The Big Bang Theory

It sounds more like science fiction than science: A growing number of people are exposed to HIV—maybe even infected—but still test negative. Some researchers call this natural immunity and hope it will unlock the secret to a cure or vaccine. Others call it a time bomb and fear a global explosion that will make today's pandemic look puny. Lawrence Goodman reports on the strange case of ESNs.

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Were they miracle patients—or PWAs waiting to happen? In the early 1990s, University of Washington immunologist Tuofo Zhu, MD, and his colleagues identified nearly 100 people in Seattle who should have tested positive for HIV. Most were gay men having unprotected sex, week in and week out, with HIV positive partners. They'd been exposed to the virus for years—yet always came up negative. By the mid-'90s, the ranks of these mysteriously HIV negative patients had swelled to include others in familiar so-called high-risk groups worldwide: sex workers in Africa, people with hemophilia who received contaminated blood products, heterosexuals in relationships with HIVers. There seemed no other explanation for their apparent good fortune than a built-in immune-system defense to the modern Black Plague. Scientists were thrilled and predicted that finding what caused their immunity would present the fastest route to a vaccine.

By the late '90s, Zhu—a meticulous researcher who has no truck with idle speculation—had the high-tech tools to determine if his initial patients were indeed HIV-free. Normally when scientists scour the immune system's hidden reservoirs for HIV, they examine a few hundred thousand CD4 cells. Zhu searched several hundred million. Also typically, researchers examine those cells' DNA just a few times. Zhu, wanting unassailable results, looked tens of thousands of times.

And he found the virus.

Zhu drew blood from only two people, but in each, one out of every 20 million CD4 cells was infected—a viral load at least a thousand times less than a HAART-hammered undetectable. Still, Zhu says, these patients are, in fact, infected: "It's a very low, persistent level of virus. But it's not a transient infection. The virus is there all the way."

Published in June's *Journal of Virology*, Zhu's findings allow that these two people may still be naturally immune to HIV. "Their immune systems just may have the irus under control," he explains. Their bodies, he says, may somehow corner the virus in a reservoir, keeping it in check. Zhu adds that over three years he found no evidence that the virus had replicated within the two patients.

But to some scientists, Zhu's duo suggest a far more disturbing scenario. Indeed, these experts contend that the patients may signal a major new public-health crisis. Sometime soon, perhaps, the virus could escape its pocket and run riot through their bodies. No one knows what might trigger such an immunity collapse. Worse, no one knows how many others worldwide also have this latent infection. "Will these people eventually seroconvert?" Zhu asks. "Can they transmit the virus? We just don't know. But you can't rule any of this out."

With AIDS already decimating whole communities around the globe, it's almost unthinkable that the pandemic could get any more dire. That's one reason this worst-case scenario has been much dismissed. Another is science. Frances Gotch, MD, a top immunologist at London's Imperial College, summarizes: "There's absolutely zero evidence" that these latent infections either are widespread or could ever roar to life.

However alarming (or alarmist), the idea that you can test HIV negative yet still house the virus isn't new. Joseph Sonnabend, MD, a researcher and clinician in New York City who has raised the theory since the late '80s, says, "I always found it offensive for scientists to be boldly declaring that infection is automatically followed by seroconversion. It may be true. It may not be true. But there could also be for some patients an in-between period of latent infection."

This mystery, like many scientific conundrums, can be traced to a petri dish. One day in 1992, Gene Shearer, MD, a National Institutes of Health immunologist, was finishing one of the first clinical trials of an AIDS vaccine. While examining a blood sample from a patient who had been exposed to the virus but tested negative on the conventional antibody test, Shearer was stunned to spot interleukin-2 (IL-2), which the immune system produces to ward off HIV.

Shearer assumed he was mistaken. And yet the patient's IL-2 level was even higher than that of an infected person. "Of course, we doubted our finding," Shearer says. "We figured there was just something wrong with our testing system that day."

Shearer reviewed his results again and again. But more tests only confirmed the observation. Here was a patient who, it seemed, had been exposed to the virus and then mounted an immune-system response that resulted in his not becoming infected—or, at least, not producing HIV antibodies. Shearer became even more confident in his theory when he learned that the patient had been having unprotected sex with an HIVer.

Describing the virological limbo between exposure and antibody production, Shearer coined the term *exposed seronegative*, or ESN. Researchers nationwide soon began identifying other ESNs—newborns of HIV positive moms, for example, and health care workers pricked by contaminated needles. Again, there was exposure to HIV, but no seroconversion.

Shearer was gratified when the discovery quickly won scientific legitimacy—but dismayed when colleagues began calling such cases *exposed uninfecteds.* Shearer well knew that *uninfected* and *seronegative* had two radically different meanings: An ESN may, in fact, "have HIV," but at a level so low that the virus could not be detected. "How did we know they were not infected in some

way? That the virus was not integrated into their DNA—and sitting there?" Shearer asks.

In fact, just over a year after Shearer's discovery, the IL-2 patient seroconverted. But as merely a control in the vaccine experiment, he hadn't had extensive DNA and RNA tests at the outset so there was no way to tell why. Perhaps the patient had originally been infected with a mutant virus strong enough to generate an immune response but too weak to withstand it—or the virus could have been lurking in the body all along and somehow managed to break free. "We didn't know why—and we still don't know why," Shearer says. "It's a mystery."

Shearer may not have been certain if ESN patients were infected, but of one thing he was: There was no immediate risk of their being infectious. To this day, the consensus among researchers is that if indeed ESNs are infected, their viral load is too low for them to transmit HIV. Mario Clerici, MD, an immunologist who worked under Shearer, cites studies in which monkeys were infected with a very low level of HIV. The animals showed immune responses similar to those of ESNs, but they did not transmit the virus. Clerici believes that only an ESN who seroconverts—and tests positive for HIV antibodies—can pose a risk of infection.

The belief that ESNs—however many there may be—present no public-health threat has made them a low research priority. "Why study people who aren't sick when millions of PWAs are dying every year?" the thinking has gone. And of those who've bothered to study them, says Clerici, now at Italy's Milano University medical school, "People tended to think we were just publishing weird things."

Not that there weren't a few significant ESN studies between Shearer's findings in the early '90s and Zhu's later in the decade. In 1995, UCLA pediatrician Yvonne Bryson, MD, announced that she had been treating a boy who seemed to have become de-infected. Bryson said she and her team had detected fragments of HIV protein and genetic material in his blood at 19 days old and then 51, but by 12 months, the child had tested negative. He was completely healthy by age 5. When a few scientists challenged Bryson's groundbreaking 1995 *New England Journal of Medicine* report, wondering if her original lab equipment had been contaminated, UCLA launched an investigation. The probe found no faults with Bryson's research, and no less an authority than the head of the National Institute of Allergy and Infectious Diseases, Anthony Fauci, MD, proclaimed Bryson's research solid.

Suddenly, ESNs were big news—with Bryson's work, involving as it did "innocent" newborns, proving especially mediagenic. "LA 'Miracle' Boy, 5, Beats HIV" ran one 1995 *Chicago Tribune* headline. Researchers fueled the hype. Over the next several years, labs worldwide claimed to have found more than 40 infants who had apparently s*ero-reverted*, clearing all traces of the virus. Based on these findings, scientists began suggesting that ESNs had "transient infections" rather than latent ones: upon exposure, they had contracted HIV and then somehow had fought off a full-blown infection. Learning how to replicate this process in HIVers might provide immune control, even a cure or vaccine (see "A Shot in the Dark).

But Bryson's and other reports of transient infections in newborns turned out to be false. A 1998

report in the journal Science declared that contaminated instruments had indeed accounted for most of the virus fragments. In some cases, lab samples had been mislabeled or confused with specimens from HIV positive babies. “The scientists were so hopeful that they could find these situations where people had spontaneously cleared HIV out of their body,” says Lisa Frenkel, MD, an associate professor of pediatrics at the University of Washington and the Science paper’s lead author. “I guess it’s good to be optimistic, but the analysis wasn’t very rigorous.”

Other ESN sightings have also proved illusory. In the mid-’90s, Canadian and British researchers thought they had found a group of about 100 Kenyan prostitutes who had natural protection against the virus. Having serviced six to 10 clients a day for years (and only rarely with condoms), the women still had no HIV antibodies—but they did have cytotoxic T lymphocytes (CTLs), an HIV-fighting white blood cell. Normally, HIV barrels through this defense, so the sex workers’ T cells were thought to be better designed or more powerful than normal.

In the late ’90s, however, 10 of the women contracted the virus. They had left Nairobi for four months to visit family, and, soon after their return, tested positive. Sarah Rowland-Jones, MD, director of the Oxford Center for Tropical Medicine and a lead researcher on the case, believes that the women did, in fact, possess temporary HIV immunity. This protection, she says, could be maintained only if their bodies had repeated daily contact with the virus, producing a constant immune-system response. Any vacation, of course, meant an interruption in this virus-as-inoculation course—their immune defense was presumably relaxed. According to Rowland-Jones, the prostitutes likely became infected by clients upon returning to work. For some reason, their immunity didn’t return with them.

It’s also possible, Rowland-Jones says, that the women were infected with the virus all along, but at a level undetectable to even the best tests. “All we can say is we looked with the best techniques currently available and found no signs of the virus,” she says. “But we can’t say it wasn’t hidden away in some lymph node.”

As one ESN promise after another failed to deliver, researchers began losing interest: Just a few teams of scientists, most from Europe, remain on the beat. They work mainly in Africa and Asia, where instrument contamination is all too frequent. “The studies haven’t shown reproducibility of the data and haven’t been independently verified,” says Bruce Walker, MD, director of the division of AIDS at Harvard Medical School and a pioneer in immune reconstitution.

Michael Lange, MD, remains interested. Lange is head of infectious diseases at St. Joseph’s Regional Medical Center, a midsize Catholic-run community hospital in northern New Jersey. He’s a clinician, not a researcher, and has done no ESN work himself. But over the years, listening to the growing number of ESN conference reports, he has developed a doomsday hypothesis. Like Sonnabend, Lange believes HIV resembles tuberculosis (TB), herpes or cytomegalovirus. People can carry all of these infections without being symptomatic or contagious. For example, when infected with TB, the body springs into action: Specialized white blood cells called macrophages trap the bacteria in your lungs and prevent it from spreading. More than two billion people worldwide have the TB bacteria. Only 10 percent, though, will ever be contagious or develop the

disease. Only when the immune system is compromised, most often because of illness, does TB become deadly. (That's why TB is the top killer of HIVers in the developing world. In fact, the rate of TB activation is 10 percent *per year*—not per lifetime—in people who are also infected with HIV.)

Accordingly, Lange says, ESNs are not immune to HIV. Like those two billion TBers, they have a latent infection, currently under control—that may surface savagely in one or 10 or even 30 years. Lange worries that the world's 42 million HIVers are only the first wave struck by the disease. ESNs constitute the second wave. The planet will face an additional health catastrophe, Lange says, when the immune systems of ESNs in the developing world founder—as a result, say, of multiple other infections such as TB and malaria. He contends that even the immune systems of ESNs in the developed world will fail in old age due to such procedures as chemotherapy and organ transplants. "This is enormously worrying," Lange says. "Could the few ESN patients we know about so far just be the tip of the iceberg? Are the millions who've gotten sick with AIDS just the beginning? This is all possible."

But is it *really*? "Absolutely," says the NIH's Shearer. He is seconded by James Mullins, PhD, a professor of microbiology at the University of Washington and Zhu's collaborator on the ESN paper. It's possible, Mullins points out, that ESN immunity "is like that of people who have been on HIV meds for a very long time—and if so, ESNs should absolutely not think they are protected."

Lange admits he's essentially reading tea leaves. He relies on the biological markers researchers have found in the blood of people with ESN, such as IL-2 and CTLs, and interprets them as signs not that the body has fought off HIV but that it has become infected. He points out that we lack an affordable test to identify latent virus on a global scale. That's why he is so intrigued by Zhu's new findings, suggesting as they do that ESNs, far from being immune to HIV, have instead a slumbering—and potentially deadly—infection.

Most top ESN researchers disagree with Lange's interpretation of Zhu's findings. They raise two main objections: Zhu's data pertain, after all, to only two patients. And if ESNs have a low-level infection capable of turning into full-blown infection, why, more than 20 years into the epidemic, have we not yet seen at least the start of this second wave? Jay Levy, MD, an immunologist and longtime HIV researcher at the University of California, San Francisco, is dismissive. "What really are the chances of that happening?" he asks. "There may be some people who have a latent infection that could break out later, but it's not going to be a major group. You are just unable to suppress HIV naturally for a long period of time without signs."

But Milano University's Clerici, who has probably done more ESN work than anyone else, says Lange may be on to something. In his most recent research, Clerici has shown that, compared to the HIV negative, ESNs have elevated levels of an HIV-fighting antibody known as IgA in their seminal fluid as well as in their vaginal and rectal lining. Clerici believes that the IgA in these most HIV-friendly spots kills the virus before infection. Still, he is troubled by his and other researchers' findings of CTLs in ESN blood. Their presence, he says, strengthens Lange's hypothesis. "The fact that we do have these T cells strongly suggests that we do have a live virus replicating in these patients," he says. "Basic science says that." So is Clerici sure ESNs are immune to the virus? "The

simple answer is," he says, "I don't know."

At least two researchers agree with Lange, though, that the likely number of ESNs worldwide is huge. Jay Levy, for his part, estimates that at least 20 percent of the globe, if exposed to HIV, would not develop antibodies. Meantime, Clerici, using survival rates from the Black Plague, puts the number closer to 70 percent. The survivors, Clerici says, probably had a kind of natural immunity akin to ESN.

"It's dishonest science to say we know for sure exposed seronegative is about immunity to HIV," Lange says. "We have to go after the answer. Right now, though, we're too busy playing ostrich." One way to go after answers, according to Lange, would be to spend more money on developing a skin test to identify ESNs. Such an exam exists for TB and is capable of determining very low levels of infection. Of course, a doctor could offer little but a pat on the back to anyone failing an ESN exam. There is no treatment. There is no way to predict an ESN's chances of developing full-blown infection. This, Lange says, is the reason that public-health officials refuse even to discuss an ESN skin test. "They're worried," he says, "that it would set off a panic."

A SHOT IN THE DARK

The ESNs hold the key to a vaccine," says Frances Gotch of London's Imperial College—and she's not the only top researcher backing the idea that a preventative vax might get the immune system to behave as it does in ESNs. Recipients would be exposed to a harmless version of HIV that wouldn't cause infection but would trigger an immune response with the same level of CTLs and IL-2 that scientists have found in ESNs—and, ideally, confer long-lasting immunity to HIV.

Only one ESN-based vaccine is now in clinical trials. Run by Oxford University scientists in East Africa, it originated with Sarah Rowland-Jones' discovery of Kenyan sex workers who seemed to have natural protection against HIV. In lab tests, the vaccine stimulated an ESN-class immune defense in mice. Yet the little critters never tested positive. Nor were they infectious. Although conclusive data are five years off, Rowland-Jones is hopeful: "As far as I am concerned, right now, this is most logical way to go after a vaccine."

Last year, several University of Medicine and Dentistry of New Jersey scientists penned an article in the journal AIDScience calling on researchers to focus more vaccine resources on ESN research. UMDNJ's Donald Louria, MD, is disappointed that scientists have so far paid the article little heed. He may get little sympathy from HIVers, though, because the ESN model would work only for a preventative—not a therapeutic—vaccine. Why? According to Louria, there is no evidence that ESNs can rid themselves of HIV once it runs riot in the body—only that they can repel it before it leads to infection. Still, he says, "I am absolutely convinced this is the way to go."

—David Gelman, MD

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