Note from the Editor-in-Chief

In this issue, which coincides with World Aids Day, we explore the scientific background for the discovery and initial characterization of the HIV retrovirus. Not only was that search aimed at one of history's most threatening public health challenges; it also generated an acrid scientific rivalry with serious political consequences, and garnered widespread media attention—not all of which aided public understanding of a complex and important scientific issue.

We'd like to promise *Science*'s readers that we're now about to dispel the fog and bring out a "true history." Alas, we cannot. What we have done is to ask the two most deeply involved protagonists, and a relatively neutral scientific observer, for their versions of that history. Sometimes it is hard to be a witness to one's own history, nevertheless, we think that these historical Viewpoints will be an important addition to a valuable archive. For coverage of these events see a collection of *Science*'s news articles at www.sciencemag.org/feature/data/aids2002/articles.shtml.

VIEWPOINT: HISTORICAL ESSAY

Discovering the Cause of AIDS

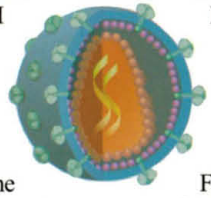
Stanley B. Prusiner

Great discoveries in science are infrequent, yet they are the grist that motivates every scientist. This source of motivation is critical because most experiments advance our knowledge little, and even when an experiment "works," the step forward is small. Great discoveries happen within different contexts. Some occur when the scientists are not anticipating the outcome—these are genuine gifts of nature. Others occur when clearly defined questions, usually with "yes" or "no" answers, are posed. And often those posing the query are not the ones making the discovery.

In 1981, the initial description of immunodeficiency in very sexually active, young gay men posed the question of causation (*1*). That report was followed by an alarming rise in the number of new cases of what became known as acquired immune deficiency syndrome, or AIDS. The immunodeficiency associated with AIDS resulted in the appearance of a rare cancer, Kaposi's sarcoma (KS), and a number of opportunistic infections caused by, for example, *Pneumocystis carinii* and *Candida albicans* (*2–4*).

As the clinical descriptions of AIDS widened in the early 1980s, the dramatic reduction in T lymphocytes and a decrease in the ratio of helper T cells to suppressor T cells became the focus of medical investigators searching for a cause. And as the number of AIDS cases exploded to reach epidemic proportions, so did the hypotheses about its possible causation (*5*). The appearance of AIDS in distinctly different populations including young gay men, intravenous drug abusers, hemophiliacs, Haitians, infants, and blood transfusion recipients argued for an infectious agent. But what kind of infectious agent would destroy the immune system of so many different groups of people?

With more than 20 million deaths from illnesses resulting from AIDS over the last two decades, learning the cause of this fatal illness was a major discovery, enabling the development of a sensitive blood test and effective drugs. Although I never worked in AIDS research, as a neurologist I examined AIDS patients with nervous system complications, and as a scientist I was engaged in defining the enigmatic infectious agent that caused degeneration of the central nervous system of immunocompetent humans and animals. Most scientists would agree that the discovery of the cause of AIDS by Luc Montagnier and his colleagues at the Pasteur Institute and by Robert Gallo and his colleagues at the U.S. National Institutes of Health ranks as a great scientific discovery. However, I became disturbed by the rancor that seemed to engulf Montagnier and Gallo at each stage in the acquisition of new knowledge about this terrifying disease. Some scientists were all too happy to involve the popular press, whose members were ready to write almost any rubbish that their editors would accept. In the mid-1980s, I had my own troubles with the press but because my work did not impact the lives of hundreds of thousands of people infected with a highly communicable, infectious pathogen, I could retreat by simply refusing to speak to reporters. AIDS researchers did not have that option—too many people were dying of this new scourge!



By both reading the literature and speaking to many scientists, I have developed what I believe is a reasonably accurate view of what Montagnier, Gallo, and their numerous colleagues contributed to our understanding of the cause of AIDS. I have taken care to determine which of my views about priority are supported by the dates of submission and subsequent publication of manuscripts in refereed journals. After all, this is the currency by which scientific discoveries have been and will continue to be judged for the foreseeable future. I did not consider abstracts, presentations at meetings, patent applications, or hearsay. In retrospect, there is no doubt that Montagnier and his colleagues were the first to report the discovery of the virus that we now call human immunodeficiency virus, or HIV (*6*). Equally important were the contributions of Gallo and his coworkers, who showed that the virus reported by Montagnier was the cause of AIDS (*7–10*). The work of both Montagnier and Gallo was made possible by the earlier discovery by Gallo's laboratory of the cytokine interleukin-2 (*11*), which is necessary for the growth of cultured T lymphocytes that support HIV replication. The propagation of large quantities of HIV in cultured T cells enabled the development of a blood test for detecting HIV by Gallo's group (*9*, *10*, *12*). Not only did the blood test allow the convincing demonstration that HIV causes AIDS but, equally important, it prevented millions of people from becoming infected with HIV through the transfusion of tainted blood. Certainly, the Montagnier and Gallo laboratories were not alone in these early days of AIDS research (*13*, *14*), but their seminal contributions dominate the field. The contemporaneous and independent isolation of HIV by my colleague Jay Levy at the University of California, San Francisco, demonstrated the presence of HIV in AIDS patients and in healthy carriers (*13*). (Levy managed not to become embroiled in the controversy and so I will not further address his research here.) Despite all of the evidence, more than a decade would pass before there was universal agreement that HIV is the cause of AIDS (*6–17*).

Identifying HIV was the critical first step in defining the cause of AIDS, but, as Robert Koch so elegantly pointed out more than a century ago, showing that a particular infectious agent causes a specific disease can be an arduous process. This process is especially complicated when exposure to the agent is followed by an incubation period of months or even years before symptoms begin to appear. Such is the case with AIDS. Compounding the delayed manifestation of AIDS

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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.

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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

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