

AN ERROR IN THE CODE

What can a rare disorder tell us about human behavior?

BY RICHARD PRESTON

Sufferers of Lesch–Nyhan syndrome are uncontrollably driven to harm themselves.

LORENZO MATTOTTI

One day in September, 1962, a woman who here will be called Deborah Morlen showed up at the pediatric emergency room of the Johns Hopkins Hospital, in Baltimore, carrying her four-and-a-half-year-old son, Matthew. He was spastic, and couldn't walk or sit up; as an infant, he had been diagnosed as having cerebral palsy and developmental retardation. The emergency room was in the Harriet Lane Home for Invalid Children, an old brick building in the center of the Johns Hopkins complex, where a pediatric resident named Nancy Esterly saw Matthew. He had strange-colored urine, Mrs. Morlen told Esterly, "and there's sand in his diaper." Esterly removed the boy's diaper. It was stained a deep, bright orange, with a pink tinge. She touched the cloth and felt grit. She had no idea what this was, except that the pink looked like blood. She learned from Mrs. Morlen that Matthew had an older brother, Harold, who was also



spastic and retarded. Harold was living at the Rosewood State Hospital, an institution for disabled children, outside Baltimore, while Matthew lived at home.

Since both brothers seemed to have the same condition, Esterly thought it likely that they had a genetic disease, but, if so, it wasn't one that she'd ever seen or heard of. Esterly also noted that Matthew was wearing mittens, even though it was a warm day. She admitted the little boy to the hospital.

Esterly took a sample of Matthew's urine, and both she and an intern looked at it under a microscope. They saw that it was filled with crystals. They were beautiful—they were as clear as glass, and they looked like bundles of needles, or like fireworks going off. They were sharp, and it was clear that they were tearing up the boy's urinary tract, causing bleeding. Esterly and the intern pored over photographs of crystals in a medical textbook. The intern asked if the crystals might be uric acid, a waste product excreted by the kidneys; however, cystine, an amino acid that can form kidney stones, seemed the most likely candidate. Esterly needed a confirmation of that diagnosis, so she carried the sample upstairs to the top floor, where William L. Nyhan, a pediatrician and research scientist, had a laboratory. "Bill Nyhan was the guru of metabolism," Esterly told me.

Nyhan, who was then in his thirties, had been studying how cancer cells metabolized amino acids, in an attempt to find ways to cure cancer in children. "It was one of my impossible projects," he said to me recently. Nyhan is now a professor of pediatrics at the University of California San Diego School of Medicine. "I love working with kids, but dealing with pediatric cancer was depressing, saddening, and, in truth, maddening," he said. Nyhan ran some tests on Matthew's urine, using equipment he had designed. The crystals weren't cystine, or any sort of amino acid. They proved to be uric acid. A high concentration of uric acid in a person's blood can lead to gout, a painful disease in which crystals grow in the joints and extremities, particularly in the big toe. Gout has been known since

the time of Hippocrates, and it occurs mainly in older men. Yet the patient here was a little boy. Nyhan had a medical student named Michael Lesch working in his lab, and together they went downstairs.

Matthew lay in a bed in an open ward on the second floor of the Harriet Lane Home. He was a spot of energy in the ward, a bright-eyed child with a body that seemed out of control. The staff had tied his arms and legs to the bedframe with strips of white cloth, to keep him from thrashing, and they had wrapped his hands in many layers of gauze; they looked like white clubs. Nurses hovered around the boy. "He knew I was a doctor and he knew where he was. He was alert," Nyhan says. Matthew greeted Lesch and Nyhan in a friendly way, but his speech was almost unintelligible: he had dysarthria, an inability to control the muscles that make speech. They noticed scarring and fresh cuts around his mouth.

They inspected Matthew's feet. No sign of gout. Then the boy's arms and legs were freed, and Lesch and Nyhan saw a complex pattern of stiff and involuntary movements, a condition called dystonia. Nyhan had the gauze unwrapped from the boy's hands.

Matthew looked frightened. He asked Nyhan to stop, and then he began crying. When the last layer was removed, they saw that the tips of several of the boy's fingers were missing. Matthew started screaming, and thrust his hands toward his mouth. With a sense of shock, Nyhan realized that the boy had bitten off parts of his fingers. He also seemed to have bitten off parts of his lips.

"The kid really blew my mind," Nyhan said. "The minute I saw him, I knew that this was a syndrome, and that somehow all of these things we were seeing were related."

Lesch and Nyhan began to make regular visits to the ward. Sometimes Matthew would reach out and snatch Nyhan's eyeglasses and throw them across the room. He had a powerful

throw, apparently perfectly controlled, and it seemed malicious. “Sorry! I’m sorry!” Matthew would call, as Nyhan went to fetch his glasses.

The doctors persuaded Mrs. Morlen to bring her older son to the hospital. Harold, it turned out, had bitten his fingers even more severely than Matthew, and had chewed off his lower lip. Both boys were terrified of their hands, and screamed for help even as they bit them. The boys’ legs would scissor, and they tended to fling out one arm and the opposite leg, like a fencer lunging. The Morlen brothers, the doctors found, had several times more uric acid in their blood than normal children do.

Nyhan and Lesch visited the Morlen home, a row house in a working-class neighborhood in East Baltimore, where Matthew was living with his mother and grandmother. “He was a well-accepted member of his little household, and they were very casual about his condition,” Nyhan says. The women had devised a contraption to keep him from biting his hands, a padded broomstick that they placed across his shoulders, and they tied his arms to it like a scarecrow. The family called it the “stringlyjack.” Matthew often asked to wear it.

Nyhan and Lesch also discovered that they liked the Morlen brothers. Lesch, who is now the chairman of the Department of Medicine at St. Luke’s-Roosevelt Hospital, in New York City, said, “Matthew and Harold were really engaging kids. I enjoyed being around them.”

Two years after meeting Matthew Morlen, Nyhan and Lesch published the first paper describing the disease, which came to be called Lesch-Nyhan syndrome. Almost immediately, doctors began sending patients to Nyhan. Very few doctors had ever seen a person with Lesch-Nyhan syndrome, and boys with the disease were, and are, frequently misdiagnosed as having cerebral palsy. (Girls virtually never get it.) Nyhan himself found a number of Lesch-Nyhan boys while visiting state institutions for developmentally

disabled people. When I asked him how long it took him to diagnose a case, he said, “Seconds.” He went on, “You walk into a big room, and you’re looking at a sea of blank faces. All of a sudden you notice this kid staring at you. He’s highly aware of you. He relates readily to strangers. He’s usually off in a corner, where he’s the pet of the nurses. And you see the injuries around his lips.”

William Nyhan is now eighty-one, a tall, fit man with blondish-gray hair and blue eyes. He has a laboratory overlooking a wild canyon near the U.C.S.D. Medical Center. One day when I visited him, two red-tailed hawks were soaring above the canyon, tracing circles in the air. In the years since he identified Lesch-Nyhan, he has discovered or co-discovered a number of other inherited metabolic diseases, and he has developed effective treatments for some of them. He figured out how to essentially cure a rare genetic disorder called multiple carboxylase deficiency, which could kill babies within hours of birth, by administering small doses of biotin, a B vitamin. Lesch-Nyhan, however, has proved to be more intractable.

Decades after the discovery of Lesch-Nyhan syndrome, it is still mysterious. It is perhaps the clearest example of a simple change in the human DNA which leads to a striking, comprehensive change in behavior. In 1971, William Nyhan coined the term “behavioral phenotype” to describe the nature of diseases like Lesch-Nyhan syndrome. A phenotype is an outward trait, or a collection of outward traits, that arises from a gene or genes—for example, brown eyes. Someone who has a behavioral phenotype displays a pattern of characteristic actions that can be linked to the genetic code. Lesch-Nyhan syndrome seems to be a window onto the deepest parts of the human mind, offering glimpses of the mechanics of the genetic code operating on thought and personality.

H. A. Jinnah, a neurologist at Johns Hopkins Hospital, has been studying Lesch-Nyhan syndrome for more than fifteen years. “This is a very horrible disease, and a very complex brain problem,” he

said. “It is also one of the best models we have for trying to trace the action of one gene on complex human behavior.”

A child born with Lesch-Nyhan syndrome seems normal at first, but by the age of three months he has become a so-called floppy baby, and can't hold up his head or sit up. His diapers may have orange sand in them. When the boy cuts his first teeth, he starts using them to bite himself, and he screams in terror and pain during bouts of selfmutilation. “I get calls in the middle of the night from parents, saying, ‘My kid’s chewing himself to bits—what do I do?’” Nyhan said. The boy ends up in a wheelchair, because he can't learn to walk. As he grows older, his self-injurious behaviors become subtle or more elaborate, more devious. He seems to be possessed by a demon that forever seeks new ways to hurt him. He spits, strikes, and curses at the people he likes the most; one way to tell if a Lesch-Nyhan patient doesn't like you is if he's being nice. (“I got beat up once by Matthew,” Lesch told me. He had leaned over the boy and asked him how he was feeling, and Matthew had punched him in the nose.) He eats foods he can't stand; he vomits on himself; he says yes when he means no. This is self-sabotage.

A few hundred boys and men alive in the United States today have been diagnosed as having Lesch-Nyhan syndrome. “I think I know most of them,” Nyhan said. One boy, known as J.J., ended up living in Nyhan's research unit for a year, when he was eleven. He was a gregarious child, whose hands seemed to hate him. Over time, his fingers had got inside his mouth and nose and had broken out and removed the bones of his upper palate and parts of his sinuses, leaving a cavern in his face. He had also bitten off several fingers. J.J. died in his late teens; in the past, many Lesch-Nyhan patients died in childhood or their teens, from kidney failure. (Both Morlen brothers died young.) Nowadays, they may live into their thirties and forties, but they are generally frail and often die from infections like pneumonia. Occasionally, a man with the disease flings his head backward with such force that his neck is broken. Many Lesch-Nyhan patients die suddenly and often inexplicably.

A Lesch-Nyhan person may be fine for days, until suddenly his hands jump into his mouth with the suddenness of a cobra strike, and he cries for help. People with Lesch-Nyhan feel pain as acutely as anyone else does, and they are horrified by the idea of their fingers or lips being severed. They feel as if their hands and mouth don't belong to them and are under the control of something else. Some Lesch-Nyhan people have bitten off their tongues, and some have a record of self-enucleation—they have pulled out an eye or stabbed it with a sharp object. When the Lesch-Nyhan demon is dozing, they enjoy being around people, they like being the center of attention, and they make friends easily. “They really are great people, and I think that’s part of the disease, too,” Nyhan said. Some Lesch-Nyhan people are cognitively impaired, while others are clearly bright, but their intelligence can’t be measured easily. “How do you measure someone’s intelligence if, when you put a book in front of him, he has an irresistible urge to tear out the pages?” Nyhan asked.

In 1967, J. Edwin Seegmiller, a scientist at the National Institutes of Health, and two colleagues discovered that in Lesch-Nyhan patients a protein called hypoxanthine-guanine phosphoribosyl transferase, or HPRT, which is present in all normal cells, doesn't seem to work. The job of this enzyme is to help recycle DNA. Cells are constantly breaking down DNA into its four basic building blocks (represented by the letters A, T, C, and G, for adenine, thymine, cytosine, and guanine). This process produces compounds called purines, which can be used to form new code. If HPRT is absent, or doesn't work, then certain purines build up in a person's cells, where they are eventually broken down into uric acid, which saturates the blood and crystallizes in the urine.

In the early nineteen-eighties, a group of researchers, led by Douglas J. Jolly and Theodore Friedmann, decoded the sequence of letters in the human gene that contains the instructions for making HPRT. It includes six hundred and fifty-seven letters that code for the protein. Researchers also began sequencing this gene in people

who had Lesch-Nyhan. Each had a mutation in the gene, but, remarkably, nearly everyone had a different one; there was no single mutation that caused Lesch-Nyhan. The mutations had apparently appeared spontaneously in each affected family. And, in the majority of cases, the defect consisted of just one misspelling in the code. For example, an American boy known as D.G. had a single G replaced by an A—one out of the three billion letters of code in the human genome. As a result, he was tearing himself apart.

The HPRT gene is found on the X chromosome. Women have two X chromosomes in each cell, and men have an XY pair. Lesch-Nyhan syndrome is an X-linked recessive disorder. This means that if a bad HPRT gene on one X chromosome is paired with a normal gene on the other X chromosome the disease does not develop. A woman who has the Lesch-Nyhan mutation carries it on only one of her X chromosomes—she doesn't develop the syndrome. Any son that she has, however, will have a fifty-per-cent chance of inheriting the syndrome, and any daughter will have a fifty-per-cent chance of being a carrier. (Examples of this type of disease include hemophilia and a form of red-green color blindness.)

Other genetic mutations have been associated with profound behavioral changes. Rett syndrome, which affects mostly girls, is caused by a mutation in a gene that codes for the MeCP2 protein. People with the syndrome compulsively wring their hands and rub them together as if they were washing them. Children with Williams syndrome have an elfin appearance, an affinity for music and language, and an extreme sensitivity to sound, and are very sociable. Williams syndrome is caused by the deletion of a bit of code from chromosome 7. There is still great uncertainty, however, about how much of a role genes play in major conditions such as depression, bipolar disorder, and borderline personality disorder. Even where there is evidence of a family history of a disease, scientists are unsure how a single gene could choreograph a suite of behaviors. There are roughly twenty-five thousand active genes in the human genome, each with about a thousand to fifteen hundred

letters of code. The genome could be thought of as a kind of piano with twenty-five thousand keys. In some cases, a few keys may be out of tune, which can cause the music to sound wrong. In others, if one key goes dead the music turns into a cacophony, or the whole piano self-destructs.

The havoc that the Lesch-Nyhan mutation causes can't easily be undone. Early on, Nyhan tried giving his patients allopurinol, a drug that inhibits the production of uric acid; it is effective with gout. It lowered the uric-acid concentration in Lesch-Nyhan patients, but it didn't reduce their self-injurious actions. The uric acid, it seemed, was another symptom, and not a cause of the behavior. Nyhan has experimented with other treatments, such as soft restraints, which seem to relax patients, and the removal of certain teeth. "I'm profligate with those upper teeth," Nyhan said. Some dentists, though, refuse to extract healthy teeth, even when Lesch-Nyhan syndrome is explained to them.

I told Nyhan that I couldn't imagine what it would be like to live with the disease.

"You could ask someone who has it," he replied.

I first met James Elrod and Jim Murphy in the winter of 1999. They were living next to each other in rented bungalows in a somewhat marginal neighborhood in Santa Cruz, California. Elrod was then in his early forties, and Murphy was just over thirty. (Murphy died in 2004; Elrod, who is now forty-nine, is one of the oldest living people with Lesch-Nyhan.) The men were clients of Mainstream Support, a private company contracted by the State of California to help people with developmental disabilities live in community settings. Before James Elrod came to Santa Cruz, he lived for eighteen years in a state institution in San Jose. Murphy had lived for most of his life at an institution in Sonoma. Mainstream employees, called direct-care staff, stayed with Elrod and Murphy around the clock, to help them with daily tasks and to make sure they didn't harm themselves. Elrod and Murphy had the

authority to hire and fire their assistants and direct their work, though an assistant could refuse an order if he thought that it would put the client in danger.

At that time, Mainstream was run by two men named Andy Pereira and Steve Glenn. “James and Jim are real down-and-gritty guys,” Pereira said, the first time I talked to him. “They are not sweet types. They’re into fast cars and women.” Glenn said that he still had difficulty seeing into the labyrinth of Lesch-Nyhan. “There are these Lesch-Nyhan moments when you feel like you’ve kind of got it,” he said. “James and Jim are pretty good at telling you when they think they’re in danger of hurting themselves, but, whenever they’re doing something, you always have to ask, Is this James or Jim, or is it Lesch-Nyhan?”

James Elrod has a square, good-looking face, which is marked with scars, and brown, hyperalert eyes. His shoulders and arms are large and powerful, but the rest of his body seems slightly diminished. One day, before he was with Mainstream, an attendant left him alone at dinner for a few minutes. To Elrod’s horror, his left hand picked up a fork and used it to stab his nose and gouge it out, permanently mutilating his face. “My left side is my devil side,” he told me. When I met him, he wore black leather motorcycle gloves that had been reinforced with Kevlar. If he thought that his left hand was threatening him or someone else, he would grab it or swat it with his right hand. He owns a pickup truck, and his assistants drive him around in it. He used to sell flowers on the Santa Cruz pier, and he carries business cards explaining that he has a rare disease that compels him to hurt himself. “I have injured myself in many ways including my nose, as you can see,” the card says. “I will even try to hurt myself by getting into trouble with others.” One day, a man bought flowers from Elrod and said, “God bless you.” “Eat shit,” Elrod replied, and handed the man his business card. While crossing a street in his wheelchair, Elrod has been known to

try to roll himself into traffic, yelling, “Slow down, you morons! Don’t you know it’s Lesch-Nyhan?” His assistants wrestle him to safety.

Elrod was sitting in front of his house in his wheelchair when I arrived. It was a sunny day. He offered me his right hand to shake. When I gripped his glove, the right index finger collapsed. “You broke my finger!” he gasped. Then he grinned and explained that he didn’t have that finger. “Some people get all upset when I do that,” he said. “Kids love it. They want to break my finger again.”

We chatted for a while. “Hey, Richard—danger,” he said.

“What’s wrong?”

He cautiously pointed at the pencil I was using to take notes. “Your pencil is scaring me. My hand could grab it and put it in my eye,” he said. “You’d better go see my neighbor.”

Jim Murphy was sitting in his wheelchair at a table in the living room of his house, and an assistant named Michael Roth cut up pancakes and fed them to him with a spoon. Murphy was a bony man with dark hair and a lean, handsome face. He had a neatly trimmed goatee and a crewcut, and his eyes were mobile and sensitive-looking. His lips were missing. Two of his brothers had also had Lesch-Nyhan, and had died when they were young. “Jimmy will be shy when you first meet him,” one of his sisters had told me on the phone. I could expect to hear a lot of swearing, though. “He doesn’t mean it,” she said. “When he swears at me, I just say, ‘I love you, too.’”

That day in Santa Cruz, Murphy stared at me out of the corners of his eyes, with his head involuntarily thrown back and turned away, braced against a headboard. His hands were stuffed into many pairs of white socks, and his chest heaved against a rubber strap that held

him in place. He started throwing punches at me, and he kicked at me. He seemed to be enduring his disease like a man riding a wild horse. The wheelchair shook.

I kept back. "It's nice to meet you," I said.

"Fuck you. Nice to meet you." Murphy had a fuzzy but pleasant-sounding voice. His speech was very hard to understand. He looked at Roth. "I'm nervous," he said.

"Do you want to be restrained?" Roth asked.

"Yeah."

Roth placed Murphy's wrists and ankles in soft cuffs fastened with Velcro.

"I'm a little nervous, too," I said, and sat down on the couch.

"I don't care. Goodbye."

I stood up to leave.

Roth explained, however, that this was one of those Lesch-Nyhan situations where words mean their opposite.

Later, Murphy tried to tell me what his disease was like. "You try to tick everybody off, and then you feel bad when you do it," he said. "If you get too close to me, I could—," he said; the ending was indecipherable.

"I'm sorry, what?"

"Coldcock you, Richard. I'll say, 'Get my water,' and I'll give you a sucker punch."

A pair of red boxing gloves hung on the wall. Every day, his assistants placed him on a wrestling mat on the floor, where he rolled around and did stretches and then boxed with them. "I could

definitely whip you,” he told me. I didn’t doubt it.

There have been about twenty autopsies of Lesch-Nyhan patients over the years. Their brains appeared to be perfectly normal. “It’s a problem in the connections, in the way the brain functions,” H. A. Jinnah, the Johns Hopkins neurologist, said. During some of the autopsies, doctors tested samples of brain tissue to see if they contained normal levels of neurotransmitters—chemicals that are used for signalling between nerve cells. In the Lesch-Nyhan brains, a lemon-size area containing structures called the basal ganglia, near the center of the brain, had eighty per cent less dopamine—an important neurotransmitter—than a normal brain. The basal ganglia are wired into circuits that run all over the brain and affect a wide range of functions: motor control, higher-level thinking, and eye movement, as well as impulse control and enthusiasm.

“People with Lesch-Nyhan have an excess number of involuntary movements,” Jinnah said. “It’s as if they are stepping on the gas too hard when they try to do something. If you ask them to look at a red ball, for instance, their eyes go to everything except the red ball, and they can’t explain why. Then, if you introduce a yellow ball into their field of view, but you don’t say anything about it, they watch the yellow ball.” The moment you draw their attention to it, however, they look away.

“Lesch-Nyhan is at the far end of a spectrum of self-injurious behavior,” Jinnah went on. “We all do things that are bad for us. We’ll sit down in front of the television and eat a quart of ice cream. We all have self-injurious impulses, too. Driving a car, we can have a strange impulse to drive it the wrong way and smash it into something.” Edgar Allan Poe called such promptings “the imp of the perverse.” The imp may be signals coming out of the basal ganglia. Normal people feel the promptings of the imp, but most of the time they don’t act on them. Lesch-Nyhan may suggest a way in which original thoughts and ideas seem to arise as impulses that aren’t suppressed, and how intimate the terrain is between the

creative and the self-destructive. “Many people bite their fingernails,” Jinnah said. “They’ll tell you it’s gross and that they don’t want to do it—‘Sometimes I get nervous and start biting my fingernails,’ they’ll say. There are people who chew their lips nervously. Now let’s turn up the volume a little: some people bite their cuticles. Turn up the volume a little more: some people bite their cuticles until they bleed. Now let’s turn the volume *way* up. Now you have someone biting off tissue and bone in his fingers, biting off the whole finger, and chewing his lips off. Where, in this spectrum of behavior, is free will?”

In some ways, Lesch-Nyhan syndrome looks like Parkinson’s disease reversed. People with Parkinson’s have trouble starting physical actions, and are said to be hypokinetic. Lesch-Nyhan people start actions too easily, and can’t stop an action once it starts; they are said to be hyperkinetic. Because Parkinson’s is also associated with a deficiency of dopamine in the basal ganglia, scientists have looked to each disease for clues to the other.

In 1973, a researcher named George Breese, at the University of North Carolina School of Medicine, was working with rats that modelled Parkinson’s disease. He was treating newborn rats with compounds that changed the dopamine levels in their brains, when, to his surprise, the rats started chewing off their paws. He had inadvertently created a rat with Lesch-Nyhan symptoms. “I’ll not go further into the details of what the rats were doing. They weren’t biting their mouth tissues, the way human patients do,” Breese told me. If he gave the self-injuring rats another compound, they stopped biting their paws—that is, he found a way to reverse the symptoms. “We treated the rat the moment we saw the animal make the first pinprick injury to its paws,” he said. The compound, however, has never been approved for use on humans.

In April, 2000, a neurosurgeon at the Tokyo Women’s Medical University named Takaomi Taira performed brain surgery on a nineteen-year-old man with Lesch-Nyhan. The young man was living with his parents in a district north of Tokyo. In addition to

exhibiting self-injurious behavior, he had the spastic, stiff, thrashing movements of dystonia. “These dystonic movements were getting more severe almost by the day, and his parents were getting desperate,” Taira said to me recently. He decided to perform a procedure called deep-brain stimulation to try to calm down the movements.

Deep-brain stimulation was developed by doctors more than twenty years ago for treating people with Parkinson’s disease. One or more thin wires are inserted through openings in the skull, and the wires are carefully navigated through the brain until they stop in a part of the basal ganglia called the globus pallidus (the “pale globe”). The wires are connected to a battery pack, which is implanted under the skin of the patient’s chest, and a faint, pulsed current of electricity runs through them into the globus pallidus, numbing a spot the size of a pea. The patient feels nothing. The procedure often helps to calm the tremors in Parkinson’s patients’ hands and limbs, and helps them walk more easily.

“After the surgery, the boy’s dystonic movement completely disappeared,” Taira said. He sent him home with the deep-brain stimulator, feeling that the operation had helped. Several months later, the young man’s parents told Taira that he had stopped biting himself. He was still in a wheelchair, and his uric-acid levels remained high, but he was reading comic books and watching television, and seemed to be enjoying life as never before. “It was completely unexpected, remarkable, almost unbelievable,” Taira said. A few years later, the young man suddenly began biting his hands again, and the parents brought him back. “I checked the device and found that the battery was flat. I replaced the battery, and his symptoms were controlled again,” Taira said.

A research group in Montpellier, France, led by a neurosurgeon named Philippe Coubes, has given deep-brain-stimulation implants to five Lesch-Nyhan patients. His method involves the insertion of four wires into the brain. “So far, we have three patients who are doing very well and two who are having an intermediate response—

the response of one of those is not poor but is not as good as the others,” Coubes said. “I’m not sure we will be able to control all their behaviors over the long term, but we are in the process of getting a better understanding of deep-brain stimulation for these patients.” The imp of the perverse can be put to sleep, but nobody knows how to make it go away.

Scientists aren’t sure why deep-brain stimulation seems to work in some patients, or if it can help others; indeed, the results are a reminder of how obscure the workings of the brain still are. Nor is it clear what the risks might be. William Nyhan was cautious about the procedure’s potential. “I see these kids as fragile, and they don’t respond very well to surgical invasions,” he said.

At Johns Hopkins, though, Jinnah was anxious to begin a study on a group of at least eight Lesch-Nyhan patients using deep-brain stimulation. He still needs to secure funding and get approval from the federal government. (The procedure has not been specifically approved for Lesch-Nyhan patients.)

Jinnah has never had an easy time getting funding and attention for Lesch-Nyhan research. He says, “People ask me, ‘Why not study more common diseases?’ My answer is that if we neurologists did that we’d all be studying Alzheimer’s disease, Parkinson’s disease, and strokes. There are thousands of other brain diseases out there, and they’re all orphans. But these rare diseases may teach us something new about the brain, something relevant to the common brain diseases which affect so many people.”

I went back several times to visit James Elrod and Jim Murphy, and began helping their staff with daily tasks. Elrod spat in my face a few times, and gave me a left jab to the jaw. Once, his Kevlarcovered fingers closed on my skin like pliers; he apologized while we both worked to get them loose. Murphy, at his thirty-third-birthday party, planted his face in his cake, and then punched me. Nevertheless, I came to like them a lot. Murphy had a passion for off-road driving, which he was not usually able to indulge. One

day, in 2001, I showed up in Santa Cruz in a rented Ford Expedition with four-wheel drive. An assistant named Tracye Overby was with Murphy, while another, named Chris Reeves, was assigned to Elrod. I drove the group to a dried-out lake bed near Watsonville called College Lake, which we'd heard was a good place for four-wheeling. On the way, I stopped to get directions from a California state trooper. "I would not advise going there with disabled people," he said.

College Lake turned out to be a mile-wide expanse of lardlike clay, covered with sand. The lake bed had a dark, wet-looking center, and was surrounded by thickets of willows. I edged the Expedition out onto the sand. "Go faster," Murphy said. "You're driving like an old lady." I gunned the engine, the Expedition leaped forward, and we raced across the sand. When I turned sharply, the men roared with delight. I performed a figure eight, then aimed the vehicle toward the center of the lake and ran it up to full power. We passed the sunken carcass of a truck, buried up to its roof in clay. The Expedition slowed. Then it began tipping over, and I realized that we were driving across what you might call quickmud. If we stopped, we would go down. I floored the engine, but it was too late. The wheels began spinning, we came to a halt and sank up to the doors, and the engine stalled.

There was a moment of silence, and then Elrod and Murphy erupted with obscenities directed at me. The two helpers seemed unperturbed. "This is just the nature of our work," Reeves said. "Everything that you plan never goes as you planned it."

After several tries on my cell phone, I reached a towing company that was willing to try to get us out, but it would need to be paid in advance, cash preferred, no results guaranteed.

"I'm nervous," Murphy said as we waited. Blood dribbled out of his mouth—he was biting himself. Overby lifted him out of the car, carried him across the sand to the shade of some willows, and sat

down, holding him in her lap. She wiped his mouth with a napkin, cradled his head in her arms, and began singing to him. He began to laugh.

Elrod, sitting in the front seat of the Expedition, began laughing, too. The men were connoisseurs of what I had done: I had ignored the advice of a police officer and driven two disabled men at high speed into the mud. They saw something familiar in my behavior.

Three years later, in 2004, Murphy came down with pneumonia. When it became clear that he was dying, I called him to say goodbye. As he came on the line, I could hear voices in the background; more than thirty people had come to see him. "I'll be all right," he said, and added, "Take care with your driving."

Another day, before Murphy died, I visited James Elrod. Tracye Overby, who was working as Elrod's assistant, needed to change the silk liners that he wears inside his motorcycle gloves.

Elrod did not like to see his bare hands. He asked me to hold his wrists while Overby removed his gloves. The hands that emerged were pale, with spindly fingers that had been gnawed close to the bone in places, and a finger was missing. "Danger," he said. His eyes took on a strange, bright, blank look. He was staring at the right hand. His arm was tense and trembling. As if a magnet were pulling it, the hand moved toward his mouth. "Help!" he called in a muffled voice.

We threw ourselves on Elrod. It took all our strength to restrain his hand. As soon as we got control of it, he relaxed. Overby got the gloves back on.

"Nobody knows about this disease. Every day I'm hoping for a cure," Elrod said. "I wanted you to see that." ♦
