

Proof Positive:
Finding the Cause of AIDS

by

Megan R. Rulison

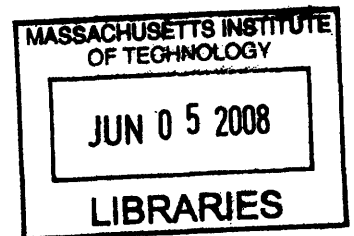
B.A. Biology and Theater
Boston College, 2006

SUBMITTED TO THE PROGRAM IN WRITING AND HUMANISTIC STUDIES IN
PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE IN SCIENCE WRITING
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

SEPTEMBER 2008

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Submitted to the Program in Writing and Humanistic Studies
on June X, 2008 in Partial Fulfillment of the
requirements for the Degree of Master of Science in
Science Writing

ABSTRACT

In 2008, it will have been 25 years since HIV was first isolated from a patient with AIDS. In the early 1980s, when the mysterious disease of the immune system spread across the globe, scientists began a race to find the cause. Through the voices of the men and women involved, this thesis tracks the discovery of HIV from the early outbreak of a deadly epidemic to the design of therapies for a fully-defined disease.

When the AIDS outbreak began, doctors and scientists had no idea what was making people sick, and the race to find a cause was a difficult and haphazard process. But it was also a successful one; scientists discovered a definite cause for the disease—the Human Immunodeficiency Virus. However, today there still remain AIDS denialists, people who do not believe HIV is the cause of AIDS. Their beliefs pose the question, why should we trust in science? This version of the history of HIV seeks to answer that question through a particular emphasis on achieving certainty in science, how the steps of the scientific process led to certainty that HIV is the cause of AIDS, through both experimental research and community acceptance.

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Christine Maggiore was pregnant and thrilled. Charlie, her five-year-old son, watched in fascination month after month as her stomach grew. But not everyone was eager to throw Maggiore a baby shower. Her doctors kept warning the Los Angeles mother to get on medication. She needed to take AZT during her pregnancy, they said. AZT is prescribed to reduce the risk of passing HIV from mother to offspring, and Maggiore tested positive for the human immunodeficiency virus in 1992.

But Maggiore didn't take the drug with Charlie, and she didn't take it with Eliza Jane, born in 2002. Maggiore breastfed both children. Neither was tested for HIV.

Maggiore is an AIDS denialist; she does not believe HIV causes AIDS. The founding director of *Alive and Well AIDS Alternatives*, a prominent AIDS denial organization in the US, Maggiore appeared on the cover of *Mothering* magazine in September 2001, pregnant with Eliza, with a red circle and slash symbolizing 'no' painted over the letters 'AZT' on her bare stomach. Charlie stands over her left shoulder, grinning.

Charlie was born a healthy, smiley boy and is now an active ten-year-old who plays the cello. Eliza Jane, who was smitten with her older brother, became sick shortly after her third birthday. She died in May of 2005. The coroner ascribed the death to "Pneumocystis Carinii Pneumonia due to Acquired Immunodeficiency Syndrome." In other words, Eliza Jane died of AIDS.

Today, Maggiore denies that HIV had anything to do with Eliza Jane's death, and does not waver in her beliefs. Seven months after Eliza's death, Maggiore told ABC News, "None of what has happened to me, and to my family, has shaken what I know to be correct and true about science and medicine and my experiences."

AIDS numbers are staggering beyond comprehension: 33 million people live globally with the disease, 2 million died from AIDS last year, more than 25 million have died since 1981. Today, Africa makes up 70 percent of those numbers.

It has been twenty-five years since the discovery of the human immunodeficiency virus, HIV, as the cause of AIDS, and scientists around the world continue to feverishly design drugs and vaccines to counter the growing death tally. Yet in the midst of the epidemic, voices of dissent rise up against scientific consensus. These are AIDS denialists, people like Maggiore who reject the link between HIV and AIDS, a position that plausibly permits them to dismiss safe sex as an AIDS prevention method and to reject anti-HIV drugs.

Within their community, different factions espouse different causes of AIDS: malnutrition, promiscuity, even the therapies used as treatment for AIDS. Yet this small but noisy band of activists is unified in one respect—its rejection of accepted medical wisdom about HIV and AIDS. Their ranks include public figures such as Foo Fighter bassist Nate Mendel, journalist Celia Farber, Peter Duesberg, a prominent molecular biologist, and President Thabo Mbeki of South Africa. Their skepticism is dangerous because, as in Eliza Jane's case, AIDS denialism can cause death. It is estimated that if South Africa had rolled out an aggressive drug therapy plan in the late 1990s, instead of Mbeki's restrictive control over anti-HIV drugs entering the country, 300,000 deaths could have been prevented.

Maggiore stands by what she knows to be "correct and true about science," but scientists say she does not understand the research. AIDS denialists and scientists are

rarely able to have constructive conversations. Most of us easily side with the scientists, but why? Why *should* we trust science?

For the general public, understanding of the scientific process is often limited: mainstream news glosses over complicated processes to get to simple, headline-worthy conclusions; textbooks present the history of science as a smooth surface of Eureka! discoveries without the turbulence of error and failure below; and scientific literature erects a wall of stupefying jargon against the casual reader. However, even with our limited knowledge of the scientific process, we accept its resulting claims: the Earth goes round the Sun, $E=mc^2$, cells are the basic structures of all living things. We're happy to sum up the reason that apples drop from trees with a word—gravity—so there's little reason, or need, to plumb the depths of Newton's law of universal gravitation.

Danger arises when others exploit our comfortable lack of curiosity. When someone refutes the idea that a virus named HIV causes a deadly disease called AIDS, they use ignorance about the scientific process as ammunition to convince others. Denialists, for example, claim that HIV has never been isolated, that blood tests are not accurate, and that things like drugs and poverty can cause AIDS. The first is outright false, the second misleading, and the latter is only indirectly related. Looking more deeply into the history of AIDS can show why we should trust the science of HIV and AIDS and why the scientific community stands steadfastly behind it.

It is a history packaged in fear and wrapped in controversy. Overnight, scientists were confronted with a deadly disease unlike anything we'd been affected by before. The illness shared none of the familiar hallmarks of past epidemics where cause and effect were often quickly discerned. Rabies results from the bite of a rabid animal and is

recognizable by distinctive symptoms of the nervous system, such as paralysis, hallucinations, and fear of water. The cause of malaria was discovered in 1880 when a French army doctor observed parasites in the red blood cells of the sick, and the disease is distinguished by a cyclical pattern of symptoms. But AIDS is a chameleon, disguising itself in many ways. First, the illness begins with rare infections and cancers. So when AIDS was new, a doctor's first diagnosis was usually some opportunistic illness, not the underlying cause. Second, AIDS has a slow onset; it often takes years to show symptoms, making it hard to pinpoint an exact moment of infection. And finally, when the AIDS outbreak first began, it was not clear how the illness was moving from one person to another. Each of these reasons is used in some form by AIDS denialists today to reject conclusions about AIDS. But in the early 1980s, when the epidemic first began, scientists and doctors confronted the challenges head-on and tracked a virus unlike any before that had infected the human population.

It is 1984, and a short blond woman, her nervous smile peeking from behind a dense gaggle of microphones, clears her throat. As the room quiets, Margaret Heckler, the US Secretary of Health, smiles again and apologizes for her laryngitis. The room is silent except for the rustling of papers; the reporters are not interested in her cough but in what she's about to say next. But she tries their patience, carrying on through an introduction, building to her climax. Finally, in a hoarse, echoing whisper, Heckler declares, "The probable cause of AIDS has been found." She continues over the growing murmur, her voice getting stronger with each hopeful assertion. Not only has the agent been identified, she boasts, but there is a new process to mass-produce the virus, which

has made a blood test possible. “With the blood test,” she wraps up, “we can identify AIDS victims with essentially 100 percent certainty.”

Why were scientists certain in 1984 that HIV was the cause of AIDS? It was only three years after the outbreak of the mysterious disease. At the onset, no one knew where the illness originated, how it was transmitted, what caused it, or how many lives it would claim. Was Heckler’s assertion a substantial claim of fact or a hopeful shot in the dark, like Robert Gallo’s papers published a year earlier linking a *different* virus to AIDS?

Heckler steps off the podium as a tall man takes her place. It is Gallo, Chief of the National Cancer Institute’s Laboratory of Tumor Cell Biology. This year, Gallo is reserved, shrouded behind dark glasses. To the chagrin of the reporters, he speaks in highly technical language. His tone is already defensive. After a burst of critical questioning, the irate Gallo makes the most declarative statement he’s willing to give: “I think the agent is at hand that produces the disease.”

What made Gallo, a scientist with a troubled history of research, success marred with mistakes, decide to stand up once again and declare a discovery of major importance to the world? And why did the scientific community believe him? Today, the scientific consensus that HIV causes AIDS is bulletproof. But we may wonder where that consensus came from. What happened that makes us so sure today?

Five months after the press conference, a reporter asked Gallo why the AIDS epidemic began. Gallo responded:

“No one can ever say with absolute certainty the origin of anything unless you’re there to document it and prove it at the time it arises. All you can do is assemble the facts that you can get your hands on after these events occur and draw the best estimate of what happened.”

There's no search for a cause until there's fear of a disease. And the first whisper of the AIDS outbreak was detected as a faint rustle in a bureaucratic web of red tape.

In 1979, the Centers for Disease Control (CDC), a national public health agency, controlled the supply of a drug called pentamidine, used to treat a rare type of pneumonia, *Pneumocystis carinii* (PCP). Jim Curran, a researcher at the CDC at the time, describes PCP as “an extremely uncommon opportunistic infection,” and “scavenger-like,” causing pneumonia only in people with damage to their immune system, such as cancer and transplant patients. The infection was so uncommon, in fact, that pentamidine was labeled “investigational” since the manufacturer never bothered to jump through the procedural hoops necessary to sell it publicly. In order to get the drug, Curran says, doctors had to petition the CDC and describe the patient's symptoms and history. The drug was rarely requested.

But in 1979, the CDC began receiving multiple requests for pentamidine to treat otherwise healthy young men. The CDC assistant filtering the requests began to suspect that “something strange” was going on and went to her supervisor. An investigator was dispatched to Los Angeles, the source of the majority of the requests, to report on the irregularity. At that point, Curran was asked to head up a task force to investigate the outbreak. He was assigned to work on the project for three months.

From the beginning, it was clear that the “otherwise healthy” men were very, very sick. The CDC investigator encouraged physicians at UCLA to circulate accounts of the unusual cases, and on June 5, 1981, the CDC published a paper on the “first five,” a small group of gay men with malfunctioning immune systems. The men suffered from not only

PCP, but another rare disorder, Kaposi's sarcoma, a cancer that manifests primarily in elderly Italian and Jewish men. A healthy immune system easily protects us from these rare maladies. Like an internal watchdog, our immune system, made up of organs, chemicals, and cells, attacks foreign invaders and defends the body against illness. Confronted with an infection like PCP or Kaposi's, a healthy immune system shrugs off these microbes like a picnicker batting away a fly. But now the "flies" were swarming around the bodies of the previously healthy thirty-year-old men. It was a clear sign to doctors that the body's defense network was down. Men who should not be getting sick were.

That was the first official government recognition of what later came to be called AIDS: in short, an illness in someone who shouldn't be getting ill. Doctors diagnosed this "accident of nature" as a weak or absent immune system in someone who shouldn't have an immune disorder. No one knew why the system was down, what symptoms would manifest, or how long it would last. Nor did they have any idea what was about to happen. Only two months after the "first five" paper, the reported number of cases jumped to 108, and at least two of the five were already dead.

As the months passed, the disease spread. One hundred and eight turned into 213, which tripled to 739 before the end of 1982. And a third of those 739 were already dead. Curran called the reported cases only the "tip of the iceberg." He wrote, "We all knew the problem was bigger than it seemed." And so the scientific community embarked on a mission to find the cause.

Over the course of history, the emergence of a new disease was not always followed with an immediate search for its cause. There was a defined moment in medical

history when ideas about disease rapidly changed. Professor K. Codell Carter, a philosopher of science at Brigham Young University, scoured through old medical literature and found striking differences in how science confronted the idea of causation before and after 1835.

Before that year, he says, “what you get is diseases always thought of in terms of a collection of symptoms, and the cause is not really interesting to people.” Carter discovered that no matter how far back you look, and he went all the way back to the Babylonian Talmud, the only references to “cause” of a disease are explanations of individual cases. For example, two mothers died after childbirth, both with a high fever, abdominal pain, and a white tongue. The “cause” of illness could likely be ascribed to an inflamed uterus in the first and to the season of the year for the second (the illness often peaked in the winter). “As long as you think in terms of symptoms, there’s no reason why two people with the same symptoms have the same cause.”

That was, however, until 1835, when five independent lines of research, culminating in the highly visible work of Louis Pasteur, rejected defining disease as a collection of symptoms. “When you get to the other end of the century,” says Carter, “the assumption is that any disease can be characterized in such a way that there will be a universal, necessary cause.” By 1880, doctors were routinely linking a single disease with a single cause, such as syphilis and anthrax with particular bacteria or rabies with a microbe from the bite of an animal. “It’s really quite remarkable,” says Carter, that over forty years, the course of one physician’s career, ideas about disease causation completely changed.

But, actually proving a link between cause and disease has never developed into an easy, regular process, even with causation in the forefront of doctors' minds. Over the last 200 years, scientists have argued over rules to follow, criteria to meet, and postulates to fulfill in order to answer that question, but a perfect checklist for proving causality has never emerged.

Thus in the early 1980s, with no definitive roadmap to guide them, researchers started off with a series of clues. The first lead was the immunosuppression of patients. Max Essex, a Harvard AIDS researcher, remembers the moment; "People first recognized, before they knew the cause, that it was a disease of depletion of the T4 cells."

Something was eating away at T-cell lymphocytes. Lymphocytes, small white blood cells characterized by a large nucleus, do the heavy lifting of the immune system. T-lymphocytes are a subclass of lymphocytes made up of two types: killer T-cells, which destroy infected cells, and helper T-cells, little lighthouse guards that secrete signals to alert the rest of the system to invaders. The physical characteristic shared by all the sick men was severely low levels of T-cells.

The second clue to the disease was the most obvious. It didn't require a lab test or even a second glance at the data. It was glaringly recorded in the first sentence of every major report—all the men were homosexual.

Perhaps the first suggested theory of the cause of AIDS was the lifestyle theory. From AIDS first appearance, it was suggested that the disease had to do with sexual behavior. Surely, people said, it was related to with the sexual practices and lifestyles of gay men. Within the theory, multiple suggestions of the cause abounded: sperm were held liable for crippling the immune system by insertion into the rectum; poppers, a

popular drug used at many gay bars, were accused; and estrogens, chemicals ingested by some gay men for feminization, were blamed. And a sexually transmitted agent was suspected; 42 of the first 200 men with the syndrome could be linked to each other through sexual contact.

Yet, as Curran's task force traveled the country, reviewing hospital charts and talking to doctors, they found a striking new piece of evidence. "The pattern after a few months was there were not only cases in gay men, but also in injecting drug users," says Curran. What was the link between the two populations? To Curran, the transmission pattern looked very similar to a model he had recently been studying, the spread of hepatitis B, which is transmitted by exposure to bodily fluids. He immediately began to suspect that an infectious agent, like the virus causing hepatitis B, was causing the new disease. But whether it was or not, the lifestyle theory was clearly bogus; gay men were not the only ones getting the disease.

Doctors searched for the next clue within the bodies of the sick. While pneumonia and Kaposi's sarcoma were obvious upon a physical examination, lab tests revealed a wider range of invaders capitalizing on the missing barricades of the immune system. Patients with the Acquired Immune Deficiency Syndrome, AIDS, as it had begun to be called in 1982, showed infections of herpes, cytomegalovirus (CMV), various bacteria, and lymphoma. Doctors wondered if one of these were the cause. Perhaps in the swarm of pathogens buzzing in the bodies of AIDS patients, one was altering the immune system and allowing the others to set up camp.

The first and greatest fear of the CDC, the National Institutes of Health (NIH), and doctors around the US, was that the cause would be an infectious agent, Curran's

first suspicion. Genetic or environmental factors merit concern, but they can be predicted or contained. Infectious agents spread.

In the first two years of the epidemic, Curran received something like 75,000 letters proposing theories for the cause of AIDS. “Some were crazy,” he recalls. “Some weren’t.” Many suggested infectious agents, such as CMV and herpes, but other causes were proposed as well. A peculiar variant of a resident protein in the immune system, found in AIDS patients and not in healthy individuals, was accused in the *New York Times*. Elsewhere, a strange fungus detected in several patients was examined. Researchers across the U.S. followed the motto, *Leave no stone unturned*.

The scary possibility of an infectious agent loomed. Curran began traveling around the US, speaking to doctors and researchers, trying to grab their interest and recruit them to pursue an infectious agent. Cases were popping up too fast, he argued, the sick had too much in common. At that point, a few women had come down with a similar condition, and several infants, born to immune-suppressed women, were also sick.

While Curran led the hunt for the agent, doctors searched for a treatment. In the medical profession, knowing the source of the illness is often critical to healing a patient, but it is not always necessary. There is no known cause for most cases of epilepsy, yet medicine is available to control the condition. With a new syndrome, if the cause of a disease is not apparent, doctors pursue treatment. All sorts of therapies were tried for AIDS, including liver replacement, bone marrow transplants, and herbal remedies. Nothing worked. The mortality rate for patients with full-blown AIDS was 100%. No one had spontaneously recovered from the illness. By 1983, after two years of attempts,

the National Cancer Institute declared, “It would seem that until the infective agent is identified, all attempts at reconstituting the immune system will fail.”

But then a surprising outbreak of the disease narrowed the hunt. “Another group of victims has been hit,” proclaimed the *Washington Post*. More than a year after the “first five” were publicized, three cases of AIDS in hemophiliacs surfaced. “I think as soon as hemophiliacs were found in late ‘82, then most of the scientific community began to believe that this was caused by a transmissible agent,” says Curran. It was such a startling development that the CDC dispatched an investigator to scrutinize the cases, hoping for shared needles or closet homosexuality as an explanation, but they found neither. It was such a surprising event, in fact, that the Assistant Secretary for Health was hesitant to make the obvious conclusion and encouraged hemophiliacs to continue to rely on their treatment.

Hemophiliacs lack factors that cause blood to clot. Every week they receive concentrates of those factors to prevent the dangers of internal hemorrhaging, including strokes and bleeding into their joints. In the early 1980s, a single concentrate was made from the factors of as many as 2,500 blood donors. So over time, hemophiliacs were being exposed to hundreds of thousands of donors, Curran recalls. “They were a perfect storm for a virus that would be in the blood supply.”

AIDS was traveling through blood. It was then, says Curran, that “people started to believe in a cause.”

A clear pattern of transmission focused the scientists on what they were looking for. Suddenly the field zoomed in tightly—not only was it certainly an infectious agent, scientists knew which type. It had to be the only microbe capable of moving through

filtered blood. It was a virus. Other infectious agents—bacteria, protozoa, fungi—are large enough to be filtered out by the processes that make blood safe for hemophiliacs. These pathogens act like a blue whale getting tangled in a fisherman’s net, while a virus is a goldfish slipping through.

In the following year, 1983, scientists tracked hundreds of viruses known to mankind, but beyond that broad classification, their certainty floundered. “We were sure it was a virus,” says Curran, “The question was which virus.”

In April, as rain spattered the streets of Washington and washed the dirt of winter away, thirty-five of the top virologists from around the nation closeted themselves in a sixth floor conference room on the NIH campus in Bethesda, Maryland. In each chair in the room sat a man waiting to present a different theory; each was a specialist for a different type of virus. Perhaps by pooling their knowledge, by connecting the dots, or simply by talking it through, they could determine which type of virus was causing AIDS.

Was it Dr. Gerald Quinnan’s popular cytomegalovirus, CMV? The nasty little ball of spikes, known for burrowing into the nucleus of a cell, had a strong case; CMV is found in virtually all AIDS patients and is shed in bodily fluids. Or did the culprit abide in the Petri dishes of Dr. Joseph Pagano, where Epstein-Barr virus grew, one of the most common human viruses? EB, the virologists knew, is transmitted through saliva and has a preference for cells of the immune system. Perhaps a mutation in its genes sent the latent intruder on a rampage. Or maybe it was one of the more exotic pets in the room, like Dr. L. E. Carmichael’s parvovirus, the smallest virus in the world. Parvoviruses

infect cats, dogs, and wolves by duplicating themselves over and over in the cytoplasm until a cell blows up, spewing the pinwheel-shaped progeny of its invader toward other cells. No strain of parvovirus had ever infected a human, or had it?

Max Essex, a researcher from Harvard, was at that meeting and remembers the ongoing debates of “everyone fighting for their own virus.” The group was so divided that even later, Essex says, after Gallo’s team showed extensive evidence for one type of virus, some were not convinced and carried on arguing for their viruses.

Certainty of a cause at this stage was elusive. The community agreed only that the agent was a virus. From there, with only methods of transmission and patient symptoms to work with, each scientist spun the sparse data to his favorite mold. “Retrovirologists like me thought it would be due to a retrovirus, herpes virus people thought it would be due to a herpes virus,” and so on, recalls Essex. The April meeting ended and the AIDS agent still had no name.

The mystery would only be unraveled by forward momentum through the scientific process. The scientists needed more data. “Everyone had their own hypothesis,” adds Curran, “because there hadn’t been a human virus of this type” before. They were questing into the unknown; the virus attacked in a never-before-seen way, dismantling immune systems with barely a whiff of its presence. The disease manifested itself differently from patient to patient; their bodies were so wracked with infections, it was hard to tell cause from effect.

The scientists dispersed that day, perhaps sharing rides back to the airport, then spreading once more across the country—San Francisco, Boston, St. Louis, New York—like the epidemic they were trying so desperately to stem.

By 1983, two years after the fateful five paper was published, only the sheer passage of time edged the scientific community closer toward a cause. As month after month went by, doctors collected data on how the disease progressed through the body.

At the initial infection of the AIDS virus, flu-like symptoms overwhelm the body for a couple of days or weeks, but the sickness is rarely serious enough to consult a doctor. Next, an asymptomatic lull calms the waters. This stage can last for years. No symptoms betray the growing invader in the body, yet the immune system is steadily undermined, like the supports of a house slowly being eaten by termites. The virus enters the cells of the immune system, then lies latent, silent, out of sight. At some point, there is a change, some threshold is crossed, either by the host or the agent, and the virus multiplies rapidly, killing the T-cells that hid it from detection, flooding the blood. Then, infections begin. On the skin, blood and cancer cells bubble up in painful red and purple clusters, the hallmark of Kaposi's sarcoma. In the gut, a worm-like parasite, *cryptosporidium*, burrows into the intestinal lining, causing cramps, diarrhea, and vomiting. In the lungs, a fungus begins to grow, covering the walls. In time, PCP can literally drown its victim. At times only one of these infections occurs, in other cases all three.

Over the two years, scientists were forced to sit and watch, waiting for the virus to act. Only time revealed that AIDS was a slow-acting infection. The virus took years to cause illness and death, so it was either slow-acting or had an incubation period. While this conclusion didn't rule out many of the viruses debated in Bethesda, scientists began

to sort through the blurry crowd of suspects and focus on one of the most promising, the retrovirus.

Retroviruses were already infamous for violating the “central dogma” of genetics. DNA, the dogma says, encodes RNA, which encodes proteins. It’s like a relay, with one racer dependent on the previous: DNA→ RNA→ protein. DNA, the genetic code, is scanned by an enzyme and copied into RNA, a long string of letters with instructions to make a protein. Now the RNA is scanned, and each section of the code cues various acids to join a growing strand, like colored beads threaded onto a necklace. This strand coils into a functional protein; the process is complete. But retroviruses defy the rules. They run the process in reverse; it’s their greatest asset and most confounding skill. But a more important fact at the time: there were two known human retroviruses, and both were slow-acting.

A retrovirus particle alone is no more dangerous than a speck of dust. It is impotent, powerless, static. Under a microscope, the virus looks like a sticky koosh ball, with suction cups at the end of each spike. Within, a string of acids—RNA—coils up, like a worm hiding in an apple. But the virus isn’t so innocent once inside the human body. The suction cups stick fast to receptors on the outside of a human cell, then the virus squeezes its way in.

Inside, the once-dormant speck becomes a dangerous tyrant. Two of the virus’ three proteins, together called reverse transcriptase (RT), scan the RNA of the virus and recreate the code as DNA, dismissing the foolish “central dogma.” RT translates RNA backward into DNA. Then, in a slick covert-ops move, the fresh viral DNA slides into

the human cell's nucleus. There, with the help of a third viral protein, the "scissors," the host DNA is cut, and the viral DNA is inserted. The infection is now permanent.

At some point in time, an event activates the cell. As cellular production begins, viral DNA hijacks the cell's machinery to produce copies of the virus. In the cytoplasm, pieces of the virus assemble: the RNA genome curls up, RT proteins latch on, a bullet-shaped shield forms around them, and the whole package pinches off a piece of the cell membrane and slides outside. A powerless cell effortlessly becomes a factory for the enemy. If production speeds up and virus particles back up in the cytoplasm, the cell will literally burst.

In the early 1980s, retroviruses were not new to science. Two decades earlier they had become a hot topic. A Scottish veterinarian, William Jarrett, found a retrovirus in cats that caused leukemia, a cancer of blood cells. At the time, it was an absurd notion that cancer could be caused by infection, but Jarrett proved it was possible. Even more peculiarly, he found that the retrovirus not only caused cells to multiply out of control (the definition of cancer), but it killed cells as well, the opposite effect. This strange behavior would be one of the early pieces of evidence to tie the AIDS virus to a retrovirus: the AIDS virus displayed both cancerous (cell-multiplying) and lytic (cell-killing) properties.

Later, Jarrett's brother Oswald and Essex, at the Harvard Public School of Health, would realize that Jarrett's cat retrovirus moved not only from mother to kitten, but from adult cat to adult cat. It was sexually transmitted. In retrospect, Essex calls it "remarkable" that a retrovirus in cats would prove so similar to a retrovirus in humans.

It might seem strange that studies of cat cancer in the 1960s would be so valuable to a human epidemic in the 1980s, but if scientists had not been familiar with retroviruses, had they not seen common symptoms in cats and humans, finding a cause for AIDS could have been set back a decade.

While scientists were learning the vices of a retrovirus, they also gained the skills to test for it. In 1970, Howard Temin, the biologist who initially proposed how retroviruses work, announced the discovery of an enzyme within a retrovirus that works feverishly to put nature in reverse, translating RNA into DNA. David Baltimore, an MIT scientist, made the discovery simultaneously, and both were awarded the Nobel Prize in 1975 for their discovery of reverse transcriptase.

Measuring the level of activity of RT would enable researchers to determine if a retrovirus was present. The activity of any enzyme is detectable with an assay, a test that looks for change in the specific ingredients an enzyme needs for its reaction: if a required ingredient is being used up, then the enzyme must be hard at work. This one diagnostic test would make the difference between a crime scene wiped of fingerprints and one streaked with muddy footprints; scientists could detect if a retrovirus was there.

Eager scientists set out in the 1970s to follow in Temin and Baltimore's footsteps and develop RT assays. With each success in the field, the ability to detect retroviruses advanced, and they were found in a variety of animals. One of the scientists tracking retroviruses was Robert Gallo, then a researcher at the National Cancer Institute, who was interested in one particular type of animal a retrovirus might infect—*humans*.

Gallo's early work in human retroviruses paved the way to the discovery of HIV. After a long search for human retroviruses, when many didn't believe that any even

existed, Gallo's team discovered the first Human T-cell Lymphotropic Virus (HTLV-I) in 1979, and found a second (HTLV-II) in 1981.

"Luckily and rather amazingly," Gallo co-wrote in a 2003 retrospective, "the conceptual and technical tools arrived in our hands just before the first patients with AIDS." In the process of discovering HTLV I and II, Gallo's team developed technologies vitally important to the AIDS epidemic. They perfected the sensitive conditions needed to perform a RT assay on human cells. They found that HTLV I and II specifically infected T-cells. They also developed methods for growing lymphocytes in culture, specifically which growth factors to use, materials that encourage T-cells to grow. Thus, Gallo wrote, "At the beginning of the 1980s, we had the essential tools required to search for a retrovirus."

These tools were immediately employed once HTLV I and II came into the spotlight. The logical way to search for the cause of AIDS was to examine other diseases with common symptoms and methods of transmission. HTLV I and II jumped off the page. The HTLVs were spread by blood, sex, and from mother to child. The resulting leukemia, cancer of the blood, occurred after a long latency period, and the virus infected T-cells specifically. It all sounded like a description of the new virus.

So when the eyes of the scientific community turned to retroviruses, Gallo was already there, hunting for a third human retrovirus. "He said, 'Let's look for a virus like HTLV-I, or related to HTLV-I, in AIDS,'" recalls Essex. "That was a hypothesis from Day One."

What would it take to declare that a particular retrovirus was the cause of AIDS? Experts suggest many principles as the litmus test for the true cause of an infectious

disease. The most common of these are Koch's postulates, a set of criteria proposed by German physician Robert Koch in the nineteenth century during his studies of anthrax and tuberculosis. Scientists and philosophers apply Koch's postulates to infectious agents to prove they cause a particular disease. But viruses are a sneaky brand of agent that does not entirely fit into these criteria. "People still try to use them," explains K. Codell Carter, "but the postulates are really just about bacteria, so you have to change them when you get to things like viruses." For example, viruses live within a cell, so they cannot be isolated on a Petri dish like bacteria or fungi, as one of Koch's postulates requires. "But [Koch's postulates] are still the route that people go when they're trying to establish causation," says Carter, and he's certain that's what they did when looking for the cause of AIDS. To prove the AIDS virus was a retrovirus, the scientific community would expect evidence to match several of Koch's points.

For a suspected agent to be the cause of an infectious disease, Koch said, it must be shown to be a living organism. This was established for AIDS when behavior and lifestyle were ruled out as the causes and a virus was found. Second, the organism must be shown to be unique to a particular disease—one organism cannot cause two different diseases and vice versa (in other words, no double dipping). This is the criterion many scientists used to argue against existing viruses like CMV or herpes as the cause of AIDS; if they already cause one disease, they don't suddenly cause an additional one.

Some scientists argue for the more nitty-gritty criteria of Koch's postulates, such as injection of the microbe into other animals to show similar symptoms or growing the microbe on an inert Petri dish, which is impossible for viruses; they only grow within

cells. But generally, the scientific community seeks to follow the spirit, not the letter, of Koch's postulates. They look for a universal, necessary cause.

"The idea of a universal, necessary cause is that every case of a given disease will have the same cause," says Carter. "The disease can't occur without it." He says that finding that necessary cause is the crucial step, "and then you can try to figure out a way to have people avoid getting the disease." Curran, Gallo, and others sought to prove a universal necessary cause by finding an agent *required* for the disease to exist, as well as *sufficient* enough to cause the disease on its own.

And they had to do it thoroughly and efficiently, because this was no ordinary footrace, but an international sprint. NIH historian of science Victoria Harden points to the international focus on AIDS as a unique feature that distinguishes it in the history of medicine. "What's different is that [AIDS] was recognized globally, whereas many other [diseases] had different names in local places and were not recognized as a global disease all at once." AIDS was in the spotlight simultaneously across Europe, in the U.S., throughout Africa, and in Central America. A single syndrome was investigated on a global scale, and that demanded a high standard of scientific proof, says Harden. "All these people reading the same journals had to be convinced by the same evidence."

It was before the Bethesda viral conference, in the spring of 1982, when Gallo's lab began looking for a retrovirus. Based on Gallo's experience, he naturally believed a retrovirus was the likely cause, but across the country, it was still only one in a wide range of candidates.

To track their suspect, the team scoured samples from AIDS patients for the smoking gun of a retrovirus, evidence of RT activity. If a retrovirus were the culprit, its

RT enzyme would be doing the dirty work; there would be traces of its activity. Gallo expected to find this activity and, more specifically, expected the virus would be a close variant of HTLV-I or II, the *only* two known human retroviruses.

In France, the Pasteur Institute was carrying out the same test but for different reasons. A subsidiary of the Institute that manufactured vaccines was concerned that plasmas used to make a hepatitis B vaccine, which were coming from America, could be infected with the AIDS agent. With that urging, Luc Montagnier, a scientist studying retroviruses at the Institute, joined forces with two colleagues, Jean-Claude Chermann and Françoise Barré-Sinoussi, to try and detect the molecular intruder. With a piece of tissue from an infected lymph node, a filter in the body that traps invading germs, viruses, and bacteria, the team tested for a virus.

Montagnier cultured the lymphocytes with growth factors to encourage the cells to multiply. He hoped that with the cell machinery churning during multiplication, the retrovirus would also burst into activity. Every day, Montagnier sat and waited, squinting at the cultures under the microscope. Once they were multiplying well, he scooped out cells from the culture every three days and gave them to Barré-Sinoussi for the RT test.

Unfortunately, an RT test is more difficult than other probes for determining the presence of an enzyme. While some enzymes produce big hunks of proteins or cause easily detectable changes in the appearance of a cell, RT assembles tiny strands of DNA, which can be nearly impossible to locate. Those strands, the end product of RT's efforts, become even harder to find once sneakily incorporated into the DNA of the human cell.

So to detect DNA assembly by RT, both teams, Gallo and Montagnier's, got colorful. They each prepared a recipe to begin the reaction, and the most important

ingredients were little DNA building blocks, called nucleotides, specially tagged with a chemical able to change color when activated (these days, scientists use a radioactive marker). Nucleotides click together like Legos to form a DNA strand. In an infected cell, RT will use the tagged blocks to assemble a new strand. Scientists can then easily separate strands out of the sample by their bright color. If an RT test results in a lot of colored DNA, scientists conclude the RT enzyme is present and hard at work.

Few definitive moments of truth exist in science, but the RT test of the AIDS virus was one of them. If the samples from AIDS patients weren't positive for RT activity, all parties would have to go back to the drawing board. It couldn't have been more straightforward: if there was no RT activity, the AIDS agent wasn't a retrovirus.

Gallo's first results were ambiguous. Some showed low-level RT activity, but many none at all. He was not encouraged. But because a similar poor result had occurred with HTLV-I, a known human retrovirus, he wasn't ready to give up. Barré-Sinoussi, on the other hand, was having more success. Montagnier's culture of lymphocytes was showing definite activity. The two tested another sample. It also confirmed RT activity—a smoking gun. It was enough evidence to continue the investigation. Now it was a question of which retrovirus was pulling the trigger.

The process of everyday science has been compared to puzzle making. Scientists working within a familiar and well-established field customarily expect certain outcomes in their experiments. The challenge is fitting all the pieces together to form the right picture. In this way, “normal” science fills up the holes in scientific thought; more puzzles are solved and more hypotheses confirmed every day. Normal science is predictive. But sometimes an anomaly arises: something behaves in an unexpected way.

In this “revolutionary” science, anomalies require a whole new perspective on the facts. Revolutionary science challenges scientists to overcome their traditional views and consider the world in a new way. It is not predictable and never easy.

Perhaps because of the strength of this mind-set, before the researchers would find the true virus causing AIDS, they rushed down the wrong path. Gallo and others expected the AIDS virus to be related to HTLV I or II. “What we were thinking,” says Essex, “was that there’d be an HTLV-III... clearly related to HTLV I and II.” It was the logical, normal approach: expect the most likely cause. They weren’t seeking a revolutionary type of virus.

Gallo reiterated his reasons for suspecting HTLV. It infects T-cells, he said, just like the AIDS virus. HTLV is also prevalent in Haiti, as is AIDS. Moreover, HTLV is transmitted by intimate contact, and viruses that cause leukemia, including HTLV, suppress animals’ immune systems. And the ideal recipe for growing the AIDS virus in culture was also ideal for HTLV. At this point, his growing certainty that the AIDS virus was a type of HTLV was influenced by past experience with HTLV I and II, as well as expectations of normal science that the virus would fit like a piece of the puzzle into the known field of virology.

Montagnier was more open to the idea of perceiving the virus as a completely new pathogen because of an early test he performed to compare the AIDS virus to HTLV. Early on, Montagnier had sent Gallo a request for antibodies, small proteins produced by lymphocytes to bind specific targets, in this case, the proteins of HTLV. Using antibodies that match to specific viruses, like a game of Memory, is a good way to identify a virus. Montagnier wanted to see if Gallo’s HTLV antibodies would tag the

mystery virus lurking in his cell cultures. Then, he could draw a conclusion either way. With a positive result, the virus was probably related to HTLV; with a negative one, he would be certain they were after a new virus.

Essex's experiments at Harvard showed that 35% of a group of samples from AIDS patients reacted to HTLV antibodies—"a tantalizing but imperfect association," Essex recalls. But Montagnier's cells, infected with what he called LAV, for lymphadenopathy associated virus, showed no reactivity to the HTLV antibodies on several separate occasions, and he concluded that his isolated virus was not related to HTLV. Montagnier was buoyed, growing more confident that LAV was the cause of AIDS, not a type of HTLV. In the back of his mind, he kept recalling the argument that the cause of a *new* disease should be a *new* virus. Now, his data fit that theory.

But Gallo was sure the AIDS virus was a variant of HTLV. "I'll readily admit that we thought it would be more closely related than it turned out to be," says Essex, who was working closely with Gallo at the time. Both were skeptical of Montagnier's tests results, which conflicted with their own. In May 1982, while testing RT activity, Gallo's team's got vigorous results from the cells of an AIDS patient labeled "EP." These showed not only RT activity but also tested positive for HTLV proteins. In addition, Gallo's lab found DNA sequences similar to HTLV-I in tissue samples from two other AIDS patients.

In April 1983, Gallo was ready to publish his and Essex's findings, and rallied Montagnier to do the same. The next month, five papers were published in *Science*: Gallo's two on HTLV antibodies in EP and the DNA evidence; two from Essex on his

antibody study and the natural immune suppression of Feline Leukemia Virus; and one from Montagnier, describing LAV.

The news release that accompanied the papers read, “Five reports in this issue of *Science* suggest a possible link between the serious new disease, acquired immune deficiency syndrome (AIDS) and human T-cell leukemia virus (HTLV).” In the center of the article was a picture of a viral capsule budding off the membrane of a cell. A little arrow points to the capsule, and the caption reads, “*Human T-cell leukemia virus. But does it cause AIDS?*” Gallo’s remarks in the article are enthusiastic, citing the number of reasons for taking a close look at HTLV as the cause of AIDS. Essex, however, was more cautious. “I definitely do not want anyone to get the impression that we have proof of cause,” he said in an interview that April. “What we do have is a good lead.”

And that’s what it seemed like, a good lead. But the research wasn’t keeping up with the epidemic. The next month, the CDC reported 1,641 AIDS cases in the US, a rise of 1,200 from the year before. With the pressure on for some degree of certainty, some scientists strode confidently forward with HTLV research, while others felt skeptical. Montagnier was one of the latter.

Montagnier, who later regretted his paper being grouped on the HTLV train, decided with Barré-Sinoussi and Chermann to devote more time to his virus. They were convinced that LAV was not related to HTLV because it did not react to HTLV antibodies. In addition, Montagnier had an even stronger, clearly visible reason the virus must be novel. The cells were dying.

The AIDS virus was lytic—it killed cells. This caused two problems: an experimental dilemma and a theoretical one. First, scientists couldn’t study the virus if

they couldn't keep it alive in the lab. There was no way to keep the virus replicating in a Petri dish without a continual supply of fresh lymphocytes, which was nearly impossible to attain. Gallo's lab continually sent out a plea for fresh samples, but unless they were taken from an AIDS patient and literally carried directly to the lab, most cells arrived in poor, unusable condition. The NIH team later found out that Gallo's ambiguous RT results were due to the poor quality of the samples; they hadn't been tested early enough. Experimental difficulty is often a roadblock in the scientific process, requiring ingenuity and hard work to take a single step forward.

Second, more theoretically, this wasn't how human retroviruses were known to work. When normal cells were infected with the HTLV (I as well as II), the cells became immortal—they grew furiously and continuously. Because of this, HTLV-infected cells multiplied easily in culture, creating a continual supply of HTLV in the lab.

But the AIDS virus was killing cells. And that was only the first of the red flags that popped up that summer to derail Gallo's HTLV hypothesis. The virus didn't look like HTLV. Under an electron microscope, HTLV budding off from a cell is a round particle with a fuzzy, diffuse center. But a virus particle isolated from AIDS looks like a small pear with a dense, black core. Also, a team at the National Cancer Institute began a molecular analysis of the virus. As they sequenced the DNA of the AIDS agent, it became clear that the viral DNA was not similar to HTLV DNA. Finally, two American researchers tested for the virus in at least 20 different samples. They found plenty of RT activity, but all the particles were HTLV-negative.

During this period, the built-in system of checks and balances of the scientific process successfully roared into gear. "The one thing that science does is self correct; if

it there is a problem, somebody will find it and pull it out,” says historian Victoria Harden. Gallo’s team, making no progress in the search for HTLV genes and proteins, began to re-work experiments, including retesting Essex’s antibody results. In addition, they more closely analyzed their own DNA results. The re-analysis provided breathing room that not only illuminated past dead-ends but revealed new, more fruitful paths of research.

First, there was a problem with Essex’s data. He had detected a reaction to HTLV-I antibodies in 35% of the AIDS patients in his study. A technician named Marjorie Robert-Gunoff tried to duplicate his results with more sophisticated technology, and repeatedly found only 10% of AIDS samples tested positive for HTLV. The percentage wasn’t high enough to support the idea that a close variant of HTLV was in every AIDS patient causing the disease. Later on, it was recognized that experimental error led to Essex’s misleading results.

Meanwhile, a scientist named Ed Gelman was reviewing the two DNA cases from Gallo’s *Science* paper. The paper declared that nucleotide sequences of two different isolates of the virus were similar to HTLV sequences. Gelman showed that the sequences were in fact *exactly* HTLV-I. The two patients had been co-infected with both HTLV-I and the new virus.

Around the table at a staff meeting, Gallo began questioning his staff. “What do you think? What do you think?” He asked each one, “Do you believe or don’t you believe that an HTLV-I variant is causing AIDS?” Many admitted it was not a variant. They believed it was another virus altogether.

As the Americans were reviewing the evidence, the Pasteur group was busy working on growing LAV in large quantities and designing a diagnostic test. However, the team was hampered by funding and resource restrictions. All three, Montagnier, Barré-Sinoussi and Chermann, cut back on other research projects to devote more time and resources to tracking the virus. In June 1983, they showed that patients with swollen lymph nodes had antibodies to LAV and not HTLV-I. Believing he had enough evidence to state his case, that LAV was causing AIDS, Montagnier strove to get the attention of his country and U.S., but received almost no attention. All eyes were on the Americans.

So Montagnier took his work to them. A month later, Montagnier presented his material to the AIDS Task Force, Curran's group of AIDS researchers including Gallo and Essex (Curran's three-month gig was now into its third year). Given a few minutes in the midst of a "festival for HTLV," Montagnier spoke to the group about LAV isolation attempts. The presentation included slide pictures of LAV particles. At some point, a NIH electron microscopist in the crowd, Matthew Gonda, was asked to review Montagnier's photos. After staring at them, he remarked to the crowd that the virus looked like a horse anemia virus, part of a subfamily of retroviruses called lentiviruses. Lentiviruses are chronic, slow in onset, and attack the immune system. And they are not closely related to HTLV.

By the fall of 1983, fewer and fewer scientists thought AIDS was being caused by a variant of HTLV, including Gallo. As many scientists do with new data thrown on their desk, Gallo began to re-formulate his hypothesis. Maybe the AIDS virus wasn't a close relative of HTLV-I or II, but perhaps in the same family. The team also accepted that their infected cells were dying, not becoming immortal as HTLV-I and II infected cells

did. There were too many major differences between the new virus and HTLV to be ignored.

It would be a shorter story if the scientific community had jumped as a group onto the retrovirus bandwagon, all throwing support toward Gallo and Montagnier, but that was not the case. Across the country, doctors continued to pursue other viruses. Even after the summer of '83, with advance after advance adding more data to the pot, a group of microscopists began to vocally spread their opinion that the virus did not look like a retrovirus; it looked like an arenavirus. Their outburst was one of many examples that other causes were still being suspected throughout the early 1980s and would continue to be until overwhelming evidence convinced the community otherwise. But Gallo and Montagnier did not waver from their one agreement; the evidence of RT activity was clear-cut. The cause of AIDS was a retrovirus.

The end of 1983 was a quest to get the virus to multiply, multiply, multiply. Montagnier needed more definitive studies to prove his point, Curran recalled, and he just couldn't make enough virus to do that. Without a large amount of virus it was close to impossible to fully characterize the virus or develop a workable blood test. The need for new tools was one of the defining aspects of the history of AIDS, says Harden. "[The scientists] were trying desperately to diagnosis a disease while trying to learn molecular biology. They were about at the place in 1981 that science was in 1900 when they started germ theory." Science simply didn't have the necessary lab techniques or intellectual theory available to deal with a T-cell virus. "They were feeling their way in a bigger intellectual superstructure," says Harden, designing hypotheses of how to get the virus to multiply in large quantities and quickly putting them into practice.

At the time, fresh cells from donors had to be routinely added to keep any sample alive. Both teams needed a group of cells that would continuously refresh itself—an immortal cell line. Eventually, Montagnier’s team found that their virus, LAV, would grow in B lymphocyte tumor cells. Tumor cells grow uncontrollably, constantly replenishing themselves. Gallo’s team had no luck with tumor lines, so they attempted a more creative approach. Mika Popovic, a Czech scientist who had joined the lab in 1980 to work on HTLV-I and II, was handed the production problem. With no success trying to grow individual patient samples, he decided to concentrate the virus by mixing up all individual virus isolates to amass a large amount of virus to work with. Then, by adding the viral juice to a variety of cell cultures, some would hopefully be hardy enough to withstand the virus’s lytic ability. Almost manically, Popovic infected practically every cell culture in the lab with his concoction. He eventually combined several different cultures and had a pool of virus and cells, to which he added more of either as needed. In the end, Popovic had isolates from ten different patients in his retroviral stew.

The drastic measure paid off. Rumor has it that the day Popovic got the results that the stew showed strong and continual RT activity, he turned to another technician and said, “One day we’ll tell our grandchildren about this moment.”

In the last days of 1983, Gallo’s lab injected the first rabbit with their replicating retrovirus, now labeled HTLV-III, the third human retrovirus. A rabbit’s immune system reacts to a virus by making antibodies in the blood, specific proteins to bind and identify the virus. The antibodies are then extracted by bleeding the rabbit and are separated out of the blood. With the sera, the leftover liquid of antibodies, it was possible to test the isolates from AIDS patients to verify that the virus was the same in all of them. By

simply adding a tagged antibody to bind to the virus if present, like a Velcro dart to a cloth dart board, they could prove that yes, this retrovirus, the one that was inoculated into the rabbit, is the same virus infecting all these AIDS patients.

Conversely, the large quantities of the virus allowed for the opposite type of testing—using the virus to test for antibodies in the blood of patients (a much easier and more realistic test than taking a tissue sample from every patient and trying to isolate the virus itself). Two tests were used, an ELISA and a Western Blot. For an ELISA test, a sample of a patient’s blood is spread onto a plate covered in the virus. If there are antibodies to the virus in the blood, meaning the body is busy reacting to an infection of the virus, the antibodies will latch onto the virus on the plate. Then, a colorful chemical that only binds to the antibody-virus complex is added, and the resulting intensity of color on the plate shows the amount of antibodies in the patient’s blood. The ELISA test allowed the first wide-scale testing of the population for the virus.

The Western Blot was used as a confirmatory test. It wasn’t a new technique, but it had never been used as a back up for the ELISA. A Western Blot detects antibodies to various-sized proteins of a virus, such as the large proteins of the virus envelope or the smaller ones of the core. Mark Kaplan, a co-author on Gallo’s 1985 paper, called the Western Blot a “critical piece” of the evidence that this virus was the cause. “It was very important in assuring accuracy of diagnosis,” he says, and what’s more, “it was important to virology, the ability to recognize specific proteins of a virus.” The search for the cause of AIDS recognized and advanced important technologies for diagnosing viral infections.

The first test results provided direct evidence that the virus isolated in both Gallo and Montagnier’s labs was the cause of AIDS. In several blind studies, where the

experimenters didn't know which blood came from which person, 88-100% (depending on the study) of AIDS patients tested positive for antibodies to the virus now called HTLV-III/LAV. A large section of known risk groups, including sexually active homosexuals and drug users, tested positive as well. And only 0.1% of healthy donors from "no-risk" groups tested positive. That convinced us, Essex recalls, because "you could find HIV specific proteins in the vast majority of people who had clinical AIDS." With antibody testing, the teams had shown that without the virus, there is no AIDS. The retrovirus growing in their lab was the cause of AIDS, Gallo would later write; "We were now totally convinced." Curran agrees: "The evidence was overwhelming, that this new virus was causing the condition."

It was time to present the virus to the public. And Gallo was the first to do so, at the April 1984 press conference. But the announcement, introduced by Secretary of Health Margaret Heckler, did not evoke shouts of joy and popping of champagne corks. Instead, the reporter onslaught began: "It looks to me like it's more circumstantial evidence than hard and fast proof." "Have you been able to take this agent, infect it into animals, and have an AIDS-like disease?" "When was HTLV first found?" "Is it the same as LAV?" "Are you resolving the differences between the two viruses?" The questions from the press led to public hesitancy to believe that one officially announced cause was the true cause. Only months before, scientists from Emory University had announced that the cause was very likely a fungus that releases a toxin that attacks the immune system. If the fungus theory was wrong, why was Gallo right? One voice at the press conference summarized the concerns of the rest: "Yesterday, just a couple of days ago, comments about the AIDS virus were very scattered... and today we're getting very

bold statements. What accounts for the difference?" Even as the scientific community rallied early behind HTLV-III/LAV, the public needed to be convinced.

The following year and a half would be later referred to as a period of "intense discovery." The teams made great strides characterizing, understanding, and treating the virus. "We accumulated more and more evidence as time went on," Essex recalls, "and it became more and more compelling." Gallo's lab sequenced the genome of the virus, which surprisingly had a large amount of variation from one isolate to the next. In fact, a single virus in a single cell line could mutate over time. Montagnier watched this occur with fascination as the virus in one of his lines became more and more lytic as months passed. DNA sequencing also showed that the virus wasn't a member of the HTLV family, although the HTLV-III nomenclature would linger a while longer.

A trio of scientists in London placed another remaining piece into the puzzle. The virus appeared to be attaching to particular receptors on T-cells, CD4 receptors. These outer proteins, like doorknobs for the virus arriving at the cell, would later become hotspots for therapies. Another potentially therapeutic advance was identification of the proteins on the outside of the virus envelope itself. Both sets of proteins were quickly characterized and later targeted for drug therapies.

The advances came so great and so fast that Gallo himself grew more and more certain. At the April press conference, Gallo's most forthright assertion was, "I think the agent is at hand that produces the disease." Five months later, in a newspaper interview, Gallo voiced a new strength. "Clearly, HTLV-III causes AIDS. Anybody who doesn't say that doesn't know the facts. There's just no question about it." Montagnier would agree: "LAV/HTLV-III was indeed the cause of AIDS, period."

When the LAV and HTLV-III genomes were finally sequenced, it was agreed that the two men who pursued the same goal with different methods had indeed found the same virus. The Parisian LAV and the American HTLV-III proved to be genetically identical. Soon, an international committee convened to pick a simpler name for the virus. It was dubbed the Human Immunodeficiency Virus, or HIV. But more important than a name change, a group of researchers at Duke University, along with Samuel Broder at NCI, found and developed a drug called zidovudine. Today we refer to it as AZT. AZT was the first drug approved for the treatment of HIV. It works by targeting the RT enzyme and inhibiting its activity.

At the end of 1985, six years after the first hints of the disease appeared in the U.S., all of the above had been accomplished. Scientists overcame the potentially paralyzing lag time between infection and disease, and they threaded through the maze of opportunistic infections to find a single cause. Because AIDS was a “unique challenge,” Montagnier and Gallo agreed, “an exceptional linkage of agent to disease had to be established,” and they believed that it was. The scientific evidence that HIV is the cause of AIDS was both direct and indirect. The most direct evidence was repeated isolation of HIV from patients with AIDS. The virus could be grown in the lab, observed under the microscope, tagged with antibodies, and monitored for reverse transcriptase activity. Second, an easily reproducible blood test enabled the general population to be tested for HIV. People with AIDS tested positive. People without AIDS tested negative.

Indirect evidence came from animal studies as well as test tubes. First, a virus closely related to HIV, simian immunodeficiency virus (SIV), caused AIDS in monkeys.

Second, evidence from the lab showed HIV's preference for killing CD4+ T-cells. The depletion of these specific cells is the hallmark of AIDS.

By that time, AIDS had infected over 10,000 Americans, taking 4,942 of their lives. Around the world, scientists and the public were eager embrace the cause and move onto ending the epidemic. But unfortunately, there was no checklist for Gallo and Montagnier to sign off on, no celebratory final dinner. Yet for a scientist there was reward enough—"acceptance in the scientific community that what we now call HIV was the cause," recalls Max Essex. "The epidemiological evidence was far better than the evidence that, say, polio virus causes polio or that adenovirus causes the common cold."

Yet doubters continued to poke and prod around the edges, to the angst of the virologists. After years of asking, questions from the media, such as, "Is this really the cause," did not easily die down, and they were spurred on by trials over blood test patents and lab misconduct that followed. In addition, some scientists continued to seek co-factors, other microbes that could be influencing the development of HIV into full-blown AIDS, an action the press regularly interpreted as doubt in HIV itself.

When Gallo was questioned in April 1986 (exactly two years after the press conference announcing that HTLV-III/LAV was the cause of AIDS) by an acquaintance, Dr. Lowell Harmison, as to whether he was *sure* that he and the French had found the *true* cause and not as associated virus, Gallo wrote:

"Lowell, for the record and for the 1,000 × 10⁶ time: I said it first unofficially; I said it officially; I will say it for the last time—I am as positive as a scientist can be that HTLV-III (or LAV or whatever one wants to call the virus), the third known human retrovirus, is the direct cause of AIDS. I am sure that if it is removed from man AIDS

will be no more. Lastly, I wish the hell I could get back to work and get all the monkeys off my back.”

Two major events in the 1980s and the 1990s ended the questioning and cemented the certainty that HIV is the cause of AIDS. The first was evidence from blood transfusions. In a 1985 study, two ELISA tests and a Western Blot were used to determine the presence of HIV in blood transfusion recipients with AIDS and their donors. Twenty-eight of twenty-eight people who had acquired AIDS through blood transfusions were infected with HIV. Even more importantly, in every one of those cases, at least one blood donor for each recipient was infected with HIV. It was compelling evidence for the direct cause-and-effect relationship between HIV and AIDS. Every transfusion recipient who developed AIDS received blood from a donor with HIV. Nine years later, 7,223 cases of AIDS in the US that resulted from blood transfusions had been reported. Virtually all could be traced to transfusions received before HIV blood bank screening began.

The second, more subtle batch of evidence had to do with drugs. When asked to reflect on his certainty that HIV is the cause of AIDS, Max Essex was quick to reminisce not to the 1980s, but to the 1990s. “In my opinion,” he says, “there’s no room whatsoever for [AIDS denialism] on a scientific basis in the last twelve years. Namely, ever since antiretroviral drugs have been used that were designed deliberately to attack virus.” He chuckles and admits, “It might sound odd,” but as far as he is concerned, evidence from drug therapies is the “ultimate proof.”

Therapy against an infection aims to either kill the agent or keep it from multiplying. For viruses, their nature makes killing a hard thing to do; they live inside of

cells, and, some would argue, aren't technically alive. Thus, killing the virus is equivalent to killing cells, which only makes a patient sicker. Instead, pharmaceuticals aim to stop the virus from multiplying.

The complex life cycle of HIV—its reversal of the central dogma and manipulation of a cell's machinery—is a bane to researchers but a benefit to drug makers; it provides many targets to stop the virus. AZT took a shot at reverse transcriptase, preventing the enzyme from synthesizing viral RNA into DNA inside a human cell, bringing the viral factory to a grinding halt.

Modern drugs called HAARTs, or highly active antiretroviral therapy, are cocktail combinations of drugs designed to hit HIV in several different stages of its life cycle. “HIV is the first case with a viral disease where drugs were directed deliberately at the virus and were shown to dramatically lower the virus's ability to replicate,” says Essex. One of these drugs is a protease inhibitor, a little molecule that disables HIV protease, an enzyme that helps reproduced virus bud off an infected cell. The protease looks like a spider hunched over its prey, its legs curled threateningly beneath it. In 1995, the first protease inhibitor, a small molecule that caught and tangled up the spider's legs, was designed to directly target HIV, and no other virus. Another type of HAART blocks HIV from binding with a T-cell by slipping snugly into the CD4 receptors on its surface, hiding the cell's doorknob.

HIV drugs are so specific, says Essex, “they don't work against even other viruses.” Specifically designed drugs that directly target and affect HIV and promote recovery in AIDS patients are further proof that HIV is the cause of AIDS. As Harden

says, “People watched people on brink of death come back after given retroviral drugs. That’s a very compelling piece of evidence.”

Christine Maggiore argues that doctors and scientists “act as if the idea that we should rigorously prove [HIV] is there” is crazy. And she’s right. The medical community thinks Maggiore and other AIDS denialists are nuts when demanding rigorous proof that HIV causes AIDS. Because they know the proof already exists.

Science has respect for criticism and doubt. It exists in competition between labs, repetition of tests, and the almost religious dogma that once a fact or law has been disproved, the community will reject it. HIV as the cause of AIDS has survived battery after battery of tests, and is now a steadfast theory in science. It was the basis for diagnostic tests to account for and track the epidemic, and it has promoted the creation and successful use of life-saving therapies. Gallo calls HIV the *sine qua non* of AIDS, meaning, “Without which it could not be.” With recent technology that can detect the virus in virtually all AIDS patients and successful drugs that target the HIV virus, the cause and effect of virus and disease are so tightly coupled that scientists will not only say, “HIV is the cause of AIDS,” they will also say, “If you don’t have HIV, you don’t have AIDS.”

We aren’t as afraid of AIDS as we used to be. Knowledge about HIV has stemmed most of that tide: we know how AIDS is transmitted, how it affects our immune systems, and how to combat it. But perhaps our newly relaxed attitude toward this epidemic, still raging at home and in Africa, but largely out of sight, has allowed denialist views to gain traction. More and more people around the world contact Maggiore on a

daily basis, including journalists. She says her book is at use at a medical school in Florida. Documentary filmmakers come to record her story. And once in awhile, a doctor will call and say she's welcome to refer clients to him.

Why organizations and individuals deny AIDS and not other viral diseases like rabies, mumps, or the flu, isn't clear. "There are enough viral diseases now that are well accepted," says Carter, that AIDS denialism cannot purely stem from the greater difficulty of recognizing and isolating a virus compared to other pathogens. According to Max Essex, some denialists argue that a disease cannot be defined as T-cell loss. AIDS, they say, should be classified as a combination of Kaposi's, tuberculosis, wasting, and other maladies. "To me, that's not fair," replies Essex. "We had TB and the others before either AIDS or the virus." These denialists are unwilling to accept the unusual nature of AIDS, that a single syndrome does not manifest with one set of symptoms. The loss of T-cells, the defining characteristic of AIDS, opens the door for a variety of microbes to enter the body and produce a range of illnesses.

And what about others, who accept the nature of AIDS but deny that HIV is the cause? "They're avoiding responsibility, or they're just ignorant of the data, or they don't understand it," Gallo said in a magazine interview. Harden, who studied both early AIDS research and AIDS denialism claims, believes that people simply love conspiracy. "There are still people who think earth's flat, still people who think we didn't go to the moon. There are people who resist," she concludes. Mark Kaplan, now Chief of Infectious Diseases at North Shore University Hospital, thinks it may go back to an age-old wisdom—it's all about the money; "Duesberg gets a lot of press for his denialist views; he gets money from denialist groups; he made a fortune." But whatever the

reason, “There’s no room for argument,” stresses Essex. “It’s just playing games and being silly saying that HIV isn’t the cause of AIDS.”

The scientific process leading to the discovery of HIV was fraught with error, feuds, uncertainty, and differences of opinion. That is to say, it was like every other major scientific advance. But not a single hiccup or bump in the road should justify the denial of an observable and proven scientific fact.

The researchers who blazed the trail, made mistakes, and tried again, proved beyond a doubt that HIV is the cause of AIDS. But, as much as we wish it were, the research on HIV and AIDS isn’t done. As Gallo and Montagnier would write nineteen years after their discovery, “finding the cause of an infectious disease is the alpha but not the omega of its eradication.” Today, no cure for AIDS has been found. Drug therapy prolongs health and lifespan, but HIV still lurks, embedding its genes in the heart of our DNA.

Biographical Note

Megan Rulison is a graduate of Boston College in Chestnut Hill, MA. Recipient of the 2005 Kennedy Center National Student Dramaturgy Award and a 2006-2007 Programs Fellow at the Museum of Science, Boston, Megan has always had one foot in the arts and the other in the sciences. This thesis is a continuation of her interest in the interaction of science and the public.

Acknowledgement

Special thanks to the Office of the Director and the Office of History at the National Institutes of Health in Bethesda, Maryland, for their gracious assistance in digging through archival material. I want to thank Jim Curran, Max Essex, and Mark Kaplan for sharing their time and memories, as well as Victoria Harden, Deborah Kraut, John Moore, Christine Maggiore, and K. Codell Carter for their insights and suggestions. Finally, my gratitude to Marcia Bartusiak, writer and thesis advisor extraordinaire, my family for their loving support, and Ryan, for sharing my enthusiasm and being my walking thesaurus.

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