Transposons

So-called junk DNA proves its worth: First in corn, now in creatures like us

BY AYALA OCHERT

Within three years, if not sooner, the Human Genome Project will be completed, and all 3 billion or so bases of the human genetic code will have been recorded. That's when biologists will face up to an uncomfortable truth: Less than 5 percent of the human genome is likely to contain functioning genes. The rest of it is stuffed—like a stranger's attic—with mysterious relics of an unknown past. Nearly half is parasitic DNA—commonly known as "transposable elements," or simply "transposons," and everything left over is just anonymous noncoding DNA. Over the years, scientists have downplayed the significance of this excess genetic baggage, referring to it disdainfully as "junk" DNA. But now the tide is turning—for transposons at least—as biologists begin to recognize that these tiniest of parasites may have been real players in evolution after all. Without their insidious presence, complex creatures

Transposons, or "jumping genes," can produce color variations in corn kernels by disrupting a gene's normal sequence.

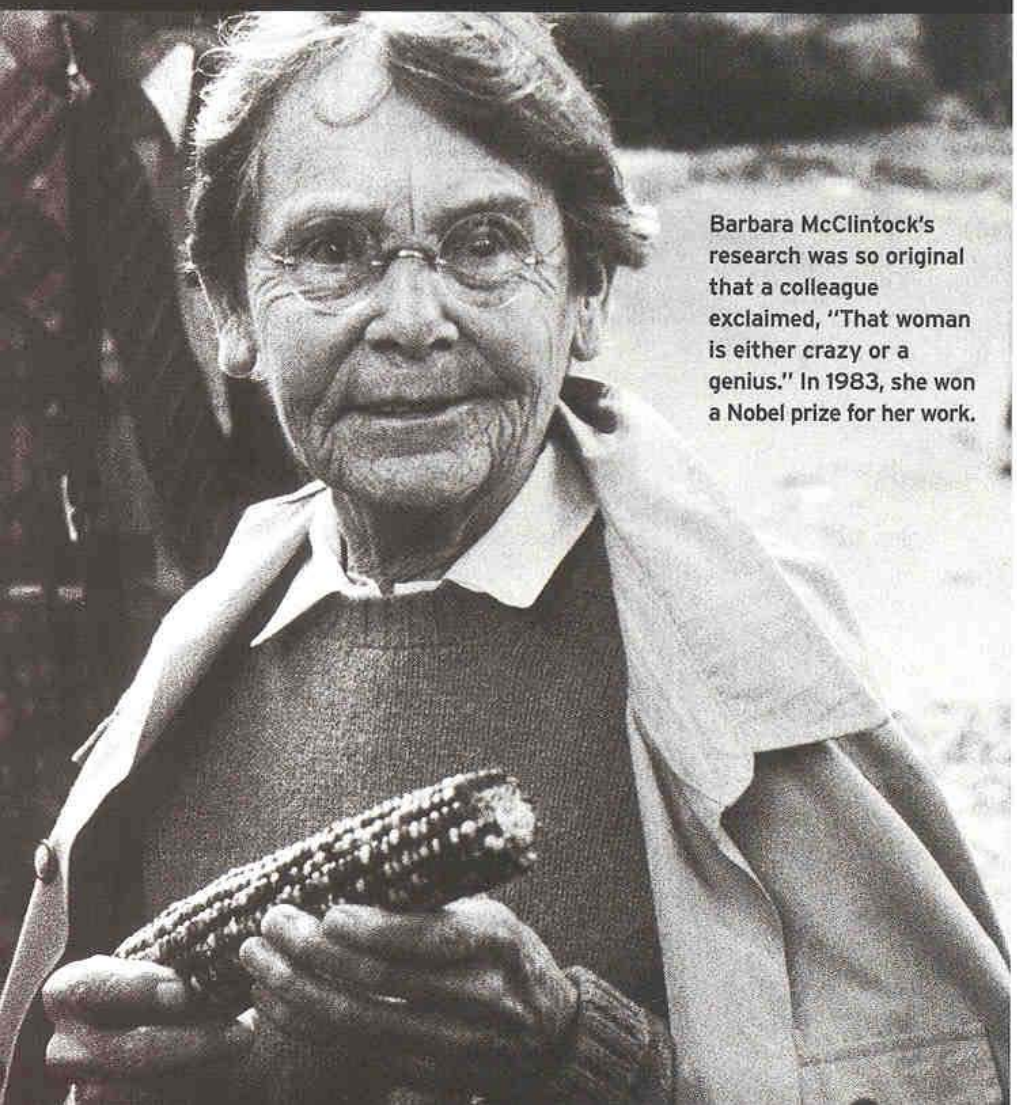
TRANSPOSONS

How Genes Jump

Transposons are sometimes whimsically referred to as "jumping genes," because they seem to hop from place to place within the genome. There are several varieties of transposon, each with its own method of jumping. The simplest use a cut-and-paste strategy: Their DNA instructs the cell to make an enzyme that can seek out the transposon, pick it up by both ends, and reinsert it at a new location. A common but more sophisticated variety is the retrotransposon. The cell treats the retrotransposon just like one of its own genes and creates RNA from it. Just after the RNA is assembled, the retrotransposon makes an enzyme called reverse transcriptase, which cunningly converts the RNA back into a DNA copy that is an exact replica of the original transposon. That duplicate then finds a new place along the genome and takes up residence.

The mode of retrotransposon movement is remarkably similar to that of retroviruses like HIV—so similar, in fact, that many scientists believe these viruses must have evolved from retrotransposons. Transposons have also managed to escape from their hosts and move to new ones, sometimes from different species, by a mysterious process called horizontal transmission. Although no one knows exactly how it happens, the transposons probably hitch a ride off an unsuspecting virus that happens to have infected its host. The transposon jumps on board, and it's free.

Entomologist Hugh Robertson of the University of Illinois at Urbana-Champaign has turned up evidence for hundreds of such cases of horizontal transmission, sometimes between very different species. That strategy, he believes, may be the transposon's only means of survival. "Within any particular host, they will eventually die by mutation and become nonfunctional. By jumping to a new host, they get a new lease on life before dying out in the old host." –AYALA OCHERT



Barbara McClintock's research was so original that a colleague exclaimed, "That woman is either crazy or a genius." In 1983, she won a Nobel prize for her work.

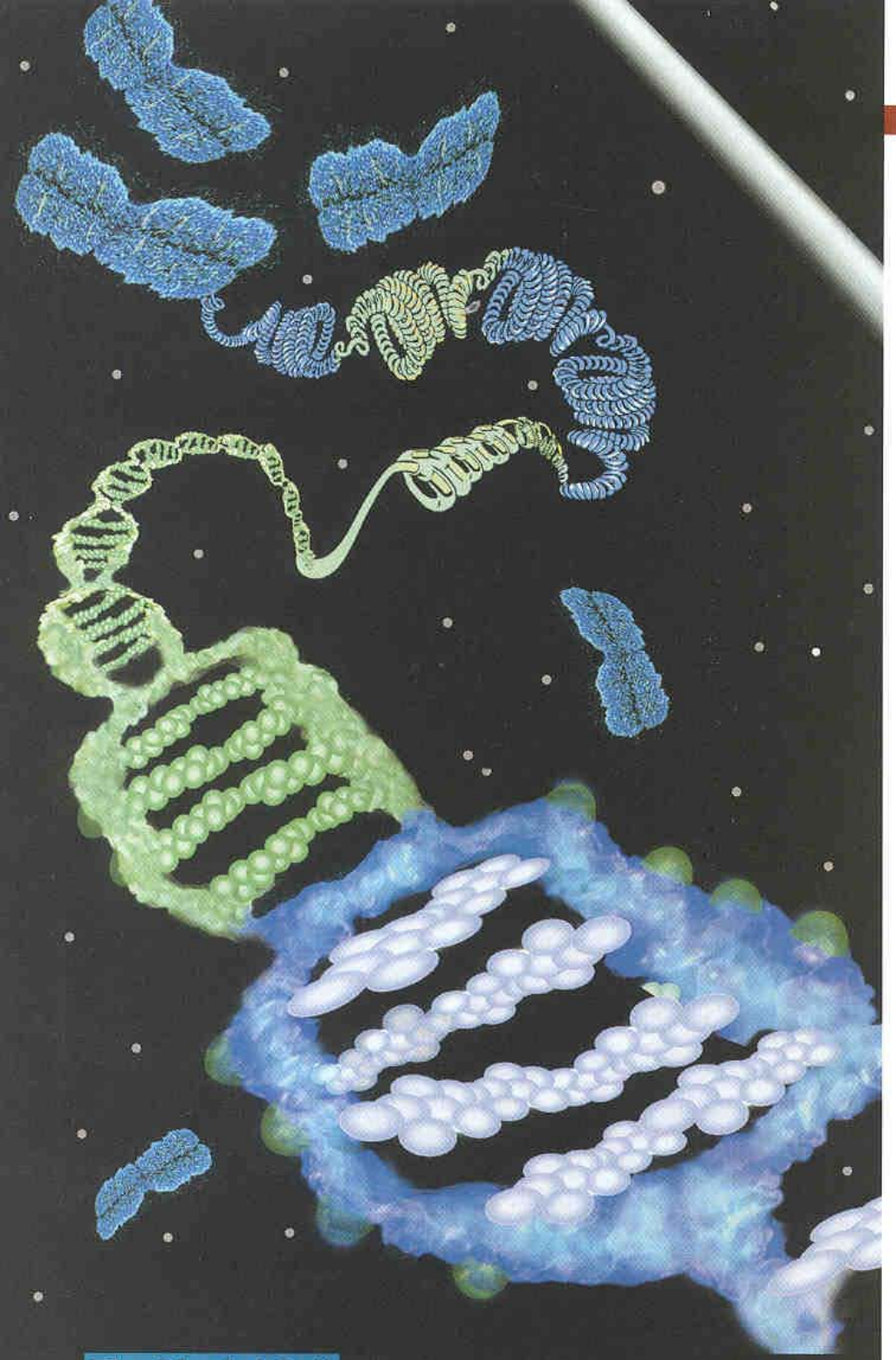
like us may never have evolved. These rogue bits of DNA may even have shaped those features that distinguish us from our closest primate kin.

Transposons are not new to biology. In the 1940s, the gifted cytogeneticist Barbara McClintock came up with the idea that DNA sequences are not always static; they sometimes move around from place to place, leaving biological peculiarities in their wake. With this idea, she was able to explain why the Indian corn she was studying didn't inherit coloring in the orderly fashion of Gregor Mendel's peas. Instead, something was causing variations to appear—more or less at random. The changes, McClintock suggested, were the handiwork of mobile genetic elements, which are today known as transposons. Unable to understand her work, other scientists were reluctant to go along with such an unorthodox idea.

By the 1960s, however, McClintock's ideas were gaining ground and, in 1983, she won the Nobel prize for her transposon research. But even now, few scientists have come to terms with just how important transposons might have been during evolution. If anyone truly appreciates their significance, it is John McDonald, a molecular biologist at the University of Georgia in Athens. He believes that without transposons nothing more interesting than a bacterium may have ever crawled out of the primordial mud.

McDonald has devoted his career to understanding the molecular tools of these rogue stretches of DNA, and he knows well their special talent for wreaking havoc in the genome. A few changes in maize kernels may not sound too worrisome, but all too often transposons are far more deadly, and many diseases—including hemophilia, leukemia, and breast cancer—have been linked to their destabilizing influence. What makes transposons so powerful—and dangerous—McDonald explains, is their mobility. Transposons piggyback on their host's genome and are copied hundreds of times over. They get a free ride down through the generations, but as they jump around at will, they can land on vital genes, blotting them out, or land near genes,

PREVIOUS PAGE: M. GERALD NEUFFER, UNIVERSITY OF MISSOURI; THIS PAGE: CORBIS BETTMANN



The Mortal Coil **Genetic sequences harboring transposons (green) tend to be stowed away in tightly coiled sections of noncoding DNA called heterochromatin. But in coding DNA (light blue), the coiled DNA relaxes, exposing genes for copying. If a transposon happens to jump into coding DNA, it can disrupt normal gene function.**

setting them off at the wrong time or in the wrong place [see "How Genes Jump," page 60].

That instability, argues McDonald, has represented a serious threat. Throughout evolution, plants and animals have had to contend with these unwelcome residents, and the force of natural selection has been a source of constant pressure to clamp down on these genetic freeloaders—to inactivate, or "silence," them, putting a halt to their disruptive spread. "The whole process is dynamic, and transposons are working constantly to escape silencing," he says. "It's a continual battle." McDonald believes that this unseen struggle at the molecular level may ultimately be responsible for two blockbuster events in the history of animal evolution.

The first occurred around two billion years ago, when multicellular creatures like worms and insects began to emerge. The new complex organisms looked different from their simpler predecessors—and their genomes looked very different too. These organisms had many more genes, and they packaged them very differently. Instead of having a loose, lengthy loop of genes, as bacteria do, these creatures had chromosomes—dense packages of DNA and proteins in the form of chromatin. McDonald thinks the need to control rowdy transposons hastened this unprecedented molecular innovation. The new chromosomal packaging allowed the cell to stow away disruptive transposons, yet somehow leave privileged genes available for use. And that ability to control access to genes would improve an organism's ability to manage a complex and varied genome.

The second event occurred around 500 million years ago, when vertebrates like fish, birds, and mammals began to appear. These organisms harbored even more genes, and their genomes were littered with molecular additions called methyl groups (CH_3s). Methylation is still poorly understood, but McDonald thinks it added a second layer of gene inactivation over and above that offered by chromatin. Genes lacking methyl groups tend to be available for making proteins; genes with methyl groups don't. It's as if these molecular ornaments work like a master switch for shutting down inappropriate activity in the genome. Like chromatin formation, methylation may have arisen as a strategy to defend against transposons, says McDonald. And it may be that once mechanisms for shutting down transposons were in place, organisms began using them to control not just invading transposons but their own genes too.

In fact, molecular biologist Adrian Bird of the University of Edinburgh in Scotland has argued that without

ILLUSTRATION BY MICHAEL ANIEL

chromatin formation and methylation, complex life would have been impossible. In multicellular organisms with lengthy complex genomes, different cells need to turn different genes on and off. Chromatin formation and methylation—with their ability to alter gene expression—were tools that made such control possible. What McDonald has added to Bird's argument is the role of transposons in prompting the evolution of these genomic features. "If we had to sit around and wait for methylation to evolve for the host function, it would probably never have happened. This molecular battle [between transposons and their hosts] just sped up evolution. It's like technology in society—would it have evolved as fast as it did if it weren't for the military-industrial complex?" he asks.

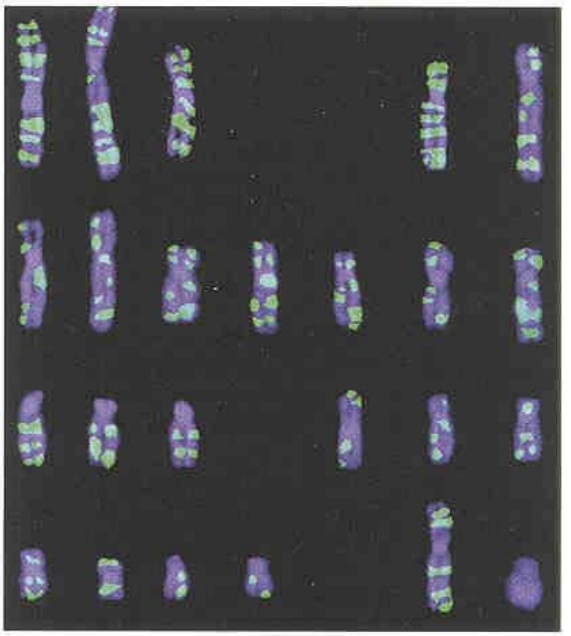
McDonald's hypothesis is provocative, although there is no way of proving conclusively whether chromatin formation or methylation evolved to inactivate transposons millions of years ago. But McDonald points to intriguing evidence that both chromatin formation and methylation are still important for reining in transposons. Chromatin, for example, performs the most remarkable feat of packaging known to biology. Within the nucleus of each human cell, nine feet of DNA must be tightly coiled into chromosomes. In its most "condensed" state, the DNA is so tightly bundled up that it's entirely inaccessible to gene-activating enzymes. As stretches of chromosome move out of this condensed state, genes are exposed and available for expression. But some sections—known as constitutive heterochromatin—are permanently condensed and packaged away. These sections are like graveyards for transposons.

If transposons move while eggs or sperm form, they can cause heritable disease

In the fruit fly *Drosophila,* for example, the constitutive heterochromatin is jam-packed with transposons. And when researchers at the Howard Hughes Medical Institute inserted a few transposons end-to-end along the *Drosophila* genome, they found that new material resembling heterochromatin would spontaneously generate where there was none before. It seems that with all their jumping around and duplicating themselves, transposons made themselves a little too conspicuous. So heterochromatin formed around them, trapping them in place.

There's also evidence that methylation, too, still defends against transposons. Timothy Bestor and his colleagues at Columbia University say that as much as 90 percent of all methylated sequences in the mammalian genome occur in transposable elements. What's more, when the methyl groups are stripped off the genome, these elements actually get reactivated. And there's even more provocative evidence of the policing power of methylation in the human genome. Nearly half of our own genome consists of transposons, yet only 0.2 percent of all spontaneous human mutations are caused by transposons. In fruit flies, transposons constitute only 10 to 20 percent of the genome, yet they are responsible for as much as 85 percent of spontaneous fruit fly mutations. Methylation may be the key. Our genomes are methylated; fruit fly genomes are not. So, although humans harbor far more transposons than fruit flies, methylation may curb their ability to do us harm.

The mariner transposon (green) is scattered throughout the human genome, according to a recent study by Lawrence Reiter of the University of California at San Diego and his colleagues. Mariner transposons don't appear to be functional, says Reiter. But they do appear guilty by association: Mariner transposons are found in 12 chromosomal regions that have been linked to genetic disorders.



But, try as it might, no organism can stop every single transposon, and occasionally one will sneak its way past all the genetic checkpoints. Much of the time transposons have no effect, but sometimes they cause an unwelcome mutation. In humans, for example, the movement of transposons from one point of the genome to another during the formation of eggs or sperm is a constant source of inherited diseases. One in 3,000 people will get type I neurofibromatosis—a disease that can cause café-au-lait patches on the skin, growths, bone deformities, and learning disabilities—and about half of these cases are caused by new mutations, which are then passed on to future generations. In some cases, the exact moment when a transposon disrupted the normal gene has been traced to a single individual, usually a father or grandfather in a family with that disease.

Despite transposons' bad reputation, they have made some surprisingly significant and lasting contributions to the genomes of animals and humans.

A 1998 study by David Schatz and colleagues at Yale, for example, helped explain how the powerful immune system of vertebrates appeared so abruptly in evolution. Almost 500 million years ago, jawed vertebrates acquired the ability to begin producing nearly infinite types of antibodies in response to bacterial or viral invaders. They do so by mixing gene fragments to create a vast array of antibody genes in millions of B cells. This recombination, which occurs very early in development, produces a diverse multitude of antibody sentinels. Schatz and his team found that this incredible genetic flexibility is made possible by the RAG transposon, which fortuitously entered our lineage around 450 million years ago. The RAG creates the protein used to "cut and paste" the gene fragments into new combinations. And, fortunately for us, RAG seems to have lost the ability to reinsert itself at random locations in the genome.

A transposon found only in humans may explain why we're so different from chimps

Transposons not only provide fodder for new genes, but they also have the power to shape organisms by influencing the intricate regulation of genes. Within the genome are enhancers and promoters—special sequences that switch genes on and off in different tissues. Transposons, too, are equipped with their own enhancers and promoters, and that can make them powerful players in evolution. "When transposons move around the genome and insert themselves near genes, they bring pre-evolved regulatory units with them, and that is prone to have a regulatory effect on nearby genes," explains McDonald.

In fact, Cal Tech molecular biologist Roy Britten, who was one of the first to spot transposons in the genomes of mammals, argues that the movement of transposons has had a much more significant effect than classical mutations—those in which a single base change results in a slightly different protein. When transposons jump to new locations, they can alter patterns of gene expression, and therefore have far more of an effect on how an organism actually turns out. Britten believes that transposons are unsurpassed as a source of natural variation. "You couldn't explain the process of evolution on the basis of single point mutations. You need a more powerful device." That powerful device, he says, is the transposon.

Britten has been particularly interested in how a transposon called the Alu element could affect patterns of gene expression. Alus are unique to primates and, for some unknown reason, they seem to have spread widely around 30 million to 50 million years ago. Although their period of intense activity occurred long before human-apes ever walked the earth, Alus have left a signature in our genome. Each of us has nearly a million Alus, and they make up more than five percent of our DNA. In fact, says Britten, the Alu element is the most abundant type of transposon in the human genome. And, according to molecular biologist Wanda Reynolds, the Alu may have played a critical role in our own evolution.

When Reynolds began studying Alu elements at the Sidney Kimmel Cancer Center in San Diego several years ago, she noticed that part of the Alu sequence bore an uncanny resemblance to something she had seen before. She had been working with distinctive DNA sequences that act as anchor points for proteins that bind to hormones. When a hormone is bound in this way, it can switch on a whole set of genes, starting a cascade of biochemical events throughout the body. When the hormone estrogen, for example, binds to such a sequence, it triggers the genes involved in ovulation. Or when growth hormone binds to a similar stretch, it triggers the genes necessary to make a child grow.

These sequences are extremely powerful, so the discovery that they reside in all Alu elements startled Reynolds. As Alus moved around during primate evolution, they would have had the power to alter which set of genes got triggered by which hormone and when. She also found that various Alus bind to several different hormones, including retinoic acid, thyroid hormone, and even estrogen—all of which are critically important in the timing of development.

"These Alus could have generated more diversity—but subtle diversity," says Reynolds. "We're not talking about knocking a gene out, but just slightly elevating or reducing its expression in certain tissues, so that you could gradually change the evolution of the species. Alus were probably very important in primate evolution, because without them you may never have had the diversity from which to select the primates," says Reynolds.

The importance of this subtle diversity becomes clear when you consider the differences between ourselves and our closest living relatives, the chimpanzees. Although they share more than 98 percent of our genes, it is less often acknowledged that such a small distinction can hardly begin to account for the very real differences between how we and they look and behave. "It's not just the sequence of the genes, it must be something about the way genes are turned on, the way they're controlled," says McDonald. "There must be different patterns of expression that are key to the differences in morphology." With their ability to bind hormones and thus switch genes on and off during development, Alus may very well have shaped the evolution of our species.

The more we learn about transposons and their powerful effects, says McDonald, the harder it becomes to think of them as mere junk. "Before, everything on the molecular level was considered random. But there's actually selection going on at the molecular level, driving evolution on the organismic level. Because these mechanisms are being driven from the inside, that speeds the whole thing up." ●

CONTRIBUTORS

'I love earthquakes and hurricanes. I like to tiptoe around risk.'

MARY ROACH

("AVALANCHE!" PAGE 88), a longtime San Francisco resident, never got over the snowdrifts of her New Hampshire childhood. "Once a year I immerse myself in snow," she says. "I missed it last year, so I made sure this would be big." Observing avalanche researchers satisfied Roach's snow cravings—and her fondness for danger. "I love earthquakes and hurricanes," she says, "but I don't want anyone to get hurt. I like to tiptoe around the edges of risk." Roach has been a contributing editor at *Discover* since 1998.

VERLYN KLINKENBORG

("NO PLACE LEFT TO HIDE," PAGE 102) learned to love his GPS receiver when September's Hurricane Floyd wiped out power lines near his home in upstate New York. Thanks to GPS, Klinkenborg could reset his clocks with accuracy. Usually, however, he tries to avoid overloading on technology, even a device that tells you exactly where you are at every second. "If I'm going fishing," he says, "I know where I am—I'm standing in a river." Klinkenborg writes about science for publications such as *The New Yorker* and *Harper's Magazine,* and is the author of *The Last Fine Time.*

JAMES BALOG

("EYE OF THE BEAST," PAGE 94, PHOTOGRAPHER) first explored nature in his hometown of Watchung, New Jersey. "As a 12-year-old with a shotgun on my shoulder, looking for animals, I could wander all day and only cross the road every so often," Balog says. The town's transformation from rural wildlands to New York City suburb had a big impact on the boy-turned-man. "My adult work became a process of looking at wilderness side by side with civilization," he says. Balog, now based in Boulder, Colorado, has contributed to *National Geographic, Rolling Stone,* and *Vanity Fair.*

AYALA OCHERT

("TRANSPOSONS," PAGE 59) gnaws on the big questions. "I want to know what it's all about," she says. "Why are we here?" Thus parasitic DNA caught her eye. "Every once in a while you come across an idea that strikes you as truly profound," she says. "What goes on in our DNA affects the whole history of how we came to be." Born and raised in England, Ochert moved to San Francisco a year and a half ago. Her articles have been published in *New Scientist, Nature,* and the *ScienceNow* Web site.

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