is the immunodeficiency that allows nonpathogenic microbes to become killers and other latent microbes to erupt. Pneumonia caused by *P. carinii* is rare in immunocompetent people but common in patients with AIDS; yet, *P. carinii* is not the cause of AIDS. KS, a rare cancer in immunocompetent people but frequently seen in AIDS patients, is caused by human herpes virus 8, also called KS-associated herpes virus (KSHV), which is transmitted sexually but remains latent in immunocompetent people (*18*, *19*). Clearly, neither KS nor KSHV is the cause of AIDS. About 10% of people infected with HIV also carry HTLV-1, the first human retrovirus causing cancer to be identified (*9*, *10*, *13*). Thus, the demonstration that HIV causes AIDS was no small task.

I have suggested to Gallo that the scientific process might be well served if he and Montagnier were to write somewhat dispassionate accounts of how the cause of AIDS was discovered. Although Gallo and Montagnier tried to do this (*20*, *21*), the need for each to be called the codiscoverer of the AIDS virus prevented resolution of the scientific dispute. The codiscoverer status had been a political solution devised by U.S. President Ronald Reagan and French Prime Minister Jacques Chirac in their attempt to resolve the dispute over patent rights covering the blood test for HIV.

The three following essays are a collaborative effort by Montagnier and Gallo that describe the different yet complementary paths that each took to discover the cause of AIDS, and both authors concur with each other's description of events.

References and Notes

1. M. S. Gottlieb *et al.*, *N. Engl. J. Med.* **305**, 1425 (1981).
2. M. S. Gottlieb *et al.*, *Morbid. Mortal. Wkly. Rep.* **30**, 250 (1981).
3. N. J. Ehrenkranz *et al.*, *Morbid. Mortal. Wkly. Rep.* **31**, 365 (1982).
4. J. M. Karon *et al.*, *Morbid. Mortal. Wkly. Rep. Recomm. Rep.* **41**, 1 (1992).
5. M. Essex, in *AIDS: Papers from* Science, *1982–1985*, R. Kulstad, Ed. (AAAS, Washington, DC, 1986), pp. 3–7.
6. F. Barré-Sinoussi *et al.*, *Science* **220**, 868 (1983).
7. M. Popovic *et al.*, *Science* **224**, 497 (1984).
8. R. C. Gallo *et al.*, *Science* **224**, 500 (1984).
9. J. Schüpbach *et al.*, *Science* **224**, 503 (1984).
10. M. G. Sarngadharan *et al.*, *Science* **224**, 506 (1984).
11. D. A. Morgan *et al.*, *Science* **193**, 1007 (1976).
12. B. Safai *et al.*, *Lancet* **1**, 1438 (1984).
13. J. A. Levy *et al.*, *Science* **225**, 840 (1984).
14. D. P. Francis *et al.*, *J. Natl. Cancer Inst.* **71**, 1 (1983).
15. J. Coffin *et al.*, *Science* **232**, 697 (1986).
16. B. J. Poiesz *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **77**, 7415 (1980).
17. Levy called the virus that he isolated AIDS-associated retrovirus or ARV (*13*), which turned out to be from the same virus family as Montagnier's LAV and Gallo's HTLV-III, all later renamed HIV (*15*).
18. Y. Chang *et al.*, *Science* **266**, 1865 (1994).
19. D. Ganem, *Cell* **91**, 157 (1997).
20. R. C. Gallo, L. Montagnier, *Nature* **326**, 435 (1987).
21. ———, *Sci. Am.* **259**, 41 (October 1988).

22. I thank F. E. Cohen, R. Gallo, H. Koprowski, J. Levy, L. Montagnier, and N. Nathanson for helpful comments, and H. Nguyen for help with the manuscript.

VIEWPOINT: HISTORICAL ESSAY

A History of HIV Discovery

Luc Montagnier

In 1972, Jacques Monod asked me to create a research unit in the new virology department of the Pasteur Institute. I baptized it the viral oncology unit because I shared the belief of many biologists that certain human cancers could be caused by viruses, in particular by retroviruses. I had some experience with chicken oncogenic viruses, having confirmed with the late Philippe Vigier the existence of infectious transforming DNA in chicken cells infected with Rous Sarcoma virus (first described by Hill and Hillova) (*1*). Yet, despite a well-funded effort, the "virus cancer program" failed to reveal a retrovirus that could cause human cancer.

In 1977, as the viral oncology unit became interested in the action of interferon, I had an illuminating idea: Perhaps we couldn't isolate retroviruses from human cancers because their expression was inhibited by production of endogenous interferon. If we could neutralize this effect by treating cancer cells with antiserum against interferon, we might be able to detect a human oncogenic retrovirus. About this time, Jean Claude Chermann and his young assistant Françoise Sinoussi, both with expertise in mouse retroviruses, joined the unit. First, we tested the idea in mouse cells and, indeed, production of exogeneous and even endogeneous retroviruses could be boosted by treating cells with low doses of antiserum to mouse interferon (*2*). Next, we investigated human cancers, selecting acute and chronic lymphocytic leukemias and breast cancers for study. We used the new T cell growth factor (now called interleukin-2) discovered in Robert Gallo's laboratory to make short-term T lymphocyte cultures from cancer patients. We hoped that the retrovirus might be hiding not only in human cancer cells but also in T cell subsets. We examined many lymphocyte samples from cancer patients, each time culturing the cells with and without antiserum to human interferon. Françoise Sinoussi measured reverse transcriptase (RT) activity (a retroviral enzyme) in the culture supernatants. We had a few (false) positive results due to RT activity associated with mycoplasma contamination of our T cell cultures. In 1982, using a DNA probe from the mouse mammary tumor virus, Michel Crepin detected by molecular hybridization a DNA sequence in a human breast tumor that resembled a sequence in the mouse oncogenic retrovirus (*3*). Strikingly, the same DNA sequence could be recovered from cultured T lymphocytes taken from the cancer patient.

It was at this time that I first heard about the "gay disease." There were only a few patients with this disease in France, but Gallo's idea that a retrovirus was the cause had already crossed the Atlantic. His idea was disseminated by a small group of clinicians and immunologists led by Jacques Leibowitch and Willy Rozenbaum. At the end of 1982, Françoise Brun-Vezinet, a former student of mine and a member of this group, proposed that we collaborate to discover if a retrovirus was the cause of this disease, now called AIDS.

We were ready to start because my laboratory was equipped to hunt for lymphotropic retroviruses in human T cell cultures. In addition, there was a risk that human plasma collected from blood in the United States and used by the Pasteur Institute's industrial subsidiary to prepare a hepatitis B vaccine might be contaminated by the AIDS agent. On 3 January 1983, Françoise Brun-Vezinet obtained a lymph node biopsy from one of Rozenbaum's patients, a young gay man (BRU) with a lymphadenopathy in the neck. I minced the lymph node, dissociated the fragments into single cells, and cultured the T lymphocytes with interleukin-2 and antiserum to human interferon. Fifteen days later, Françoise Sinoussi (by then Barré-Sinoussi) found the first traces of RT in the supernatant of the lymphocyte culture, indicating the presence of a retrovirus. The only retroviruses then known were the human T cell leukemia viruses, HTLV-1 and HTLV-2, identified by Gallo's group. So, we tested whether the viral proteins in the supernatant could be recognized by Gallo's antibodies against HTLV. Surprisingly, our labeled viral supernatant could not be immune precipitated with the HTLV antibodies, but could be precipitated with the patient's own serum (*4*). A protein with a molecular mass of about 25 kD precipitated by the patient's serum seemed to be the counterpart of the p24 protein of HTLV-1. The virus could not be isolated from blood lymphocytes, a fact that is now explained by the early stage (lymphadenopathy) of this patient's disease when the virus is almost exclusively located in lymphatic tissues. Louis Pasteur's quote that "luck in science smiles on prepared minds" certainly applied to us. We

The author is President of the World Foundation for Aids Research and Prevention, 1 rue Miollis, Paris F-75015, France.

received a biopsy from another young gay male patient (MOI), who was infected with both HTLV and the new lymphadenopathy-associated virus. If MOI had been our first patient, we would have been very confused.

A few months later, I received a blood sample from a young hemophiliac (LOI) with full-blown AIDS, and blood and lymph node samples from a young gay man (LAI) with advanced Kaposi's sarcoma. The LAI virus could be isolated from the patient's blood cells and grew very quickly in the patient's cultured T lymphocytes, killing them as well as killing T lymphocytes from blood donors. In September, we isolated a similar virus from the blood of a Zairian woman, ELI, who died of AIDS a week later. All of the isolated viruses showed cross-reactivity between their gag proteins (p25 and p18) (*5*). The viruses isolated from full-blown AIDS patients were more aggressive than the BRU virus, and so I called them immune deficiency–associated viruses (IDAV). The viruses like BRU that were isolated from patients who only suffered from lymphadenopathy were termed lymphadenopathy-associated viruses, or LAV. This classification corresponded to the later terminology of syncitium and nonsyncitium-inducing strains.

The retrovirus was new, as was the disease. My collaborator, the electron microscopist Charles Dauguet, showed me pictures of the viral particles whose dark, cone-shaped centers suggested that this virus was not the same as HTLV. Fellow virologist Edwald Edlinger suggested that I compare the new virus with animal lentiviruses, and, indeed, the pictures of viral particles we obtained in June 1983 looked identical! As I told Robert Gallo, I was convinced that we were dealing with a virus quite different from the HTLV family.

To better characterize the new virus, we tried (unsuccessfully) to grow the BRU isolate in different T cell lines. If we had tried the LAI isolate instead, we would have been able to grow the virus without any trouble. In October 1983, we were finally able to grow the BRU isolate in Epstein-Barr virus–transformed B cell lines, although we discovered later that the LAI virus had contaminated our BRU culture (*6*). At least six laboratories received the LAI sample (under the name BRU) from our group and experienced the same contamination. We think that the LAI virus readily contaminated the BRU culture because it associates with a mycoplasma species, *Mycoplasma pirum*, usually present in T cell lines. This physical association makes a fraction of the LAI virus highly infectious, and, in fact, this fraction can be neutralized with antibodies against *M. pirum*. As mycoplasmas are common contaminants of cultured cells, an infectious pseudotype virus (LAI associated with *M. pirum*) may have caused several contaminations between 1983 and 1984 in different laboratories.

New evidence that this strange retrovirus was the cause of AIDS came from our team in the fall of 1983 and the winter of 1984 (*7*). We observed a high frequency of antibodies against the virus in lymphadenopathy patients, and noted the favored tropism of this virus for $CD4^+$ T lymphocytes. Our results were still controversial, however, and we had difficulty in obtaining the funding needed to better characterize the virus and to develop a blood test. The tide only turned in France when Robert Gallo and his group in the United States made a similar discovery. In the spring of 1984, Gallo published more convincing evidence that HIV causes AIDS (*8*) (see the Viewpoint by Gallo on page 1728), a finding that was confirmed by Jay Levy's group (*9*). In 1985 came the cloning and sequencing of the HIV genome with identification of new open reading frames specific for lentiviruses (*10*). This was followed by identification of the HIV large surface glycoprotein (*11*) and of T cell CD4 as the receptor for HIV (*12*, *13*). In 1986, HIV-2 was isolated from West African patients (*14*).

Over the past 20 years, the scientific and legal controversies between our team and Gallo's group have faded. We are left with the salient fact that HIV was identified and shown to be the cause of AIDS less than 2 1/2 years after this disease was first identified. It took only another 2 years for blood tests to become commercially available, reducing almost to zero the transmission of AIDS through blood transfusion in developed countries. In 1987, the first anti-HIV drug, AZT, which blocks HIV RT activity, was introduced. With the arrival of the HIV protease inhibitors and triple drug therapy in 1995, many patients are alive today who would otherwise have died.

But we must not be complacent—the task ahead is immense. We still do not understand the origin of the AIDS epidemic; the slow destruction of the immune system by factors in addition to HIV infection of $CD4^+$ T cells; the importance of cofactors in AIDS progression and virus transmission; and the nature of the HIV reservoir that resists triple drug therapy. The next wave of advances in the fight against this worldwide scourge will require the contribution and energy of us all.

References and Notes

1. P. Vigier, L. Montagnier *Int. J. Cancer* **15**, 67 (1975).
2. F. Barré-Sinoussi *et al.*, *Ann. Microbiol.* (Inst. Pasteur) **130 B**, 349 (1979).
3. M. Crepin, *Biochem. Biophys. Res. Commun.* **118**, 324 (1984).
4. F. Barré-Sinoussi *et al.*, *Science* **220**, 868 (1983).
5. L. Montagnier *et al.*, in *Human T Cell Leukemia and Lymphoma Viruses*, R. C. Gallo, M. E. Essex, L. Gross, Eds. (Cold Spring Harbor Laboratory, New York, 1984), pp. 363–379.
6. S. Wain-Hobson *et al.*, *Science* **252**, 961 (1991).
7. Between 1983 and 1985 the team included the superb retrovirologists Jean-Claude Chermann and Françoise Barré-Sinoussi and the following talented individuals to whom I am indebted: M. Alizon, C. Axler-Blin, F. Brun-Vezinet, J. B. Brunet, S. Chamaret, F. Clavel, S. Cole, O. Danos, C. Dauguet, J. C. Gluckman, J. Gruest, D. Guetard, D. Klatzmann, B. Krust, N. T. Nugeyre, F. Rey, C. Rouzioux, W. Rozenbaum, P. Sonigo, E. Vilmer, and S. Wain-Hobson.
8. R. Kulstad, Ed., *AIDS: Papers from* Science, *1982–1985* (AAAS, Washington DC, 1986).
9. J. A. Levy *et al.*, *Science* **225**, 840 (1984).
10. S. Wain-Hobson *et al.*, *Cell* **40**, 9 (1985).
11. J. S. Allan *et al.*, *Science* **228**, 1091 (1985).
12. A. G. Dalgleish *et al.*, *Nature* **312**, 763 (1984).
13. D. Klatzmann *et al.*, *Nature* **312**, 767 (1984).
14. F. Clavel *et al.*, *Science* **233**, 343 (1986).

VIEWPOINT: HISTORICAL ESSAY

The Early Years of HIV/AIDS

Robert C. Gallo

Animal retroviruses were among the earliest viruses discovered, and by the 1960s some were shown to cause cancer. These findings prompted the formation of the U.S. Virus Cancer Program, which aimed to identify human tumor viruses, especially human retroviruses. By the late 1970s, however, a mistaken consensus emerged that viruses did not cause human cancer and that human retroviruses did not exist, leading to termination of the program. Even more perplexing was the assertion that serious epidemic diseases were limited to the "Third World," culminating in the closure of certain U.S. medical school microbiology departments and a disturbing lack of support for the U.S. Centers for Disease Control and Prevention (CDC). In the midst of this complacency, my co-workers and I made human retroviruses one of our primary research objectives. We were interested in leukemia and began to characterize the DNA polymerases in blood cells (*1*, *2*). Howard Temin had proposed that retroviruses replicate through an integrated DNA intermediate, a notion supported by his discovery with David Baltimore of a retroviral reverse transcriptase (RT).

This discovery provided me with an entry point into the field because RT is a DNA polymerase. We developed sensitive assays to de-

The author is at the Institute of Human Virology and Department of Microbiology and Immunology, University of Maryland, Baltimore, MD 21201, USA.