

KENNETH S. KOSIK

Luis González Palma, *Litanies II*, 1994

The Fortune Teller

*Will the secrets of genetic destiny bring comfort
or only more sorrow to a remote land ravaged by violence?*

THE LOCALS OF Medellín, Colombia, joke that when God created the world, one of the angels asked him why he was putting so many natural wonders in one place. God replied, "It will even out. Wait till you see the character of the people I'm going to put there." Self-effacement aside, among the people of Colombia there is a curious mixture of pride and bafflement, sorrow and theatricality, regret and resignation about their unusually bloody history—a history from which the country has not yet emerged. Violence and beauty intertwine in Colombia in complicated ways, just as the folk saying implies; that much I have learned during the many trips I have made there to conduct research and genetic testing on a rare form of Alzheimer's disease.

The lush valley of the Cordillera Central, the range of the Andes where

Medellín is situated, is striking. From the airport, it is an hour-long winding descent to the city on a mountain road bordered by verdant slopes. At night, the soft lights in the valley suggest the mythical golden city of El Dorado, the way the first Spanish settlers must have pictured it some 400 years ago. But daylight exposes the urban sprawl that extends well up the sides of the surrounding mountains, and the cruel poverty that penetrates the choked streets. On the far outskirts of Medellín, a few swimming pools and enormous mansions dot the landscape. Some of them are the vast estates of the drug lords, who can be identified in the city by their powerful four-wheel-drive vehicles, and whose pursuits a few years ago gave Medellín one of the highest murder rates of any city not at war.

This highly insular world, where Internet access coexists with ancient folk beliefs, opened to me in 1991. A neurologist at Brigham and Women's Hos-

pital in Boston, I visited Colombia that year with the support of the Fogarty International Center, a branch of the National Institutes of Health, to help develop neuroscience in Latin America. In October 1992 I traveled to the University of Antioquia School of Medicine in Medellín, where I gave a talk on the biology of Alzheimer's disease—the degenerative brain disorder that strikes so many people at the end of their lives. There I was introduced to the neurologist Francisco Lopera.

Lopera told me of a fascinating find he had made. About a decade earlier, while evaluating a forty-four-year-old man complaining of memory loss, he had been struck by how closely the man's symptoms resembled Alzheimer's disease, except for the patient's young age. More disturbing was the man's family history: he mentioned many relatives with similar problems back in his village. Beginning with mildly annoying symp-

toms such as asking the same question repeatedly, the affected people later developed personality changes, became disoriented, and about a decade later died, usually of pneumonia after a prolonged vegetative period.

Lopera began investigating, and by the time I met him he had developed a series of detailed genealogies that tracked twelve interrelated families. Intrigued by this mysterious early-onset form of dementia, I agreed to help Lopera try to find the gene mutation at work and unlock its secrets.

But genes are not isolated entities that live only in laboratory test tubes; they are part of the fabric of a person's individual and cultural identity. Thus our quest turned out to be more than a scientific search for a snippet of mutant DNA: it became, for me, an odyssey both geographical and personal. The work has connected me to people whose lives would otherwise be quite foreign—Spanish-speaking farmers who are provincial and unsophisticated, yet uncannily wise. Their fates are enmeshed in that microscopic skein of genetic material, the human genome—a tangled scroll that I know how to read, but whose dictates they will have to live with.

LIKE MANY NEUROLOGISTS, LOPERA brings a depth of scholarly and esoteric knowledge to his work, though his patients usually suffer from commonplace maladies such as headaches and epilepsy. He has a nearly fixed smile that conveys his genuine good nature, but that can shift with ease to an ironic grin. Our collaboration has included many earnest discussions over late-night bottles of wine, and has led to several articles written for professional journals.

The task that brought us together was a classic one. Geneticists are always on the lookout for inherited diseases that show up within a single extended family. Such case studies offer exceptional opportunities to isolate the faulty gene responsible, because family members tend to share certain idiosyncratic stretches of DNA that reappear through the generations. When investigators find that one of those unusual stretches of DNA always occurs in the family members who have the disease, but is not present in the other family members, they can assume the faulty gene is nearby, and zero in on it.

When Lopera and I began working together, our first task was to make certain the disease in question was Alzheimer's. A definitive diagnosis requires the microscopic study of brain

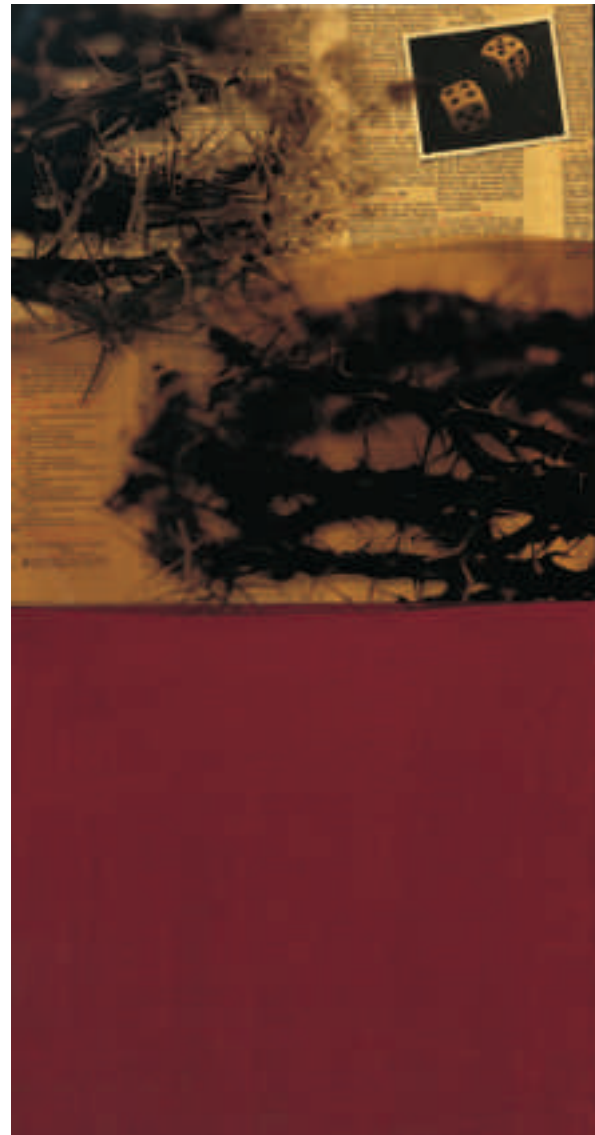
tissue after death. But because funeral rites in Colombia invoke so many local traditions and superstitions, no one had yet been able to conduct a postmortem examination, even years after the afflicted families had come to light.

Nearly all the families live in a region of the country called Antioquia, of which Medellín is the capital, in a few rural pueblos: Angostura, Belmira, Caldas, Ituango, Sabanalarga, Santa Rosa de Osos and Sopetrán; San José de la Montaña, perched high in the mountains; and Yarumal—by far the largest, with paved streets and a sizable town square. About a year after I met Lopera, he learned that a middle-aged woman who had had early-onset dementia for eleven years had died in Angostura. Quickly he enlisted Juan Carlos Arango, a neuropathologist colleague at the University of Antioquia School of Medicine, to accompany him on the five-hour drive from Medellín.

When they arrived, the *lloronas*, professional mourners, had already joined family and friends around the body, which was laid out in the sitting room. People cried and talked, and some drank to excess through the night. Gradually one of the dead woman's sons became suspicious about why the city doctors wanted his mother's brain tissue. Perhaps they planned to sell it to the gringos. All the other children agreed to have the brain examined, but this son lent a sinister tone to the negotiations. People whispered that he was connected to the *narcotraficantes* as a *sicario*, or hit man, because he had been a member of the local police, a common route to the mafia. His gold chains, his remoteness from the townspeople and the bullyish way he carried himself enhanced that impression. He made the situation tense, and as he drank, the possibilities for trouble increased.

The mayor of Angostura came to the house, followed by the vaccine man, a village medical worker known to be very *simpático*, and both attempted to resolve the situation. Finally, with further entreaties from Lopera and other family members, the angry son relented. In a brief stop at the local infirmary on the way to the church, Lopera and Arango removed the dead woman's brain. Arango flew with it straight to Boston; there, in my laboratory, he proved the case was Alzheimer's disease.

LOPERA, MEANWHILE, CONTINUED TO labor over the genealogies. What had come to his attention as a few cases of early-onset dementia turned out to be a concealed epidemic involving nearly 4,000 people. Lopera's handwritten family trees began to fill large rolls of paper, enough to cover a huge wall. Each entry distilled an entire life story into a few spare symbols—age, gender, affected or non-affected, alive or dead. The names read like a dark, enchanted poem—Gilma,



Resfa, María, Epifanía, Altagracia, Rosa, Fabiola. Lopera was struck by the inexorable appearance of the disease in one generation after the next. When one parent was affected, about half the children, regardless of gender, later developed the disease. In genetics that pattern of inheritance is called autosomal dominance, and it strongly suggested that a single mutation was responsible.

The gene involved was discovered—by someone else—a couple of years after we began the project. In 1995 the molecular geneticist Gerard D. Schellenberg of the Veterans Affairs Medical Center in Seattle identified an approximate site on chromosome 14 where one of the mutant genes for early-onset Alzheimer's resided. Within months the geneticist Peter St. George Hyslop of the University of Toronto zeroed in on the gene and named it *presenilin 1*.



Luis Gonzlez Palma, *The Only Hope*, 1998

When the *presenilin 1* gene is intact, it causes no problems for its bearer. But more than fifty different mutations—misspellings of DNA—can exist in *presenilin 1*, and wherever they occur, they lead to early-onset Alzheimer's. (In addition to *presenilin 1*, two other genes are known to cause early-onset Alzheimer's, and workers think there are still others waiting to be found.) Later in 1995, I enlist-

ed the help of Alison M. Goate, a geneticist at Washington University in Saint Louis, and together we were able to identify the specific mutation responsible for the Colombian families' disease.

It is important to understand that Alzheimer's disease comes in two distinct flavors. The most common type, afflicting about four million elderly Americans, is not caused by a genetic mutation, though some people may have a gene that makes them more than usually susceptible. That form of Alzheimer's generally strikes people sixty-five or older; no one knows why. But in about 1 percent of cases—including those among the families in Colombia—Alzheimer's strikes the young and the cause is clearly a faulty gene. Both kinds of Alzheimer's leave the same telltale marks in the brain: knotty clumps of a protein called beta-amyloid. As investigators, we hope that an understanding of the relatively rare, genetic form of Alzheimer's will lead to a treatment for the more common type.

SHORTLY BEFORE OUR TEAM learned the precise location of the Alzheimer's mutation, we invited the families involved to a meeting at the hospital in Yarumal. There we were greeted by the mayor, who assigned me two bodyguards: he said he had no fears about the people in his town, but could not be sure about people from other villages. Nearly a hundred people came—in donkey carts, on horseback and by bus. We gathered them together in an open auditorium, told them about our work and invited questions. They asked about a local superstition that the disease could be contracted by touching a tree, though they were unsure which tree was the contagious one. They also asked about marrying their first cousins. Although they were aware of the risk posed by intermarriage, still, the limited choice of a mate in their small villages meant that sometimes

love outweighed more abstract concerns. To the people gathered there, most of whom had no more than a first- or second-grade education, some genetic principles seemed to make intuitive sense, whereas others did not. No one had trouble, for instance, understanding that traits can be inherited. But the fact that the probability of inheriting a trait is unrelated to the previous births

was more difficult to grasp. If one parent has the Alzheimer's mutation, there is a 50 percent risk that each child will have it too. But, just as parents who have had three girls in a row may expect their chance of having a boy to increase, the villagers endorsed a logical fallacy. One man announced to the assembled group: "We the families in which there are only a few affecteds must be grateful to those families with many affecteds." Local ideas of guilt and collective burden were deeply ingrained, and clashed with the principles of population genetics.

Where did the Colombian Alzheimer's mutation come from? *Paisas*, as the people of Antioquia call themselves, are generally regarded as different from other Colombians. Some say they are related to the Basques; others consider them a lost tribe of Israel. Various indigenous groups once ruled their land—principal among them the Chibchas, who originated the legend of El Dorado. Excellent goldsmiths, the Chibchas anointed their chiefs by rolling them in gold dust, which the new leaders then washed off in Lake Guatavita. In the sixteenth century Spain conquered the area, and for three centuries governed it with a harsh grip.

Even tracing back seven generations, it is impossible to find a common ancestor who links any of the twelve extended families that carry the Alzheimer's gene. Yet undoubtedly they are all related to a single individual, the first person in whom the deadly mutation occurred. Perhaps that person was a pre-Columbian, whose own people are now extinct, and whose only legacy is the defective Alzheimer's gene propagating in retribution among the Spanish usurpers of her land. Or perhaps the curse originated with a Spaniard—a sailor whose forgettable fling left an indelible genetic memory. Indeed, the mutation may have spread by any of the myriad entanglements through which human beings accomplish genetic recombination.

AFTER THE DISCOVERY OF THE mutation it became possible to predict, from a simple blood test, who within the Colombian families would get Alzheimer's—even whether a pregnant woman's fetus would one day contract the disease. We then were ethically bound to find out how such powerful information, if made available, would affect the local people. There is no known way to dodge the illness or even to postpone it. If someone carries the mutation, early-onset Alzheimer's is inevitable—unless another cause of

early death makes a pre-emptive strike.

The village of Caldas is not far from Medellín. To get there we turned off the road onto a dirt path that runs along an abandoned railroad track. Near the end of a row of houses a smiling señora, her face lined with creases, greeted us with a litany of salutations. Her middle-aged daughter, a ruddy, dough-faced woman, stood beside her. We sat in their simple living room while the daughter brought out the Colombian coffee they call *tinto*. After chatting a bit, the señora Autila asked whether we would like to see her son, Rodrigo.

She told us Rodrigo's disease had begun five years earlier, at age forty-four, when they had found him lost and wandering in a field. It was the same field where another of her sons had been shot dead. The murder was not unusual. Nearly every family we visited had been touched by the violence that permeates Colombian society, and often it struck me that the biological disease my colleagues and I were trying to defeat was dwarfed by another, equally deadly condition—one that had none of the predictability of an inherited gene defect, and about which we understood almost nothing.

In a small room next to the dining area, Rodrigo was neatly tucked into white sheets, unconscious and, except for his breathing, quite still. Occasionally this peaceful picture was interrupted by the gnashing of teeth and quick jerking movements that are typical of late-stage Alzheimer's. The room, bare of ornament, resembled a mortuary, with its white walls and the small cross at the head of the iron-railed bed—as if to ease Rodrigo's transition to the next world.

OUR NEXT STOP WAS MANRIQUE, A poor and violent barrio in Medellín. That was where Nubia lived with her demented mother and an unclear number of other family members. To reach the house we had to drive deep into what felt like a Brueghel painting. Blackened, distorted human faces looked out from dingy garages and the platforms of abandoned warehouses; vultures perched patiently overhead. Nubia's front door opened directly onto a busy street. Only

a thin wall separated the inhabitants of the house from the noise and squalor outside.

Here was none of the tranquillity that surrounded Rodrigo in his whitewashed room. Nubia's mama was on display, visible to every passerby through the open front door. Emaciated, she sat contorted, her hands gnarled and stuck in an unnatural position, a feeding tube protruding from her nose. Motionless except



Luis Gonzales Palma, *The Critical Gaze* (detail), 1998

for her aimlessly roving eyes, she was a constant reminder to her children of the fate that lay ahead for those among them who carried the mutant gene.

I told the grown children that we could now determine which of them would get the disease, and I asked whether they would want to take the test. "Before answering," I told them, "remember that there is no treatment." All the children said they would want to take the test. What would they do differently, once they knew the result? I asked. At that point no one had an answer, except twenty-three-year-old González, who later told our nurse that if his test were positive, he would shoot himself.

ONCE THE PROVINCE OF SHAMANS and *curanderos*, revealing the future of an otherwise healthy person is a very modern responsibility for physicians. When

the genes tell a cruel story, we must be prepared for the power and danger of that information. In the United States, genetic counselors are trained to help people make sense of such news. Faced with someone like González, a counselor would sympathize with his despair while reminding him that many more worthwhile years lay ahead. But Colombia has no genetic counselors, and so, adhering to well-established ethical guidelines, Lopera and I have decided that the gene test will be given for research purposes only: the results will not be made available to the person tested or to anyone else. I am not fully comfortable with that arrangement, however, because I know there are, among the Colombians, people who might limit the number of children they chose to have if they knew they carried the mutation.

CURIOSLY, THE *PRESENILIN 1* mutation found among the Colombians does not strike all its victims at the same age. Some people with the mutation get Alzheimer's in their early thirties, and others are not stricken until their late fifties. The question is, Why? One possibility is that something in the environment triggers the disease. But if that were the case, one would expect family members with different onset ages to have divergent lifestyles. Instead, the affected

people have similar habits and occupations: the men work on coffee plantations, and the women are housewives.

A more likely explanation, therefore, is a modifier gene—a second gene that controls when the *presenilin 1* mutation begins to do its damage. It is not unusual for two genes to work in tandem—one doing damage, the other dictating when the damage will occur and how bad it will be. Modifier genes are among a growing group of known "risk factor" genes, genes that increase a person's chances of getting a disease. For example, a specific variant of the *APOE* gene predisposes people to the more common kind of Alzheimer's (the kind that strikes elderly people), and may cause them to contract it earlier.

So the hunt is on among the Colombians. We have obtained blood samples from siblings who developed the disease

at widely disparate ages, and we have begun the tedious search among the billions of nucleotides that make up the enormous stretches of human DNA. If a modifier gene exists, we will find it in two or three years. And the payoff could be enormous: if, for instance, a drug could be developed that inhibited the protein made by the modifier gene, physicians could delay the onset of Alzheimer's by as many as twenty years—not only in the Colombian families, but potentially also among the people who suffer from the more common version of the disease. Pushing back the age at which the widespread form of Alzheimer's strikes—from, say, age seventy to age ninety—would be nearly tantamount to a cure.

AT ONE POINT IN THE NOVEL *ONE Hundred Years of Solitude*, by the Nobel-prize-winning Colombian writer Gabriel García Márquez, the inhabitants of the fictional village of Macondo mysteriously begin to lose their memories. In a haunting parallel to the real disease that afflicts the families in Antioquia, the novel describes how the villagers first forget the names of objects, and then lose the ability to use them. The cure comes eventually in the form of “a drink of a gentle color,” brought to town by a traveling gypsy.

Armed with the tools of modern genetics, are we biologists the gypsies who bring the campesinos the cure? Or are we dangerous intruders instead, one more band of exploiters in a long line of outsiders who, beginning with Cortés, have invaded and betrayed Latin America? Just as foreigners have historically plundered the continent's natural resources, so we, the prospectors of the late twentieth century, come to harvest genes.

Our work, however, has the feel of something predestined. Whether because of a Faustian pact or naïve curiosity, knowledge cannot be denied. Sooner or later we will know our genes; if we do not, our children will. We stand poised to be expelled from an Eden of genetic ignorance into a society where every talent and weakness, every wrinkle and freckle may be predicted from our genomes. More disturbing is the possibility that our genomes will become public property, that employers and insurance companies will peer into our DNA and then discriminate against us as a result—that the knowledge of our genetic destiny will rob us first of opportunity, and later of all hope.

Like magical concoctions from a Márquez novel, geneticists' devices can predict a tragic fate for children playing along the railroad tracks of Caldas or in

the sunny church square of Yarumal. I worry particularly about the impact of newfound genetic knowledge in a land far from the microtiter plates, DNA chips and fluorescent gel bands of my laboratory. Ultimately, however, such qualms are pointless.

Scientific revolutions derive from small, incremental discoveries. Lopera and I, and other neurologists, who contribute a jigsaw piece here or there, cannot envision the completed puzzle. My experiences in Colombia have helped me put the genetic enterprise in perspective. What I have learned in that colorful yet tortured land, where the threat of violence is constant and senseless murder is accepted as a fact of life, is that no matter how much progress we scientists make toward understanding the present and controlling the future, destiny will always hold the trump card. We cannot know, in advance, the eventual impact of genetic knowledge. We can only strive to untangle its secrets with a sense of responsibility toward the communities that hold the precious genetic clues. ●

KENNETH S. KOSIK is a professor of neurology at Harvard Medical School and an attending physician at Brigham and Women's Hospital in Boston, where he was a cofounder of the Memory Disorders Clinic.



THE BEST OF THE SCIENCES COLLECTORS' EDITIONS SALE



March/April 1993

The five sexes; life in amber; Modern Homers in Bosnia; ultraviolet and X rays

September/October 1997

Special Issue: Cloning
1998 National Magazine Award
Best single-topic issue

July/August 1998

Special Issue: Frontiers of Life
Radiation-resistant bacterium; Mars rocks; impact theory; life underground

March/April 1995

Chasing tornadoes; estimating extinction rates; the secret life of American slaves; combating insecticide resistance

July/August 1994

What makes the number *e* so special; the hypercello; timing drug treatment; flood control in the Midwest

September/October 1995

Can hormones delay aging?; spider silk; multidimensional space; the Internet and education

November/December 1996

Perspectives on science ± 35 years; ancient wine; biology of homosexuality

May/June 1992

The naked mole-rat; origin of mass; deadly African lake; culture of a weapons lab

May/June 1996

How climate change destroyed ancient civilizations; biology of memory; the end of science?

Please send me _____ issues at \$7.50 each. Allow 4-6 weeks for delivery.

Total amount _____.

Name _____
Address _____
City _____
State _____ Zip Code _____
Country _____

Check enclosed SCICOLL
 Please charge my:
 Master Card Visa American Express
ACCOUNT # _____ EXPIRATION DATE _____
SIGNATURE _____

Return to: Publications, New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021
For questions or for credit card orders, call 212-838-0230, ext. 342, or E-mail: publications@nyas.org