SCIENCE FICTIONS

A SCIENTIFIC MYSTERY, A MASSIVE COVER-UP, AND THE DARK LEGACY OF ROBERT GALLO

JOHN CREWDSON

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threatened to "come out in public and tell everybody" how the cancer-virus program "almost destroyed NCI."[19]

Cancer still killed more Americans by far. But AIDS was the disease of the moment, and the Reagan administration's priority was putting Gallo's blood test into service. At least twenty-three million tests a year, the government estimated, would be needed to keep the blood supply virus-free. In case the blood banks and other prospective customers might be tempted to buy the Pasteur ELISA, Gallo offered a reminder that "no one else but our NCI laboratory has the cell line that produces this virus. Without the specific virus, they can't have a specific test."[e]

Gallo's professions of uncertainty about whether LAV and HTLV-3 were the same virus had dampened enthusiasm for the Pasteur ELISA, and within days of Heckler's news conference companies had begun lining up for licenses to manufacture the Gallo test. First to apply was Baxter-Travenol, which took the opportunity to praise Gallo for "the outstanding work you have just reported on the relationship between AIDS and HTLV."[20] Within a week, more than twenty other companies had requested applications, prompting the official in charge of licensing government patents to complain that "the phone is ringing off the hook regarding Dr. Gallo's inventions."[21]

The applicants ranged from pharmaceutical powerhouses like Becton Dickinson and Warner-Lambert, to biotech boutiques like Seragen, Chiron, and Cetus. Even Max Essex's Cambridge BioScience, apparently hoping to recoup its misbegotten investment in the test for HTLV-MA, had submitted an application.[22] Also on the list were the three Gallo contract companies that had helped grow the AIDS virus and perfect the blood test: Biotech Research Laboratories, run by Gallo's one-time postdoc, Bob Ting; Electronucleonics, which had been put in charge of culturing the Chardon virus; and Litton Bionetics, where Samgadharan had developed the Gallo ELISA.

The most formidable competitor by far was Chicago's Abbott Laboratories, which had pioneered the field of diagnostic blood testing and dominated the worldwide market. Although Abbott's consumer items were household names, the bulk of Abbott's business was done with hospitals and laboratories, to many of which Abbott already was selling an ELISA for antibodies to the hepatitis B virus.

Racing to meet Heckler's six-month deadline, an HHS committee charged with evaluating the competing applications chose Abbott

first and Baxter-Travenol second, followed by the three Gallo contractors — but only after Electronucleonics and Biotech had formed hasty commercial partnerships with Organon and DuPont to manufacture and distribute their tests.[23] Vince DeVita remembered being concerned that the three contractors, who had been working with HTLV-3 for months, had taken advantage of an inside edge in what was supposed to be an impartial government competition. "The companies who heard about it and tried to compete from scratch were at a competitive disadvantage," DeVita said.

For Margaret Heckler, who evidently didn't have similar concerns, the licensing agreements marked "an important milestone in our drive to conquer AIDS."[24] *Science* headlined its story "Five firms with the Right Stuff," but there wasn't anything magic about the number five.[25] The government had been free to issue as many licenses as it liked, or as few. "If all of the applications had met the criteria," declared the committee's chairman, a senior HHS executive named Lowell Harmison, "all would have been awarded a license." But Harmison didn't explain how three government contractors in the Maryland suburbs had rated ahead of Becton Dickinson, Warner-Lambert, Chiron, and Cetus.

The official reason for requiring government licenses at all was to ensure the quality of the AIDS test.[26] In fact, the licenses were royalty agreements that had nothing to do with the accuracy of the individual tests. No AIDS test could reach the market until its quality had been verified by the U.S. Food and Drug Administration, the agency charged with approving all medical devices. The real reason for the patent licenses, an HHS lawyer acknowledged, was to give the five chosen companies "the opportunity to develop a strong market position."[27]

In return for HTLV-3B and the H-9 cell line, Abbott and the four other companies agreed to pay HHS five percent of their gross sales. Assuming the companies sold twenty million tests a year at three dollars apiece, HHS would pick up an extra $3 million annually — a miniscule sum by government standards. The real benefit for the government, one HHS attorney admitted, was "scientific pride."[28]

The theology of the biotech industry held that small companies could move faster than large ones, and Abbott was a gargantuan bureaucracy. But the head of the company's diagnostics division, Jack Schuler, intended to beat the smaller companies at their own game by

creating a small company inside a large one. To head Abbott's ELISA team, Schuler chose a twenty-eight-year-old researcher and gave him ten people. Schuler's only instructions were that Abbott must be first to win FDA approval. "I told them, nobody is going to remember who was second," Schuler said.

The HTLV-3B carried to Frederick by Larry Arthur in April as seed stock for the ELISA virus production had gotten off to a faltering start.[f] HHS had hoped to have enough virus to supply the five companies at the end of May, but two weeks before the deadline Arthur sent Gallo an urgent request for more virus.[29] It was mid-June when representatives of the five companies finally gathered in Frederick to pick up HTLV-3B, the Abbott contingent arriving in one of the company's fleet of corporate jets — a gesture, Schuler said later, that he hoped would send a message to the rest of the company that Abbott was serious about being first.

Although Gallo claimed to have more than fifty isolates of HTLV-3, Popovic's *Science* article had identified just five, including R.F. But scientists eager to begin work on a cure or a vaccine for AIDS were all being given the isolate Gallo called HTLV-3B. "We received the HTLV-3B isolate in May of '84," recalled Robin Weiss. "We got none of the ones listed in Popovic's paper. We asked for them and we never received them. And we kept asking and not getting them."

Gallo's research had been paid for with millions of taxpayer dollars, and Gallo had long been aware of the NIH policy that its cell lines and other discoveries be made available to any qualified scientist who requested them.[g] But Gallo treated HTLV-3B and the H-9 cell line in which it grew best like his personal property. Anyone who wanted either would first have to promise, in writing, not to provide them to another laboratory without Gallo's permission. Moreover, all experiments performed with 3B or H-9 would be done in collaboration with Gallo, who was to be kept informed of his competitors' research in progress, and who retained the option of appearing as a co-author on any resulting publications.[h]

To what was already an unprecedented collaboration agreement for a government laboratory, Peter Fischinger and Lowell Harmison added the admonition that recipients must "maintain in confidence" all information relating to HTLV-3B and H-9. Written confidentiality

agreements would have to be obtained "from all employees to whom the proprietary materials or information will be made available."[30] The reason for the secrecy, Fischinger told Jim Wyngaarden, was to protect the possibility of "further patents by the Government"— particularly those involving H-9, which would be released only at Gallo's discretion, and only then after "a discussion of the resulting collaborative plan."[i]

Between May and December 1984, at least sixty-three laboratories received either HTLV-3B, H-9, or both.[j] The rules, however, were stricter for some than for others. Daniel Zagury got HTLV-3B more than a week before the Heckler news conference.[k] Before the *Science* articles were in print, several of Gallo's other friends had received private invitations to take HTLV-3B and H-9 into their labs.[31] Jerry Groopman, who had introduced Gallo at the Park City symposium, got H-9 three weeks after Margaret Heckler's news conference. When a request arrived from Mike Gottlieb, who had interceded for Chermann at Park City, it was turned down.[32]

For a few others, Gallo tried to impose conditions on which experiments they could perform and which they could not. The agreement drafted for Jim Mullins's signature provided that he could infect H-9 only with viruses that *didn't* cause AIDS — an absurd condition for an AIDS researcher. Disgusted, Mullins never bothered to sign the form.

Bill Haseltine, whom Flossie Wong-Staal considered her principal competitor, got H-9 with the caveat that it could be used only "for the specific purpose of studying expression of HTLV-LTR linked genes."[l] The only scientist explicitly exempted from the collaboration requirement was Robin Weiss. "Collaboration *at will* for Dr. Weiss," Gallo noted on Weiss's agreement, meaning that it was up to Weiss whether to include Gallo as a co-author on his own papers.[m]

"There were lots and lots of people who got reagents from Bob Gallo," Vince DeVita said later. "One of the issues, though, is whether or not there were people who were excluded by a mechanism we could not get a handle on. There were rules that you had to send out to everybody. Would Bob quietly prevent something from going out to a single individual? My guess is he would. If he doesn't like you, you could die of thirst before he'd give you a drink."

Gallo was generous with Murray Gardner, but he was worried about some of Gardner's California colleagues. "Please feel *free* to do

any research you want with HTLV-3," Gallo told Gardner. "My colleagues and I would be pleased to collaborate with you at any time, but we should be involved only when we make real contributions. The cell line is *yours* now. I would appreciate if periodically you keep me informed of projects and collaborators. Obviously, there are some people in your part of the country one can only wonder about."[33]

Gallo didn't say whom he had in mind. But the day Gallo's *Science* articles were published, Jay Levy had written to request Gallo's reagents. "In our studies of AIDS in San Francisco," Levy explained, "we have also isolated retroviruses and now would like to know if any of them are related to the HTLV-3." Levy was growing his AIDS viruses from San Francisco patients in HUT-78, but he wanted Gallo's H-9 cell line as well. Gallo never replied to Levy's request.[n]

Mal Martin's boss, the head of the National Institute of Allergy and Infectious Disease, had underlined for Vince DeVita the urgent need to know whether HTLV-3 and LAV were different viruses — a comparison Martin could easily have performed in his lab with HTLV-3 and the LAV sample Martin obtained in Paris.[34] But the collaborative agreement Gallo prepared for Martin contained the provision that any work with HTLV-3B "not be published without prior approval by Dr. Gallo," and it required Martin's written agreement not to use HTLV-3 "in comparisons with other viruses."[35]

The uninfected H-9 cell line, especially useful to any researcher wanting to make his own isolations of the AIDS virus, had been shared with a half-dozen labs — but not the Pasteur, and Mal Martin wouldn't get it either. The reason, Gallo informed Martin, was that H-9 was "still being characterized." In the event it did become available, Gallo wanted to know what Martin intended to do with the cells. "For instance," Gallo wrote, "I do not think it would be appropriate for you to put the French isolate in them. That is for them to do in collaboration with me and my co-workers and is on-going."

Martin never got either HTLV-3B or H-9. The real reason, Gallo admitted later, was his reluctance to provide his virus or cell line to those he "could not trust," who might "stab me in the back" or "embarrass me or call me dishonest if there was something wrong."[36] Apparently, that description also fit the CDC, whose blood-testing program was expanding rapidly and which faced the same dilemma outlined by Martin's boss: which virus, LAV or HTLV-3B, should be the gold standard for AIDS testing?

That question couldn't be answered without comparing LAV to 3B. But when the CDC met Gallo to take delivery of his virus, the occasion was described by Fred Murphy as "a tense moment, fraught with the possibility of non-delivery."[37] Gallo began by insisting the CDC promise in writing not to compare 3B with LAV. "Our tack," Murphy reported later to Walt Dowdle, "stated in several different ways, was that public health purposes were paramount."

According to Murphy, "Dr. Gallo agreed" with the urgency of the situation. But when Murphy offered "to have certain comparative tests between his HTLV-3 and the French LAV done at CDC, Dr. Gallo declined each time, stating that such work would be done in his lab."

When Murphy pointed out that Max Essex and other collaborators had HTLV-3B in *their* labs, Gallo replied that he viewed the CDC not as a collaborator but a competitor. Only after the CDC complained to Ed Brandt did Gallo agree to release a small quantity of HTLV-3B.[38] But the CDC still couldn't make any comparisons with LAV, and it would have to *pay* the NCI for the virus, at a cost of $72 per liter.[39]

"Gallo's friends received tons of virus for free," recalled Berge Hampar, the manager of the NCI-Frederick facility. Every two weeks, Hampar said, Max Essex was sent the virus-rich cells left over from growing virus for others, including the CDC. When Jim Mason told Jim Wyngaarden that the H-9 cell line was also badly needed by the CDC, Wyngaarden replied that H-9 was being given only to those "who want to collaborate" with Gallo.[40]

Gallo had promised to send Sarngadharan to Paris "very soon" to take part in a formal comparison of HTLV-3B and LAV. But when Robin Weiss arrived in Bethesda on May 11 to pick up his sample of HTLV-3B, he found Gallo on the verge of canceling Sarngadharan's trip.

Weiss spent "much time persuading Gallo that Sarngadharan should indeed go," he told Montagnier later. "Much politics is going on at the moment in the USA," Weiss explained, and Montagnier's name was "being used by CDC to exacerbate difficulties that I believe you yourself have no part in whatsoever. I therefore persuaded Bob that it was imperative for your laboratories to co-operate. In that sense my weekend in Bethesda was probably more valuable than all the research we are pursuing in London."[41]

By the time Sarngadharan arrived in France it was the middle of May. The anger over Gallo's remarks at the news conference, and the Pasteur's treatment in his *Science* articles, was still palpable, and Sarngadharan remembered being greeted by "some animosity."[42] Gallo had initially agreed to let Sarngadharan carry only inactivated HTLV-3B to Paris, which would have been adequate for the comparative studies but wouldn't have been able to grow in the Pasteur labs. "But at the last minute he changed his mind," Montagnier said, "and Dr. Sarngadharan brought live HTLV-3B growing in H-9 cells to our lab."

The unexpected arrival of Gallo's live virus presented the unwelcome possibility of a cross-contamination with LAV, and a nervous Montagnier decided to keep HTLV-3B locked in his own lab, in a different building from where Chermann and Barré were working with LAV. "We both went to his lab," Sarngadharan recalled. "He took a key, opened the door. We walked in and the door automatically locked behind us. And then he took the sample and he gave it to his technician to put it in the hood."[43]

It took Sarngadharan and Chermann four days to agree that the proteins that comprised LAV and HTLV-3B were the same sizes and weights — and, more important, that the core protein Gallo called p24 and the French called p25 was the same molecule, despite their different designations.[o] The two viruses behaved the same way in culture, and AIDS patients had antibodies to both. It was Montagnier's idea to make a chart comparing their principal features —"to show that there were some points that he agreed on," Sarngadharan said later, "and there were some points that we needed to work out."[44]

The only real disagreement concerned a protein, gp41, that Sarngadharan thought was part of the viral envelope. The AIDS patients tested at Pasteur didn't appear to have gp41 antibodies, and Montagnier had reasoned that gp41 must be actin, a cellular protein found in muscles and other contracting tissues.[45] Sarngadharan had been wrong himself, in concluding that the AIDS virus RT had a molecular weight of 100,000 (nearly twice its actual size). But he thought Montagnier was wrong about gp41, and that HTLV-3B and LAV were the same kind of virus.[p]

Sarngadharan's conclusions were confirmed upon his return to Bethesda, when he repeated the experiments using a fresh sample of LAV. As they had been in Paris, the core proteins of the two viruses were a perfect match.[46] When another NIH researcher asked

Gallo whether he should use HTLV-3 or LAV in an upcoming series of experiments, he was advised that "LAV is identical."[47]

As Sarngadharan was leaving Paris, Montagnier asked whether he should destroy the live HTLV-3B culture. "It gave me a shock," Sarngadharan said. "I mean, I was really not expecting that kind of a question from him. I immediately said, 'No. I brought it for you to use. Please keep it. Don't destroy it.' For a second I was confused, but I knew right away if I said, 'Yes, destroy it,' absolutely no way would I know that he indeed destroyed it. The moment I walked out of the lab I stopped knowing anything about the culture."[48]

Don Francis heard about the Paris experiments from an excited Chermann, for whom they represented proof positive that the French had discovered the cause of AIDS.[q] Gallo didn't think it mattered. "I don't give a crap that they are the same or not," Gallo told Francis, who was taking his customary telephone notes.[49] "I'm honest," Gallo told Francis. "I am not trying to say that I was the first to isolate the cause of AIDS. We started the field. We predicted AIDS. We were the first to find cause. You created the problem. If anyone asks who first identified the virus I say the French."

That wasn't what Gallo had been saying in the weeks and months leading up to the Heckler news conference, or at the news conference itself. Gallo had planned a post–news conference visit to France, to attend a small convocation in the village of Talloires near lac d'Annecy. When he canceled at the last minute, Francis and Chermann approached the session chairman, Robin Weiss, who had just published a commentary in *Nature* suggesting that the similarities between 3B and LAV were more striking than the differences.

"We said, 'If you would like, we can update you on LAV and AIDS,'" Francis recalled. "There was a tremendous amount of pressure on Robin to cancel Jean-Claude and me, but Robin allowed us to speak. Robin's a straight guy." Chermann gave what Weiss described as "his usual disorganized talk, bringing the Institut Pasteur group's work up to date." When Francis's turn came, he talked about the CDC's transfusion pair, describing it as "a very tight natural experiment, very important for determining the natural course of AIDS."

"At that point we broke up," Francis said. "We were sitting around a table, and Bill Haseltine came up to me and said, 'Don, how could you possibly have given those specimens to Institute Pasteur and not given them to Bob? How can you justify that?' I turned to him and I

said, 'Bill, we gave all those specimens to Bob. Don't stick your goddamn nose in something you don't know anything about.'"

His encounter with Haseltine still fresh in his mind, when Francis got home he composed an appeal to Gallo, reminding him of the tripartite meeting in Montagnier's office three months before.[50] "I tried to tell you all," Francis said. "I opened our printouts on the serologic results and showed you my summaries. Unfortunately, I understand from you, I did not succeed since you still don't feel that those data have been shared. But I tried to show you that either isolate, when used as a target antigen, scored similarly."

> I tried to reinforce the fact that probably what you had, what we had and what the French had were the same. Jim Curran did the same and encouraged you to complete comparisons before making any broad announcement. On the Sunday before your press conference, I tried again to show you that the bugs were probably the same. The lack of pre-announcement comparison, the lack of substantial mention of the French work at the press conference, and the minimum of credit given the French at subsequent talks and interviews made it look like you wanted to be given credit for first identifying the cause of AIDS. Thus, the perception (and I agree, Bob, it is perception) by me was that you did not want to give due credit to the French. My defense of the French has been because I perceived that they were not being given the credit that I knew they were due.

Due credit aside, in the United States the French were being portrayed as sore losers. According to *Science Digest*, it was Gallo who had "solved the most compelling medical mystery of our time."[51] The *Baltimore Sun* thought Gallo had been victimized by the CDC, which "wanted to ride on the French coattails and share in the credit" for one of the most important medical discoveries in decades.[52] When the *Boston Globe* dispatched its chief science correspondent, Loretta McLaughlin, to find out why there was such bitterness at the Pasteur, Montagnier again blamed Gallo.[53] "He could have grown our virus and analyzed it when we sent it to him," Montagnier said. "But that is not his way. His way is not to confirm the work of others."

Chermann thought Gallo's behavior was explained by the fact that "they have been under more pressure in the States to come with some answers fast. They were very concerned with a molecular biology approach. We were looking for a virus. It was sort of like they were looking for a door with one or two keys — HTLV-1 and HTLV-2 — while we were also looking for a door, but telling ourselves that an entirely different type of key might open it."[54]

The correspondence flying between Bethesda and Paris was more embittered than the public statements. It wasn't "easy or pleasant" to revisit the past, Gallo told Chermann in a letter he copied to Jim Wyngaarden, Ed Brandt, Vince DeVita, and Peter Fischinger. But Gallo thought a proper accounting of recent history was necessary, "after the peculiar press treatment we have received . . . and the statements attributed to you, Luc Montagnier, and the 'unnamed' people at the Pasteur Institute."[55]

The package Montagnier delivered to Gallo's house in July, Gallo said, had contained "no detectable virus particles." The second shipment, sent by Françoise Barré in September, did contain LAV, but Popovic had only grown it in fresh T-cells, not HUT-78 or any other continuous cell line. Despite what the French obviously suspected, Gallo had never "mass-produced" the French virus. "We assumed that was your job," Gallo told Chermann. "We also did not want to cross contaminate our lines."

Gallo mainly wanted Chermann to know that the French hadn't been first to find the AIDS virus. "Our first identification of HTLV-3," Gallo declared, "was November 1982. We had several more isolates in February 1983, but did not choose to report on our electron microscopy or reverse transcriptase studies until we had further characterized the virus."[56]

"I am confused," an astonished Chermann replied, "by your statement that your first isolate of HTLV-3 was in November 1982. Is this a typographical error or did you really withhold this information from me for that long of a period?"[57]

Gallo and Montagnier found themselves face-to-face in mid-June, at a tumor virus meeting in Denver, whose organizers had arranged a joint news conference.[58] In the corridors at the Denver meeting, the consuming topic of conversation was the mounting tension over the rela-

tionship between HTLV-3B and LAV; Fred Murphy recalled being assured by a member of Gallo's lab that, whatever the CDC might think, 3B and LAV were different viruses.[59] At the news conference, Gallo was equivocal. "There is data now," he said, "that they *could* belong to the same virus group of the same virus family."

But Gallo cautioned that the data was only preliminary. A final determination would have to await the comparison of the two viruses at the DNA level.[60] Montagnier tried to point out that the comparisons by Chermann and Sarngadharan had established that the two viruses were the same, but his attempts to explain the subtleties of competitive radioimmunoassays hadn't succeeded. "I was not quite happy about that press conference," Montagnier said later. "Gallo speaks faster than me in English."

According to Gallo, one of those spreading "the plot and innuendo" in Denver "about HTLV-3 and LAV being the same" was George Todaro, who had landed in Seattle after leaving the NCI.[61] Besides running a lab at the University of Washington, Todaro was serving as scientific adviser to a small Seattle company, Genetic Systems, that had been among the losers in the competition to license the Gallo AIDS test.

The Harmison committee had credited Genetic Systems with superior scientific experience and technology. Its only shortcoming, the panel said, was the fact that the company had never marketed an ELISA. But Genetic Systems's CEO, a flamboyant thirty-six-year-old scientist named Robert Nowinski, was convinced the real reason for the rejection was the longstanding enmity between Gallo and Todaro. "George and I probably had more experience in retroviruses than all the applicants put together," Nowinski said.

Genetic Systems's only products, a set of monoclonal antibodies for the diagnosis of herpes, chlamydia, and other sexually transmitted diseases, had come on the market the year before. But most of the company's value had been created by Wall Street's fascination with biotech stocks, and that fascination wouldn't last forever without some earnings. Genetic Systems was looking for a score, and the AIDS test was a guaranteed moneymaker. If Nowinski and Todaro couldn't sell the Gallo ELISA, they would get around the Gallo patents by going to France.

Todaro remembered having been impressed by Montagnier's presentation at the scientific sessions in Denver. "His data were so much

better than anyone else's," Todaro recalled, "and they were ignoring him. I convinced Montagnier to change his plans and come out to Seattle to meet with the executives at Genetic Systems."

The Pasteur had everything Genetic Systems needed: an AIDS virus and a cell line in which to grow it, and a patent application that had been filed months before Gallo's.[62] "We made our deal with the Pasteur in one day," Nowinski recalled. "We flew to Paris, we arrived at four o'clock and by eleven o'clock that night we had the arrangement made. The collaboration was really exceptional." "Let them bark in the wind," Gallo told the *Wall Street Journal*. "Genetic Systems is interested in money. I'm not."[r]

Once the discovery of HTLV-3 was in print, the appetites of the medical and scientific journals for articles about AIDS became insatiable. The French, whose efforts to publish their most important findings had been stymied for months, were quick to take advantage of the opening.

Montagnier sent *Science* an article on his successful transmission, the previous February, of LAV to a continuous B-cell line.[63] Françoise Brun submitted a report of her detection, also in February, of LAV antibodies in 90 percent of Peter Piot's Zairian AIDS patients.[64] Hoping the third time would be a charm, David Klatzmann included the manuscript on T-4 tropism that had been rejected by *Nature* and *PNAS*.[65] Appearing in the same issue of *Science* with Klatzmann's paper was the CDC's report on the transfusion pair.[66]

Had any of those papers appeared before Gallo's publication of HTLV-3, they would have created enormous excitement. But when the articles from Paris and Atlanta finally saw print, they were virtually ignored. Another long-overdue paper to appear was the manuscript Brun and Rouzioux had sent *The Lancet* the previous December, and which unaccountably had languished in the journal's offices for nearly six months.[s] The data in that article was from the fall of 1983, but the *Lancet* editors had permitted Brun to update her results with an addendum.

"Since submission of this paper," it read, "we have introduced . . . technical modifications to the ELISA [which have] increased the sensitivity of the test." With the new test, 75 percent of the AIDS patients and more than 90 percent of those with pre-AIDS were positive for

antibodies to LAV. The last of the backlogged articles, Jay Levy's isolation of ARV from seven San Francisco AIDS patients, appeared in *Science* at the end of August.[67] "We published it third," Levy said, "but that doesn't mean we found it third. We've always been like, 'Oh, yes, there was Jay Levy,' when actually we were right there at the beginning."

In the world outside the laboratory, facts mattered less than perceptions. It appeared to be true, as Levy claimed, that he was the first American researcher to have isolated the AIDS virus.[t] But Levy was a long way from Harvard and the NIH. He wasn't a major player in the retrovirological establishment. He didn't chair major scientific meetings or edit their proceedings. He didn't command half a hundred scientists and technicians, and he didn't have any contract laboratories to call on for help. No editors were expediting the publication of his papers, and the secretary of health and human services wasn't announcing his discoveries. At a critical moment Jay Levy had done some outstanding science, but that mattered less than who Jay Levy was — or wasn't.

"It's all Hollywood," said Flossie Wong-Staal's husband, Steve Staal, on the verge of leaving the NCI to set up a private oncology practice. "The whole business has the ethics of a used-car lot. It's what you can get away with. The older-style scientists are falling by the wayside. To be a success in science these days, you need a big operation. You need a different sort of talent than just the ability to be a good experimenter or to ask the right questions or be good at the bench. It's become an entrepreneurial business, and Gallo's good at that. He enjoys most of all making contacts and wining and dining and traveling. He works the European connection very heavily."[68]

In the wake of the discovery of the cause of AIDS, the awards and honors flowed in Gallo's direction. From Detroit, the General Motors cancer prize, conferred in recognition of Gallo's "profound" influence on cancer research. From Bombay, the Second Triennial Rameshwardas Birla International Award. From Tokyo, an invitation to deliver the Henry Kaplan Memorial Lecture at the annual meeting of the Princess Takamatsu Cancer Research Fund. From the Italian-American Foundation, headed by frozen pizza magnate Jeno Paulucci, an award for scientific achievement that compared Gallo to Galileo.[69]

Mindful of how much the Nobel Prize had done to enhance Sweden's stature in the world, the Japanese had created their own scien-

tific prize, richer even than the Nobel. Consisting of a gold medal and ten million yen, the Japan Prize was to be awarded each year "on an auspicious day in November."[70] When the National Cancer Institute nominated Gallo, it cited the discovery of HTLV-1 and HTLV-2. In the NCI's opinion, however, it was the discovery of the AIDS virus for which Gallo most deserved to be rewarded.[71]

The NCI's citation didn't mention the French. But Robin Weiss, who was among those asked by the Japanese to submit nominations, did. "They wanted an opinion from a non-French, non-American retrovirologist," Weiss said. "So I had to write a reasoned appraisal of who was prizeworthy. I pushed Françoise Barré. She's the one who did the work. I knew perfectly well they were never going to pick Françoise, because they don't pick women. Women are assistants."[72]

The judges ignored Barré's contribution and selected Montagnier to share the prize with Gallo. But half of the first Japan Prize was cold comfort for the French. To the rest of the world, Robert Gallo was the discoverer of the cause of AIDS, and the Institut Pasteur and Jay Levy among the also-rans.

[e] Robin Weiss observed that Jay Levy in San Francisco was growing ARV-2 in the HUT-78 cell line, and that the CDC in Atlanta was growing LAV, and that even if Gallo's lab had never worked on AIDS, companies interested in making an AIDS test could have sought a license from another laboratory "or done a deal with Institut Pasteur for the U.S. market. I have a feeling that the screening of blood might not have been delayed by a single day without Gallo" (R. Weiss to the author, January 15, 1993).

[f] Arthur's notebooks show that the viability of the AIDS virus culture declined from 34 to 31 percent on April 20, 1984.

[g] In a July 15, 1981, deposition in the case of *Hoffman-LaRoche, Inc., v. David W. Golde, et al.*, Gallo confirmed that NIH's policy was to make cell lines available "to everybody on publication who asks who's a qualified investigator, whether they work in any place, any affiliation, race, color, or creed, and so on. The lines are available on publication."

[h] Many of those who signed the agreement never included Gallo as an author on their subsequent papers, but many others did.

[i] P. Fischinger to J. Wyngaarden, June 27, 1984. Fischinger and Lowell Harmison backed down on the secrecy clause, which Ed Brandt hadn't known about and wouldn't have agreed to (E. Brandt, to SOI, February 24, 1993). Their retreat came after Elkan Blout, dean for academic affairs at the Harvard School of Public Health, protested that the clause placed "unacceptable restrictions on research, is inconsistent with long-standing policies of this and many other major research institutions and threatens to inhibit vital research activity on a major threat to public health" (E. Blout to P. Fischinger, October 10, 1985). In an October 23, 1985, reply, Fischinger assured Blout "that in the University or any other non-profit research environment, secrecy agreements or any attempt from [*sic*] public disclosure be disregarded."

[j] In chronological order: Daniel Zagury; Dani Bolognesi and Bolognesi's Duke University colleague Bart Haynes; Mark Wainberg, a young Canadian researcher who had worked in Gallo's lab; Robin Weiss; the New York Blood Center's Fred Prince (3B only); the CDC's Fred Murphy (3B only); John Sever of NIH (3B only); Gallo's Italian colleague Paolo Rossi; Luc Montagnier; Louis Gazzolo, a French researcher who had worked in Gallo's lab; Antti Vaheri; Martin Hirsch and Bill Haseltine from Harvard; Gallo's cancer-virus colleague Wade Parks, then at the University of Miami; Jean-Claude Chermann; Rubin Sher; Reinhard Kurth; Paul Jolicoeur; George Miller; Fred Jensen of the Cytotech Corporation (3B only); Ian Gust; Fausto Titti; Max Essex; Carel Mulder (3B only); John Sullivan (3B only); M. A. Koch; Friedrich Deinhardt; Gunnel Biberfeld of the Karolinska Institute in Stockholm; Tony Chu (3B only); Gerhard Hunsmann; Gerry Robey at the NCI's Frederick center (3B only); Olivia Prebble (3B only); Jim Curran of the CDC (3B only); Leon Epstein (3B only); Sam Broder (3B only); Francis Barin; Don Burke of San Francisco General Hospital (3B only); Hubert Schoemaker (3B only); Paul Bunn, Adi Gazdar's boss; Kai Krohn; Murray Gardner; Steve Sherwin (3B only); Fredrich Dorner; Arye Rubinstein (3B only);

Joseph Pagano (3B only); Arwin Diwan (3B only); Jerry Groopman; Emin Kansu; Ferenc Toth; Jaap Goudsmit; Otto Thraenhart; Jeff Laurence (3B only); Franz Heinz; John Fahey; Richard Emmons (3B only); Robert Downing; Jun Minowada; Arsene Burny; Volker terMeulen; Peter Wernet; Jim Hoxie; and Phil Hartig.

[k] On April 13, 1984, ten days before the Heckler news conference, Zagury signed a receipt stating that "I received from Dr. Robert C. Gallo (LTCB, NCI, NIH) HT cells (clone 4) and HT cells infected with HTLV3 from AIDS patients as well as antibody anti HTLV3 virus only for research purposes. This material will not be used for any other reasons."

[l] F. Wong-Staal to G. Franchini (undated). When a similar request arrived from Jim Mullins, Ann Sliski advised Gallo that "Flossie may want to write in some further restrictions as she did with Haseltine" (handwritten note appended to letter from J. Mullins to R. Gallo, June 4, 1984).

[m] Weiss's noncollaboration clause proved helpful on at least one occasion. A month before the Heckler news conference, Marguerite Pereira of the Public Health Laboratory Service in London wrote to thank Gallo for having sent HTLV-1 reagents to aid her in tracking the U.K.'s incipient AIDS epidemic (M. Pereira to R. Gallo, March 15, 1984). Gallo waited until the day of the news conference to let Pereira know that he had sent her the wrong virus, and that the actual cause of AIDS was "a new variant" called HTLV-3. Even though Daniel Zagury in Paris had had the virus for over a week, Gallo told Pereira he wasn't able to send the British Public Health Service any HTLV-3 because "we have to have papers published and other assurances" (R. Gallo to M. Pereira, April 23, 1984). When no HTLV-3 was forthcoming from Bethesda, Pereira simply borrowed some from Robin Weiss (M. Pereira to H. Streicher, February 20, 1985).

[n] J. Levy to R. Gallo, May 4, 1984. The letter bears a handwritten notation by someone in Gallo's lab: "Save for staff meeting to decide what to do." Gallo told another researcher, James McDougall of the Fred Hutchinson Cancer Research Center in Seattle, that "we are still in the middle of characterizing some clones. It will be a while before we can distribute them." Gallo added a handwritten note: "Jim, write to me again in about 6 weeks." When McDougall asked again six weeks later, Gallo scribbled "No" across the top of his letter.

[o] M. Sarngadharan to OSI, June 13, 1990. Montagnier named the core protein of LAV p25, to reflect its molecular weight of almost exactly 25,000 daltons. Gallo incorrectly labeled the same protein p24, to artificially enhance the similarities between HTLV-3B and HTLV-1 and HTLV-2, whose core proteins weigh closer to 24,000 daltons.

[p] "We could not detect gp41," Montagnier said later. "Sarang used a Western Blot and he could detect gp41. I could detect a p42, but it was cellular. We missed the gp41 at that time. That's Gallo's contribution. We didn't use the Western blot. We used only

immune precipitation, and if you label the virus you don't label this protein." In less than three weeks Sarngadharan had resolved the temporary discrepancy by putting both HTLV-3B and LAV through a Western Blot. In the middle of the LAV blot was gp41, the protein Montagnier had missed (M. Sarngadharan laboratory notes, June 15, 1984; M. Sarngadharan to OSI, June 13, 1990).

[q] D. Francis telephone notes, May 21, 1984. "Competition — Sarang — infected cells: competition by Françoise — p25 [the viral core protein] same. French side of comparison done."

[r] *Wall Street Journal*, July 5, 1984. Three weeks after Nowinski's announcement, Gallo and Popovic applied for an American patent on the CEM cell line as a method of producing the AIDS virus (U.S. Patent Application 602,946, July 29, 1984). However, Betsy Read's lab notes show that she first infected CEM with the AIDS virus on May 28, 1984, a few days after Sarngadharan's return from Paris — where, according to Robin Weiss, Sarngadharan encountered Weiss's assistant, Rachanee Cheingsong-Popov, delivering the LAV-producing CEM line infected by Weiss three months before.

[s] Brun-Vézinet, F., *et al.* "Detection of IgG antibodies to lymphadenopathy-associated virus in patients with AIDS or lymphadenopathy syndrome." *Lancet* (8389): 1253, June 9, 1984. Ian Munro, editor of *The Lancet* at the time the paper was published, said he could not recall why the manuscript was held up, although he was certain it had not been negatively reviewed by Dr. Gallo "or any of his close (or even remote) colleagues" (I. Munro to the author, August 2, 1993). As for whether Gallo's March 5, 1984, letter to Munro, touting the discovery of HTLV-3 and denigrating the Pasteur's discovery of LAV, had played a role in delaying publication of the Pasteur paper, Munro replied that "I cannot refrain from refuting in the strongest terms the apparent implication that the *Lancet* was a party to some scheme to delay publication of the French paper." Munro's successor, Robin Fox, agreed that any suggestion the journal might intentionally have delayed publication on the basis of Gallo's letter is "far from *The Lancet's* way of working — then and now. . . ." (R. Fox to the author, August 24, 1993).

[t] Judging from his published data, Levy's first isolate of ARV was accomplished prior to November 15, 1983 — the day the cells that produced four of the five isolates identified in Popovic's *Science* article — R.F., B.K., L.S., and W.T. — were first unfrozen and placed in culture. The fifth *Science* isolate, from the patient S.N., was first cultured in cord blood cells on November 16 (C359/SN; B. Read lab notes. R. Gallo to OSI, December 10, 1990). Levy delayed announcing his discovery until he could complete an experiment that hadn't been attempted by either Gallo or the French. "Hemophiliacs had gotten AIDS," Levy said. "The only thing I couldn't explain was how could a retrovirus get into Factor VIII. So I decided before we published we better put a retrovirus through Factor VIII treatment and show that it does, or does not, survive. If it doesn't survive then this is not the cause." Levy had gotten in touch with Cutter Laboratories, a principal manufacturer of Factor VIII, across the

San Francisco Bay in Berkeley. "We set up an experiment in which we used a mouse retrovirus, because it was easy to measure," Levy said. "That took three months, and in March we saw that the mouse retrovirus survived. We realized that a human retrovirus could do it as well, and we set out to find out how do we get rid of it. And we did a heating experiment, which shows that you have to heat it for three days in order to kill it. We put that together and we sent it off to *Lancet*. And then we put together the paper on the isolation for *Science*."

Chapter 7. "Only Because There Are So Many"

[a] "I enclose a complete 1981 list of the Academy including sectional breakdowns," Gallo wrote Fischinger on July 30, 1982. "As we discussed the section most appropriate for me would have been #41 (Medical Genetics, Hematology, and Oncology). Hillary [Koprowski] has, however, nominated me for section 22, Cellular and Developmental Biology. This is likely to be more difficult. I have circled what I feel sure are friends in 41, and those who I hope are at least useful in 22 — just in case you have any chances. Takis Papas has contacts to Dr. Kafatos. He is very good and respected. He is at Harvard. Takis feels he could and would really help. However, he is in Greece until early September. There is a 'straw' vote mid-late August. If I make it in section 22 that is the time for the contacts to key people in this section via Kafatos and Hillary or anyone else."

[b] "Four win awards for cancer work." *New York Times*, June 21, 1984. "Dr. Gallo, a physician, was cited for discoveries that have 'profoundly influenced modern cancer research' by showing that a virus called HTLV-1 is a cause of leukemia in humans . . . [h]is team has recently discovered two related viruses, HTLV-2 and -3. The latter is strongly suspected of causing acquired immune deficiency syndrome, known as AIDS."

[c] According to Gallo's lab records, the four other *Science* cultures, B.K., L.S., S.N., and WT, were discontinued either shortly before, or shortly after, the *Science* paper was published. Betsy Read's lab notes show that while 80 percent of the cells in the H-4/R.F. culture were producing virus on March 1, 1984, by April 11 the number had fallen to less than 20 percent. That none of the five original isolates had been distributed to other laboratories bothered Robin Weiss. "One should be able to continuously propagate them," Weiss said. "If one couldn't, I'd say, 'Well, hold on a minute, they ought to be hardy enough to send to other labs.'"

[d] B. Read lab notes, June 28, 1984. The R.F. culture reported in *Science* was in the less-productive H-4 cell line.

[e] B. Hahn to R. Gallo, April 6, 1990. The viruses were J.K., J.R., L.S., M.R., L.W., and mROD.

[f] In her April 6, 1990, letter to Gallo, Beatrice Hahn states that R.F. was "identified as an independent and genetically distinct isolate" on June 5, 1984.

to say that the etiology was sound. And he was overwhelmingly convinced. Not one fucking picture, but forty-eight isolates. You're being taken for a ride because of big, commercial, economic reasons. The French simply followed my reasoning and followed me."

Years later, Sattaur shook his head at recalling the conversation. "Gallo has this ability to just absorb everything," Sattaur said. "He's wonderful at it. He's so good at manipulating things that I'm pretty sure that unconsciously he's doing it most of the time. If you talk to him about other people's work, he'll say, 'Well, he worked in my lab for six weeks. I taught him everything he knew.' He's a real megalomaniac. I think that's why I got quite angry with myself — I felt I'd been duped, when I found out the other side of things."

Margaret Heckler's October 1984 deadline for putting the AIDS blood test into service had come and gone, with Abbott Laboratories and the other licensees still field-testing their ELISAs in cities where significant numbers of potential blood donors were presumed to be infected with the AIDS virus.[28] Lowell Harmison, the senior HHS official charged with getting the blood test to market, had promised the blood banks the ELISA would be at least 98 percent accurate.[29] But the computer printouts Abbott was sending the Food and Drug Administration showed that at least 60 percent of blood samples scoring positive contained no AIDS virus antibodies at all.[e]

So inaccurate was the American ELISA, the FDA conceded, that it would be necessary to use a more complicated and expensive test, the Western Blot, which registers the presence of antibodies to specific viral proteins, to confirm any ELISA-positive result.[f] When health groups threatened lawsuits to keep the AIDS test from being licensed until its accuracy could be assured,[30] the FDA, which had planned to license all five tests simultaneously, shifted its strategy to putting at least one reasonably accurate test in the hands of the blood banks as quickly as possible.[31] The American Red Cross, which collected more than half the blood donated in the United States and which was the world's biggest purchaser of blood antibody tests, announced that it would buy its AIDS tests from whichever company received the first FDA license.

By the end of January 1985 Margaret Heckler was promising that the AIDS test would be licensed by mid-February. Attempting to

assuage concerns about the risk from unscreened blood, Heckler assured Americans that infection with the AIDS virus didn't mean most people would get AIDS. Only "a small number of those with positive test results," Heckler said, would go on to develop the disease itself.[32] It wasn't true, but it wasn't Heckler's fault. Three days earlier, the Public Health Service's Executive Task Force on AIDS had estimated that only 5 to 20 percent of those infected with the AIDS virus would ever get AIDS.

When mid-February arrived with no AIDS test in sight, Heckler explained that the FDA needed still more field data from Abbott and the other manufacturers.[33] The Red Cross was already negotiating a draft contract with Abbott Laboratories, whom the FDA had pushed to the front of the line.[34] But the Red Cross technicians working with the prototype Abbott test were finding it "extremely cumbersome and labor intensive," and the Red Cross's Boston blood center had "major concerns" about the test's ability to catch every virus-infected blood sample.[35] The Abbott ELISA, a senior Red Cross official complained, had "the potential for causing undue concern for a number of healthy donors" by registering too many false positives, "while not removing from the blood supply all the units that are potentially infectious for AIDS."[36]

In the Reagan administration's view, any AIDS test was better than no test, and on a Saturday afternoon in early March 1985, timed to make the Sunday papers, Margaret Heckler announced that the FDA at last had approved a blood-antibody test for HTLV-3.[37] Jack Schuler, the Abbott executive, recalled being summoned to meet with Heckler early that morning, then watching from her anteroom sofa as a delegation from Electronucleonics, one of the other licensees, filed out of the secretary's office.

Schuler's first thought was that both Abbott and Electronucleonics were being approved at the same time, which would have cost Abbott a substantial share of Red Cross business. Once the Electronucleonics team departed, Heckler reassured Schuler that the FDA had decided to approve Abbott first. She had merely been explaining to Electronucleonics that the approvals were being issued in alphabetical order.[38]

The following day, Abbott closed a deal to supply the Red Cross with a year's worth of ELISA kits at the cut-rate price of ninety-three cents apiece. When the stock market opened on Monday morning,

Abbott's shares began a long upward climb that would see them more than double in price over the next two years.[g] The first blood bank in the world to get the AIDS test was the Red Cross Blood Center on Ohio Street in downtown Chicago, a thirty-minute drive from Abbott's North Chicago headquarters.[39] Accompanying each of the two thousand test kits delivered that Saturday afternoon was a warning that "false positive test results can be expected with a test kit of this nature."[40]

Because of the delays in field-testing, Abbott only had sixty thousand ELISA kits on hand, not nearly enough to fill the nationwide demand. The AIDS test would be rationed among fourteen cities,[h] with no tests available for the rest of the country. A month after the test was approved, the Red Cross was still testing only half its new blood donations, and none of the blood that had been stored in its freezers when the test became available.[41] Testing the stored blood might raise concerns that the blood was unsafe and discourage hospitals from buying it.[42]

Such concerns would have been justified. At the end of March, an Arkansas patient received a pint of blood donated four days after Abbott received its FDA license. Although routine blood testing in Arkansas had begun five days *before* the patient's surgery, the blood used for the man's transfusion hadn't been screened. He later got AIDS. There were other such cases,[43] and not until mid-April of 1985, after nearly three million AIDS tests had been distributed, was Heckler able to report that the domestic backlog had been filled. "As a result," she told researchers attending an international AIDS conference at the CDC, "our manufacturers will now be able to turn their attention to *your* needs — meeting the foreign demand for the test, which has been significant. That is a contribution to the international community we are very proud to make."[44]

Some eight thousand Americans had been diagnosed with AIDS.[45] But there were less than four hundred cases in France, barely two hundred in Germany, and fewer than that in Great Britain. There was plenty of AIDS in Africa, but those cases weren't the result of hospital transfusions, and in the countries whose health systems could afford it, the demand for an AIDS test was less than overwhelming. Gallo reminded a physicians' convention in London that, because of the long lag-time between infection and disease, the number of reported cases was no guide to the number of people actually infected with the virus.

Two million Americans, Gallo declared, were already carrying the AIDS virus — a number that later proved to be far beyond the actual scope of the epidemic.[i] In another two years, Gallo predicted, a half million British would be infected with HTLV-3. Although the actual numbers in Britain would never surpass a tenth of that figure,[j] the headlines generated by Gallo's warning—"British doctors told of massive new AIDS crisis," cried the *Observer* — prompted questions in Parliament and elsewhere about why there was no AIDS test in Britain.

In fact, there was a British AIDS test. Months before, Robin Weiss had developed a laboratory ELISA and used it to test nearly two thousand Londoners, including a thousand randomly selected blood donors, for Weiss's *Lancet* paper concluding that LAV and HTLV-3B were both the cause of AIDS.[46] That none of the randomly selected blood donors had been positive suggested there wasn't much AIDS virus circulating in England. But the National Health Service, hoping to head off what might be an incipient epidemic, wanted to begin precautionary screening of donated blood at a few of its Regional Transfusion Centres.

Weiss had made his ELISA with HTLV-3B, and like everyone who received Gallo's virus he had been required to promise not to use it for commercial purposes. The National Health Service was an agency of the British government, not a private company, and an NHS blood test hardly fit the description of a commercial product. But when British officials asked the Reagan administration for permission to scale-up Weiss's ELISA, they were told to buy their AIDS tests from Abbott or Electronucleonics.[47]

"We are prevented from using a perfectly good and reliable test because the Americans want to make money," one of Weiss's assistants, Angus Dalgleish, told the *Daily Telegraph*. "The American test is worse than useless. It has produced false negative results and even false positives. It's not surprising that the American health department delayed giving it a license. Commercial considerations are absolutely hampering the containment of the disease in Britain. We've allowed AIDS to get a year's start."[48]

A *Daily Telegraph* reader who happened to be a hemophiliac sent a copy of the article to President Reagan with a demand for an explanation. Replying on the president's behalf, Lowell Harmison explained that unfortunately no British company had applied for a license to sell

the Gallo ELISA, and now no more licenses were being issued. The writer and his fellow hemophiliacs would simply have to await the arrival of the AIDS test from one of the American manufacturers.[49]

An angry Robin Weiss responded to the American rebuff by putting "more effort into growing our own isolates." In short order Weiss had isolated an AIDS virus called CBL-1, named for the Chester Beatty Laboratories where Weiss was scientific director, that appeared to grow even better in culture than HTLV-3B. What Weiss did with his own discoveries wasn't governed by his agreement with Gallo or the American government, and CBL-1 was licensed to the British pharmaceutical firm Burroughs Wellcome, which lost no time producing an ELISA — only to receive a stern warning from the United States Department of Commerce that the company had not "been granted any rights under our pending patent rights to market such a kit" in the United Kingdom.[50]

When a rival British company, Amersham Laboratories, announced its intention to make an ELISA with an AIDS virus obtained from Don Francis, the HHS lawyers warned Amersham to cease and desist.[51] Although the CDC virus had been isolated independently of Gallo, the HHS decreed that any competing blood test "would discourage the development of the inventions already made by our licensees."[52] Amersham turned to Abraham Karpas, who provided the company with his own AIDS virus isolate, C-LAV.

The American laboratory and blood-bank technicians called upon to deploy the Gallo AIDS test had little information about how it performed under real-world conditions. When Murray Gardner compared the commercial ELISAs, he found that both Abbott and the new test from Electronucleonics "repeatedly" scored antibody-negative blood samples as positive.[53] The Red Cross was finding the same. Of every four positive blood samples tested with the Abbott ELISA, three were antibody-negative when tested by the Western Blot.[54]

The excessive number of false positives produced wasn't due, as first thought, to technician error or variation in the quality of the test kits, although there was plenty of both. As it happened, the source was Gallo's "revolutionary" method of growing the AIDS virus, the H-9 cell line, which Abbott and the other licensees were using to produce the virus for their ELISAs.

The H-9 phenomenon had first been noticed in Germany, where a surprising number of middle-aged women had begun testing positive

for the AIDS virus —"staid matrons who had only ever been married to one man," said Robin Weiss.[55] "They turned out to have the same HLA group, these women, as H-9 cells. Or their husbands had, and they had had children with their husbands, so they had made antibodies against their fetuses. So they had this antibody that gave positive reactions." So, apparently, did thousands of Americans, including a group of black farmers in rural South Carolina, whose risk for AIDS was virtually zero and who had exhibited a false-positive rate of 300 percent.[56]

Despite efforts to purify the virus from which the tests were being made, some debris from the H-9 cells inevitably remained, apparently including the HLA protein in question.[57] "All five of the licensees who were making virus out of that cell line had this contamination," said Bob Nowinski, whose Genetic Systems was gearing up to manufacture the Pasteur ELISA with virus grown in a different cell line. When the Red Cross sent Nowinski fifty coded blood samples, it discovered that the Genetic Systems test didn't share the false-positive problem —"complete concordance," Nowinski said later, "between the Western Blot and our test."

Like the Pasteur in Paris, Genetic Systems was growing virus in the C-30 cell line David Klatzmann had cloned from CEM, which didn't have the errant protein that was causing all the trouble with H-9.[k] The C-30 clone had grown out of another of Klatzmann's precocious discoveries, that a particular molecule on the surface of T-4 cells seemed to disappear a few hours after those cells were infected with LAV. This, Klatzmann reasoned, must mean the molecule, called CD-4, was the receptor, or portal, through which the AIDS virus found its way to the interior of the cell before beginning to reproduce.

To prove his hypothesis, Klatzmann exposed a batch of uninfected T-4 cells to a synthetic antibody designed to adhere only to the CD-4 protein, then tried infecting the cells with LAV. When no infection occurred, Klatzmann concluded the antibody was blocking the pathway used by the virus. "Maybe because I was not such a hot scientist at that time, it came very easily in my mind," Klatzmann said. "I saw the patient — no T-4 cells. I looked for the tropism, I saw decreasing CD-4 on the cells. It's disappearing because it's the receptor. I started reading a little bit about receptors. All my experiments were very simple."

The identification of the AIDS virus receptor represented a major advance, since once the virus's pathway into the T-4 cell was known,

various strategies could be considered for blocking its entry. Robin Weiss and Mika Popovic also were struggling with the receptor problem, but Weiss had taken a more circuitous route, methodically testing scores of monoclonal antibodies one at a time.

"We didn't know which was which," Weiss recalled. "We went through 150 and we picked out fourteen that blocked, and they were all CD-4. Klatzmann got the same results, but we thought our work was a little bit nicer." Popovic had tried the single-antibody approach, but unlike Klatzmann he had used the wrong antibody. "Mika was unlucky," Weiss said.[58]

Having identified CD-4 as the point of entry for the AIDS virus, Klatzmann sorted through CEM looking for the cells with the most CD-4 proteins, on the assumption that they would the best for growing LAV. "Some cells had quite a lot of CD-4," Klatzmann said, "and some not at all. We made clones, I and the technician in Montagnier's lab. She picked up cells and gave me back the clones. I came out with the C-30 clone, and that was a good virus producer."

The Pasteur might have the best cell line and the most reliable AIDS test, but it didn't have an FDA license or an American patent. In May of 1985, with the French patent application filed seventeen months before still pending before the United States Patent and Trademark Office, the American patent was awarded to the Gallo AIDS test.[59]

The Gallo application had been approved in near-record time — thirteen months, less than half the average for biotechnology patents. The reason, it would later develop, was that the American application had received expedited handling from a special branch of the patent office which examined patents related to national security and nuclear energy.[60] The AIDS test didn't have anything to do with national security, but the number of pending applications in that group was much shorter than in the biotechnology group, where the Pasteur application still languished near the end of the line.[61]

The day after the Gallo patent was awarded, a patent office supervisor named Charlie Van Horn got a call from Bert Rowland, a biotechnology specialist with the Pasteur's San Francisco law firm of Townsend and Townsend.[62] How, Rowland demanded to know, could a patent have been issued to Gallo and the HHS, who had filed *last*, instead of the Institut Pasteur, which had filed first?

Rowland's call was the first Van Horn had heard about a French AIDS test. When the Pasteur application was tracked down and dusted off, the cardboard "wrapper" around the application and its attached documents told the story. The first examiner to whom the Pasteur patent was assigned had protested her lack of qualifications in that particular area of biotechnology. The application had been reassigned to a second examiner, who soon afterward had quit the patent office. A third examiner had inherited the Pasteur file, but had put it aside for later consideration. Now *he* was about to leave. The French application had fallen between the cracks, and nobody at the patent office seemed to have noticed. Or at least that was the story.

To keep track of potential conflicts, the patent office compiles a short description of each application in a central index. As she was expected to do, the examiner who issued the Gallo patent had searched the index to see whether anyone else was claiming to have invented a blood test for AIDS. But the examiner hadn't found any trace of the Pasteur application, because it had never been indexed.[1] Had she known there was a competing application on file, she said later, rather than issuing the Gallo patent she would have requested an "interference," an administrative proceeding intended to sort out competing claims.[63]

Bert Rowland had no idea what had happened to the Pasteur application when he called the NIH patent coordinator, Tom Ferris.[64] Looking at the government's case in the best possible light, Rowland said, the most Gallo could claim was that he had been first to establish a cell line in which the AIDS virus could be continuously grown. But the H-9 cell line was the subject of a separate patent, and considering the false positives H-9 was causing, the Americans were welcome to it. The ELISA was another question, and the Pasteur thought it deserved the patent on the blood test. In Rowland's opinion, the simplest solution would be for HHS to add Montagnier, Chermann, and Barré as co-inventors on the Gallo patent and to split the royalties fifty-fifty with the French.

Rowland asked for a chance to carry the Pasteur's complaint to NIH higher-ups, and Ferris suggested he call Peter Fischinger. When Rowland replied that he would prefer to speak to someone "less apt to be biased," Ferris suggested Lowell Harmison. When Rowland rang Harmison, he was assured that the HHS was as interested in an amicable settlement as the French. Suppose, Harmison said, HHS agreed

to add Montagnier and the other French inventors to the Gallo patent. Would Pasteur be willing to add Gallo, Popovic, and Sarngadharan to its own application? No, Rowland replied. The French had developed the AIDS test first, and without any help from Gallo, whereas Gallo had developed his AIDS test second, and with considerable help from the French.[65]

Another Pasteur lawyer, Gerard Weiser, tried to explain to the patent office that LAV and HTLV-3B were two names for the AIDS virus, and that the blood tests made with those viruses must be the same invention. With the DNA sequences in print and Gallo's own acknowledgment in *Nature* that HTLV-3B and LAV were "variants of the same AIDS virus,"[66] Weiser's task should have been easy. But the patent office hadn't been persuaded.[67] Fischinger, Harmison, and other senior HHS and NCI executives had seen copies of Gallo's correspondence with Montagnier, Barré, and Chermann, and they had known for more than a year how angry the French researchers were. But the calls from Rowland and Weiser were the first indications the government might be in for a serious fight with the Pasteur Institute itself.

Gallo, on a visit to Paris when the French began tossing grenades, had erupted himself upon learning that Rock Hudson, the American actor, was being treated for AIDS at the Institut Pasteur.[68] "Something is very wrong," Gallo wrote Vince DeVita, "when this man and many other Americans are heading to the Pasteur for treatment." According to Gallo, the National Cancer Institute had "much retrovirus talent, much more molecular biology talent, considerably greater facilities, [and] much more experience" than the Pasteur, not to mention "far more ideas."[69]

DeVita, who had just finished responding to inquiries from at least two senators whose constituents were complaining of "scientific impropriety" surrounding the discovery of HTLV-3,[m] lost his patience when he saw Gallo's memo. "I hardly need to be reminded of your accomplishments," he shot back, "since I have watched them with great interest and have played a role in assuring you receive proper credit including the national recognition that has come with the receipt of many prizes in the past three years. I believe that Dr. Montagnier would probably feel that he has been under recognized if

[b] B. Read lab notes, June 28, 1984. To Popovic's consternation, by the time the *Science* papers were published in May of 1984 Matt Gonda hadn't been able to photograph any virus in R.F.'s cells (Visiting Associate, LTCB, DTP, DCT, NCI, to Chief, Laboratory of Tumor Cell Biology, DPT, DCT, NCI. November 28, 1984). Struggling over the summer of 1984 to get HTLV-3_{RF} "out the door" of Gallo's lab, Popovic asked Gonda to try one more time to find the AIDS virus in the original R.F. cells. "Mika was extremely aggravated," Gonda recalled, "and wanted us to go back until we found virus." In October 1984, after re-examining the original R.F. sample from early in the year, Gonda finally found a solitary particle of HTLV-3 — the equivalent of one virus per six thousand cells, an indication that the R.F. culture hadn't been very productive (M. Gonda to M. Popovic, October 17, 1984; M. Gonda to OSI, August 13, 1990).

[c] According to a summary of Francis's March 11, 1992, interview with the General Accounting Office, "Dr. Gallo telephoned Dr. Francis to express in a caustic manner his displeasure that he had hired 'Kaly' away from him. During the conversation Dr. Gallo made direct references to Dr. Francis that he would prevent him from publishing in the future or perform any work in the area of retrovirology."

[d] In a letter to the author dated June 14, 1991, Kalyanaraman's attorney stated that "Dr. Kalyanaraman did not make the statements referred to" by Omar Sattaur.

[e] Abbott Laboratories, Inc. Product License Application for the Manufacture of Human T-Lymphotropic Virus, Type III, December 19, 1984. Of 7,758 blood samples from "normal healthy donors," forty-two tested positive. Of these, seventeen were true positives and twenty-five false positives.

[f] FDA AIDS workshop, December 26, 1984. "Initial studies indicate that all tests successfully identify HTLV III reactive samples but confirmatory testing will be required since a significant proportion of donor samples yield false positive results."

[g] Electronucleonics received its license on Thursday, March 7, 1985.

[h] Philadelphia got 8,000 tests, followed by Boston (7,300), Los Angeles (7,000), Detroit (6,000), Cleveland (5,000), Washington, D.C. (4,500), and Atlanta (4,000).

[i] At the time Gallo spoke, between 200,000 and 300,000 Americans were believed to be infected with the AIDS virus. Subsequent epidemiological studies have shown that, even at the epidemic's peak, there were never more than 750,000 at any one time, and probably substantially fewer.

[j] By the end of 1999, according to the U.K. Public Health Laboratory, 32,200 British had been diagnosed as infected with the AIDS virus, and 15,500 of those had subsequently developed AIDS, 12,800 of whom had died.

[k] Montagnier credited Robin Weiss for "the beginning of our knowledge that the virus could grow in CEM." According to Montagnier, however, the LAV-infected CEM

line Weiss delivered to Pasteur in the spring of 1984 contained mycoplasma. Rather than go through the laborious process of removing the bacteria, Montagnier had obtained a mycoplasma-free sample of CEM from the American Type Culture Collection and given it to Klatzmann to clone.

[l]The patent office case file shows the Pasteur application, "Antigens, Means and Method for the Diagnosis of Lymphadenopathy and Acquired Immune Deficiency Syndrome," was filed on December 5, 1983, but not "docketed" until December 27, 1984. The examiner's interference search was performed on November 15, 1984.

[m]D. Bassett to S. Nunn, July 26, 1985; B. Chabner to A. D'Amato, August 8, 1985; P. Fischinger to C. Dodd, July 22, 1985. To Senator Christopher Dodd of Connecticut, Peter Fischinger replied that HTLV-3 was "very similar to but clearly different from the LAV isolate. Accordingly, Dr. Gallo did not 'steal' the virus from France. In fact, he had many of his own isolates, each of which could have been used for the development of diagnostic tests."

[n]The "Chermann history" provided by Gallo to the OSI was dated July 1985. However, in a September 8, 1986, note to James Wyngaarden, Gallo gives March 8, 1986, as the date Chermann signed the document "in the presence of Professor Daniel Zagury and Dr. Escoffier-Lambiotte." In a letter to the author dated August 4, 1995, Escoffier-Lambiotte stated that "Of course, I was *not present* at Zagury's home" when the history was written. NIH travel order 636356 shows that Gallo was supposed to have been attending an AIDS symposium at the University of Genoa on March 8.

Chapter 9. "I Don't Want to Go to Jail"

[a]Transcript of telephone conversation between B. Hampar and J. Roberts, August 7, 1985, as provided by Roberts to the SOI. Although Hampar was unaware at the time that Roberts was recording their conversation, he agreed to the use of the transcribed conversation in this book.

[b]M. Popovic to OSI, December 21, 1990, p. 29. According to Betsy Read's notes, on September 20, 1983, reverse transcriptase was detected in fresh lymphocytes infected with the July LAV sample, the cells in which Matt Gonda first photographed the AIDS virus. The September LAV grew continuously from October 24, 1983 — not in "fresh T-cells" but in two continuous T-cell lines, HUT-78 and Ti7.4.

[c]In a July 16, 1992, interview with the General Accounting Office, Fischinger acknowledged having known about the CDC blood-test results with the French ELISA in the spring of 1984, and having concluded at that time that LAV was the cause of AIDS.

[d]Fischinger's report conceded the French apparently had some kind of test, but one designed to pick up antibodies primarily to the core protein of the AIDS virus, p24. "We now know that many AIDS patients do not have detectable anti-p24 antibodies,"

At this point I told him he was behaving not as a scientist and that his presence in Naples was no longer of interest to me. He invited me to leave. A few days before the seminar, a letter was received by the Naples newspaper where he said that we had fabricated everything and that he did not even know us. We had exploited his name without his knowledge for publicity purposes."[37]

The blood test for AIDS was proving even more profitable than its manufacturers had predicted. During the first four months of testing, Abbott Laboratories had sold $8 million worth of ELISA kits. Despite Margaret Heckler's assurance of a few months before that American manufacturers were prepared to meet the foreign demand for the AIDS test, Abbott still couldn't make enough tests to satisfy the domestic demand.[38] Unable to increase its inventory beyond a one- or two-day supply, Abbott had asked the FDA for permission to change its method of producing the AIDS virus.[39]

The change increased the amount of available virus, but it did nothing to resolve the false positives the test was producing. During the last six months of 1985, the Red Cross blood center in Springfield, Illinois, reported that two hundred blood donors had tested positive after the first Abbott ELISA. Only eighty-six remained positive after a second ELISA. When the eighty-six double-positives were run through the Western Blot, only two donors proved actually to be infected with the AIDS virus — an astounding false-positive rate of ninety-nine in every hundred.

The FDA required that donated blood be discarded if the first ELISA was positive,[40] and the Abbott test had cost the Springfield Red Cross 198 pints of perfectly good blood.[41] Nationwide, nearly four out of five Red Cross blood samples testing positive by the Abbott ELISA were falsely positive, and in addition to losing blood the Red Cross and the other blood banks were losing donors.[42] Anyone who was ELISA-positive was no longer permitted to donate blood, even those who were subsequently negative by Western Blot.[43]

Despite its increasing alarm, the Red Cross was finding it difficult to get Abbott's attention. "It has taken us over two weeks to convince persons at Abbott Laboratories that indeed a crisis situation does exist," the head of the Los Angeles blood center wrote Abbott in early November.[44] Not until the Gallo ELISA had been on the market for

eight months did Abbott form an "HTLV-3 Task Force" to address the false positive problem.[45]

The Red Cross contract with Abbott didn't prevent it from evaluating other AIDS tests, and in mid-November of 1985 a competition was arranged: blood samples from thousands of donors would be tested in sequence by the Abbott ELISA and the Pasteur test from Genetic Systems.[46] Genetic Systems won the competition hands down. Not only was the Pasteur test far more precise, the Red Cross technicians found it much easier to use. "WE LOVE IT!!!!! Easy to learn. Easy to run," exclaimed the Red Cross blood center in San Jose.[47]

The superiority of the Pasteur ELISA was well-confirmed by independent studies.[48] But the Red Cross wouldn't be switching to the French AIDS test any time soon. A year before, Genetic Systems had applied to the FDA for permission to sell the Pasteur ELISA in the United States, and the company still didn't have an FDA license.[49] Considering Mac Haddow's rebuff of Raymond Dedonder, it seemed unlikely that a license would be forthcoming soon, and without a license the Pasteur ELISA couldn't be employed for the testing of human blood.

The more intransigent Washington became, the more Dedonder's resolve stiffened. "I am left with no choice," he wrote Haddow in September 1985, "but to turn the matter over to our attorneys. They are instructed to proceed quickly and efficiently. We are now compelled to present all the facts to the community, so it may judge the actions of those involved."[50]

It wasn't the solution Dedonder would have chosen. "At the beginning," he said later, "we did not want to start a big fight. We wanted to share. We were really aware of the importance of the AIDS problem, of the fact that such kits to test the people who were contaminated by the virus were very deeply needed. I didn't want to stop the production of any of the firms that were putting kits on the market, because of the important public health problem of AIDS."

Not really expecting a reversal, Dedonder appealed Haddow's rejection to Jim Mason, who privately put the government's chances of winning a lawsuit against the French at no better than sixty-forty.[51] "I think Mason was rather sympathetic," Dedonder said, "but he was not in a position to do something." Most of what Mason knew about the dispute came filtered through Lowell Harmison, and Mason's knowledge was fragmentary. "I

think I know pretty well what [Harmison] found out from Fred Murphy and his people in Atlanta. But I do not know what he discovered in Bob Gallo's lab."

Realizing he would have to make good on his threat to take the United States to court, Dedonder retained a brace of New York City law firms and set them on parallel paths. The out-of-court negotiations would be handled by Weil, Gotshal & Manges, whose managing partner, Ira Millstein, sat on the board of the American affiliate of the Pasteur Foundation, and who had a longstanding relationship with the French government that previously had brought him the Legion of Honor. "For something else I did for them," was all Millstein would say about the rosette in his buttonhole, except that "it gets me better tables" in Paris restaurants.

If the negotiations failed, Dedonder wanted a lawsuit ready to file, and his New York connections introduced him to James B. Swire, a senior litigation partner in the Manhattan firm of Townley & Updike. The offices of Weil, Gotshal, on the upper floors of the General Motors Building in Midtown Manhattan, were modern, light, and airy, and housed many, many attorneys. Townley, on the twenty-sixth floor of the Chrysler Building a mile away, was smaller and more conservative, all dark wood and polished brass. The Weil, Gotshal letterhead listed trendy branch offices in Miami, London, Singapore, and Budapest. The letterhead of Townley & Updike, which had no branch offices, bore only the names of its partners.

A product of Princeton and Harvard Law and a Reagan Republican to the core, Jim Swire once had been interviewed for a job by Richard Nixon's White House counsel, John W. Dean 3d. The interview took place a few months before the Watergate break-in, and Swire recalled with amusement Dean's interest in an article Swire had written on wiretapping for the *Harvard Journal on Legislation*. To his everlasting relief, Swire turned Dean down, only to find himself later helping to defend Nixon's onetime FBI director, L. Patrick Gray 3d, against lawsuits by members of the Weather Underground.

Jim Swire was to be the Pasteur's stick, Ira Millstein its carrot. If HHS didn't give Millstein what Pasteur wanted, Swire would get it in court. "We fought in both directions," Dedonder said.

Before becoming Ronald Reagan's HHS Secretary, Heckler had represented Massachusetts in the House of Representatives, where her principal distinction had been her seniority among the female members of Congress. Heckler thought her political career had

• 10 •

"French Virus in the Picture"

The dispute with Pasteur raised Robert Gallo's profile to the point where Gallo could complain that "I get press calls every day. Every day. I'm invited on 'Good Morning America,' 'Hello America,' 'Wipe-the-Dust-Out-of-Your-Eyes America.'"[1] According to the *Washington Post*, Gallo was "tired of all the fury, but is caught up in it as one story adds to another, and as rumors become 'facts' because they are published repeatedly. He is also caught up because he is a competitive, emotional man who has difficulty not fighting back. 'Gossip occurs about people who are visible,'" Gallo said. "It can give you a bad weekend sometimes."[2]

Gallo's disposition improved in early February of 1986, with a visit to Bombay and Delhi as an honored guest of the Indian Oncological Society,[3] a trip he later described as one of the best he had ever taken. "They treated me like a maharajah," Gallo said. "They put garlands of flowers around my neck and sprinkled me with oil. What a place."[4]

While Gallo was out of the country, the Food and Drug Administration notified Genetic Systems that the company had been approved to make and sell the Pasteur AIDS blood test in the United States. Abbott Laboratories had gotten its license in just nine weeks; it had taken Genetic Systems nearly nine months.[a]

In the interim, a Red Cross task force had christened Genetic Systems its "test of choice" and recommended that the company be awarded at least 80 percent of the Red Cross business currently going

to Abbott.[5] "Our test brings a new accuracy standard to AIDS testing," declared Bob Nowinski. "With this accuracy, it should be possible to virtually eliminate the transmission of AIDS virus through the blood supply system."[b]

The lack of an American patent didn't preclude Genetic Systems from selling the Pasteur test in the United States, since the most the Reagan administration could do was to sue the French for patent infringement. Indeed, several of the companies selling the Gallo AIDS test had begun pushing for such a suit.[6] But patent infringement cases can take years, and the French, who had been first to apply for an American patent, stood an excellent chance of winning.

In the meantime, the FDA license made the sales legal, or so Bob Nowinski imagined. But when the company tried to bid on the enormous military contract for AIDS antibody tests, Genetic Systems representatives couldn't even get a meeting with the Pentagon brass. It would be un-American, they were told, for the United States military to buy a French AIDS test. The Pentagon contract went to Electronucleonics, whose false-positive rate was many times higher than the Pasteur's.

The French found it a further insult that their FDA license described the Pasteur ELISA as a test for antibodies to HTLV-3.[7] "The FDA knows perfectly well," Dedonder protested to the FDA commissioner, Frank Young, "that the Genetic Systems kit works with LAV, the virus isolated by the Pasteur group in January, 1983, more than one year before the description of HTLV-3 by Gallo and his co-workers. Thus, requiring Genetic Systems to call its product HTLV-3 is simply wrong, both historically and scientifically . . . it also does a disservice to the discoverers of the AIDS virus, *Montagnier et al.*, who, though having made an important scientific breakthrough, are apparently not to be allowed the ordinary right to see in everyday use, on their own product, the name they chose for the AIDS virus."[8]

Young replied that if Pasteur wanted to sell its AIDS test in the United States, HTLV-3 was the name it would have to use. "Please be assured," he told Dedonder, "that it is not in any way meant to slight the very important work of scientists like Dr. Montagnier and others on whom research advancement is depending."[9] It sounded like a conciliatory letter. But within a few days the FDA was warning Pasteur that its advertising shouldn't mention any of the independent

studies showing the Pasteur test to be more accurate than the Gallo version.[10]

That information might have been welcome at the Blood Center of Southeast Louisiana, where two-thirds of the donors testing positive with the Gallo/Abbott ELISA weren't infected with the AIDS virus at all.[11] Or at the North Colorado Medical Center in Greeley, where false positives were running over 70 percent.[12] Or in tiny Hays, Kansas, where there was no AIDS, but whose town doctor complained to the FDA that unless something were done about the false positives there soon wouldn't be anyone left who was eligible to donate blood.[13]

With the advent of blood screening for the AIDS virus, the ramifications of false positives reached far beyond the relatively small number of prospective blood donors. The military had begun testing all new recruits and active duty personnel, the State Department foreign service officers and their dependents, the Peace Corps and Job Corps anyone who applied to join. The state of Illinois, where Abbott had its headquarters, was gearing up to require mandatory AIDS tests for anyone who wanted to be married.[14]

The consequences of a false positive AIDS test could prove horrendous. A Michigan college student, advised by his county health department to begin making final arrangements on the basis of a false-positive test, dropped out of school and spent what he thought were his last months on earth working for an AIDS support group.[15] A Philadelphia man, having taken a required premarital blood test for syphilis — and been tested, without his knowledge, for the AIDS virus — lost his fiancée when the test proved falsely positive.[16]

A Los Angeles teacher with a false-positive test lost his job.[17] A pregnant soldier who volunteered for an Army blood drive discovered her positive test was false only after having the abortion urged by her doctor.[18] An Alabama housewife became celibate, stopped kissing her children, and started seeing a psychiatrist until she, too, was discovered to be the victim of a false-positive ELISA.[19]

The FDA official in charge of monitoring the performance of the AIDS test was Tom Zuck, a hematologist and army colonel from Letterman Army Hospital in San Francisco who had been temporarily assigned to FDA headquarters in Rockville, Maryland. "They wanted a blood banker," said Zuck, "and they couldn't find anybody on short notice, and I was available. So I got the job."

Zuck had been in San Francisco when the Abbott test was approved, and he believed that the decision had been made in haste.

"There's no doubt that Abbott was rushed to market," Zuck said. "Absolutely no doubt about it. Part of the problem with those tests was *because* they were rushed to market. They were bound to be lousy tests. They were hastily concocted. The issue was, is it better to have a bad test than no test at all? And I think everybody involved said, 'We'll worry about the nonspecificity later.'"

Later was now, and Zuck saw the false positives as a huge problem, not only because they were costing the blood industry money but also because of the human consequences. Even when the follow-up Western Blot was negative, the news that their initial "AIDS test" had been positive unhinged donors who didn't comprehend the complexities of blood-antibody diagnostics. "A lot of blood centers told people, 'You're repeatedly reactive but you don't confirm, so you can't give blood,'" Zuck said. "A lot of these people were hysterical and believed they really had some kind of unusual AIDS."

When the complaints about the Abbott test began piling up on Zuck's desk, he ordered the company to send him its "action plan" for eliminating the false positives.[20] The Abbott test was an old-style configuration, in which tiny polystyrene beads coated with inactivated AIDS virus are placed in small indentations, or wells, on a plastic plate, each filled with a tiny drop of the blood being tested. If the blood contains AIDS virus antibodies, in theory the antibodies adhere to the virus on the bead, triggering an enzyme to change color.

To eliminate the aberrant H-9 cell proteins on the bead that were adhering to nonviral antibodies and triggering false-positive reactions, Abbott had enhanced its virus-purification techniques. That hadn't worked, and now the company was proposing to reduce the length of time the bead was exposed to the blood.[21]

When Zuck saw the company's newest proposal, he realized that Abbott was trying to reinvent the AIDS test from the ground up. "You don't know what's wrong, do you?" Zuck told Marijane Sidote, Abbott's liaison with the FDA.[22] Sidote admitted Zuck was right, and that Abbott was worried. The company had been hearing rumors that the FDA had put Abbott "on probation," Sidote said — or, worse, that it was about to pull the Abbott test off the market. Zuck replied that there was no such thing as "FDA probation," and that in order to withdraw the license the FDA would have to take Abbott to court.[23] The FDA just wanted Abbott to fix its test.

Zuck's decision to award a license to Genetic Systems hadn't been well received by the executive hierarchy at HHS. In mid-March of 1986,

Zuck was summoned for interrogation by no less than Lowell Harmison, whom Vince DeVita had come to view as "hostile toward the French" because he thought they were "stealing American technology."[24]

"It got really kind of ugly," Zuck recalled. "I had to show cause, actually defend myself, for licensing a French test. Remember, we're in the middle of this lawsuit at the time. It was a very difficult meeting. You've got one active-duty army colonel in uniform, surrounded by a whole bunch of one- and two-star Public Health Service officers. The meeting was a political meeting, but the science won the day."

According to notes taken by one of the HHS lawyers present, Zuck explained that the greater a blood test's specificity, the fewer false positives it will record. The Pasteur ELISA was "widely regarded as superior," Zuck said, because "it was considerably more specific" than the Gallo test. In fact, the accuracy of the Genetic Systems test approached "the benchmark criteria," the Western Blot.

The main reason the French test was so much better, Zuck told Harmison, was the Pasteur's CEM cell line, which meant the test resulted in less wasted blood. But the blood banks also liked the test because there were no little beads to deal with, and because the Genetic Systems kits were "more complete than any of the other licensees."[25]

Moving quickly to head off the notion that the French had made a better AIDS test, Gallo declared that *his* lab had been first to grow the AIDS virus in CEM, a claim with which Robin Weiss would have taken issue.[c] The problem with CEM, Gallo told Harmison, was that it had to be reinfected periodically with virus — which happened to be precisely how Genetic Systems was growing huge quantities of pristine LAV in Seattle. Gallo nonetheless insisted that CEM "offers no intrinsic advantage in virus production and may have yet to be discovered disadvantages. Therefore, I would strongly urge our FDA officials to get input from very experienced people (like us) before making public quality pronouncements."[26]

Momentarily, Zuck had a call from Gallo. "Every time you dealt with Lowell," Zuck said, "it always seemed there was a Gallo connection somewhere. Gallo called and shouted at me that the French virus was 'incompletely integrated' in their cell line, which is bullshit. The Public Health Service, particularly in the person of Lowell Harmison, tended to always side with Gallo. There were a whole lot of financial interests floating around there too, which I don't even

want to touch. But we all know there were royalties on this and royalties on that."

Developing a blood test that could accurately detect antibodies to a single AIDS virus had proved difficult enough. But there was no reason there should be only *one* kind of AIDS virus. If the virus had come into man from African monkeys, as most researchers believed, many monkeys must have been infected before the first human acquired the virus.

Waiting to leap the "species barrier," an event which probably occurred sometime in the 1940s, the virus would have mutated in each of those monkeys. Nobody could say how it had finally crossed over — a monkey bite, a wounded hunter, incompletely roasted monkey meat — but Gallo had his own ideas. "Maybe there's some ritual with monkey blood," he suggested. "Who knows? They do a lot of funny things in Africa, like when they make the lower lip stick out or when they put things through their noses."[27]

However it had happened, there was no reason to think the AIDS epidemic should have been confined to a single monkey virus that had passed into a single human. Why not two or three such viruses, or even more?

The second AIDS virus, like the first one, was discovered at the Institut Pasteur in Paris, this time by a genial, thirty-one-year-old doctor named François Clavel. Like David Klatzmann before him, Clavel had given up clinical medicine to pursue a fascination with research. Clavel counted himself lucky to have landed in Montagnier's lab, where one of his first assignments was to search for a virus in T-cells from an AIDS patient languishing in a Lisbon hospital.[d]

Nobody was sure what it meant, but the man's cells had tested positive for reverse transcriptase and negative for antibodies to LAV. Clavel began by hybridizing the cells to a LAV DNA probe. When the probe failed to detect any LAV, he repeated the experiment under increasingly less stringent conditions, searching for the point at which some annealing was bound to occur. Eventually he could see some genetic similarities between LAV and whatever was growing in the Lisbon cells, but they were faint.

According to his doctors, the Lisbon patient, code-named *Mir*, had come to Portugal from one of that country's former African colonies,

Paris until April 22, 1984 — not to assist the French, but to "consult with Dr. Chermann, to learn serological techniques and perform serology on AIDS-related sera [and] to obtain information on virus growth and isolation techniques. . . ."

[k]There are only about ninety nucleotide differences between 3B and LAV, not 150, and those ninety differences would have been more or less evenly divided between the two virus cultures, with forty-five occurring in Paris and the other forty-five in Bethesda. Before HTLV-3B was cloned by Beatrice Hahn it had been growing in Gallo's lab for more than six months, not six weeks. Fewer than fifty nucleotide changes over six months is well within the mutational realm of a retrovirus comprised of more than nine thousand nucleotides and which changes its overall genetic makeup by 5 percent a year.

[l]Popovic evidently referred to the restriction analyses showing the genetic identity of LAV and HTLV-3B contained in the unpublished paper by Flossie Wong-Staal.

Chapter 10. "French Virus in the Picture"

[a]E. Esber to D. Awberry, February 19, 1986. Abbott's application for an FDA license was filed on December 24, 1984, and granted March 2, 1985. Genetic Systems's application was filed on May 16, 1985, and granted on February 19, 1986.

[b]Genetic Systems news release, February 19, 1986. A few months earlier, Genetic Systems had been purchased for $300 million by Bristol-Myers, which retained Bob Nowinski and George Todaro as the company's chief executive officer and scientific director.

[c]First to successfully infect CEM with the AIDS virus was Robin Weiss, on February 29, 1984. The first mention of CEM in Gallo's lab notes is dated May 28, 1984, a month after Weiss had told Gallo of his success with CEM in Cremona.

[d]According to Montagnier's notebook, the cells, code-named *Mir,* sent by a Portuguese microbiologist, Odette Santos-Ferreira, arrived in his laboratory on September 16, 1985.

[e]In the current nomenclature, HTLV-3B and LAV_{Bru} are designated $HIV\text{-}1_{Lai}$. ARV-2 is $HIV\text{-}1_{SF2}$. $HTLV\text{-}3_{RF}$ is $HIV\text{-}1_{RF}$. For consistency, the original designations will be retained throughout this book.

[f]Besides Robin Weiss, the other signatories were John Coffin, Ashley Haase, Jay Levy, Luc Montagnier, Steven Oroszlan, Natalie Teich, Howard Temin, Kumao Toyoshima, Harold Varmus, and Peter Vogt.

[g]The correction states that "In the several months preceding preparation of the composite in question, electron micrographs of cultures infected with our HTLV-3 iso-

man had arranged an off-the-record lunch with Lowell Harmison. According to Montagnier, Gallo's first words after shaking hands were "'Believe me, I didn't steal your virus.' He was very upset." The conversation that followed was strained until Harmison suggested, halfway through the meal, that a public pronouncement by Montagnier that HTLV-3B and LAV had come from different patients might be worth a million dollars.

Where such a sum of money might come from, Montagnier recalled, "was not really said in proper words." But he remembered thinking that if the Americans were willing to pay him a million dollars, "something was being hidden by the NIH." Berneman quickly interjected that any payment from the Americans would have to go to the Pasteur, not to Montagnier directly. But, Berneman said, money alone was not enough to resolve the dispute. At a minimum, the Pasteur wanted the lion's share of the patent royalties and co-inventorship for the blood test.

Jim Wyngaarden received the same message over lunch from Michèle Barzach, the French minister of health. When Wyngaarden got home, he warned the HHS lawyers they were in for a tough fight. The French were "going all out for a share of [the] patent," Wyngaarden said. "It is open and shut." Not only did the French see the dispute as "a bell-weather [*sic*] patent case," they were saying they could "prove that HTLV-3 was cultivated from LAV."[7]

According to Wyngaarden, the view from within NIH and HHS had been that the French "were trying to take credit for Bob's work. Everyone felt that — of course, relying on Bob's account of what he had done."[8] But the HHS lawyers were coming to the conclusion that the French had a case. "A significant part of this dispute is whether LAV and HTLV-3 are the same virus," one HHS attorney wrote. "NCI is very firm in its view that HTLV-3 is different. However, they are very similar viruses and this is a weak thread to rely on . . . we might better settle now."[9]

Among the speakers in Paris was the head of the Red Cross's blood-testing laboratory, who presented his evaluation of the five AIDS blood tests on the market. Of the five, only the test made with LAV recorded a perfect score, both for false positives *and* false negatives. But the false-positive rate for the Abbott ELISA was still through the

roof.[10] While Abbott experimented with reducing the bead-coating time from three hours to fifteen minutes, Mike Ascher was boarding a plane for Florida and the Second Annual Clinical Virology Symposium. Ascher was deputy chief of the Viral and Rickettsial Disease Laboratory at the California Department of Health Services. For more than a year, Ascher's urgent preoccupation had been developing an accurate HIV-antibody test for the state's diagnostic blood laboratories. Now he had some bad news.

Ascher had used Jay Levy's ARV to search for viral antibodies in a unique set of blood samples, drawn from hundreds of San Francisco men for a hepatitis-B study in the mid-1970s. Although the existence of AIDS wouldn't be recognized for another six years, some of the men were already infected with HIV at the time their blood was taken. Fortunately, the blood samples from the "City Clinic cohort" had been preserved in the freezers of the San Francisco Health Department, an invaluable serological archive of the natural progression of the AIDS virus. Using a home-made blood test, Ascher had been able to identify with great precision which of the samples were infected with decade-old HIV and which were not. But when Ascher tested the same HIV-positive samples with the commercial Abbott ELISA, several had been *negative*.

There had been indications from the start that the Gallo ELISA produced *false negatives* as well as false positives, but they had been overlooked or ignored.[b] Before the Abbott test was licensed, the Boston Red Cross had expressed "major concerns" about its sensitivity.[11] Murray Gardner had done the same shortly afterward.[12] Gardner had been joined by the Canadian CDC, which discovered that the Abbott ELISA couldn't detect HIV antibodies in blood samples from seven AIDS patients.[13] Even Max Essex, whose Cambridge BioScience was attempting to market its own version of an HIV ELISA, warned that the Abbott test was failing to detect one HIV-positive sample in every twenty — a false-negative rate of 5 percent.[14]

It was Murray Gardner who first recognized that all the false-negative blood samples contained antibodies to a single HIV protein, p24. The Canadians had found the same thing. When Mike Ascher ran *his* false negatives through the Western Blot, the only antibody that showed up was anti-p24. In every case, the false-negative samples had come from men infected with HIV a relatively short time before their blood was drawn. The reason some HIV-infected people were show-

ing up as negative on the Abbott ELISA was that the Gallo test simply couldn't see antibodies to p24.

After warning California's public health laboratories about a "gray zone" in the commercial AIDS tests, Ascher had presented his data in Clearwater.[15] A number of people at the meeting expressed interest, but Ascher recalled that two seemed more interested than the rest: the representative from Abbott Laboratories, and Gallo's deputy lab chief, Prem Sarin.

When Ascher performed his initial tests, the Pasteur ELISA hadn't been approved by the FDA. Now that it was approved, Ascher was curious to see how the French test handled blood samples containing only p24 antibodies. The Pasteur test scored all twelve samples positive. The new prototype Abbott ELISA with the reconfigured bead missed every one. In fine-tuning the test to reduce the number of false positives, Abbott had somehow increased its propensity for false negatives, which meant the Pasteur test was now more precise than Abbott at both ends of the scale. Bob Nowinski thought it was the batch virus production process about which Gallo complained to Lowell Harmison that accounted for the advantage in false negatives.

"You grow up a batch of CEM," Nowinski said, "put in the virus, and it releases a large amount of virus. You grow huge liters of it, you let it go through a cycle of ten days and you harvest the fluid. You purify the virus from it, and then do a second infection, a third infection, and so on. You can do this forever." The only reason Gallo used a continuous cell line like H-9, Nowinski said, "was that in all retroviruses up to then, everyone had used continuous cell lines. But you grow as much virus by our method as you grow in any other method. Genetic Systems could produce enough virus for the entire nation without any problem."

Five weeks after the Clearwater meeting, the FDA approved the reconfigured Abbott test for clinical use. In granting certification, the agency agreed that Abbott could advertise its new ELISA as providing fewer false positives, and no more false negatives, than the original ELISA.[16] When Ascher heard what the FDA had done, he asked Tom Zuck "'What the hell's going on?' I said, 'Why did you relicense Abbott?' "He said, 'Ascher, what's your problem?' "I said, 'My problem is that we're still getting false negatives with Abbott, and the improvements you just licensed have made the problem worse.'"

Zuck retorted that the FDA had been checking for false negatives too, and *it* hadn't found any difference between Abbott and Genetic Systems. When Ascher asked *how* the FDA was measuring sensitivity, Zuck explained that it was using the standard laboratory method, by successively diluting blood samples and testing for antibodies at ever-lower levels of virus concentration.

No, Ascher said. Dilution might work for ordinary viral antibodies, but it was the worst possible way to measure sensitivity to HIV antibodies. With the AIDS virus, Ascher explained, it wasn't a question of how *many* antibodies there were in a given sample of blood, but rather *which* of the viral proteins had given rise to them. The only way to measure HIV sensitivity was with blood samples from recently infected individuals, "early seroconverters" who had just begun producing antibodies. Still skeptical, Zuck asked Ascher to test more sera and send him the results. When Abbott scored eight out of eight early seroconverters as HIV-negative and the Genetic Systems ELISA scored the same samples positive, "the FDA was fairly responsive," Ascher said.

Before the summer of 1986, the unnecessary expense and wasted blood caused by false positives had seemed a more pressing concern than the likelihood of false negatives, which remained largely theoretical. False positives were immediately visible, by comparing ELISA results with Western Blots. Because AIDS often took years to develop, there hadn't been any way to know for sure whether HIV-contaminated blood was passing through the ELISA screen and into transfusion patients or hemophiliacs who might remain healthy for years.

That changed in mid-June of 1986, when the CDC reported the case of a thirty-one-year-old Colorado man who had made a donation at his local blood-transfusion center the previous August.[17] Tested with the Abbott ELISA, his blood had registered HIV-negative. When the man donated another unit three months later, he was HIV-positive. According to what the donor told local health officials, he had had only one male sex partner in his entire life, and their first contact had occurred three months before the first donation.

The records of the hospital to which the first donation had gone showed it had been divided between two middle-aged patients, both of whom had undergone cardiac surgery. The first recipient was now HIV positive, but because he was also a homosexual there was no way

to say whether he had acquired the virus from the donated blood. The second recipient, a sixty-year-old man, had been married for thirty years and denied any extramarital sexual contacts with either sex, as well as intravenous drug use. But when the second man's blood was tested by Western Blot, it too was HIV-positive. The only way he could have become infected with HIV was from the blood the Abbott ELISA had scored as HIV-negative.

The same thing happened on a more devastating scale two months later, following the fatal shooting during an armed robbery of a Virginia gas station attendant, William "Pete" Norwood. Before he died, Norwood's mother agreed to donate her son's vital organs for transplantation, and Norwood's blood was tested twice for HIV. Both tests were negative, but both negatives were false. At least seven recipients of Norwood's organs and tissues, including his heart and kidneys, contracted the AIDS virus.[18] "It's like Petey died all over again," his aunt Emma said.[19]

Three months later, in nearby Richmond, a thirty-three-year-old woman underwent surgery to remove a uterine cyst, not a life-threatening condition but a procedure her doctor said was necessary if she wanted to have children. The blood the woman was given had tested HIV-negative; it, too, was infected with the AIDS virus.[20] Such cases, the Red Cross declared, didn't represent "a test failure," because no ELISA was capable of detecting antibodies in early seroconverters. "We know the test can't do the impossible," a Red Cross official said.[21]

Mike Ascher had data showing that what was impossible for the Gallo AIDS test was possible for the Pasteur/Genetic Systems ELISA, and Ascher was no longer alone. At the NIAID in Bethesda where Mal Martin worked, a researcher named Al Saah was coming independently to the same conclusion. Saah was working with a collection of blood samples as unique in their way as the City Clinic cohort, taken from gay men in several cities over a period of years beginning with the dawn of the AIDS epidemic. At the outset of the study, the subjects had been healthy. As it progressed, many had become infected with HIV and developed symptoms of AIDS. By studying the samples in chronological order, it was possible to construct a time-lapse picture of how the human immune system responded to the AIDS virus.

Saah and his collaborators noticed that the earliest postinfection samples didn't always test positive by ELISA. Or, rather, that *some* of

those samples tested positive only with *some* of the commercial ELISAs. When Saah tried to figure out what was different about the positive samples, he discovered what Murray Gardner and Mike Ascher already knew. The earliest samples contained only p24 antibodies, whereas those taken from the same subjects later had antibodies to a host of HIV proteins.

When Saah used the ELISA from Litton Bionetics to test thirty early seroconverters, it scored only two HIV-positive, next to useless for blood-testing purposes. The test from Electronucleonics did scarcely better, only four positives out of thirty. Abbott recorded thirteen of the thirty samples positive — better than the others, but still a false-negative rate of 57 percent. The Pasteur/Genetic Systems ELISA caught twenty-five of the thirty samples.[22]

A major blood-testing conference was about to convene at NIH, the first time in a year that the test manufacturers and blood bankers, including a large contingent from the Red Cross, would be in the same room at the same time. When Al Saah got a postcard from *Science* rejecting the paper reporting his blood-test comparisons, he packed up his charts and graphs and joined Mike Ascher at the NIH conference. Neither was on the conference program, and they listened from the audience while one speaker after the next described a world in which the blood supply had been made as safe as possible from HIV. When the time came for questions, Ascher and Saah asked permission to present their data from the floor.[23]

The reporters covering the conference hadn't heard much about false negatives, and the impromptu presentation made headlines. "Despite a concerted effort to screen blood donations," the *Washington Post* reported, "a small percentage of blood throughout the country remains contaminated with the AIDS virus." The *Post* quoted Saah's boss, Anthony Fauci, as saying the bad news was "something that we have suspected for a long time. It tells us that we have got to get a better test."[24]

Not until the eighteenth paragraph did the *Post* reveal that there already *was* a better test, made by "the French [*sic*] company Genetics [*sic*] Systems." The story didn't say that, a month before, the Commerce Department had begun preparing a patent infringement suit against Genetic Systems.[25] An Abbott spokesman said the company needed "to look at the methodology" used by Ascher and Saah before commenting on their data. But the Abbott representative at the con-

ference informed his superiors in Chicago that "Litton and ENI [Electronucleonics] clearly take a dive on this, and the implications for our test are not exactly favorable."[26]

The United States market for the HIV ELISA, once estimated at $20 million a year, had passed $34 million and was headed upward,[27] and the news had implications for Abbott's bottom line. As it happened, Abbott had known about the false negatives for months. The company had seen Mike Ascher's data in the middle of June.[28] The previous April, the Red Cross chapter in Burlington, Vermont, had encountered a false negative on a blood sample with the newly configured Abbott test.[29] When the Burlington sample, from a man recently infected with HIV, was tested by Western Blot, it had antibodies only to p24. In May, Abbott had learned that the Red Cross blood center in Syracuse, one of the sites testing the new ELISA, had found another false-positive blood sample from another early seroconverter.[c]

Abbott hadn't told the FDA.[d] Now, however, the story was out, and Abbott headquarters was on maximum alert. "Action plans" were drafted to "immediately address the critical need for increased sensitivity" in the Abbott ELISA. Project teams were formed, under orders to meet daily until the crisis was resolved.[30] Having no idea what was causing the false negatives, Abbott decided to make *two* new ELISAs, one spiked with extra p24 and the other with extra gp41, the transmembrane protein that connected to the HIV envelope.[31] But new tests meant new field trials, and new field trials would take months, and the Ascher-Saah revelations put the American Red Cross in a bind.

Months before, the Red Cross task force had selected the Genetic Systems ELISA as its "test of choice." Sensitive to the political implications of buying the French test over the American version, senior Red Cross officials had reversed the recommendation. When the second-year contracts were signed, Abbott had 80 percent of the Red Cross business, with 20 percent split between Genetic Systems and DuPont — the opposite of what the task force had recommended.[32]

The new Abbott–Red Cross contracts had been signed only a few days before the NIH conference. Now the *Washington Post* was telling its readers that the Abbott test, whose principal user was the Red Cross, missed more than half of all HIV-infected blood samples. When the Red Cross blood centers demanded to know what headquarters was doing about the situation, Gerry Sandler invited Al Saah to present his data to the monthly meeting of the Center Directors'

Council. "What we learned from Al Saah's presentation was that there was a better way to determine sensitivity than the way we had been doing it," Sandler said later. In the end, the Red Cross had "agreed with Saah's analysis." The Abbott test "did not pick up samples that could be picked up."

Among the Red Cross officials alarmed by Saah's presentation was the director of its Miami blood center, Peter Tomasulo. "It is not impossible," Tomasulo wrote to a Red Cross executive after returning home from the meeting, "that, within the next month, we will run across another seronegative viremic donor. We know we have a better chance of detecting such an individual by using the Genetic Systems assay. Delaying the switch even one month may be wrong. Should we move ahead as quickly as possible to use the best p24 test that is now available? If one person in South Florida develops AIDS from a seronegative blood donor after July 30, 1986 which was processed by Abbott, I will wonder if I did everything I could have done."[33]

The American Red Cross wasn't a government agency. But it was a public trust, chartered by Congress. Although the Red Cross's original purpose had been wartime disaster relief, its real business had become the selling of blood.[e] While paying no taxes and collecting tens of millions of dollars each year from United Way and other charities, the Red Cross used free television advertising to persuade Americans to roll up their sleeves, for free, at blood centers, Bloodmobiles, and office blood drives. The millions of pints of donated blood were sold to hospitals for a "processing fee" approaching $400 a pint, affording the Red Cross an annual operating profit of nearly $40 million. Now the Abbott test had placed that business in jeopardy.

The Red Cross contract had an escape clause that could be invoked if another test became available that was more sensitive by at least 5 percent, and the Pasteur ELISA was much more sensitive than that.[34] Seizing the opportunity, Genetic Systems told the Red Cross it was "willing and able to expand to additional Red Cross centers," whenever the Red Cross wished.[35]

"When the Saah study came out," Bob Nowinski recalled, "Genetic Systems received an inquiry from the Red Cross asking to submit a bid for one hundred percent of all their business. Just before the bid was ready, they called back and said, 'Don't submit the bid.' They then held a closed session of which no minutes were taken, which is unusual at the Red Cross. At that point Abbott made a repre-

sentation to them that they could correct the test in a certain period of time. So the Red Cross took Abbott at its word. I think Abbott promised them three months."[36]

A few days after Saah's presentation to the Red Cross, a thirty-year-old North Carolina man was admitted to Moses Cone Memorial Hospital in Greensboro following an auto accident. The man was in a coma, and his condition was critical. As part of the hospital's admitting procedure, a blood sample was drawn for typing. Over the next eleven hours, the man's doctors transfused him with fifty-six units of blood. Despite the transfusions, the man's condition worsened, and his name was added to a list of prospective organ donors. A second sample of blood was taken for HIV antibody testing. The Abbott ELISA scored it negative for HIV.

Forty-eight hours later the man was declared brain dead and his heart, kidneys, and liver were distributed to other medical centers for transplantation, each accompanied by another blood sample to be double-checked by the receiving center for HIV. At three of the four centers the blood tested negative, and the donor's liver and kidneys were transplanted into waiting patients. At the fourth center — the only one to use the Genetic Systems ELISA — the blood tested positive.[37] Within weeks, the patients who had received the donor's other organs were also HIV-positive.

While Gallo and Montagnier parried in Paris and Genetic Systems did battle with Abbott and the Red Cross, the Institut Pasteur and the Reagan administration were crossing swords in the Court of Claims. None of the government lawyers was a scientist, and in characterizing Gallo's research for the court they depended on Gallo and his people to interpret his data and explain its significance.[38]

Not only had Gallo *not* stolen LAV, the government declared, the French virus hadn't contaminated Popovic's cultures, even by accident. The scientific evidence was "clear" that HTLV-3 and LAV had come from different patients,[39] and it showed "conclusively" that "HTLV-3 is *not* LAV by another name."[f] Finally, neither the Gallo blood test nor the H-9 cell line had "depended on," much less been "derived from," LAV.[40]

The claims court judge, James F. Merow, perceived the existence of "a major factual dispute" as to whether LAV, in the Pasteur's view,

[v] A May 26, 1983, report from Electronucleonics to the Laboratory of Tumor Cell Biology states that plates 7081-7086, made from virus extracted from C-103 + W3731 (Chardon co-culture with C103 cord blood cell line) and W-3731 contain "C-type particles." HTLV-1 and HTLV-2 are type-C retroviruses — but not the AIDS virus, which has some features of a D-type retrovirus but belongs to the lentivirus subgroup of retroviruses.

[w] An Electronucleonics technician wrote Gallo in December 1985 that "Relative to my discussion with you and Dr. Striker [*sic*] about early HTLV cultures which we received from your laboratory for cultivation and EM, Dr. Kramarsky has found two thin, cell pellet sections (attached) which have aberrant morphology, neither HTLV-1 nor HTLV-2." Electronucleonics produced a second version of the letter, dated the same day but with a different first paragraph, in which the new particles were described as "morphologically-distinct HTLV-3 virus."

Chapter 11. "Bingo. We Win"

[a] When Weiss asked Karpas for samples of the "Karpas T-cell line" and the AIDS virus, C-LAV, Karpas claimed to have isolated in December of 1983, Karpas pretended not to be reassured by Weiss's promise that neither the virus nor the cell line would leave Weiss's laboratory. "I regret very much having to say that I do not feel able at present to place my trust and confidence in your assurances," Karpas wrote Weiss. "Might not my cell line end up with a new name and a rediscovery?" Weiss replied that he was "dismayed that you express doubt as to my academic propriety and integrity, which remarks I must ask you to withdraw. . . . I am returning your letter with this one, and I invite you, upon reflection, to destroy both of them. I have kept copies of this correspondence, but will be happy to destroy these on hearing within the next two weeks that you have done the same to the originals." Karpas responded by thanking Weiss for his letter, "which in fact I will not destroy. I may even frame it next to mine. Unfortunately I remain tormented by doubts and therefore am unable to withdraw any of my remarks about your academic propriety and integrity. I am also reminded of your writing in *Nature* about the French '. . . skimpy data . . .' — an odd way of thanking Dr. Montagnier for providing you with the French AIDS virus isolate."

[b] According to Sarngadharan's May 1984 article in *Science,* the original Gallo ELISA detected HTLV-3 antibodies in 88 percent of AIDS patients tested, a 12 percent false-negative rate. There is no indication in the article that the sera tested were coded, which would represent a major protocol violation. With coded sera sent by other laboratories, however, the Gallo ELISA did much worse. When Sarngadharan tested blind samples from Sloan-Kettering, 52 percent of AIDS patients were negative (Safai, B., *et al.* "Seroepidemiological studies of human T-lymphotropic retrovirus Type III in acquired immunodeficiency syndrome." *Lancet* 1438. June 30, 1984), and only 60 percent of the coded AIDS sera provided by David Ho at the Massachusetts General Hospital (D. Ho to M. Sarngadharan, May 25, 1984). In both

cases, Gallo's score was about the same as his original tally with the CDC blood samples before it was enhanced by Jim Curran.

[c] In a May 20, 1986, letter to Abbott's Sally Hojvat, Nancy Dock of the Red Cross blood center in Syracuse wrote that "[w]e are extremely concerned about the Abbott modified EIA which detects this sample as reactive only 2 of 3 times tested, and about certain lot numbers of the current Abbott assay which do not detect it as reactive at all . . . the donor of this sample has been documented to be an HTLV III/LAV seroconverter and is viral culture positive by RT assay. Information regarding this sample was brought to the attention of Mr. Bill Stall at Abbott by Dr. Harold Lamberson on April 28, 1986, and they have discussed the problem at length." Tabulation of the Syracuse data shows that the modified Abbott ELISA missed HIV antibodies in two AIDS patients. See also M. Klamrznski telephone notes (conversation with S. Risso), May 15, 1986.

[d] FDA Conversation Records, S. Risso and M. Klamrznski, May 15, 1986; S. Risso and M. J. Sidote, May 16, 1986. Of her conversation with Abbott's Sidote, the FDA's Sharon Risso wrote "that at least one site [Red Cross Syracuse] indicated to FDA that they had data from a study requested by Abbott, but that Abbott had not asked that the data be reported to them. I asked her to contact all sites in order to provide assurances to FDA that all data requested had been received and for her to submit any additional data to FDA. She assured me that Abbott had not censored any data and had provided all data available to them. She said they had contacted Syracuse based on my call yesterday and that Syracuse had indicated that all data had been received to Abbott except raw data listings which they would provide." In a May 27, 1986, letter to the FDA, Abbott acknowledged that the problem with Syracuse sample 313 had been discussed by the Syracuse center director, Dr. Harold Lamberson, and Abbott's William Stall on April 29, 1986 — but that Lamberson's call had been recorded by Stall "as a current product quality issue," not a false-negative report.

[e] According to the *Philadelphia Inquirer*, by 1988 fifty-nine cents of every dollar spent by the Red Cross went to operate its blood program, while less than ten cents went to disaster relief. The best account of the American Red Cross's blood business is contained in the Pulitzer Prize–winning *Inquirer* series by Gilbert M. Gaul, which appeared in that newspaper September 24–28, 1989.

[f] Defendant's Reply to Plaintiff's Opposition to Defendant's Motion to Stay Discovery. *Institut Pasteur v. The United States*, 730-85C. United States Court of Claims, May 19, 1986. Although the government informed the court that the genetic difference was 1.8 percent, or about 165 nucleotides out of 9,213, the actual difference is only 86 nucleotides, or less than 1 percent (Weiss, R. A., *et al. RNA Tumor Viruses*, 1107–1123. New York: Cold Spring Harbor Laboratory, 1985). Gallo later acknowledged that the real difference was less than 100 nucleotides.

[g] Reply Affidavit of James B. Swire in Further Support of Motion to Compel. *Institut Pasteur v. The United States*. United States Claims Court, 730-85C, May 8, 1986. In

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"Just Show Us the Proof"

By the autumn of 1986 the Red Cross had been aware for months that the Abbott ELISA produced false-negative results. But Red Cross blood banks had continued using the Abbott test while the company searched for a solution. When Abbott's Marijane Sidote called the FDA to report that the false-negative problem at last had been solved, the FDA's Tom Zuck wasn't persuaded. "I told him we have process change to improve sensitivity," Sidote wrote in her telephone notes.[1] "He asked what? I said enriched with p41. He said no, it's p24 we miss. I explained our position. He said he doesn't believe it, that we have a circular argument. He said it will be hard to convince."

Zuck was "upset," Sidote told Abbott executives a few days later, "that he has been asking for confirmation of 'What's on the bead' for seven months and we still haven't told him. He said he can't work the science of the assays for dealing with lawyers and executives. He said he's so angry with Abbott, 'There are several stacks to work on, and we won't pick Abbott first.'"[2]

At the end of July 1986 a flock of specialists from Abbott headquarters descended on the FDA. Zuck's concerns about p24 aside, the data presented by the Abbott group seemed to show that the more gp41 on the bead, the fewer false negatives. Mike Ascher, now employed as a consultant to Abbott, surmised that antibodies to *both* gp41 *and* p24 must be produced early in the infection, but that for some reason only p24 antibodies showed up on a Western Blot.

In the FDA's view, it wasn't necessary to understand what was going on serologically as long as the Abbott test improved its reliability and sensitivity. Then Abbott confided that while gp41 enrichment had worked with its laboratory model test kits, the company didn't have the capacity to purify enough gp41 to make the same change in its product line.[a]

Abbott asked the FDA to approve a lesser bead modification without additional field testing, but Zuck refused. Abbott would have to present the gp41-enriched bead as an entirely new product, rather than an improvement on a product that already had an FDA license. That meant more field tests.[3] But no sooner had those evaluations begun than Abbott told the Red Cross to put everything on hold. A new problem had cropped up — an unexpected reappearance of the false positives Abbott thought had been resolved.[4]

When the Red Cross Blood Center Directors' Council met in Washington in October, the topic was the performance of the new Abbott ELISA. The new test was clearly better than the one the Red Cross and the blood banks were still using. The bad news was that it still missed nearly half the samples the Western Blot called HIV-indeterminate. Considering the manufacturing challenges involved, Abbott couldn't say when it could put the new test on the market. In the meantime, sentiment was growing among the Red Cross blood bank directors for dumping Abbott altogether in favor of Genetic Systems, whose AIDS test was already being used on a trial basis by seven of the fifty-five Red Cross blood centers.[5]

The Red Cross lawyers warned that dropping Abbott completely would probably violate the Abbott contract, and someone suggested using the Genetic Systems ELISA to back up the Abbott test. But if the Red Cross were going to buy the Genetic Systems test anyway, it didn't need the Abbott test. In the end, the blood center directors agreed that Abbott would be given an ultimatum: If the company's new test hadn't been approved by the FDA in ninety days, the contract with Abbott would be terminated. Less than a week after that decision, the Red Cross blood-testing chief, Gerald Sandler, assured the American public that "the blood supply is as safe as it can possibly be made."[6]

Bob Nowinski, the head of Genetic Systems, knew it wasn't true. "Statistically, bad blood got into the system," Nowinski said. "You can make a calculation, which in fact we did. If one test is twelve weeks

later in picking up a newly infected individual and you make various suppositions of what's the rate of new infection, then you can calculate given the number of transfusions, given the number of new infections, and given whatever the latency is. You can come up with a number that can be anywhere from eight hundred to several thousand a year."

As the Red Cross directors reconvened in San Francisco in November, Sandler was saying something quite different from what he had been telling the news media. The Red Cross lawyers, Sandler said, had decreed that if the agency wanted to protect itself from lawsuits down the road, it "could wait no longer" before putting a better HIV-antibody test into service. The formal ninety-day notice had never been given to Abbott, but the company had been made "aware" that the Red Cross was ready to replace it if the new test didn't become available "in the immediate future."

In the meantime, one council member suggested that the Red Cross stop making reassuring public statements and admit that the AIDS test was flawed. That might at least discourage people who thought they were HIV-positive from giving blood. His suggestion was rejected out-of-hand. But France Peetoom from the Portland Red Cross, one of the seven centers using the Genetic Systems ELISA, implored his colleagues to take "rapid action" in switching the entire system to Genetic Systems. If they didn't, Peetoom warned, it would soon be a full year since the Red Cross had learned about the false-negative problem.[7]

In mid-November Abbott sent the FDA its latest field data on the new ELISA, which now had a gp41 enriched bead, a new diluent *and* an improved conjugate.[8] The new test, Abbott assured the FDA, no longer would misread any blood samples containing HIV antibodies as antibody-free. When Tom Zuck saw the data, he fired a broadside at Abbott.[9] "You threw us a curve," he told Marijane Sidote. "You've made more changes — bead, diluent, buffer. It may be a new product. We can't keep putting Abbott before other reviews. We've been asked to take Abbott off the market because of poor sensitivity. We've had complaints that we handle Abbott changes as amendments instead of as a new product. You've made too many changes. You wasted our time with enriched bead and it didn't work. Now you have more changes coming. You've got to stick to an assay configuration for at least 60 days and quit changing it!"

The FDA had tried to tell Abbott "you had a sensitivity problem," Zuck went on, "and we told you the enriched bead would cause a specificity problem. Heller heard us, but the rest of you wouldn't listen. We wasted half a day talking to the Red Cross about your improved bead. Now we're concerned with the cell lysate. We don't know what it will do to the product. I've now been hauled in front of the Commissioner three times. We tell him you don't know what's in your product. You gave us 4 manufacturing options and asked us to help and we're not going to design your product for you . . . if you can't produce [the new test] then why should we approve the change? We don't think you've got a product you can make."

While Abbott sweated and Zuck fumed, the Red Cross continued to stall. At the beginning of October, the blood center directors had voted to give Abbott ninety days. Now it was nearly Christmas, and Red Cross headquarters executives hadn't even obtained a price quote from Genetic Systems for supplying the entire Red Cross system, as the directors' council had also requested. In a late-December conference call, the center directors demanded that Abbott be given an ultimatum. Headquarters promised the company would be told the following day that its contract would be canceled if the new test didn't receive a license within sixty days.[10]

On the second day of January, seventeen-year-old Kandra Kae Crosby of Fort Walton Beach, Florida, gave birth to her first child, a son she named Michael. During childbirth, Kandra Kae received four units of blood. One was from an early seroconverter who had tested HIV-negative prior to transfusion.[11] "She's never going to see her son graduate from high school," said her attorney, Dennis Webb.

While Jim Swire awaited the appeals court's ruling, the Institut Pasteur and the Department of Health and Human Services prepared to square off before the United States Patent and Trademark Office. According to *Time,* the PTO's decision to grant Pasteur's request for an interference represented a "minor triumph" for the French.[12]

On its face, the question of who deserved credit for inventing the HIV blood test seemed open-and-shut. The first-ever ELISA for AIDS virus antibodies had been performed in Paris in July 1983, using LAV from Frédéric Brugière. In September of that year the French had applied for a European patent on their blood test. In December

the middle of the 'rush to save the blood supply'. . . suddenly decide to perform a laborious experiment" by attempting to culture a virus he had already grown for more than three months, and then send those cultures to Gonda when he already had plenty of pictures of LAV?

[m]S. Arya laboratory notes, January 19, 1983, *et seq.* The page dated January 19 is headed, "HTLV cloned DNAs x LAV (BN1) cDNA." Similar entries exist dated January 27, January 30, February 5, February 7, February 23 ("LAV provirus Human cells"), February 25 ("LAV/Htu [Bn-1] [Mika virus]"), February 29 ("LAV/Htu [Bn2]: Mika Cell Culture"), March 5 ("Probe cDNA LAV [Bn2]"), March 16, March 21 ("Hybridization c LAV cDNA"), March 29 ("LAV [Mo(v)] from Biotech [#4BT]"), April 2 ("LAV (PZ-2)").

[n]A September 21, 1986, memo from Arya to Gallo fails to mention that the first appearance of LAV in Arya's notebook actually occurred on January 19. A number of Arya's other LAV entries are also missing, including those for restriction and hybridization experiments performed on January 27 and 30, February 5, 23, and 29, and March 5 and 21.

[o]S. Arya lab notes, January 19, 1984. As Maddox, Newmark, and Palca could have deduced from Popovic's notes, the only other candidate AIDS virus was MOV, then growing in sufficient quantities that Popovic had been able to send liters of concentrated virus to Sarngadharan two weeks before.

[p]M. Popovic lab notes. "Infection sup HUT 78/MOV →Htu4." November 29, 1983. Gallo to S. Broder, June 3, 1994. The evidence that MOV had been used to make the DNA probes used in Arya's experiments was deleted from documents provided by Gallo's lab to OSI but was uncovered by the House Subcommittee on Oversight and Investigations.

[q]Sarngadharan, the third inventor listed on the blood-test patent, also qualified for annual $100,000 payments. But under Sarngadharan's arrangement with his employer, Litton Bionetics, all such royalties were owned by the company.

Chapter 13. "Just Show Us the Proof"

[a]"Abbott can't make enough gp41 to coat beads with 13% enriched lysate," wrote one attendee at the July 29 meeting. "At best can enrich about 4%."

[b]The principal difference between the two tests, declared Byrnes, was that the French ELISA was attuned to antibodies to p24, while the Gallo test was focused on gp41. What Byrnes didn't mention was that the Gallo test had been producing false-negatives precisely *because* it failed to pick up antibodies to p24 — the flaw Abbott was working frantically to resolve. Byrnes next argued that the two tests were different inventions because the virus used in Gallo's test was being grown in the H-9 cell