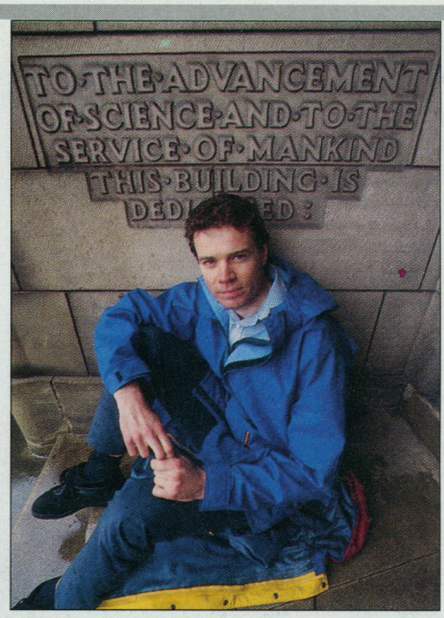
Unlikely Recruit: Andrew Leigh Brown



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AIDS is such a complex, multifaceted process that it has drawn researchers from many fields of research. There are virologists and immunologists, molecular biologists and epidemiologists, pharmacologists, oncologists, primatologists, experts in drug use, sexual behavior, hemophilia, and pregnancy. But even in that list a researcher trained to study *Drosophila* genetics stands out. And, indeed, Andrew Leigh Brown of the University of Edinburgh sees the differences between his original field and his current one. "AIDS is a lot harder work, and the problems are much bigger."

Actually, as Leigh Brown's promising start in AIDS research shows, it makes good scientific sense that the field should attract a population geneticist with a firm understanding of *Drosophila melanogaster*. In 1990, Leigh Brown, a 40-year-old Anglo-Scot, became a familiar name to AIDS researchers when he showed how his brand of molecular genetics could track the spread of HIV from a single infected batch of clotting Factor VIII through an entire cohort of hemophiliacs. A large study like this had never been done, and it opened up a window on the history of the epidemic that had seemed to be shut tight.

Accomplishments like those have attracted the notice of some well-known investigators. Leigh Brown is "bright and young and he'll continue to become a researcher who is at the forefront," says Gerald Myers, a Los Alamos National Laboratory researcher who tracks the spread of HIV through the world. "His potential is considerable."

That potential appeared at a tender age. At 24, possessor of a brand new Ph.D. from England's University of Leicester, Leigh Brown had already had his first publication in *Nature*, a single-author report on enzyme polymorphism in field mice. From there he moved on to *Drosophila* work, first at London's Imperial Cancer Research Fund, later at the University of Sussex, studying the evolution of "transposable elements" in flies. These genetic sequences, also known as "endogenous" retroviruses, can move from place to place in a host cell's genome, causing mutations as they go.

Leigh Brown moved to the University of Edinburgh in 1984, and 2 years later he experienced a pivotal career moment while reading a paper that analyzed changes in HIV over time in a single patient. The paper "posed a number of questions that were unresolvable, but the nature of the questions made me realize there was a role for a population geneticist in AIDS," he says.

After studying the published genetic sequences of HIV, Leigh Brown began wondering what forces influenced the changes in viral genetic sequences in any given infected person. That's when he began investigating a cohort of hemophiliacs. He observed how the swarm of HIV strains in each person changed, and, using genetic analysis, he traced the infections in each member of the cohort back to a single lot of the blood clotting protein known as Factor VIII. When he presented that data at the 1990 international AIDS conference in San Francisco, it put him on the AIDS research map. "People were surprised that this kind of analysis could be used with HIV," Leigh Brown says.

What was initially surprising, however, has since become a key part of the field. Leigh Brown has gone on to examine in detail the selective forces that act on HIV as it spread through a heterosexual cohort in Edinburgh and plans to begin similar analyses on samples from Uganda. In addition, he heads the newly opened Centre for HIV Research on the Edinburgh campus.

Leigh Brown's current research involves going beyond epidemiologically linked cohorts to find out what type of HIV is initially transmitted among the population at large. His work shows that even though people who have been infected for some time harbor many forms of HIV, among newly infected the various isolates show remarkable genetic similarities.

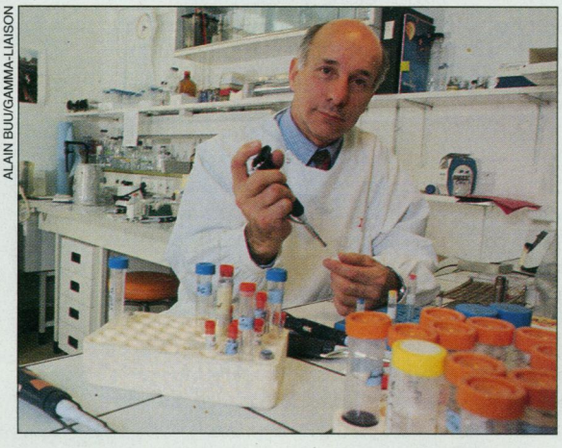
Leigh Brown is currently trying to find out whether one type of virus is preferentially transmitted and, if so, why that happens. The answers could significantly influence AIDS vaccine development. Sounds like a job cut out for a population geneticist.

–J.C.

Laughing Last: Marc Girard

Marc Girard remembers skiing in Keystone, Colorado, in the winter of 1989 and being ribbed by several top immunologists. They had come to Keystone for the annual AIDS conference held there and Girard was a target because he was one of the few researchers attempting to protect chimpanzees with HIV vaccines, something that, at the time, had never been reported. "They were laughing at me, saying, 'Marc, you can go back and try for years and it will never work.'"

By the fall of 1989, there was a new punch line and the joke was on Girard's colleagues, because he and his collaborator, Patricia Fultz of the University of Alabama, had protected a chimpanzee with an HIV vaccine. "I was very comforted by the observation that it worked," says Girard, a deputy director of the Pasteur Institute in Paris. He was also relieved, since the joke might well have continued to be on him: "I thought [success] was easier than could have been anticipated."



ALAIN BUU/GAMMA-LIAISON

Following that success, Girard, 56, is viewed as one of the world's leading authorities on AIDS vaccines and chimpanzees. "Marc is a major force in AIDS vaccine development," says Duke University's Dani Bolognesi, himself an influential AIDS vaccine researcher. Girard heads a French government-sponsored AIDS vaccine task force and organizes the annual Cent Gardes meeting, a much-praised AIDS conference.

In many ways it seems fate steered Girard to his current work. "I do believe in serendipity," says Girard. "The word doesn't exist in French, and it's the best English word I know." For starters, his father was a veterinarian who developed a foot-and-mouth disease vaccine for livestock.

The younger Girard grew up in Lyon and earned a doctorate of veterinary medicine in 1960. The field never really gripped him, though, and soon he had moved on to his real passion: human viruses. In 1965, a young researcher at California's Salk Institute offered him a fellowship to study poliovirus. That young researcher was David Baltimore, now a Nobel laureate, who says: "[Girard's] ability to handle problems at the level of the whole animal really distinguishes him. Only someone with a training in virology and animals could pull off what he does."

After sharpening his wits with Baltimore, Girard returned to France where he earned a Ph.D. in 1967 from the University of Paris. Having obtained his degree, he went to work at the Pasteur, attempting to make a polio vaccine from a component of the virus rather than the whole viral particle as other researchers had done. Having little luck, in 1970 he moved to the Cancer Research Institute in a Parisian suburb, where he spent a decade before returning to the Pasteur and his passionate interest in polioviruses.

A few further career twists and turns later, Girard became interested in AIDS and struck up a fruitful collaboration with Fultz. In their first experiment with chimpanzees, they vaccinated animals with several different combinations of whole, killed HIV (see p. 1261) and genetically engineered HIV proteins. This work became known as "the kitchen sink" experiment to many AIDS researchers—in reference to the only thing Girard didn't throw into the chimps. Says Girard: "We were under the simplistic assumption that hopefully we'd get protection and then we'd start removing [components of the virus] one by one" to reach the minimal combination needed for a vaccine.

In fact, Girard and Fultz found that by *adding* a particular HIV peptide—the V3 loop—they raised the levels of the antibodies that they believe are critical. They have now shown that a vaccinated chimpanzee can resist infection when "challenged" with an injection of HIV that is either inside or outside of cells. And they hope to break new ground soon with tests that are more like what happens in the real world of AIDS: challenging with strains of virus that don't match the strain in the vaccine as well as vaginal or rectal challenges. In addition to his chimpanzee work, Girard is helping to test HIV vaccines in 45 uninfected humans.

In spite of his successes so far, Girard is well aware of the difficulties that makers of AIDS vaccines face. "It's going to take as many years as it's taken so far. I'm not the optimistic kind, like the American companies that, for their shareholders, say there will be a vaccine in 3 years." And at this last thought, he lets out a throaty laugh.

–J.C.

On a Rollercoaster: James Stott

At an international AIDS vaccine conference in 1990, James Stott combed the halls posing a question to colleagues: Which experimental vaccine would they take, he wanted to know, if 6 months hence they became infected with HIV? Stott, a primate researcher at the National Institute for Biological Standards & Control in Potters Bar, England, wasn't making a ghoulish joke— he had a scientific agenda. At the time, Stott and others who tested AIDS vaccines in monkeys were having dramatic success with an old-fashioned vaccine approach based on the whole, killed virus. But the entire field, it seemed, was wedded to a modern, high-technology approach—genetically engineered vaccines—even though those vaccines were failing monkey test after monkey test. To Stott, the situation seemed unbelievable.

A year later Stott turned the world of AIDS vaccines on its head by showing that the successful monkey results he was using to chide his colleagues were due to an artifact. People working with vaccines in monkeys are still recovering. But one of the first to recover—and even find a silver lining in this catastrophe—was Jim Stott.

Then again, Stott's research career has had a number of twists. Born in England's industrial north 54 years ago, he earned an undergraduate degree at Cambridge University in 1960. His early career was spent on subjects that don't get nearly as much media attention as AIDS. After studying respiratory illnesses in children at Glasgow University, he completed a Ph.D. at the Medical Research Council's (MRC) Common Cold Research Unit in Salisbury, England, where he concentrated on rhinoviruses, the cause of most colds.

In 1972, Stott took a job in the countryside outside of London with the government's Agricultural and Food Research Council. The task was to investigate calf pneumonia, and though Stott assumed he had moved beyond the kind of work he was doing in Glasgow, "we discovered—surprise, surprise—that one of the major causes was respiratory syncytial virus. Here we were back again with the thing I started with in Glasgow."

Fifteen years later, after having developed a successful whole, killed vaccine for the cows, Stott decided to move on. It so happened that Geoffrey Schild of the MRC was just setting up an AIDS vaccine research program. "Geoffrey had made the decision, with great wisdom actually, that the vaccine program of the MRC was to be built around animal models," says Stott. Monkeys, which develop AIDS when infected with SIV, a simian cousin of HIV-1, were to be the main focus.

At first the work went swimmingly: Stott, working with Martin Cranage at the Centre for Applied Microbiology and Research in Salisbury, repeatedly protected monkeys against experimental "challenges" with live SIV. It was at that point that Stott began "challenging" not only the monkeys, but his colleagues at AIDS conferences. Not long after, however, the roof fell in.

DAVID LEVENSON/BLACK STAR

Stott found that using human white blood cells alone as a vaccine—with no virus—could provide the same result: protecting monkeys from SIV challenges. He quickly came up with a dispiriting explanation. The SIV used in the challenges had been grown in human white blood cells. Stott knew that as the viruses budded from human cells, they brought with them human cell-surface proteins. He reasoned that when the viral vaccine preparation was injected into monkeys, they made antibodies to the human proteins caught on the surface of the virus. When they were challenged, antibodies against those same proteins—and not against viral proteins—caused protection. And that meant the vaccine makers were no closer to knowing what components of the virus they needed to include in a successful vaccine.

Of that result Stott says wryly: "It may not be knowledge we wanted, but it's better to face reality than to run along with an illusion, thinking that you are getting to where you're going." But all is not doom and gloom to Stott. Since the same types of white blood cell proteins are found in many strains of HIV, it is possible that an HIV vaccine based on cellular proteins could offer protection against multiple viral strains. "This was the great hope when we recovered from the great shock of our results," Stott says. That's a remarkable turnaround for a gloomy finding. But unexpected reversals seem to be a leitmotif in the career of Jim Stott.

–J.C.