Probing the AIDS Virus and Its Relatives

Nothing illustrates the spectacular growth of research on AIDS (acquired immune deficiency syndrome) better than the expansion of the annual international congresses devoted to the disease. The III International Congress on AIDS, which was held on 1 to 5 June in Washington, D.C., drew more than 6000 participants and nearly 800 journalists. This year's attendance was more than double that of the second congress, held last year in Paris, and nearly triple that of the first one in Atlanta in 1985.

The meeting offered over 1250 talks, posters, and round-table discussions covering every aspect of current AIDS research from the medical, psychological, and social problems experienced by the patients to the efforts to understand the molecular biology of the virus that causes AIDS. Situated as it was in the nation's capital, the meeting also offered excellent opportunities for political protests.

Both Vice President George Bush and Secretary of Health and Human Services Otis Bowen were booed during their talks, especially with regard to the U.S. government's decision to extend AIDS testing, now required for members of the the military and foreign service, to federal prisoners and persons wishing to immigrate to this country. A picket line, also protesting U.S. government policies on AIDS, materialized for a time on 1 June outside the Washington Hilton, the congress headquarters, and the meeting exhibits featured one by an individual distributing antihomosexual materials. However, for the most part the meeting participants went about their business with little discomfort beyond that imposed by crowding roughly 7000 people into space intended for about 4500.

This may in any event be the last of such all inclusive meetings, which are becoming unwieldy for their size, if not for the opportunities they offer for disruption. The congress next year will be held in Stockholm, Sweden, and researchers from the Karolinska Institute there, who are involved in planning the meeting, say that it may be subdivided, perhaps with the politically and psychosocially oriented sessions held separately from those devoted to AIDS virus genetics and biology.

However the next congress is organized, the growth of the research effort reflects the seriousness of the AIDS problem. More than 50,000 cases of the deadly disease have been reported worldwide, with more than 36,000 in the United States. The World Health Organization estimates that a total of perhaps 5 to 10 million people have been infected with the AIDS virus. At least one-third of the infected individuals will develop the disease.

A large part of AIDS research is aimed at dissecting the causative virus with the aim of identifying any vulnerable points at which it might be attacked. Herewith follows a selection of developments reported at the congress about the AIDS virus and how it acts. (A discussion of the epidemiological findings presented at the meeting appeared in the 12 June issue of Science.*)*

Questions Raised About Peptide T's Action

A recent functional dissection of the AIDS virus protein called gp120 has raised questions about a proposed new therapy for the disease. The therapy involves the use of a peptide, designated peptide T by its discoverer Candace Pert of the National Institute of Mental Health, to block the infection of cells by the AIDS virus. According to Pert, the peptide acts by binding to the receptor for the AIDS virus on cell surfaces, thereby preventing binding of the virus and its entry into the cells.

The Food and Drug Administration is apparently on the verge of granting approval for clinical testing of peptide T in AIDS patients, although officials at NIMH have not yet received formal notification of that approval, news reports and an NIMH press release notwithstanding.

Other investigators have failed to confirm that the peptide blocks the ability of the AIDS virus to enter cells, however. For example, William Haseltine of Harvard's Dana-Farber Cancer Institute says, "We are forced to conclude that there is no scientific basis for consideration of peptide T as an antiviral drug."

Entry of the AIDS virus into most of the cells it infects requires an interaction between gp120, which is located on the envelope covering the viral particle, and a receptor on the target cells, which is called the CD4 antigen. Peptide T contains an amino acid sequence corresponding to one that is maintained in the gp120's of the various AIDS virus isolates.

The results of Pert and her colleagues suggest that the peptide T region in gp120 should be part of the binding site for the CD4 antigen, but that supposition is not supported by the functional dissection of the envelope protein that has been performed by Haseltine, Joseph Sodroski, and their Dana-Farber colleagues. By introducing mutations at various sites in the gene encoding the envelope protein, these researchers defined three segments in gp120 that are needed for binding to the CD4 antigen.

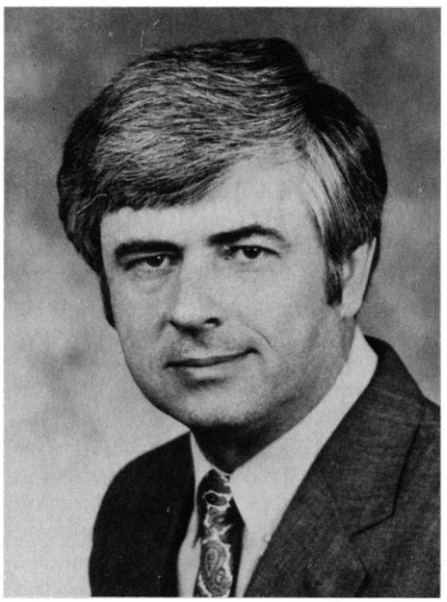
Lawrence Lasky and his colleagues at Genentech, Inc., in South San Francisco independently defined one of those same three regions as important for binding. None of those regions contained peptide T, however. "We were puzzled by peptide T," Haseltine says, "because it fell into a region that was not important by any of our mutagenic studies." Consequently, the Harvard workers tested the ability of the peptide to block gp120-CD4 antigen interactions in three separate assays and found it ineffective.

Pert was traveling in Italy and could not be contacted for comment before this issue of *Science* went to press. However, researchers at Genetic Systems Corporation in Seattle have been able to inhibit AIDS virus infection of T cells with a slightly modified form of peptide T.

Meanwhile, NIMH issued a press release at the AIDS congress stating that the FDA had approved clinical trials with peptide T. According to Frederick Goodwin, the scientific director of the institute, the release was based on a verbal assurance by an FDA official that the approval would be granted, pending the submission of information on a few technical details, such as drug formulation. Those details have been submitted, Goodwin says, and the formal notification of the approval is expected.

Taking a Closer Look at AIDS Virus Relatives

In late 1985, researchers began picking up signs indicating that people in West Africa are infected with one or more viral relatives of the AIDS virus. Since then, the research has become enveloped in confusion, not the least of which concerns whether the West African virus is pathogenic the way the AIDS virus itself is. In addition, questions have been raised about the virus isolated as the new West African virus by Myron Essex, Phyllis Kanki, and their colleagues at the Harvard School of Public Health. The questions concern whether they have inadver-



Myron Essex, *who has been tracking a West African relative of the AIDS virus.*

tently isolated not the true West African virus but a contaminant, namely, the previously known simian T-lymphotropic virus–3 (STLV-3), which is also related to the AIDS virus and has been under study in the Essex laboratory.

At the Washington meeting, researchers presented for the first time comparisons of the complete gene sequences of a number of isolates of these various AIDS virus relatives. Although the knowledge of these gene sequences has not resolved the controversy over the pathogenicity of the West African virus, the sequences do provide a possible clue that may help in this regard. The gene sequences also support the view that the Harvard group did isolate an STLV-3 contaminant, although the case for this conclusion is not ironclad and Essex says that he can find no evidence for the proposed contamination.

Despite the still unsettled nature of the research on the West African virus isolates, two points are not in doubt. West African populations carry an AIDS virus relative (or relatives), and it resembles STLV-3 more closely than the AIDS virus. Essex, Kanki, and their colleagues originally detected the presence of this virus on the basis of antibodies carried by many healthy West Africans that react poorly with proteins of the AIDS virus and much more strongly with those of STLV-3. When they then went on to attempt to isolate the West African virus, they came up with the agent they call human T-lymphotropic virus–4 (HTLV-4), which is the center of the current dispute.

Meanwhile, Luc Montagnier and his colleagues at the Pasteur Institute in Paris were identifying a very similar virus, with a comparable geographical distribution and antigenic composition, but in patients who had an AIDS-like condition with no indication of infection by the typical AIDS virus. The Paris workers are convinced that the virus they have isolated and called human immunodeficiency virus–2 (HIV-2) causes AIDS.

The Essex group is equally convinced on the basis of extensive epidemiological studies in West Africa that the virus they have identified there is not a major cause of AIDS. These studies are based on the detection of antibodies as evidence of infection by the AIDS virus relative and their validity will not be affected by the outcome of the controversy over the origins of HTLV-4.

The discrepancy in the findings concerning the pathogenicity of the West African virus might be resolvable if the Harvard and Pasteur groups are seeing the effects of different virus variants, one pathogenic and the other not. Comparison of the HIV-2 sequence, which was obtained in the Montagnier laboratory, with that of HTLV-4, which was obtained by Robert Gallo, Flossie Wong-Staal, and their colleagues at the National Cancer Institute, shows that the two viruses are about 80% identical. The 20% difference leaves room for a possible variation in pathogenic behavior.

The problem with the HTLV-4 sequence is its near identity to that of STLV-3. The first indication of this came from James Mullins' group at the Harvard School of Public Health, who used restriction enzymes to map the viral DNAs and found the maps to be almost identical. This apparent genomic stability is surprising in view of previous findings that AIDS virus isolates show a great deal of genomic variability, as much as 20 to 25%. And the Montagnier group has demonstrated that the HIV-2 genome also varies from isolate to isolate.

Restriction maps do not give a base-by-base comparison of gene sequences, but the complete genomic sequences also show little difference between STLV-3 and HTLV-4. "We compared an STLV-3 isolate and an HTLV-4 isolate," says Beatrice Hahn of the Gallo–Wong-Staal group. "The sequences are 99% identical and we conclude they are the same virus."

Essex says that it is unlikely a monkey virus contaminant has been isolated instead of a West African human virus. Since becoming aware of the close relation between HTLV-4 and STLV-3, the Harvard workers have tried to pinpoint any possible source of contamination by the monkey virus, and have failed. This includes looking for signs of STLV-3 presence in the human cells originally used to isolate HTLV-4. No evidence of the monkey virus was detected, Essex says, and the cells were examined in the laboratories of Gallo and Mullins.

Essex has also ruled out the possibility that the cells were contaminated with rare STLV-3–infected cells that might have taken over the cultures during HTLV-4 isolation. "There's no conventional cellular contaminant," Essex says, "but we can't rule out an aerosol contaminant." He points out, however, that there are examples of retroviruses with stable genomes, so that the type of stability proposed for HTLV-4 and STLV-3 is not unprecedented.

Finally, the sequence data provide a possible clue that might help to explain differences in pathogenicity among isolates of the AIDS virus, HIV-2, and HTLV-4. The sequences of the HIV-2 and HTLV-4 genomes differ by about 55% from the that of the AIDS virus genome, although all have a similar overall organization. In particular, HTLV-4 and STLV-3 and some isolates of HIV-2 have a "stop" codon in the gene coding for the transmembrane protein of the viral envelope.

The presence of the stop codon can lead to the synthesis of a truncated transmembrane protein in which nearly all of the internal portion is missing. Viruses having this altered protein may have a decreased ability to infect and kill cells. HTLV-4, for example, does not show the cell-killing ability of the AIDS virus. The hypothesis about the stop codon's proposed effects on pathogenicity needs to be verified by more work—as does much else about the nature and origins of the AIDS virus's relatives.

New Human Retrovirus Detected

The more researchers look for new human retroviruses the more they find. The AIDS virus family, for example, appears to be acquiring a new branch, according to Robert Gallo of the National Cancer Institute. He said that physician Chris Williams of the University of Ibadan, Nigeria, had identified ten patients with a constellation of symptoms, including immune suppression. The patients were apparently not infected either with the AIDS virus or with its relative, human immunodeficiency virus–2 (HIV-2), but they did have antibodies that react weakly with the core proteins of HIV-2, a finding that indicates that they are infected with a related virus. "This and a series of other studies have led us to conclude that this is still another human retrovirus," Gallo says.

A great deal remains to be learned about the new virus. The virus may be less pathogenic than the AIDS virus and, Gallo indicates, there is no reason to believe that it is anywhere except Nigeria.

A Test to Distinguish HIV-1 from HIV-2

As the number of related human retroviruses increases, the need for a simple test that will accurately distinguish one from another also increases. Erling Norrby of the Karolinska Institute in Stockholm and his colleagues have developed a new type of test that can distinguish between infection by the AIDS virus, which is also known as human immunodeficiency virus–1 (HIV-1), and its relative HIV-2.

Whereas current AIDS tests use whole proteins from HIV-1 to detect antibodies to the virus in infected individuals, the new method, called "site-directed serology," detects the antibodies by means of a short synthetic peptide corresponding to a segment of a viral protein. The peptide segment used, Norrby says, has to be a good elicitor of antibody production, and also conserved among the many variants of HIV-1 or HIV-2. A peptide that fits this description and the one chosen by Norrby and his colleagues, who include Richard Lerner of the Research Institute of Scripps Clinic in La Jolla, California, is from the outer segment of the viral transmembrane protein.

The researchers synthesized the peptide, which contains 22 amino acids, for HIV-1 and they also made the corresponding peptide for HIV-2. When they tested the peptides against 20 serum samples each from healthy individuals and from persons with known HIV-1 or HIV-2 infections, the results, Norrby says, were "beyond expectations." None of the serum samples from healthy individuals reacted with either of the peptides, whereas all 20 of the samples from persons infected with HIV-1 or HIV-2 reacted with the corresponding peptide. Only one sample from each group showed low cross-reactivity with the other peptide.

These new generation tests, which are under development in several laboratories in addition to those of Norrby and Lerner, should have a number of advantages over the original AIDS virus tests, especially in developing countries where medical facilities may be limited. The need for a specific HIV-2 test is greatest in West Africa, where the virus is endemic.

Tests based on site-directed serology are both sensitive and specific because they detect a single antigenic site of a particular virus. Moreover, Norrby says, the materials used are more stable than those in the current tests. But perhaps the greatest advantage of the newer tests is that they can be completed in one step. Current tests require two. With the new methods, Norrby says, "The screening test gives you the final answer." ■ JEAN L. MARX

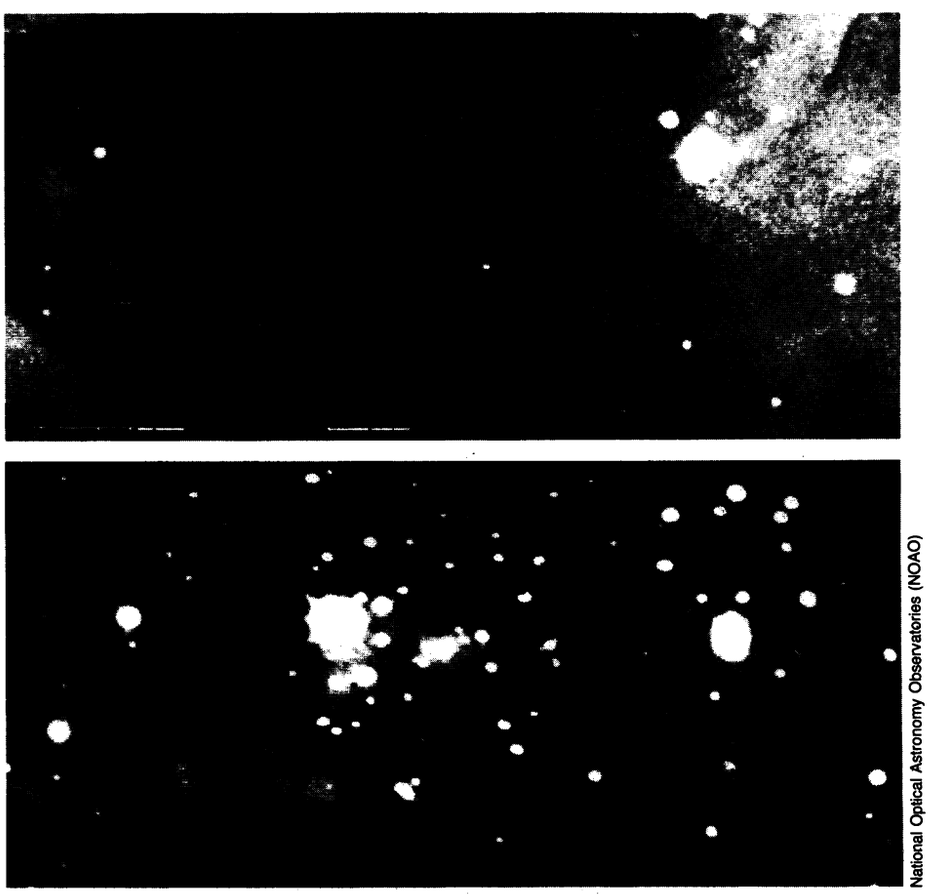
Imagery Comes to Infrared Astronomy

A new semiconductor detector should greatly speed up data taking; the infrared astronomers are understandably excited

A tiny, cryogenically cooled detector derived from military space research is being hailed as a milestone in infrared astronomy comparable to the invention of the photographic plate in optical astronomy. Not only is the device as much as 100 times more sensitive than conventional infrared detectors, but it is also among the first sensors in this wavelength band that can actually form images of the sky instead of just taking data one point at a time. Certainly it is the first to be generally available to the whole astronomical community. Thus, astronomers will no longer have to construct their infrared maps by painstakingly scanning their telescopes back and forth.

"You do what used to be a night's work in a few minutes," says one astronomer at the National Optical Astronomy Observatories (NOAO) in Tucson, where the new sensor is being tested. "It represents a marvelous advance in what we can do," agrees Fredrick Gillett, project scientist on the NOAO infrared team. "It opens up all sorts of applications where before you had to say, 'No, that's just too difficult.' "

At the heart of the new sensor is a 58 by 62 matrix of individual detectors etched on an indium antimonide crystal, which is about the size of a flake of confetti. Each of these individual detectors produces an electronic signal when exposed to photons, with the strength of the signal being almost exact-



National Optical Astronomy Observatories (NOAO)

Stellar nursery. *The nebula NGC 2024, a dense region of interstellar dust and gas, is nearly opaque at visible wavelengths (top). As seen by the new infrared array detector, however, it is swarming with newborn stars (bottom).*