiology, it helped replace the simplistic Pavlovian scheme of conditional reflexes, based on a telephone switchboard metaphor, with more sophisticated models that compared the brain to an information processor. Even the law turned its attention to "judicial cybernetics"; legal scholars dreamt of making their concepts "as exact as [those] of mathematics, physics, and chemistry." The Soviet computer had been rebooted.

The cybernetics agenda in economics and management was especially daring. In a remarkable pre-Internet vision, researchers proposed to link together all Soviet enterprises through a unified national computer network which would process economic information in real time and optimize the entire economy. The proposal caused serious alarm among CIA analysts, who began to suspect that cybernetics was becoming too powerful a tool in the hands of the Soviet government. They raised concern with the Kennedy administration, and in October 1962 Arthur Schlesinger, Jr., President Kennedy's special assistant, wrote a memo in which he gloomily predicted that the "all-out Soviet commitment to cybernetics" would give the Soviets "a tremendous

MACHINES OF COMMUNISM SERVE THE PEOPLE Leonid Brezhnev, General Secretary of the Communist Party (third from the right, front row), watches a demo of a specialized Soviet computer for engineering applications at an exhibit in Moscow.

IMAGES COURTESY OF BORIS MALINOVSKY

advantage." Schlesinger warned that, "by 1970 the USSR may have a radically new production technology, involving total enterprises or complexes of industries, managed by closed-loop, feedback control employing self-teaching computers." A special expert panel was set up to investigate the Soviet cybernetic threat.

What Schlesinger may not have appreciated is the degree to which the Soviet establishment was appropriating cybernetics for the purpose of maintaining their administrative hierarchies, and resisting reform. When the Soviet government launched a mammoth effort to introduce computerized management systems into the economy for production control and planning in the 1970s, it did so without fundamentally changing management structures or the balance of power.

This proved to be a grave mistake. The centrally planned Soviet economy was poorly prepared for computerization. Its cumbersome bureaucracy was too slow to implement rapid changes in production and distribution, and it was ruled by industrial ministries which, like separate fiefdoms, did not want to share their information or decision-making power. Each ministry therefore created its own information management system, disconnected from and incompatible with the others. Instead of transforming the top-down economy into a self-regulating system, bureaucrats used their new cybernetic models and computers to protect their power. Expensive and largely useless information management systems were strewn across the country.

The results of top-down computerization were devastating. New computer systems accumulated ever-increasing amounts of raw data and generated terrifying heaps of paperwork. In the early 1970s, roughly 4 billion documents per year circulated through the Soviet economy. By the mid-1980s, after Herculean efforts to computerize the bureaucratic apparatus, this figure rose by a factor of 200 to about 800 billion documents, or 3,000 documents for every Soviet citizen. All this information still had to pass through narrow channels of centralized, hierarchical distribution, squeezed by institutional barriers and secrecy restrictions. Management became totally unwieldy. To get an approval for the production of an ordinary flat iron, for example, a factory manager had to collect more than 60 signatures. Technological innovation became a bureaucratic nightmare.

Big Brother, who wanted to see everything and know everything, became overwhelmed with information that was often distorted by lower-level officials trying to present a rosy picture. Vast clogs of inaccurate information paralyzed the decision-making mechanism, while accurate information was exchanged only locally, like black-market goods or forbidden books in the samizdat. Computers, once vilified and now championed, were constant in one thing: They amplified the virtues and deficits of the system that implemented them. After all, the key idea behind cybernetics was control via feedback. In the hands of self-motivated free agents, it was a powerful economic engine. In the hands of a single controlling agency, it brought stagnation. Or, as computer scientists like to say, "garbage in, garbage out." Called in to prove the superiority of socialism, information technology eventually proved the ineffectiveness of the Soviet regime.

The irony of the situation was not lost on Soviet humor. As one joke tells it, Brezhnev is gifted with the latest in artificial intelligence, so he asks it "When will we have built communism?" The computer responds, "In 17 miles." Brezhnev thinks, "There must be something wrong," and repeats the question. The computer again replies, "In 17 miles." Angered by the incomprehensible reply, Brezhnev orders a technician to investigate the machine. "Everything is correct," replies the technician after some time. "You said it yourself: Every five-year plan is one step toward communism."

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“GROUPTHINK”
ILLUSTRATION BY **CARMEN SEGOVIA**

24

FOR THE PHILOSOPHER OF SCIENCE Karl Popper, the process of science came down to this equation: PS1 → TT1 → EE1 → PS2. A problem situation (PS) leads to tentative theories (TT), then error elimination (EE), then another set of problems. Much of the work of science lies in the error elimination step, and the objective experiments that it requires.

But what if, as the biologist and science historian Stephen Jay Gould argued, the promise of science can't be realized until "scientists give up the twin myths of objectivity and an inexorable march toward the truth?" There is certainly a factual reality out there and science can discover it, Gould wrote, but even the act of observation can be biased by our expectations. Popper called this being "theory-laden."

Error runs rife through the other segments of Popper's equation, too. Nature is full of "mistakes," from improperly copied genes to animals deceiving each other. Even foundational physics has shed some of its air of mathematical inevitability, and wrestles with why we live in a universe that is "right" for life.

Is there a "wrong" universe out there? Or is this question laden with the wrong theory? And how does the scientist negotiate this hall of mirrors, and come out clutching the Truth?

Welcome to "Error."

—MS

"The worst data are better than the best theory. If you look for reasonable results, you will never make a discovery, or at least you will never make an unexpected discovery."

RANSOM STEPHENS

"The Data That Threatened to Break Physics" p. 110

Error

SOMETHING WRONG?

SCHEMAS
Genuine
Flaming Red head
Sneaky
Self serving
dumb blond
apple of my Eye
Stone deaf
Liar
cheeky
Fishy
Red neck
Ambitious
Perceptive

The Bugs in Our Mindware

Many obstacles lie on the path to rational thought

THREE BASEBALL UMPIRES ARE talking about how they play the game. The first says, "I call 'em as they are." The second, "I call 'em as I see 'em." And the third says, "They ain't nothin' till I call 'em."

Most of the time all of us are like the first umpire, thinking that we're seeing the world the way it really is and "calling 'em as they are." That umpire is what philosophers and social psychologists call a "naive realist."[1] He believes that the senses provide us with a direct, unmediated understanding of the world. But in fact, our construal of the nature and meaning of events is massively dependent on stored schemas and the inferential processes they initiate and guide.

We do partially recognize this fact in everyday life and realize that, like the second umpire, we really just "call 'em as we see 'em." At least we see that's true for other people. We tend to think, "I'm seeing the world as it is, and your different view is due to poor eyesight, muddled thinking, or self-interested motives!"

The third umpire thinks, "They ain't nothin' till I call 'em." All "reality" is merely an arbitrary construal of the world. This view has a long history. Right now its advocates tend to call themselves "postmodernists" or "deconstructionists." Many people answering to these labels endorse the idea that the world is a "text" and no reading of it can be held to be any more accurate than any other.

Among the three umpires, the second is closest to the truth.

WE AREN'T TOO DISTRESSED when we discover that lots of unconscious processes allow us to correctly interpret the physical world. We live in a three-dimensional world and we don't have to worry about the fact that the mind makes mistakes when it's forced to deal with an unnatural, two-dimensional world. It's more

ILLUSTRATIONS BY HENRIK DRESCHER

unsettling to learn that our understanding of the nonmaterial world, including our beliefs about the characteristics of other people, is also utterly dependent on stored knowledge and hidden reasoning processes.

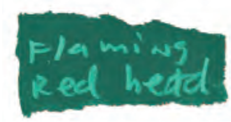
> Donald spent a great amount of his time in search of what he liked to call excitement. He had already climbed Mt. McKinley, shot the Colorado rapids in a kayak, driven in a demolition derby, and piloted a jet-powered boat—without knowing very much about boats. He had risked injury, and even death, a number of times. Now he was in search of new excitement. He was thinking, perhaps, he would do some skydiving or maybe cross the Atlantic in a sailboat. By the way he acted one could readily guess that Donald was well aware of his ability to do many things well. Other than business engagements, Donald's contacts with people were rather limited. He felt he didn't really need to rely on anyone. Once Donald made up his mind to do something it was as good as done no matter how long it might take or how difficult the going might be. Only rarely did he change his mind even when it might well have been better if he had.[2]

Meet "Donald," a fictitious person experimenters have presented to participants. One study describes him as follows:

Before reading the paragraph about Donald, participants first took part in a bogus "perception experiment" in which they were shown a number of trait words. Half of the participants saw the words "self-confident," "independent," "adventurous," and "persistent" embedded among 10 trait words. The other half saw the words "reckless," "conceited," "aloof," and "stubborn." Then the participants moved on to the "next study," in which they read the paragraph about Donald and rated him on a number of traits. The Donald paragraph was intentionally written to be ambiguous as to whether Donald is an attractive, adventurous sort of person or an unappealing, reckless person. The perception experiment removed the ambiguity and shaped readers' judgments of Donald. Seeing the words "self-confident," "persistent," and so on resulted in a generally favorable opinion of Donald. Those words conjure up a schema of an active, exciting, interesting person. Seeing the words "reckless," "stubborn," and so on trigger a schema of an unpleasant person concerned only with his own pleasures and stimulation.

Since the 1920s, psychologists have made much use of the schema concept. The term refers to cognitive frameworks, templates, or rule systems that we apply to the world to make sense of it. The progenitor of the modern concept of schema is the Swiss developmental psychologist Jean Piaget. For example, Piaget described the child's schema for the "conservation of matter"—the rule that the amount of matter is the same regardless of the size and shape of the container that holds it. If you pour water from a tall, narrow container into a short, wide one and ask a young child whether the amount of water is more, less, or the same, the child is likely to say either "more" or "less." An older child will recognize that the amount of water is the same. Piaget also identified more abstract rule systems such as the child's schema for probability.

We have schemas for virtually every kind of thing we encounter. There are schemas for "house," "family," "civil war," "insect," "fast food restaurant" (lots of plastic, bright primary colors, many children, so-so food), and "fancy restaurant" (quiet, elegant decor, expensive, high likelihood the food will be quite good). We depend on schemas for construal of the objects we encounter and the nature of the situation we're in.



Schemas affect our behavior as well as our judgments. The social psychologist John Bargh and his coworkers had college students make grammatical sentences out of a scramble of words, for example, "They her send she usually."[3] For some participants, a number of the words—"Florida," "old," "gray," "wise"—were intended to call up the stereotype of an elderly person. Other participants made sentences from words that didn't play into the stereotype of the elderly. After completing the unscrambling task, the experimenters dismissed the participants. The experimenters measured how rapidly the participants walked away from the lab. Participants who had been exposed to the words suggestive of elderly people walked more slowly toward the elevator than unprimed participants.

If you're going to interact with an old person—the schema for which one version of the sentence-unscrambling task calls up—it's best not to run around and act too animated. (That is, if you have positive attitudes toward the elderly. Students who are not favorably disposed toward the elderly actually walk faster

My grandfather was bankrupted by his reliance on the representativeness heuristic. As a consequence, I'm a psychologist rather than a wheat baron.

after the elderly prime!)[4]

Without our schemas, life would be, in William James' famous words, "a blooming, buzzing confusion." If we lacked schemas for weddings, funerals, or visits to the doctor—with their tacit rules for how to behave in each of these situations—we would constantly be making a mess of things.

This generalization also applies to our stereotypes, or schemas about particular types of people. Stereotypes include "introvert," "party animal," "police officer," "Ivy Leaguer," "physician," "cowboy," "priest." Such stereotypes come with rules about the customary way that we behave, or should behave, toward people who are characterized by the stereotypes.

In common parlance, the word "stereotype" is a derogatory term, but we would get into trouble if we treated physicians the same as police officers, or introverts the same as good-time Charlies. There are, however, two problems with stereotypes: They can be mistaken in some or all respects, and they can exert undue influence on our judgments about people.

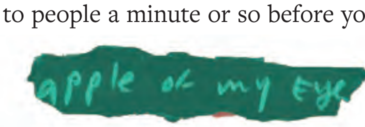
Psychologists at Princeton had students watch a videotape of a fourth-grader they called "Hannah."[5] One version of the video reported that Hannah's parents were professional people. It showed her playing in an obviously upper-middle-class environment. Another version reported that Hannah's parents were working class and showed her playing in a run-down environment.

The next part of the video showed Hannah answering 25 academic achievement questions dealing with math, science, and reading. Hannah's performance was ambiguous: She answered some difficult questions well but sometimes seemed distracted and flubbed easy questions. The researchers asked the students how well they thought Hannah would perform in relation to her classmates. The students who saw an upper-middle-class Hannah estimated that she would perform better than average, while those who saw the working-class Hannah assumed she would perform worse than average.

It's sad but true that you're actually more likely to get a correct read on Hannah if you know her social class than if you don't. In general, it's the case that upper-middle-class children perform better in school than working-class children. Whenever the direct evidence about a person or object is ambiguous, background knowledge in the form of a schema or stereotype can increase accuracy of judgments to the extent that the stereotype has some genuine basis in reality. The much sadder fact is that working-class Hannah starts life with two strikes against her. People will expect and demand less of her, and will perceive her performance as being worse than if she were upper middle class.

A serious problem with our reliance on schemas and stereotypes is that they can get triggered by incidental facts that are irrelevant or misleading. Any stimulus we encounter will trigger spreading activation to related mental concepts. The stimulus radiates from the initially activated concept to the concepts that are linked to it in memory. If you hear the word "dog," the concept of "bark," the schema for "collie," and a mental representation of your neighbor's dog "Rex" are simultaneously activated.

We know about spreading activation effects because cognitive psychologists find that encountering a given word or concept makes us quicker to recognize related words and concepts. For example, if you say the word "nurse" to people a minute or so before you ask them



to say "true" or "false" to statements such as "hospitals are for sick people," they will say "true" more rapidly than if they hadn't just heard the word "nurse."[6]

INCIDENTAL STIMULI THAT DRIFT into the cognitive stream can affect what we think and what we do, including even stimuli that are completely unrelated to the cognitive task at hand. Words, sights, sounds, feelings, and even smells can influence our understanding of objects and direct our behavior toward them. That can be a good thing or a bad thing, depending.

Which hurricane is likely to kill more people? One named Hazel or one named Horace? Certainly seems it could make no difference. What's in a name? Especially one selected at random by a computer. In fact, however, Hazel is likely to kill lots more people.[7] Female-named hurricanes don't seem as dangerous as male-named ones, so people take fewer precautions.

Want to make your employees be more creative? Expose them to the Apple logo.[8] And avoid exposing them to the IBM logo.

It's also helpful for creativity to put your employees in a green or blue environment (and avoid red at all costs).[9–11] Want to get lots of hits on a dating website? In your profile photo, wear a red shirt, or at least put a red border around the picture. Want to get taxpayers to support education bond issues? Lobby to make schools the primary voting location.[12] Want to get the voters to outlaw late-term abortion? Try to make churches the main voting venue.

Want to get people to put a donation for coffee in the honest box? On a shelf above the coffee urn, place a coconut like the one pictured below. That would be likely to cause people to behave more honestly. A coconut with a different pattern of dots would likely net you nothing. The coconut pictured here is reminiscent of a human face (coco is Spanish for head) and people subconsciously sense their behavior is being monitored. (Tacitly, of course—people who literally think they're looking at a human face would be in dire need of an optometrist or psychiatrist, possibly both.)

Actually, it's sufficient to just have a picture of three dots in the orientation of this coconut to get more contributions.[13]

Want to persuade someone to believe something by giving them an editorial to read? Make sure the font type is clear and attractive. Messy-looking messages are much less persuasive.[14] But if the person reads the editorial in a seafood store or on a wharf, its argument may be rejected.[15] If the person is from a culture that uses the expression "fishy" to mean "dubious," that is. If not, the fishy smell won't sway the person one way or the other.

Bodily states also find their way into the cognitive stream. Want to be paroled from prison? Try to get a hearing right after lunch. Investigators found that if Israeli judges had just finished a meal, there was a 66 percent chance that they would vote for parole.[16] A case that came up just before lunch had precisely zero chance for parole.

Want someone you're just about to meet to find you to be warm and cuddly? Hand them a cup of coffee to hold. And don't by any means make that an iced coffee.[17]

You may recall the scene in the movie *Speed* where, immediately after a harrowing escape from death on a careening bus, two previously unacquainted people (played by Keanu Reeves and Sandra Bullock) engage in a passionate kiss. It could happen. A man who answers a questionnaire administered by a woman while the two are standing on a swaying suspension bridge high above a river is much more eager to date her than if the interview takes place on terra firma.[18] The study that found this effect is one of literally dozens that show that people can misattribute physiological arousal produced by one event to another, altogether different one.

If you're beginning to suspect that psychologists have a million of these, you wouldn't be far wrong. The most obvious implication of all the evidence about the importance of incidental stimuli is that you want to rig environments so that they include stimuli that will make you or your product or your policy goals attractive. It's obvious when stated that way.

Less obvious are two facts: (1) The effect of incidental stimuli can be huge, and (2) you want to know as much as you possibly can about what kinds of stimuli produce what kinds of effects. A book by Adam Alter called *Drunk Tank Pink* is a good compendium of many of the effects we know about to date. (Alter chose the title because of the belief of many prison officials and some researchers that pink walls make inebriated men tossed into a crowded holding cell less prone to violence.)

A less obvious implication of our susceptibility to "incidental" stimuli is the importance of encountering objects—and especially people—in a number of different settings if a judgment about them is to be of any consequence. That way, incidental stimuli associated with given encounters will tend to cancel one another out, resulting in a more accurate impression. Abraham Lincoln once said, "I don't like that man. I must get to know him better." To Lincoln's adage, I'd add: Vary the circumstances of the encounters as much as possible.

WE OFTEN ARRIVE AT JUDGMENTS or solve problems by use of heuristics—rules of thumb that suggest a solution to a problem, and can introduce errors in judgment. Dozens of heuristics have been identified by psychologists.

Several of the most important heuristics were identified by the Israeli cognitive psychologists Amos Tversky and Daniel Kahneman. The most important of their heuristics is the representativeness heuristic.[19] This rule of thumb leans heavily on judgments of similarity. Events are judged as more likely if they're similar to the prototype of the event than if they're less similar. The heuristic is undoubtedly helpful more often than not. Homicide is a more representative cause of death than is asthma or suicide, so homicides seem more likely causes than asthma or suicide. Homicide is indeed a more likely cause of death than asthma, but there are twice as many suicide deaths in the United States in a given year than homicide deaths.

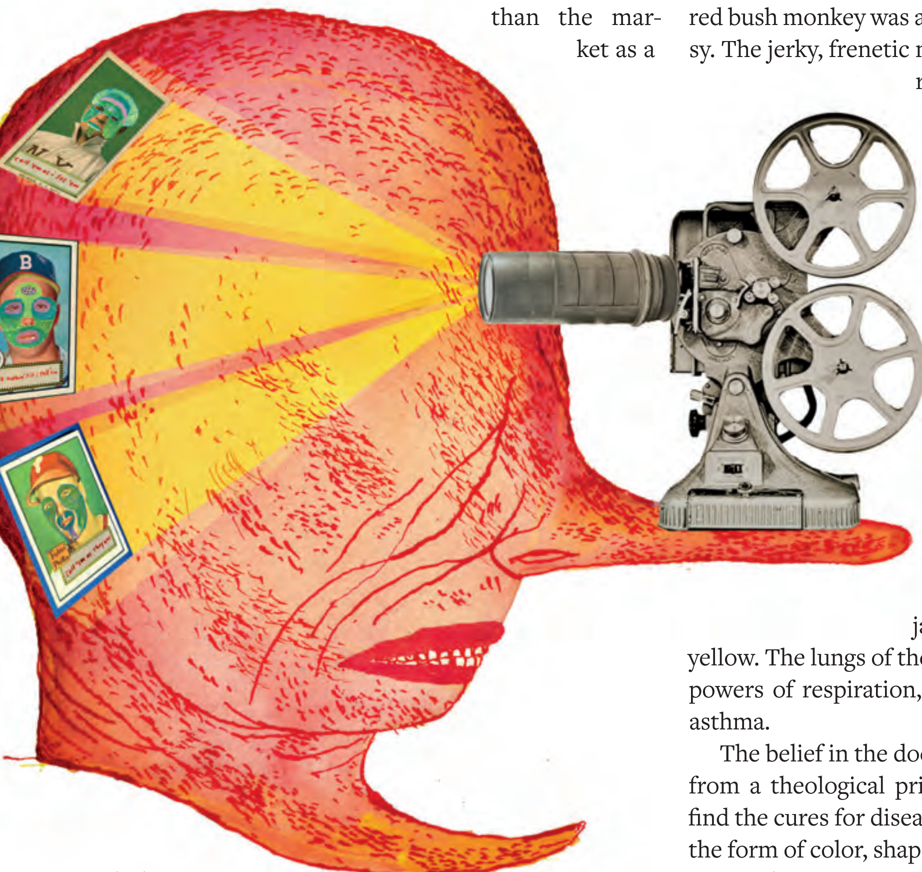
A particularly unnerving example of how the representativeness heuristic can produce errors concerns one "Linda." "Linda is 31 years old, single, outspoken, and very bright. She majored in philosophy. As a student, she was deeply concerned with issues of discrimination and social justice and also participated in antinuclear demonstrations." After reading this little description, people were asked to rank eight possible futures for Linda.[20] Two of these were "bank teller" and "bank teller and active in the feminist movement." Most people said that Linda was more likely to be a bank teller active in the feminist movement than just a bank teller. "Feminist bank teller" is more similar to the description of Linda than "bank teller" is. But of course this is a logical error. The conjunction of two events can't be more likely than just one event by itself. Bank tellers include feminists, Republicans, and vegetarians. But the description of Linda is more nearly representative of a feminist bank teller than of a bank teller, so the conjunction error gets made.

Representativeness judgments can influence all kinds of estimates about probability.

The representativeness heuristic can affect judgments of the probability of a limitless number of events. My grandfather was once a well-to-do farmer in Oklahoma. One year his crops were ruined by hail. He had no insurance, but he didn't bother to get any for the coming year because it was so unlikely the same thing would happen two years in a row. That's an unrepresentative pattern for hail. Hail is a rare event and so any particular sequence of hail is unlikely. Unfortunately, hail doesn't remember whether it happened last year in northwest Tulsa or southeast Norman. My grandfather did get hailed out the next year. He didn't bother to get insurance for the next year because it was really inconceivable that hail would strike the same place three years in a row. But that, in fact, did happen. My grandfather was bankrupted by his reliance on the representativeness heuristic to judge probabilities. As a consequence, I'm a psychologist rather than a wheat baron.

When you see a basketball player score points five times in a row, there's no reason to keep passing the ball to him any more than to some other player. The player with the "hot hand" is no more likely to make the shot than another player with a comparable record for the season.[21] (The more familiar you are with basketball, the less likely you are to believe this. The more familiar you are with statistics and probability theory, the more likely you are to believe it.)

The basketball error is characteristic of a huge range of mistaken inferences. Simply put, we see patterns in the world where there are none because we don't understand just how un-random-looking random sequences can be. We suspect the dice roller of cheating because he gets three 7s in a row. In fact, three 7s are precisely as likely as 3, 7, 4 or 2, 8, 6. We hail a friend as a stock guru because all four of the stocks he bought last year did better than the market as a whole. But four hits is no less likely to happen by chance than two hits and two misses or three hits and one miss. So it's premature to hand your portfolio to your friend.



The representativeness heuristic sometimes influences judgments about causality. I don't know whether Lee Harvey Oswald acted alone in the assassination of John F. Kennedy or whether there was a conspiracy involving other people. I have no doubt, though, that part of the reason so many people have been convinced that there was a conspiracy is that they find it implausible that an event of such magnitude could have been effected by a single, quite unprepossessing individual acting alone.

Some of the most important judgments about causality that we make concern the similarity of a disease and treatment for the disease. The Azande people of Central Africa formerly believed that burnt skull of the red bush monkey was an effective treatment for epilepsy. The jerky, frenetic movements of the bush monkey resemble the convulsive movements of epileptics.

The Azande belief about proper treatment for epilepsy would have seemed sensible to Western physicians until rather recently. Eighteenth-century doctors believed in a concept called the "doctrine of signatures." This was the belief that diseases could be cured by finding a natural substance that resembles the disease in some respect. Turmeric, which is yellow, would be effective in treating jaundice, in which the skin turns yellow. The lungs of the fox, which is known for strong powers of respiration, were considered a remedy for asthma.

The belief in the doctrine of signatures was derived from a theological principle: God wishes to help us find the cures for diseases and gives us helpful hints in the form of color, shape, and movement. He knows we expect the treatment to be representative of the illness. This now sounds dubious to most of us, but in fact the representativeness heuristic continues to underlie alternative medicine practices such as homeopathy and Chinese traditional medicine—both of which are increasing in popularity in the West.

Representativeness is often the basis for predictions when other information would actually be more helpful. About 20 years out from graduate school a friend and I were talking about how successful our peers had been as scientists. We were surprised to find how wrong we were about many of them. Students we thought were sure to do great things often turned out to have done little in the way of good science; students we thought were no great shakes turned out to have done lots of excellent work. In trying to figure out why we could have been so wrong, we began to realize that we had relied on the representativeness heuristic. Our predictions were based in good part on how closely our classmates matched our stereotype of an excellent psychologist—brilliant, well read, insightful about people, fluent. Next we tried to see whether there was any way we could have made better predictions. It quickly became obvious: The students who had done good work in graduate school did good work in their later career; those who hadn't, fizzled.

The lesson here is one of the most powerful in all psychology. The best predictor of future behavior is past behavior. You're rarely going to do better than that. Honesty in the future is best predicted by honesty in the past, not by whether a person looks you steadily in the eye or claims a recent religious conversion. Competence as an editor is best predicted by prior performance as an editor, or at least by competence as a writer, and not by how verbally clever a person seems or how large the person's vocabulary is.

IT'S POSSIBLE TO MAKE fewer errors in judgment by following a few simple suggestions.

Remember that all perceptions, judgments, and beliefs are inferences and not direct readouts of reality. This recognition should prompt an appropriate humility about just how certain we should be about our judgments, as well as a recognition that the views of other people that differ from our own may have more validity than our intuitions tell us they do.

Be aware that our schemas affect our construals. Schemas and stereotypes guide our understanding of the world, but they can lead to pitfalls that can be avoided by recognizing the possibility that we may be relying too heavily on them. We can try to recognize our own stereotype-driven judgments as well as recognize those of others.

Remember that incidental, irrelevant perceptions and cognitions can affect our judgment and behavior. Even when we don't know what those factors might be, we need to be aware that much more is influencing our thinking and behavior than we can be aware of. An important implication is that it will increase accuracy to try to encounter objects and people in as many different circumstances as possible if a judgment about them is important.

Finally, be alert to the possible role of heuristics in producing judgments. Remember that the similarity of objects and events to their prototypes can be a misleading basis for judgments. Remember that causes need not resemble effects in any way. And remember that assessments of the likelihood or frequency of events can be influenced simply by the readiness with which they come to mind.

In other words, call that pitch as you see it.

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REFERENCES

1. Ross, L. & Ward, A. Naive realism in everyday life: Implications for social conflict and misunderstanding. In Reed, E.S., Turiel, E., & Brown, T. (Eds.), *Values and Knowledge* Psychology Press, New York, NY (2013).

2. Higgins, E.T., Rholes, W.S., & Jones, C.R. Category accessibility and impression formation. *Journal of Experimental Social Psychology* **13**, 141-154 (1977).

3. Bargh, J.A. Automaticity in social psychology. In Higgins, E.T. & Kruglanski, A.W. (Eds.), *Social Psychology: Handbook of Basic Principles* The Guilford Press, New York, NY (1996).

4. Cesario, J., Plaks, J.E., & Higgins, E.T. Automatic social behavior as motivated preparation to interact. *Journal of Personality and Social Psychology* **90**, 893-910 (2006).

5. Darley, J.M. & Gross, P.H. A hypothesis-confirming bias in labeling effects. *Journal of Personality and Social Psychology* **44**, 20-33 (1983).

6. Meyer, D.E. & Schvaneveldt, R.W. Facilitation in recognizing pairs of words: Evidence of a dependence between retrieval operations. *Journal of Experimental Psychology* **90**, 227-234 (1971).

7. Jung, K., Shavitt, S., Viswanathan, M., & Hilbe, J.M. Female hurricanes are deadlier than male hurricanes. *Proceedings of the National Academy of Sciences* **111**, 8782-8787 (2014).

8. Alter, A. *Drunk Tank Pink* Penguin Books, New York, NY (2014).

9. Berman, M.G., Jonides, J., & Kaplan, S. The cognitive benefits of interacting with nature. *Psychological Science* **19**, 1207-1212 (2008).

10. Lichtenfeld, S., Elliot, A.J., Maier, M.A., & Pekrun, R. Fertile green: Green facilitates creative performance. *Personality and Social Psychology Bulletin* **38**, 784-797 (2012).

11. Mehta, R. & Zhu, R. Blue or red? Exploring the effect of color on cognitive task performances. *Science* **323**, 1226-1229 (2009).

12. Berger, J., Meredith, M., & Wheeler, S.C. Contextual priming: Where people vote affects how they vote. *Proceedings of the National Academy of Sciences* **105**, 8846-8849 (2008).

13. Rigdon, M., Ishii, K., Watabe, M., & Kitayama, S. Minimal social cues in the dictator game. *Journal of Economic Psychology* **30**, 358-367 (2009).

14. Song, H. & Schwarz, N. If it's hard to read, it's hard to do: Processing fluency affects effort prediction and motivation. *Psychological Science* **19**, 986-988 (2008).

15. Lee, S.W. & Schwarz, N. Bidirectionality, mediation, and moderation of metaphorical effects: The embodiment of social suspicion and fishy smells. *Journal of Personality and Social Psychology* **103**, 737-749 (2012).

16. Danziger, S., Levav, J., & Avnaim-Pesso, L. Extraneous factors in judicial decisions. *Proceedings of the National Academy of Sciences* **108**, 6889-6892 (2011).

17. Williams, L.E. & Bargh, J.A. Experiencing physical warmth influences personal warmth. *Science* **322**, 606-607 (2008).

18. Dutton, D.G. & Aron, A.P. Some evidence for heightened sexual attraction under conditions of high anxiety. *Journal of Personality and Social Psychology* **30**, 510-517 (1974).

19. Kahneman, D. *Thinking, Fast and Slow* Farrar, Straus and Giroux, New York, NY (2011).

20. Tversky, A. & Kahneman, D. Extensional versus intuitive reasoning: The conjunction fallacy in probability judgment. *Psychological Review* **90**, 293-315 (1983).

21. Gilovich, T., Vallone, R, & Tversky, A. The hot hand in basketball: On the misperception of random sequences. *Cognitive Psychology* **17**, 295-314 (1985).

“THE MAN WHO BEAT HIV AT ITS OWN GAME FOR 30 YEARS”
ILLUSTRATION BY **AAD GOUDAPPEL**

In Mathematics, Mistakes Aren't What They Used To Be

Computers can't invent, but they're changing the field anyway

BY SIOBHAN ROBERTS

VLADIMIR VOEVODSKY HAD no sooner sat himself down at the sparkling table, set for a dinner party at the illustrious Institute for Advanced Study in Princeton, New Jersey, than he overturned his empty wine glass, flipping bowl over stem and standing the glass on its rim—a signal to waiters that he would not be imbibing. He is not always so abstemious, but Voevodsky, that fall of 2013, was in the midst of some serious work.

Founded in 1930, the Institute has been called "the earthly temple of mathematical and theoretical physics," and is a hub for all manner of rigorous intellectual inquiry. Einstein's old house is around the corner. In the parking lot a car sports a nerdy bumper sticker reading, "Don't Believe Everything You Think"—which might very well be aimed directly at Voevodsky. Because during the course of some professional soul-searching over the last decade or so, he'd come to the realization that a mathematician's work is 5 percent creative insight and 95 percent self-verification. And this was only reinforced by a recent discovery around the time of the dinner party: He'd made a big mistake.

BORN IN MOSCOW IN 1966, Voevodsky developed an interest in mathematics largely on his own—initially because he wanted to understand physics, later because he unexpectedly fell in love with abstract algebra. Disliking the formalities of academia and neglecting to attend classes, he was "rusticated," as he puts it, from Moscow State University. After the fall of Communism in 1989, it didn't matter so much that he never technically completed his undergraduate mathematics degree. He established his credentials working and publishing with his betters, namely the mathematicians Yuri Shabat and Misha Kapranov. He and Kapranov shared a passion for developing the mathematics of new higher dimensional objects and categories, and they published an important result in 1990.

On the weight of Kapranov's recommendation, Voevodsky found himself accepted for graduate studies at Harvard, without even having applied. His 1992 doctoral thesis marked the beginning of a line of ideas in algebraic geometry that 10 years later earned him the Fields Medal, the so-called Nobel of mathematics. And, the year before, in 2001, by the young age of

ILLUSTRATION BY RICHIE POPE

36, he'd become a full professor at the Institute, the most esteemed of intellectual sanctuaries (after being a long-term member since 1998).

But along the way he met a bump in the road. In 1998, the American mathematician Carlos Simpson published a paper indicating there might be a mistake in Voevodsky and Kapranov's 1990 result. For years Voevodsky sifted through the details without making much progress. He remained convinced the result was right. Then, in the autumn of 2013, as the leaves changed color and summer gave way to autumn, he made a breakthrough. Of sorts. He confirmed the error. The important result was no longer quite so important.

"It is plainly wrong. The main theorem is incorrect," he says. "It's not that there is some gap in the proof. It's that the main theorem is plainly wrong." The mistake, he explains, was in failing to question the obvious. "We had proved that an assertion was indeed true in all of the difficult cases, but it turned out to be false in the simple case. We never bothered to check." In confirming the error, he added an addendum to the original citation in his official publications list—"Warning: The main theorem of this paper was shown by Carlos Simpson to be false."

But even in clearing up the matter and making amends, the broader implications left him unsettled. The error was confirmed a quarter century after it was committed, having passed unnoticed in a paper that had been widely read and roundly discussed and, for a time, repeatedly applied in an ever-evolving field (until doubts percolated post 1998). And, in fact, this was the second time an error had been found in his published work—there'd been another incident in 1999, a smaller error, easily routed.

Not a bad margin, two errors in about 60 papers. Nonetheless, he found it troubling. It clearly was not an accident, as Voevodsky himself is quick to note, in a talk about the predicament he's given at least a dozen times in the intervening years—he is determined to communicate his concern. It was a complicated paper. And readers of such papers essentially get lazy. "A technical argument by a trusted author, which is hard to check and looks similar to arguments known to be correct, is hardly ever checked in detail."

What were the implications for mathematics on the grand scale?

> "For most people the computer is only a tool, like a vacuum cleaner. For me, it's like a colleague."

"I got very worried," he says. Worried, and scared. Since around the same time that he confirmed the error, he'd also been working on something new and exciting—something he called "2-theories," similar to the higher-dimensional mathematics he and Kapranov had been exploring. It was technically complex and innovative. But his passion for pursuing it evaporated because there was no way of knowing that he might not make a mistake. And, as he'd just learned, no one was likely to be checking up with any diligence. These worries killed his creativity. "I stopped doing curiosity driven research. Because the areas where my curiosity led me, areas of value and interest and beauty, I didn't have the tools to explore."

Not with any certainty, anyway. According to Voevodsky's own insight-to-verification ratio, for every hour he spent on an idea he'd need to spend 19 hours ensuring it was correct. Or more. "The more original the insight," he says, "the more one has to pay for it later in self-verification." Too steep a price.

Voevodsky decided that the only way he could proceed would be to employ a "proof assistant"—a computer program that would prevent him from wandering too far down errant paths. He had already been investigating the prospects of a computer-assisted formalization of mathematics, since 2003. The error, he says, "was just like a little present for me, to make my argument stronger."

The experience of working with a proof assistant, as he describes it, is a bit like playing a video game. He's jousting with the computer. He instructs it to try this, try that—he can even instruct it to try something known to be wrong, just to see what happens. "It's very

PETER BADGE

WORRIED NO LONGER Vladimir Voevodsky uses a computer proof assistant to ensure his work is error-free.

interactive," he says. "It can be fun and exciting, and kind of addicting." When he makes a mistake, all the assertions he's typed in, lines and lines and lines, vanish before his very eyes (though he saves the work in a file called "leftovers").

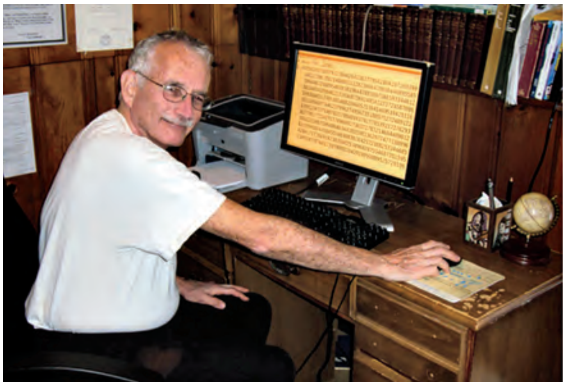
This way, once Voevodsky has proved something, he knows for certain it's true. He doesn't wonder if there are any mistakes lurking within arguments, and he doesn't worry about how to convince his colleagues. The proof assistant provides a stamp of authenticity.

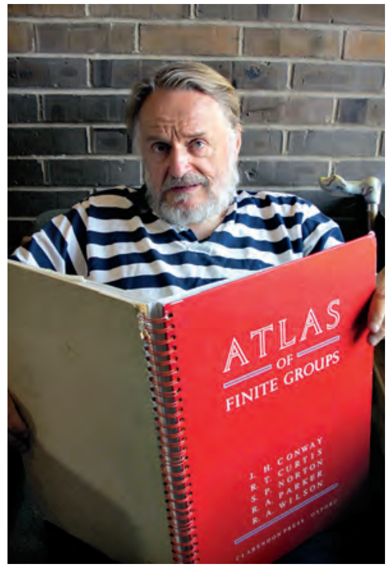
VOEVODSKY IS CONSIDERED a pioneer in this arena, but the notion of proof assistants has been around for a while. The first, "Automath," dates to 1968. Over time a vast ecosystem of proof assistants evolved, with a myriad of setups whereby the computer is used as a tool that mimics how traditional mathematics is done. The computer is essentially taught how humans do mathematics, programmed with axioms and asked to deduce proofs using the laws of logic.

Another approach is to deploy computers in pursuit of discovering altogether new mathematics, new approaches and procedures. For instance, Rutgers mathematician Doron Zeilberger has cited his co-author Shalosh B. Ekhad, the name he gave to his various computers along the way, with numerous papers he's published since the 1980s. "For most people," Zeilberger says, "the computer is only a tool, like a vacuum cleaner. For me, it's like a colleague." He hopes the effect will be nothing short of revolutionary. "Traditional mathematics is based on the notion of rigorous formal proof, and I think this is going to be obsolete," he says. "I think since computers are so powerful, they open up new vistas, and the old agenda of proving everything so rigorously is not as exciting as it was before."

And then there are the purists, the old guard. "I'm not interested in a proof by computer," says Princeton mathematician John Horton Conway. "I prefer to think." He notes the irony that his official title is the John von Neumann Professor in Applied and Computational Mathematics, sponsored by IBM—"I sit and compute all day, but I don't use a computer to do it."

Conway is best known for discovering the Conway groups in mathematical symmetry, the aptly named surreal numbers, and the cellular automata Game of Life. He has a penchant for recreational mathematics and he was keen on the four color map theorem, but





DIFFERENT STROKES Doron Zeilberger (left) regularly lists his computer as a co-author of his papers. John Horton Conway (right), on the other hand, thinks computers are a buzzkill.

when in 1976 it became the first theorem proved by computer—at the behest of mathematicians Kenneth Appel and Wolfgang Haken and hailed in *The New York Times* as "a major intellectual feat"—he wasn't as interested in the result as he might have been otherwise. He was fond, too, of tinkering with the Kepler conjecture about the maximum density for packing spheres in three-dimensional space, but when Thomas Hales solved it in 1998 using linear programming, Conway was left dissatisfied. For Conway, computers kill the buzz. Though he isn't one to judge. He doesn't mind if others use computers. "It just isn't me."

Historically, the purists have not always regarded the issue with such equanimity. The computer proof of the four-color conjecture caused controversy and most mathematicians refused to accept it: Computers + math = verboten. And as the Berkeley professor Edward Frenkel told *The New York Times* upon Appel's death in 2013, "Like a landmark Supreme Court case, the proof's legacy is still felt and hotly debated."

Broadly speaking, the argument against the use of computers is a lament for the loss of the human element: intuition and understanding. Acknowledging something as true because the computer says so is not the same as knowing *why* it is true. One might reckon it's analogous to relying on an Internet mash-up of reviews about the mysteries of Venice, rather than going there and splurging on the water taxi and experiencing the magic for oneself. But then again, the same conundrum arises in building upon previous results rather than working from scratch.

"Computers are good—and generally much better than humans—at what they are designed to do," says Frenkel, author of *Love and Math*. "And that is computation ... But we must realize that mathematical research is not about numbers or calculations. It is about finding connections between things that are seemingly disconnected, it's about seeing the invisible.

> At the actual moment of discovery, you actually *stop thinking*. Like an artist, you connect to something that lies far beyond logic, thinking, and computation.

That can *not* be achieved by computation alone. As a professional mathematician, I can tell you that mathematical discoveries come to us as insights. At the actual moment of discovery, you actually *stop thinking*. Like an artist, you connect to something that lies far beyond logic, thinking, and computation. And that's the beauty of math."

Voevodsky himself is careful to distinguish the various ways computers should or shouldn't be put to use. "Lots of people don't understand the difference between using computers for calculation, for computer-generated proofs, and for computer-assisted proofs," he says. "The computer-generated proofs are the proofs which teach us very little. And there is a correct perception that if we go toward computer-generated proofs then we lose all the good that there is in mathematics—mathematics as a spiritual discipline, mathematics as something which helps to form a pure mind."

But very gradually, he says, the use of computers in mathematics is coming to be accepted as inevitable. And with respect to calculation and computation, especially among up-and-coming generations, it is already quite pervasive, if under-acknowledged. Frenkel agrees, saying that the use of computers to verify proofs is both an expected and welcome trend. As the towering mathematical enterprise reaches new heights, with more intricately and esoterically turreted peaks, each practitioner drilling down into minutiae that could never be understood by colleagues even in the same field, computers will be necessary for advancing the enterprise, and authenticating the integrity of the structure—a structure so complex in detail and so massive in scale that adjudication by mere human referee will no longer be feasible.

Voevodsky goes even further, arguing that the role of proof assistants—and the use of computers in general—extends beyond the isolated practical instances of avoiding errors. Because the broader culture and practice of how errors occur is an even larger roadblock threatening the foundation and future of mathematics. Error can be symptomatic of a certain disregard for what is really involved in proving something properly. Error, he says, can motivate "the direct dishonesty of claiming to have proved something without actually having done it. That's a big force in mathematics today."

"Nobody intentionally does something less well than one could," he reckons. But if a mathematician must choose between publishing sooner without working through all the nuances of a proof, or publishing later and allowing a competitor to get ahead, the temptation is to glide over the details and sacrifice the quality of the proof and publish now. "And then if you read somebody else's paper and there are even fewer details, you think, 'Well if that's what's normal today then I'll just be normal and next time put even fewer details.' [Then] your student looks at your proofs and learns that this is how things are done, and then the student goes around and thinks completely honestly that he is doing the right thing." It's a gradual slippage—a "dissolution of standards." Proof assistants nudge mathematicians in the other direction.

Besides, errors are rarely, if ever, enlightening. Even Conway, who likes to show off the odd error here and there in allowing others to witness his imperfections, protests that he has never encountered an error that was in any shape or form advantageous. And Voevodsky dismisses the notion that taking an errant mathematical turn might be like getting lost in New York City and stumbling upon a magnificent hidden garden. "Well, first of all you'd have to be in Manhattan, or you might find something not so desirable."

So these days, Voevodsky goes back and forth between his proof assistant, rigorously laying down definitions and theorems line by line by line, and his more traditional efforts with pencil and paper, drawing diagrams and sketching out ideas. "Working with a proof assistant reminded me what a real proof is," he says. "It grounded me back into being able to provide more detailed proofs when I write mathematics by hand." Whenever he is tempted to take a shortcut—to say something like, *The proof of this is similar to the proof of that* or *This is straightforward* … or *This is obvious* … —he is forced to ask himself, *Would I be able to get away with such shaky reasoning in the company of my trusty proof assistant?*

"Obviously not."

SIOBHAN ROBERTS is a Toronto-based writer. Her new book, *Genius At Play: The Curious Mind of John Horton Conway*, will be published this July by Bloomsbury.

The Data That Threatened to Break Physics

What does a rational scientist do with an impossible result?

BY RANSOM STEPHENS

ANTONIO EREDITATO INSISTS that our interview be carried out through Skype with both cameras on. Just the other side of middle age, his salt-and-pepper hair frames wide open eyes and a chiseled chin. He smiles easily and his gaze captures your attention like a spotlight. An Italian accent adds extra vowels to the end of his words.

We talk for 15 minutes before he agrees to an on-the-record interview. He tells me he has no desire to engage journalists who might subvert his words into a sensational, insincere story. The reason he agreed to Skype with me is because I am *not* a journalist, but a physicist and writer who spent 13 years in the trenches of experimental particle physics. And he has no tolerance for entering another debate about behavior rather than science. But finally, he says, "Okay. I've looked in your eyes. I trust you. Maybe that is my problem. Maybe I trust too easily, but I trust you." He laughs and leans back in his chair with his arms out and open.

Ereditato is the former leader of the 160 physicists from 13 countries that compose the OPERA collaboration, whose goal is to study neutrino physics. It was first proposed in 2000, and Ereditato led it from 2008 to 2012. Then in late winter of 2011, the impossible seemed to happen. "The guy who is looking at the data calls me," Ereditato tells me from my computer screen. "He says, 'I see something strange.' " What he saw was evidence that neutrinos traveled through 454 miles of Earth's crust, from Switzerland to Italy—which they are supposed to do—at such a high speed that they arrived 60.7 nanoseconds faster than light could travel that distance in outer space—which should have been impossible.

Over the last century, Einstein's observation that no massive object can travel faster than the speed of light in a vacuum, enshrined in his theory of special relativity, has become a keystone of how we understand the universe. If the OPERA measurement was correct, it would mark the first-ever violation of that theory: An atom bomb in the heart of our understanding of the universe.

I ask Ereditato if he thought it must have been a mistake. "I don't think it's fair to say this," Ereditato tells me. "If we say that, we bias our analysis. So when we got this indication that something was so astonishing, the first reaction was, well, let's find why this is so."

ALBERTO PIZZOLI/AFP/GETTY IMAGES

WOLFGANG PAULI POSTULATED the existence of neutrinos in 1930 to solve a simple problem. When nuclei undergo beta decay through the emission of an electron or a positron, the electron's antimatter equivalent, something is missing. Either something invisible is emitted along with the electron or positron, or energy must disappear. Since no repeatable experiment of anything flying, falling, moving, colliding, decaying, or staying put had ever seen energy disappear, Pauli proposed the neutrino, an invisible particle with all the properties necessary to bring beta decay into accord with the first law of thermodynamics. By invisible, I mean that when neutrinos pass through matter they rarely leave a trace. So rarely that it took almost 30 years before an experiment (by Frederick Reines and Clyde Cowan) found physical evidence of them.

Today, neutrinos are an integral part of the Standard Model's periodic table of particle physics. Here you'll find the particles that make up matter listed in pairs separated into three categories: electron neutrinos are paired with electrons, muon neutrinos with muons, and tau neutrinos with, you guessed it, taus. Neutrinos can morph from one flavor into another. For example, an electron neutrino can oscillate into a muon neutrino, and a muon neutrino can flip into a tau neutrino. "Neutrino oscillations are the first indication of physics *beyond* the Standard Model," Ereditato tells me. Laughing, he adds, "That's the reason why I like neutrinos."

Which brings us back to the OPERA experiment. When it was conceived, evidence for neutrino oscillations was plentiful but all of it came from *disappearance* experiments. That is, the evidence consisted of either electron or muon neutrinos disappearing. An *appearance* experiment was needed, and that was OPERA's goal. The idea was for CERN, the European Organization for Nuclear Research in Geneva, to produce a beam of muon neutrinos aimed at a detector buried deep beneath Italy's Gran Sasso Mountain range, 454 miles away. If any tau neutrinos were detected there, then neutrino oscillations were happening. Following the particle physics tradition of snazzy acronyms for experiments, "Oscillation Project with Emulsion-tRacking Apparatus" became OPERA.

Measuring the speed of neutrinos as they traveled from the CNGS (CERN Neutrinos to Gran Sasso) beam to the OPERA detector was not mentioned in the proposal. But in February of 2011, OPERA turned most of its focus to exactly that.

TOOLS FOR THE SEARCH A scientist studies the OPERA detector at the Gran Sasso National Laboratory.

"I THINK AS ANY SCIENTIST, [I was] very, very, very skeptical from day one," says Ereditato. "You make a check list: timing, receiver, GPS, transmitter from the receiver to the detector, … you check everything." Some options were checked immediately, while others required them to wait. The CERN beam, for example, could not be stopped. In the meantime, Ereditato drove his team hard. "You could not imagine how I was handling this business with my colleagues—check this, check that, do this, do that, do this, let's cut the chain, do it again, do it again—we did this from spring to September 23rd!"

The team tried and tested every permutation of software, hardware, and theory that they could think of, and through every step, every bug they fixed, every increment of understanding they earned, the evidence for faster than light neutrinos stood as solid as the mountain above the experiment. Then, the inevitable happened: News of the data leaked. People outside the experiment started gossiping about a violation of relativity, a result that would rattle the foundation of physics like it hadn't been rattled since 1900, when Max Planck discovered quantum physics. The rumors "spread at the speed of light," Ereditato tells me.

"And then what do you do? Think about yourself taking the position of spokesperson. Do you say: No, no comment? And then everyone will blame you, all journalists: 'Oh you hide it. We want to know what is happening. We are taxpayers giving support to you, we have the right to know!' Or you make a claim." In a sinister voice, he adds: "I discovered the superluminal neutrinos."

In this case, it wasn't just up to Ereditato. Large experimental collaborations like OPERA have bylaws for dealing with controversy, and voted to announce the results in public by a large majority of the collaboration. Just a few individuals voted against the announcement. "Which I respect very much. And they were right, eventually, kudos."

OPERA announced its results on September 23rd, 2011 at a special seminar at CERN. The team did not state that it had observed a violation of relativity, and instead of using phrases like "evidence for" or "discovery of," it called the data an "anomaly." But that pivotal caveat was lost in the sensation of human interaction. While the conditional made it into *The New York Times* headline, "Tiny Neutrinos May Have Broken Cosmic Speed Limit," it did not make an appearance in *The Daily Telegraph* ("CERN Scientists 'Break the Speed of Light' ") or *The Guardian* ("Faster Than Light Particles Found, Claim Scientists") or *Scientific American* ("Particles Found to Travel Faster Than Speed of Light.")

The worst data are better than the best theory. If you look for reasonable results, you would never make a discovery, or at least you will never make an unexpected discovery.

The physics community, on the other hand, received the announcement skeptically, even cynically. No practicing professional physicist was willing to abandon special relativity any more than Wolfgang Pauli was willing to abandon conservation of energy in 1930. Still, what if? Since the confirmation of the core tenets of the Standard Model by the UA1 and UA2 experiments at CERN in 1983, every discovery in particle physics (except for neutrino oscillations) had just added another checkmark to that annoyingly venerable Standard Model. How could particle physicists resist the temptation to hope that something, anything, might open up the field during their lifetimes?

Even Ereditato dared to hope. "You come out in a science conference, a seminar, and you start saying, 'Hey guys, I have something which I don't understand. Please help us in understanding.' " He pauses for a second and nods more to himself than to me. "I think it was a good choice to be modest. And second, is that everybody was dreaming that we were right. Everybody."

In one direction lay epic, ground-breaking physics—and in the other, potential embarrassment. Should OPERA have waited? How many more months could they have spent analyzing and reanalyzing the result? Leaning forward and pointing at me through the camera, Ereditato explains why a scientist can't ignore a measurement just because it seems absurd. "You don't kill this … nature is talking to us, not through theories, but

ALBERTO PIZZOLI/AFP/GETTY IMAGES

through experimental results. The worst data are better than the best theory. If you look for reasonable results, you would never make a discovery, or at least you will never make an unexpected discovery. You only make—this is a contradiction in terms—an expected discovery."

One thing is certain: The announcement got OPERA the help they had hoped for. A few days afterward, with the operators of the CNGS beam, they started developing a new approach to the measurement. The original analysis had to use a statistical technique to determine the neutrino's arrival time because the beam was spread out in space. The new approach was to generate neutrinos in tight bunches so that they would arrive at the detector together, making it much easier to determine their arrival time.

News of the data leaked. People outside the experiment started gossiping about a violation of relativity, a result that would rattle the foundation of physics.

It took two months to reconfigure the neutrino beam, perform the experiment and analyze the results—unprecedented speed for an experiment of this complexity.

The faster-than-light measurement was still there.

"Then I started to feel fear," Ereditato says. "I said, 'Oh my God.' And not only me, many people who were very critical, in front of this result, they had no more argument."

PARTICLE PHYSICS EXPERIMENTS CONSIST of complex, building-sized detectors and particle accelerators. Design and construction begin years before the first bit of data is acquired. By the time both the detector and collider are up and running, the experimentalists have developed analysis software to sift through the data and separate signals from backgrounds, the rare and exotic from the common and mundane, music from noise. They use a version of blind analysis, like the double-blind tests of biomedical research that requires a "hidden signal box." Instead of testing their techniques on real data, they test them on simulated data created by replicating the response of the detector hardware to known processes. This way, when they "open the box," their measurements shouldn't be biased by any conscious or unconscious desire for discovery.

Yet OPERA's faster-than-light neutrino data persisted. The next step would be to seek independent confirmation outside of OPERA itself, which is common practice. The Higgs, for example, was observed by both the ATLAS and CMS experiments. But there were no other experiments that could confirm or deny OPERA for at least several years. There was, however, another experiment at the base of Gran Sasso, called the Large Volume Detector (LVD), that could at least check OPERA's timing system. The idea was to make sure the clocks of each experiment were synchronized by comparing the arrival times of cosmic ray muons in their respective detectors.

"This was really the killing experiment," Ereditato tells me. Looking back through all five years of OPERA data, the teams found a period when OPERA's timing was off by about 73 nanoseconds. Then another mistake was found with the timing circuit that affected the bunched beam experiment: The frequency of OPERA's clock wasn't locked to the timing of the bunches. The combination of the two problems accounted completely for the 60 nanosecond early arrival time of the CNGS muon neutrinos.

The source of the timing problem was traced to a fiber optic cable that carried GPS timing signals from the surface of Gran Sasso, down 8.3 kilometers to the OPERA detector. The cable presented two insidious challenges: First, if it was poorly connected, one would reasonably expect that the receiver wouldn't respond at all. If the receiver sees the light, it should fire the starting pistol for the neutrinos racing to the detector. If the receiver doesn't see the light, the starting pistol shouldn't be fired—an obvious bug. But neither of these happened. Instead, it took this particular receiver 73 nanoseconds to acquire *enough* light energy to fire the starting pistol and trigger the electronics; in effect, the starting pistol was fired 73 nanoseconds after the neutrinos left the starting line back at CERN. "I would have expected that you either get a signal, or you don't. But you don't get a delayed signal," says Ereditato. Second, the cable's connector seems to have moved. "The cable was in a good situation maybe one week before we started data taking, and it was in a good position when we checked again everything," Ereditato says. "The nasty thing is that in the middle, where we took data for the neutrino velocity, the cable was in a strange situation."

With the mistake found and fixed, OPERA's measurement of the neutrino velocity is now the most accurate in the world. And it is perfectly consistent with Einstein's special theory of relativity. The faint hope for new physics that wasn't predicted by the venerable Standard Model was dead. But the performance of the OPERA team in finding a single loose cable among the thousands of electrical channels of experimental equipment was remarkable. "I am proud," Ereditato tells me. "I should say very frankly, I was always thinking the solution would have come from very strange effects. Second order effects, somewhere that nobody thought about. I never thought such a thing (the cable), never." Nor did the collaboration overstate the data, or make claims that were unwarranted. In fact, they made no claims at all, and worked closely with other teams in their investigation.

Nevertheless, it seemed clear that someone, somewhere, had made a mistake. Maybe it was the person who attached the cable or designed the receiver, or someone else entirely. In March of 2012, as the dust settled, the OPERA collaboration held another vote, this time to determine whether the collaborators had confidence in the leaders of the experiment. Each member institution got one vote. The tally ended at 16 to 13 favoring no confidence with several abstentions, well short of the two-thirds majority required to impeach the leadership, but enough to send a strong message. Both the OPERA leader, Ereditato, and the experimental coordinator, Dario Autiero, resigned.

Ereditato's resignation letter made it clear he was resigning for the benefit of his team: "… as a result of the enormous media interest, the OPERA Collaboration found itself under anomalous and in some respects irregular pressure … External tensions do not take long to transfer to the inside of a social system comprising over 150 people … leading to the potentially dangerous outcome of potentially losing sight of scientific objectives … This is a risk too great to run. To avert it, the position of individuals must take a back seat."

But did Ereditato do anything wrong? People make mistakes. I spent 13 years working on experiments at SLAC, Fermilab, Cornell, CERN, and even the long dead Superconducting Super Collider. Maybe I'm more forgiving than people who haven't crawled around under counting houses, routing and connecting cables. Connectors fail for lots of reasons and with thousands of channels, it's probably safe to say that there is no particle physics experiment that doesn't have to deal with a bum connector or two. They're usually easy to find, but not this time. Some said OPERA should have done still more tests, but by the time of the no-confidence vote, a whole year had passed. How many more months should they have spent? Should their allegiance to special relativity have compelled them to wait until they found the problem? No, then they would be playing into the absurd concept that scientists are bound to uphold a scientific creed.

Maybe the frustration exhibited by the OPERA collaboration's no confidence vote testifies to how much scientists, especially experimentalists, want to find something new, something that hasn't been predicted, and how angry they get when it slips away.

I ask Ereditato to reflect on the whole experience. "Society likes black and white," he answers. But answers in science are not always so cleanly resolved. "We have to be careful because if we give the impression that science never says yes or no, says always maybe, then people say, 'Well, then I should not trust science.' It is very delicate how to give this message." Most science journalists are not scientists. "They pretend to treat scientific information the same way as murder or kidnapping." As for his own role? "I learned that we are all actors in this field."

Today, Ereditato is the director of the University of Bern's Laboratory for High Energy Physics, and continues to participate in a variety of neutrino experiments. The OPERA experiment, meanwhile, has different leaders and continues to hunt for neutrino oscillations and collect tau neutrinos. They have four so far.

RANSOM STEPHENS is a physicist, novelist, technologist, and science writer. His first popular science book, *The Left Brain Speaks, but the Right Brain Laughs: an irreverent (but accurate!) look at the neuroscience of talent & skill, innovation & discovery, and art & science* is coming out in October, 2015.

How the Biggest Fabricator in Science Got Caught

Yoshitaka Fujii falsified the data behind 183 science papers before statistics exposed him

BY ADAM MARCUS & IVAN ORANSKY

IN APRIL OF 2000, the journal *Anesthesia & Analgesia* published a letter to its editor from Peter Kranke and two colleagues that was fairly dripping with sarcasm. The trio of academic anesthesiologists took aim at an article published by a Japanese colleague named Yoshitaka Fujii, whose data on a drug to prevent nausea and vomiting after surgery were, they wrote, "incredibly nice."

In the language of science, calling results "incredibly nice" is not a compliment—it's tantamount to accusing a researcher of being cavalier, or even of fabricating findings. But rather than heed the warning, the journal, *Anesthesia & Analgesia*, punted. It published the letter to the editor, together with an explanation from Fujii, which asked, among other things, "how much evidence is required to provide adequate proof?" In other words, "Don't believe me? Tough." *Anesthesia & Analgesia* went on to publish 11 more of Fujii's papers. One of the co-authors of the letter, Christian Apfel, then of the University of Würzburg, in Germany, went to the United States Food and Drug Administration to alert them to the issues he and his colleagues had raised. He never heard back.

Fujii, perhaps recognizing his good luck at being spared more scrutiny, mostly stopped publishing in the anesthesia literature in the mid-2000s. Instead, he focused on ophthalmology and otolaryngology, fields in which his near miss would be less likely to draw attention. By 2011, he had published more than 200 studies in total, a very healthy output for someone in his field. In December of that year, he published a paper in the *Journal of Anesthesia*. It was to be his last.

Over the next two years, it became clear that he had fabricated much of his research—most of it, in fact. Today he stands alone as the record-holder for most retractions by a single author, at a breathtaking 183, representing roughly 7 percent of all retracted papers between 1980 and 2011. His story represents a dramatic

ILLUSTRATION BY LOUISA BERTMAN

RGC-5
Retina
Thy-1
GFAP
8A1
HPC-1
Neuritin
NMDA-R
GABA-B R

fall from grace, but also the arrival of a new dimension to scholarly publishing: Statistical tools that can sniff out fraud, and the "cops" that are willing to use them.

STEVE YENTIS ALREADY HAD a fairly strong background in research ethics when he became editor in chief of the journal *Anaesthesia* in 2009. He'd sat on and then chaired an academic committee on the subject and even gone back to school part-time for a master's degree in medical ethics. He'd also been serving on the Committee for Publication Ethics, or COPE, an international group based in the United Kingdom devoted to improving standards in scholarly publishing.

Still, he said, he had "no real inkling that the ceiling was about to fall in" so soon after he assumed the journal's top post. Like *Anesthesia & Analgesia* a decade earlier, *Anaesthesia* published a 2010 editorial about Fujii's corpus of work by a group of authors that did not believe in its findings, and called on the field to conduct reviews of the literature to weed out bogus results.

As Yentis detailed in a later article, titled "Lies, damn lies, and statistics," the editorial—which he himself had commissioned—prompted a flood of letters, including one by a reader "who bemoaned the fact that the evidence base remained distorted by that researcher's work" and challenged anaesthetic journal editors to do something about it. The author of that letter was John Carlisle, a U.K. anesthetist.

The timing was fortuitous in a way. The field of anesthesiology was still reeling from an epic one-two punch of misconduct. The first hit involved Scott Reuben, a Massachusetts pain specialist who'd fabricated data in clinical trials—and wound up in federal prison for his crimes. The second, barely a year later, came in the form of Joachim Boldt, a prolific German researcher who was found to have doctored studies and committed other ethics violations that led to the retraction of nearly 90 papers.

Anaesthesia had published six of Boldt's articles, and Yentis felt a bit chastened. So when he read Carlisle's letter he saw an opportunity. He effectively told Carlisle to put his money where his keyboard was: "I counter-challenged the correspondent to perform an analysis of Fujii's work," Yentis says. Carlisle admits that he had no special expertise in statistics at the time, nor was he a particularly well-known anesthesiologist

If it seems too good to be true, math will tell you it probably is.

whose word carried weight among his colleagues. But his conclusion was simple, and impossible to ignore—it was extremely unlikely that a real set of experiments could have produced Fujii's data.

Top-tier evidence in clinical medicine comes from randomized controlled trials, which are essentially statistical egg sorters that separate chance from the legitimate effects of a drug or other treatment. "The measurements that are usually analyzed are those subsequent to one group having a treatment and the other group having a placebo," Carlisle explains. "The two unusual things that I did were to analyze differences between groups of variables that exist before the groups are given a treatment or a placebo (for instance weight), and to calculate the probability that differences would be less than observed, not more than observed."

Carlisle compared the findings from 168 of Fujii's "gold standard" clinical trials from 1991 to 2011 (an eyebrow-raising average of about eight papers a year) with what other investigators had previously reported, and what would be expected to occur by chance. He looked at factors ranging from patient height and blood pressure at the start of a study to rates of side effects associated with the drugs Fujii was reportedly testing.

Using these techniques, Carlisle concluded in a paper he published in *Anaesthesia* in 2012 that the odds of some of Fujii's findings being experimentally derived were on the order of 10^{-33}, a hideously small number. As Carlisle dryly explained, there were "unnatural patterns" that "would support the conclusion that these data depart from those that would be expected from random sampling to a sufficient degree that they should not contribute to the evidence base." In other words: If it seems too good to be true, math will tell you it probably is.

Carlisle's conclusion was much like that of the anesthesiologists who called out Fujii in 2000—only this time, people paid attention. Shortly after Carlisle's findings appeared, a Japanese investigation concluded that only three of 212 published papers by Fujii contained clearly reliable data. For 38 others, evidence of fraud was inconclusive. Eventually 171 papers were deemed to have been wholly fabricated. As the Japanese report concluded: "It is as if someone sat at a desk and wrote a novel about a research idea."

ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN & IRELAND

THE COP Steve Yentis, editor in chief of *Anaesthesia*, challenged a reader to perform a statistical analysis of Fujii's work.

CARLISLE'S STATISTICAL ANALYSIS technique isn't limited to anesthesia, or even to science about people. "The method I used could be applied to anything, plant, animal, or mineral," he says. "It requires only that the people, plants, or objects have been randomly allocated to different groups." It would also be "fairly simple" for other scholarly journals to implement it.

At least one journal editor agrees. "It is still evolving, but John Carlisle's basic approach is being generalized as a tool to detect research fraud," says Steven Shafer, a Stanford anesthesiologist and current editor in chief of *Anesthesia & Analgesia*. Shafer, Yentis, and others are involved in that effort, and Carlisle plans to publish a revised methodology soon. One of the goals, Shafer says, is to automate the process. (Disclaimer: Shafer is on the board of directors of the Center for Scientific Integrity, home to Retraction Watch, which the authors of this article co-founded.)

Shafer says he personally used Carlisle's method to identify a paper about insertion of breathing tubes, submitted to his journal in 2012, as fraudulent. He rejected it, then learned that it had been submitted to another journal. "Same paper, different data!" says Shafer. "The authors invented new numbers, since I implied in my rejection letters it was a fraudulent paper." Shafer and his fellow editor sent a note to the authors' department chair, who responded, "These people won't be doing research anymore."

Nor is the technique limited to catching fraudsters. Carlisle says groups like the Cochrane Collaboration—a U.K. body that conducts reviews and meta-analyses of the medical literature—could potentially use it to check the reliability of any pooled result. These meta-analyses, which pool findings from numerous studies of a particular intervention, such as drugs or surgery, are considered powerful evidence-based ways to inform treatment guidelines. If the data in the studies on which they're based is flawed, however, you end up with "garbage in, garbage out," making them useless.

But this is an approach that requires journal editors to be on board—and many of them are not. Some find reasons not to fix the literature. Authors, for their part, have taken to claiming that they are victims of "witch hunts." It often takes a chorus of critiques on sites such as PubPeer.com, which allows anonymous comments on published papers, followed by press coverage, to generate any movement.

In 2009, for example, Bruce Ames—made famous by the tests for cancer-causing agents that bear his name—performed an analysis similar to Carlisle's together with his colleagues. The target was a group of three papers authored by a team led by Palaninathan Varalakshmi. In marked contrast to what later resulted from Carlisle's work, the three researchers fought back, calling Ames' approach "unfair" and a conflation of causation and correlation. Varalakshmi's editors sided with him. To this day, not a single one of the journals in which the accused researchers have published their work have done anything about the papers in question.

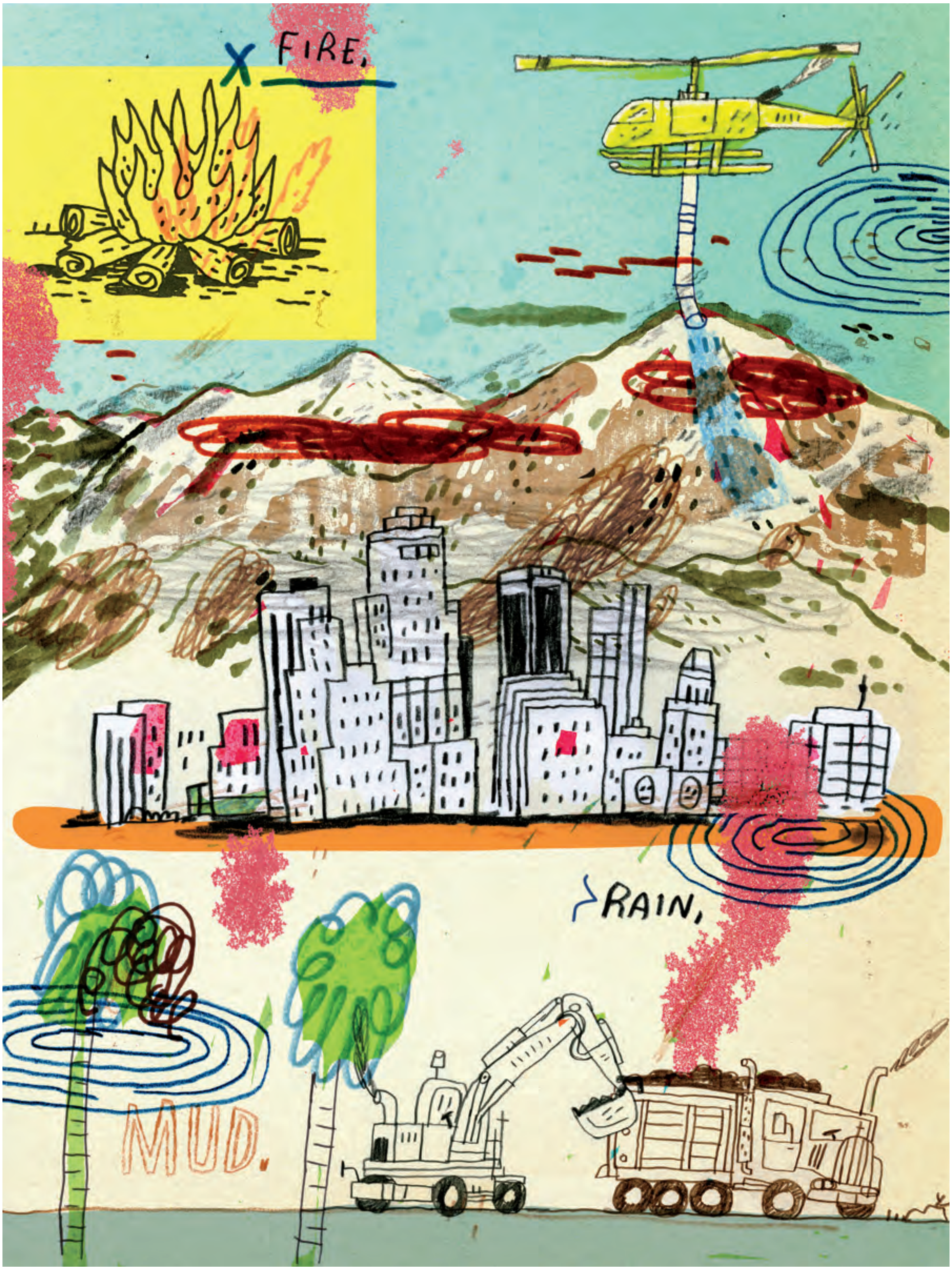
Sadly, this is the typical conclusion to a scholarly fraud investigation. The difficulty in pursuing fraudsters is partly the result of the process of scholarly publishing itself. It "has always been reliant on people rather than systems; the peer review process has its pros and cons but the ability to detect fraud isn't really one of its strengths," Yentis says.

Publishing is built on trust, and peer reviewers are often too rushed to look at original data even when it is made available. *Nature*, for example, asks authors "to justify the appropriateness of statistical tests and in particular to state whether the data meet the assumption of the tests," according to executive editor Veronique Kiermer. Editors, she notes, "take this statement into account when evaluating the paper but do not systematically examine the distribution of all underlying datasets." Similarly, peer reviewers are not required to examine dataset statistics.

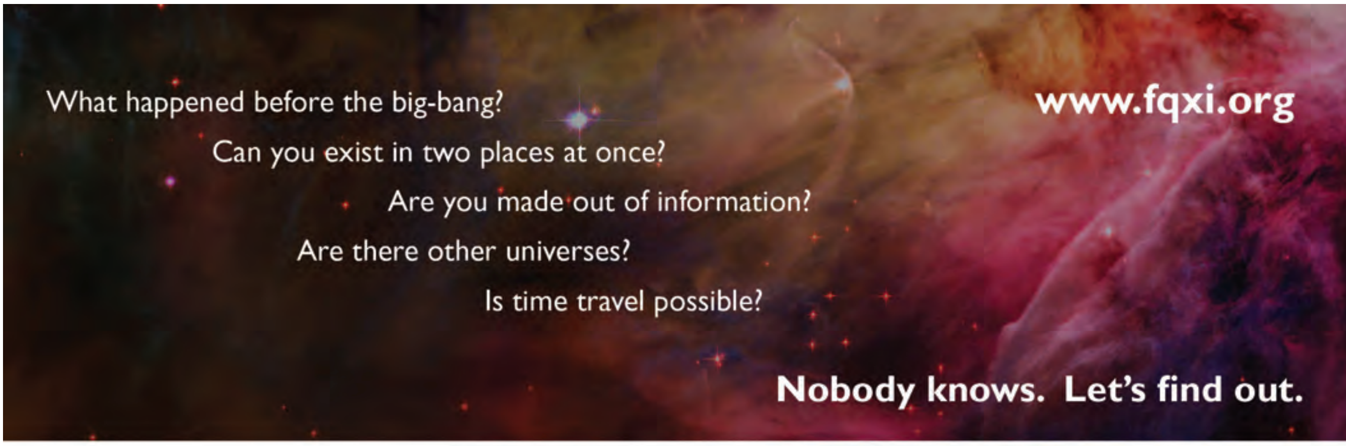
When *Nature* went through a painful stem cell paper retraction last year, which led to the suicide of one of the key researchers, they maintained that, "we and the referees could not have detected the problems that fatally undermined the papers." The journal argued that it took post-publication peer review, and an institutional investigation. And pushing too hard can create real problems, *Nature* wrote in another editorial. Journals "might find themselves threatened with a lawsuit for the proposed retraction itself, let alone a retraction whose statement includes any reference to misconduct."

Nature might be content to leave the heavy-duty police work to institutions, but Yentis has learned his lesson. While he commissioned the 2010 editorial that brought the red flags in Fujii's work to the attention of his readers, he also all but ignored the editorial's message. It took a brace of letters—including one from his eventual sleuth, Carlisle—to goad him into action, and as a result he didn't publish the definitive analysis until 2012. "Were such an accusation to appear in an editorial now," he says, "I wouldn't let it go by me."

ADAM MARCUS, the managing editor of *Gastroenterology & Endoscopy News*, and IVAN ORANSKY, global editorial director of *MedPage Today*, are the co-founders of Retraction Watch (http://retractionwatch.com), generously supported by the John D. and Catherine T. MacArthur Foundation.



“LOS ANGELES SHOULD BE BURIED”
ILLUSTRATION BY **MARK TODD**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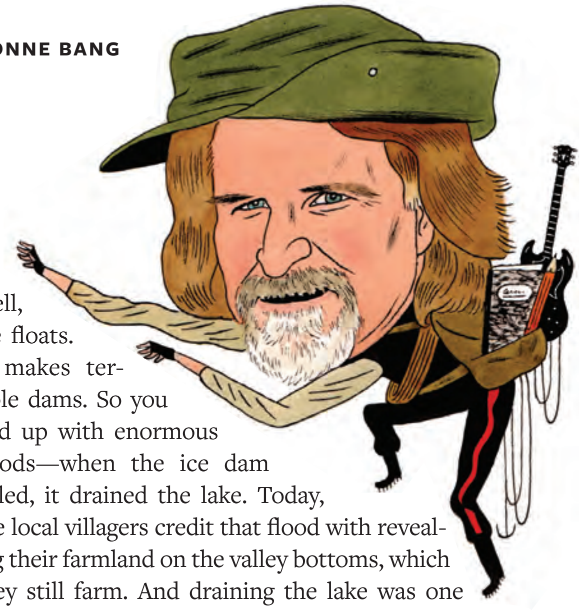
David R. Montgomery

Geologist, MacArthur fellow, Big Dirt guitarist, and author of Dirt *and* The Rocks Don't Lie *reflects on the themes in* Nautilus

INTERVIEW BY YVONNE BANG



ON SLOW

Everyday change adds up to really big effects, given enough time. And geologic time is a hard concept to wrap your mind around because it's both big and slow. Our lives are so short, in comparison. Consider the history of salmon runs in Europe. Gradual change to rivers added up to tremendous impacts on salmon. Some ancient Scottish fisheries laws were really good laws designed to protect salmon. Since salmon was what a lot of people ate, it was important to preserve. You had to let the salmon return to their spawning ground. A fish that made it back was off limits—King's orders! And you couldn't dam a river in a way that would prevent a salmon from going up or down it, because they knew the juvenile fish got big at sea and came back to spawn. But over time, what happened in England is that a lot of little dams got built and there was this constant whittling away of habitat accessible to salmon. None of those individual changes—one little dam at a time—destroyed the Atlantic salmon. It was the aggregate played out over centuries. The same story is essentially unfolding on the West Coast; we're just not as far along in it.

ON DOMINOES

Natural phenomena can sometimes have an effect on cultural evolution. On a trip from Lhasa to study the geological evolution and topography of the Tsangpo Gorge, we noticed these terraces made out of gravel, silt, and clay along the one paved road. We had not expected to see these flat surfaces rising above the valley bottom. What had happened? Slowly, over the course of a couple of weeks, we found that a massive ice dam down at the bottom of the study area had impounded a tremendous lake. But what happens when you dam a river with a plug of ice? Well, ice floats. It makes terrible dams. So you end up with enormous floods—when the ice dam failed, it drained the lake. Today, the local villagers credit that flood with revealing their farmland on the valley bottoms, which they still farm. And draining the lake was one of the miracles credited to Guru Rinpoche—one of the guys who brought Buddhism into Tibet.

ON ERROR

We've spent the last century trying to kill microbes. "They're all evil, they're germs, they're bad." But there's a new perspective. In the last decade or two, we've discovered that populations of microbes living around plant roots and in our own gut are actually critical to the health of plants and people. In college, I was taught that the fertility of the soil was all about the physical chemistry of the clays and the soils. That was only part of the story. What it misses is the role that microbial life plays in liberating nutrients and putting them into soluble forms that plants can suck up through the roots. In our new book, *The Hidden Half of Nature*, my wife and I describe how this oversight led to erroneous practices, like the overapplication of fertilizers, which then led to a rise in crop diseases. It's like that old Mark Twain quote: "It ain't what you don't know that gets you into trouble. It's what you know for sure that ain't so."

ILLUSTRATION BY ANDY FRIEDMAN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