1

The virus now known as Hendra wasn't the first of the scary new bugs. It wasn't the worst. Compared to some others, it seems relatively minor. Its mortal impact, in numerical terms, was small at the start and has remained small; its geographical scope was narrowly local and later episodes haven't carried it much more widely. It made its debut near Brisbane, Australia, in 1994. Initially there were two cases, only one of them fatal. No, wait, correction: There were two *human* cases, one *human* fatality. Other victims suffered and died too, more than a dozen—equine victims—and their story is part of this story. The subject of animal disease and the subject of human disease are, as we'll see, strands of one braided cord.

The original emergence of Hendra virus didn't seem very dire or newsworthy unless you happened to live in eastern Australia. It couldn't match an earthquake, a war, a schoolboy gun massacre, a tsunami. But it was peculiar. It was spooky. Slightly better known now, at least among disease scientists and Australians, and therefore slightly less spooky, Hendra virus still seems peculiar. It's a paradoxical thing: marginal, sporadic, but in some larger sense representative. For exactly that reason, it marks a good point from which to begin toward understanding the emergence of certain virulent new realities on this planet—realities that include the death of more than 30 million people since 1981. Those realities involve a phenomenon called zoonosis.

A *zoonosis* is an animal infection transmissible to humans. There are more such diseases than you might expect. AIDS is one. Influenza is a whole category of others. Pondering them as a group tends to reaffirm the old Darwinian truth (the darkest of his truths, well known and persistently forgotten) that humanity *is* a kind of animal, inextricably connected with other animals: in origin and in descent, in sickness and in health. Pondering them individually—for starters, this relatively obscure case from Australia—provides a salubrious reminder that everything, including pestilence, comes from somewhere.

2

In September 1994, a violent distress erupted among horses in a suburb at the north fringe of Brisbane. These were thoroughbred racehorses, pampered and sleek animals bred to run. The place itself was called Hendra. It was a quiet old neighborhood filled with racecourses, racing people, weatherboard houses whose backyards had been converted to stables, newsstands that sold tip sheets, corner cafes with names like The Feed Bin. The first victim was a bay mare named Drama Series, retired from racing and now heavily in foal—that is, pregnant and well along. Drama Series started showing signs of trouble in a spelling paddock, a ragged meadow several miles southeast of Hendra, where racehorses were sent to rest between outings. She had been placed there as a brood mare and would have stayed until late in her pregnancy, if she hadn't gotten sick. There was nothing drastically wrong with her—so it seemed, at this point. She just didn't look good, and her trainer thought she should come in. The trainer was a savvy little man named Vic Rail, with a forceful charm, swept-back brown hair, and a reputation for sharp practice in the local racing world. He was "tough as nails, but a lovable rogue," Vickie was, by one judgment. Some people resented him but no one denied he knew horses.

It was Rail's girlfriend, Lisa Symons, who took a horse trailer out to collect Drama Series. The mare was reluctant to move. She seemed to have sore feet. There were swellings around her lips, her eyelids, her jaw. Back at Rail's modest stable in Hendra, Drama Series sweated profusely and remained sluggish. Hoping to nourish her and save the foal, he tried to force feed her with grated carrot and molasses but she wouldn't eat. After the attempt, Vic Rail washed his hands and his arms, though in hindsight perhaps not thoroughly enough.

That was September 7, 1994, a Wednesday. Rail called his veterinarian, a tall man named Peter Reid, sober and professional, who came and looked the mare over. She was now in her own box at the stable, a cinderblock stall with a floor of sand, close amid Rail's other horses. Dr. Reid saw no discharges from her nose or eyes, and no signs of pain, but she seemed a pale image of her robust former self. "Depressed," was his word, meaning (in veterinary parlance) a physical not a psychological condition. Her temperature and her heart rate were both high. Reid noticed the facial swelling. Opening her mouth to examine her gums, he noticed remnants of the carrot shreds that she hadn't bothered or been able to swallow, and he gave her injections of antibiotic and analgesic. Then he went home. Sometime after four the next morning, he got a call. Drama Series had gotten out of her stall, collapsed in the yard, and was dying.

By the time Reid rushed back to the stables, she was dead. It had been quick and ugly. Growing agitated as her condition got worse, she had staggered out while the stall door was open, fallen down several times, gouged her leg to the bone, stood up, fallen again in the front yard, and been pinned to the ground for her own protection by a stable hand. She freed herself desperately, crashed into a pile of bricks, and then was pinned again by joint effort of the stable hand and Rail, who wiped a frothy discharge away from her nostrils—trying to help her breathe—just before she died. Reid inspected the body, noticing a trace of clear froth still at the nostrils, but did not perform a necropsy because Vic Rail couldn't afford to be so curious and, more generally, because no one foresaw a disease emergency in which every bit of such data would be crucial. Drama Series's carcass was unceremoniously carted away, by

the usual contract hauler, to the dump where dead Brisbane horses routinely go.

Her cause of death remained uncertain. Had she been bitten by a snake? Had she eaten some poisonous weeds out in that scrubby, derelict meadow? Those hypotheses crumbled abruptly, thirteen days later, when her stable mates began falling ill. They went down like dominoes. This wasn't snakebite or toxic fodder. It was something contagious.

The other horses suffered fever, respiratory distress, bloodshot eyes, spasms, and clumsiness; in some, bloody froth surged from the nostrils and mouth; a few had facial swelling. Reid found one horse frantically rinsing its mouth in a water bucket. Another banged its head against the concrete wall as though maddened. Despite heroic efforts by Reid and others, twelve more animals died within the next several days, either expiring horrifically or euthanized. Reid later said that "the speed with which it went through those horses was unbelievable," but in these early moments no one had identified "it." *Something* went through those horses. At the height of the crisis, seven animals succumbed to their agonies or required euthanasia within just twelve hours. Seven dead horses in twelve hours—that's carnage, even for a casehardened veterinarian. One of them, a mare named Celestial Charm, died thrashing and gasping so desperately that Reid couldn't get close enough to give her the merciful needle. Another horse, a five-year-old gelding, had been sent from Rail's place to another spelling paddock up north, where it was sick on arrival and soon had to be put down. A vet up there necropsied the gelding and found hemorrhages throughout its organs. And in a neighbor's stable on the corner beside Rail's place in Hendra, at the same time, still another gelding went afoul with similar clinical signs and also had to be euthanized.

What was causing this mayhem? How was it spreading from one horse to another, or anyway getting into so many of them simultaneously? One possibility was a toxic contaminant in the feed supply. Or maybe poison, maliciously introduced. Alternatively, Reid began wondering whether there might be an exotic virus at work, such as the one responsible for African horse sickness (AHS), a

disease carried by biting midges in sub-Saharan Africa. AHS virus affects mules, donkeys, and zebras as well as horses, but it hasn't been reported in Australia, and it isn't directly contagious from horse to horse. Furthermore, Queensland's pestiferous midges don't generally come biting in September, when the weather is cool. So AHS was not quite a fit. Then maybe another strange germ? "I'd never seen a virus do anything like that before," Reid said. A man of understatement, he recalled it as "a pretty traumatic time." He had continued to treat the suffering animals with what means and options he had, given the inconclusive diagnosis—antibiotics, fluids, antishock medicine.

Meanwhile, Vic Rail himself had taken sick. So had the stable hand. It seemed at first that they each had a touch of flu—a bad flu. Rail went into the hospital, worsened there, and, after a week of intensive care, died. His organs had failed and he couldn't breathe. Autopsy showed that his lungs were full of blood, other fluid, and (upon examination by electron microscopy) some sort of virus. The stable hand, a big-hearted man named Ray Unwin, who merely went home to endure his fever in private, survived. Peter Reid, though he had been working on the same suffering horses amid the same bloody froth, stayed healthy. He and Unwin told me their stories when I found them, years later, by asking around Hendra and making a few calls.

At The Feed Bin, for instance, someone said: Ray Unwin, yeah, most likely he'll be at Bob Bradshaw's. I followed directions to Bradshaw's stable and there on the driveway was a man who turned out to be Unwin, carrying grain in a bucket. At that point he was a middle-aged working bloke with a sandy red ponytail and a weary sadness in his eyes. He was a little shy about attention from a stranger; he'd had enough of that already from doctors, public health officials, and local reporters. Once we sat down to chat, he professed that he wasn't a "whinger" (complainer) but that his health had been "crook" (not right) since it happened.

As the horse deaths came to crescendo, the government of Queensland had intervened, in the form of veterinarians and other personnel from the Department of Primary Industries (respon-

sible for livestock, wildlife, and agriculture throughout the state) and field officers from Queensland Health. The DPI veterinarians began doing necropsies—that is, cutting up horses, looking for clues—right in Vic Rail's little yard. Before long there were horse heads lying around, severed limbs, blood and other fluids flowing down the gutter, suspect organs and tissues going into bags. Another neighbor of Rail's, a fellow horse man named Peter Hulbert, recollected the gruesome pageant that had transpired next door, while serving me instant coffee in his kitchen. As the kettle came to a boil, Hulbert recalled the garbage containers used by DPI. "These street wheelie bins here, there was horses' legs and heads . . . —do you have sugar?"

No thanks, I said, black.

". . . horses' legs and heads and guts and everything, going into these wheelie bins. *It—was—horrendous.*" By midafternoon that day, he added, word had spread and the TV stations showed up with their news cameras. "Agh. It was bloody terrible, mate." Then the police arrived too and threw a tape cordon around Rail's place, treating it as a crime scene. Had one of his enemies done this? The racing world had its underbelly, like any business, and probably more so than most. Peter Hulbert even faced pointed questioning about whether Vic might have poisoned his own horses and then himself.

While the police wondered about sabotage or insurance scam, the health officials had other hypotheses to concern them. One was hantavirus—which is actually a group of viruses, long known to virologists following outbreaks in Russia, Scandinavia, and elsewhere but newly conspicuous since a year earlier, 1993, when a new hantavirus emerged dramatically and killed ten people around the Four Corners area of the American Southwest. Australia is justifiably wary of exotic diseases invading its borders, and hantavirus in the country would be even worse news (except for horses) than African horse sickness. So the DPI vets packed up samples of blood and tissue from the dead horses and sent them on ice to the Australian Animal Health Laboratory, a high-security institution known by its acronym, AAHL, pronounced "*aahl*," in a town

called Geelong, south of Melbourne. A team of microbiologists and veterinarians there put the sample material through a series of tests, attempting to culture and identify a microbe, and to confirm that the microbe made horses sick.

They found a virus. It wasn't a hantavirus. It wasn't AHS virus. It was something new, something the AAHL microscopist hadn't seen before but which, from its size and its shape, resembled members of a particular virus group, the paramyxoviruses. This new virus differed from known paramyxoviruses in that each particle carried a double fringe of spikes. Other AAHL researchers sequenced a stretch of the viral genome and, submitting that sequence into a vast viral database, found a weak match to one subgroup of these viruses. That seemed to confirm the visual judgment of the microscopist. The matching subgroup was the morbilliviruses, which include rinderpest virus and canine distemper virus (infecting nonhuman animals) and measles (in humans). So the creature from Hendra was classified and given a name, based on those provisional identifications: equine morbillivirus (EMV). Roughly, horse measles.

About the same time, the AAHL researchers tested a sample of tissue that had been taken from Vic Rail's kidney during his autopsy. That sample also yielded a virus, identical to the virus from the horses, confirming that this equine morbillivirus didn't afflict only equines. Later, when the degree of its uniqueness became better appreciated, the label "EMV" was dropped and the virus was renamed after its place of emergence: Hendra.

Identifying the new virus was only step one in solving the immediate mystery of Hendra, let alone understanding the disease in a wider context. Step two would involve tracking that virus to its hiding place. Where did it exist when it wasn't killing horses and people? Step three would entail asking a further cluster of questions: How did the virus emerge from its secret refuge, and why here, and why now?

After our first conversation, at a café in Hendra, Peter Reid drove me several miles southeast, across the Brisbane River, to the site where Drama Series took sick. It was in an area called Cannon

Hill, formerly pastoral land surrounded by city, now a booming suburb just off the M1 motorway. Tract houses on prim lanes had been built over the original paddock. Not much of the old landscape remained. But toward the end of one street was a circle, called Calliope Circuit, in the middle of which stood a single mature tree, a Moreton Bay fig, beneath which the mare would have found shelter from eastern Australia's fierce subtropical sun.

"That's it," Reid said. "That's the bloody tree." That's where the bats gathered, he meant.

3

Infectious disease is all around us. Infectious disease is a kind of natural mortar binding one creature to another, one species to another, within the elaborate biophysical edifices we call ecosystems. It's one of the basic processes that ecologists study, including also predation, competition, decomposition, and photosynthesis. Predators are relatively big beasts that eat their prey from outside. Pathogens (disease-causing agents, such as viruses) are relatively small beasts that eat their prey from within. Although infectious disease can seem grisly and dreadful, under ordinary conditions it's every bit as natural as what lions do to wildebeests and zebras, or what owls do to mice.

But conditions aren't always ordinary.

Just as predators have their accustomed prey, their favored targets, so do pathogens. And just as a lion might occasionally depart from its normal behavior—to kill a cow instead of a wildebeest, a human instead of a zebra—so can a pathogen shift to a new target. Accidents happen. Aberrations occur. Circumstances change and, with them, exigencies and opportunities change too. When a pathogen leaps from some nonhuman animal into a person, and succeeds there in establishing itself as an infectious presence, sometimes causing illness or death, the result is a zoonosis.

It's a mildly technical term, zoonosis, unfamiliar to most people, but it helps clarify the biological complexities behind the ominous headlines about swine flu, bird flu, SARS, emerging diseases in general, and the threat of a global pandemic. It helps us comprehend why medical science and public health campaigns have been able to conquer some horrific diseases, such as smallpox and polio, but unable to conquer other horrific diseases, such as dengue and yellow fever. It says something essential about the origins of AIDS. It's a word of the future, destined for heavy use in the twenty-first century.

Ebola is a zoonosis. So is bubonic plague. So was the so-called Spanish influenza of 1918–1919, which had its ultimate source in a wild aquatic bird and, after passing through some combination of domesticated animals (a duck in southern China, a sow in Iowa?) emerged to kill as many as 50 million people before receding into obscurity. All of the human influenzas are zoonoses. So are monkeypox, bovine tuberculosis, Lyme disease, West Nile fever, Marburg virus disease, rabies, hantavirus pulmonary syndrome, anthrax, Lassa fever, Rift Valley fever, ocular larva migrans, scrub typhus, Bolivian hemorrhagic fever, Kyasanur forest disease, and a strange new affliction called Nipah encephalitis, which has killed pigs and pig farmers in Malaysia. Each of them reflects the action of a pathogen that can cross into people from other animals. AIDS is a disease of zoonotic origin caused by a virus that, having reached humans through just a few accidental events in western and central Africa, now passes human-to-human by the millions. This form of interspecies leap is common, not rare; about 60 percent of all human infectious diseases currently known either cross routinely or have recently crossed between other animals and us. Some of those—notably rabies—are familiar, widespread, and still horrendously lethal, killing humans by the thousands despite centuries of efforts at coping with their effects, concerted international attempts to eradicate or control them, and a pretty clear scientific understanding of how they work. Others are new and inexplicably sporadic, claiming a few victims (as Hendra does) or a few hundred (Ebola) in this place or that, and then disappearing for years.

Smallpox, to take one counterexample, is not a zoonosis. It's

caused by variola virus, which under natural conditions infects only humans. (Laboratory conditions are another matter; the virus has sometimes been inflicted experimentally on nonhuman primates or other animals, usually for vaccine research.) That helps explain why a global campaign mounted by the World Health Organization (WHO) to eradicate smallpox was, as of 1980, successful. Smallpox could be eradicated because that virus, lacking ability to reside and reproduce anywhere but in a human body (or a carefully watched lab animal), couldn't hide. Likewise poliomyelitis, a viral disease that has afflicted humans for millennia but that (for counterintuitive reasons involving improved hygiene and delayed exposure of children to the virus) became a fearsome epidemic threat during the first half of the twentieth century, especially in Europe and North America. In the United States, the polio problem peaked in 1952 with an outbreak that killed more than three thousand victims, many of them children, and left twenty-one thousand at least partially paralyzed. Soon afterward, vaccines developed by Jonas Salk, Albert Sabin, and a virologist named Hilary Koprowski (about whose controversial career, more later) came into wide use, eventually eliminating poliomyelitis throughout most of the world. In 1988, WHO and several partner institutions launched an international effort toward eradication, which has succeeded so far in reducing polio case numbers by 99 percent. The Americas have been declared polio-free, as have Europe and Australia. Only five countries, as of latest reports in 2011, still seemed to have a minor, sputtering presence of polio: Nigeria, India, Pakistan, Afghanistan, and China. The eradication campaign for poliomyelitis, unlike other well-meant and expensive global health initiatives, may succeed. Why? Because vaccinating humans by the millions is inexpensive, easy, and permanently effective, and because apart from infecting humans, the poliovirus has nowhere to hide. It's not zoonotic.

Zoonotic pathogens can hide. That's what makes them so interesting, so complicated, and so problematic.

Monkeypox is a disease similar to smallpox, caused by a virus closely related to variola. It's a continuing threat to people in central and western Africa. Monkeypox differs from smallpox in one

crucial way: the ability of its virus to infect nonhuman primates (hence the name) and some mammals of other sorts, including rats, mice, squirrels, rabbits, and American prairie dogs. Yellow fever, also infectious to both monkeys and humans, results from a virus that passes from victim to victim, and sometimes from monkey to human, in the bite of certain mosquitoes. This is a more complex situation. One result of the complexity is that yellow fever will probably continue to occur in humans—unless WHO kills every mosquito vector or every susceptible monkey in tropical Africa and South America. The Lyme disease agent, a type of bacterium, hides effectively in white-footed mice and other small mammals. These pathogens aren't *consciously* hiding, of course. They reside where they do and transmit as they do because those happenstance options have worked for them in the past, yielding opportunities for survival and reproduction. By the cold Darwinian logic of natural selection, evolution codifies happenstance into strategy.

The least conspicuous strategy of all is to lurk within what's called a reservoir host. A reservoir host (some scientists prefer "natural host") is a living organism that carries the pathogen, harbors it chronically, while suffering little or no illness. When a disease seems to disappear between outbreaks (again, as Hendra did after 1994), its causative agent has got to be *somewhere*, yes? Well, maybe it vanished entirely from planet Earth—but probably not. Maybe it died off throughout the region and will only reappear when the winds and the fates bring it back from elsewhere. Or maybe it's still lingering nearby, all around, within some reservoir host. A rodent? A bird? A butterfly? A bat? To reside undetected within a reservoir host is probably easiest wherever biological diversity is high and the ecosystem is relatively undisturbed. The converse is also true: Ecological disturbance causes diseases to emerge. Shake a tree, and things fall out.

Nearly all zoonotic diseases result from infection by one of six kinds of pathogen: viruses, bacteria, fungi, protists (a group of small, complex creatures such as amoebae, formerly but misleadingly known as protozoans), prions, and worms. Mad cow disease is caused by a prion, a weirdly folded protein molecule that triggers

weird folding in other molecules, like Kurt Vonnegut's infectious form of water, ice-nine, in his great early novel *Cat's Cradle*. Sleeping sickness results from infection by a protist called *Trypanosoma brucei*, carried by tsetse flies among wild mammals, livestock, and people in sub-Saharan Africa. Anthrax is caused by a bacterium that can live dormant in soil for years and then, when scuffed out, infect humans by way of their grazing animals. Toxocariasis is a mild zoonosis caused by roundworms; you can get it from your dog. But fortunately, like your dog, you can be wormed.

Viruses are the most problematic. They evolve quickly, they are unaffected by antibiotics, they can be elusive, they can be versatile, they can inflict extremely high rates of fatality, and they are fiendishly simple, at least relative to other living or quasi-living creatures. Ebola, West Nile, Marburg, the SARS bug, monkeypox, rabies, Machupo, dengue, the yellow fever agent, Nipah, Hendra, Hantaan (the namesake of the hantaviruses, first identified in Korea), chikungunya, Junin, Borna, the influenzas, and the HIVs (HIV-1, which mainly accounts for the AIDS pandemic, and HIV-2, which is less widespread) are all viruses. The full list is much longer. There is a thing known by the vivid name "simian foamy virus" (SFV) that infects monkeys and humans in Asia, crossing between them by way of the venues (such as Buddhist and Hindu temples) where people and half-tame macaques come into close contact. Among the people visiting those temples, feeding handouts to those macaques, exposing themselves to SFV, are international tourists. Some carry away more than photos and memories. "Viruses have no locomotion," according to the eminent virologist Stephen S. Morse, "yet many of them have traveled around the world." They can't run, they can't walk, they can't swim, they can't crawl. They ride.

4

Isolating the Hendra bug had been a task for virologists, working in their high-security labs down at AAHL. "Isolating," in this sense of the word, means finding some of the virus and growing more. The isolate becomes a live, captive population of virus, potentially dangerous if any were to escape but useful for ongoing research. Virus particles are so tiny they can't be seen, except by electron microscopy, which involves killing them, so their presence during isolation must be detected indirectly. You start with a small bit of tissue, a drop of blood, or some other sample from an infected victim. Your hope is that it contains the virus. You add that inoculum, like a dash of yeast, to a culture of living cells in a nutrient medium. Then you incubate, you wait, you watch. Often, nothing happens. If you're lucky, something does. You know you've succeeded when the virus replicates abundantly and asserts itself sufficiently to cause visible damage to the cultured cells. Ideally it forms plaques, large holes in the culture, each hole representing a locus of virus-caused devastation. The process demands patience, experience, expensively exact bench tools, plus meticulous precautions against contamination (which can falsify results) or accidental release (which can infect you, endanger your co-workers, and maybe panic a town). Laboratory virologists are not generally knockabout people. You don't meet them in bars, waving their arms and bragging lustily about the perils of their métier. They tend to be focused, neat, and still, like nuclear engineers.

Discovering where a virus lives in the wild is work of a very different sort. It's an outdoor job that entails a somewhat less controllable level of risk, like trapping grizzly bears for relocation. Now, the people who look for wild viruses aren't rowdy and careless, no more so than the lab specialists; they can't afford to be. But they labor in a noisier, more cluttered, more unpredictable environment: the world. If there is reason to suspect that a certain new virus infecting humans is zoonotic (as most such viruses are), the search may lead into forests, swamps, crop fields, old buildings, sewers,

caves, or the occasional horse paddock. The virus hunter is a field biologist, possibly with advanced training in human medicine, veterinary medicine, ecology, or some combination of those three—a person who finds fascination in questions that must be answered by catching and handling animals. That profile fits a lanky, soft-spoken man named Hume Field, midthirtyish at the time he became involved with Hendra.

Field grew up in the provincial towns of coastal Queensland, from Cairns to Rockhampton, a nature-loving kid who climbed trees, hiked in the bush, and spent school holidays on his uncle's dairy farm. His father was a police detective, which seems only too prefigurative of the son's later role as a viral sleuth. Young Field earned an undergraduate degree in veterinary science at the University of Queensland, in greater Brisbane, and volunteered at an animal refuge on the side, helping to rehabilitate injured wildlife. After graduation in 1976, he worked in a mixed veterinary practice in Brisbane for some years and then as a temporary fill-in (the Australians call it "doing locums") all over the state. During that time, he doctored a lot of horses. But he became increasingly aware that his deepest interest was wildlife, not livestock and pets, so in the early 1990s Field returned to the University of Queensland, this time for a doctorate in ecology.

He focused on wildlife conservation and, in due time, needed a dissertation project. Because feral cats (domestic cats gone wild on the landscape) cause considerable damage to native Australian wildlife, killing small marsupials and birds and acting as a source of disease, he undertook a study of feral cat populations and their impact. He was trapping cats, fitting them with radio collars to track how they lived, when the outbreak occurred at Vic Rail's stable. One of Field's doctoral mentors, a scientist who worked with the Department of Primary Industries, asked Field whether he would be interested in changing projects. The department needed someone to investigate the ecological side of this new disease. "So I forgot my feral cats," Field told me, when I visited him long afterward at the Animal Research Institute, a DPI facility near Brisbane, "and started off looking for wildlife reservoirs of Hendra virus."

He began his search by going back to the index case—the first equine victim, its history and locale. That was Drama Series, the pregnant mare, fallen ill in the paddock at Cannon Hill. The only clues he had were that this virus was a paramyxovirus and that another Queensland researcher had found a novel paramyxovirus in a rodent some years earlier. So Field established a trapping regime at the paddock, catching every small and medium-sized vertebrate he could—rodents, possums, bandicoots, reptiles, amphibians, birds, the odd feral cat—and drawing blood from each, with a particularly suspicious eye to the rodents. He sent the blood samples to the DPI lab to be screened for antibodies against Hendra.

Screening for antibodies is distinct from isolating virus, just as a footprint is distinct from a shoe. Antibodies are molecules manufactured by the immune system of a host in response to the presence of a biological intruder. They are custom-shaped to merge with and disable that particular virus, or bacterium, or other bug. Their specificity, and the fact that they remain in the bloodstream even after the intruder has been conquered, make them valuable as evidence of present or past infection. That's the evidence Hume Field was hoping to find. But the rodents from Cannon Hill had no antibodies to Hendra virus. Neither did anything else, leaving him to wonder why. Either he was looking in the wrong place, or in the right place in the wrong way, or at the wrong time. Bad timing might indeed be the problem, he thought. Drama Series had sickened in September, half a year had passed, and here he was searching in March, April, May. He suspected that "there could be some sort of seasonal presence of either the virus or the host" at the Cannon Hill paddock, and that maybe now it was out of season. Screening the cats, dogs, and rats around Rail's stable yielded no positives either.

Seasonal presence of the virus was one possibility. Coming and going on a shorter time scale was another. Bats, for instance, fed in large numbers at the Cannon Hill paddock by night but returned to their roosts, elsewhere, to sleep out the day. Peter Reid heard a Cannon Hill resident say that, during hours of darkness in the neighborhood, "flying foxes were as thick as the stars in the sky."

Reid had therefore suggested to AAHL that the bats should be looked at, but his suggestion evidently wasn't passed along. Hume Field and his co-workers on the reservoir hunt remained stumped until the following October, 1995, when an unfortunate event gave them a helpful new lead.

A young cane farmer named Mark Preston, who lived near the town of Mackay, about six hundred miles north of Brisbane, suffered a spate of seizures. His wife got him to a hospital. Preston's symptoms were especially alarming because they signaled a second health crisis for him in barely more than a year. Back in August 1994, he had endured a mysterious illness—headache, vomiting, stiff neck, then a provisional diagnosis of meningitis, cause unspecified—from which he had recovered. Or had seemingly recovered. Meningitis is a term applicable to any inflammation of the membranes that cover the brain and the spinal cord; it might be caused by a bacterium, a virus, even a reaction to a drug, and it might go away as inexplicably as it appeared. Preston continued to live a robust life on the farm with his wife Margaret, a veterinarian who based her practice there amid the sugar cane and the stud horses.

Did Mark Preston's seizures now indicate a recurrence of his indeterminate meningitis? Admitted to the hospital, he sunk into severe encephalitis—that is, brain inflammation, cause still unknown. Medication controlled his seizures but the doctors could watch storms of distress flickering on the electroencephalograph. "He remained deeply unconscious with persisting fever," according to a later medical report, "and died 25 days after admission."

Blood serum taken during Preston's final illness tested positive for antibodies to Hendra virus. So did his serum from a year earlier, which had been taken during the first episode, stored, and was now tested in retrospect. His immune system had been fighting the thing back then. Postmortem examination of his brain tissue, as well as other tests, confirmed the presence of Hendra. Evidently it had attacked once, subsided, lingered in latent form for a year, and then reared up and killed him. That was scary in a whole new way.

Where had he gotten it? Investigators, working backward to assemble the story, learned that in August 1994 two horses had

died on the Preston farm. Mark Preston helped his wife care for them during their sudden, fatal illnesses and assisted her, at least marginally, when she performed the necropsies. Preserved tissue that Margaret Preston had drawn from both horses now also tested positive for Hendra. Despite her own exposure, though, Margaret Preston remained healthy—just as Peter Reid would remain healthy despite his exposure weeks later at Vic Rail's place. The good health of the two veterinarians raised the question of just how infectious this new virus might be. And the Preston case, at such distance from the first outbreak, caused the experts to wonder—to worry—about how far it might already have spread. Take the mileage from Hendra to Mackay as a radius of potential distribution, draw circles with that radius around the site of each outbreak, and you would circumscribe about 10 million people, nearly half the population of Australia.

How big was the problem? How widely was the virus dispersed? One group of researchers, led by an infectious diseases man named Joseph McCormack, based at the Brisbane hospital where Vic Rail had died, took a broad look. They screened serum from five thousand Queensland horses—every horse they could put a needle in, evidently—and from 298 humans, each of whom had had some level of contact with a Hendra case. None of the horses contained Hendra antibodies, nor did any of the humans. Those negatives, we can assume, brought sighs of relief from the health authorities and deepened the puzzled scowls on the faces of the scientists. "It seems," McCormack's group concluded, "that very close contact is required for transmission of infection to occur from horses to humans." But they were whistling in the dark. To say that "very close contact is required" didn't explain why Margaret Preston had outlived her husband. The reality was this: that very close contact, plus bad luck, plus maybe one or two other factors were necessary for a person to become infected, and nobody knew what the other factors were.

But the Mark Preston case gave Hume Field valuable clues—a second point on the map, a second point in time. Hendra virus in Mackay, August 1994; Hendra virus at the Cannon Hill paddock and in Rail's stable, September 1994. So Field went up to Mackay

and repeated his method, trapping animals, drawing blood, sending serum to be tested for antibodies. And again he found nothing. He also drew samples from injured or otherwise debilitated wildlife of various types, creatures being nurtured in captivity until they could be released (if possible) back to the wild. The people who do such nurturing, a loose network of good-hearted amateurs, are known in Australian parlance as wildlife "carers." They tend to specialize by zoological category. There are kangaroo carers, bird carers, possum carers, and bat carers. Hume Field knew of them from his years of veterinary practice; he had virtually been one of them, during his student days at the animal refuge. Now he sampled some of the animals in their care.

But damn it: still no trace of Hendra.

In January 1996, with the search for a reservoir host at impasse, Field took part in a brainstorming session of agency officials and researchers, called by his supervisor at DPI. What were they doing wrong? How could they better target their efforts? Where would Hendra strike next? Queensland's racing industry stood in jeopardy of multi-million-dollar losses, and human lives were at risk. It was an urgent problem of governance and public relations, not just a medical riddle. One useful line of thought was explored at the meeting: biogeography. It seemed obvious that the reservoir host (or hosts), whatever type of animal it was (or they were), must exist both at Mackay and at Cannon Hill—exist there for at least part of each year, anyway, including August and September. This pointed toward animals that were either broadly distributed in Queensland or else *traveled* broadly across the state. The brainstormers (partly guided by genetic evidence suggesting there was no localization of distinct viral strains—that is, the *virus* was moving and mixing) leaned toward the second of those two possibilities: that the reservoir host was quite mobile, an animal capable of traveling hundreds of miles up and down the Queensland coast. That in turn directed suspicion at birds and . . . at bats.

Provisionally, Field and his colleagues dismissed the bird hypothesis, on two counts. First, they were unaware of any other paramyxovirus that spills over from birds into humans. Second, a

mammalian reservoir simply seemed more likely, given that the virus infects humans and horses. Similarity of one kind of host animal to another is a significant indicator of the likelihood that a pathogen can make the leap. Bats are mammals, of course. And bats get around. Furthermore, bats famously harbor at least one fearful virus, rabies, although Australia at that time was considered rabies-free. (Many other bat-virus-human connections would be discovered soon afterward, including some in Australia; but at this time, 1996, the link seemed less obvious.) From the meeting, Field took away a new mandate: Look at bats.

Easily said. But catching bats on the wing, or even at their roosting sites, isn't so simple as trapping rodents or possums in a meadow. The most conspicuous and far-ranging bats native to Queensland are the so-called flying foxes, which belong to four different species within the genus *Pteropus,* each one a magnificent, fruit-eating megabat with a wingspan of three feet or more. Flying foxes customarily roost in mangroves, in paperbark swamps, or high in the limbs of rainforest trees. Special trapping tools and methods would be required. Short of gearing up immediately, Field returned first to the "carer" network. These people already had bats in captivity. At a facility in Rockhampton, up the coast toward Mackay, he found that the wounded animals under care included black flying foxes (*Pteropus alecto*). Bingo: Blood drawn from a black flying fox had antibodies to Hendra.

But one bingo moment wasn't sufficient for a scientist so fastidious as Hume Field. That datum proved that black flying foxes could be infected with Hendra, yes, but not necessarily that they were a reservoir—let alone *the* reservoir—from which horses became infected. He and his colleagues kept looking. Within a few weeks, Hendra antibodies turned up in all three other kinds, the grey-headed flying fox, the spectacled flying fox, and the little red flying fox. The DPI team also tested old samples from flying foxes, which had been archived for more than a dozen years. Again, they found telltale molecular tracks of Hendra. This showed that the bat population had been exposed to Hendra virus long before it struck Vic Rail's horses. And then, in September 1996, two years after

the Rail outbreak, a pregnant grey-headed flying fox got herself snagged on a wire fence.

She miscarried twin fetuses and was euthanized. Not only did she test positive for antibodies; she also made possible the first isolation of Hendra virus from a bat. A sample of her uterine fluids yielded live virus, and that virus proved indistinguishable from Hendra as found in horses and humans. It was enough, even within scientific bounds of caution, to identify flying foxes as the "probable" reservoir hosts of Hendra.

The more that Field and his colleagues looked, the more evidence of Hendra they found. After the early bat surveys, about 15 percent of their flying foxes had tested positive for Hendra antibodies. This parameter—the percentage of sampled individuals showing some history of infection, either present or past—is called *seroprevalence*. It constitutes an estimate, based on finite sampling, of what the percentage throughout an entire population might be. As the team continued testing, the seroprevalence rose. At the end of two years, having sampled 1,043 flying foxes, Field and company reported Hendra seroprevalence at 47 percent. In plain words: Nearly half of the big bats flying around eastern Australia were present or former carriers. It almost seemed as though Hendra virus should have been raining down from the sky.

While the scientists published their findings in periodicals such as *Journal of General Virology* and *The Lancet*, some of this stuff got into the newspapers. One headline read: BAT VIRUS FEAR, RACING INDUSTRY ON ALERT. The crime-scene tape and the dismembered horses at Rail's place had been an irresistible starting point for television crews, and their interest continued. A few of those journalistic reports were accurate and sensible, but not all, and none were soothing. People became concerned. The identification of flying foxes as reservoir hosts, plus the high levels of seroprevalence within those bat populations, caused public-image trouble for a group of animals that had a legacy of such trouble already. Approval ratings for bats are never high. Now in Australia they went lower.

One eminent racehorse trainer gave me his view of the matter at

a track in Hendra on a sunny Saturday during an interlude between races. *Hendra virus!* This man exploded at the mention. They shouldn't *allow* it! "They" were unspecified governmental authorities. They should get *rid* of the bats! Those bats *cause* the disease! They hang upside down and *shit* on themselves! (Can that be true? I wondered. Seemed biologically unlikely.) And they shit on *people*! It's *backwards*—let the people shit on *them*! What *good* are they? *Get rid* of them! Why doesn't that *happen*? Because the *sentimental Greenies* won't have it! he groused. We were in the Members Bar, a social sanctum for track professionals, to which I had been admitted in company with Peter Reid. The government should *protect* people! Should protect *vets*, like our friend Peter here! Harrumph, harrumph, and furthermore harrumph! et cetera. This trainer, a legendary figure in Australian racing, was a short, bantam-cocky octogenarian with gray hair combed back in dandy waves. I was a guest in his clubhouse and owed him a little respect—or anyway, a little slack. (In fairness, too, he was speaking not long after still another human victim, a Queensland veterinarian named Dr. Ben Cunneen, had died of Hendra contracted while treating sick horses. The mortal risk to horse people, and the economic risk to the entire Australian racing industry, were undeniably large.) When I showed genial interest in quoting this trainer on the record, he spoke more temperately but the gist was the same.

Among the "sentimental Greenies," he would have included bat carers. But even some of those softhearted activists, the carers, grew concerned as evidence piled up. They had two worries, uneasily counterbalanced: that the virus would make bats even more unpopular, leading to calls (like the trainer's) for bat extermination, and that they themselves might become infected in the course of their well-meaning work. The second was a new sort of anxiety. It must have caused some reexamination of commitment. They were *bat* lovers, after all, not *virus* lovers. Does a virus constitute *wildlife*? Not in most people's minds. Several such carers asked to be screened for antibodies, which opened doors for a broad survey, quickly organized and led by a young epidemiologist from the University of Queensland named Linda Selvey.

Selvey tapped into the wildlife-carer networks in southeastern Australia, eventually finding 128 bat carers willing or eager to be tested. She and her field team drew the blood and asked each participant to complete a questionnaire. The questionnaires revealed that many of these people had had prolonged and close contact with flying foxes—feeding them, handling them, not infrequently getting scratched or nipped. One carer had been bitten deeply on the hand by a Hendra-positive bat. The most unexpected finding of Selvey's survey was the percentage of those 128 carers who tested positive for antibodies: zero. Despite months and years of nurturing, despite scratches and bites and cuddling and drool and blood, not one person showed immunological evidence of having been infected with Hendra virus.

Selvey's report appeared in October 1996. She was a grad student at the time. Later she became head of the Communicable Diseases Branch of Queensland Health. Still later, as we sat over coffee in a noisy Brisbane café, I asked her: Who *are* these bat carers?

"I don't know how to describe them," Selvey answered. "People with a passion for animals, I guess." Both women and men? "Predominantly women," she said, speculating gently that women without kids might have more time and more desire for such surrogacy. Generally they do the caring in their own homes, equipped with a sizable, comfortable cage where the bats can roost when not being handled. It seemed mystifying to me that such intimate bat-human relations, combined with such a high level of bat seroprevalence, had yielded not a single case of human infection to be detected by Selvey's study. Not a single antibody-positive person out of 128 carers. What did that tell you, I asked her, about the nature of this virus?

"That it needed some sort of amplifier," she said. She was alluding to the horse.

5

Let's think about foot-and-mouth disease for a moment. Everybody has heard of it. Everybody has seen *Hud.* Most people aren't aware that, at least tenuously, it's a zoonosis. The virus that causes foot-and-mouth disease (FMD) belongs to the picornaviruses, the same group that includes poliovirus and some viruses similar to those that cause the common cold. But infection with FMD virus is a rare misfortune in humans, seldom causing worse than a rash on the hands, the feet, or the mouth lining. More frequently and consequentially, it afflicts cloven-hoofed domestic animals such as cattle, sheep, goats, and pigs. (Cloven-hoofed wildlife such as deer, elk, and antelope are also susceptible.) The main clinical signs are fever, lameness, and vesicles (little blisters) in the mouth, on the snout, on the feet. In a lactating female, the teats sometimes become blistered and then, as the blisters break, ulcerated. Bad for the mother, bad for the calf. Lethality from FMD is relatively low but the morbidity (incidence of the disease within a population) tends to be high, meaning that the disease is very contagious, making livestock ill, putting them off their feed, and causing losses of productivity that, in big-volume operations with narrow profit margins, are considered disastrous. Because of such losses, plus the swiftness of contagion, it's often treated as a terminal condition in commercial terms: Infected herds are slaughtered to prevent the virus from getting around. Nobody wants to buy stock that might be carriers, and the export trade drops to zilch. Cows, sheep, and pigs become worthless—less than worthless, an expensive liability. "Economically, it is the most important disease of animals in the world," according to one authority, who reports that "an FMD outbreak in the US could cost $27 billion in lost trade and markets." The virus spreads through direct contact, and in feces, and in milk, and is even capable of transmission by aerosol. It can travel from one farm to another on a humid breeze.

Impacts of FMD differ from one kind of animal to another.

Sheep tend to carry the infection without showing symptoms. Cattle suffer openly and pass the virus to one another by direct contact (say, muzzle to muzzle) or vertically (cow to calf) by suckling. Pigs are special: They excrete far more of the virus than other livestock, and over a longer period of time, broadcasting it prodigiously in their respiratory exhalations. They sneeze it, they chuff it, they oink it, they wheeze it and burp it and cough it into the air. One experimental study found that pig breath carried thirty times as much FMD virus as the breath of an infected cow or sheep, and that once airborne it could spread for miles. That's why pigs are considered an amplifier host of this virus.

An amplifier host is a creature in which a virus or other pathogen replicates—and from which it spews—with extraordinary abundance. Some aspect of the host's physiology, or its immune system, or its particular history of interaction with the bug, or who knows what, accounts for this especially hospitable role. The amplifier host becomes an intermediate link between a reservoir host and some other unfortunate animal, some other sort of victim—a victim requiring higher doses or closer contact before the infection can take hold. You can understand this in terms of thresholds. The amplifier host has a relatively low threshold for becoming infected, yet it produces a vast output of virus, vast enough to overcome the higher threshold in another animal.

Not every zoonotic pathogen requires an amplifier host for successful infection of humans, but some evidently do. Which ones, and how does the process work? The disease scientists are exploring those questions, among many others. Meanwhile, the concept is a hypothetical tool. Linda Selvey didn't mention the FMD paradigm when she used the word "amplifier" in our conversation about Hendra virus, but I knew what she meant.

Still . . . why horses? Why not kangaroos or wombats or koalas or potoroos? If the horse fills that amplifying role, one obvious fact deserves fresh attention: Horses aren't native to Australia. They are exotic, first brought there by European settlers barely more than two centuries ago. Hendra is probably an old virus, according to the runic evidence of its genome, as read by molecular evolution-

ists. Distantly diverged from its morbillivirus cousins, it may have abided unobtrusively in Australia for a very long time. Bats too are an ancient part of the native fauna; the fossil record in Queensland shows that small bats have been there for at least 55 million years, and flying foxes may have evolved in the region during the early Miocene, about 20 million years ago. Human presence is more recent, dating back only tens of millennia. More precisely, humans have inhabited Australia since the pioneering ancestors of Australian aboriginal peoples first made their way, island hopping daringly in simple wooden boats, from southeastern Asia by way of the South China Sea and the Lesser Sunda Islands to the northwestern coast of the island continent. That was at least forty thousand years ago, possibly much earlier. So three of the four principals in this complex interaction—flying foxes, Hendra virus, and people—have probably coexisted in Australia since the Pleistocene era. Horses arrived in January 1788.

It was a small change on the landscape, compared to all that would follow. Those earliest horses came aboard ships of the First Fleet, under command of Captain Arthur Phillip, who had sailed out from Britain to establish a convict colony in New South Wales. After five months of navigating the Atlantic, Phillip stopped at a Dutch settlement near the Cape of Good Hope to take on provisions and livestock before continuing eastward from Africa. He rounded Van Diemen's Land (now Tasmania) and sailed north along mainland Australia's east coast. Captain James Cook had already come and gone, "discovering" the place, but Phillip's group would be the first European settlers. At a spot near what is now Sydney, within the fine natural harbor there, his penal arks put ashore 736 convicts, 74 pigs, 29 sheep, 19 goats, 5 rabbits, and 9 horses. The horses included two stallions, four mares, and three foals. Until that day there was no record, either fossil or historic, of members of the genus *Equus* in Australia. Nor were there any oral traditions (none shared with the world so far, anyway) of Hendra virus outbreaks among aboriginal Australians.

As of January 27, 1788, then, the elements were almost certainly gathered in place—the virus, the reservoir hosts, the amplifier host,

plus susceptible humans. And now another riddle presents itself. From the horses of Captain Arthur Phillip to the horses of Vic Rail is a gap of 206 years. Why did the virus wait so long to emerge? Or had it indeed emerged previously, maybe often, and never been recognized for what it is? How many past cases of Hendra, over two centuries or more, have been misdiagnosed as snakebite?

Answer from the scientists: We don't know but we're working on it.

6

Hendra virus in 1994 was just one thump in a drumbeat of bad news. The drumbeat has been sounding ever more loudly, more insistently, more rapidly over the past fifty years. When and where did it start, this modern era of emerging zoonotic diseases?

To choose one point is a little artificial, but a good candidate would be the emergence of Machupo virus among Bolivian villagers between 1959 and 1963. Machupo wasn't called Machupo at the start, of course, nor even recognized as a virus. Machupo is the name of a small river draining the northeastern Bolivian lowlands. The first recorded case of the disease came and went, almost unnoticed, as a bad but nonfatal fever afflicting a local farmer. This was during the wet season of 1959. More such illnesses, and worse, occurred in the same region over the following three years. Symptoms included fever and chills, nausea and vomiting, body aches, nosebleeds, and bleeding gums. It became known as El Tifu Negro (the Black Typhus, for the color of vomit and stool), and by late 1961 had struck 245 people, with a case fatality rate of 40 percent. It continued killing until the virus was isolated, its reservoir identified, and its dynamics of transmission understood well enough to be interrupted by preventive measures. Mouse trapping helped enormously. Most of the scientific work was done under difficult

field conditions by a patched-together team of Americans and Bolivians, including an intense young scientist named Karl Johnson, pungently candid with his opinions, deeply enthralled by the dangerous beauty of viruses, who caught the disease himself and nearly died of it. This was before the Centers for Disease Control and Prevention (CDC) in Atlanta sent out well-equipped squads; Johnson and his colleagues invented their methods and tools as they went. Having struggled through his fever at a hospital in Panama, Karl Johnson would play a large and influential role in the longer saga of emerging pathogens.

If you assembled a short list of the highlights and high anxieties of that saga within recent decades, it could include not just Machupo but also Marburg (1967), Lassa (1969), Ebola (1976, with Karl Johnson again prominently involved), HIV-1 (inferred in 1981, first isolated in 1983), HIV-2 (1986), Sin Nombre (1993), Hendra (1994), avian flu (1997), Nipah (1998), West Nile (1999), SARS (2003), and the much feared but anticlimactic swine flu of 2009. That's a drama series more glutted and seething with virus than even Vic Rail's poor mare.

A person might construe this list as a sequence of dire but unrelated events—independent misfortunes that have happened to us, to humans, for one unfathomable reason and another. Seen that way, Machupo and the HIVs and SARS and the others are "acts of God" in the figurative (or literal) sense, grievous mishaps of a kind with earthquakes and volcanic eruptions and meteor impacts, which can be lamented and ameliorated but not avoided. That's a passive, almost stoical way of viewing them. It's also the wrong way.

Make no mistake, they are connected, these disease outbreaks coming one after another. And they are not simply *happening* to us; they represent the unintended results of things we are *doing*. They reflect the convergence of two forms of crisis on our planet. The first crisis is ecological, the second is medical. As the two intersect, their joint consequences appear as a pattern of weird and terrible new diseases, emerging from unexpected sources and raising deep concern, deep foreboding, among the scientists who study them. How do such diseases leap from nonhuman animals into people,

and why do they seem to be leaping more frequently in recent years? To put the matter in its starkest form: Human-caused ecological pressures and disruptions are bringing animal pathogens ever more into contact with human populations, while human technology and behavior are spreading those pathogens ever more widely and quickly. There are three elements to the situation.

One: Mankind's activities are causing the disintegration (a word chosen carefully) of natural ecosystems at a cataclysmic rate. We all know the rough outlines of that problem. By way of logging, road building, slash-and-burn agriculture, hunting and eating of wild animals (when Africans do that we call it "bushmeat" and impute a negative onus, though in America it's merely "game"), clearing forest to create cattle pasture, mineral extraction, urban settlement, suburban sprawl, chemical pollution, nutrient runoff to the oceans, mining the oceans unsustainably for seafood, climate change, international marketing of the exported goods whose production requires any of the above, and other "civilizing" incursions upon natural landscape—by all such means, we are tearing ecosystems apart. This much isn't new. Humans have been practicing most of those activities, using simple tools, for a very long time. But now, with 7 billion people alive and modern technology in their hands, the cumulative impacts are becoming critical. Tropical forests aren't the only jeopardized ecosystems, but they're the richest and most intricately structured. Within such ecosystems live millions of kinds of creatures, most of them unknown to science, unclassified into a species, or else barely identified and poorly understood.

Two: Those millions of unknown creatures include viruses, bacteria, fungi, protists, and other organisms, many of which are parasitic. Students of virology now speak of the "virosphere," a vast realm of organisms that probably dwarfs every other group. Many viruses, for instance, inhabit the forests of Central Africa, each parasitic upon a kind of bacterium or animal or fungus or protist or plant, all embedded within ecological relationships that limit their abundance and their geographical range. Ebola and Marburg and Lassa and monkeypox and the precursors of the human immunodeficiency viruses represent just a minuscule sample of what's there,

of the myriad other viruses as yet undiscovered, within hosts that in many cases are as yet undiscovered themselves. Viruses can only replicate inside the living cells of some other organism. Commonly they inhabit one kind of animal or plant, with whom their relations are intimate, ancient, and often (but not always) commensal. That is to say, dependent but benign. They don't live independently. They don't cause commotion. They might kill some monkeys or birds once in a while, but those carcasses are quickly absorbed by the forest. We humans seldom have occasion to notice.

Three: But now the disruption of natural ecosystems seems more and more to be unloosing such microbes into a wider world. When the trees fall and the native animals are slaughtered, the native germs fly like dust from a demolished warehouse. A parasitic microbe, thus jostled, evicted, deprived of its habitual host, has two options—to find a new host, a new *kind* of host . . . or to go extinct. It's not that they target us especially. It's that we are so obtrusively, abundantly available. "If you look at the world from the point of view of a hungry virus," the historian William H. McNeill has noted, "or even a bacterium—we offer a magnificent feeding ground with all our billions of human bodies, where, in the very recent past, there were only half as many people. In some 25 or 27 years, we have doubled in number. A marvelous target for any organism that can adapt itself to invading us." Viruses, especially those of a certain sort—those whose genomes consist of RNA rather than DNA, leaving them more prone to mutation—are highly and rapidly adaptive.

All these factors have yielded not just novel infections and dramatic little outbreaks but also new epidemics and pandemics, of which the most gruesome, catastrophic, and infamous is the one caused by a lineage of virus known to scientists as HIV-1 group M. That's the lineage of HIV (among twelve different sorts) that accounts for most of the worldwide AIDS pandemic. It has already killed 30 million humans since the disease was noticed three decades ago; roughly 34 million other humans are presently infected. Despite the breadth of its impact, most people are unaware of the fateful combination of circumstances that brought

HIV-1 group M out of one remote region of African forest, where its precursor lurked as a seemingly harmless infection of chimpanzees, into human history. Most people don't know that the real, full story of AIDS doesn't begin among American homosexuals in 1981, or in a few big African cities during the early 1960s, but at the headwaters of a jungle river called the Sangha, in southeastern Cameroon, half a century earlier. Even fewer people have caught wind of the startling discoveries that, just within the past several years, have added detail and transformative insight to that story. Those discoveries will get their place later ("The Chimp and the River") in this account. For now I'll just note that, even if the subject of zoonotic spillover addressed nothing but the happenstance of AIDS, it would obviously command serious attention. But as mentioned already, the subject addresses much more—other pandemics and catastrophic diseases of the past (plague, influenza), of the present (malaria, influenza), and of the future.

Diseases of the future, needless to say, are a matter of high concern to public health officials and scientists. There's no reason to assume that AIDS will stand unique, in our time, as the only such global disaster caused by a strange microbe emerging from some other animal. Some knowledgeable and gloomy prognosticators even speak of the Next Big One as an inevitability. (If you're a seismologist in California, the Next Big One is an earthquake that drops San Francisco into the sea, but in this realm of discourse it's a vastly lethal pandemic.) Will the Next Big One be caused by a virus? Will the Next Big One come out of a rainforest or a market in southern China? Will the Next Big One kill 30 or 40 million people? The concept by now is so codified, in fact, that we could think of it as the NBO. The chief difference between HIV-1 and the NBO may turn out to be that HIV-1 does its killing so slowly. Most other new viruses work fast.

I've been using the words "emergence" and "emerging" as though they are everyday language, and maybe they are. Among the experts, they're certainly common parlance. There's even a journal dedicated to the subject, *Emerging Infectious Diseases*, published monthly by the CDC. But a precise definition of "emergence" might

be useful here. Several have been offered in the scientific literature. The one I prefer simply says that an emerging disease is "an infectious disease whose incidence is increasing following its first introduction into a new host population." The key words, of course, are "infectious," "increasing," and "new host." A re-emerging disease is one "whose incidence is increasing in an existing host population as a result of long-term changes in its underlying epidemiology." Tuberculosis is re-emerging as a severe problem, especially in Africa, as the TB bacterium exploits a new opportunity: infecting AIDS patients whose immune systems are disabled. Yellow fever re-emerges among humans wherever *Aedes aegypti* mosquitoes are allowed to resume carrying the virus between infected monkeys and uninfected people. Dengue, also dependent on mosquito bites for transmission and native monkeys as reservoirs, re-emerged in Southeast Asia after World War II due at least partly to increased urbanization, wider travel, lax wastewater management, inefficient mosquito control, and other factors.

Emergence and spillover are distinct concepts but interconnected. "Spillover" is the term used by disease ecologists (it has a different use for economists) to denote the moment when a pathogen passes from members of one species, as host, into members of another. It's a focused event. Hendra virus spilled over into Drama Series (from bats) and then into Vic Rail (from horses) in September 1994. Emergence is a process, a trend. AIDS emerged during the late twentieth century. (Or was it the *early* twentieth century? I'll return to that question.) Spillover leads to emergence when an alien bug, having infected some members of a new host species, thrives in that species and spreads among it. In this sense, the strict sense, Hendra hasn't emerged into the human population, not yet, not quite. It is merely a candidate.

Not all emerging diseases are zoonotic, but most are. From where else might a pathogen emerge, if not from another organism? Well, granted, some novel pathogens do seem to emerge from the environment itself, without need for shelter in a reservoir host. Case in point: The bacterium now called *Legionella pneumophila* emerged from the cooling tower of an air-conditioning system at a

hotel in Philadelphia, in 1976, to create the first-known outbreak of Legionnaires' disease and kill thirty-four people. But that scenario is far less typical than the zoonotic one. Microbes that infect living creatures of one kind are the most likely candidates to infect living creatures of another kind. This has been borne out statistically by several review studies in recent years. One of them, published by two scientists at the University of Edinburgh in 2005, looked at 1,407 recognized species of human pathogen and found that zoonotic bugs account for 58 percent. Of the full total, 1,407, just 177 can be considered emerging or re-emerging. Three-fourths of those emergent pathogens are zoonotic. In plain words: Show me a strange new disease and, most likely, I can show you a zoonosis.

A parallel survey, from a team led by Kate E. Jones of the Zoological Society of London, appeared in the journal *Nature* in 2008. This group considered more than three hundred "events" of emerging infectious disease (EIDs, in their shorthand) that occurred between 1940 and 2004. They wondered about changing trends as well as discernible patterns. Although their list of events was independent of the Edinburgh researchers' list of pathogens, Jones and her colleagues found almost the same portion (60.3 percent) to be zoonotic. "Furthermore, 71.8% of these zoonotic EID events were caused by pathogens with a wildlife origin," as distinct from domestic animals. They cited Nipah in Malaysia and SARS in southern China. Further still, the increment of disease events associated with wildlife, as opposed to livestock, seems to be increasing over time. "Zoonoses from wildlife represent the most significant, growing threat to global health of all EIDs," these authors concluded. "Our findings highlight the critical need for health monitoring and identification of new, potentially zoonotic pathogens in wildlife populations, as a forecast measure for EIDs." That sounds reasonable: *Let's keep an eye on wild creatures. As we besiege them, as we corner them, as we exterminate them and eat them, we're getting their diseases*. It even sounds reassuringly doable. But to highlight the need for monitoring and forecasting is also to highlight the urgency of the problem and the discomfiting reality of how much remains unknown.

For instance: Why did Drama Series, the original mare, fall sick in that paddock when she did? Was it because she shaded herself beneath a fig tree and munched some grass besmeared with bat urine containing the virus? How did Drama Series pass her infection to the other horses at Vic Rail's stable? Why did Rail and Ray Unwin get infected but not the devoted veterinarian, Peter Reid? Why did Mark Preston get sick but not Margaret Preston? Why did the outbreaks at Hendra and Mackay occur in August and September 1994, close in time though distant geographically? Why did all those bat carers remain uninfected, despite their months and years of fondling flying foxes?

These local riddles about Hendra are just small forms of big questions that scientists such as Kate Jones and her team, and the Edinburgh researchers, and Hume Field, and many others around the world are asking. Why do strange new diseases emerge when they do, where they do, as they do, and not elsewhere, other ways, at other times? Is it happening more now than in the past? If so, how are we bringing these afflictions upon ourselves? Can we reverse or mitigate the trends before we're hit with another devastating pandemic? Can we do that without inflicting fearful punishment on all those other kinds of infected animals with which we share the planet? The dynamics are complicated, the possibilities are many, and while science does its work slowly, we all want a fast response to the biggest question: What sort of nasty bug, with what unforeseen origins and what inexorable impacts, will emerge next?

7

During one trip to Australia I stopped in Cairns, a balmy resort city about a thousand miles north of Brisbane, for a conversation with a young veterinarian there. I can't recall how I located her, because she was wary of publicity and didn't want her name

used in print. But she agreed to talk to me about her experience with Hendra. Although her experience had been brief, it included two roles: as doctor, as patient. At that time she was the only known Hendra survivor in Australia, besides the stable hand Ray Unwin, who had also suffered infection with the virus and lived. We spoke in the office of a small veterinary clinic where she worked.

She was an ebullient woman, twenty-six years old, with pale blue eyes and hennaed brunette hair pulled back in a tight bun. She wore silver earrings, shorts, and a red short-sleeve shirt with a clinic logo. While an earnest border collie kept us company, nudging my hands for affection as I tried to write notes, the vet described a night in October 2004 when she had gone out to attend to a suffering horse. The owners were concerned because this particular animal, a ten-year-old gelding, seemed "off color."

The horse was named Brownie, she remembered that. He lived on a family farm down at Little Mulgrave, about twenty miles south of Cairns. She remembered it all, in fact, a night full of vivid impressions. Brownie was a quarterhorse-thoroughbred cross. Not a racer, no, a pet. The family included a teenage daughter; Brownie was her special favorite. At eight o'clock that evening the horse seemed normal, but then something went suddenly wrong. The family suspected colic, bad stomach—maybe he had eaten some toxic greens. Around eleven o'clock they phoned for help and got the young vet, who was on call that night. She jumped in her car, and when she arrived Brownie was in desperate condition, panting heavily, feverish, down on the ground. "I found the horse had a heart rate through the roof, temperature through the roof," she told me, "and there was bloody red froth coming out the nose." Giving him a quick look, taking his vitals, she came close to the horse and, when he snorted, "I got quite a degree of bloody sort of red mucousy froth on my arms." The teenage girl and her mother were already smeared with blood from having tried to comfort Brownie. Now he could barely lift his head. The vet, a fiercely caring professional, told them the horse was dying. Knowing her duty, she said: "I want to euthanize it." She ran back to her car, got the euthanasia solution and tools, but by the time she returned Brownie was dead.

In his last agonal gasps, he had brought up more bubbly red froth through his nostrils and mouth.

Were you wearing gloves? I asked.

No. The protocol was to use gloves for a postmortem, but not for live animals. Then the one situation led so swiftly to the other. "I was wearing exactly what I'm wearing now. A pair of shoes, short socks, blue shorts, and short sleeves."

A surgical mask?

No, no mask. "You know, in the laboratory all those precautions are easy to take. When it's twelve at night and it's pouring down rain and you're out in the middle of the dark and you're operating via the car headlights with a hysterical family in the background, it's not always easy to take the proper precautions. And the other thing was, that I just didn't know." Didn't know what she was confronting in Brownie's case, she meant. "I wasn't really thinking infectious disease." She was defensive on these points because there had been second-guessing of her procedures, an investigation, questions about negligence. She had been exonerated—in fact, she made her own complaint about having not been properly warned—but it couldn't have been helpful to her career, and that's presumably why she wanted anonymity. She had a story to tell, yet she also wished to put it behind her.

In the minutes after Brownie's death, she had changed into boots, long pants, and shoulder-length gloves and begun the postmortem exam. The owners were keen to know whether Brownie had eaten some sort of poisonous grass that might threaten their other horses too. The vet sliced opened Brownie's abdomen and found his guts looking normal. No sign of twisted bowel or other blockage that might cause colic. In the process, "I got a couple of splashes of abdominal fluid on my leg." You can't do a postmortem on a horse without getting smeared, she explained. Next she looked into the chest, by way of a modest incision between the fourth and fifth ribs. If it wasn't colic it was probably cardiac trouble, she suspected, and saw that hunch immediately confirmed. "The heart was massively enlarged. The lungs were wet and full of bloody fluid and there was just fluid right through the chest cavity. So he died of congestive

heart failure. That was all I could conclude. I couldn't conclude whether it was infectious or not." She offered to take samples for lab testing, but the owners declined. Enough information, enough expense, too bad about Brownie, and they would simply bury the carcass with a bulldozer.

Were there bats around this property? I asked.

"There's bats everywhere." Everywhere throughout northern Queensland, she meant, not just at Little Mulgrave. "If you walk out the back here, you'll see a couple hundred bats." The entire area of Cairns and its environs: warm climate, plenty of fruit trees, plenty of fruit-eating bats. But the subsequent inquiry turned up nothing about Brownie's situation that seemed to have closely exposed him to bats. "They couldn't say, other than random chance, why this particular horse got infected." Buried beneath ten feet of dirt, having left behind no samples of blood or tissue, he couldn't even be labeled "infected" except by later inference.

Immediately after the postmortem, the vet washed her hands and arms thoroughly, wiped down her legs, and then went home to take a Betadine shower. She keeps a large supply of Betadine, the professional antiseptic of choice, for such occasions. She gave herself a good surgical scrub and got into bed, after a hard but not too unusual night. It wasn't until nine or ten days later that she started feeling headachy and sick. Her doctor suspected the flu, or a cold, or maybe tonsillitis. "I get tonsillitis a lot," she said. He gave her some antibiotics and sent her home.

She missed a week's work, languishing with symptoms that felt like influenza or bronchitis: mild pneumonia, sore throat, a bad cough, muscle weakness, fatigue. At one point a senior colleague asked whether she had considered the possibility that the dead horse had infected her with Hendra virus. The young vet, trained in Melbourne (way down in temperate Australia) before she moved up to tropical Cairns, had scarcely heard Hendra virus mentioned in veterinary school. It was too obscure, too new, and not an issue in the Melbourne area. Only two of the four kinds of reservoir bats range that far south, and evidently they had yet to cause concern. Now she went to the hospital for a blood test, then

another, and yes indeed: She had antibodies to Hendra virus. By that time she was back on her feet, working again. She had been infected and shaken it off.

When I met her, more than a year later, she was feeling fine, apart from a little weariness and more than a little anxiety. She knew well that the case of Mark Preston—his infection during a horse postmortem, his recovery, his interlude of good health, then his relapse—cautioned against complacency that the virus had left her forever. State health officials were tracking her case; if the headaches returned, if she felt dizzy or suffered a seizure, if her nerves tingled, if she started coughing or sneezing, they wanted to know it. "I still go and see the infectious disease control specialists," she said. "I get weighed by the Department of Primary Industries on a regular basis." From blood tests they charted her antibody levels, which continued to fluctuate peculiarly down and up. Lately the numbers were back up. Did that portend a relapse, or did it just reflect her robust acquired immunity?

The scariest part, she told me, was the uncertainty. "It's the fact that this disease has been around for so little that they can't tell me whether there's going to be any future health risk." How would she be in seven years, ten years? How high was the chance of recrudescence? Mark Preston died suddenly after a year. Ray Unwin said his health was still "crook." The young vet in Cairns only wanted to know, in her own case, the same thing we all want to know: What next?

II

THIRTEEN GORILLAS

8

Not many months after the events at Vic Rail's stables, another spillover occurred, this one in Central Africa. Along the upper Ivindo River in northeastern Gabon, near the border with the Republic of the Congo, lies a small village called Mayibout 2, a sort of satellite settlement just a mile upriver from the village of Mayibout. In early February 1996, eighteen people in Mayibout 2 became suddenly sick after they participated in the butchering and eating of a chimpanzee.

Their symptoms included fever, headache, vomiting, bloodshot eyes, bleeding from the gums, hiccupping, muscle pain, sore throat, and bloody diarrhea. All eighteen were evacuated downriver to a hospital in the district capital, a town called Makokou, by decision of the village chief. It's less than fifty miles as the crow flies from Mayibout 2 to Makokou, but by pirogue on the sinuous Ivindo, a journey of seven hours. The boat wound back and forth between walls of forest along the banks. Four of the evacuees were moribund when they arrived and dead within two days. The four bodies, returned to Mayibout 2, were buried according to traditional ceremonial practice, with no special precautions against the transmission of whatever had killed them. A fifth victim escaped from the hospital, straggled back to the village, and died there. Secondary cases soon broke out among people infected while caring

for the first victims—their loved ones or friends—or in handling the dead bodies. Eventually thirty-one people got sick, of whom twenty-one died: a case fatality rate of almost 68 percent.

Those facts and numbers were collected by a team of medical researchers, some Gabonese, some French, who reached Mayibout 2 during the outbreak. Among them was an energetic Frenchman named Eric M. Leroy, a Paris-trained veterinarian and virologist then based at the Centre International de Recherches Médicales de Franceville (CIRMF), in Franceville, a modest city in southeastern Gabon. Leroy and his colleagues found evidence of Ebola virus in samples from some patients, and they deduced that the butchered chimpanzee had been infected with Ebola. "The chimpanzee seems to have been the index case for infecting 18 primary human cases," they wrote. Their investigation also turned up the fact that the chimp hadn't been killed by village hunters; it had been found dead in the forest and scavenged.

Four years later, I sat at a campfire near the upper Ivindo River with a dozen local men who were working as forest crew for a long overland trek. These men, most of them from villages in northeastern Gabon, had been walking for weeks before I joined them on the march. Their job involved carrying heavy bags through the jungle and building a simple camp each night for the biologist, one Mike Fay, whose obsessive sense of mission drove the whole enterprise forward. Fay is an unusual man, even by the standards of tropical field biologists: physically tough, obdurate, free-spirited, smart, and fiercely committed to conservation. His enterprise, which he labeled the Megatransect, was a two-thousand-mile biological survey, on foot, through the wildest remaining forest areas of Central Africa. He took data every step of the way, recording elephant dung piles and leopard tracks and chimpanzee sightings and botanical identifications, tiny notations by the thousands, all going into his waterproof yellow notebooks in scratchy left-handed print, while the crewmen strung out behind him toted his computers, his satellite phone, his special instruments and extra batteries, as well as tents and food and medical supplies enough for both him and themselves.

Fay had already been walking for 290 days by the time he reached

this part of northeastern Gabon. He had crossed the Republic of the Congo with a field crew of forest-tough Congo men, mostly Bambendjellés (one ethnic group of the short-statured peoples sometimes termed Pygmies), but those fellows had been disallowed entry at the Gabonese border. So Fay had been forced to raise a new team in Gabon. He recruited them largely from a cluster of gold-mining camps along the upper Ivindo River. The hard, stumbling work he demanded, cutting trail, schlepping bags, was evidently preferable to digging for gold in equatorial mud. One man served as cook as well as porter, stirring up massive amounts of rice or *fufu* (a starchy staple made from manioc flour, like an edible wallpaper paste) at each evening's campfire, and adorning it with some sort of indeterminate brown sauce. The ingredients for that variously included tomato sauce, dried fish, canned sardines, peanut butter, freeze-dried beef, and *pili-pili* (hot pepper), all deemed mutually compatible and combined at the whim of the chef. No one complained. Everyone was always hungry. The only thing worse than a big portion of such stuff, at the end of an exhausting day of stumbling through the jungle, was a small portion. My role amid this gang, on assignment for *National Geographic*, was to walk in Fay's footsteps and produce a series of stories describing the work and the journey. I would accompany him for ten days here, two weeks there, and then escape back to the United States, let my feet heal (we wore river sandals), and write an installment.

Each time I rejoined Fay and his team, there was a different logistical arrangement for our rendezvous, depending on the remoteness of his location and the urgency of his need to be resupplied. He never diverted from the zigzag line of his march. It was up to me to get to him. Sometimes I went in by bush plane and motorized dugout, along with Fay's trusted logistics man and quartermaster, a Japanese ecologist named Tomo Nishihara. Tomo and I would pile ourselves into the canoe amid whatever stuff he was bringing for the next leg of Fay's trek: fresh bags of fufu and rice and dried fish, crates of sardines, oil and peanut butter and pili-pili and double-A batteries. But even a dugout canoe couldn't always reach the spot where Fay and his crew, famished and bedraggled,

would be waiting. On this occasion, with the trekkers crossing a big forest block called Minkébé, Tomo and I roared out of the sky in a Bell 412 helicopter, a massive 13-seater, chartered expensively from the Gabonese army. The forest canopy, elsewhere thick and unbroken, was punctuated here by several large granite gumdrops that rose above everything, hundreds of feet high, like El Capitan standing out of a green ground fog. Atop one of those inselbergs was the landing zone to which Fay had directed us. It was forty miles due west of Mayibout 2.

That day had been a relatively easy one for the crew—no swamps crossed, no thickets of skin-slicing vegetation, no charging elephants provoked by Fay's desire to take video at close range. They were bivouacked, awaiting the helicopter. Now the supplies had arrived—including even some beer! This allowed for a relaxed, genial atmosphere around the campfire. Quickly I learned that two of the crewmen, Thony M'Both and Sophiano Etouck, had roots in Mayibout 2. They were present when Ebola virus struck the village.

Thony, an extrovert, slim in build and far more voluble than the other fellow, was willing to talk about it. He spoke in French while Sophiano, a shy man with a body-builder's physique, an earnest scowl, a goatee, and a nervous stutter, sat silent. Sophiano, by Thony's account, had watched his brother and most of his brother's family die.

Having just met these two men, I couldn't decently press for more information that evening. Two days later we set off on the next leg of Fay's hike, across the Minkébé forest, heading southward away from the inselbergs. We got busy and distracted with the physical challenges of foot travel through trackless jungle terrain, and were exhausted (especially they, working harder than I) by nightfall. Halfway along, though, after a week of difficult walking, common miseries, and shared meals, Thony loosened enough to tell me more. His memories agreed generally with the report of the CIRMF team from Franceville, apart from small differences on some numbers and details. But his perspective was more personal.

Thony called it *l'épidémie*, the epidemic. This happened in 1996,

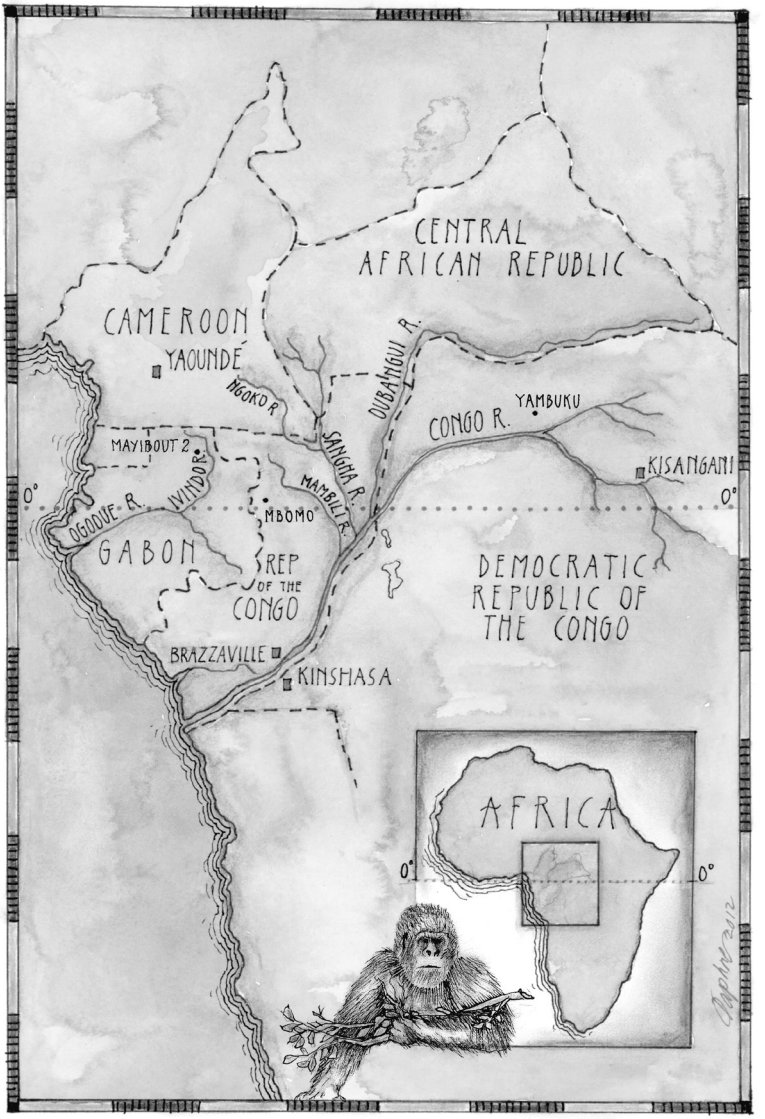
yes, he said, around the same time some French soldiers came up to Mayibout 2 in a Zodiac raft and camped near the village. It was unclear whether the soldiers had a serious purpose—rebuilding an old airstrip?—or were just there to amuse themselves. They shot off their rifles. Maybe, Thony guessed, they also possessed some sort of chemical weaponry. He mentioned these details because he thought they might have relevance to the epidemic. One day some boys from the village went out hunting with their dogs. The intended prey was porcupines. Instead of porcupines they got a chimp—not killed by the dogs, no. A chimp found dead. They brought it back. The chimp was rotten, Thony said, its stomach putrid and swollen. Never mind, people were glad and eager for meat. They butchered the chimp and ate it. Then quickly, within two days, everyone who had touched the meat started getting sick.

They vomited; they suffered diarrhea. Some went downriver by motorboat to the hospital at Makokou. But there wasn't enough fuel to transport every sick person. Too many victims, not enough boat. Eleven people died at Makokou. Another eighteen died in the village. The special doctors quickly came up from Franceville, yes, Thony said, wearing their white suits and helmets, but they didn't save anyone. Sophiano lost six family members. One of those, one of his nieces—he was holding her as she died. Yet Sophiano himself never got sick. No, nor did I, said Thony. The cause of the illnesses was a matter of uncertainty and dark rumor. Thony suspected that the French soldiers, with their chemical weapons, had killed the chimpanzee and carelessly left its meat to poison the villagers. Anyway, his fellow survivors had learned their lesson. To this day, he said, no one in Mayibout 2 eats chimpanzee.

I asked about the boys who went hunting. Them, all the boys, they died, Thony said. The dogs did not die. Had he ever before seen such a disease, such an epidemic? "*No*," Thony answered. "*C'etait le premier fois*." Never.

How did they cook the chimp? I pried. In a normal African sauce, Thony said, as though that were a silly question. I imagined chimpanzee hocks in a peanutty gravy, with pili-pili, ladled over fufu.

Apart from the chimpanzee stew, one other stark detail lingered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