A REPORTER AT LARGE

THE VACCINE

Has the race to save Africa from AIDS put Western science at odds with Western ethics?

BY MICHAEL SPECTER

At forty-one, Hala has five children and eight grandchildren. Her first husband left when their second child was born. Her second husband died of AIDS nearly twenty years ago, in the earliest days of the epidemic. Hala often tells people that she sells charcoal, doughnuts, or cooking oil on the streets, but that isn't true. She is a prostitute, who has spent nearly half her life working out of a wattle hut in Pumwani, one of Nairobi's most crowded—and violent—slums. On an average day, she might see ten men, most of them truck drivers from Tanzania. Her "office" has just enough room for a single bed, a stool, a customer, herself, and a wicker basket filled with condoms. The basket is a recent addition; only in the past year or so have her clients agreed to use condoms with any regularity.

None of these details make Hala unusual. Despite the severity of the AIDS epidemic, Kenyans have only just begun to speak openly about the disease, and the epidemic has certainly done little to deter prostitution. As many as two and a half million people in Kenya, one in six adults, are infected with H.I.V. In Pumwani, more than ninety per cent of prostitutes—and many of their clients—test positive for the virus. Hala has engaged in unprotected sex with hundreds of H.I.V-positive men. Her best customer—a man who visited her regularly for seventeen years, and never used a condom—recently died of AIDS. Remarkably, though, she has never become infected.

The day I was introduced to Hala, at a clinic not far from where she lives, she was draped in black robes and wore a purple shawl with gold piping down the sides. She is a handsome, businesslike woman, and she is completely baffled by her fate. "I have no idea why I of all people have been spared," she told me. "But if my luck can be useful to the doctors then I will be grateful."

Hala belongs to an increasingly famous cohort of research subjects, known by AIDS experts throughout the world as "the Nairobi prostitutes." In the late nineteen-eighties, the Canadian infectious-disease expert Francis Plummer noticed something startling: in a study of two thousand Nairobi prostitutes, as many as two hundred remained uninfected, despite years of constant high-risk behavior. Later, when Plummer and his colleagues examined the data more closely, they realized that if the prostitutes didn't become infected within five years of their first exposure to the virus, they were unlikely to become infected at all.

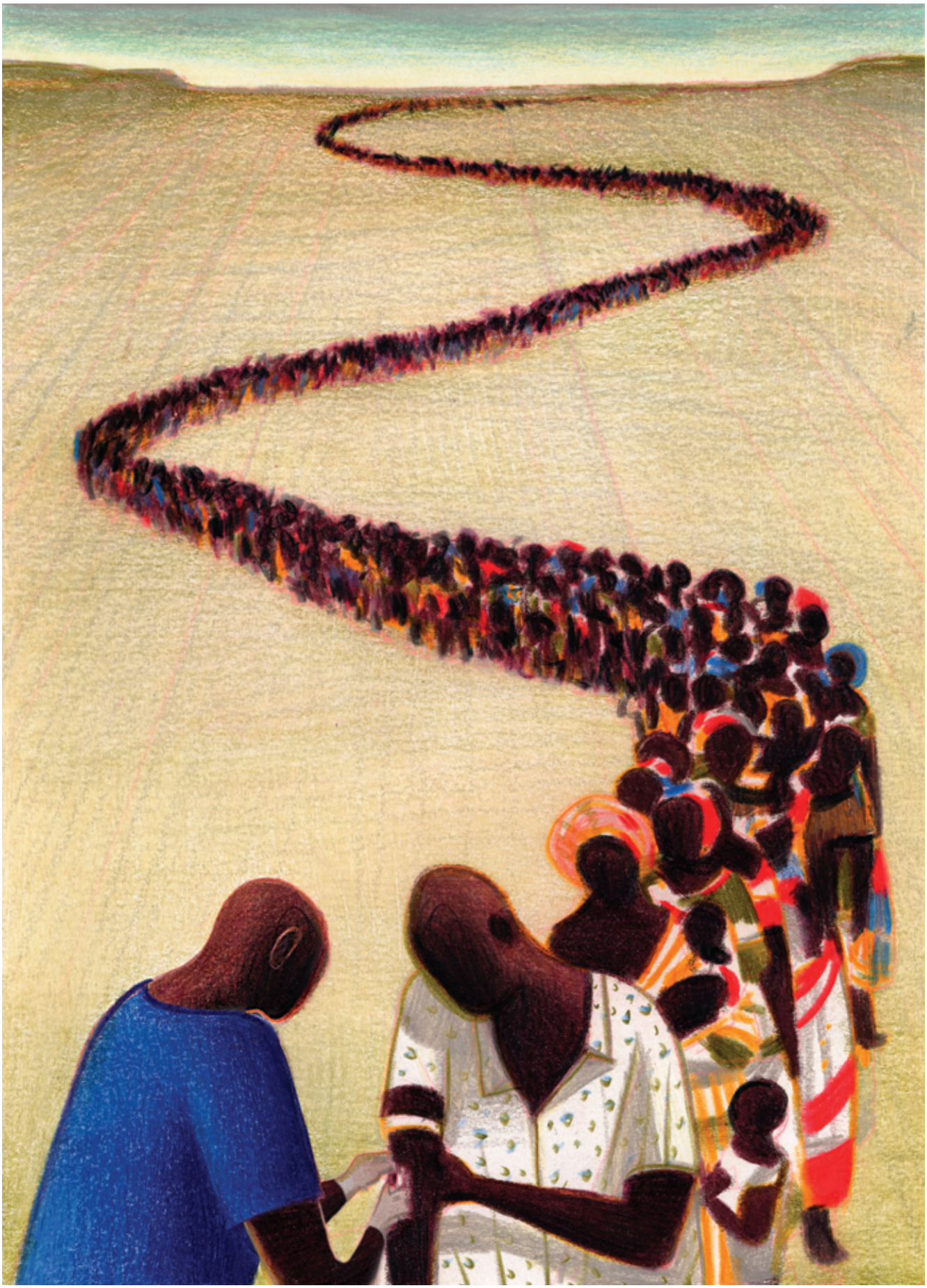
How, exactly, were these women protected when millions who engaged in the same behavior fell ill and died? It couldn't have been luck; nobody gets lucky a thousand times in a row. Nor was it good nutrition; the women often lived on plantains and rice, and many were weak, undernourished, and sickly. Plummer concluded that these women harbored a rare defensive weapon within their immune systems. To many vaccine researchers, the implications were thrilling: if they could identify that weapon and somehow bottle it, they might help to end the world's most devastating epidemic. "We all held our breath for a while," Job J. Bwayo, the director of the International AIDS Vaccine Initiative in Kenya, told me when I went to see him at the University of Nairobi. "Nobody expected a simple solution to come from it, but we have all kept hoping that somehow the girls will provide the key."

The search for a solution has become desperate. Twenty-one years after the first cases of "slim disease," as AIDS was initially called in Africa, appeared in a Ugandan village on the shores of Lake Victoria, scientists are only marginally closer to producing a successful vaccine than they were when they identified the virus that causes it. A great deal has changed for people with AIDS in those two decades: medicines are now routinely available throughout the developed world. But, of the forty million people who are living with H.I.V., less than five per cent have access to them. Because that percentage will not change dramatically in the next decade, the world has never needed a medical intervention more urgently than it needs an AIDS vaccine today.

Thanks in part to a United Nations special session devoted to AIDS, the plight of Africa has finally gained at least a measure of attention. Last fall, I watched at a clinic in Nairobi as a farmworker received a new kind of H.I.V. test, one that provides almost instant results. A nurse took a few drops of his blood, the man sat quietly on a bench for half an hour, and then he had his answer. Even a year ago, this man, and tens of thousands like him, would have had to make a second journey to the clinic—often on foot—to get the test results; many would not have been able, or willing, to do that. While I was in Nairobi, I attended a support group for infected mothers, visited well-maintained clinics in the most fetid slums, and was surprised to see billboards on the main highway urging precautions. After years of denial, even politicians acknowledge that AIDS poses a serious threat to the future of the nation. In Uganda, where President Yoweri Museveni long ago established himself as the African leader most willing to speak openly about the disease, the epidemic has ebbed. In each of the past ten years, there have been fewer new H.I.V. infections than in the year before, a feat managed by no other African country. Although six per cent of the adults in Uganda remain infected—a toll that would be horrifying almost anywhere else on earth—the figure a decade ago was more than twenty per cent.

Still, the news in Africa can only be described as profoundly distressing. The life expectancy of sexually active Ugandans has fallen from sixty-four years before the epidemic to forty-two today. In Kenya, the decline has been from sixty-six

LORENZO MATTOTTI



Producing a life-saving vaccine will require scientists to compare thousands of people who receive it with thousands who do not.

"On balance, Estelle, your party was not helpful."

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years to forty-eight in the past ten years alone, and life expectancy continues to drop. Studies by the United Nations show that H.I.V. not only is contributing to the famine in southern Africa but may be a cause of it. Seven million farmworkers have died from the disease in Africa since 1985; sixteen million more are likely to die by 2020 if prevention programs aren't improved. Agricultural productivity has plummeted, even as the nutritional needs of the sick have become greater than ever. To date, sixty-five million people around the world have become infected with H.I.V., most of them in Africa. Twenty-five million have died. In the next twenty years—as the epidemic moves swiftly through India, Russia, and China—the number could more than double. There are no scenarios for any kind of war which project the type of complete destruction, the numbers of dead, or the social collapse that can already be attributed to AIDS. The disease represents the worst disaster that we can reasonably expect to befall humanity in our lifetime.

That is why Hala and the other women of Pumwani are essential. "You do the research where the problem is," Kevin De Cock, the chief representative in Kenya for the Centers for Disease Control, told me. "Africa needs the answer, the world needs the answer. But you are not going to solve the AIDS crisis in a convent in Montana." To gauge the effectiveness of an AIDS vaccine, scientists will need to compare thousands of people who receive it with thousands who do not. That will never happen in the United States or Europe—regions where less than one per cent of the population is infected, and where most patients have access to effective treatments. Only extensive human trials among groups with high infection rates will produce a vaccine. In practice, this means that tens of thousands of Africans and Asians from remote villages and overcrowded cities will have to be recruited for tests on a scale never seen before.

The scientific challenges presented by the epidemic have proved to be humbling: in laboratories across the world, researchers have thrown everything they have at H.I.V., but nearly every time they manage to move one step forward, the virus seems to move two. As great as the scientific and logistical hurdles are, however, the ethical problems associated with long-term vaccine trials in the developing world—funded by Western donors and designed, largely, by Western scientists—may be tougher still. In 1796, after Edward Jenner noticed that dairymaids seemed immune to smallpox, he simply inoculated a healthy young boy with cowpox, and then, a few weeks later, exposed him to the human disease, at great risk to the child. No scientist could do such a thing today. There are rules that prohibit researchers from gambling with the lives of their subjects: they have to minimize the risks, obtain consent, and provide the volunteers with "appropriate treatment." But what, exactly, constitutes appropriate treatment? In America or Europe, such a trial would have to include the requirement that every infected participant receive the best care available today—a lifetime commitment to expensive antiretroviral medicine. Should such a promise be made to Africans? Is appropriate treatment for a community in northern Uganda the same as it would be in Manhattan?

The issue of whether Western ethics and the rules of medical care which accompany them should prevail in Africa has for many people become the central debate of the AIDS epidemic. Several prominent American physicians, led by Marcia Angell, who teaches at Harvard and is a former editor of the *New England Journal of Medicine*, have argued that medical ethics has no borders: what is morally right in America is morally right in Africa, too. They believe that international rules of medical experimentation require that volunteers in such trials receive the best treatment available, not simply the level of care typical of an impoverished community.

No country in Africa, and few countries elsewhere in the developing world, can afford Western levels of treatment. So the principal question for researchers and public-health officials is both simple and

harsh: Will scientific objectives drive the search for an AIDS vaccine, or will a series of ethical imperatives imposed by the West take precedence? Because that question has gone unanswered, fear of exploitation and abuse hangs over the trials, threatening not only to impede their progress but to prevent them altogether.

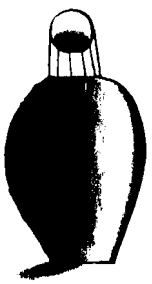
Issues of equity in clinical research preoccupy Western ethicists and public-health officials. Will people used as subjects benefit from the research? (Africans served as essential participants in trials for the principal vaccine now used against hepatitis B; yet when the vaccine finally arrived they could not afford it.) Should volunteers get better medical care than other people in their villages? Should they get better treatment than other members of their own families? Are we exploiting research subjects if we don't promise special treatment? Are we bribing them if we do?

"I am very worried about these trials," Peter Lurie, the deputy director of Public Citizen's Health Research Group, told me when we met one rainy day in the organization's offices, just off Dupont Circle, in Washington, D.C. Lurie and his colleague Sidney Wolfe have long been concerned about what they regard as the cavalier attitude of American researchers toward Third World subjects. "Instead of seeing themselves as activists for better care in Africa, scientists will use the poor quality of care to justify what they want to do anyway," Lurie said. "But you are not permitted simply to use subjects in order to collect data because it is useful to you. That is exploitation and abuse. That is what Tuskegee was." In the Tuskegee experiment, which ran from 1932 until 1972, researchers allowed poor black men with syphilis to go untreated, in order to study the long-term effects of the disease; it remains America's signature instance of research undisciplined by ethical oversight. Lurie fears that, in the name of science, doctors could again withhold treatments that they know will work. "If we aren't careful," Lurie said, "we could be in for the greatest injustice in the history of medicine."

The Windsor hotel, just a few miles from the center of Entebbe, has a commanding view of Lake Victoria. It sits at the end of a rutted dirt road crowded with men selling tomatoes and fresh Nile perch, not far from the Uganda Virus Research Institute. U.V.R.I. scientists have led investigations into many of the continent's infectious scourges, including polio, measles, yellow fever, and West Nile fever (which was initially isolated and identified in 1937 from the blood of a febrile Ugandan woman). Uganda was the first country to be visibly decimated by the AIDS epidemic, and, since the mid-eighties, the institute's researchers have worked almost exclusively on H.I.V.

Nearly every significant global health organization—among them, the United States' Centers for Disease Control and Britain's Medical Research Council—has been allotted workspace at the institute. Its extensive studies—from natural history to molecular biology—have turned Uganda into one of the world's most informative scientific field projects. Among those groups, though, none play a more significant role than the International AIDS Vaccine Initiative.

I went to the Windsor late one afternoon at the urging of Pontiano Kaleebu, a virologist who is the Vaccine Initiative's principal investigator in Uganda. The group's community advisory board was planning its first serious discussion of the Phase III trials that the I.A.V.I. hopes to conduct in Uganda. Once vaccines have shown promise in the laboratory and in animals, they are generally tested on humans in three stages. In the first phase, a few people are given the vaccine, simply to insure that it causes no serious side effects. Next, scientists try to find out whether the vaccine can stimulate people's immune systems. The final phase, and the one that matters most, requires thousands of volunteers (and several years) in order to provide reliable statistical evidence of whether a vaccine actually prevents disease. The vaccine for which Kaleebu was trying to recruit volunteers had been developed by Andrew McMichael, Tomâs Hanke, and their collaborators at Oxford, based in part on immunological information gleaned from the blood cells of the Nairobi prostitutes. It is one of dozens of vaccines currently under development (and among several that the I.A.V.I. is supporting), but it has shown particular promise. The plan is to expand that trial to include thousands of people in at least three African countries. But first Kaleebu and his colleagues would have to convince a group of Ugandan civic leaders—educators, newspaper editors, and clergy among them—that the people of their country should once again subject themselves to the inconvenience and uncertainty involved in testing a vaccine.



It was the beginning of the monsoon season, and the intense daily rain had just ended as the members of the advisory board arrived at the hotel. The scent of jasmine filled the air, and a family of monkeys played on the lawns. It is never easy to persuade people to submit to medical experiments, even in a country like Uganda—which is both enlightened about AIDS and has nearly been destroyed by it. People are instinctively wary of offering their bodies for research. Meetings like this, where risks and benefits are explained, are essential if any drug or vaccine is to succeed.

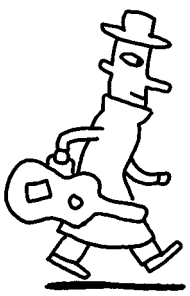
Kaleebu had confided to me that he was nervous about the meeting, because without the support of community leaders a vaccine trial could never be completed. "We have asked the people of this country to be guinea pigs before, and they have responded admirably," he told me. "But we have not been able to come back and say, 'Here is your reward.' I worry about how many times we can ask for the sacrifice. But, of course, I worry far more about what we would do if people gave up and said, 'No, go away.' "

The group gathered in a large, muggy conference room on the second floor. Fred Nakwagala, a young medical officer for the I.A.V.I. program, explained how the vaccine works. He is a thin, unprepossessing man, and at first he spoke too softly to be heard. "We need to create a world without AIDS," he said. "In order to do that, we need a safe, effective, and affordable vaccine. This is up to you. No one else can do it." Sweat poured from his brow as he began explaining, in the simplest possible terms, that a vaccine is a scientific product that prepares your body to fight infection.

Father Christopher Kiwanuka, the leader of an Entebbe Catholic parish, asked if a vaccine was really the only thing that could eliminate the threat of

H.I.V. "There are drugs now," he said. "They are getting cheaper. Won't they eventually be here, too?"

Antiretroviral therapies, which stop H.I.V. from replicating, are already available to Ugandans rich enough to pay for them. When the drugs are purchased by agencies like Doctors Without Borders, they cost no more than three hundred dollars a year, less than a dollar per day. That doesn't seem like much, but, as it happens, it is Uganda's annual per-capita income. The government spends an average of about six dollars a year on health care for each of its citizens; a dollar a day might as well be a thousand. Nakwagala explained that, even with falling prices, antiretroviral therapies will never resolve Uganda's AIDS crisis. "Neither will prevention," he continued. "Prevention has had limited success. Education and condoms work only up to a point. We have one million people in our country currently infected. Half a million are dead. I wish I could offer you different news, but we have run out of things we can try."



Silence filled the room. The people on the advisory board were polite, informed, and supportive. But they were also unhappy with the lack of medical progress. AIDS is the first disease of globalization. No other infectious epidemic has attacked both the richest and the poorest parts of the world at the same time. These people read newspapers and watch television; many of them travel. They know what the citizens of their country are missing. Uganda has often been presented as a model to the world because it has "turned around its epidemic." But one reason death rates have fallen is that so many people have already died. And, with a million residents infected, the risk to the population remains grave.

One member of the board asked whether the vaccine could cause the disease, since many vaccines are made from weakened versions of the virus they are designed to provide immunity against. "Just as a tomato cannot cause AIDS," Nakwagala told the group, "this vaccine cannot cause AIDS." The analogy produced puzzled looks around the room. "This vaccine also cannot cure AIDS—we won't be able to tell for years if it works."

"But why us?" a prominent journalist asked. "It seems it's always us. For how many years does Uganda have to be the test case?" There were murmurs of agreement.

It is an awkward fact that the very countries where vaccine trials must take place are usually the poorest, and the most politically unstable. Before researchers can invest hundreds of millions of dollars in a scientific study, they need some assurance that the government will allow it to run for years. In Africa, that is asking a lot. Earlier that day, Kaleebu told me that he had made plans to attend an AIDS conference in the Ivory Coast later that week. But, he said, as if he were passing along an unpleasant weather report, "I had to cancel because of the coup."

Nakwagala spoke frankly to the advisory board: "There are no answers right now. Only questions. There will be none tomorrow, either. But if we ever want anything to change we have to do this." After an hour, tea was served, everyone agreed that there was no real choice except to go forward, and the meeting came to an uneasy end.

The campus of the Uganda Virus Research Institute is spread across a few dozen acres, and most of the offices are housed in airy little bungalows that face Lake Victoria. After the meeting, I followed Kaleebu back to his office there. Kaleebu is an urbane and reflective man with a sad smile; a thin oval of hair surrounds his mouth. He was brought up in Kampala and finished his medical studies at Makerere University, in 1986. He then moved to London, where he earned a Ph.D. Since returning to Uganda, he has been in charge of the U.V.R.I.'s immunology division. "I am worried that the question of how to do the trials, and whether they can be done fairly and ethically, will overshadow the science itself," he said, in a soft British accent. "There is an endless amount of talk—in the West, not here—about what kind of treatment all the volunteers should receive and whether it's fair to use them. I know people in America think this discussion is for our benefit, but they are wrong. I am Ugandan and, believe me, I have no stake in taking advantage of anyone in this country for my research. We will give people the best care they can get, the best care we can afford. That is fair. If we could distribute antiretroviral drugs, I would be thrilled. But I don't see how, and I don't see when. And the debate is a bit patronizing. We are not blind here. This is not an issue of individual rights—as American ethicists would like it to be. It is the opposite: a public-health emergency."

Kaleebu is married and has four young children. He lives near the institute so that he can walk to work. He stays at the lab until dinner, spends an hour with his family, and then returns until ten. "That's my life," he said with a shrug. "And it will be my life as long as AIDS is with us."

Earlier in the day, I had seen a heavy-set man leaving his office in tears. Kaleebu has a gentle demeanor. He did not appear to be the type to make a man cry. "What happened?" I asked.

"That was a man I have known for many years," he told me. "He came here today and showed me the drugs he was prescribed and the amount he had to pay for them. I didn't know he had AIDS. He can't afford the drugs, and he asked if there were cheaper alternatives. I told him there were not." The sun was setting on the lake, and Kaleebu's eyes glistened in the fading light. "This is a person from my life. I was surprised to see him sick, and I look at him and it's frustrating, because what is his future? He will die without drugs, and I can do nothing for him. I had to let him leave my office with no hope. I am a doctor, and it is humiliating to tell people we can't do well enough for you."

He sighed and waved sadly at the darkening lake behind him. "There was AIDS here before my wife and I had children. I see my daughters and sons growing up, and not long ago I realized—really, I guess, admitted to myself—that they are going to have the same problem. I never thought that would be true. AIDS will be in all their futures. I have come to realize that now. And it frightens me."

The International AIDS Vaccine Initiative has its main offices in Manhattan, high above the financial district. With money from a coalition of public and private donors—not least the Bill & Melinda Gates Foundation, which has made the discovery and distribution of

an AIDS vaccine its most significant project—the initiative acts both as a medical gateway and as a sort of philanthropic venture-capital firm dedicated to funding the effort to find a vaccine.

I went there one morning to talk with Seth Berkley, the man who runs the initiative. Berkley is a rangy forty-six-year-old physician who was trained at Brown and at Harvard, and worked as an epidemiologist in Brazil and Uganda during the nineteen-eighties. He was in Africa just at the time that the full horror of AIDS became clear. When I saw Berkley, he was walking with a severe limp, the result of an accident last year in the Fish River Canyon, in southern Namibia. Since he was the only doctor on the trip, he was forced to set his own badly fractured leg and then wait for a day until a helicopter could lift him out of the gorge.

I asked Berkley whether he thought the search for a vaccine was at last fully under way. His office has a spectacular view of the city, and its one free wall is covered with a giant map of the world. "You have to ask yourself what on earth the people on this planet are doing," he replied, in a typical burst of unhinged honesty. He limped over to the map. "If you stand back and think about what the world will look like a hundred years from now, and you look at even the most conservative numbers, you will see that in the end only a vaccine will matter. Nothing else. The projections are that bad—in Africa, India, China, Russia—yet the world has just not gotten serious enough. Even now, we are still fooling around on the edges."

Berkley is often criticized for his single-minded pursuit of this goal. But his assertions are hard to dismiss; in 2001, less than two per cent of the twenty billion dollars spent on AIDS prevention, treatment, and research across the world was devoted to the search for a vaccine. After millions of deaths, only a single vaccine has made it into the late stages of human trials.

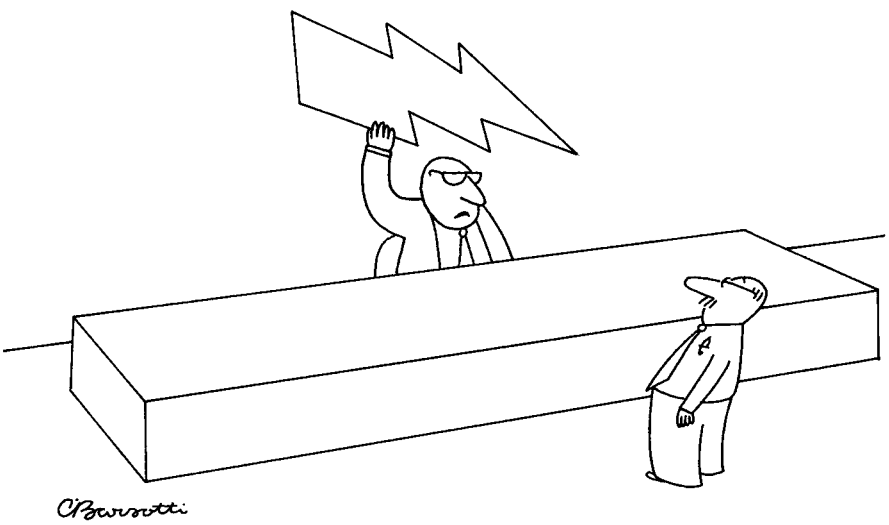
The International AIDS Vaccine Initiative exists for a strange reason: an AIDS vaccine may be a global necessity, but it is really in no single country's or company's interest to spend the sort of money that would be necessary to find one. Most pharmaceutical firms view any such vaccine as a liability nightmare; and the demand would be greatest among the populations that are least able to pay. Making drugs, by contrast, involves a much greater financial incentive and much lower risk. "We have left vaccine development to the commercial sector as if there were an incentive for companies in the marketplace to make a product," Larry Corey, the head of the H.I.V. Vaccine Trials Network and a professor of medicine at the University of Washington, told me. "But there is no incentive. And what is society's response? Well, society can't get it together. Remember, these trials can cost hundreds of millions of dollars. Do we use public-private partnerships? Does the government fund it all? We are just asking all these questions today. Twenty years after the epidemic began."

Much has been written about whether governments have spent enough money developing an AIDS vaccine—whether there should have been a sort of viral Manhattan Project—and whether existing resources have been used wisely. It is a difficult matter to resolve. There is no question that more money, particularly in the early years, would have helped push research forward. But scientific discovery isn't linear; it moves in unpredictable patterns. Billions of dollars have been spent on the war on cancer in the past thirty years, and, many would argue, to little avail.

One reason progress toward an AIDS vaccine has been limited is that we live in a time of scientific transition; our growing knowledge of molecular genetics has put biologists in a scientific netherworld. In the past, vaccine programs were run by empiricists, who relied on scientific intuition and common sense. Often, they tried compounds without knowing in detail how they worked; like Jenner's smallpox vaccine, either the shots prevented an infection or they didn't. We still do not fully understand, for example, why the pertussis vaccine offers protection. But biology is now driven by genomics, not by trial and error. Researchers seek, above all, to understand the functions of the specific proteins and genes that form a sophisticated and mutable virus like H.I.V., and then to concoct clever ways of preventing those genes from doing their job.

"We all want to move in medicine from empiricism, where we have been, to design," says Richard Klausner, who is a former director of the National Cancer Institute and is now at the Gates Foundation, which has increasingly become a sort of shadow National Institutes of Health. "Design makes sense. It would be more effective, less toxic, more efficient. There is no question it's a better alternative. It turns out, however, that we are not quite ready for it. Our desire is far beyond our ability to apply the knowledge we have. It all sounds great, but we don't have a model for this disease. We don't even know what it takes to create a successful AIDS vaccine."

From the start of the epidemic, researchers, instead of trying every vaccine that might conceivably work, turned the principal responsibility over to molecular biologists—who sought to reduce the AIDS virus to its smallest genetic



"The board of directors has given me new powers."

components. "It cost us at least a decade," Berkley told me. Then, as more people in the United States and Europe became ill, advocacy groups began to clamor for governments to emphasize treatment, and they were successful. The vaccine effort suffered considerably.

Since 1984, when H.I.V. was first identified as the cause of AIDS, there have been occasional pronouncements that a vaccine would soon become available. The first, and most ridiculed, of these claims was made by Margaret M. Heckler, who was then the Secretary of Health and Human Services. During a press conference at which she announced the discovery of the virus, she confidently predicted that there would be an effective vaccine within two years. In May, 1997, after thirteen years and thousands of disappointing experiments, President Bill Clinton, in a conscious echo of John F. Kennedy's electrifying 1962 promise to put a man on the moon, set a new national goal for science. In a speech delivered at Morgan State University, Clinton said, "Today let us commit ourselves to developing an AIDS vaccine within the next decade."

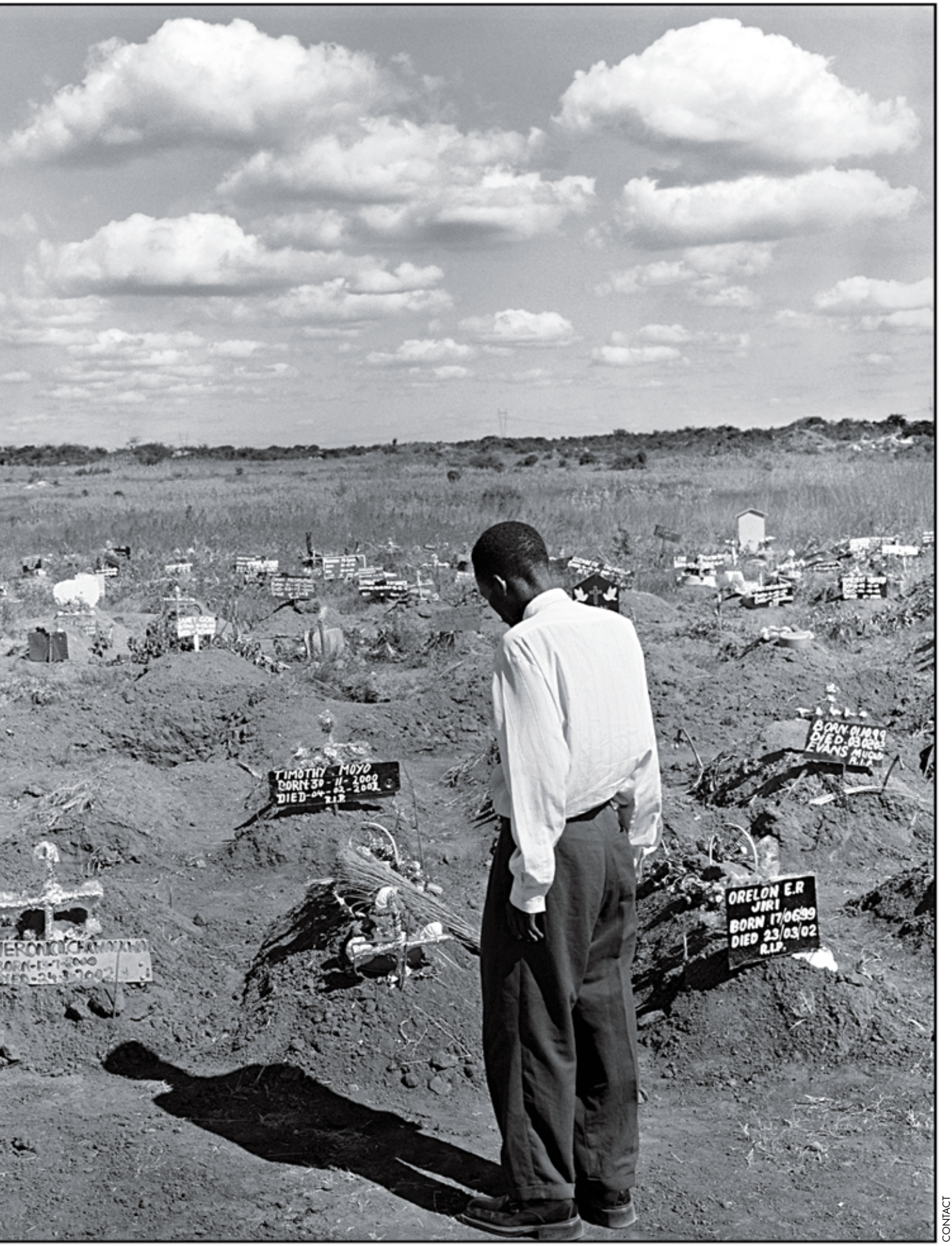
It is already clear that his goal will not be met. The vaccine that is furthest along is made by a company called VaxGen, based in California. VaxGen recently completed a study that enrolled nearly eight thousand people, including twenty-five hundred intravenous drug users in Thailand. The company's scientists are currently analyzing the data. The vaccine is a genetically souped-up version of a single protein from the outer shell of the AIDS virus. Unfortunately, the shell changes so rapidly that such approaches have failed several challenges in the past; most scientists are skeptical that this vaccine will prove capable of protecting many people for very long. Don Francis, the president of the company—and among the first to warn the world about the epidemic—has said that he would be pleased if the vaccine worked a third of the time. By contrast, vaccines for measles, yellow fever, and pertussis have success rates that are greater than ninety per cent.

"Please don't say that I am pessimistic, because I am not," Anthony Fauci told me when I went to visit him at the N.I.H., where, as the director of the National Institute of Allergy and Infectious Diseases, he is responsible for funding much of the AIDS research in the United States. "A fully effective vaccine against H.I.V. is by no means impossible. It will eventually happen. But there are many problems we need to solve in order to produce one. The best ways to vaccinate don't work with H.I.V. We need to come up with something new."

Late last year, I went to Oxford to visit Andrew McMichael. McMichael is chief of the human-immunology group at the Weatherall Institute of Molecular Medicine, part of Oxford University, where he is also a professor of medicine. Most scientists who study vaccines concentrate on the function of antibodies; McMichael was among the first to focus on a different phenomenon—T-cell immunity. He started with the flu virus and moved into H.I.V. research in the mid-eighties. His laboratory has designed one of the most promising AIDS vaccines currently being tested. McMichael is a shy, donnish man. He is pale and partly bald, with soft brown hair. He tends to mumble, and, as an experienced, cautious researcher, he abhors hype. He rarely discusses his vaccine work without mentioning that it might all come to nothing.

McMichael and the infectious-disease expert Sarah Rowland-Jones work with about a dozen others in a boxy glass building hidden behind the maternity ward of Oxford's John Radcliffe Hospital. The research facility is laid out in identical grids on four floors. The most expensive and cumbersome equipment sits in the center of each floor, and the researchers work around it. The labs, which are only a few years old, are filled with machines for sequencing DNA and with centrifuges for analyzing blood that researchers collect from volunteers nearly every day. The place is crowded with young graduate students, and space is so scarce that some of them are forced to work in the halls. Oxford is not known for its cheery weather, but the day I was there blinding sunlight bounced off the highly polished chrome hoods and glove

An H.I.V.-positive man at the grave of his son, who died of AIDS. The epidemic has claimed some twenty million African lives. Photograph by Kristen Ashburn.



boxes that lined the walls of the lab.

In the mid-nineteen-nineties, McMichael and Rowland-Jones began to look closely at the Nairobi prostitutes, in an attempt to see why they remain uninfected. It turned out that most of the women possessed high levels of a type of white blood cell designed specifically to kill H.I.V.-infected cells. So, with financial support from the International AIDS Vaccine Initiative, they decided to make a vaccine that would trigger the same kind of response they had seen in the prostitutes.

Most vaccines train the immune system to defend itself by using a harmless piece of virus—or a clever imitation—to trick the body into thinking it has been infected. Our white blood cells create a range of weapons, but the immune system relies most heavily on two of them. The first, proteins known as antibodies, rush to attack viruses as they circulate in the bloodstream. The other kind of response involves cytotoxic T lymphocytes, better known as killer T cells, which detect infected cells and destroy them.

Vaccines are made in a couple of basic ways. Those created by killing the disease-causing germ are usually able to train blood cells to secrete the specific antibodies needed to recognize and overcome infection. Most of these vaccines produce only a weak response, however, which means they have to be given more than once. Live, attenuated vaccines are often more effective; they are composed of a virus that has been weakened or altered in order to reduce its ability to cause disease. After exposure to such a vaccine, lymphocytes called memory cells learn to fight the infection, and they normally stay in a person's immune system for the rest of his or her life. If the infection returns, the cells recognize it and can rapidly swarm the bloodstream to defeat the invader. You never even know you were exposed.

By contrast, scientists have discovered no way to eliminate H.I.V. once it infects a cell. Killed-virus vaccines haven't worked, and researchers are afraid of infecting a healthy person with any live form of the virus, even one that seems to have been disabled. The virus mutates so rapidly, unpredictably, and lethally that such an approach would be too dangerous. Infections like influenza and polio can often be eliminated even without the help of medicine. But once H.I.V. insinuates itself into the machinery of a cell, it is there until that cell is dead. It would, in fact, be difficult to design a more successful or insidious pathogen. Unlike the other viruses that commonly afflict humans, H.I.V. is a retrovirus: it doesn't simply attack our cells; it takes control of them by incorporating its genetic material into their DNA. The virus then becomes a permanent part of every infected cell, and, whenever those cells divide, H.I.V. goes with them.

"When we looked at the Nairobi women who were coming into the cohort, virtually none of them had H.I.V.-specific T-cell immunity that we could detect," Rowland-Jones said. She explained that in a laboratory dish it was easy to infect their cells—but it wasn't in life. "If you look at the women after a couple of years, about twenty-five per cent show an increase in the number of T cells that can specifically fight off H.I.V. After three or four years, by which time they have met our definition of resistance, it was more than fifty per cent."

Armed with these findings, Rowland-Jones, McMichael, and their colleagues took an entirely new approach to designing a vaccine. They noticed that the Pumwani women's killer T cells were able to zero in on fragments of two particular proteins, which are produced by the H.I.V. virus and which then move to the surface of the infected cells. The Oxford team identified the DNA sequence that makes these proteins, and, on the assumption that they were particularly likely to attract killer T cells, used it to create a vaccine.

There are several subtypes of H.I.V., so a vaccine that proved effective in Thailand, say, might fail to protect Africans. What works in Kenya might not work in France. Different strains of the virus can even appear within the same city (and, at times, within the same person). The vaccine designed by McMichael, Hanke, and their colleagues is the first to address the specific viral subtype that is most prevalent in East Africa.

The vaccine has two components. The first is simply the naked DNA—an artificial copy of the relevant genes. The other component, used to further boost the immune response, is called M.V.A., or modified vaccine Ankara. It is a benign virus into which the researchers have inserted a copy of the same DNA sequence. Early evidence sug-

"If I had it to do all over again, I wouldn't change much—maybe part my hair on the other side."

gests that, together, the DNA and the M.V.A. stimulate a bigger immune response than either would alone. "Whether that will be enough to stop the virus most or much of the time, and for how long, we just don't know," McMichael told me. "But we are encouraged. We are cautiously encouraged."

It is impossible to test these agents fully in animals or in the lab. What seems to succeed in mice often fails in macaques. Vaccines that work in some primates don't necessarily work in others. In the end, although animal experiments are essential, we cannot know whether a vaccine will protect us unless we try it on human subjects.

McMichael's vaccine—and those like it currently under development by researchers at Harvard and at Merck—is not ideal. The body builds permanent immunity to many infections—mumps, for instance, or measles. But when the Nairobi prostitutes stopped having sex with H.I.V.-positive people, their immune systems often lost the power to protect them. When they came back to the job, they were vulnerable to infection. "It means you need a constant level of exposure to the virus to stimulate T cells," Rowland-Jones explained. "And, of course, that might mean you need frequent booster shots." If so, it would defeat one of the main advantages of vaccines, which is that they can be delivered cheaply and don't require a high degree of compliance.

The likelihood of a partially effective vaccine—most researchers think the first vaccine on the market will be no more than forty or fifty per cent effective—is a troubling prospect. If used properly in high-risk groups, such a vaccine could slow the epidemic and save many lives. But people generally associate the word "vaccine" with the idea of total prevention. Once they get those shots, people may feel free to engage in the type of behavior that causes AIDS to spread. In fact, several studies have suggested that a partially effective AIDS vaccine, if its recipients became less vigilant about taking other precautions, could actually cause as much harm as it prevents.

This is one reason that researchers are so anxious about the results of the VaxGen trial. The company has said that it will distribute the vaccine only if it is effective at least thirty per cent of the time. What if the figure is thirty-two per cent? Even putting aside the epidemiological complications, its existence would mean that no future vaccine could be tested against a placebo: it would be unethical to do so, according to standard experimental guidelines, unless you have nothing better to offer. Yet the logistical and financial challenges of trying to get the VaxGen vaccine to every control group in every trial would be enormous. In addition, many researchers—including David Baltimore, a Nobel Prize winner, and Sarah Rowland-Jones—have wondered publicly how many times you can go back to the same communities and ask for their help. If the vaccine doesn't protect enough people, you will simply lose their support when a better candidate comes along.

"Let's be realistic for five minutes," Larry Corey, who is responsible for organizing the N.I.H.-supported network of vaccine trials, told me. "To create a vaccine that works maybe forty per cent of the time, that costs a thousand dollars, and that has side effects such that you have to go to a lab and get a blood test every six weeks"—which is the case with drug regimens—"is crap. What we need is a ninety-per-cent biologically active product that has no side effects, and that, at the most, costs around a hundred and fifty to two hundred dollars."

Almost no one who does AIDS research thinks that a genuine cure will be discovered soon. "I would have to say the virus is winning, not us," Anthony Fauci told me. Fauci is among the most forthcoming members of the American AIDS establishment. When I asked him whether we will have anything significant ten years from now, he winced. "My God, I hope so," he said. "I really do."

"Before you sentence me, I'd like to remind the court that I was just passing through the building looking for a bathroom."

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Bouncing along on one of Uganda's few good roads, you can easily spend three hours on the ninety-five-mile journey from Kampala to the Masaka district. The drive takes you straight across the equator, around the western edge of Lake Victoria, and toward the border with Tanzania. I went there early one morning with Anatoli Kamali, who works as an epidemiologist for the region's Medical Research Council, which is funded by the British government. The road passes through some of the world's lushest land; Churchill called Uganda the "pearl of Africa," and it is easy to see why. Not long after leaving behind the snarled traffic of the city, one is all but engulfed by a tangled cor-

"Would you take the guy at Table 4? I used to be his broker."

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ridor of vegetation. Equatorial butterflies hover at the edge of the roadway. Ebony, mahogany, teak, and fig trees fill the forest, which has more shades of green than I ever knew existed.

Nearly a million people live in Masaka—most of them scattered in small communities. The Medical Research Council has been following the lives and health of several thousand adults in twenty-five villages there since 1988. By now, the council has accumulated enough statistical documentation to fill warehouses on more than one continent: data on the rates of every possible sexually transmitted disease; how often condoms are used and under what circumstances; who is most likely to seek counselling; who wants to be tested for H.I.V.; and who comes back to get the results. Blood and DNA samples have been collected, stored, and analyzed by the truckload. This attention has made the people of Masaka unusual; the community is relatively well informed about what causes AIDS, there are dozens of clinics, and nobody goes hungry. If there is going to be a vaccine trial involving thousands of people and lasting up to a decade, Masaka has to be among the best places on earth to carry it out.

It is in regions like Masaka that the debate about the standard of medical treatment for volunteers turns into a question of how long, and how well, someone will live. At the same time, volunteers face basic uncertainties about whether the AIDS-vaccine trials will benefit them at all. "We are asking the Third World to take risks that we have actually never taken ourselves," Larry Corey told me. "Every other time that we have gone in with a vaccine—whether polio, measles, mumps—we have been able to say, 'It works on our people.' With AIDS, we can't say that. Now I have to build a global H.I.V. network, and I have to go to my colleagues in Botswana, Kenya, or Malawi and say, 'I have no idea if I have schlock or I have gold. But you need it and we need it, so we will have to test it on you.' There are really no other choices."

I never met a health-care professional in Africa who didn't understand this. African doctors live every day with uncertainty and inequity. More clearly than any disease before, AIDS has demonstrated the vast and unbridgeable gulf between the affluent north and the impoverished south. How can one compare the health care available in the United States or Europe with that of the Third World? Curable illnesses like diarrhea still kill more people every year than AIDS does. Even in Uganda, the rate of childhood vaccination—perhaps the best way to judge the over-all health of a nation—has declined recently, from forty-seven per cent in 1995 to thirty-seven per cent last year.

In Masaka, I toured the village of Kalungu with a census-taker named Irene. Her goal was simply to identify all the people who lived in the pale-yellow huts of the village, and then to ask basic questions about their age and marital status. You can't just walk up to a stranger—in Uganda or Utah—pull out a clipboard, and begin to ask about his sexual habits or health history. First, you have to lay the groundwork. So a local leader, somebody the villagers know and respect, always accompanies the census-takers. We were guided by a regal-looking woman named Teddy Nabwami. Dressed in a flowing brown-and-white tribal gown, her hair tied in a tight bundle to protect her head from the punishing sun, Nabwami led us from hovel to hovel, then sat silently on a straw mat while Irene asked questions.

Mostly for my benefit, I suspect, she tried to find out what people knew about H.I.V. The majority said that it would probably kill them. Many knew that it was transmitted sexually, but they didn't have the vaguest notion of how it might be prevented.

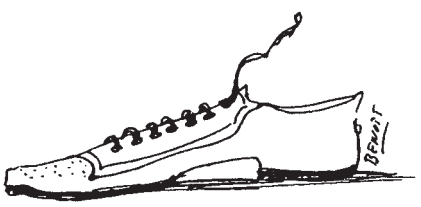
We walked over to the local clinic, where a young medical student was on duty. I asked whether he thought it would be fair for the people in this village to enter a trial for a new AIDS vaccine if those who became infected did not receive antiretroviral drugs. He snorted and made a dismissive wave at the shelves

on the wall. There were about two dozen neatly lettered red labels for a variety of pharmaceuticals. Half the labels—including those for aspirin and Paracetamol—had empty spaces above them. The selection was spotty; there was Fansidar (a highly effective malaria drug), but no ordinary, inexpensive antibiotic. Eight women sat on a bench in the waiting room; they all had children with them. A couple of the babies were crying, but most just stared blankly into space. "We are not getting the care you get," the medical student told me without a shred of bitterness in his voice. "We never will. But I would line up tomorrow to test anything that might help us in any way. And I am sure the rest of the village would, too."

Anyone who offers himself as a test subject for a vaccine that could end a plague surely deserves the best possible medical care. Perhaps that care should be better than the care that other people would receive in the same community; or perhaps entire villages should be entitled to the first access to new treatments. But medicine in Uganda will never be as good as it is at the Mayo Clinic, or even at a typical hospital in Moscow. Most people in Africa can't even afford to take a bus to get care at a free clinic. "Where does it start, and where does it end?" Seth Berkley asked me when we spoke one day. "Is it the best treatment for people in the trial? Is there an obligation to pay for current therapies? What about better therapies in the future? Are we supposed to pay for the state of the art for eternity? Nobody could afford it." There is a malady called Chagas' disease, or American trypanosomiasis. It can destroy the esophagus, the bowel, and the heart. End-stage Chagas' disease often results in heart failure. The only treatment is a heart transplant. Does this mean that in order to try to cure this disease in places like Mexico and Brazil, where it is endemic, everyone should receive a transplant? "We have always had this idea, which is simplistic, that justice requires treating everyone, everywhere exactly the same way," Ezekiel Emanuel, who is the chief of the bioethics branch at the N.I.H., told me. "Justice requires no such thing. Justice simply requires us to treat people fairly." If the rules of clinical trials required participants to receive the best care on earth, there would be no clinical trials.

Some activists in the West talk as if this were a price worth paying to avoid the risk of exploitation. In a speech that Marcia Angell gave at Princeton, she said, "People are not guinea pigs. Research must hold human welfare above the interest of society and science. If you breach this principle, you're on a slippery slope where first humans are exploited for worthwhile purposes, then for not so worthwhile purposes." This position suggests that one cannot hold the interests of society above the interests of an individual, that individual well-being is paramount. Yet in countries that have been devastated by AIDS, balancing the needs of society against those of the individual has never seemed more essential.

Five years ago, Angell led a highly public attack on Western scientists who were conducting trials in Africa, attempting to find a cheap, effective way to prevent a mother from passing the AIDS virus to her child at birth. The research was based on one of the more exciting discoveries of the past decade: that women who took the drug AZT during pregnancy could cut the risk of transmission by as much as two-thirds. But the drug regimen was too expensive and complicated for the women who needed it most, and public-health officials began looking for cheaper alternatives. They decided to follow more than fourteen thousand women in Thailand and Africa and gave AZT to a third of them in various doses. The rest received placebos. At the time, Angell wrote that allowing the women to go without AZT—when doctors knew it worked and Western women would have received it—was "a retreat from ethical principles," and she invoked that most incendiary of comparisons the Tuskegee experiment. Peter Lurie, who is South African and is no stranger to the clinics of the Third World, said that the tests proved there was a two-tiered standard for health care in the world—one set of rules for rich people and another for those who are poor. The recriminations were harsh, and their effects have lingered.



African scientists saw it differently, however. "The women were not going to get any treatment anyway," Pontiano Kaleebu told me. "Instead, thousands received AZT, and that saved their babies. And we found out that it works in much smaller doses—and it has been one of the great discoveries for us in the entire epidemic. If Marcia Angell had her way, though, we still wouldn't know what works, because we would never have been able to do the studies."

The day I left Uganda, I went to see Edward Mbidde, who is the director of the Uganda Cancer Institute and among Africa's most internationally prominent vaccine advocates. Mbidde is a powerfully built, imposing man. He wore a dark-green dashiki, and speaks in the rich, deliberate tones of the English-educated African élite. His office is at the Old Mulago Hospital, which for years was at the center of the AIDS epidemic, and it sits on a hill overlooking the streets of Kampala. Despite ample reason for despair, Mbidde has always remained determined and optimistic.

"In many ways, these last fifteen years have been the best Uganda has ever seen," he told me. I must have gasped, because he laughed, and then said, "What I mean by that is simple enough. We have leadership, we have support, and we are united. Who else in Africa can say that? Can you imagine what would have happened to Uganda if AIDS had come along during the time of Idi Amin?" Mbidde travels widely, and he long ago decided that without an AIDS vaccine Africa is in peril, and that the only way to find one that works is to experiment on people—his people.

"If you are living in New York or Florida, you can sit on the beach or work in a skyscraper. You have a different view of what the world is like than we do," he said. "Perhaps it is a better world. Yet if we need to go to work, and we cannot afford a Mercedes-Benz, should we refuse to ride on a motorcycle? Or should we get there by the best route we have? You do what you can in this life, and in Kampala we cannot do everything. Principles matter as much to us as they do to Americans. But we have been dying for a long time, and you cannot respond to death with principles." ♦