Has French AIDS Research Stumbled?

Once, French scientists were at the forefront of AIDS research; now, they are struggling to keep up. Most say the country's hierarchical research system is the culprit

PARIS AND MARSEILLES—During the early days of the AIDS epidemic, it seemed that France could do no wrong. In 1983, a multidisciplinary team of physicians and researchers, including virologist Luc Montagnier of the Pasteur Institute in Paris, was first to isolate HIV, the virus that causes the disease. French scientists went on to sequence HIV's genome—narrowly beating an American team led by Robert Gallo, then at the National Cancer Institute in Bethesda, Maryland, into print. A French group shared the credit, along with a British group, for identifying the CD4 molecule as the primary receptor used by the virus to dock onto T lymphocytes, its major target cells. And French scientists first isolated HIV-2, a viral strain common in West Africa.

France is still a major player in AIDS, particularly in clinical studies of anti-HIV therapies, and it spends more than any other country apart from the United States on HIV research. But there is a widespread perception among scientists here and abroad that France is no longer on the cutting edge, particularly in basic research into how the virus destroys the immune system. "What major AIDS discovery has France made in the last 10 years?," asks immunologist David Klatzmann of the Pitié-Salpêtrière Hospital in Paris, who was a key contributor to the CD4 work. In 1996, for example, French scientists were on the sidelines when one of the most important breakthroughs of the past decade was announced: the discovery, by several American-led teams, that receptors for immune system signaling molecules called chemokines act along with CD4 as coreceptors for HIV. "The French were not in the wave; they missed the coreceptor story altogether," says Pasteur Institute virologist Marc Girard, a leader in France's AIDS vaccine effort.

In discussions with *Science*, AIDS researchers based in France and their international colleagues identified a number of possible reasons why the nation has lagged behind after its fast start. Some cited competition with the United States, pointing out that despite the French government's generosity compared to other European countries, the United States still outspends France on AIDS research by more than 30 to 1. But for the most part, researchers say, the problem lies within France's borders—and it is not limited to AIDS research.

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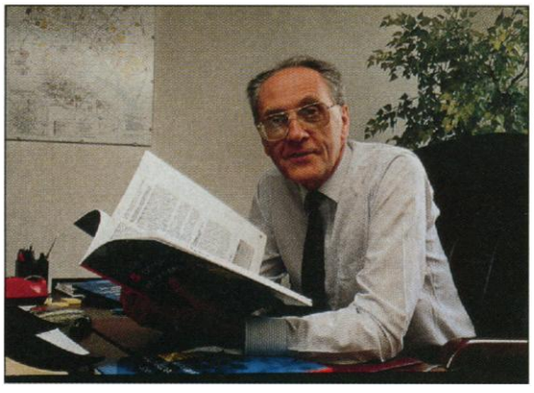
Hallowed hall. The AIDS virus was first isolated in the Emile Roux building at the Pasteur Institute in Paris.

Many put the blame on France's highly centralized research system, which, they say, lacks the flexibility and dynamism they see as key to American scientists' domination of the AIDS field. And while French scientists are not always unanimous in their views about why France has fallen behind, AIDS researchers who spoke with *Science* generally agreed that the French system stifles creativity, rewards mediocrity, and—the greatest sin of all, in the view of many—places serious obstacles in the way of young scientists seeking an independent career.

To observers outside the country, France's failure to keep up with its international competitors is a tragedy, given its earlier successes. "They had the courage to put together the first reports and push through the idea that AIDS was caused by a new retrovirus," says virologist Jay Levy of the University of California, San Francisco. "But afterward, it's difficult to know whether the resources available to them, both clinical material and [funds], were sufficient to allow them to go forward."



FLORENCE DURAND

AIDS czar. Jean-Paul Lévy, head of the National Agency for AIDS Research, manages a $40 million budget.

At times, French efforts to recapture the glory of the early years have gone badly awry. In 1993, for example, a team of scientists at Pasteur announced, to the accompaniment of much media fanfare on both sides of the Atlantic, that they had identified a molecule called CD26 as the long-sought coreceptor for HIV (*Science*, 5 November 1993, p. 843). But these results were soon discredited after other researchers—including some of France's leading AIDS investigators—were unable to reproduce the findings.

French researchers who spoke with *Science* repeatedly laid the blame for France's lackluster performance in AIDS research on the hierarchical nature of its scientific institutions. "We still have a very feudal system of organization," says Girard. "In most labs, there is a big boss, a baron, who has command of everything, and your future depends on him. If a young scientist wants to take risks, the system will not let him do much." Simon Wain-Hobson, an AIDS researcher at the Pasteur Institute and a member of the team that sequenced HIV's genome, agrees: "The bosses are too influential, while 35-year-old scientists are still considered young wolves, rather than equals. In the United States, 35 is getting on."

Indeed, some believe that French AIDS researchers made so much progress in the beginning precisely because they were working outside the scientific establishment. "At first, the disease didn't interest anyone, and so we were left free," says Klatzmann, who was a member of the band of mostly young

The Twin Icons of French AIDS Research

PARIS—Ask the average French person to identify France's leading AIDS researcher, and one name is likely to come up immediately: virologist Luc Montagnier of the Pasteur Institute in Paris. Montagnier came to public attention in 1983, when he emerged as spokesperson for the group of physicians and scientists that first isolated HIV, the virus that causes the disease. And thanks in part to constant media exposure ever since, he has come to personify French AIDS research both within the country and internationally.

But ask a French AIDS researcher to name the most important figure in HIV research, and you are likely to hear a different name: virologist Jean-Paul Lévy. As director of the National Agency for AIDS Research (ANRS), the government's primary AIDS funding agency, Lévy's power to chart the course of French efforts against the disease is second to none. "If you want to do something, the only person you have to convince is Lévy," says a leading French AIDS researcher who asked not to be identified.

Yet, ironically, members of the original AIDS research team say it was Lévy's unwillingness to take the helm of AIDS research during the early days of the epidemic that paved the way for Montagnier's rise to fame. In 1982, suspecting that a retrovirus might be the cause of AIDS, immunologist Jacques Leibowitch, an early member of the group, asked Lévy and his coworkers at the Cochin Hospital in Paris—where Lévy now directs the Cochin Institute in addition to his ANRS duties—to help identify it. "I tried to involve them," Leibowitch recalls, "but they were reluctant and referred me to other groups." The team then approached Montagnier, who, together with Pasteur virologists Jean-Claude Chermann and Françoise Barré-Sinoussi, eventually succeeded in isolating HIV.

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High public profile. Luc Montagnier of the Pasteur Institute.

As the senior member of that pioneering team, Montagnier became its spokesperson. "Montagnier had an openness of spirit and did not have preconceived ideas" about the cause of AIDS, says Willy Rosenbaum of the Rothschild Hospital in Paris, who was one of the first physicians to treat AIDS patients in France. Immunologist Jean Claude Gluckman of the Pitié-Salpêtrière Hospital in Paris says Montagnier "played an important role" in those early days. "He agreed to work on the subject, which others refused to do."

There is another side to the coin, however. Many French AIDS researchers have come to feel that the intense media focus on Montagnier has downplayed his colleagues' roles. "To see him on television all the time is intolerable," says one former member of the team. Indeed, in a 1993 letter to *Science*, Gluckman attempted to set the record straight by detailing the important contributions made by other members of the group (*Science*, 26 March 1993, p. 1809).

Moreover, a number of researchers told *Science*, in recent years Montagnier's continuing media exposure has been less and less justified by his actual contributions to AIDS research. "He has come to occupy a place he doesn't deserve," says a Paris-based AIDS researcher privately. For example, several French AIDS investigators who spoke to *Science* cited Montagnier's long-running but unsuccessful attempts to prove that mycoplasma—a microbe that resembles bacteria but lacks a cell wall—works together with HIV to cause AIDS (*Science*, 18 January 1991, p. 271). Montagnier has also been criticized for associating himself with a widely publicized, but quickly discredited, claim by a group at the Pasteur Institute that a molecule called CD26 was a long-sought coreceptor for HIV (see main text). "He has lost a lot of credibility in the scientific world," says Rosenbaum.

In an interview with *Science*, Montagnier conceded that neither the mycoplasma nor the CD26 story has played out the way he expected. "It is now clear that some strains of HIV can produce AIDS without any cofactors," Montagnier says, although he believes that mycoplasma infection might have been an important cofactor when the virus first jumped from monkeys to humans, as has been proposed as the origin of the disease. As for CD26, he still believes that the protein "could play a role in infection, or could be yet another coreceptor." Montagnier also cites his group's ongoing work on the effect of HIV on apoptosis, or programmed cell death, of T lymphocytes as evidence that he has continued to make important contributions to AIDS research.

But whether Montagnier's high profile is still justified, he has little influence over the funding of AIDS research in France, apart from a considerable amount he has received from the AIDS telethon Sidaction for an independent research center he created at the St. Joseph Hospital in Paris. The real power, for the most part, is wielded by Lévy. About half of the ANRS's $40 million annual spending on AIDS research is reserved for special "coordinated actions," such as vaccine development and therapeutic trials, over which Lévy has considerable discretion; the remainder is awarded to investigators after peer review by scientific committees, whose members are appointed with Lévy's approval.

Some researchers complain that Lévy keeps too tight a grip on the reins of French AIDS research. "He is very authoritarian," says Gluckman, adding that the "policy of the ANRS has been to push people to have short-term results, and that kills risky research." Most ANRS grants run only 2 years, which many scientists complain is not long enough to make significant progress. "This favors unidisciplinary, academic research and does not allow a quick adaptation to new research challenges," says immunologist Brigitte Autran of the Pitié-Salpêtrière Hospital in Paris.

But Lévy disputes the contention that risky research is being stifled. "You will find very few proposals that have been refused," he argues. "The problem for the committees is to find something original. When we do find it—something truly original and not a fantasy—we support it." Lévy also argues that the system of 2-year grants encourages rather than inhibits shifts to new lines of research. "This field evolves so rapidly that it's not logical to support research for 5 years; it would be stupid. In most cases, the research is reevaluated, and if it is good, there is no problem with renewing it."

Despite the grumbling, however, most researchers who spoke to *Science* believe Lévy is the best person to lead French AIDS research. Says Simon Wain-Hobson, an AIDS researcher at the Pasteur Institute: "He has made mistakes, but he has probably done better than anyone else could have done." **–M.B.**

physicians and scientists that met regularly in Montagnier's office during the early 1980s. "All that was suffocated when the [government research agencies] CNRS and INSERM became more interested, and things moved to the classic French system."

This perception is shared by some other members of the early group. Jean Claude Gluckman, an immunologist at Pitié-Salpêtrière Hospital, says that "the government discovered the problem in 1986, when a big AIDS conference was organized in Paris. They put people in charge who had never worked on the subject and who did not establish a dialogue with those who had." A similar view is held by Willy Rosenbaum, who, as an infectious-diseases expert at Claude Bernard Hospital in Paris, was one of the first physicians in France to treat AIDS patients. Rosenbaum, now at Paris's Rothschild Hospital, believes that the group, which included physicians, immunologists, and virologists, succeeded because it took a multidisciplinary approach. "I regret that we have lost this synergy in AIDS research," Rosenbaum says. "When the field was virgin terrain, it was easier to communicate. Now it is more and more specialized." Girard agrees that the lack of communication between research groups is a major problem in France. "In the United States, people know what is being done at any given time, even when they're not supposed to know, whereas I don't know what is being done in Montagnier's lab, and I'm not sure he knows what is being done in mine."

What some researchers call the "institutionalization" of AIDS research was completed by 1989, when the French government created the National Agency for AIDS Research (ANRS), under the leadership of virologist Jean-Paul Lévy, now France's undisputed AIDS czar (see sidebar). The ANRS now funds the overwhelming majority of French AIDS research, but Lévy takes issue with the idea that innovative research is being stifled. "This is not true at all," he says. "We didn't make progress in the beginning because we had cowboys who were outside the system, but because we were at a different historical point in AIDS research. The time of the cowboys is dead."

Wain-Hobson agrees with that analysis. He says the creation of a central agency like the ANRS was "essential" once it became clear that AIDS was a very complex disease that was not going to be cured overnight. "In the early days, the questions were very simple," says Wain-Hobson. "What was the virus? What was its receptor? But now we are interested in all sorts of difficult questions. Look how long it took to find the coreceptor: 10 years."

Despite these differing viewpoints, there is general agreement that France's scientific culture lacks the pugnacious dynamism that has made American science both envied and resented by European researchers. "Once the American machine gets going, there is no stopping it," says Wain-Hobson. The highly competitive spirit that characterizes much research in the United States does not come naturally to most French scientists. "The Americans abandon everything to jump on something new, like the coreceptor," says Robert Vigne, director of INSERM's Pathogenesis of Lentivirus Infections Unit in Marseilles. "But that is not our culture." Virologist Josephine Sire, also of the lentivirus unit, agrees: "We are not opportunistic. We are afraid for our [doctoral] students. We don't tell them to stop working on their theses and do something else."

Indeed, researchers say, the relatively unaggressive nature of French science may be key to understanding why France is lagging in AIDS research. "Those with less desire to win are going to lose," Gluckman says. "When you need to put on a major push to get something done, we don't know how to do that." And Girard laments that even when French researchers do discover something new, they are slow to publish their results. "When an American scientist has a new finding, the first reflex is to decide whether it's going to *Cell* or *Science* or *Nature* or [the *Proceedings of the National Academy of Sciences*]. In France, someone will make an interesting observation, and then they will start talking about it, and dream about it, and develop an interesting theory."

While researchers who spoke with *Science* offered a myriad of criticisms of France's research institutions, they were unanimous on one point: The French system does a poor job of preparing young scientists for future careers. "I am always impressed when I go to the U.S.," says Girard, "because any young American Ph.D. has been trained to think on his own and really express his creativity. But we have been trained in a very different fashion. We are good at producing administrators who think according to the rules, but we have not been brought up to find out new things." As a result, says Quentin Sattentau, a British immunologist at the Centre for Immunology in Marseilles, French doctoral students find it difficult to work independently. "In the United Kingdom, there is a tendency to let Ph.D. students fend for themselves. But students in France expect a lot of day-to-day supervision. They are neither well equipped nor very willing to think for themselves."

Moreover, once French science students do receive their Ph.D.s, they face a new hurdle: the almost total lack of government-funded postdoctoral positions in French labs. "It is easier to go anywhere in the world for a postdoc than in France," says Gluckman. "This is very bad for the French research system," says Brigitte Autran, an immunologist at Pitié-Salpêtrière Hospital. "Researchers between 25 and 35 years old, who are at the height of their creativity, go to the United States or other countries." And Rosenbaum says that the difficulties faced by young scientists do not bode well for the future of AIDS research in France. "I have seen very capable young researchers who were working on AIDS, but for strategic reasons they have decided to stop, either because they went abroad or their institution asked them to work on something else." The only hope for the future, Rosenbaum concludes, would be a "complete reconstruction" of French research institutions.

But this seems unlikely, at least anytime soon. In the meantime, France's AIDS researchers carry on making modest contributions and trying to keep up with the competition as best they can. "There is a big potential in France, even if we are not often in first place," says Lévy. And French scientists can still dream of making the historic discoveries that marked those heady days back in the 1980s. "Who knows?" says Gluckman. "Perhaps right now there is a lab in France writing up a paper that will revolutionize everything."

–Michael Balter

FRANCE'S HOTTEST AIDS RESEARCHERS

Name	Institution	Research Area
Marc Alizon	Cochin Institute, Paris	Coreceptors, HIV cell entry
Brigitte Autran	Pitié-Salpêtrière Hospital, Paris	Anti-HIV therapies and immune function
Alberto Beretta	St. Joseph Hospital, Paris	Coreceptor mutations, immunology
Christine Katlama	Pitié-Salpêtrière Hospital, Paris	Anti-HIV therapies
Quentin Sattentau	Centre for Immunology, Marseilles	HIV cell binding, antibody neutralization
Jean-Louis Virelizier	Pasteur Institute, Paris	Chemokines and HIV
Simon Wain-Hobson	Pasteur Institute, Paris	HIV molecular biology, lymph nodes

Pick of the bunch. In an informal poll carried out by *Science*, these researchers came out as France's finest.