Crash Development of AIDS Test Nears Goal

Impending ability to screen U.S. blood supply meets political and public health goals and paves the way for an epidemiological study that is raising ethical dilemmas

The recent discovery of a virus that is almost surely the cause of AIDS (acquired immune deficiency syndrome) has turned the need for a highly visible AIDS crusade on the part of the federal government into a real political imperative. Ever since the devastating immune system disease was first identified in homosexual men 3 years ago, the Reagan Administration has been criticized by "gay" activists for its alleged failure to mount a well financed war on AIDS. So this spring, when Administration officials learned that Robert C. Gallo, a government scientist with the National Cancer Institute, had isolated and grown the AIDS virus, they were quick to seize the moment to do something visible and to do it fast.

Secretary Heckler and Robert Gallo

The AIDS virus has been isolated and grown successfully.

The 23rd of April was a landmark day. That morning, government attorneys filed patent applications covering the Gallo work. Hours later, news that the AIDS virus had been discovered made headlines around the world following a press conference in Washington, D.C., at which Gallo reported that acquired immune deficiency syndrome is caused by a human retrovirus called HTLV-III, which is a variant of a class of human tumor viruses that were previously discovered in his laboratory. Four papers on HTLV-III by Gallo and his many colleagues appeared in the 4 May issue of *Science*.

Margaret M. Heckler, the former Republican congresswoman who is now Secretary of the Department of Health and Human Services (HHS), and whose office orchestrated the press conference, stood by Gallo's side. Lauding him for his achievement, she went on to promise that within 6 months there would be a test to screen the U.S. blood supply for evidence of the AIDS virus. Although AIDS occurs primarily in promiscuous homosexual men and intravenous drug users, it also afflicts hemophiliacs who become infected by contaminated blood products. And, to date, at least 50 cases of AIDS have been diagnosed in persons who most likely became infected when they received transfusions of AIDS-positive blood. Thus, a blood test for AIDS would be useful for diagnosing early disease among high-risk populations and for screening the nation's blood supply. Secretary Heckler promised not only that the test would be available within 6 months but also that it would provide "100 percent certainty."

The Secretary promised. This is an election year and AIDS is a significant public health problem that could figure in the campaign. Out of a combination of scientific accomplishment and political necessity, HHS has launched its own campaign to make the Secretary's promise come true. Five U.S. drug and biotechnology companies have been awarded licenses by the government which give them access to HTLV-III for commercial development. Competition among them to come out with a test kit is fierce and there is every reason to bet success is not far off.

The five competitors, selected from a field of some 20 corporate applicants, are Abbott Laboratories, North Chicago; Electro-Nucleonics, Columbia, Maryland; E. I. du Pont de Nemours, Wilmington, Delaware, in collaboration with Biotech Research Laboratories, Rockville, Maryland; Litton Bionetics, Kensington, Maryland; and Travenol Genentech Diagnostics, Cambridge. In June, each of the five received 25 liters of HTLV-III infected cells, which are being produced in large quantities at the cancer institute's facility in Frederick, Maryland. It is expected that most of them will be ready to file "investigational new drug applications" any day now with the Food and Drug Administration (FDA) which must approve clinical trials of the test kits and which has ultimate say over their approval for commercial marketing. (For a discussion of how the five companies were chosen, see accompanying box on p. 1129.)

While federal health officials are monitoring the progress toward development of a mass screen for the blood supply, they are also anxiously trying to put in place a relatively large-scale study that will also contribute answers to crucial questions about the transmissibility of the disease. Is AIDS spreading beyond what is currently identified as the high-risk population to the population at large? If so, how? Although there is evidence that the disease is transmitted by the transfusion of AIDS-positive blood, frankly little is known about how great a risk that is. Will most people who receive contaminated blood come down with AIDS or only a few?

To answer questions about the natural history and epidemiology of the disease, the National Heart, Lung and Blood Institute began designing a study several months ago (before Gallo reported on HTLV-III) to enable investigators to track the distribution of blood from four of the country's largest voluntary blood banks, namely those in New York, Miami, Los Angeles, and San Francisco, cities where the incidence of AIDS is highest. The idea behind the study is to collect blood samples now for subsequent testing so that it will be possible in a 6- to 7-year follow-up to see what happens to patients who receive a unit or more of transfused AIDS-positive blood. Will they get AIDS? Or a milder "pre-

Five Firms with the Right Stuff

On 23 April, the Department of Health and Human Services (HHS) filed patent applications covering the discovery by National Cancer Institute scientists of a virus called HTLV-III that causes AIDS (acquired immune deficiency syndrome). Isolation and characterization of HTLV-III was made by Robert C. Gallo and his colleagues at the cancer institute. Driven by determination to turn that achievement in basic science into a medically useful tool that would be evidence of the Reagan Administration's commitment to fighting AIDS, HHS quickly made plans to grant private companies licenses to use HTLV-III and the cells in which it grows for commercial development of a test to detect evidence of the virus in human blood.

It is standard practice for the federal government to award licenses to private companies, but the extraordinary speed and special attention that was devoted to the licenses for HTLV-III–related techniques bespeak the Administration's desire to refute allegations that it is moving too slowly in its effort to combat this devastating, infectious immune system disorder that primarily afflicts promiscuous homosexuals, intravenous drug users, and hemophiliacs and others who may contract AIDS from transfused blood.

Exactly 2 weeks after government patent applications were filed, a request for proposals appeared in the *Federal Register* and *Business Commerce Daily*. Companies interested in developing a test to screen the nation's entire blood supply were given 10 days to get their applications in. According to Lowell Harmison, science adviser to HHS assistant secretary for health Edward Brandt, some 20 companies were standing in line for a license before the application deadline closed on 17 May.

Meanwhile, scientists at the NCI's facility in Frederick, Maryland, were gearing up for large-scale production of HTLV-III–infected cells to distribute to the companies that would soon be awarded licenses. Frederick scientists with long experience in growing viruses proved remarkably successful at moving into large-scale production but, nonetheless, it was clear that supplies of HTLV-III would be relatively limited. For this reason, and in order to guarantee success by distributing HTLV-III with companies most likely to come through, tough criteria were established for getting a license and, thereby, access to the government's store of AIDS virus. An officer of one competing biotechnology firm said, "They were looking for the companies with the right stuff."

Ten criteria were established, among them these: i) Experience in handling human retroviruses, a family of RNA tumor viruses of which HTLV-III is a subgroup. The government wanted companies that already know how to purify, characterize, and grow these viruses. ii) Because biosafety was a major concern, the companies were required to have existing P-3 containment facilities. iii) The first diagnostic test will most likely be based on a radioimmunoassay system known as ELISA (enzyme-linked immunosorbent assay). A technique for detection of antibodies in AIDS and pre-AIDS patients using the HTLV-III core protein, p24, in an ELISA test is covered by one of the federal patent applications. Experience in using ELISA and related tests was another important criteria.

Another criteria of paramount importance, Harmison noted, was proved ability to produce and market a product for mass distribution. There are some 1700 blood banks in the United States and estimates of the numbers of units of blood that might be tested per year range as high as 20 million. Clearly, the potential for profit is enormous, but in order to compete successfully in the race to meet HHS's goal of a mass screening test to be ready within months, the ability to operate on a national scale is also obvious. Any company that failed to meet even one of the ten criteria was scrubbed from the list of potential licensees, which meant that several of the smaller biotechnology companies with skill in science but not in marketing lost out.

"Seven or eight of the applicants met the criteria," Harmison reports and HHS officials then site-visited the companies to verify such things as the existence of a P-3 facility and a staff of experienced retrovirologists. "If all of the applicants had met the criteria, all would have been awarded a license," Harmison said. But as it turned out, only five had enough of the right stuff: Abbott Laboratories, which already commands a major share of the market for testing blood for hepatitis B; Electro-Nucleonics; DuPont, in collaboration with Biotech Research Laboratories, which was working in collaboration with NCI's Gallo before HTLV-III was nailed down; Litton Bionetics, another biotechnology company with which Gallo has close scientific ties; and Travenol Genetech Diagnostics.

Accuracy, reliability, and cost will play important roles in determining which of the five companies ultimately wins the greatest share of the commercial market once one or more tests are given final approval by the Food and Drug Administration. From a technical point of view, each is taking a slightly different and closely guarded tack, while government officials meet with them regularly to monitor progress as investigational new drug applications to FDA are prepared. Harmison is betting that some of the companies will be ready for clinical trials of test kits by October. Indeed, on a strictly experimental basis, some already are testing blood at the rate of 1000 or more samples a day with assays that can be completed in a matter of hours. Once the test kits are on the market, blood banks will choose which of the approved tests they want to use as the companies vie for their business and for profit.

Another scientifically important challenge in AIDS that also has commercial implications is the development of a vaccine. A number of the companies that failed to win licenses in June now want access to the government's supply of HTLV-III for use in vaccine studies. Although work can proceed without a government license, access to its store of cells confers an advantage. At present, HHS officials are designing criteria for a new round of license awards. Harmison notes that the government is not trying to be unduly restrictive (a contested view) but, rather, is interested in making sure that a limited resource is distributed to people who have the capacity to make good scientific use of it. Unless something quite unexpected happens, it is a good bet that in the short term the market for a blood test will be captured by one or more of the five present licensees. But the contest for vaccine development is wide open. That's another story.—**B.J.C.**

AIDS'' infection? Or might they be unaffected?

Researchers concerned with the natural history and epidemiology of AIDS recognize an urgent need to get at these questions—a need that, for ethical reasons, has been made all the more urgent now that a means of screening blood before it is transfused is so close on the horizon. Using the argot of the space program, HHS officials talk about a brief ''window of opportunity'' for this study which will close once mass screening removes from the blood supply those units that test positive for AIDS.

''Between now and the time a test is commercially available, we have a unique scientific opportunity to learn about the transmission of this disease,'' says heart institute director Claude Lenfant. ''But it is important to emphasize that this study can only take place because the blood we want to collect and screen will be used in the usual course of blood banking now whether we do our study or not. An informed consent form must clearly explain that we are not deliberately transmitting AIDS.''

The design of the first phase of the study is this. Some 200,000 normal, healthy blood donors, who do not fall into any of the high-risk groups for AIDS, will be asked now to consent to having a sample of their blood stored at the blood bank for testing a few months from now. Meanwhile, their blood will be available for transfusion just as is usually the case. Then, when test kits are in hand, the samples will be screened. Researchers expect that somewhere between one-half and one percent of the blood from these normal donors will test AIDS-positive. Both the donors and the patients who received their blood will then become part of a long-term research project.

From a medical point of view, this study makes an enormous amount of sense. If AIDS is spreading slowly among the general population through the blood supply, it is vital to know that. But from an ethical and public relations point of view, this study, which has been under intense—virtually daily—discussion by federal health officials for the past 8 weeks, is creating terrible dilemmas.

For weeks, government scientists and blood bank officials have been arguing over the informed consent form that the blood donors will be asked to sign. A major sticking point was the question of notification of donors. According to one source at the National Institutes of Health (NIH) representatives of three of the blood banks argued vigorously against notifying the donor that his or her blood tested positive for AIDS. The argument was twofold. Weighing the duty to do no harm against the good to be done, some believe notification can only be harmful at present because the meaning of an AIDS-positive test is unclear. Full-blown AIDS is a baffling and nearly 100 percent fatal disease for which there is at present no known cure. It also carries a heavy social stigma. Because the first mass screening tests will be able only to detect antibody to AIDS in the blood, they will provide little clear information about whether the person is at risk of getting a full-blown infection or whether he has simply been exposed to HTLV-III and mounted a successful immune response. Heterosexual blood donors who test AIDS-positive could be falsely labeled homosexuals if the information leaked out. Healthy, nonpromiscuous homosexuals also worry about the stigma that an AIDS-positive test would attach to them. All around, there is concern about what the information would mean to prospective employers or health insurance companies. The issue of confidentiality has been central but is not easily resolved, especially in states where AIDS is a reportable disease. Thus, for many reasons, the likelihood that giving the donor complex, unclear, but frightening information will cause at least psychological stress is very high. The consent form itself will include a statement that says, ''the significance of a positive finding and the reliability of the test are not known at this time.''

A second argument raised against informing the donor rested on concern that members of high-risk populations who are not readily identifiable as such will lie about their status and donate blood just to find out whether they have AIDS antibodies. By telling the donor, one in effect turns the test into a diagnostic service. Were this to happen, not only would the validity of the data be altered but the risk of actually attracting high-risk donors and contaminating the blood supply increases.

Arguments in favor of informing the donor, espoused by the majority of HHS and NIH scientists involved in the debate, were equally strong and, apparently, have prevailed. As things stand now, for several reasons the decision has been made to tell the donors who agree to participate in the study that they will be notified if the test shows them to be AIDS-positive. First, a positive test will have to be confirmed and the individuals will be closely followed medically for several years for symptoms of AIDS or pre-AIDS. Second, they must be told not to donate blood any more. And third, even though the significance of a positive test is presently unclear, it was agreed that persons have a legal right to know and, in this case, medical professionals have an ethical duty to tell them.

Now that federal officials and blood bank representatives have agreed to the wording of the informed consent, the study has to clear one final hurdle before any blood can actually be collected and stored. Ethical approval of human experimentation rests legally with Institutional Review Boards composed of professionals and laymen who scrutinize research proposals at their respective institutions. If they give their okay, the first stages of this study may begin within a few weeks—a couple of months later than investigators hoped but nonetheless in time to collect samples before the window of opportunity slams shut. Says Amoz Chernoff of the heart institute, ''I'm optimistic that the study will go forward.''

If it does, unresolved issues will be put on hold for the time being. One crucial matter which has found no consensus yet is the question of what to tell the unwit-

Viruses Across the Sea

At present, research on the viral etiology of AIDS focuses on the putative role of two viruses: HTLV-III (human T-cell lymphotropic virus) found by National Cancer Institute scientists and a closely related agent, LAV (lymphadenopathy virus), which was reported a year ago by researchers from the Pasteur Institute in Paris.* Whether HTLV-III and LAV are in fact the same virus, as many virologists expect, ought to be known for certain within a matter of weeks. Whether they match up nucleotide for nucleotide under molecular analysis or not, there is little doubt that from a clinical point of view, these nearly identical viruses cause the disease. The outcome of disputes over priority for finding the AIDS virus has implications not only in terms of scientific credit but also with regard to patent rights and commercial activity. However, the HTLV-III/LAV question does not appear to be central in the short run to the results of the crash program to develop a simple assay for detecting evidence of AIDS virus in the blood supply.—**B.J.C.**

*A set of papers on AIDS virus by American and French scientists was published in the 20 May 1983 issue of *Science* (**220**, pp. 859–871). Papers on HTLV-III appeared in the 4 May 1984 issue (**224**, pp. 475–477 and pp. 497–508).

ting recipient of an AIDS-positive transfusion. The arguments about creating anxiety with sketchy information versus a person's right to know and to be medically followed pertain here as they did in the case of the donor. But the recipient, unlike the donor, cannot be asked for prior informed consent because there is no way of knowing in advance that he or she would get AIDS-positive blood. According to Robert Gordon of NIH, the decision about notifying the recipient is being held in abeyance in the hope that by the time the issue has to be faced, enough knowledge will have accrued in this rapidly moving field to permit researchers to convey more useful, clear information than they could now. For instance, within several months it might be possible to screen widely for the presence of viral antigen, rather than just antibody, in the recipient, which would give a better indication of his exposure and risk.

The ethical dilemmas surrounding the consent form in the heart institute's proposed long-term study will be echoed to a degree when the five competing U.S. companies begin clinical trials of the test kits they are now rushing to develop. Estimates are that as many as 20,000 blood samples will be screened as part of the investigational new drug clearance that precedes FDA approval for marketing. Likewise, once a test is available commercially so that the entire blood supply can be tested, questions of what to tell an AIDS-positive donor will be troublesome until the time comes that individuals either can be reassured that the presence of AIDS antibody is not an inevitable harbinger of serious infection or that successful therapy is at hand. However, health officials point out, despite the thorny issues that rapid test development is raising, the goal of trying to safeguard the blood supply is paramount.—**BARBARA J. CULLITON**

OSTP Seeks Advice on Export Controls

In a surprise move, the White House Office of Science and Technology Policy (OSTP) has decided to establish an advisory committee to assist in drafting regulations governing the release of unclassified but militarily sensitive information. The decision to appoint the committee is being interpreted by outsiders as a move to help prevent the adoption of unpalatable controls on basic research.

The focus of the committee's work will be the Department of Commerce's export control regulations, which the Reagan Administration has been trying to redraft for at least 18 months. A version circulated among government agencies in July last year provoked outcries from scientists because it would have clamped down on the conduct and publication of research in several areas. A second draft, circulated recently, is said to be no more palatable.

The purpose of the proposed revisions is to restrict access by non–U.S. citizens to technical information in areas included in the Defense Department's militarily critical control list, a massive compendium of technologies that the department considers to have potential military applications. Currently, academic research not closely related to industrial processes is exempt from the export control regulations. But the revisions proposed by Commerce would require researchers in fields covered by the critical control list to obtain export licenses before publishing their results or delivering papers at meetings at which foreigners are present.

A meeting of researchers potentially affected by the regulations, convened by the National Science Foundation early this year, concluded that the draft circulated last July "would, if read literally, reach an enormous amount of cutting edge research, as well as development, production, and utilization." Export licenses would probably be required before conducting university research projects involving foreign graduate students or faculty members, and multinational companies would have difficulties in exchanging people and information between U.S. and overseas subsidiaries, the meeting concluded. One academic participant estimated that his own research and teaching would probably require between 100 and 200 licenses a year.

The regulations were drafted chiefly by the Department of Commerce, with substantial input from the Departments of Defense and State. OSTP got into the act more recently. When the drafts ran into heavy fire, an interagency committee was established to try to reach a consensus on a final version and OSTP was given the chairmanship. (The job has gone to Andrew Pettifor, an NSF official who has been on detail to OSTP for the past 2 years.) The establishment of an advisory committee to assist OSTP in its task was quietly announced by President Reagan's science adviser, George A. Keyworth II, with a notice in the 29 August *Federal Register*.

The announcement caught groups that have been closely following the moves on export controls by surprise, but the immediate speculation is that OSTP is hoping to gather support from the scientific community to head off restrictive provisions. They note, in particular, that the committee will consist of "an appropriately balanced representation of the scientific and engineering communities in those areas of science and engineering most directly impacted" by the regulations—those most affected will, presumably, be the loudest in protesting overly strict controls. No appointments have yet been announced; the committee is expected to consist of about 18 people and have a 6-month lifetime.

Deputy OSTP director John McTague says, however, that "right now, there is unanimity across the government agencies" that strict controls on basic research are unwarranted, and he implied that the Commerce revisions have been scrapped. OSTP is establishing the advisory committee, he said, "to get good expert advice. We want to see what the impacts [of the regulations] will be."

In the meantime, Congress is struggling to rewrite the Export Administration Act, the legislation that governs the export control regulations. Both the House and Senate have approved versions of the bill, and an endless series of conference committee meetings have attempted to reconcile the many differences between them. Agreement has apparently been reached on wording that would discourage the use of export controls to restrict communication of basic research, but the chief sponsors of the two bills are still so far apart on many other key issues that the chances of getting a bill passed this year are now considered no better than even. If no new bill is passed, the Administration will have a much freer hand to rewrite the regulations.

—**COLIN NORMAN**