

THE NETHERLANDS

Access to Patients Is Key to Success of Dutch Quartet

AMSTERDAM—Back in the 1980s, when most of the important AIDS discoveries were coming out of the United States, France, and the United Kingdom, Dutch AIDS researcher Frank Miedema had a credibility problem. “I would get up at a meeting, and people would say, ‘Who is this strange guy from Amsterdam; what does he have to tell me?’” Miedema recalls. But he soon got people’s attention. Thanks to their access to two large cohorts of HIV-infected people in Amsterdam, gay men and intravenous drug users, Miedema and his colleagues accumulated enough data to convince skeptical researchers of a groundbreaking insight: In many patients, progress to AIDS is associated with HIV’s evolution from strains that do minimal damage to their T lymphocyte target cells into viruses that easily kill T cells.

The Amsterdam team went on to map these differences in virulence to small changes in the amino acid sequences of proteins that make up HIV’s outer coat, a finding that helped make sense of more recent discoveries that different viral strains use different cell surface receptors to latch onto T cells. And over the past 15 years, this unusual collaboration—led by public health expert Roel Coutinho of Amsterdam’s Municipal Health Service, clinician Joep Lange and virologist Jaap Goudsmit at the University of Amsterdam’s Academic Medical Center, and Miedema, an immunologist with the Netherlands’ Red Cross Blood Transfusion Service—has made a number of other important contributions to AIDS research, including key findings on AIDS epidemiology, markers of disease progression, antiviral therapies, and the interplay between HIV and the immune system.

“They are the number one group in Europe for impact on AIDS research,” says immunovirologist Guido Poli of the San Raffaele Scientific Institute in Milan. And Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, adds that the Amsterdam group has “made very significant inroads in understanding [HIV] pathogenesis. If you look at the size of their country [15 million people] and the size of its [financial] commitment, as opposed to some larger countries that have committed many more resources, their contributions really stand out.” Indeed, the Amsterdam team has accomplished so much that the Dutch health ministry—which had given the group more than \$40 million over the past decade—

cited its very success as the rationale for stopping the collaboration’s funding after this year (*Science*, 19 September 1997, p. 1757).

The team’s own members ascribe their success to being in the right place at the right time. “When the AIDS epidemic started, it was clear from the beginning a virus was involved,” says Coutinho. “So we started discussing it with the virology group at the University of Amsterdam.” That brought in Goudsmit, who began trying to devise a blood test for the disease. Soon after, the group was joined by Lange, who was treating AIDS patients at the university’s medical



Cohort cabal. From left: Frank Miedema, Roel Coutinho, Joep Lange, and Jaap Goudsmit.

center, and Miedema, who was doing his doctoral research at the blood bank.

When the first AIDS cases were diagnosed in the Netherlands in the early 1980s, the Amsterdam health service and the Red Cross blood bank were already running programs involving the city’s gay male community. These included an effort to combat sexually transmitted diseases and a large-scale clinical trial of vaccines against hepatitis B. The team’s access to these cohorts of people at high risk for HIV infection allowed it to gather valuable data on the course of the disease from the time of initial infection to the development of full-blown AIDS, usually many years later.

Yet researchers who know the Amsterdam group well say that the collaboration has not always gone smoothly, particularly because each member of the team is endowed with a forceful personality and strong views about AIDS research. One Dutch scientist, who asked not to be identified, says that rivalries soon emerged over “priorities of research, distribution of money, and authorships.” Indeed, in an interview with *Science*, the group admitted that members often disagreed. “There were moments when I thought we couldn’t go on,”

says Coutinho. “Everyone is very ambitious, and everyone has certain goals.” But in the end, they realized that their success was based on their dependence on each other and on close contact with the cohorts. “Without these cohorts, we would be nowhere,” Coutinho says. “If we had split up, we all would have lost.”

In recent years, as the team has gained international recognition, some members have become outspoken in broader debates in the AIDS research community as well. For example, Lange, who has been principal investigator on numerous clinical trials sponsored by the pharmaceutical industry, wrote a blistering critique in *Science* last year of the way many anti-HIV drug trials are conducted (*Science*, 25 April 1997, p. 548). Biting the hand that feeds much of his research, he condemned drug companies for their reluctance to carry out multidrug trials that include products of their competitors, even if such combinations might provide the best therapy.

And Miedema has come out swinging in the fierce debate over just how HIV infection leads to the drastic loss of T cells that heralds the destruction of the immune system. In particular, he has tangled with David Ho, director of the Aaron Diamond AIDS Research Center in New York City, over Ho’s theory that the immune system becomes exhausted in its battle with HIV when it can no longer produce T cells faster than they are destroyed by the virus (*Science*, 21 November 1997, p. 1399). Miedema, along with

Hanneke Schuitemaker of the blood transfusion service and other Dutch colleagues, argues that the virus destroys the immune system by interfering with the regeneration of new T cells rather than by directly killing large numbers of mature T cells.

The Amsterdam group’s prominence on the international AIDS research scene makes it all the more ironic that the health ministry has decided to stop funding it. The collaboration’s future is now in the hands of a committee appointed by the Dutch Medical Research Council, which is part of the Netherlands’ science ministry. The committee is expected to make a recommendation this autumn on whether the project should continue, and if so, who should fund it. “We have funding until the end of this year,” says Coutinho, adding that if new money is not found before September, “we will have to stop the cohort studies.” Given the contributions of the Amsterdam group over the years, researchers say, that would be a major blow not only to AIDS research but to HIV-infected people throughout the world.

—Michael Balter