4/30/86

History of Key Events and Side Issue of the HTLV-III/LAV Discovery

1. Idea for Cause of AIDS - as a retrovirus

   - Gallo, 1982 with input from M. Essex

   - evidence idea came from us:

     (a) published (from symposia, talks)

     (b) publicly stated September 1984 International Retrovirus meeting in Leriche, Italy by Chermann that "idea came from Gallo"

     (c) Jacques Leibowitch of Paris states he brought idea to Pasteur Inst. and heard one of the Administrators tell Pasteur group to work on this idea from Gallo

2. Technology for detection of HTLV-III/LAV

   Essentially identical as that for HTLV-I and -II. Pasteur group made a modification: antibody to alpha interferon. This is useful but not essential.

3. First detection of HTLV-III in Gallo lab (not called HTLV-III until mass produced and characterized and proven to be cause of AIDS) was December 1982.

   Evidence: Reverse Transcriptase (RT) + particles, cytopathic, negative for HTLV-I and -II. No electron microscopy.

4. First detection of HTLV-III in Gallo lab with above data plus electron microscopy was February 1983.

   Many more detections, several with electron micrographs, prior to Montagnier sending us virus particles on September 23, 1983.

   All the above can be documented and conclusively proven.

5. Pasteur group, by their own statements, did their first experiments in January 1983.

6. January to March 1983: Montagnier and Pasteur group asked for and received from me reagents to distinguish their particles from HTLV-I and -II.

7. May 1983: Montagnier and co-workers report new Human T-Lymphotropic Retrovirus in one case of a man with lymph node enlargement. Data is an electron micrograph and RT. No serology.

   No characterization of viral proteins or nucleic acids. Virus not grown in a cell line. I reviewed and accepted the paper. On publication: the paper is attacked in France and U.S. in writing and at meetings by leading virus electron microscopists (Jack Dalton, Francoise Hayneau, John Moloney, R. Zeigel) with statements that this is not a retrovirus but an irrelevant arena virus. I defended against this attack.

8. In same May 1983 issue of Science I describe an HTLV-I-like (or identical) retrovirus in 2 of 33 AIDS cases, emphasizing that it may be HTLV-I itself and hence not the cause, but important to note because it can cause leukemia and may be prevalent in the same risk groups. Alternatively, this may be a variant of HTLV-I and a cause of AIDS. In fact, Gallo's idea at that time was that the causative retrovirus was likely to be a variant of HTLV-I, varying in the 3' half of the viral genome. Subsequent detailed molecular analysis of these two isolates showed that they were not variants but HTLV-I themselves, and eventually when the cause of AIDS (HTLV-III or LAV) was proven and sufficient molecular analyses completed, it became clear to everyone for the first time that this retrovirus differed from HTLV-I more substantially than anyone thought or could have possibly expected.

   It is important to understand that in 1983 in peer reviewed journals there is just the one case report of the new retrovirus later to be called LAV. It is important to note that in this 1983 paper the Pasteur group do not call the virus LAV. They call it a human T-lymphotropic virus.

   It is important to note that on that 1983 paper the Pasteur group report a significant cross reaction with HTLV-I. Later they conclude that this was a mistake.

   It is also important to note that in testing sera of AIDS patients for antibodies to a human retrovirus, Max Essex used HTLV-I as a test virus and by looking for a cross reaction with this (wrong virus) he did better (35% of AIDS sera and in blind tests) than the Pasteur group did almost a year later with LAV (less than 20% AIDS sera +)!

   It is obvious then that it is no wonder that all of us expected the causative agent to be more related to HTLV-I than has turned out.

   We elected not to publish on the new virus because no one had reagents to it in early-mid 1983, no one could mass produce it, and we felt for us to describe a new virus demanded more detail. In fairness to the Pasteur group, however, they certainly were pushing their one detection at this time. Our attitude was a "wait and see" while characterizing it and other retroviruses from these patients. The key point is that even many months after their publication they only detected what was to be LAV or HTLV-III a few times and not having a single reagent to the virus could never demonstrate that any two detections were detections of the same virus.

9. July 1983: Montagnier sends us a sample of "LAV." No virus was present by: EM, RT, or nucleic acid analyses.

   September 1983: Chermann prepares a sample for Montagnier to send to us with a paper for us to sign. Popovic signs the paper which states we cannot sell the virus, but the agreement gives us freedom to do anything else (nucleic acids, cell biology, virology). Also, Chermann appreciates the magnitude of the cytopathic effect of the virus and lets me know this.

10. Analysis of LAV: In view of Montagnier's conclusion that it is impossible to grow the virus in a cell line; in view of the complete absence of any available reagents to this virus; and in view of the controversy that it may

not be a retrovirus, there were only two things we could do: a) EM & b) RT. We did both and confirmed it was a retrovirus and immediately told them so. To try to do EM's and to try to grow it, Popovic transmitted it to human cord blood T-cells, to a T-cell line - HUT 78 and another T-cell line. All transmissions were transient. The virus was never mass produced and never put into our H9 clonal cell line. This is true to this day.

We do not do electron microscopy. We sent all our labeled samples to Electronucleonics, Inc. In September 1983, Peter Fischinger, Deputy Director of NCI requested that we use the Frederick, Maryland facilites, especially the subcontract with Program Resources Incorporation, because it would be less expensive and because he wanted Frederick to be involved. So at this time we began sending samples to Dr. M. Gonda and Dr. R. Gilden of this company. We sent LAV, labeled as LAV. At first we failed to detect RT so Popovic collected the samples for EM. They found the virus and informed us.

They made 20 pictures. One was inadvertently used by them later in making a composite to show stages of maturation of HTLV-III. (HTLV-III & LAV are not distinguishable by morphology. The Pasteur lawyers have unethically acquired EM pictures and letters between Gonda and Gilden and have made much of the positive EM report. This is ridiculous because they know we have a + EM of LAV. What they conveniently leave out is that all future reports were negative; i.e., we could not keep LAV growing, thus this is a fake issue.)

11. In the same month (Sept. 1983) the Pasteur filed for a patent for a diagnostic test for AIDS using LAV. Critical points to note about this patent claim:

    1. They had but a few detections of the virus.

    2. They could not grow the virus except transiently, precluding any blood bank test.

    3. The patent was directed - not at a blood test to protect against blood transfusions with virus - but as a diagnostic test for AIDS.

    4. The patent states the virus cannot be mass produced.

    5. The patent states only 20% of patients with AIDS have serum antibodies to LAV - 80% are negative!! It is a description of an ELISA test.

    6. The patent states there are not antibodies to the envelope protein. We know that the envelope is the main antigen. They now admit this.

    7. The patent provides no data that this virus is the cause of AIDS.

    8. We were not aware that they made a patent.

    9. A year earlier, Biotech Laboratories patented the same ELISA test for HTLV-I and for other human retroviruses, based to a major degree on technology and samples and information from Gallo's laboratory. Consequently, Gallo is on that patent.

12. November 1983: Our laboratory succeeds in the first mass production of the AIDS virus HTLV-III. Because of this, reagents are available for the first time. Because of that we can type all previous samples we suspected from the past (48 stored in the freezer; including 6 with positive electron microscopy). Also, because of this we can get enough quality viral proteins to do real sero-epidemiology. These studies and the numerous isolates prove HTLV-III is the cause of AIDS by Christmas 1983 to February 1984. Because of this we can also make virus and reagents available all over the world and, of course, have the first workable blood bank test.

We mass produced two immediately. One is called HTLV-III B; the second is called HTLV-III-RF or HAT (a Haitian isolate). We do the first molecular cloning of the viral genes in early 1984 and are first to publish molecular cloning of HTLV-III or LAV.

13. Later sequence analyses of HTLV-III B shows it differs from LAV by 150 nucleotides, also by insertions, deletions and duplications. Yet because it is closer to LAV than many other isolates and because the less sensitive restriction maps are so similar, Montagnier and Mal Martin imply they are the same. They do not mention that there are 47 other isolates, restriction maps on numerous, mass production of many (2 from the start), and that HTLV-III RF differs by about 1,000 nucleotides. It is worth noting that LAV was obtained from a French homosexual who went to New York in 1979. The sample from which LAV was obtained was from a biopsy in early 1983. HTLV-III was obtained from a New York homosexual in January 1983. Although substantial variation among isolates can occur in the same time and place, we have four pairs (including HTLV-III B and LAV) which are very similar - from the same time and place, including one pair from New Jersey, 1984 which are closer than LAV and HTLV-III. We have since published on over 100 isolates.

14. Early 1984 (don't know exact date). We tell NCI administrators we are sure we know the cause of AIDS and have a blood test.

15. Late January 1984. Gallo calls James Curran of CDC and tells him the same, asking for coded sera from CDC to prove it to them.

16. February, 1984. CDC sera arrives. 1st week of March 1984: Curran, Gallo, and Sarngadharan meet in Bethesda, "break the code" and results are, as anticipated, clear cut.

17. March - April 1984. 6 papers are submitted for publication: 4 to Science, 1 to Lancet, 1 to Advances in Internal Medicine. These results prove cause of AIDS. We say it in print (for the first time anyone says it) May 1984.

18. March 1984. Gallo visits Pasteur Institute; tells them his conclusions. Tells Montagnier that it is likely he (Gallo and his co-workers) will receive attention, but after appropriate comparisons with LAV if the viruses are essentially the same, they will make joint announcement.

19. April 1984. While at a meeting in Cremona, Italy and while papers on HTLV-III were in press, word on papers leaks into a British publication. Secretary Heckler asks Dr. Gallo and Dr. Wyngaarden to return for an urgent press conference where announcement of blood test and cause being known will be made. However, through input from CDC and Mal Martin of NIAID, New York Times is told "French" have the cause. Yet no new data is published from the Pasteur and the NCI data is published two weeks later.

New York Times writes a bitter editorial. This is led to Dr. Larry Altmann, a Times science writer with close affiliation (and past association) with CDC. At press conference, first words from Gallo are: "It is true we are sure of the cause of AIDS. It is true we have a blood test. The cause is a virus and it may be the same as the one detected last year in a case of lymphadenopathy by the Pasteur group." This is the first time anyone publicly makes either of these claims.

20. Following publication of the papers - May 1984, the cell lines producing HTLV-III are made available to people all over the world. CDC and the Pasteur group are the first to receive them. This is the first time anyone has a cell line permanently producing HTLV-III/LAV.

Soon, a committee (without me) is formed to select 5 companies (26 bid) to put the blood test into worldwide application to protect blood banks.

Earlier, in February 1984, I am advised by Dr. DeVita and Dr. Fischinger to patent the blood test. We patent a blood test with data included that shows: a) HTLV-III is the cause of AIDS
b) that we can mass produce the virus and make the necessary reagents available all over the world for the first time.
c) that the purpose is to protect the blood supply.
d) that the envelope is important in the assay.
e) that sera tested "blindly" (coded) slow less than 0.1% of the healthy population to be positive but 90% to 100% of AIDS sera are positive.

This is the first time I have ever filed a patent, i.e., I did not patent our discovery of T-cell growth factor (IL-2); nor numerous human cell lines making commercially valuable lymphokines; nor HTLV-I; nor HTLV-II.

21. June 1984: M. Sarngadharan, a close co-worker of Gallo, goes to Paris, brings the cell line producing HTLV-III and with Montagnier makes comparisons of LAV, to our prototype HTLV-III known as the B strain (HTLV-III B).

* They prepare a table signed by Montagnier in which Montagnier argues for significant differences between HTLV-III B and LAV.

22. Visit by George Todaro of Genetic Systems.

Some time around the summer of 1984, former NCI Branch Chief, George Todaro visits me and tells me:

1. It is not in "my interest" that the arrogant U.S. Government selected only 5 companies. I will have many "enemies" as a consequence.

2. When I admit he has a point and perhaps I should discuss making it open to more companies, Todaro changed the argument and states "only Genetic Systems is really qualified." I laugh and say good-by. Knowing that NCI Deputy Director Peter Fischinger was on the selection committee (and being that Todaro was formerly Fischinger's Branch Chief), Todaro vows to me "he will get Fischinger if its the last thing he does."

23. When we began getting the key information of a retrovirus role in AIDS, CDC hired one of our senior post-doctorals who was doing the immunochemistry of various HTLVs. His name is V. Kalyanaraman. When we began to link HTLV-III to AIDS (winter 1983 - early 1984), Kalyanaraman is sent by CDC to the Pasteur Institute to help Montagnier.

24. Nomenclature:

1. 1983 - Pasteur in their only paper call the virus an HTLV.

2. Late 1983 - Pasteur calls virus LAV.

3. Early 1984 - Pasteur calls virus IDAV.

4. Until we know it is cause of AIDS, we use a variety of code names. When we publish we call it the 3rd human T-lymphotropic retrovirus or HTLV-III.

5. When we know LAV is a strain of the same virus we recognize Pasteur contribution and call virus HTLV-III/LAV generically, and then use the specific strain name such as HTLV-III B, HTLV-III RF, or LAV-I.

6. In fact, we followed an internationally agreed upon nomenclature system made in September 1983 by European, U.S., and Japanese scientists - all working in the field, that new human retroviruses infecting T-cells would be called HTLV-III, IV, V .... etc.

   As of April 1986 there are four categories of human retroviruses. All chiefly infect T-cells.

7. In 1985 Harold Varmus, not working on human retrovirology, forms a committee to name these viruses. After one year of disagreements, a generic name for HTLV-III/LAV is suggested. HIV. I strongly believe this will cause more confusion than help. The committee is divided but this is the majority vote. However, Varmus promises strict confidence and sensitivity as well as approval of the committee before any statements are made public on the recommendation for a new generic name.

   Early April 1986: Montagnier announces through a public relations New York firm a "new" virus LAV-2. No data are publisned. It appears that it is the same as a retrovirus discovered six months earlier by M. Essex and called HTLV-4. The Essex isolate does not cause disease. Montagnier's "new" virus is widely published in the lay press.

   Two weeks later Montagnier is invited by Mal Martin of NIAID to give a lecture at NIH in a special auditorium. The press is called to be present by Montagnier, Martin, or both. Montagnier breaks the agreements with the nomenclature committee to announce HIV-I (formerly LAV) and now HIV-II (probably Essex's HTLV-IV)! Now the nomenclature committee is in disarray.

25. By 1985 with the help of Genetic Systems of Seattle, Pasteur group now have a workable blood test for the first time. When this occurs they hire 3 or 4 law firms, 1 or 2 public relation firms, and they file suit against our patent. Our U.S. government lawyers tell me they have never seen such an extensive, aggressive, and unethical policy as occurs in the coming months.

26. Misbehavior by Pasteur lawyers or collaborators.

1. June 1984, Denver Colorado meeting on Human Retroviruses. George Todaro approaches R. Gilden of Program Resources, Inc. about possibly working together to show "Gallo has Montagnier's virus." This is before any analytical comparative data are available on LAV-1 vs. HTLV-III B! Gilden reports this to Fischinger and Gallo.

2. Summer 1984. George Todaro's visit to me and gives his threat discussed above.

3. February 1986. Mr. Swire, one of the many Pasteur lawyers lies to Gonda and tells him they are a company seeking scientific advice. Instead, they attempt to entrap Gonda. Gonda reports this.

4. Private correspondence and copies of electron micrographs are in the hands of the Pasteur lawyers. It is only information from Gonda and Gilden. This same information was given to our Health Department lawyers. In other words, it could only have been obtained by Pasteur lawyers by illegal entry and theft or from Gonda - Gilden or from a Health Department lawyer or from someone in their office.

5. Swire and company attempt to get Jim Curran of CDC to go for a ride to talk privately.

6. Swire and company come to scientific meetings where I am scheduled to talk. Also, they call people at Nature and Science, stating if we have an EM picture of LAV it is bad for me . . . etc.

27. April 1986. Yamamoto et al. in Japan find biological, immunological, and new nucleic acid differences between LAV I and HTLV-III B.

P. Fischinger and Kobey have immunological differences.