of the French group. Montagnier and Chermann did not realize that virus from a patient called LAI had contaminated their LAV/BRU isolate. Although Montagnier believed he was sending LAV/BRU to us—and so did we—one culture consisted predominantly of LAI. The properties of LAI are very different from those of LAV/BRU, which does not grow in cell lines. Compounding the complexity, although IIIB was clearly derived from LAI, it is not identical with LAI, but rather is a variant that grows vigorously because of mutations in some of its regulatory genes. All of this was acknowledged by our group and the French group in 1991 (*18*) (see the Viewpoint by Montagnier, on page 1727).

The period after the May 1984 publication of our papers was marked by rapid advances (*15*, *19*). The HIV-1 genome was sequenced, HIV antigenic variation was discovered, the virus was found in the brain of AIDS patients, genomic sequence variation was found in viral populations from the same patient, macrophages were found to be targets for HIV, various modes of HIV transmission were elucidated, all of HIV's genes and most of its proteins were defined, and the blood supply in most developed nations was rendered safe as a result of screening for HIV. Next, came identification of the HIV receptor (CD4), the discovery of SIV in chimps, and the development of the first anti-HIV drug, AZT.

The late Jonathan Mann heralded the years 1982 to 1985 as a period of intense discovery, noting that the pace of research was the fastest in medical history. For some scientists, these were also years of disquiet and frustration; years in which we would encounter in an unprecedented manner the negative face of politics, the media, patient activists, and legal issues. For myself and others trained in science and disciplined by the rigor and analysis that are the essence of scientific endeavor, the rough and tumble of the outside world provided harsh and bitter lessons. In retrospect, it is clear that these lessons needed to be learnt, and I can say we are better for the experience. But our job is far from over, and it is up to the scientists to ensure eradication of the AIDS epidemic that continues to rage in many regions of the world.

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VIEWPOINT: HISTORICAL ESSAY

Prospects for the Future

Robert C. Gallo and Luc Montagnier

With close to 70 million people already infected with HIV and more than 20 million dead, AIDS is one of the greatest pandemics in medical history. Not only is this a human tragedy of unimaginable dimensions, it is also a threat to world security because of the potential for political destabilization. The AIDS epidemic must be halted soon. We need a policy of prevention that can be adapted to the sociological and cultural conditions of the most devastated countries in Africa and Asia, and that encompasses sustained international political will. New developments in AIDS research will contribute decisively to the decline of the epidemic and eventually its eradication. From the beginning of the epidemic, science has produced the most important practical advances: from discovering the cause of AIDS to developing a blood test and anti-HIV drugs. Now, science must develop new therapies that are practical alternatives for the developing world, as well as new microbicidals that block sexual transmission, until an efficacious vaccine arrives.

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In developed nations, the judicious use of combination anti-HIV drug therapy has substantially benefited HIV-infected people and has ended the pediatric epidemic. The Global Fund to Fight AIDS, Malaria and Tuberculosis—launched by Koffi Annan, the secretary-general of the United Nations—is spearheading efforts to translate these advances worldwide. However, the challenge is huge and has been complicated by many factors, including the emergence of multidrug-resistant HIV mutants. New antivirals that target not only dividing cells but also "resting" cells, and strategies that augment intracellular levels of active drug through modulation of metabolic pathways, may improve the suitability of existing drugs (*1, 2*). New classes of drugs, particularly HIV entry inhibitors, show promise. They have the advantage of stopping HIV before it establishes new infections in host cells. Preliminary studies show impressive results with inhibitors that block each stage of HIV entry: attachment and binding to $CD4^+$ T cells, coreceptor binding, and fusion of the viral and cellular membranes (*3, 4*).

What can be done to bring anti-HIV therapy to developing countries with limited infrastructure? Administering these therapies is complex, and patient compliance is a major challenge. If compliance and careful follow-up of patients is not achieved, we will see a dramatic increase in multidrug-resistant HIV mutants whose further spread will only exacerbate the epidemic. With our 20 years of experience, we propose the following priorities for eliminating AIDS worldwide.

Access to Antiretroviral Treatments

One of the main objectives of the Global Fund to Fight AIDS is to make anti-HIV drugs accessible to all of the developing world. The problem of cost can be partly solved by reducing drug prices (through lower pricing acceptable to pharmaceutical companies, use of generic drugs, and financial help from the Global Fund). But the infrastructure necessary for performing follow-up of patients during treatment will be costly and difficult, and the duration of such treatments will make them ultimately unaffordable for patients in poor countries. This is an unprecedented situation. The decrease in plasma viral load achieved with triple drug therapy does not stabilize after treatment interruption, which results in a rapid increase in circulating virus. Moreover, there are severe limitations to antiretroviral therapy, including toxic side effects (lipid

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deposition, increased risk of diabetes and cardiac infarcts, muscular and neurological toxicity). Therefore, it is imperative to launch clinical trials to test additional treatments that are less toxic and less expensive.

Therapies for the Developing World

After 6 months of continuous antiretroviral therapy, a patient's immune system is usually partly restored, and it is then possible to mount a relatively potent immune response against HIV. We suggest that patients on drug therapy for 6 months might benefit from being vaccinated at this stage. The efficacy of vaccination could be rapidly assessed by comparing the intensity of viral rebound in unvaccinated versus vaccinated patients after cessation of drug therapy.

Vaccines and Microbicidal Agents

Developing a vaccine is, of course, the ideal way to contain and even eradicate the AIDS epidemic, but there are serious difficulties:

- It is impossible to use a "live" attenuated retroviral vaccine in humans, for safety reasons.
- Experimental data are disappointing, and there are hazards with "killed" whole-virus vaccines.
- There is extreme variability in the dominant epitopes of the HIV surface glycoprotein.
- A vaccine needs to stimulate both systemic and mucosal immunity.
- It is difficult to run Phase III trials involving thousands of volunteers who are already highly exposed to HIV.
- HIV's capacity to integrate its genetic information into the DNA of target cells quickly establishes infection. This means that a vaccine response must be quick and effective in preventing HIV entry (by inducing production of neutralizing antibodies) and potent in finding and killing infected cells (by inducing activation of killer T cells).

AIDS vaccines are based on HIV subunits—that is, on one or more HIV proteins or portions of such proteins that are delivered directly or in the form of DNA that is then expressed in the target tissue. First attempts at developing a vaccine from 1984 to about 1990 used unmodified forms of the HIV protein envelope gp120. The goal was to induce neutralizing antibodies that could block virus entry and thereby possibly achieve complete protection from infection. But this approach failed in monkey tests (and may fail in humans) because the neutralizing antibodies are often short-lived and unable to block infection by a broad range of HIV strains. Consequently, in the 1990s the emphasis switched to inducing T cell–mediated immunity, involving production of killer T cells. Trials in monkeys infected with SIV or SHIV did not produce complete protection but kept virus at levels too low to cause disease for more than 1 year, creating optimism for trials (now ongoing) in humans (*5*). There are two arguments in favor of this approach. First, successful vaccines do not necessarily have to achieve complete protection; for example, in vaccinated individuals exposed to poliovirus, the virus replicates in the gut before the recall immune response targets the virus. Second, some argue that with AIDS there is no other choice because we cannot achieve broadly reactive, long-lasting neutralizing antibodies. However, we point out that poliovirus is ultimately eliminated after vaccination, whereas HIV is a retrovirus that integrates its genes into target cell DNA such that cells may express the virus at variable levels after vaccination. In addition, there have been some reports of broadly reactive neutralizing antibodies raised against primary isolates of HIV (*6*) and of new candidate vaccines that achieve this goal (*7*). However, adequate levels of the immune response would need to be maintained by boosting (which exposure to HIV might achieve).

To quickly evaluate the efficacy of immunization, we propose that candidate subunit vaccines be tested in HIV-infected persons as therapeutic supplements after initial antiretroviral therapy. The endpoint—a lack of viral rebound after interruption of drug therapy—should be easy to measure. From such therapeutic trials the best subunit combination could then be selected for testing in a full-scale clinical trial. There have been encouraging data with candidate microbicidal agents such as the cyclodextrins, which block infection when delivered at portals of entry (*8*).

Blocking Mother-to-Infant Transmission

In developed countries, mother-to-infant transmission has been blocked by several approaches: blood testing of mothers and, if they are positive, advising them to avoid breastfeeding; caesarian delivery when intrapartum risks are great; reducing HIV levels in mothers by treating them with triple drug therapy throughout pregnancy; and postpartum prophylactic treatment of the exposed newborn for its first week of life. In Africa, a single dose of a reverse transcriptase inhibitor given to mothers and their newborns decreased transmission from approximately 30% to 10% (*9*). However, postpartum infection continues to be a major problem in developing nations because of HIV transmission through breast-feeding. We are collaborating with colleagues in Rome on a program called "Families First Africa." In sites in West Africa, we plan to administer prophylactic antiretroviral therapy to pregnant mothers and to vaccinate their newborns with HIV peptides matching their HLA genotype; we will take advantage of the BCG vaccination routinely given to newborns in these countries by adding the HIV peptides to the BCG vaccine, which acts as a strong adjuvant. This approach will primarily induce cellular immunity without excluding an antibody response.

Prevention, Treatment, and Research

Scientists and clinicians in developed countries must contribute to the creation of infrastructure in the countries worst hit by AIDS. They need to train health care specialists in these countries, help to conduct clinical trials, and set up laboratories to analyze viral strains. There needs to be a transfer of technology from the North to the South and a two-way exchange of information. A center was created in 1996 in Abidjan by the World Foundation for AIDS Research and Prevention under the aegis of the government of Côte d'Ivoire and UNESCO for this purpose. The center integrates three activities under one roof: prevention by education (training of industry and administrative managers), treatment of ambulatory patients (within the UNAIDS initiative program), and laboratory and clinical research (in preparation for clinical trials). The Institute of Human Virology has also established programs in Africa and the Caribbean with similar goals. We suggest that each country create and develop a reference center integrating these three activities, with the possibility of radiating to rural regions through satellite mobile units. This will require close interactions between local governments, United Nations international agencies, and nongovernmental organizations. There needs to be a strong political will on the part of the governments of developing nations and generous financial contributions from the developed world, conveyed through a United Nations organization, such as WHO or UNESCO, in coordination with UNAIDS. It is also important that developing countries themselves participate financially. We suggest that the amount of funding from developing countries for AIDS projects should be deducted from their national debts to developed countries. More than ever, a global coordinated response is required to fight the scourge of AIDS.

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