PERSPECTIVE

RETROSPECTIVE

The Discovery of HIV as the Cause of AIDS

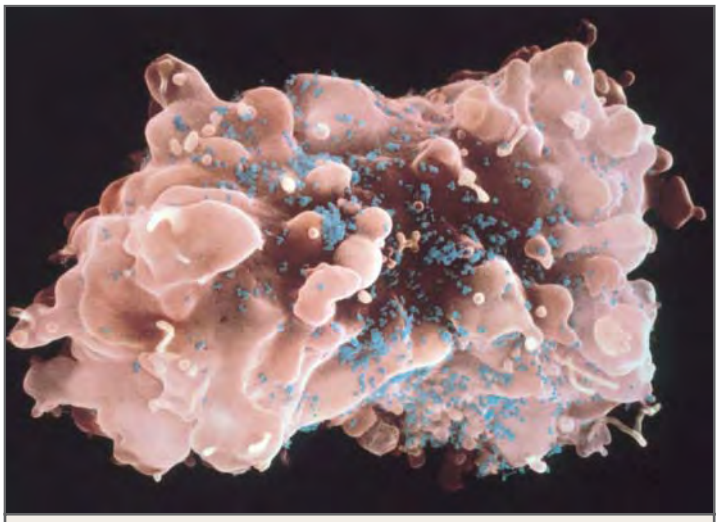
Robert C. Gallo, M.D., and Luc Montagnier, M.D.

Progress in scientific research rarely follows a straight path. Generally, it entails many unexpected meanderings, with a mix of good and bad ideas, good and bad luck. The discovery of the human immunodeficiency virus (HIV) as the cause of AIDS did not avoid this pattern.

The story began in an unfavorable environment: during the late 1970s, many people thought that epidemic diseases caused by microbes, including viruses, no longer posed a threat in industrialized countries. Other prevailing beliefs were that viruses did not cause any human cancers and that there was no such thing as a retrovirus that infected humans. Some of these beliefs were justified, since attempts to find tumor viruses and, in particular, retroviruses in cancers or other diseases in humans had a troubled history, and many of the groups that had the greatest expertise in the study of retroviruses had turned their efforts toward research on oncogenes. Luckily and rather amazingly, however, the conceptual and technical tools arrived in our hands just before the first patients with AIDS were identified in 1981. In addition, there remained a few heretical or "old-fashioned" groups — among which were our two laboratories — that persisted in searching for retroviruses in human cancers, particularly breast cancers and leukemias. This search finally paid off with the discovery of human T-cell leukemia virus types 1 and 2 (HTLV-1 and HTLV-2), the first of which was shown to cause an unusual T-cell leukemia. This discovery was made possible by 15 years of basic research on leukemogenic retroviruses in animals, including the design and development of highly sensitive biochemical assays that were based on reverse transcriptase — the enzyme that is present in all retroviruses, which was discovered in 1970 by Temin and Baltimore.

An additional important contributor was the development of methods for growing T lymphocytes in culture for a period sufficient to allow the expression of putative latent retroviruses. This effort was helped greatly by the isolation of specific factors — in particular, the T-cell growth factor (now called interleukin-2) in Bethesda, Maryland. The role of interferon in repressing the production of retroviruses in mouse cells was demonstrated in Paris, and this discovery led to the use of anti-interferon serum in the search for human retroviruses. Thus, at the beginning of the 1980s, we had the essential tools required to search for a retrovirus in this new and menacing disease called AIDS. But why search for a virus, and specifically a retrovirus, in AIDS? The answer was far from obvious in 1982.

At that time, AIDS had already appeared as a long-lasting disease, with an extremely long lag time between exposure to the agent (through blood or sexual activity) and the profound state of immune suppression characterized by the occurrence of opportunistic infections or cancers. Many factors — fungi, chemicals, and even an autoimmunity to leukocytes — were invoked at that time as possible causes. However, for us, there were clues. First, the various manifestations of AIDS were unified by a biologic marker: a decrease in the levels of a specific subgroup of T cells that harbored the CD4 surface antigen. CD4 and other CDs had been identified only a few years earlier with the use of specific monoclonal antibodies, thanks to the work of Milstein and Kohler. The findings regarding the T-cell subgroup suggested an agent that specifically targeted CD4+ T cells, and HTLV was one such agent. Moreover, there were animal models in which lymphotropic retroviruses caused not only leukemias or lymphomas, but also an AIDS-like wasting syndrome. Furthermore, HTLV was transmitted through blood and sexual activity, as well as from mother to infant, which was consistent with some of what we learned early on about the epidemiology of AIDS. Finally, the Centers for Disease Control and Prevention (CDC) reported cases of AIDS in patients



T Lymphocyte Infected by HIV.
Photograph by Lennart Nilsson, M.D., Stockholm, Sweden, 1985.

with hemophilia who had received only filtered clotting factors, which seemed to eliminate the possibility that the agent was a microorganism larger than a virus.

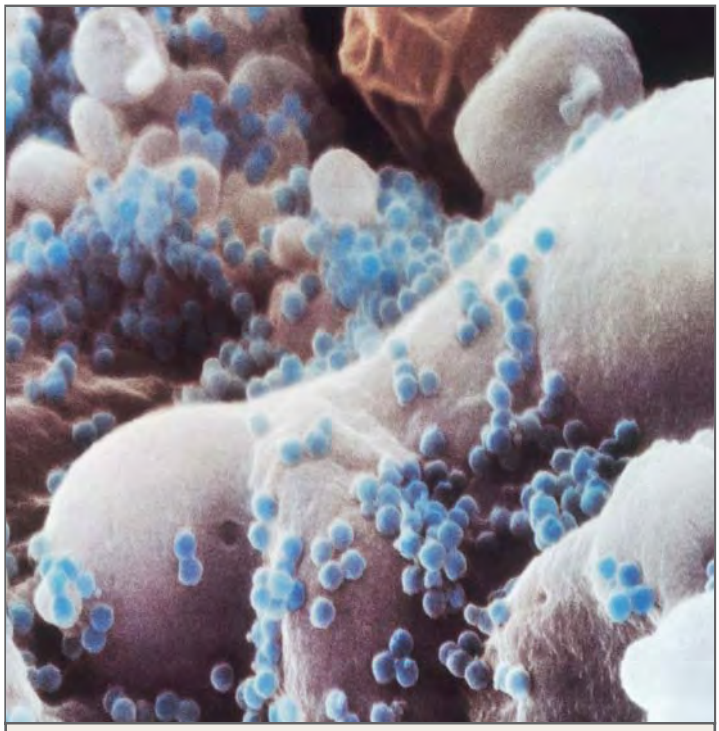
This set of arguments convinced us, as well as Max Essex in Boston, each independently to start a search for an HTLV-like virus in patients with AIDS. We began conducting this research at the National Institutes of Health in Bethesda and at the Pasteur Institute in Paris. The theory that a retrovirus caused AIDS was correct, but the hypothesis that it was a close relative of HTLV proved to be wrong. In Bethesda, an earlier survey involving the use of molecular and immunologic probes seemed to favor a variant similar to HTLV-1. In fact, some patients with AIDS were doubly infected with HTLV-1 and the new agent, which complicated the interpretation of the nature of the virus causing AIDS.

In early 1983, a clear-cut isolate was obtained in Paris, with the help of interleukin-2 and anti-interferon serum, from cultured T lymphocytes derived from a lymph-node–biopsy specimen from a patient with lymphadenopathy, a syndrome that was considered to be a precursor of AIDS. This virus proved to be different from HTLV in terms of antigenicity and morphology, but it could be propagated only in fresh cultures of T lymphocytes and not in permanent T-cell lines, which impeded its full characterization. The idea that the causative agent of AIDS should be sought in swollen lymph nodes was partly right, since we now know that lymph nodes are the main site where the virus hides during the presymptomatic phase. At this early stage, it seemed more likely that the isolate was causative than that it was opportunistic, since the immunosuppression was very mild. In some ways, however, it was also a misleading idea that delayed the full characterization of the virus and its mass production for seroepidemiologic studies, because only some viral isolates from patients with fully developed AIDS grow quickly in permanent cell lines, as we would soon learn.

This technical breakthrough was first achieved in late 1983 in Bethesda. Among a few strains in the Bethesda laboratory that grew in continuous cell lines, one came, unbeknownst to both of us, from the third isolate from a patient with Kaposi's sarcoma in Paris. The origin of the HIV strain with a very high capacity for growth that could readily overcome other HIV strains in culture — and which contaminated cell cultures in several laboratories, beginning with both of ours — was unraveled only in 1991, thanks to the use of the polymerase-chain-reaction technique.

The year 1984 was a time of both intense excitement and harsh discussions between members of our two groups. Identifying the cause of AIDS presented a unique challenge, because unlike other viral diseases responsible for past epidemics (or, more recently, the severe acute respiratory syndrome), AIDS was characterized by clinical signs that developed years after the infection had occurred, and by then, patients usually had numerous other infections. Thus, an exceptional linkage of agent to disease had to be established. This linkage was made (particularly in Bethesda) through the repeated isolation of HIV from patients with AIDS and, more important, through the development of a readily reproducible blood test. The growth of the putative virus in T-cell lines was an enormous step, facilitating the development of a blood test for HIV, which became available in blood-transfusion centers in 1985 and produced convincing evidence of the association between HIV infection and AIDS. The blood test also helped in the cloning and molecular characterization of the genetic material of the virus at the end of 1984, which clearly proved that the new virus belonged to the subfamily of lentiretroviruses; this finding, in turn, opened the way for the design of specific drugs and vaccines.

Other indirect evidence that HIV was the cause of AIDS came from the demonstration, in 1984, of its high degree of tropism for the subgroup of CD4+ T cells, its consistent isolation from patients of different origins who had AIDS, and the isolation of



Surface of a T Lymphocyte Infected by HIV.
Photograph by Lennart Nilsson, M.D., Stockholm, Sweden, 1985.

similar viruses that cause AIDS in nonhuman primates (specifically, macaques). Thus, the causative relation between HIV and AIDS was accepted by the scientific and medical community in 1984 and was further verified through the later isolation of HIV type 2 in West African patients with AIDS. The relation was also supported by the clinical efficacy of drugs that specifically inhibit HIV enzymes and the demonstration that mutations in one of the coreceptors for HIV (CCR5) make some persons highly resistant to HIV infection and AIDS.

Many lessons can be drawn from this early intense period, and most suggest that science requires greater modesty. Our experience with AIDS underscores the importance of basic research, which gave us the technical and conceptual tools to find the cause less than three years after the disease was first described. The work of numerous researchers is required for such efforts, and we have described the contributions of many scientists in other publications.[1,2] It has also become clear that finding the cause of an infectious disease is the alpha but not the omega of its eradication. The identification of HIV has allowed us to eliminate transmission of the disease through the transfusion of blood and blood products, create rational policies for prevention, and design efficient antiretroviral therapies. These therapies are not a cure, however, and the epidemic is still growing in many countries for lack of accessible treatments and preventive vaccines. Moreover, we must recognize that we are still far from having exhausted the list of potential new pathogens. Finally, one lesson that should be clear is that effective collaboration among groups of scientists and clinicians is essential — and that it is possible to achieve such collaboration without excluding a certain dose of the competitive spirit as a stimulant.

From the Institute of Human Virology, University of Maryland Biotechnology Institute and University of Maryland, Baltimore (R.C.G.); and the World Foundation AIDS Research and Prevention, Paris (L.M.).

1. Gallo RC. Virus hunting. New York: Basic Books, 1991.
2. Montagnier L. Virus. New York: Norton, 2000.

Unstable Coronary-Artery Plaques

Donald D. Heistad, M.D.

It is ironic and instructive that in the age of cellular and molecular biology, great advances in our understanding of the pathophysiology of cardiovascular disease continue to be made by pathologists who perform meticulous and imaginative studies. The concept of stable and unstable atherosclerotic plaques and implications for coronary thrombosis and myocardial infarction can be attributed to several great cardiovascular pathologists during the past century.

What characterizes an arterial plaque that is vulnerable to rupture? What causes the vulnerable plaque to rupture? How can plaque rupture be prevented? These are critically important questions in