MEDICAL DISPATCH

UNINFECTABLE

To learn how to immunize people against AIDS, it may help to know why some people are already immune. And that's Janis Giorgi's grail.

BY JON COHEN

In his younger, wilder years, Glen Redman estimates, he had between two thousand and three thousand sexual partners. With Jeff, one of his longtime lovers, he had what AIDS researchers antiseptically refer to as "unprotected receptive anal intercourse." After the relationship ended, Redman learned that Jeff had tested positive for H.I.V. and had probably contracted the virus while they were together. By the time of Jeff's death, from AIDS, in 1986, Redman had a new partner. A tattoo on Redman's right arm displays what amounts to a tombstone for that man. It says simply "Max"—in lettering that Redman describes as a blend of "Old English and East L.A."—framed by the years "1940" and "1991." Max, too, died from AIDS.

As Redman sits in the antique-decorated living room of his plaster-walled Spanish home in the old Los Angeles neighborhood of Eagle Rock, he recounts how he used to spend his evenings at sex clubs like Basic Plumbing or at bathhouses like HealthWorks. On bargain night at the Corral Club, a bathhouse near Studio City, he and another man often put on a show for the crowd. "Everybody would stand around and watch and appreciate," recalls Redman, who has adorned his torso with a dozen tattoos. "And afterward, you know, we'd split up and go do our business and hook up again later on. It was a whole different time."

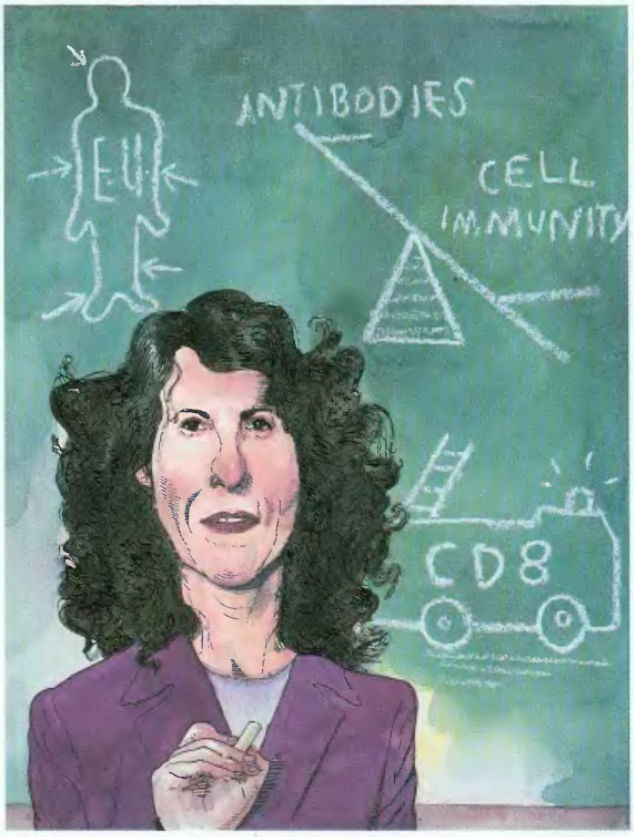
Then the AIDS epidemic began to close in, killing acquaintances, friends, and eventually lovers. Redman's blue eyes grow wide when he talks about this. "I was absolutely floored when they told me I was negative," says Redman, who is fifty-two, gym-solid, tanned, and the picture of health. "I was unbelieving then and I still am amazed."

Janis Giorgi, an AIDS immunologist at the University of California at Los Angeles, has never met Glen Redman, but she knows him intimately, as No. 41001. In 1984 and 1985, Giorgi and her U.C.L.A. colleagues began taking blood samples from No. 41001 (the number insures confidentiality) and sixteen hundred and thirty-six other homosexual and bisexual men every six months, charting the spread of H.I.V. and AIDS through this population and preserving the life stories of their immune systems in test tubes. Over the years that followed, the Los Angeles Men's Study, a branch of a large "multicenter AIDS cohort study," found that H.I.V. behaved differently in different people. The virus usually killed a person in about twelve years, but some people died within a few years of becoming infected, and others lived with H.I.V. for well over a decade with no obvious damage done. Still others, despite having practiced "high risk" sex, never lit up the antibody test that can detect an infection within weeks of transmission. Redman is one of those men, and Giorgi is now conducting a new, intensive study of the immune systems of No. 41001 and thirty-one other E.U.s—shorthand for "exposed uninfecteds."

E.U.s have now been found among heterosexual spouses, hemophiliacs, injection-drug users, and health-care workers, and among prostitutes in Kenya, Gambia, and Congo. Researchers are investigating two kinds of factors. One is genetic, and several labs revealed last year that some E.U.s carry mutant genes that remove the knobs to the cellular doors through which H.I.V. must pass to establish an infection. But that genetic quirk plays no role in ninety-five per cent of E.U.s, Glen Redman among them. A more likely explanation for most of them—and the one that Giorgi is focussing on—is immunologic. Maybe the route by which the virus first entered their bodies didn't allow H.I.V. to establish an infection but somehow trained

their immune systems to fight it: oral sex, say, might have exposed them to low, "subinfectious" doses of the virus. Maybe the H.I.V. that entered their bodies was in a defective, noninfectious form. Maybe their genes predisposed their immune systems to tilt one way or the other. Maybe it's a combination of route, dose, viral type, and genetics.

Giorgi's specialty is teasing out which specific immune responses succeed and fail against H.I.V. It's a messy business, the occasion for many heated controversies. One camp—largely populated by virologists, who pioneered the field of AIDS research—is convinced that the body's most powerful weapons against H.I.V. are antibodies, Y-shaped proteins that patrol the blood for trespassers and try to prevent them from entering cells. In the last few years, though, a number of leading AIDS researchers have grown disenchanted with the antibody-centered approach. This camp—one led by immunologists—focusses on the role of "cellular immunity." As the name implies, cellular immunity occurs when living cells—not simply lifeless proteins like antibodies—identify and obliterate cells that have already been infected. Janis Giorgi doesn't scant the importance of antibodies, but her work suggests how powerful cellular immunity might prove to be against H.I.V. And it has done so with the help of E.U.s like Glen Redman.



The test subjects were like the milkmaids who didn't get smallpox and so caught the attention of Edward Jenner two centuries ago.

BARRY BLITT

What's at stake, finally, is something that AIDS researchers agree is the only way to end the epidemic—an effective vaccine. Already, data from E.U.s have helped raise doubts about the AIDS vaccine furthest along in human tests, a preparation, made by VaxGen, which was designed to spur the production of antibodies and will shortly be put to a real-world trial in the United States and Thailand. But even if this trial proves disappointing, learning what makes people like Glen Redman immune may teach vaccine researchers how to confer immunity on the rest of us.

JANIS GIORGI doesn't exactly fit the image that people have of a middle-aged woman scientist: white lab coat, sensible shoes, pulled-back hair. She's been known to go two-step dancing in her cowboy boots, and to roar up mountain roads on the back of a Harley. Today, she is dressed in a chic black suit and clogs; waves of curly raven hair spill to her shoulders. She leads me down a hallway of labs to five flow cytometers that her sixteen-person group maintains for the university. For immunologists like Giorgi, the flow cytometer is the most important tool to have been invented since the microscope: the laser inside its cream-colored metal housing can probe a treated blood sample for specific types of immune cells and count their numbers with astonishing accuracy. You feed a sample to the machine by slipping a finger-size test tube filled with cells under a strawlike device that gradually sucks up the liquid and delivers the cells, single file, into the beam of the laser. A large computer monitor next to the machine displays a pattern of dots, which reveals, to the trained eye, the type and quantity of cells in the sample.

Giorgi, who regularly questions the accuracy of her own work, is cautious about moving from such empirical results to conjectural explanations. As she puts it, "I want to avoid being deceived by what I'm trying to find out in the experiments I'm doing." Even as a high-school student, she had a knack for science; she was one of only two girls in her high-school physics class, in Jacksonville Beach, Florida. In 1972, she embarked on what has proved to be her lifelong area of expertise: she began graduate studies in immunology at the University of New Mexico School of Medicine. Ellen Goldberg, an immunologist there at the time, helped recruit Giorgi, and she remembers the moment when the twenty-five-year-old pulled into Albuquerque in a dark-blue 1962 Cadillac Fleetwood loaded with all her possessions, one of which was a four-foot red-tailed boa constrictor coiled in a tall boot. "She's very smart and doesn't show it off," Goldberg, who is now president of the Santa Fe Institute, says. "She absolutely doesn't care whether she receives recognition for what she does."

Giorgi's Ph. D. dissertation focussed on what was then the esoteric question of the relationship between antibodies and cellular immunity and on a curious observation that would lay the foundation for her work with E.U.s. Researchers had just discovered in mouse studies that these two kinds of immunology had a seesaw relation to each other: when an animal had made a lot of antibodies, its cellular response was dampened, and vice versa. Some studies even suggested that if you gave a mouse a very low dose of bacterial components

you could "lock" its immune system into a cellular response without triggering the production of antibodies. As a young scientist, Giorgi worked in the under-explored area of cellular immunity, and acquired a mastery of specialized laboratory techniques like flow cytometry. In 1983, when U.C.L.A.'s nascent AIDS program wanted to set up its own flow-cytometry lab, it hired Giorgi for the job.

IN August of the following year, the thirty-eight-year-old Glen Redman, a clerk typist who had worked his way up into management in the Los Angeles Department of Water and Power, joined the L.A. Men's Study. Redman explained to an interviewer with the study that he often visited sex clubs and that he "swallowed semen like a fish." Redman also reported the unprotected receptive anal intercourse he had regularly had with Jeff, over a period of about eleven years. The U.C.L.A. researchers classified him as being at high risk for the disease.

By then, Jeff had moved back to his home town, in Ohio, but the two men stayed in touch. That fall, Jeff complained to Redman of flu symptoms that would not go away. In March of 1985, a blood test came on the market which could detect H.I.V. antibodies—the first reliable indicator that a person was infected. Although the L.A. Men's Study began checking for H.I.V. antibodies in the blood of all its participants, Redman chose not to learn his status, because he "just assumed" that he, too, had the virus. In February, 1986, Jeff died; not long afterward, Redman's new lover, Max, began having problems with his health. Max, too, was part of the L.A. Men's Study, and as he was going to find out his H.I.V. status he suggested that Redman do the same. Max was H.I.V.-positive. Redman was not, but he dismissed the results. "I just couldn't believe that I wasn't infected," he says.

GIORGI'S investigation of Redman and other E.U.s is part of her attempt over the past fourteen years to determine the specific way that H.I.V., which now infects thirty million people around the world, depletes the immune system and causes disease. Anthony Fauci, an immunologist, who heads the National Institute of Allergy and Infectious Diseases, the single largest funder of AIDS research in the world, says, "She's done very classical, solid immunology over the years," and singles her out for "maintaining the immunologic approach to H.I.V. pathogenesis."

Fauci mentions Giorgi's "immunologic approach" pointedly. Most virologists have maintained that H.I.V. wreaks havoc in a straightforward way: it's an arsonist that burns down firehouses. In this model, H.I.V. infects and then kills the class of immune cells—they're known as "helper T cells," or CD4s—that orchestrate the attack against invaders. The relatively few immunologists who work in AIDS research, like Fauci and Giorgi, tend to think that this direct-killing model is overly simplified.

Back at her meticulously organized office desk, Giorgi offers a vision of an indirect route to AIDS. Without any immune defenses, she estimates, H.I.V. would annihilate the body's helper T cells in about two weeks, and within the next four weeks the person would get sick and die. But, even without any anti-H.I.V. drugs, adults live with the virus for an average of ten years before their immune systems can no longer defend them. Two more years typically pass before these people die. The point is that the immune system is remarkably robust and can replace destroyed cells for years on end, but H.I.V. finally wears people down by keeping their immune systems

THE BLOSSOM

A May morning. Light starting in the sky.
I have come here
after a long night.

The blossom on the apple tree is still in shadow,
its petals half white and filled with water at the core,
in which the secrecy and freshness of dawn are stored
even in the dark.

How much longer will I see girlhood in my daughter?

In other seasons,
I knew every leaf on this tree.
Now I stand here almost without seeing them

and so lost in grief
I hardly notice what is happening
as the light increases
and the blossom speaks

and turns to me with blond hair
and my eyebrows and says—

Imagine if I stayed here
even for the sake of your love.
What would happen to the summer? To the fruit?

Then holds out a dawn-soaked hand to me
whose fingers I counted at birth
years ago

and touches mine for the last time

and falls to earth.

—EAVAN BOLAND

hyperactivated. "They deteriorate," she says. Though she agrees with the virologists that direct killing of helper T cells occurs, she believes that even more of the deterioration can be explained by the way the virus constantly calls into action certain other cells—warrior cousins of helper T cells known as "killer T cells," which are the main players in the cellular immune response. After the virus infects a cell, it hoists what amounts to a pirate flag on the surface. When killer T cells see these flags, they destroy the infected cell.

With help from the flow cytometers, Giorgi's lab has provided compelling evidence for the hypothesis that H.I.V. prematurely ages the immune system. One groundbreaking study specifically revealed that the killer T cells in H.I.V.-infected patients showed signs of deterioration similar to that seen in people who have lived a hundred years or longer. Giorgi has also discovered a protein on the surface of certain T cells which can be used to predict the course of someone's disease, and so help patients make treatment decisions, in the way that measures of "viral load" and helper T cells do now. "Very few other people have studied this marker, even though it is more predictive than viral loads," Giorgi says. "Why? I think it is because no one, not even me, knows the biological significance of the association. For me, the fact that it cannot be explained is what makes it so interesting."

In 1989, that attitude drew her to the study of E.U.s, who had similarly defied explanation. Did these people have an immunologic head start on H.I.V.?

AFTER watching a close friend with AIDS return to his mother's home to die, Ed, a gay man who is now forty-seven years old, was determined that this would never be his fate. As soon as he learned that he was H.I.V.-positive, he figured, he would "just go on and end it right away." Ed, who has never spoken of his homosexuality to his family, says, "They would have accepted me, but it was like you'd have to be a child back at home, and I just didn't want to do that." To Ed's continuing surprise, however, he has never had to make any such decision.

Ed had joined the L.A. Men's Study in 1984. "All of my friends were terrified that they were going to catch this and just die," Ed, who now lives in San Diego, says. "I felt the same, because I had been pretty wild with the sex all over the place." He says he once tallied the number of partners he'd had and it came to more than a thousand men over a period of five years. In late 1989, Giorgi recruited men uninfected with H.I.V. who had had unprotected receptive anal intercourse twice or more in the preceding nine months with an H.I.V.-infected partner. Ed was one of five men who signed up.

Giorgi had decided to launch this study after attending an immunology meeting and bumping into Gene Shearer, a widely respected AIDS immunologist at the National Cancer Institute. Shearer's lab had discovered, by accident, a man who had recently been infected by H.I.V. but had yet to produce antibodies. The man's blood sample, however, did show evidence of cellular immunity to H.I.V. "That really caught my attention," Shearer recalls. "Geez, you can have cellular immunity without antibodies."

At that point, nearly every AIDS vaccine under development had as its aim to trigger the immune system's production of antibodies against H.I.V.—an aim based largely on the rationale that antibodies explained the success of many, if not all, human vaccines on the market. The AIDS-vaccine search hadn't taken into account E.U.s like Ed, and the questions raised by their resistance to H.I.V. What if people could gain cellular immunity by a low dose of the virus? And what if stimulating antibody production actually worked against that mechanism of protection? "It's so basic to what I did as a graduate student," Giorgi says. "It just seemed as if it would be the explanation for the exposed uninfected." Soon, she and Shearer decided to collaborate, testing blood from some E.U.s in the L.A. study with a sensitive assay that Shearer and his understudy, Mario Clerici, had developed to measure cellular immunity against H.I.V.

No microscope slide can hold a person's immune system, a dynamic network of cells that communicate their constantly changing battle plans through an array of chemical messengers, but researchers can, with varying degrees of difficulty, look at separate parts of the whole. The simplest actors to observe are antibodies, which researchers can easily and cheaply isolate from blood. Peering into the cellular immune system, by contrast, is like walking through the woods at night: even with a strong light, it's easy to get lost. To get a look at the cellular immune systems of Ed and the four other men who had volunteered for the study, Clerici and Giorgi had to separate out their white blood cells and tickle them with pieces of H.I.V., and then test for a specific chemical messenger that the cells would secrete only if they had previously seen the virus. This laborious task was worth it: the results showed that the helper T cells of all five men recognized H.I.V. Clerici was beside himself with

"Are we there yet?"

"Oh, how very French."

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excitement. The men had no antibodies, but they did manifest cellular immunity.

Clerici was staying at Giorgi's, and at the end of their long workdays they had animated conversations in her gray Mustang convertible as they drove from Westwood to her San Fernando Valley house. "Every night, I had to convince her how good the data are," says Clerici, who is now based at the University of Milan and is a leading researcher of E.U.s. "You can talk to her for one hour and she just gives you this look back. She gives you this big cat look. 'Janis, just tell me what you think.' "

Clerici says he was certain that they "were on to something very big." To him, these men were like the milkmaids who didn't get smallpox and caught the attention of the British country doctor Edward Jenner two centuries ago. Jenner demonstrated that the milkmaids had been protected from smallpox because they had previously contracted cowpox, a related but milder disease. Jenner did this by inoculating a boy with sludge taken from a cowpox pustule on a milkmaid's hand and showing that the boy became immune to smallpox. This was the first human vaccine—and one that eventually banished the contagion of smallpox from the earth. "I'm still absolutely convinced that figuring out what these guys have is going to be the only way that we can build a vaccine," Clerici says.

Giorgi's reluctance to believe the data reflects in part her cautious attitude toward making scientific declarations of any sort. When I ask whether she thinks the work with E.U.s will uncover the ingredients needed for an AIDS vaccine, she gives *me* the big cat look. The work, she suggests, will lead to a better understanding of how to manipulate the immune system, which may well help in the search for vaccines. "Almost all the research that we do is associative," Giorgi says. "We don't know which things are necessarily the cause of something that comes downstream to us."

After Giorgi, Shearer, and Clerici had re-assayed the samples and confirmed the results, she finally agreed that the data were real. Still, many prominent AIDS researchers challenged the work vigorously. "The whole AIDS thing was a virologist's game," Shearer says. "Everybody went after antibodies because the assays were easy and available." Since cellular immunity was difficult to evaluate, he says, "there was just a reluctance to look at it."

Clerici describes AIDS researchers as buffaloes on the prairie. "What Gene and I have always thought is that the buffaloes are running in the wrong direction," Clerici says. "It's difficult to stop them and make them turn. I'm not saying we have the answer. But maybe after almost twenty years of failing to develop a vaccine, it would be time to stop and search for other ways to fight the disease." In addition, ignoring research on E.U.s may muddle data from vaccine trials; after all, they enroll people who are at high risk *and* H.I.V.-negative—the very population where researchers find E.U.s. So vaccine developers must test volunteers for cellular immunity at the start of a trial to be able to distinguish between protection conferred by a vaccine and natural immunity.

Though Giorgi's research has been controversial, she takes the skepticism in stride. "Everybody criticizes everybody for everything. It's part of being a scientist who is doing things that are novel." And, criticized or not, the work has spawned a new field of inquiry, and has helped persuade many researchers that antibody-based vaccines (including the VaxGen preparation) are less likely to be effective than vaccines that also trigger broad cellular immunity.

WHEN Glen Redman visited the U.C.L.A. clinic on May 31, 1996, he had a friend drive him. Redman usually made the twenty-five-mile trip from his Eagle Rock house to Westwood by himself, but this time his donation for the L.A. Men's Study was not a simple biannual bleed. The reason he needed someone to drive him home was that researchers wanted to sample the lymph nodes in his groin, which help drain the anal canal. "There's barely a scar," says Redman, who notes that the biopsy didn't interfere with any of his tattoos. Both the node and his blood showed evidence of cellular immunity to H.I.V. The virus, it seems, was once in his body; it isn't there now.

Redman says he's staggered by the results of the research done on his body to date. "It was amazing to me to learn that the study showed that I had been exposed and that I continued to be not infected," he says.

Researchers in Oxford, Nairobi, Paris, and Dallas are building on the kind of work Giorgi has done. Several have found evidence of cellular immunity without antibodies, and Clerici recently added further complexity to the story when he examined sixteen unin-

fected heterosexuals who had had unprotected sex with infected partners "multiple" times over at least a two-year period. He found evidence of special anti-H.I.V. antibodies that cluster around mucosal surfaces such as those in the vagina and the rectum.

Giorgi continues to subject samples from Redman and thirty-one other E.U.s to a battery of immunologic and genetic tests. As she points out, the work is arduous: evaluating someone's freshly drawn blood for cellular immunity is like transplanting a kidney—time is of the essence, and the process is brutally unforgiving of mistakes. Still, the lessons from E.U.s have become impossible to ignore. After all, these are people who, by some felicitous accident, seem to have been naturally immunized, like Jenner's milkmaids. Not only do they suggest that an effective vaccine should be possible, but they raise questions about why, over the past fifteen years, more of an effort hasn't been made to come up with one. Indeed, historically the National Institutes of Health has spent ten per cent or less of its AIDS research money on vaccine R. & D. And vaccine development has been further impeded by a reluctance to test imperfect ones. (Tellingly, the VaxGen vaccine has been around since 1985.) The fact remains that no disease has ever been eradicated without a vaccine.

Many researchers have great hopes for combining antibody-based vaccines with a preparation now in trials which contains H.I.V. genes stitched into the harmless canary-pox virus; the specially engineered virus fools the body into thinking it has been infected, and so triggers the right kind of cellular immune response. Other potentially important leads—such as the idea that a low-dose vaccination with a harmless version of H.I.V. might be protective—have yet to be vigorously followed up in animal and human experiments. Given that H.I.V. now infects an estimated sixteen thousand people a day, even an AIDS vaccine that only works half the time might save millions of lives.

It's because E.U. research holds such promise that Glen Redman doesn't mind being probed and prodded and bled. "I'm very willing to let them draw out as much blood as they want," he says. "There is this thing that may help the world—who knows?" ♦