Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

The San Francisco AIDS Oral History Series

THE AIDS EPIDEMIC IN SAN FRANCISCO: THE MEDICAL RESPONSE 1981-1984

VOLUME VIII

Jay A. Levy, M.D.

ANIMAL VIROLOGY AND THE DISCOVERY OF THE AIDS VIRUS

With an Introduction by
James Chin, M.D., M.P.H.

Interviews Conducted by
Sally Smith Hughes, Ph.D.
in 1993

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of northern California, the West, and the nation. Oral history is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is indexed, bound with photographs and illustrative materials, and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

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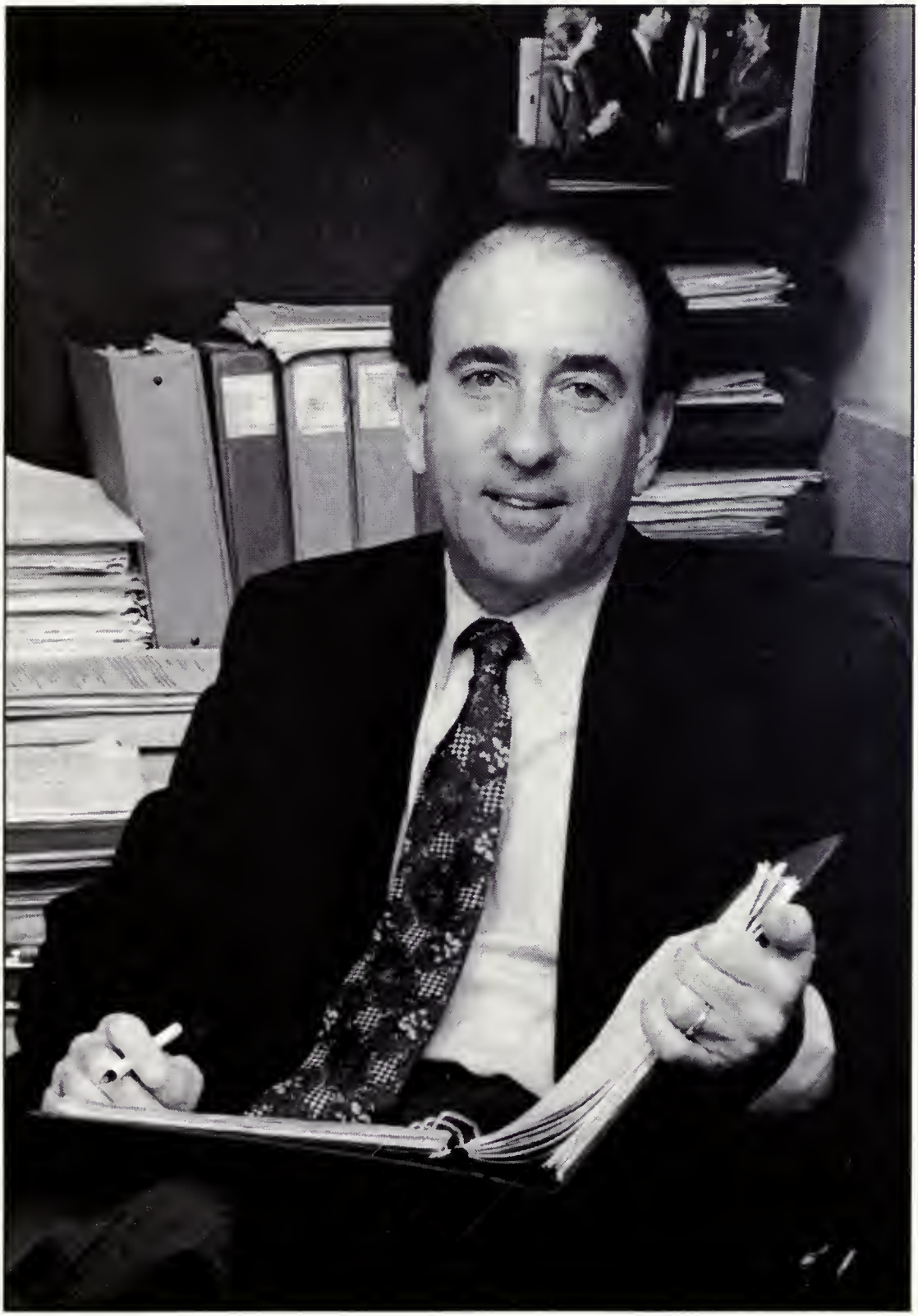

Jay A. Levy, M.D., 1996.

Photograph by Karen Preuss

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Jay A. Levy, M.D. (b. 1938), "Animal Virology and the Discovery of the AIDS Virus": virologist. Education at Wesleyan and Columbia, internship, residency, and research at University of Pennsylvania; pre-AIDS career and research at the National Cancer Institute, UCSF, and in France; Kaposi's Sarcoma Clinic, UCSF, visit to Haiti; 1983 State AIDS research grant; heat treatment of blood products and viral cause of AIDS; Robert Gallo at NCI, Luc Montagnier and Pasteur Institute group, and Levy laboratory in race to identify AIDS virus, and ensuing claims for priority; controversy over AIDS antibody tests; cloning and sequencing AIDS virus, Chiron Corp.; naming the virus HIV, and research on immune mechanisms and CD8 cells in long-term AIDS survivors; comments on Robert Gallo, Gertrude (Brigitta) and Werner Henle, and William J. Rutter.

Introduction by James Chin, M.D., M.P.H., Clinical Professor of Epidemiology, School of Public Health, University of California, Berkeley.

Interviews conducted in 1993 by Sally Smith Hughes, Ph.D. for the San Francisco AIDS Oral History Series, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

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PREFACE--by David A. Lennette, Ph.D., and Evelyne T. Lennette, Ph.D.

As two young medical virologists working in Pennsylvania, we experienced first hand some of the excitement of medical detective work. We had our first glimpse of how personalities can shape the course and outcome of events during the swine influenza and Legionnaires' disease outbreaks.

On our return to California, we were soon embroiled in another much more frightening epidemic. In 1981, our laboratory began receiving samples for virologic testing from many of the early San Francisco AIDS patients--whose names are now recorded in Randy Shilts' book *And the Band Played On*. Our previous experience with the legionellosis outbreak had primed us for this new mystery disease. While the medical and scientific communities were hotly debating and coping with various issues during the following three years, we were already subconsciously framing the developments in an historical point of view. In San Francisco, dedicated junior physicians and researchers banded together to pool resources and knowledge out of necessity, and in doing so, organized part of the local medical community in a very unusual way. Once again, we were struck by how the personalities of each of these individuals shaped the course of events. Even before HIV was discovered, we knew we were witnessing a new page in the history of science and medicine.

The swine flu and legionellosis outbreaks were both very local and short lived. We now speak of them in the past tense. The AIDS epidemic, sadly, is still spreading unimpeded in much of the world. We know that it will be with us for a long time and that it is very unlikely that either of us will live long enough to read the closing chapter on AIDS.

Future generations will some day want to know how it all got started. The existing scientific reports and publications provide depersonalized records of some of the events, while newspaper articles and books give glimpses as summarized by observers. What are missing are the participants' own accounts and perspectives.

It is now more than a dozen years after the recognition of the AIDS epidemic in the United States. So much has happened and changed--already, some of the participants in early events have retired, records are being discarded and destroyed, and memories of those days are beginning to fade. We felt their oral histories had to be recorded without delay.

We had previously sponsored oral histories on virology with Dr. Edwin H. Lennette, David's father, and Dr. Harald N. Johnson, and were familiar with the methods and work of the Regional Oral History Office. We met to talk over the recording of the AIDS epidemic with Willa Baum, head of the office, and Dr. Sally Smith Hughes, medical history interviewer. After

some discussion, we agreed that the events from 1981-1984 needed to be documented and we would fund it. This was a time when many crucial decisions on the clinical, public health, social, and political issues pertaining to AIDS were made with little scientific information and no precedents to rely on. The consequences of many of these decisions are still being felt today. With the discovery of HIV, however, the framework for decision making shifted to different ground, and a pioneering phase was over. Once we decided on the scope of the project, it was a simple task to identify prospective interviewees, for we worked with many of these individuals during those years.

Dr. Sally Hughes has shared our enthusiasm from the beginning. We are pleased that her efforts are now coming to fruition.

David A. Lennette, Ph.D.
Evelyne T. Lennette, Ph.D.

November 1994
Virolab, Inc.
Berkeley, California

SERIES INTRODUCTION--by James Chin, M.D., M.P.H.

As the California state epidemiologist responsible for communicable disease control from the early 1970s to the late 1980s, I had the privilege and opportunity to work with all of the participants who were interviewed for the San Francisco AIDS Oral History Project. I consider it an honor to have been asked to provide a brief introduction to the role that these individuals played in the history of AIDS in San Francisco during the early years. Before I begin, the following quote from Dr. James Curran, in a December 1984 issue of the *San Francisco Chronicle* sums up what has happened to all of the participants in this oral history project:

> I'd like to sound more upbeat about this, but there are some unavoidable facts we need to face. AIDS is not going away. Gay men don't want to hear that. Politicians don't want to hear that. I don't like to hear that. But for many of us, AIDS could well end up being a lifelong commitment.

The first recognized cases of AIDS were reported in the *Morbidity and Mortality Weekly Report (MMWR)* on June 5, 1981. I recall this report vividly. A few months earlier, the Centers for Disease Control (CDC) had begun sending an advance copy of the *MMWR* text to state health departments. The advance text of the June 5 *MMWR* had a lead article on the sudden and unexplained finding of five apparently unrelated cases of *Pneumocystis carinii* pneumonia in five young gay men from Los Angeles. The *MMWR* text was received in my office just before our weekly Tuesday afternoon staff meeting was to start. I handed the text to Tom Ault, who was responsible for the state's venereal disease field unit and asked him to have some of our federal- or state-assigned staff in Los Angeles assist in the investigation of these cases. I remember saying to him that it may not turn out to be much of anything, but it may be the start of something. I never imagined that that something would eventually develop into a worldwide epidemic of disease and death.

In the ensuing weeks and months, it became apparent that the mysterious illness reported from Los Angeles was also present among gay men in San Francisco. From 1981 to 1984, the numbers of AIDS cases reported from San Francisco rose almost exponentially--from a handful in mid-1981 to well over 800 towards the end of 1984. The impact that AIDS has had in San Francisco is unequaled on a per capita basis anywhere in the developed world. If the AIDS prevalence rate of about one AIDS case per 1,000 population that was present in San Francisco at the end of 1984 was applied nationally, then there would have been about a quarter of a million AIDS cases nationwide instead of the 7,000 that were actually reported. During the first few years of what was initially referred to as GRID (gay-related immune deficiency), there was general denial of the severity of this newly

recognized mystery disease even in San Francisco. The enormity of the AIDS problem was first fully accepted by the gay community in San Francisco, and physicians and researchers in the city rapidly became the leading experts in the country on the medical management, prevention, and control of AIDS. In contrast to Los Angeles and New York, which also have had large concentrations of AIDS cases, the gay community in San Francisco has been more unified and organized in developing political and community support for the treatment and care of AIDS patients.

The epidemiology of AIDS, namely, that it is caused primarily by a sexually transmitted agent, was fairly well established by 1983, well before HIV was eventually isolated and etiologically linked to AIDS in 1984. Public health investigations in San Francisco, spearheaded by Selma Dritz in 1981 and 1982, provided much of the key epidemiologic data needed to understand the transmission and natural history of HIV infection. The more formal epidemiological studies of AIDS among gay men in San Francisco were carried out by Andrew Moss at San Francisco General Hospital (SFGH) and Warren Winkelstein at the University of California at Berkeley. All of these studies were helpful to Mervyn Silverman (who during this period was director of the San Francisco Department of Public Health) to support his decision in October 1984 to close the San Francisco bathhouses. Selma Dritz retired from her position with the health department in 1984, and Mervyn Silverman has moved on to become the premier HIV/AIDS frequent flier in his current position as president of the American Foundation for AIDS Research, which is now supporting studies internationally.

Jay Levy was an established virologist when AIDS was first detected and reported in 1981. His laboratory isolated and characterized a virus which he initially called ARV--AIDS Related Virus. He continues to play a prominent role in the quest to better understand the pathogenesis of HIV. Herbert Perkins was the scientific director of the Irwin Memorial Blood Bank in San Francisco during the critical period around 1982-1985 when data began accumulating to indicate that the cause of AIDS might be an infectious agent which could be transmitted via blood. Under his direction, the Irwin Memorial Blood Bank in May 1984 was the first blood bank in the country to begin routine surrogate testing of blood units for the AIDS agent using a hepatitis B core antibody test. He retired as director of Irwin Memorial in April 1993, but remains very much involved in defending the blood bank from legal suits arising from transmission of HIV via blood transfusions during the early years. Don Francis did not work in California during the early 1980s, but directed epidemiologic and laboratory studies on AIDS as the first head of the AIDS laboratory at CDC in Atlanta during this time period. Following his request to become more directly involved with field work and HIV/AIDS program and policy development, he was assigned to work in my office in Berkeley in 1985. Don took an early retirement from CDC in 1992 and continues to actively work in the San Francisco Bay Area as well as nationally and internationally on the development of an AIDS vaccine.

The clinical staffs of San Francisco General Hospital and the University of California at San Francisco established the two earliest AIDS clinics in the country, and in 1983, Ward 5B at SFGH was set up exclusively for AIDS patients. In the early 1980s, Don Abrams and Paul Volberding were two young physicians who found themselves suddenly thrust into full-time care of AIDS patients, a responsibility which both are still fully involved with. As a result of their positions, experience, and dedication, both are acknowledged national and international experts on the drug treatment of HIV and AIDS patients. Merle Sande, John Ziegler, Arthur Ammann, and Marcus Conant were already well established and respected clinicians, researchers, and teachers when AIDS was first detected in San Francisco. Their subsequent work with HIV/AIDS patients and research has earned them international recognition. The Greenspans, Deborah and John, have established themselves as the foremost experts on the oral manifestations of HIV/AIDS, and Constance Wofsy is one of the leading experts on women with HIV/AIDS. There is rarely a national or international meeting or conference on AIDS where most, if not all, of these San Francisco clinical AIDS experts are not present and speaking on the program. The number of HIV/AIDS clinicians and research scientists from San Francisco invited to participate in these medical and scientific meetings usually far exceeds those from any other city in the world. All of these individuals have made tremendous contributions to the medical and dental management of HIV/AIDS patients in San Francisco and throughout the world.

As of late 1994, more than a decade since the advent of AIDS in San Francisco, Jim Curran's remark in 1984 that "...for many of us, AIDS could well end up being a lifelong commitment" has been remarkably accurate for virtually all the participants in this San Francisco AIDS Oral History Project.

James Chin, M.D., M.P.H.
Clinical Professor of Epidemiology
School of Public Health,
University of California at Berkeley

September 1994
Berkeley, California

SERIES HISTORY--by Sally Smith Hughes, Ph.D.

Historical Framework

In 1991, Evelyne and David Lennette, virologists and supporters of previous Regional Oral History Office (ROHO) projects in virology and horticulture, conceived the idea for an oral history series on AIDS. They then met with Willa Baum (ROHO director) and me to discuss their idea of focusing the series on the medical and scientific response in the early years (1981-1984) of the AIDS epidemic in San Francisco, believing that the city at this time played a particularly formative role in terms of AIDS medicine, organization, and policy. Indeed San Francisco was, with New York and Los Angeles, one of the three focal points of the epidemic in the United States, now sadly expanded worldwide.

The time frame of the oral history project is historically significant. Nineteen eighty-one was the year the epidemic--not until the summer of 1982 to be officially christened "AIDS"--was first recognized and reported. A retrovirus was isolated in 1983, and by early 1985, diagnostic tests were being marketed. These achievements signaled a turning point in the response to the epidemic. Its science shifted from a largely epidemiological approach to one with greater emphasis on the laboratory. As soon as the virus was determined, scientific teams in the United States and Europe raced to characterize it in molecular terms. Information about the molecular biology of the human immunodeficiency virus (HIV), as it was named, was in turn expected to transform AIDS medicine by providing a basis for treatment and prevention of the disease through new drugs and vaccines.

San Francisco continued to make important contributions to combating the epidemic, but by early 1985 it had lost its pioneering role. The AIDS test showed that the epidemic reached far beyond the three original geographic centers and involved large numbers of symptomless HIV-positive individuals, who were not identifiable prior to the test's advent. AIDS funding increased; the number and location of AIDS researchers expanded; research interest in the newly identified virus took center stage. San Francisco's salient position in the AIDS effort faced competition from new players, new research interests, and new institutions. The first phase of the epidemic was history.

Project Structure

Within the limits of funding and the years of the project (1981-1984), the Lennettes suggested eight potential interviewees whom they knew to have played important medical and scientific roles in the early years of the San Francisco epidemic. (Both Lennettes have close connections with the local AIDS research community, and Evelyne Lennette was a scientific collaborator of three interviewees in this series, Jay Levy and John and

Deborah Greenspan.) I then consulted Paul Volberding, an oncologist at San Francisco General Hospital with an international reputation as an AIDS clinician. He and others in the oral history series made several suggestions regarding additional interviewees, expanding my initial list to fourteen individuals.[1] My reading of primary and secondary sources and consultation with other authorities confirmed the historical merit of these choices.

The series consists of two- to ten-hour interviews with seventeen individuals in epidemiology, virology, public health, dentistry, and several medical specialties. By restricting phase one to San Francisco's early medical and scientific response to the epidemic, we aim to provide in-depth documentation of a major aspect, namely the medicine and science it generated in a given location, at a given time, under near-crisis conditions. Like any human endeavor, medicine and science are embedded in the currents of the time. As these oral histories so graphically illustrate, it is impossible to talk about science and medicine without relating them to the social, political, and institutional context in which they occur. One of the strengths of oral history methodology is precisely this.

This concentration on physicians and scientists is of course elitist and exclusive. There is a limit--practical and financial--to what the first phase of a project can hope to accomplish. It was clear that the series needed to be extended. Interviews for phases two and three of the oral history project, a series with AIDS nurses and a third with community physicians with AIDS practices, have been completed and serve to broaden the focus. The long-range plan is to interview representatives of all sectors of the San Francisco community which contributed to the medical and scientific response to AIDS, thereby providing balanced coverage of the city's biomedical response.

Primary and Secondary Sources

This oral history project both supports and is supported by the written documentary record. Primary and secondary source materials provide necessary information for conducting the interviews and also serve as essential resources for researchers using the oral histories. They also orient scholars unfamiliar with the San Francisco epidemic to key participants and local issues. Such guidance is particularly useful to a

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[1]A fifteenth was added in 1994, when the UCSF AIDS Clinical Research Center provided partial funding for interviews with Warren Winkelstein, M.D., M.P.H., the epidemiologist directing the San Francisco Men's Health Study. A sixteenth and seventeenth, with Lloyd "Holly" Smith, M.D., and Rudi Schmid, M.D., were recorded in 1995 when the UCSF Academic Senate allocated funds for transcription.

researcher faced with voluminous, scattered, and unorganized primary sources, characteristics which apply to much of the AIDS material. This two-way "dialogue" between the documents and the oral histories is essential for valid historical interpretation.

Throughout the course of this project, I have conducted extensive documentary research in both primary and secondary materials. I gratefully acknowledge the generosity of Drs. Arthur Ammann, Marcus Conant, John Greenspan, Herbert Perkins, Warren Winkelstein, and John Ziegler in opening to me their personal documents on the epidemic. Dr. Frances Taylor, director of the Bureau of Infectious Disease Control at the San Francisco Department of Public Health, let me examine documents in her office related to closure of city bathhouses in 1984. Sally Osaki, executive assistant to the director of the health department, gave me access to documents from former Mayor Dianne Feinstein's papers on her AIDS activities. I am grateful to both of them.

Dr. Victoria Harden and Dennis Rodrigues of the NIH Historical Office assisted by sending correspondence and transcripts of a short telephone interview with John Ziegler, which Rodrigues conducted.[1] I thank Dr. James Chin for his introduction to this series, which describes his first-hand experience of the epidemic as state epidemiologist at the California Department of Health Services where he was responsible for communicable disease control. I also thank Robin Chandler, head of Special Collections, UCSF Library, and Bill Walker, former archivist of UCSF's AIDS History Project and the San Francisco Gay and Lesbian Historical Society, for their assistance in accessing these rich archival collections.

The foregoing sources have been crucial in grounding the interviews in specifics and in opening new lines of questioning. A source to be noted, but untapped by this project, is the California AIDS Public Policy Archives, which is being coordinated by Michael Gorman, Ph.D., at San Francisco General Hospital.

Of the wealth of secondary historical sources on AIDS, the most pertinent to this project is Randy Shilts' *And the Band Played On*.[2] Although criticized for its political slant, it has been invaluable in providing the social, political, and ideological context of early AIDS efforts in San Francisco, particularly in regard to San Francisco's gay community.

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[1]Telephone interview by Dennis Rodrigues with John L. Ziegler, M.D., January 5, 1990. Tapes and transcripts of the interview are available in the NIH Historical Office, Bethesda, MD.

[2]Randy Shilts, *And the Band Played On: Politics, People, and the AIDS Epidemic*, New York: Penguin Books, 1988.

Oral History Process

The oral history methodology used in this project is that of the Regional Oral History Office, founded in 1954 and producer of over 1,400 archival oral histories. The method consists of background research in primary and secondary sources; systematic recorded interviews; transcription, editing by the interviewer, and review and approval by the interviewee; deposition in manuscript libraries of bound volumes of transcripts with table of contents, introduction, interview history, and index; cataloging in UC Berkeley and national on-line library networks (MELVYL, RLIN, and OCLC); and publicity through ROHO news releases and announcements in scientific, medical, and historical journals and newsletters and via the UCSF Library web page (http://www.library.ucsf.edu/).

Oral history as an historical technique has been faulted for its reliance on the vagaries of memory, its distance from the events discussed, and its subjectivity. All three criticisms are valid; hence the necessity for using oral history documents in conjunction with other sources in order to reach a reasonable historical interpretation.[1] Yet these acknowledged weaknesses of oral history, particularly its subjectivity, are also its strength. Often individual perspectives provide information unobtainable through more traditional sources. For example, oral history in skillful hands provides the context in which events occur--the social, political, economic, and institutional forces which shape the evolution of events. It also places a personal face on history which not only enlivens past events but also helps to explain how individuals affect historical developments.

The foregoing criticisms could be directed at the AIDS oral history series. Yet this series has several mitigating characteristics. First, it is on a given topic in a limited time frame with interviewees focused on a particular response, namely the medical and scientific. Thus although each interviewee presents a distinctive view of the epidemic, multiple perspectives on the same events provide an opportunity for cross-checking and verification, as well as rich informational content. Furthermore, most of the interviewees continue to be actively engaged in AIDS work. Hence, the memory lapses resulting from chronological and psychological distancing from events discussed are less likely to occur than when the interviewee is no longer involved.

An advantage of a series of oral histories on the same topic is that the information each contains is cumulative and interactive. Through individual accounts, a series can present the complexities and interconnections of the larger picture--in this case, the medical and scientific aspects of AIDS in San Francisco. Thus the whole (the series)

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[1]The three criticisms leveled at oral history also apply in some cases to other types of documentary sources.

is greater than the sum of its parts (the individual oral histories), and should be considered as a totality. To encourage this approach, we decided to bind several oral histories together in most of the volumes.

Another feature of an oral history series is that later interviews tend to contain more detailed information because as the series unfolds the interviewer gains knowledge and insight from her informants and from continued research in primary and secondary sources. This was indeed the case in the AIDS series in which the later interviews benefited from my research in private document collections made available to me as the project progressed and by the knowledge I gained from the interviews and others connected with the AIDS scene.

A feature of this particular series is its immediacy, a characteristic less evident in oral histories conducted with those distanced from the topic of discussion. These are interviews with busy people who interrupted their tight schedules to look back, sometimes for the first time, at their experiences of a decade or so ago. Because many have not had the luxury of time to contemplate the full meaning of their pasts, the oral histories could be criticized for lacking "historical perspective." But one could also argue that documents intended as primary historical sources have more scholarly value if the information they contain is not filtered by the passage of years and evolving personal opinions.

The oral histories also have a quality of history-in-progress. With few exceptions, the interviewees are still professionally engaged in and preoccupied by an epidemic which unhappily shows no sign of ending. The narrators are living the continuation of the story they tell. Neither they nor we can say for sure how it will end.

Other Oral History Projects Related to AIDS

Oral history projects on other aspects of the San Francisco epidemic are essential for full historical documentation and also mutually enrich one another. Unfortunately, not enough is currently being done in this regard. Two local projects are Legacy, directed by Jeff Friedman, which focuses on the Bay Area dance community tragically decimated by AIDS, and Clarissa Montanaro's AIDS Oral History Project, which interviews people with AIDS. An installation, "Project Face to Face", directed by Jason Dilley and using excerpts from interviews with people with AIDS, was exhibited around the San Francisco Bay Area and in 1991 was part of the inaugural exhibit at the Smithsonian's Experimental Gallery.

AIDS oral history projects outside San Francisco include documentation by Victoria Harden, Ph.D., Caroline Hannaway, Ph.D., and Dennis Rodrigues of the NIH Historical Office of the contribution made by NIH scientists, physicians, and policymakers to the AIDS effort. Gerald

Oppenheimer and Ronald Bayer at Columbia, with support from the National Library of Medicine and the Royal Marx Foundation, are conducting interviews with AIDS physicians in several cities across the United States. The New Jersey AIDS Oral History Project, sponsored by the University of Medicine and Dentistry of New Jersey, interviews faculty and staff involved in the epidemic and representatives of organizations providing AIDS support services. Rosa Haritos, Ph.D., at Stanford relied substantially on oral history in her dissertation on the controversy between the Pasteur Institute and NIH over the discovery of the AIDS virus.[1] In England, Virginia Berridge, Ph.D., co-director of the AIDS Social History Programme at the London School of Hygiene and Tropical Medicine, employs oral history in her research on AIDS policy in the UK.[2] And Maryinez Lyons, Ph.D., at the University of London, uses interviews in her work on the political economy of AIDS in Uganda.[3] In France, Anne Marie Moulin, M.D., Ph.D., Director of Research at INSERM, Paris, has relied on oral history in some of her work on the epidemic in France. The anthropologist, Paul Farmer, used interviews heavily in his work on AIDS in Haiti.[4]

Emerging Themes

What themes can be extracted from these oral histories? What do they convey about the medical response to AIDS in San Francisco? Was it unique, or are there parallels with responses to other epidemics? What do these interviews tell us about the complex interweaving of factors--social, political, economic, and personal--which shaped reactions to this epidemic, in this city, in these years?

The short answer is that it is too soon to attempt definitive answers. This is the third volume in a lengthy series, and most of the oral histories are not completely processed nor has the information they contain been fully assessed.

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[1]Rosa Haritos, "Forging a Collective Truth: A Sociological Analysis of the Discovery of the AIDS Virus," Ph.D. dissertation, Columbia University, 1993.

[2]See: Virginia Berridge and Paul Strong, eds., *AIDS and Contemporary History*, Cambridge: Cambridge University Press, 1993.

[3]Maryinez Lyons, "AIDS and the Political Economy of Health in Uganda," paper presented at a conference, AIDS and the Public Debate: Epidemics and their Unforeseen Consequences, sponsored by the AIDS History Group of the American Association for the History of Medicine, Lister Hill Center, NIH, Bethesda, MD, October 28-29, 1993.

[4]Paul E. Farmer, *AIDS and Accusation: Haiti and the Geography of Blame*, Berkeley: University of California Press, 1992.

Furthermore, there is an inherent danger in reaching definitive conclusions on the basis of oral histories with only seventeen individuals. Obviously, this is not a statistical sampling. On the other hand, because these seventeen have been at the front line of the epidemic and in a city hit hard by the epidemic, their voices "count" more than their numbers might suggest. They also "count" because these individuals helped devise organizations and policies that have served as models for AIDS programs across the country and around the world. Thus, if used in conjunction with the traditional documentary sources, these oral histories "count" as rich historical sources on several levels.

Remembering these caveats, I will make some tentative suggestions about a few of the many themes which come to the fore as I put the first volume together. My thoughts will doubtless be modified and extended as I examine the oral history collection as a whole and assess it in the context of the existing literature on AIDS history.

--Professional and personal "preparation" for the epidemic:

Narrators invariably mentioned how their prior education and professional training and experience had prepared them for participation in the epidemic. Their training as oncologists or epidemiologists or infectious disease specialists "fitted them" in a deterministic sense to take notice when the epidemic was first recognized in San Francisco. Their interest piqued, they chose to become engaged because their professional knowledge, experience, and responsibility placed them in a position to contribute. How then to explain why others with similar backgrounds chose not to become involved? The interviews indicate that psychological makeup, humanitarian concerns, career ambition, sexual orientation, and simply being needed and on the scene also played a role.

--Organizing for the epidemic:

The oral histories describe at length, in detail, and on many levels how the academic medical profession in San Francisco organized to respond to the epidemic. The focus is on university physicians, but the oral histories show that it is impossible to talk about the medical response without at the same time mentioning its interconnections with the community physician, nursing, psychiatric, and social service professions, the gay community, and volunteer AIDS support organizations. Discussion of the coordinated medical system created in the early years of the epidemic, capsulized in the so-called San Francisco model of comprehensive AIDS care, permeates the oral histories. The complex process by which a community organizes to diagnose, investigate, and treat a newly recognized disease is detailed here, as are the spinoffs of these activities--the foundation of two AIDS clinics, an AIDS ward, and a specimen bank; funding efforts; education and prevention programs; epidemiological and laboratory studies; political action at the city, state, and national levels; and so on.

--The epidemic's impact on the professional and personal lives of physicians and scientists:

Surprisingly, despite the flood of AIDS literature and the centrality of the medical profession in the epidemic, there are few accounts by physicians of the epidemic's professional and personal impact.[1] The physicians' voices which speak--at times poignantly, but always with immediacy--through these oral histories are a small corrective to the impersonality of most of the literature on AIDS.

On a professional level, the narrators describe commitment, concern, cooperation, camaraderie, and conflict as attributes of their engagement in the epidemic. Clinicians and epidemiologists confronted by what they perceived as a medical emergency described the prevailing sense of urgency and dedication of the epidemic's early years--to stop the insidious spread of disease, to discover its cause, to devise effective treatments, to establish community care arrangements. Narrators talked of concern for an articulate, informed, and youthful patient population, with whom some identified and for whom most felt great sympathy. They also spoke of the camaraderie and cooperation of the physicians, nurses, social workers, and community volunteers assembled at UCSF and San Francisco General to run the AIDS clinics and ward. But they also mentioned conflict--personal and institutional rivalries, funding problems, and run-ins with the university administration, city politicians, and gay activists.

On a personal level, the interviews recount the epidemic's impact on individual lives--of fear of a devastating and lethal infection, of stigma and homophobia involved in dealing with socially marginal patient populations, of exhaustion and burnout, and of growth in human experience and insight.

--The epidemic as a social and cultural phenomenon:

These oral histories describe the complex interactions between disease and its social and cultural context. They indicate how the unique circumstances of San Francisco in the early 1980s--its large and vocal gay community, its generally cooperative medical and political establishments, the existence of a city budget surplus--shaped the response to the epidemic.

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[1]A few personal accounts by physicians do exist. See, for example: G. H. Friedlander, "Clinical Care in the AIDS Epidemic," *Daedalus* 1989, 118 (2):59-83. H. Aoun, "When a House Officer Gets AIDS," *New England Journal of Medicine* 1989, 321:693-696. The Oppenheimer/Bayer oral history project, mentioned above, also seeks to document physicians' responses.

AIDS, like all disease, reflects social and cultural values. Implicit and explicit in the oral histories are evidence of stigma and homophobia, the politicization of the AIDS effort and those associated with it, and the tension between individual rights and social welfare.

The foregoing themes are but a few of those inherent in these oral histories. I hope that scholars will be persuaded to explore these further and to discover and research those unmentioned. To serve as a rich, diverse, and unique source of information on multiple levels is after all a major purpose of this oral history series.

Locations of the Oral Histories

The oral history tapes and bound volumes are on deposit at The Bancroft Library. The volumes are also available at UCSF, UCLA, and other manuscript libraries.

Note Regarding Terminology

In this series, both interviewer and interviewee occasionally use the term "AIDS" to refer to the disease before it had been officially given this name in the summer of 1982. "AIDS" is also used to refer to the disease which in recent years has come to be known in scientific and medical circles as "HIV disease." In these oral histories, the term "AIDS" has been retained, even when its use is not historically accurate, because it is the term with which readers are most familiar.

Sally Smith Hughes, Ph.D.
Project Director

October 1996
Regional Oral History Office

December 2001

THE AIDS EPIDEMIC IN SAN FRANCISCO: The Medical and Nursing Response, 1981-1984

AIDS PHYSICIANS ORAL HISTORY SERIES: The Medical Response, 1981-1984

Volume I
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William F. Owen, Jr., M.D., "AIDS Clinical Practice in the Private Sector."

INTERVIEW HISTORY--Jay A. Levy, M.D.

Jay Levy was interviewed for this series because of his role as virologist in the small group of physicians and scientists following AIDS patients at the University of California San Francisco [UCSF] and San Francisco General Hospital [SFGH] in the early days of the epidemic. As he describes in the oral history, he began at this time to attend the Kaposi's Sarcoma Study Group at UCSF and to establish cell lines for research on the disease agent. Only subsequently did the group recognize that Kaposi's sarcoma [KS] was only one manifestation of the syndrome which came to be known as AIDS.

The oral history is largely a recounting of Levy's science from his undergraduate days through the discovery and early depiction in the mid-1980s of the virus which we now know as HIV. The first interview is almost wholly devoted to his pre-AIDS research in animal virology, some of it in exotic parts of the world. It is a revealing account of mid-century virological research and sets the stage for Levy's entry into AIDS science. As he explains, it was his decades-long research on viral links to cancer that sparked his interest in Kaposi's sarcoma, the skin cancer being reported in gay patients by his physician colleagues at UCSF and SFGH as early as 1981. He remarks that the discovery of AIDS in hemophiliacs in 1982 convinced him to switch to investigating the blood of AIDS patients in his search for a causal virus. In the process, he demonstrated that heat treatment destroyed the infectious agent in blood clotting factors used by hemophiliacs. The finding he took to be evidence that the agent was likely a virus and gave impetus to his attempt to identify what he now suspected was a new virus, rather than a variant of a known type, as he and others originally believed.

Although science is center stage in this account, science politics is also much in evidence. AIDS has been called the most highly politicized disease in history and no episode was more highly politicized than the race to isolate and characterize the virus. The contenders were Robert Gallo at the National Cancer Institute with its ready access to the abundant resources of the National Institutes of Health, the Pasteur Institute group in Paris under Luc Montagnier with far more modest support, and Jay Levy in his under-equipped and meagerly staffed lab at UCSF. As a participant in the contentious race to discover the virus, Levy conveys an insider's view of the scientific and political chaos and discord of this period. In the end, Gallo's claim to be discoverer of the AIDS virus was discredited, the French group at the Pasteur Institute in Paris acknowledged as the winner, and Levy, working with his own viral isolate (AIDS-Associated Retrovirus), credited as the second to isolate the virus and the first to confirm the Pasteur group's finding.

But Levy's description of intense scientific competition does not end with this episode. He goes on to describe bitter controversy over the patent on the AIDS antibody test and the lavish royalties expected to flow from it, the multi-party race to clone and sequence the AIDS virus, and the eventual agreement to name the virus human immunodeficiency virus, the now-familiar

HIV. All this is set against Levy's long-standing battle, as he sees it, for sustained institutional support and recognition.

The Oral History Process

Three interviews were conducted in Levy's cramped and colorful office in the Cancer Research Institute at UCSF--colorful because several of his "primitives" (oil paintings) hang on the walls. With characteristic exuberance and enthusiasm, Levy recounted his story, not always adhering to standard chronology nor the detached language of science. His colorful and outgoing personality can be glimpsed in the pages of this volume. Not surprisingly, he was intent on establishing his place in AIDS history, particularly in regard to the discovery of the AIDS virus. Much more remained to be clarified at the conclusion of the interviews, but Levy felt compelled to stop recording and get on with yet another hot research topic, the role of the immune system in preventing the appearance of AIDS in long-term survivors of the disease.

Dr. Levy reviewed the transcripts twice, in a few instances taming off-the-cuff remarks. The history stands as a distinctively personal view of banner episodes in early AIDS history, as well as of less-publicized areas of virology.

The Regional Oral History Office was established in 1954 to augment through tape-recorded memoirs the Library's materials on the history of California and the West. Copies of all interviews are available for research use in The Bancroft Library and in the UCLA Department of Special Collections. The office is under the direction of Richard Cándida Smith, Director, and the administrative direction of Charles B. Faulhaber, James D. Hart Director of The Bancroft Library, University of California, Berkeley. The catalogues of the Regional Oral History Office and many online oral histories can be accessed at http://library.berkeley.edu/BANC/ROHO.

Sally Smith Hughes, Ph.D.
Historian of Science and Project Director

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
November 2001

Regional Oral History Office
Room 486 The Bancroft Library

University of California
Berkeley, California 94720

BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

Your full name JAY A. LEVY

Date of birth 11/21/38 Birthplace Wilmington, DE.

Father's full name Charles

Occupation Physician Birthplace Minsk, Russia

Mother's full name Ruth Blank

Occupation House wife Birthplace Newark, N.J

Your spouse Sharon

Occupation Interior Decorator Birthplace Philadelphia, Pa

Your children None

Where did you grow up? Wilmington, Del.

Present community San Francisco

Education

Occupation(s) Physician - Scientist

Areas of expertise Virology
Infectious Diseases
Internal Medicine

Other interests or activities French literature; Samuel Beckett; Sports (tennis, squash, golf, swimming, skiing)

Organizations in which you are active

on CV

INTERVIEW WITH JAY LEVY

I EDUCATION AND EARLY RESEARCH

[Interview 1: February 16, 1993] ##[1]

Undergraduate Research at Wesleyan University and Research in Paris

Hughes: Dr. Levy, let's start with where you were born and educated.

Levy: I was born on November 21, 1938, in Wilmington, Delaware. I am an identical twin, second born. My education was in public schools up until I went to college in 1956. I graduated from Wesleyan University in 1960 with a major in biology. I almost had a double major, because I had almost the same number of units in French studies. I became a teacher's assistant in the biology laboratory for students, so that made me put my major emphasis in biology.

At college, I also did research on the anaerobic respiration of fungi and what biochemical aspects are involved in regulation of this process. It involved very intricate biochemical measurements as well as assessing physiological parameters. Actually, the topic was not very interesting, but I had no choice since Dr. Vince Cochrane was the only professor who was free to take a student for a research project. I already knew then I wanted to do research.

Vince Cochrane had a reputation of being a tyrant and he proved to live up to that reputation with me! I finally told him off on my twenty-first birthday, when he reprimanded me for breaking a Warburg vessel during the washing after a long experiment. I announced I was treated like a robot by him and did not feel comfortable in his lab. I left to celebrate my birthday. Ironically, after that everything changed for the better and

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[1]## This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

Cochrane treated me with more respect, I thought. I even got a paper out of this research.[1] But I always say, this experience was the easiest way to turn a student off, to work under a man like that. He had a nice heart, but was a very strange person in the lab.

Fellowships at the University of Paris, Orsay, France, 1961

Levy: Then I won Fulbright and French government fellowships to go to France in 1961. I went there to take a break and do research. Unfortunately, there again, I got into a topic that wasn't the most demanding. I studied regeneration of planaria and the effects of different heavy metals on the ability of these freshwater flatworms to regenerate their heads and tails.

Hughes: Was that a pet project of one of your mentors?

Levy: When you were accepted into the fellowship program, you were assigned to a laboratory. You didn't have much choice, but I did request Paris. So I was assigned to the Laboratoire de Biologie Animale at the University of Paris in Orsay. I worked under Professor Theodore Lender, who was a former student of Etienne Wolff, one of France's most illustrious embryologists and cell biologists.

I had a twenty-minute train ride from Paris to the Orsay lab. I thus lived in Paris and commuted. It was a new experience, because I did nothing but research the whole time--no course work. The first week I got there, Lender told me to go out and find planaria. That was my first week's job. I was lucky; I found them the first day. But I also was clever; I didn't tell Lender until the end of the week, so I had a week to enjoy Paris [laughter] and do what I wanted. I love to paint, so I made sketches by the Seine. That was such a nice way of getting to know Paris.

Hughes: Are these your paintings on the wall?

Levy: Yes, these are my "primitives."

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[1]V. W. Cochrane, S. J. Berry, F. G. Simon, et al., "Spore germination and carbon metabolism in *Fusarium solani*. III. Carbohydrate respiration in relation to germination," *Plant Physiology* 1963, 38:533-541.

Medical Student, Columbia University, College of Physicians and Surgeons, 1961-1965

Levy: When I finished in Paris, I went to medical school at Columbia. I had been accepted there in 1960 but took a leave of absence to do research in Paris.

Hughes: Had medical school always been your ambition?

Levy: Well, at one point, I thought I wanted to be in international affairs. In my third year at Wesleyan, I went to see Sigmund Neumann, who was head of the Ford Foundation and professor of history at Wesleyan and a brilliant historian. Everyone idolized him. I was one of those students who looked up to the really great professors and enjoyed being around them and hearing them talk.

Neumann got to know me through one of his classes. I said to him I couldn't make up my mind between being a doctor and going into international affairs. He's the only one in my whole life who has ever told me what to do, and I don't know why he did it. He said, "You can always do international affairs as a hobby. If you like medicine, go after that degree." I love that story, because what I'm doing now is international medicine.

Moreover, when I went to Columbia in 1961, I got into the International Fellows Program, which was a new program which brought people together from all the different disciplines. I was the only representative from the medical school. They had law, art, journalism, writing--it was fantastic. I did my thesis on "The Role of International Medicine," and it went very well.

During all the summers at medical school, as you can see in my curriculum vitae,[1] I chose to do research and medicine. Sputnik had come out in '57, so there was tremendous thrust on the part of the U.S. government to put young people into research. I took advantage of that effort.

Hughes: Had you thought that rather than practice medicine as a clinician you would go into research or an academic career?

Levy: Yes. That's why I did research at Wesleyan even with that difficult professor. I wanted to teach and do research at a college--then realized I wanted a medical school career.

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[1]See the appendix to this volume.

Research in Medical School

Levy: As I mentioned, I applied and received fellowships every summer during medical school. The first summer [1962], I went to Israel and did public health in a clinic at Hebrew University. The next summer, I went to Sweden and worked at the Karolinska Institute with the famous couple, Elizabeth and Giovanni (Joe) Bertani. I worked with bacteriophages, which are viruses of bacteria. I studied ways in which one could activate these viruses out of bacteria that did not show their presence. I was very interested in the possibility that cancers were caused by viruses that inserted themselves into the DNA of a cell and set up a state of silence or hidden existence but exerted their transforming effects on the cell. The lysogenic bacteriophages that can remain silent in a host bacterium are a good model, and the Bertanis were studying these agents. I recall that at Wesleyan I had read a paper by Raymond Latarjet at the Institut Radium in Paris on this issue in 1960 in *Cancer Research*.[1] So I pursued latent viruses in relationship to cancer. (My twin brother Stuart later with Latarjet in Paris in 1962. Ironically, Luc Montagnier was in the lab as a student at the same time.)

Hughes: Was this before the topic was fashionable?

Levy: Well, I don't know if it was or wasn't fashionable. It wasn't unusual for me to talk about it, and this theory that viruses cause cancer in humans was considered at that time. In the late fifties, they knew there were various viruses that caused cancers in animal species, so I don't think it was a novel idea. But in human cancer, perhaps, the process of lysogeny provided a theory of why you couldn't find a virus. I thought it was hidden in the cell.

Research on Bacteriophage

Levy: In my second year of medical school, I also did research with Herbert Rosenkranz on these viruses of bacteria and discovered some interesting things about drugs, like hydroxyurea, that were being developed for possible anti-cancer therapy. We chose hydroxyurea because it resembled hydroxyamine that activated viruses from bacteria. To my surprise, I found that hydroxyurea

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[1]R. Latarjet, "Viruses in relation to other carcinogenic agents: Discussion of Dr. Stanley's paper," *Cancer Research* 1960, 20:807-815.

blocked the ability of the bacterium to divide, and it just got bigger and bigger.

That's one of my great examples for students of serendipity, because if you looked at the protein content of the bacteria you were studying, it went up and up, so I assumed that the bacteria were replicating like crazy. But when I plated them, I found the number had not changed over an eighteen-hour period. Under the microscope, we saw these huge bacteria. So with hydroxyurea, while we stopped the bacteria from dividing, they could still continue protein synthesis.[1] It was pretty exciting to be involved in those early phases of work on hydroxyurea--now an anticancer drug.

Research on Burkitt's Lymphoma

Levy: I continued to do research in my junior year of medical school and did some work with Harry Rose on vaccinia virus. I wanted to get into human virus systems. I was fascinated by Burkitt's lymphoma. In 1959, Denis Burkitt had described this tumor in children and thought it might be caused by a virus. I wanted to find the virus that causes that human cancer. So I did what I advise my students to do: I listened to one of Parkinson's laws, which is energy expended in one direction can come back in another direction. I used to send out letters immediately when I returned from one summer trip, in order to find a position for another summer. I wanted to go to Africa. The only possibility was a Louisiana State University Medical Fellowship, but they were all given for studies in Latin America. I wrote the organization anyway and told them why they should pick me to go to Africa to do research in tropical medicine.

Hughes: That was their emphasis?

Levy: Yes, their emphasis was tropical medicine. I wanted to study Burkitt's lymphoma. I was lucky. They gave the fellowship to me. Well, it had wonderful ramifications. I worked with Denis Burkitt in surgery and with Thomas Bell at the East African Virus Research Institute in Entebbe, Uganda. In fact, it was the first time I worked with animal viruses. For this work, I needed normal monkey kidney cells. Therefore, I had to sacrifice a rhesus monkey, take

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[1]H. S. Rosenkranz, J. A. Levy, "Hydroxyurea: A specific inhibitor of deoxyribonucleic acid synthesis," *Biochimica et Biophysica Acta* 1965, 96:181-183.

out the kidneys, put the kidneys in culture, and then look in the Burkitt tumor cells for viruses that could cause Burkitt's lymphoma. Thomas Bell had found a virus called reovirus type 3 in a tumor, and I was there to see if he was right about this virus's involvement in Burkitt's lymphoma.

That research led me into working with Alexander Haddow, who was head of the institute, who I think had discovered more viruses than anyone I know by just grinding up mosquitoes. These were arboviruses. In some of my studies, I actually climbed trees to catch mosquitoes.

Hughes: This was for research on Burkitt's lymphoma?

Levy: Yes, in part. Arboviruses are transferred by mosquitoes.

We thought maybe the virus that causes Burkitt's was transmitted by a mosquito, because the distribution of the cases mirrors the distribution of mosquitoes in Uganda. We were interested in trying to find reovirus type 3 in mosquitoes. The experience was unbelievable: I climbed a tree with an African counterpart, and we were asked to expose our legs, because Haddow and Bell were only interested in the *Aedes aegypti* mosquito, which only bites the lower legs. We were to be paid one shilling a mosquito. Each of us collected mosquitoes from the other. My African counterpart needed the money more than I did, so he always let the mosquito bite him for me to collect it. I found that I always hit and killed the mosquito on me when it bit me--and if it wasn't living, it wasn't any good for the studies. So he lost a little bit of money with me. But it was lots of fun and a new experience.

Hughes: What did you accomplish?

Levy: Not much with the mosquitoes, although we tried to find a virus in them using the monkey kidney cells. I collected sera from patients with Burkitt's lymphoma, and, toward another objective, sera from normal children. I traveled all over Uganda looking at Burkitt's lymphoma cases, but I also did some work with malaria transfer through placentas, and I did work in the country with nutrition. It was an unbelievable experience--tropical medicine and research, combined with living out, taking care of people in the outer parts of Africa, working in clinics and so forth.

Research on Reovirus

Levy: I came back to my fourth year at Columbia, and because of my interest in reovirus type 3, Ed Curnen, who was head of pediatrics and a virologist, offered me space in his lab to work in my spare time. So actually I was able to do research in my second, third, and fourth years of medical school.

In that experience, I met Eru Tanabe who was a Japanese technician who ran the diagnostic virology lab for Curnen. She became my teacher and an unbelievable friend who taught me everything that I know about various ways of finding viruses, including hemagglutination assays, hemadsorption procedures--everything. I am very grateful. She and I wanted to prove that anti-reovirus type 3 antibodies were increased in Burkitt cases versus normal controls.[1] That meant that we had to run our hemagglutination assays around the clock, so we had alarm clocks, and we'd sleep in the lab, and we'd wake each other to change shifts. Thus we would do the assays alternately. We had to finish the study, so when I went to Philadelphia the next year [1965], Eru came for a visit, and we did the alarm clock routine again and completed the work. My training with Eru was a wonderful introduction to the varied fields of virology.

We proved that we were right. There were more antibodies to reovirus type 3 in Burkitt cases than in the controls. Then we learned what you have to learn in research, that controls must be well selected. The ones I used came from outside the hospital. If we had gotten our controls from the hospital, we would have seen no difference, because reovirus type 3 was circulating around the hospitals! [laughs]

So that introduction to virologic questions was very interesting. I got a lot of experience, and Burkitt's lymphoma got a lot of my attention. And I was right there, at the very beginning. Sixty-four, I was in Africa, and '64 the Epstein-Barr-Achong paper came out describing herpes virus-like particles in Burkitt's lymphoma cells.

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[1]J. A. Levy, E. Tanabe, E. C. Curnen, "Occurrence of reovirus antibodies in healthy African children and in children with Burkitt's lymphoma," *Cancer* 1968, 21:53-57.

Internship, 1965-1966, and Residency in Medicine, 1966-1967, University of Pennsylvania

Research at the Wistar Institute

Levy: When I finished at Columbia, I went to the University of Pennsylvania for my internship and residency in medicine. When I got to the University of Pennsylvania, I didn't want to stop doing research, so I went to the Wistar Institute, which is across the street from the medical school and hospital. I was doing an internship and residency, two years there, and I had gotten accepted at the NIH [National Institutes of Health] to do research as a public health officer instead of going to Vietnam. I was to work under Robert Huebner, one of the country's leading virologists at the time. And that, of course, was a great way of putting in military service.

However, in that first year at Penn [1965], during my physical examination at the military unit for induction into the army or Public Health Service, I stupidly showed the physician that my left foot was deformed because I had osteomyelitis when I was a child. Well, that then opened up a whole can of worms, and they said they couldn't accept me in the Public Health Service because they didn't want anyone with a previous history of osteomyelitis, because it might flare up again, and the Public Health Service didn't want to pay the cost of treatment. Of course, almost immediately the army wrote that it was inducting me into Vietnam. So this was just a horrible period for me. I wanted so much to go to NIH.

The University of Pennsylvania was fantastic. It built a wonderful case for me on why the Public Health Service shouldn't worry about me. I agreed to sign all sorts of waivers, although the Public Health Service said there was no such thing as a waiver. The person who really did it for me was the former surgeon general, Luther Terry, who was the well-known advocate against smoking. Luther Terry became vice president of the University of Pennsylvania, and I went to see him. He had all the connections, and with the help of several department heads at Penn, he got me into the Public Health Service, and I was able to go to NIH.

So with that assured, I went to Wistar, and told Hilary Koprowski, the director, I wanted to continue my work with reovirus type 3 and Burkitt's. He said he didn't want to have a new virus in his institute, and that I should talk to Vittorio Defendi and learn about lymphocytes. So I went to see Dr.

Defendi, who was a well-known immunologist/virologist. He agreed that I could work with him on lymphocytes. All these things have played beautifully into my career, but they were decided by crazy quirks of fate. I'm very much a fatalist.

My medical colleagues at the University of Pennsylvania used to call me the Wistar fellow, because I had a beeper and it was only fifteen seconds from the Wistar Institute down the steps, across the street, into the emergency room or to the ward. So it wasn't any different than being on call in your dorm. So I just did research at Wistar when I had some free time and used my beeper.

That first week after speaking to Koprowski, I ran into Angus Graham, whom my brother had known at Penn. I have a twin brother, Stuart, who was a medical student at Penn and did research in microbiology, and then moved up to New York for his internship. We kind of exchanged places. He went to Mt. Sinai [Hospital], and actually inherited some of my patients who were at Columbia, because there was a connection between Mt. Sinai and Columbia. And I went to Penn and inherited some of his patients.

I ran into Angus Graham at the Wistar Institute and I said, "What are you working on?" He said, "Well, my usual subject: reoviruses." I said, "Reoviruses? I didn't think reoviruses were in this institute." He said, "They sure are, on the third floor." [laughing] That's how I realized that Hilary Koprowski just didn't want me to work with Angus Graham, and he assigned me to Vittorio Defendi. When I told Hilary about it, he laughed. He said, "Why do you want to work with animal viruses? You should get into human systems." Sounds providential now.

Hughes: Did you switch projects?

Levy: I stayed in lymphocytes and was among the first to describe transformed B lymphocyte cell lines. They were first made in the early sixties, and we wrote one of the first papers.[1] We weren't the first. The lymphocytes were transformed because they had Epstein-Barr virus. That finding was ironic since I had begun work on that virus with the Henles.

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[1]J. A. Levy, M. Virolainen, V. Defendi, "Human lymphoblastoid lines from lymph node and spleen," *Cancer* 1968, 22:517-524.

Research with the Henles on Burkitt's Lymphoma

Levy: While I was in the emergency room at Penn the first few months, I got a phone call from Werner Henle whom I wanted to meet. Now, Werner Henle was the thesis advisor of my sister, Ellen [Levy], who's also in research and now a doctor. She was doing research on interferon and was working with Kurt Paucher in Werner Henle's laboratory unit. Henle and his wife, Gertrude (Brigitta), were among the world's great virologists.

Anyway, Werner Henle called, and he said that he was giving a lecture on Burkitt's lymphoma at Columbia and that he had been looking all over for sera from children with Burkitt's lymphoma versus children that didn't have Burkitt's. So one of the doctors in the pediatrics department at Columbia, Hatie Alexander, said, "Well, we just had a student who came back from Africa, and he has all these sera." "Who is it?" "Jay Levy." "Where is he?" "He's at the University of Pennsylvania." That's all part of Brigitta Henle's "blue flower story." The blue flower story is about the man who looks all over the world for this famous blue flower, comes back to his house twenty years later, goes to the back garden, and there it is, growing.

When the Henles were looking for the virus of Burkitt's lymphoma, their technician got infectious mono[nucleosis], and they had the clever insight to look to see if her white cells might be established in culture, and they found Epstein-Barr virus in this infectious mono case. They had their African sera through my connection to Ellen.

I went down to Children's Hospital, and the Henles said, "We're going to teach you immunofluorescent testing, and if you like you can do this research in the late evenings and over the weekends." So I worked in the evenings and on weekends at Children's Hospital way down in a really miserable part of Philadelphia, Bainbridge Avenue, and I handled as well a very heavy clinical program as an intern and resident.

But I was able to pull it off, and I had some nice publications with the Henles. In fact, the first one that we published,[1] showing differences in antibodies to the Epstein-Barr agent, (we didn't know what it was then) got selected in *JAMA* for an editorial. And I'll never forget it, because Mrs. Henle called

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[1]J. A. Levy, G. Henle, "Indirect immunofluorescence tests with sera from African children and cultured Burkitt's lymphoma cells," *Journal of Bacteriology* 1966, 92:275-276.

me in and said, "Jay, you've made it. They actually call you a scientist in this editorial." [laughter] And there it was, "Levy and Henle, scientists at the--" Of course, they didn't know who the hell I was.

I worked on the reovirus problem with the Henles as well, and actually showed that reovirus could affect EBV [Epstein-Barr virus] replication and came up with a good publication in *Nature*.[1] And with Vittorio Defendi, I worked on B cell lymphomas, and then the two subjects came together, because EBV [Epstein-Barr virus] is involved in both. Very ironic.

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[1]J. A. Levy, G. Henle, W. Henle, et al., "Effect of reovirus type 3 on cultured Burkitt's lymphoma tumor cells," *Nature* 1968, 220:607-608.

II PRE-AIDS RESEARCH

Staff Associate, National Cancer Institute, National Institutes of Health, 1967-1970

Robert J. Huebner

Levy: After Penn, I went to NIH and I was told by Robert Huebner, who was now my mentor, that I was to throw away the work with Epstein-Barr virus--that was in '67--that I was to work on RNA tumor viruses.

Hughes: Why did he say that?

Levy: Because he didn't think much of herpes viruses. Actually, he didn't want me to work on RNA tumor viruses right away; he advised me to work on the adenoviruses, which had been found in the early sixties to produce tumors in hamsters by John Trentin. Huebner thought maybe these viruses would be involved in human cancers, so they needed reagents to test the hypothesis. They wanted me to grow up adenoviruses and polyoma viruses.

Huebner was one of those enormous giants in virology, made all sorts of discoveries, and of course it hits me hard when no one knows him anymore. Unfortunately, he now has Alzheimer's and is in an institution. But brilliant, and I'll always remember his energy.

Hughes: As I remember, he revitalized the cancer virus story, which had been a theme that had waxed and waned since Peyton Rous's work around 1912.

Levy: Oh, yes. Huebner was one of the key people to convince Nixon to set up the cancer virus program.

Huebner farmed me out--he was criticized later for having all these contracts at different companies--to this company in

Rockville [Maryland] where they had been working for two years to grow up lots of adenovirus and to express viral proteins. Then the protein can be concentrated and used for detection assays. One can look for antibodies to specific viral proteins in cancer patients. They weren't able to accomplish this objective, however, with the adenoviruses and the polyoma viruses.

Huebner said, "You're to work on this problem. You're not to work on the herpes viruses." Well, I hadn't finished up my last experiments on some of the B cell lines. I tell this story because it was so amusing. He'd come in to visit me and he'd go to the incubator and he'd say, "What's this? Are they the lymphoma cells? Throw them out." I did, but I always had another incubator with the cells growing. Finally, I finished up the research. He was right. That last paper on established B cell lines infected by the herpes virus Epstein-Barr wasn't all that important, but I had to complete the work.

For this new challenge with adenovirus I was able to draw from my work with hydroxyurea at Columbia. I said, "Look. If hydroxyurea makes a bacterium produce more protein but not divide, maybe hydroxyurea will cause the virus to make more and more protein but not destroy the cell, because the virus can't replicate." And it worked.

But apparently I was too young to be given credit for that discovery. The people at the company who had been working on it for a long time became jealous. They started to bad-mouth me. I'm not really sure what they said, but I know that they said enough that Huebner took me off the project completely. I fortunately was still able to publish the paper that showed the effect of hydroxyurea. One man even poisoned my animals. So all the things you hear about what can go on in labs can unfortunately be correct at times. So I'd say that was the second trauma in my life, the first being my almost going to Vietnam and not NIH.

Now I'm at NIH with Robert Huebner, and now I'm in his bad favor and I don't know how to tell him otherwise, and I see this all as a conspiracy against me, alone and young. I did not know what to do. Fortunately I could go see Mike Oxman, who had befriended me--a nice young fellow working with Wallace Rowe. Now, Wally Rowe was one of the great virologists working with Huebner. He discovered adenovirus and cytomegalovirus. I really wanted to work with Rowe, not be off the NIH campus. But you had to go where your mentor wanted you. Janet Hartley was also there with Rowe, and I admired them both. Mike talked to Rowe, and Rowe spoke to Huebner--that was lucky.

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Levy: But I was soon called into Huebner's office, and I was given what everyone later told me was the "annihilation" speech, which led me to tears. Huebner said: Who was I to talk against these people I was working with? I was a young person, only been at NIH a few months; how did I know what was going on?

Hughes: So this was a theme with Huebner--if the speech had a name, it had happened before.

Levy: Yes, that had happened to other young people who came in.

The most amazing thing about Huebner is after the whole speech is over and I'm absolutely distressed, he then turns to me, smiles, and says, "Now, let's go to dinner." I said, "I can't." I couldn't! And I left.

Well, we became good friends after that. Huebner assigned me to Wally Rowe. I had glorious times with Wally Rowe and Janet Hartley. I'll never forget an early experience. Huebner had a mouse that had arrived from Miriam Finkel that was infected with a virus that causes bone tumors. Rowe said, "Jay, this is your project. You're to get the virus out, and you're to figure out why it does what it does."

I worked alone, lots of hours, but I had a wonderful time in Washington. I was a bachelor; my brother Stuart was there at the same time, and we lived together and often had parties for our friends. We had a cute little carriage house in Georgetown--three of the most marvelous years. I didn't make much money, but it was more money than I'd ever had in my life. The research went well.

Discovery of Xenotropic Viruses

Levy: I didn't have many publications until the third (last) year when things really hit. It was at NIH that I discovered the xenotropic viruses, and that was again serendipity, like the Henles finding EBV. There was a mouse called the New Zealand Black [NZB] mouse, which I always say is the most published mouse in history. It gets autoimmune disease and cancer, and I was interested in these diseases. Many had described virus particles in these mice, but no one could get the virus out. They all said the virus was defective.

Here I drew from my first independent project with Wally, Jan, and Huebner. I had been working with the Miriam Finkel sarcoma virus, and other viruses, and I realized that transforming

genes in tumors can be rescued by helper viruses, by other RNA viruses that may induce leukemia or may not. If you mix the cells together under the right conditions, you'll rescue the sarcoma virus genome in the envelope coat of the helper virus. And then, you can look for that transforming virus by cell transformation. In other words, you take the culture fluid from mixed cells (the transformed and the virus-producing) and add it to a new flat monolayer of cells. If the sarcoma virus is rescued, you see foci of transformation in culture. Well, I said, maybe the NZB mice have such a helper virus; it isn't an infectious virion, but perhaps it will rescue a sarcoma virus genome. So I can at least show some biologic effect of the NZB virus.

Hughes: This system had been previously worked out?

Levy: This system had been worked out by Huebner, Rowe, and Hartley for the rescue of sarcoma virus genomes from cells.

Now another story came into play: Huebner, Rowe, and Hartley (I called them the triumvirate) didn't know why you needed two particles to get cell transformation in mouse embryo cells or chicken embryo cells plated in a dish. I worked with a friend and colleague named Robertson Parkman, who was also one of the young public health appointees, non-Vietnam group. It was a marvelous group. It was highly competitive to get to NIH; if you were lucky enough to get there, you met some wonderful future productive scientists.

Robbie was interested in transformation of rat cells. In the midst of working with him, I discovered that in mouse embryo cells you need two particles for transformation, but in rat cells you only needed one particle.[1] And it became clear that the reason you needed two particles in mouse embryo cells is that the transformed cell died, and you had to constantly produce virus progeny to recruit cells into a transformed focus big enough to see. In rat cells, the transformed cell didn't die; the rat cell grew autonomously into a transformed focus.

So I said, "This is a great system when I go to find out if this NZB mouse virus can rescue a sarcoma virus genome from a tumor cell containing that gene. I'll put the fluid from the co-cultured cells into mouse embryo cells to see if the NZB-rescued virus replicates. And if I put the fluid into rat cells, at least I'll know if the NZB virus is biologically active and can rescue the sarcoma virus." So if the NZB was a defective virus, it

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[1]R. Parkman, J. A. Levy, R. C. Ting, "Murine sarcoma virus: The question of defectiveness," *Science* 1970, 170:326-327.

wouldn't grow, and I wouldn't see anything in the mouse cells but I would in rat cells if I just got a rescue of the sarcoma virus genome. Foci of cell transformation would appear. Well, it happened unbelievably: I got foci of transformation in rat cells, and I didn't get anything in the mouse cells.

I went to see Wally Rowe, and he didn't think I filtered the culture fluid correctly, so I put lots of bacteria in the co-culture fluid and then passed it through the filter. Sure enough, the bacteria were filtered out, and I got transformation in the rat cells. He still didn't believe it, and he had Ted Pincus, who was in the lab as well, a good friend of mine, do the experiment independently. So Ted did it independently with my coaching. Then Rowe believed the observation, and he allowed us to publish it on our own.[1] So that is the Levy-Pinkus story on xenotropic viruses, but at the time we called the virus the NZB virus. I couldn't really get good replication of the NZB virus, but I knew this virus would not infect mouse cells even though it came from a mouse. I thought it was unique for NZB.

Second-year Resident in Medicine, University of California, San Francisco [UCSF], 1970-1971

Levy: When I left NIH [in 1970], I came to San Francisco to complete my residency training. During that year I helped a bit in Tim Crocker's lab on chemical transformation of cells.

Hughes: How had you originally gotten to UC as a second-year resident?

Levy: John Mills, who was a friend of mine, worked with Bob Chanock at NIH on influenza virus. He said, "Jay, you ought to go out to California to do your last year of clinical training as a second-year resident--just for a lark." [Lloyd Hollingsworth] Holly Smith, the head of the medicine department, accepted me. There was a group here headed by Tim Crocker doing research on chemical carcinogenesis, chemical transformation of human cells, and they had money from the Council for Tobacco Research, which is a research organization funded by tobacco companies.

The council asked if I'd be willing to be a consultant to them on a grant on cell transformation. Well, that was a great

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[1]J. A. Levy, T. Pincus, "Demonstration of biological activity of a murine leukemia virus in New Zealand Black mice," *Science* 1970, 170:326-327.

opportunity. I started asking questions about viruses as co-carcinogens with chemicals. So I had that wonderful opportunity to interact with basic research at the level of co-carcinogenesis while I was doing my second-year residency.

Visiting Scientist, France, 1971-1972

Hôpital St. Louis, Paris

Levy: Then in May [1971] I went off to France on an invitation to teach retrovirus techniques to Michel Boiron's group in Paris. Interestingly, when I got to the Hôpital St. Louis, they were looking at transformation of human cells with a mouse retrovirus.

Hughes: And they didn't know any retrovirology?

Levy: They knew some, but they wanted me to do special assays with them. Well, I began working there, and in the midst of looking at transformation of human cells, I began thinking about the NZB virus and wondering whether it could infect human cells. But I didn't do anything with this idea for a year, and no one took up the NZB story. In fact, I was not beloved by many in the scientific community, especially Frank Dixon, who worked as well on the NZB mouse and said, "Levy has a rat virus."

Hughes: Which was a retrovirus?

Levy: Yes, they're all retroviruses, but that was in 1970 when they were known as RNA tumor viruses.

Hughes: Did people believe that retroviruses could not infect human cells?

Levy: Yes.

Hughes: But you didn't believe that?

Levy: I wasn't buying into any of the dogmas.

Collaboration with Claude Jasmin, Mirek Hill, and Jana Hillova, Hôpital Paul Brouse, Villejuif

Levy: After six months with Boiron in which I studied transformation of human cells by an unusual mouse virus (because we incorrectly thought it was unique), I then went to work with George Mathé at the Cancer Institute in Villejuif, which is a very well-known research center. There, I worked on transformation of cells as well. The lab I went into was Claude Jasmin's, who's a very close friend and France's leading oncologist now. We were peers, and Claude turned his lab over to me and asked if I would direct it. He had tuberculosis and had to leave for six months for the mountains. So I directed his lab and worked on Friend leukemia [virus], which is a mouse leukemia virus. Most of my studies, however, dealt with inhibitors of the mouse virus and not so much with Friend virus.

During this time, I began trying to transform cells with DNA. It was a brand-new technique that had been discovered by the couple, Mirek Hill and Jana Hillova from Czechoslovakia. I became friends of theirs. They extracted DNA from cells that were infected with the avian RNA tumor virus, Rous sarcoma virus, which is a retrovirus--that is, it makes a DNA copy of itself in the cells and then integrates into the cell chromosomes. They showed that you could take that integrated DNA from the cell and put it into another cell through transformation and you got back the whole virus again. In those days, that was unbelievable. *Nature* turned their paper down twice. I helped them to rewrite it. It was just that the editors of *Nature* didn't believe it.

Hughes: What was the basis of that disbelief?

Levy: Dogma was if you took DNA and you put it into cells, the virus couldn't be alive, couldn't regenerate itself. How did it happen? You need an infectious virus. Here, you just put the DNA of the virus in, and out came the entire virus. Today, it seems like, "Of course it works." In those days, "no." Today we are using pure DNA for vaccines, and that rather recent discovery was not believed at first.

Anyway, I wanted to do the same procedure in a murine system, which was more complicated. But the difference in the mouse system was, we didn't have a competent virus, a transforming virus. We had the transforming gene, but then we couldn't get the virus to replicate out. So it was very tough to see if you had transferred the viral DNA.

This approach was based on transfer of a virus via DNA into a recipient cell. If replication of the virus took place, it was easy to find since it would spread through the culture. If it transformed the cells, you could detect it. This procedure is the beginning of oncogene research that was pioneered by Bob Weinberg. He put tumor cell DNA into mouse 3T3 cells and found transformation. I started working on it in 1971 because I thought it was an exciting observation and wanted to prove it in the mouse system, but I couldn't.

The University of California, San Francisco

Assistant Professor of Medicine, 1972-1977

Levy: When I came back from France in 1972, I was given a position at UCSF in the Cancer Research Institute by David Wood, who was a great mentor. He's now eighty-eight years old. He was then the head of the institute. Sid Salmon, who's a very well-known oncologist working with tumor cell resistance, and Marty Klein, who is a hematologist and was co-director of the institute, realized they needed a virologist in the cancer institute, and they asked me if I was interested.

So in 1971 during my residency Dr. Wood called me in, offered me this lab space, and offered to renovate it for me. I said, "I'll be back in two months." In two months, he wrote me, "Stay in France, because it's not ready yet." And then two months became a year, and that was the most unbelievable year I've ever had. We already discussed it.

Research on Endogenous Viruses

Levy: Now in 1972 when I came back to UCSF after that year in France, my goal was to try to figure out why the DNA transformation wasn't working better. Mistakenly, I was trying to save the long pieces of DNA, to really make the method work better than what the Hills had done. The Hills had more primitive approaches, and they would just grind the viral DNA up and bring it back and forth through needles. When I did it, I made very small DNA.

Hughes: Why did you get short lengths of DNA?

Levy: I was extracting the DNA, purifying the DNA, and then putting it through a small needle, and this breaks the DNA up automatically.

Hughes: So you didn't use restriction enzymes.

Levy: No, I didn't. When I came back from France, I rejoined my interactions with Mike Bishop's group with Harold Varmus. We were good friends. We'd interact a lot when I just arrived at UCSF. The association began in 1970, before I had my own lab, when I was just a resident. Huebner knew them, and I think when one of Huebner's fellows came to UCSF, they invited me to join their group and to be in the journal clubs and meet their fellows. So for a long period of time, I had tremendous interaction with Mike's and Harold's groups. I heard lots of stories about the discovery of oncogenes, from not only Mike but also from Dominique Stehelin, who was the one who did much of the research and was the first author on the paper, though it was Mike and Harold's idea.

In any case, Harold also wanted to get the DNA system working in his lab and agreed to help by measuring the DNA so we could use the right lengths. It was annoying that he had a French woman working on it as well but others said that was Harold. I didn't really appreciate that competition. But Harold did work with us, and so he's a co-author on the paper, which was the first paper to confirm the Hill and Hillova research.[1] But we were never cited much, because Howard Temin did the same thing, published it in a Cold Spring Harbor journal, and for some reason everyone referred to that paper. Our paper in *Virology* was the first confirmation of the Hill paper and showed that you needed low molecular weight DNA to get it to work.

The person who was the first author in the Temin paper was a researcher named Geoff Cooper who then went on to do a lot of this work in oncogenes. So again our work really was part of that trend to look for transforming genes. Actually, I have never thought about that until our discussion here.

Further Research on Xenotropic Viruses

Levy: So anyway, when I came back in 1972 and I opened my lab, I had a little group. Besides the DNA work, I started revitalizing the

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[1]J. A. Levy, P. M. Kazan, H. E. Varmus, "The importance of DNA size for successful transfection of chicken embryo fibroblasts," *Virology* 1974, 61:297-302.

NZB story. It's wonderful how things happen--we were trying to figure out why the NZB mouse has this virus, which was called the NZB virus. And Beatrice Mintz, who is a very well-known scientist, had formed what we call tetraparental mice. They have four parents. She took eggs of two couples and just pelleted them together and put them into a foster mother. By that procedure, she got offspring that had a certain percentage of NZB and a certain percentage of C57 Black in their genetic background.

Norman Talal, who was head of immunology at the Veterans Hospital here, and who was a friend of mine at NIH, said, "Jay, I have these animals, and you can do some work with them." I said, "I would like to see how easily we can get virus out of the tetraparental mice: if there's only 10 percent NZB or only 5 percent and so forth."

So we got tissue from these animals, and did the sarcoma rescue and found the NZB virus again. And in the midst of it, I said, "Let's see if we can get it to go into human cells." And sure enough, we got transformation of human cells with the rescued virus. What was even better is that I got virus replicating in the human cells. It doesn't replicate very well in the rat cell so I couldn't get much virus progeny. So now I had a replicating NZB agent.

In the midst of doing all this work, I found that there was one animal that gave me virus, and it wasn't supposed to have any NZB genes in it. It was supposed to be completely C57 Black. So I got another C57 Black mouse, and sure enough, I got virus out of that one. This was another serendipitous discovery.

Let me tell you about NZB mice. If I had considered better their origin I might not have been so surprised about the C57 Black observation. Marianne Bielschovsky derived the NZB mice from a wild mouse colony at her institute in New Zealand. I visited her in New Zealand before she died. My biggest regret is that she willed me all her books, but I never received them from her lab. She became a good friend. You know that movie, "Harold and Maude"? That's what we were. She and I bummed around together all over Dunedin, and she showed me the places. It was really cute. Her husband Franz had died and in many ways I could see she enjoyed visitors.

She told me how she made these mice. She just had random mice that had been collected in New Zealand (you couldn't import any into New Zealand), and whatever was left, she used. Eventually out comes this mouse with an autoimmune disease.

Well, in retrospect that meant the NZB virus had to come from some wild mouse. So I should have thought to myself, "There's nothing unique about NZB. Other mice strains must have this agent." But I didn't take that leap. I was too set in looking at NZB. But it didn't matter, because in the midst of doing the work, I found C57 Black mice had this virus. And I said, Well, if they have them, what about the NIH Swiss? That's a mouse that was said to have no RNA tumor virus at all, according to the dogma. Then, I got the virus out of NIH Swiss. That was a big step.

About this time, Wally Rowe calls me on the phone and he says, "Jay, you know the NZB virus that you isolated?" (Wally was always very critical; I always thought I had to prove myself to Wally Rowe.) I wasn't sure what he would say. "People are now doing work on NZB here, and there are rumors that George Todaro is finding the NZB virus grows in rabbit cells."

I said, "Wally, I'm sitting on a big discovery. Now I have the virus in C57 Black and NIH Swiss mice." He said, "Well, you better write this up." Then I said, "Well, not only do we know it grows in human cells and rabbit cells and all these other cell types as well, but it does not grow in mouse cells. It's probably a universal virus, and must be inherited since it cannot infect the mouse." He encouraged me very much, and I feel that was fate at my door.

So I wrote it up immediately, and we didn't know what to name the virus.[1] Riding back in the car from a Gordon conference the summer of 1973, I was talking it out with my brother, and we were trying to figure out a name. Since I love Greece and I love Greek people--I think I was Greek in one past lifetime--I drew from the Greek xenos for "foreign" and tropic for "turning," and I said, "Let's call them xenotropic viruses." And we did, and the name stuck. It's a virus that comes out of a species and does not go back into the same species; it goes into foreign species.

Then I chose to name the virus that comes out of one species and likes to go back into the same species. We called them ecotropic viruses, which comes from the Greek word oikos, home, as in ecosystem, ecology. So I had the pleasure of naming the two major species of retroviruses in animals. Then Suraya Rasheed and Murray Gardner in southern California and Janet and Wally at NIH discovered a virus in a wild mouse that will grow both in mouse cells and in foreign cells. Wally asked me to name it. So I took

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[1]J. A. Levy, "Xenotropic viruses: Murine leukemia viruses associated with NIH Swiss, NZB, and other mouse strains," *Science* 1973, 182:1152-1153.

the Greek amphos, for both, like amphibians, and called them amphotropic viruses. So those are the three virus groups. And they all are different; they have different envelope coats and so forth.

Well, that now put my laboratory on the map. I was here a year, and we had xenotropic viruses, and there was tremendous excitement. There was newspaper coverage but I never capitalized on it. I never said, "Now I should do this to advance our reputation." I just continued to work in my lab on it. Someone else would have really publicized it and maybe assured themselves of better security than what I had.

Hughes: Why didn't you?

Levy: Not part of my nature, and it was not how I was trained. Scientists stayed in their lab; they didn't go after publicity. I was embarrassed by the publicity. Not that I didn't like it, but I was embarrassed by it.

The paper was published December 2, 1973, in *Science*. I was visiting my sister in the Dominican Republic. I picked up the newspaper, and on the front page it said in Spanish, "New Discovery on Viruses that Has an Application to Human Cancer." I said to my sister, "Once again, someone claiming they have the cure for cancer." [laughing] Then I discovered it was my article they were discussing! It was picked up by the newspaper reporter David Perlman and written up. I wasn't even around! They even interviewed the [UCSF medical school] dean, Julius Krevans, who really was nice but never that supportive of me. Yet here he was on the TV talking about this work. I was then thirty-five years old.

I grew up with the Rowes and the Henles and the Huebners--well, Huebner was a little more flamboyant--who said as a scientist, you do the work, and you allow people to read about it, and you're not the one to talk to newspapers and make big publicity out of it. In fact, when the newspaper article came out on NZB, Wally Rowe wanted to know how it came about, and I didn't know if he was upset or not. I said it was by chance; I had nothing to do with it. Well, he had heard it on the radio, NPR [National Public Radio], I think.

Hughes: Why wasn't Krevans supportive of you?

Levy: I have no idea.

Hughes: It was nothing to do with science?

Levy: Well, yes. UCSF had Mike Bishop and Harold Varmus working on avian retroviruses. They didn't need someone in mouse retroviruses. This campus isn't big enough. So I was an extra. Huebner and the Henles used to argue that Mike and Harold did molecular studies and were not looking at the biology and pathogenesis, but it didn't matter to this school. They had one retrovirus group.

Research on Xenotropic Viruses in Humans

Levy: I then plunged into looking for characteristics of these xenotropic viruses, and at the same time got a grant, through the help of Bob Huebner, to look for xenotropic viruses in human tissues. After all, that was what we really wanted to see: there must be a human xenotropic virus. People thought maybe that's why you can't get the human cancer virus, because when you try to grow it in human cells, it won't grow; you have to put it animal cells. So several groups embarked on taking extracts of tumors and putting them into all sorts of different animal cells.

We went after the human placenta for this virus, because Sy Kalter had shown that there were virus-like particles in human placentas. We thought that since NZB mice had these viruses in placentas, they could be expressed in humans. We should look at tissues from autoimmune patients for a human virus. And that's another dramatic time.

I was looking for a placenta from a woman with lupus [erythematosus], and one came in almost immediately. I remember going over to the VA Hospital, coming back, and actually passing Julie Krevans on the steps. Julie, very friendly and all, said, "What's going on?" I said, "Julie, this is my attempt to find the xenotropic virus in humans. I've got this lupus placenta." I have no idea what he thought.

One of the things I did was to send some of the placenta tissue down to Ellen Dirksen, who had been in the Cancer Research Institute at UCSF but left after they didn't appreciate her work. She did some very nice studies on epithelial cells in the lung and in the trachea and was a superb electron microscopist. Anyway, she found the virus-like particles in human placentas and we

published the confirmation of Kalter's work,[1] but she found them in normal placentas as well as in lupus placentas. Now we considered these agents possible viruses of normal development.

To isolate a human virus I had what I called zooion lines--obviously from the word "zoo". We took various cell lines from all different animals. Since I was working in xenotropic viruses, our liquid nitrogen freezer was literally a zoo. You would walk into this lab--I wish I had pictures of it--and we'd have fish cultures growing on top of the incubator, because they grew at 20 degrees [centigrade]. We had some animal cell cultures inside at 37 degrees, and then we had mosquito cultures on the shelf, because they did better at 17 degrees. And all of them were being inoculated with xenotropic viruses.

Some researchers had raised the issue that xenotropic viruses might bring harm to humans if infected, but we were able to prove that it would be very difficult to get humans infected, especially since human blood lyses the virus. So we weren't put under the pressure to have special safety precautions that you now have with HIV. Nevertheless, we worked with the human placentas and, when possible, with human fetuses in a small eighty-square-foot room renovated for me from a former hot room used at the Cancer Research Institute.

Our lab was flourishing in the mid-seventies. I was always fighting for space, and Julie Krevans was the one who handled it. He gave me space, and then the next person who saw him, he gave it to him. So we always said you had to see Julie Krevans last in order to make sure you got it. I remember we had a chair outside the lab in the corridor, and we would have people sitting on the chair waiting to come into the lab to use the hood--we only had one hood--and it was very, very hot. The university didn't believe in air conditioning. They finally allowed us to get an air conditioner.

By the way, the paint in the lab was brand-new. In 1970 when I first built this lab, I didn't want to have it painted in yellow and green, which were the institutional colors. When I called color experts to find out what are the colors that are conducive for work, what do you think they said? Yellow and green. And I said, "Well, I can't stand them." So we got chartreuse and violet and sky blue, and made a very exciting lab. And then after we did it, other labs came in to see it, and they

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[1]E. R. Dirksen, J. A. Levy, "Virus-like particles in placentas from normal individuals and patients with systemic lupus erthematosus," *Journal of the National Cancer Institute* 1977, 59:1187-1192.

all started doing it; they changed the face of labs in the university. Well, we were really the first, I think, and we needed special permission.

Then Julie Krevans gave me the room across the hall to do work and we expanded into that space. I had a lot of money to work, and we were going after the human xenotropic virus. We were also trying to insert the xenotropic virus gene into ducks; we were inoculating duck eggs. We went up to Petaluma Farms and got duck eggs, brought them back, hatched them. We kept the ducks on the roof of the animal tower, and I had a woman technician, Oksana, to care for them. We wanted the ducks to lay eggs and have the eggs fertilized so we could put the xenotropic virus gene into the fertilized egg. I'm loaded with funny stories about how you try to get a duck to fertilize the egg. This was a very exciting and fun period.

I was working with a xenotropic virus of mice and hoped that it would have some relevance to humans, but it didn't look like it was the cause of autoimmunity or cancer. We began to derive a theory that these were viruses of normal development, and that they were needed in the placenta. And that was a way-out idea. We published a few papers on that theory, and actually talked a lot on it. And I think people just said, "Ah, relatively young, naive guy, just ideas--."

Hughes: Your theory was unpopular because people thought all viruses were pathogens?

Levy: They thought all viruses are pathogenic. They didn't care about the fact that you have bacteria in your gut to help you. To think that a virus might be helpful was unheard of.

In pursuing this interest I conducted work with JoAnn Leong up in Oregon in the mid-seventies. She had been a postdoc with me for six months and then went to Oregon to begin her career. We have remained close colleagues and friends. Thus I would fly up

to Oregon every other month to work on placentas. Jay Nelson, who's now a wonderful molecular biologist, was a student with JoAnn. In a way, he was with both of us. Essentially, we would get a placenta and work it up for virus over a long weekend.

Now, in Oregon in those days, finding a woman that had fourteen children wasn't unusual, so getting placentas was easy as can be. I would arrive there on Friday and we put the word out we wanted a placenta, and we had it. We then extracted the placenta to look for virus, and we searched by measuring reverse transcriptase in the placenta, which is the enzyme for retroviruses.

Hughes: That was a recognized technique for identifying retroviruses?

Levy: By that time. But we had to work out all the procedures. Reverse transcriptase in the placenta was very labile, and you sometimes saw it and sometimes you didn't. We did maybe eighty placentas. It would be all-nighters. We'd start on Friday morning, and we'd go straight through until Saturday at noon, and do the whole thing.

Hughes: You went to Oregon because the placentas were readily available?

Levy: Right, but mostly since JoAnn Leong and I had begun the work in my lab, and we decided this would be a collaborative work.

Also, I did not have any ultracentrifuges nor money to buy this equipment. Her lab could do the molecular work. This becomes important with HIV research since I did not have an ultracentrifuge at the time I needed it. I had none of the molecular techniques ongoing in the lab. Everything I did was biology: how the viruses infect; how can you manipulate them? It was not the kind of subject that attracted students, because they wanted fast results, and fast results came with molecular approaches. The Herb Boyer [recombinant DNA] techniques weren't quite there. Reverse transcription was there to work on, but not with as advanced technology as there is today. But still, a student could work with Mike or Harold and get a result much quicker than coming to my lab. So I always had a hard time finding postdocs, and Mike would sometimes send me the list of people that he didn't take. One did come to my lab and was disappointed she was not with him, so it didn't work well.

Research on Anti-xenotropic Virus Neutralizing Factor

Levy: JoAnn had come from Mike's lab to work with me in biology and pathogenic systems. While she was here, I put her on an exciting project. We found that in the serum of mice, there was neutralizing activity against the xenotropic virus. Other people had also seen it, and they had reported the finding of high titers of antibodies to xenotropic virus.

It didn't make sense to me: Why would an animal make an antibody against something it inherits in its genes? I always say it was naiveté, because I thought I had a new finding. I felt the animal should not be making antibodies. And I remember saying that maybe it's not an antibody.

Sir Macfarlane Burnet was here at the time, and I met him. I told him about xenotropic viruses and about our antiviral serum factor. I'll never forget what happened. He looked at me and said in his Australian accent, "Well, that would be terribly novel." [laughter] And we went after it.

And here's another lucky event: I had met a scientist named Ron Barnes in England. He worked on NZB and mouse viruses. I didn't have the procedures for doing a lot of immunoprecipitation of antibodies and he offered to help. He did it for me in England and sent the material here, and we tested them. The results were exciting. The antibodies in the mouse serum had no antixenotropic virus activity, and the non-antibody fraction did. I'll never forget, I was so excited. This was two years <u>after</u> the discovery of xenotropic viruses. I had another new thing to report that was nonconventional and anti-dogma.

Huebner was visiting at the time and I brought him into my small office. I recall he sat on this desk--well, at that time, it wasn't as nice a desk. But it was in the same room. And I said, "I have some very important information to tell you, and I would like you to submit it to the [*Proceedings of the*] *National Academy of Sciences*." In those days, you did that to protect yourself, because other people might rush in and try to take the discovery away. This way, he could direct it to trustworthy people. He was equally impressed. At the same time, he had grown fond of me, partly, I felt, because his wife, Harriet, who was formerly his secretary, was such a very good friend of mine.

In any case, what was nice about Huebner was once he submitted the paper, then he told <u>everybody</u> about it, and they didn't dare take it away. And that's what he did for me for xenotropic viruses, too. I give him credit for getting everyone

to accept the term, because he went around calling everything, "xenotropic, ecotropic," and everybody just accepted it. You need people to get the word out, and I wasn't the one to do it--at least then.

Hughes: Well, not only people, but people of the stature of Huebner.

Levy: Right.

I knew very good immunologists at NIH, whom I called and asked, "I would like you to prove I'm right on this observation," and they did it, and came up with the same finding. Thus I could note in the article that they confirmed the observation. This became known as a neutralizing factor. No one knew what it was biochemically. Then JoAnn and I did all sorts of really very primitive biochemical and protein assays, and we proved the neutralizing factor was a lipoprotein. With that finding I joined with John Kane in the Cardiovascular Research Institute here, and we proved it was an apolipoprotein. What an interesting time--to learn antibody purification techniques and then all about lipoproteins. I tell my students that is where science can be so exciting--never dull. Then I got invited to lipid and cardiovascular meetings, because this finding was the first example that a lipoprotein had some biologic activity aside from transporting lipids.

So in '75, '76, '77 we tied in the neutralizing factor in the mouse with the xenotropic viruses. And now xenotropic viruses were being found in cats, in deer, in mink, and they became a theme. So while working on the placenta virus we were looking as well for neutralizing factors in human serum. But none were found.

All of this work came about up to 1977. I was asked to write a review of xenotropic viruses, which took a lot out of me. It was through Werner Henle, and it was a very good review, and I got lots of praise for it, particularly from him. A lot of things happened that year. I had been wanting to be an associate professor, and since I didn't have any great strong advocates--Dr. Wood had retired; I was inherited by the department [of medicine]. Anyway, finally I got it with the wonderful statement that it was about time that I received this promotion. And I got married to Sharon in that year [September 1977].

Visiting Scientist, Weizmann Institute, July 1978-January 1979

Levy: All this happened at the end of the seventies, and I decided, I need a sabbatical. I received money through the Eleanor Roosevelt Foundation and another fund to go to Israel [Weizmann Institute] to work on T-cell leukemias with Nechama Haran-Ghera. I had met her at the Gordon conference in 1973 and really appreciated her approach to research using live animal models. For five months in Israel I learned about T-cell leukemogenesis. I was there to work on viruses that could induce these tumors, and it was a very interesting time. We showed how the mouse virus could affect the immune system of the animal and thus lay the basis for leukemia development--not a too distant cry from HIV.

I also had a very active lab in San Francisco. I bet I had about fifteen people. There were no fax machines. Mail would come to Israel three weeks later. By the time I got it, I'd forgotten the questions I'd asked. I got hepatitis while I was there from eating the wrong food, and then I was out for about five weeks. It was terrible but I have great memories of my time there, and Sharon and I remain very active in Weitzmann Institute events.

Visiting Scientist, Institut Pasteur, January 1979-July 1979

Levy: After Israel then we moved on to Paris, where I couldn't drink wine for three months because of the hepatitis. I worked with [François] Jacob on embryocarcinoma cells. This was again a different subject for me. I wanted to show that viruses could affect differentiation. I was, as I said before, directed at looking at viruses in cancer and normal development. So I studied T-cell differentiation and leukemogenesis and how viruses would manipulate that system.

Then, I wanted to go to the Pasteur Institute to study the effects of retrovirus on embryogenesis. Also I was happy to work with Jacob and experience the Pasteur Institute. And I loved Paris ever since I spent the year there in 1960. I decided in 1960 that I was going to return to Paris every decade and spend time learning and teaching. Well, it hasn't worked out because of AIDS, and I just haven't been able to get away. I went to Paris in '60-'61, '71-'72, and then '78-'79, when I spent eight months there. It was very difficult then, I have to say. They weren't used to working with viruses. In fact, Jacob didn't want viruses

in his lab, so I had to take my embryocarcinoma cell cultures from his lab across the center quad to Jean-Claude Chermann's lab in a small makeshift one-story building.

Now, Jean-Claude Chermann--the name will later become important--had been a friend of mine, because in 1971 and '72, when I had been with Jasmin for six months in Villejuif, Jean-Claude was often around. At the time I had described a factor that NZB cells make that inhibits murine retrovirus replication. I thought that this substance might have something to do with the block in xenotropic virus infection. But it didn't. However, this factor still stands today as one of those substances, not an interferon, that is antiviral. But I didn't get very far with it.

Jean-Claude had seen something similar, so we interacted, but initially on his research subject. He and Dani and Sharon and I would socialize in Paris. He actually established reverse transcriptase assays in my lab in 1973 or '74. We used the procedure, especially for searching for the placenta virus. Up until about '78 or '79 the reverse transcriptase assays, which were very good, were a major biochemical approach used for our work.

In '78-'79 when I was at the Pasteur, Luc Montagnier was the head of the lab where Jean-Claude worked. In fact, Luc had been a student with my brother Stuart in Raymond Latarget's lab in the early sixties. You recall I was also influenced by Latarget and his ideas on cancer viruses. So I knew Luc because they were colleagues together. Luc was interested in interferon, and Jean-Claude and Françoise Barré-Sinoussi, who was a very good friend of mine as well, were interested in viruses. So I interacted with them with my embryocarcinoma cells. When I proved that you could actually influence development with retroviruses, we published it.[1] I was very pleased that Jacob agreed to be on the paper. He really did not want much to do with viruses.

Hughes: Because they were infectious?

Levy: Yes. He wanted the lab clean. When I showed him that every mouse cell has a virus [laughing], he still just smiled wryly and I traveled to Chermann's lab.

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[1]J. A. Levy, H. Jakob, D. Paulin, F. Kelly, J.-C. Chermann, F. Jacob, "Productive infection of embryonal carcinoma cells with ecotropic mouse type C viruses and subsequent arrest of differentiation," *Virology* 1982, 120:157-170.

I worked very hard at the Pasteur, I think harder than most of the French researchers there. I didn't end up with a lot of papers, but I ended up at least proving what I came to do. I wanted to learn about embryocarcinoma cells; I wanted to learn about differentiation and how viruses could affect it.

Research Cuts

Levy: I came back to this lab in '79 and set out to revitalize it; wrote up all my grants. Then 1980 hit, Reagan was elected, and all my grants failed. I was reduced from fifteen people to me, a part-time secretary, Michelle Ramirez (who by the way was most important). Dr. Wood told me: "Your secretary is one of your most important people. Don't ever give her up." Anyway, I ended up with four people. I had a student and a postdoc on her own salary. Everyone else had to go.

Then I got a letter from the dean, [Robert H.] Credé, saying, "Dear Dr. Levy, since you have no more money for your support, if you do not find any funds within a year, you must leave the university." I found that letter so cold, callous. Not even, "We thank you for all the money you brought in and what you've done for us in the past."

I then talked to Marty Petrakis, who was head of contracts and grants here; she was a good friend. She said, "Jay, this is the saddest part about this place. They don't care a thing about what you've done in the past." With her, I tallied up all the money I had brought the university--it was close to $2 million--but the overhead didn't matter either. The school agreed they would pay my salary for one year.

My wife was the best thing that ever happened; Sharon was fantastic. I was so depressed; I couldn't believe this was happening. It happened to me first among my research colleagues. It happened to the others later. Some left science completely. Sharon said it was one of my most creative periods. If so, it was also very difficult. It can, however, be your most creative period, because you have to sit back and figure out what you're going to do.

I could be a physician but I didn't think I really wanted to do it, though I knew I'd be a good one. I have a nice way with people, because I enjoy taking care of them. But I wanted the excitement of research. So I wrote grants. I have a file

on that project. I must have sent out a hundred grant applications. Letters. Met with foundations.

Fortunately I had a friend whom I met through Ellen Dirksen, the electron microscopist. This woman worked at the National Science Foundation. And I'll never forget what happened: In 1980 or '81, I applied for a grant on embryocarcinoma cells. It was for $39,000 for three years. This lady knew that I was in terrible financial shape, and she fought for me, and I got the grant. I got the news at the same time that I got an award notice that I was given a month grant to return to the Weizmann Institute to finish up some work on T-cell leukemia with Haran-Ghera. Then I got another grant for another small amount of money from some local people, so that I was able to get by. My luck had finally changed. That history brings us up to August of '81.

Let me say in retrospect that 1976-'80 was also difficult for me emotionally since I had as the new head of the Cancer Research Institute Stephen Shohet.

Hughes: Why?

Levy: Because he just wanted his own people. I had a Research Career Development Award [1972-1977] that Julie Krevans had sponsored me for, which was nice of him. That really was a commitment by the university to me.

I remember when Steve Shohet in '76 said he couldn't even spell "virus." He was nasty, tried everything to get rid of me, and forced me out of the room across the hall that we were using. He kept it empty, but we always snuck back and used it. Just terrible behavior. You just can't believe the atmosphere of this place in '76-'77. Well, I'm sure it's true at a lot of places.

And then to have Julie Krevans when I went to see him say to me, "Well, Jay, he's the director of the institute. If he wants to get rid of you, he can." Think about how insecure that would make one feel, when I had a fine research group. So I have never really felt a great security at this university, but I kept working.

I'm telling you this because I actually don't know why I continued here. Maybe part of it is to just prove that I don't care what they do, we're going to get this research done anyway. Xenotropic viruses weren't that important to them. If my research turned out to be exciting, great: they'd take the credit, thank you very much, goodbye. And the neutralizing factor is a very unique observation. Our research in biologic

systems has always been novel and adventuresome. That made it fun.

Hughes: Were your financial troubles in the early eighties related to the fact that Nixon's war on cancer was petering out?

Levy: Well, Reagan got in and said that government was not going to support research. You had to go to the companies for support. He cut the budget. I wrote Dick Rauscher at the American Cancer Society and said, "I'm going to have to close my lab. This is terrible." I wrote him about the neutralizing factor. He got me $50,000 to continue. So that helped. Those kinds of grants really help people through the tough times. But many did not survive and left science.

The reason I'm building this up is to show that the atmosphere here was not great. Steve Shohet was the director of the Cancer Research Institute; he seemed to be an unhappy person and obviously did not like the job. They then got rid of him in the six-year review, and they brought in Ed Cadman, who was better and was more supportive of me. Nevertheless, even then the institute did not recover the importance it had under David Wood.

III THE AIDS EPIDEMIC

Kaposi's Sarcoma, August, 1981

Levy: Paul Volberding came to do his oncology fellowship here while I was in Paris and Israel. He had done work in retroviruses in Minnesota. He spent two years working with me in '79 and '80. In 1981, he moved to San Francisco General to become an oncologist. He saw the problem of getting money for research.

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Levy: Then in August of '81, Paul calls me and says, "Jay, we have Kaposi's sarcoma [KS] occurring in homosexual men. It's a small number of cases, but we'd like you to come over [to San Francisco General Hospital] to grand rounds and discuss it, because I think this is an opportunity for you to look at human cancer."

Judy Luce, an oncology fellow with me then, and I went over, and Don Abrams talked about the case; Don was then a fellow. I got up and explained why, if Kaposi was caused by a cytomegalovirus (the leading idea for a virus causing this cancer), you couldn't get the virus out. I went back to the fact that if a DNA virus was causing the cancer, it would be locked in and wouldn't express the total particle. Back to 1962 and lysogeny and bacteriophages. It's the same story, because if the virus replicates out of the cell, it kills the cell. I said it might be a defective cytomegalovirus and that we would like to work on this problem. But I had no money.

Hughes: Why were they even thinking viruses?

Levy: Well, Burkitt's lymphoma had been linked to a herpes virus, EBV [Epstein-Barr virus]. Kaposi's sarcoma in Africa had been linked with cytomegalovirus by Gaetano Giraldo. There has been a close association with cytomegalovirus with this cancer, but no one can prove it as the cause. So Kaposi's sarcoma was now suddenly

occurring in these young men, where usually it's in much older Mediterranean people and in Africa. It was an opportunity to move into human cancer, and we needed to get the tumors out and grow them. I had no money. That was in August of '81.

Then it became clear that Kaposi's was really hitting as an epidemic. In San Francisco, *Pneumocystis* [*carinii* pneumonia] was not as emphasized then in association with AIDS. In February of '82, Marc Conant called me and said, "I've got a case of Kaposi's; do you want to get started on your growth of Kaposi cells? Come on over." I went over, and I met Dan Turner. Dan Turner was a young, vivacious, handsome guy. He had a KS lesion on his foot. Marc took it off, gave it to me. I came back here, and it was the first Kaposi's tumor that we established in cell culture. That was in early '82, and I subsequently established about thirty cell lines in this early period.

National Cancer Institute Grant for AIDS Research, 1983

Levy: In the beginning of '83, end of '82, a group of us at the university decided to write a grant to work on AIDS. The NIH had announced that requests were being considered. Paul decided to put the grant together with John Ziegler. I give a tribute to Paul; Paul had just been my fellow, remember. He had a name that no one could pronounce, and he was going to go for this first grant on AIDS. He was an unknown in research, and we all were saying, "Paul, it's not good for you to be head of this research grant; it should be John Ziegler." Ziegler had worked in cancers in Africa; he was well known to NIH. Paul said, "No. I'm going to see a lot of these cases at San Francisco General. If I'm going to do this, I want to be co-investigator." And there was nothing we could do. Today, if you can't pronounce his name, it's not because you haven't thought about it. So he became the co-investigator with John Ziegler on the grant.

Hughes: I have heard it postulated that it was that grant that established the hierarchy of the San Francisco AIDS workers;[1] that it gave Volberding the edge.

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[1]See the oral history in this series with Andrew Moss. This and many of the other oral histories in the AIDS series are available online at: http://www.lib.berkeley.edu/BANC/Biotech/.

Levy: Absolutely. But who else was around? I mean, it was Paul calling me in to see Kaposi's sarcoma in '81, then Marc Conant seeing patients and then starting the Kaposi's Sarcoma Clinic.

The Kaposi's Sarcoma Clinic, UCSF

[Interview 2: February 22, 1993] ##

Hughes: Dr. Levy, last time we talked about your first encounter with the AIDS epidemic. What we should do now is record your memories of how the KS Clinic was founded and set up.

Levy: In February, 1982, as you recall, I saw Dan Turner in Marc Conant's office, and began to work on Kaposi's sarcoma. Marc Conant invited me to what had just been opened [in September 1981] as the Kaposi's Sarcoma Clinic[1] over in the [UCSF] Clinics Building. The study group was held, I think, at lunchtime every Thursday, or every other Thursday. I would go there representing a basic researcher and virologist.

There weren't very many of us at first. I think John Mills was there, Dan Stites, several epidemiologists. Selma Dritz would come. It was an excellent format for describing what was going on in KS, this new disease. I can remember having discussed with Don Abrams whether lymphadenopathy, swollen lymph glands, was part of this syndrome or not. We discussed whether other viruses could cause lymphadenopathy and did we know if homosexual men got swollen lymph glands. I believe that I said that I thought lymphadenopathy probably was related to the new disease.

I can recall Larry Drew arguing for cytomegalovirus as a possible cause. At that clinic evolved the separation of our two approaches, where I wanted to go for a new agent and Larry was looking for a mutant of a known agent as the cause of AIDS.

Hughes: Why did you suspect a new agent?

Levy: We hadn't seen Kaposi's sarcoma, and later *Pneumocystis* disease, occur at this level, ever before.

Hughes: In this age group?

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[1]Levy and others use the term "clinic" to embrace both the KS Clinic and the KS Study Group, which followed the clinic.

Levy: Yes, in this age group, and like an epidemic or a minor epidemic in cities, among people that were of certain backgrounds and risk groups and sexual persuasions. We had some very good discussions in the Kaposi's Sarcoma Clinic.

This clinic was an excellent opportunity to have this information exchange, and I do not know why it stopped. Partly, money ran out. Partly, people after a time didn't attend as often, although I always went. But you met everybody who was anybody in public health and working on this new disease. I was really one of the only basic researchers, along with Larry. Larry didn't come as often as I, because he's at Mt. Zion and I think had a more difficult commute.

Hughes: What was the usual format?

Levy: Marc or his assistant would set up lectures, and you'd hear a lecture or two. I can't remember; I think sometimes it was two.

Hughes: Which were sometimes by outside people?

Levy: Some outside visitors came.

Hughes: Were there patient presentations?

Levy: No. You had people discuss various aspects of KS or a related topic. They wouldn't present a problem, but they might use a case to illustrate one of the points they were making. While we focused at first on KS, later it was on lymphadenopathy and AIDS in general.

Visit to Haiti and the Dominican Republic

Levy: I went to Haiti at the end of '82 to look into the possibility that the virus that causes AIDS, as it was then called then, might have originated in Haiti. You may recall that fingers were pointing there. I also went to the Dominican Republic where I had been doing work with Ellen Koenig, who is my sister and is a virologist. We had been looking at AIDS in the Dominican Republic as a third-world country. Since the country has Haitians working in the sugar cane factories, I thought that we might see a difference in the disease among the two populations. We collected blood in 1982-'83 and then with the discovery of HIV could trace the onset of infections in the Dominican Republic. And that

turned out to be a rather major observation, published in *JAMA*.[1] We found a high rate in Haitians and a very, very low rate in the Dominican homosexual community.

For collecting the blood in that country, I would go dressed in a white jacket with Dr. Koenig and her public health coworkers to gay bars and hotels, bleed the men, and keep the blood, because in '82, '83 we didn't know what the cause of AIDS was but felt it could be a virus. Every December at the holiday season, I go down there. We set up this collaboration with the national laboratory and it turned out to be very interesting. We could watch HIV enter the Dominican Republic and spread, as I was able to do as well in Zimbabwe, which is another story.

Hughes: How was HIV entering Haiti?

Levy: It was entering with tourists and Haitians. It was quite clear that the concentration of cases in Dominicans was in the port cities, and we showed that fact in our first paper.

Hughes: Gay men were bringing in HIV?

Levy: It was mostly gay men.

Hughes: From the United States?

Levy: Wherever, but most likely, yes. We didn't think the infection of Dominicans came from Haitians; they don't mix very much, although you have a few Haitian prostitutes. Ellen went on to prove that most of the prostitutes in the Dominican Republic are negative for HIV. It's the international prostitutes who are infected, being moved around the world. That was one of Ellen's comments: "Stay away from international prostitutes."

In December 1982 I arranged to go meet Bob Elie in Haiti, who was my host. It was really an amazing trip. Because I was going to Haiti, I called Berkeley and asked if there was anyone there in Haitian studies and met a young Haitian teacher named Michel Laguerre who was a history of Haiti scholar. He had a lot of contacts in Haiti with a very intellectual group. One of his friends, Max Blanchard, became a friend, and I serve with him on a Haitian-American committee in San Francisco.

So I went to Haiti armed with all these contacts, and I met many of them. One was a famous historian and lecturer, and I had

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[1]R. E. Koenig, L. G. Brache, J. A. Levy, "HIV in the Dominican Republic," *Journal of the American Medical Association* 1987, 258:47.

an incredible time. In fact, I even met with the minister of health. My hotel was empty because AIDS had been just talked about and no tourists came. I think I spent four days, and there were meetings all the time. I met some of Michel's friends and the head voodoo priest. I photographed a voodoo ceremony and raised the question of whether the virus could come from chickens, because they drink chicken blood.

At that time, Jane Teas had her African swine fever virus article published in *Lancet*, which captured the imagination of lots of readers and the gay community. And Jane was here in San Francisco, talking about it. I decided to examine further the idea though I thought it was a bit far-fetched. While in Haiti I checked on the pigs that were supposed to be infected by this virus, and although all the pigs had been ordered killed, there were plenty of pigs left in Haiti. No one bothered to kill them all. In the voodoo ceremony, they smear themselves with pig blood. So I looked around for swine fever virus as a possible cause of AIDS and learned some very interesting things while I was there. For certain the swine fever virus did not seem responsible.

One reason was that most of the wild animals were gone; they had all been eaten. The second was that there had been in 1977 a conference of gays in Haiti, and a lot of gay people had come down from New York for this conference. After all, Haiti was a great spot for gay vacations. The poverty there had lots of young boys acting as prostitutes. There apparently were some there when I was there, but it wasn't as evident. There was a hotel that had a lot of famous homosexuals staying there. I saw the hotel; I can't remember the name of it. I also learned that one guy had given a party in which rhesus monkeys were featured, running around wild at the party. So that led me to think again about viruses spreading from an animal to humans, or--I always laugh--the other way, too.

I came away with a wonderful appreciation of Haitian culture, despite the short visit. The voodoo priest was wonderful; really it was a privilege to be there for a special voodoo ceremony, and I was permitted to take many photos. Years before I had been in Haiti with friends and actually went to a voodoo ceremony that we paid for. It was like $10 and went on for three days. We saw the first six hours and then excused ourselves, but it went on forever. So I had a feeling for it and met some voodoo priests then. I came back to San Francisco and gave a talk on this visit at the KS Clinic. It was really very well received. I had marvelous pictures, which I still use. I said then that I thought perhaps in '77 the virus was brought to Haiti via New York.

I continued my connections with Haiti, but it became impossible to do research with them. I tried very hard, even tried to get blood samples from them and found that the best way of doing it was getting the blood from Haitian sugar cane workers in the Dominican Republic. They go back and forth over the border. So that's where I did most of my work in the Caribbean. I looked at the Caribbean as a third world country for us to study. I maintain some wonderful Haitian friends here in the city. I still see Max Blanchard, who is a prominent Haitian businessman here--or he may be a lawyer--and, as I mentioned, I'm an advisor to the Haitian-American Foundation that strives to bring up the level of attention to Haiti.

I tell you that story because it adds a certain dimension to my own life, but it also gave me insight. You go there; you see it. As a result of that experience, I went to Africa at my own expense so I would not be just hearing about it and reading about it; I would see it myself. And that added tremendous dimensions to my appreciation of the HIV problem.

Hughes: Did these trips add to your science? Was what you were doing in the laboratory affected by where this virus originated?

Levy: Well, at that time, I thought these trips might give me a hint as to what animal cells to culture the virus in, and ways in which it could be transferred. But as a medical person trained in virology, I'm also very interested in epidemiology and disease transmission. So I cover quite an area when I look at pathogenesis. I'd like to know how a virus gets transmitted as well as how it causes the disease.

Hughes: Now, why did it have to be a virus? Why were you convinced that it wasn't another type of infectious agent?

Levy: I was convinced it was a virus because in early '82 there was the case of immune deficiency in a hemophiliac who received only blood products, not blood transfusions, and all the Factor VIII material is filtered. So it therefore became really rather silly when a prominent researcher published in the *New England Journal of Medicine* in 1983 that a fungus could cause this disease.[1] That to me was ruled out. Also, it couldn't be a bacterium, because bacteria are also blocked by filtration. The cause had to be a virus.

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[1]K. W. Sill, T. Folks, K. T. Kwon-Chung, J. Coligan, and W. L. Maloy, "Cyclosporin immunosuppression as the possible cause of AIDS," *New England Journal of Medicine* 1983, 309:1065.

Hughes: Was a viral etiology pretty well accepted in the KS group?

Levy: No. Some people thought it was amyl nitrate.

The Peter Duesberg story that Peter still maintains was considered: hypersexuality, drugs.[1] Males have this one enzyme in their T cell and homosexuals may have more of it, et cetera.

San Francisco AIDS Researchers

Levy: I have to say, without romanticizing the time in San Francisco, it was a small cadre of people who got together and took this disease seriously when the university couldn't give a damn. And we as an outside crowd really went after it to try to get an answer. There were people who shared information. There was no one who demanded top attention. You had great personalities that to this day remain in wonderful rapport, which highlights this AIDS program on the campus. There is only one group, which has recently come to UCSF, that has not made any efforts to collaborate, and that's the Gladstone [Institute of Virology and Immunology] group. They kind of came after everything, and they're kind of staying separate. The group from the early days has maintained tremendously close association. I'll get on the phone and call Larry Drew or John Greenspan or Andrew Moss or John Ziegler or Marc Conant.

Hughes: What you're describing is a cooperative situation.

Levy: It was partly because we each came from a different discipline. If there were two prominent virologists, perhaps we would have been at each other. Larry's a good virologist, but he took herpes as the cause. I took the probability of a new virus.

Hughes: This choice of research areas just happened to be what you each were interested in?

Levy: They became partitioned in the Paul Volberding grant application to the National Cancer Institute [NCI] in 1982. That's where it was decided. Larry said, "I'll take cytomegalovirus," and I said, "I'm taking a new agent." So if I found a herpes virus, it went to Larry. If he found something new, it came to me. Anyway, that was the principle.

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[1]For more on Duesberg's views on AIDS, see the oral history in this series with Warren Winkelstein.

Hughes: And that went on down the line?

Levy: Everyone had their turf. There were problems when people felt they didn't get the credit or that someone was encroaching on their research area. And I, and John Greenspan[1] as well, would very often negotiate settlements so that we could retain very close rapport, and it worked. Always worked.

Hughes: Why was it you two?

Levy: Partly maybe because I've been around a long time, and I was after the virus, and after I found the virus, I became important for everybody because I did all the [HIV] antibody tests for them. And maybe because we took it seriously. We felt that everyone should get along, and this should be a part of what we do. We took pride in the fact that our group was different from UCLA, New York--there everyone was grabbing and trying to get the credit. And that spirit of cooperation here, as I said, maintains today.

So from the KS Clinic, we devised this grant application to NCI, and we defended it in May of 1983. It was a very exciting period of time. What I had was thirty-three KS cell lines and the review committee liked my work and the algorithm for finding the AIDS virus. I could not isolate any virus in a serious way; I had no ultracentrifuges. What became famous from Randy Shilts's book,[2] my old flow hood did not have a filter that would pass inspection, and it was to cost $1,500 to buy a new filter.

Well, as I mentioned to you, in 1980 I lost all my money when Reagan came in, so I had no money to upgrade my facility, no less go after an infectious agent, but I took on the challenge. And I had at the time very few people. Judy Luce was here; an undergraduate student from University of San Francisco, Tony Hoffman; a secretary, Michelle Ramirez; and Martha Szoenyi, who's been with me for seventeen years and is the woman who maintains the lab supplies, cleans up, et cetera.

Later I was able to accept John Morrow on a fellowship from England, but he began working on autoimmune diseases, which was part of a big research effort looking at viruses and autoimmunity --a confirmation of my NZB studies, neutralizing factor of xenotropic viruses. John took on the challenge of isolating an AIDS agent in small animals--and later primates. Here again I

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[1]See the oral history in this series with John Greenspan.

[2]Randy Shilts, *And the Band Played On: Politics, People, and the AIDS Epidemic*, New York: St. Martin's Press, 1987, pp. 173-174.

used my contact with a former virology colleague, Sy Kalter, who arranged for me in 1984 to have chimps in which to inoculate our virus, ARV-2 [AIDS-associated retrovirus-2] (second isolate). I find this another example of how previous work in the field came together with the contacts I had from former years. In 1983 I also accepted a postdoc, Leslie Tobler. She began working in the small room which we had for the human virus research.

The State of California Appropriation for AIDS Research, 1983

Levy: I went to the dean, Julie Krevans, who is the chancellor now. I asked for money in '82, just $1,500, and he said, "Well, you have to apply; I can't give it to you."

Hughes: This was for the filter?

Levy: Yes. I applied, but it took months, so Marc Conant called the state legislators, and they got on the chancellor. Then the chancellor called Marc in and gave him hell for going above his head.[1] But it got me my filter.

Hughes: Did you go down to the Los Angeles meeting with [California State Assembly Speaker] Willie Brown?

Levy: Yes. There were a group of us. We heard through Marc Conant that Willie Brown was going to submit an AIDS appropriation bill to the legislature. So I got up at five o'clock in the morning, took a cab to the airport, met Art Ammann, Dan Stites, John Greenspan, Paul Volberding, and Murray Gardner from UC Davis, and we flew down to L.A. to Willie Brown's office. We got there at eight o'clock in the morning, and we were to work on a budget. There were six secretaries with word processors assigned to us. Now, at the time, I had never even seen a word processor. There were some very nice people there from UCLA, Irvine, and San Diego, but I was the more senior person. I headed the virology group.

Hughes: What virology group?

Levy: Well, all the people interested in looking for a virus [in association with AIDS].

Hughes: All those campuses had ongoing AIDS research in place?

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[1]For Conant's viewpoint, see his oral history in this series.

Levy: They were getting started. We were well ahead of them; we really were.

We set up a budget to go after finding the virus. I set up my own budget, which was about $190,000--most of it being for an ultracentrifuge to do the enzyme assays I needed. You could not get funds for machines from NIH. I couldn't get money for salaries, no less machines, and that really was important to me.

At the L.A. meeting we came up with this budget, and they counted it all up as $2.9 million. Well, you could have picked me off the floor. I said, "No way. We'd better get that down below $2 million--$1.2 million or something--or we'll never get it." And the others said, "Jay, you're wrong. The legislature is all hepped up to do this; this is a major issue. The legislature has a lot of pressure on it from homosexual groups, and so forth. You'll be surprised. This is not a lot of money; it will go through, and you will be able to get started." So sure enough, in June 1983, the bill passed.

Now there are some interesting political aspects to this. I was playing squash with John Ziegler, because we had a regular squash game, and he said to me, "Dave Golde is saying that he is going to prevent us from getting the money unless he gets just as much money as you." Dave Golde had been here as a fellow in hematology and oncology when I was already an assistant professor and for some reason developed an envy. He seemed above coming to that meeting with Willie Brown, so he didn't have any request for money, and no budget.

The legislators wanted to take money away from other people so that Dave Golde wouldn't mess it up, and I insisted to John that I would not give in: Dave Golde should not get this funding; we should call his bluff. There was no way he was going to challenge the state, and it would be more embarrassing to him. I'll never forget that. That was really unbelievable. I was furious. But it indicates what goes on here. So in July of 1983, the bill was voted on and approved. Golde didn't get his funds.

I had just published the *Lancet* paper where I said that AIDS was an opportunistic infection,[1] and it had gotten a fair amount of publicity. So I had established myself as thinking about the AIDS problem and also the cause of Kaposi's. So it wasn't like I was an unknown.

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[1]J. A. Levy, J. L. Ziegler, "Acquired immune deficiency syndrome (AIDS) is an opportunistic infection and Kaposi's sarcoma results from secondary immune stimulation," *Lancet* 1983, ii:78-81.

I remember Rudi Schmid coming up to me at a dinner at Steve Shohet's house (after Cadman took over the cancer institute) and saying, "Jay, it's very good what happened, and don't worry, you'll get your money in time. But we can't just have the state money for AIDS research given like that." Someone else had also said, "There's going to be trouble, because Rudi Schmid is not going to allow us to have the money. He's going to seize it and make us all go through a review."[1]

Hughes: Which was not the legislature's idea?

Levy: No.

Hughes: They wanted the funds to go immediately to the AIDS researchers?

Levy: That's right. I had to go off to a meeting, and during that period of time, Art Ammann came out very adamant against Rudi and was in the newspaper about this.[2] Shortly thereafter, Art left the university.[3]

Rudi Schmid was very demanding. I went down to see Dick Littlejohn, who was his assistant and vice dean, and said to him, "Dick, this is wrong." Dick and I had known each other from social events. He said, "Jay, Rudi is adamant about this but I think you'll get some money."

Hughes: Schmid was adamant that AIDS funds should go through university channels?

Levy: That it should be peer reviewed. Now, we kept saying, "We're not fly-by-night researchers; we are major people in research; we've gotten grants before, and we need this money to get going right away." Eventually in September I received money (three months late) to buy my ultracentrifuge so we could begin doing reverse transcriptase assays for detecting the virus. That machine did not get purchased until October, 1983.

At the time, I was anti enveloped viruses--herpes and retroviruses--being the cause of AIDS, mostly because I did not think they could survive the treatments used to make Factor VIII

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[1]For Schmid's viewpoint, see his oral history in Archives and Special Collections, UCSF Library.

[2]Randy Shilts, "UC Assailed for Delay on AIDS Funds," *San Francisco Chronicle*, August 25, 1983.

[3]See the oral history in this series with Arthur Ammann.

for hemophiliacs.[1] In mid-'83 I was thinking along the lines of a parvovirus or small DNA virus. I like parvoviruses, because they're hard to grow.

My grant from the state of California was to isolate the AIDS virus in animals. So when the grant came through in July of '83, John Morrow was here looking at xenotropic virus expression, nutrition, and autoimmune disease, and Larry Kaminsky joined me as a dermatology fellow. Now I could hire some technicians. But the grant gave me, for the whole year, only $19,000 for supplies. That hardly would pay for much.

I called the NIH and I told Jack Gruber, whom I had known for years in cancer, that there was not enough money. I said, "It is so little money that when the press asks me, 'Is there enough money for AIDS research?', I am going to have to tell them, 'Absolutely not.'" He said, "Are you threatening me?" I said, "Take it as you will. I'm called by the press all the time." He blew up, apparently called everybody, and he said, "I am working like crazy to get you more money and don't mess it up." Within a week, I had $20,000 more for each year. That's the way NIH seemed to work.

Now, Jack was tied to the National Cancer Institute, and I can tell you that that group was tied to Gallo, and that whole area of research [AIDS] was cordoned off for Gallo, and not much support for anybody outside. At that time, 1982-1983, Bob Gallo and I were good friends, but he had all the money he wanted, and I had no money. So I always was hoping Gallo would help me, and I did various things at his advice, like writing a letter to Congress in defense of Vince DeVita so he would be maintained as the head of the NCI. I never got even a letter of thanks from him.

AIDS Etiology and Heat Treatment of Blood Products

Levy: Meanwhile, I had come up with this great idea, I thought. I had worked with mouse retroviruses, and I knew they were very sensitive to acid. If you lyophilized them, freeze-dried them, you could keep them living, but they lost some infectivity. I

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[1]Stephen Follansbee, M.D., remembers receiving at one of the KS Study Group meetings a document giving Levy's reasons why the AIDS agent was probably not a retrovirus. See Follansbee's oral history in this series.

felt that the procedures for making Factor VIII would probably kill them. How then could a retrovirus give AIDS since the chance of this virus surviving Factor VIII preparation would be low?

I called Bruce Evatt at CDC [Centers for Disease Control] to find out whether all hemophiliacs with AIDS had received whole blood, because if they had, then my idea wouldn't work. They could get the virus from blood transfusions. Well, I found out that no, there were some hemophiliacs who only got Factor VIII concentrate, and they had AIDS. Everyone then was rushing to look at Factor VIII concentrates by DNA hybridization in search of a virus--I mean, what were they going to look for?--but they were looking. And they were trying to culture the virus.

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Levy: To examine this idea, in the fall of 1983, I contacted five companies manufacturing Factor VIII. Armour, Abbott, Highland, and one other said that they couldn't work with me. I wanted to have them prepare the mouse retrovirus according to their procedure and see what happened to it.

Hughes: Why did they say they couldn't work with you?

Levy: They said their procedure was under a patent and they couldn't reveal it--not that they'd have had to--and they just didn't want to work on this project.

I wanted to figure out what this virus was, and the only clue I had was that it was passed in a product (Factor VIII concentrate) that had been subjected to acid, pH changes, filtration, pelleting, centrifugation, all these procedures. So I thought, This virus has a physicochemical property that may not be characteristic of a retrovirus, and I ought to figure out first if I should just forget about the retroviruses as a cause of AIDS. So I contacted the companies, and Cutter, a subdivision of Miles Laboratory, was the only one that said, "We'll do it with you," and that was George Mitra and Milt Mozen. So we set up some experiments. The phone calls were in the fall of '83. I had even written up a letter for submission to a journal saying retroviruses might not cause this disease, but it was never published.

Everyone else who had said it could be a retrovirus, like Gallo and [Myron] Essex and all, hadn't given this [heat treatment of Factor VIII] any thought. Although I had the idea, I had to prove to myself that it was right or wrong, so I needed to do it [purification of Factor VIII] exactly the way the companies did it, and Cutter agreed to do it. So we set up some experiments at

the end of '83 with the mouse retroviruses, and they were ongoing for several months.

Hughes: At Cutter?

Levy: Yes. I sent the mouse virus over to Cutter in Berkeley; they prepared the Factor VIII material, brought it back here, and we tested all the fractions; we measured how much virus was left after purifying the Factor VIII. And those studies ended up in March of '84 revealing that the virus survived in the freeze-dried product.[1]

Having observed this result, we agreed to test heat treatment as a means of eliminating the virus. We found that it took up to seventy-two hours at sixty-eight degrees C. to kill off all the mouse virus added to the plasma sample and remaining in the lyophilized product. We then went to the National Hemophilia Foundation and asked them immediately to ask that heat treatment be the accepted therapy. They refused.

Hughes: Why?

Levy: They said, "You did it with the mouse virus and not with the human virus." This is my second biggest regret in AIDS; the first is that I didn't go to Park City in February 1984. I would have been ahead of the NIH as I would have known about the emphasis on retroviruses and heard Jean-Claude's [Chermann] talk.[2] The second is that I didn't go to the National Hemophilia Foundation [NHF] meeting. I was in Europe. Milt Mozen went, and Milt came back and said, "Jay, no, they don't want to do it." Peter Levine, then head of NHF, wouldn't advocate it, we thought because it required too much money and the evidence was not conclusive. It would have cost millions of dollars to recall all of the blood products and have them heated.

Hughes: But AIDS is a fatal disease!

Levy: At the time, even I didn't think that many hemophiliacs would get contaminated product. We didn't know how widespread HIV was in blood products. In fact, if we had heated blood products in '84, we would have protected a number of people--but not the vast majority. They had already been infected with HIV.

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[1]J. A. Levy, G. Mitra, M. M. Mozen, "Recovery and inactivation of infectious retroviruses added to Factor VIII concentrates," *Lancet* 1984, ii:722-723.

[2]See below for more on this topic.

So now we had to repeat all that work with HIV, and then I had a hard time getting the human virus work published by *Lancet*. They said, "You're just repeating the mouse work!" But we finally got it published, I think in '85, as a letter.[1]

The CDC [Centers for Disease Control] did the same thing we did, and they came up with a similar but not as quantitative a result. But to this day, the work that we did showing three days of heat treatment is needed is the only treatment of blood products that protects against blood product transmission of HIV. There are people who have been infected by products heated for two days at sixty degrees, not sixty-eight degrees. In this regard, I feel good that we made an impact on hemophiliac care.

Hughes: Was heat treatment a recognized technique in virology?

Levy: It had just been developed at Cutter.

Hughes: For what?

Levy: For hepatitis B, and it worked okay, but not consistently, I don't think.

Hughes: What was the theoretical basis?

Levy: They were afraid that if you heated the concentrate too long, you'd kill the Factor VIII. So you had to work out conditions in which you would not inactivate Factor VIII but you would kill virus. Which they did.

Hughes: Was heat ever thought of as a possible treatment for AIDS patients?

Levy: You can't heat the blood. You'd kill the white cells. So it's only useful for plasma.

Hughes: In the pre-antibiotic era, hyperthermia was used to raise body temperature with the idea of killing micro-organisms.

Levy: Yes, with syphilis. And some people said this might work for HIV, but it has not.

Interestingly, the only recognition I received in those early years for all the work I did in HIV came from the heat

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[1]J. A. Levy, G. A. Mitra, M. F. Wong, M. M. Mozen, "Inactivation by wet and dry heat of AIDS-associated retroviruses during Factor VIII purification from plasma," *Lancet* 1985, i:1456-1457.

treatment process. I got the Murray Thelin Award [1986] from the National Hemophilia Foundation for finding a way of making blood products safe.

Hughes: Did you go to the blood bank meeting in Atlanta in January '83?

Levy: No. I was unable to attend.[1]

Chasing the Virus

The Gallo and Montagnier Teams

Levy: Now, I was in Paris in October of '83 for my brother's wedding. I had had my sabbatical with Jacob at the Pasteur in 1979, and I had maintained close contact with Jean-Claude Chermann and Françoise Barré-Sinoussi, and I was now quite proud of them. I have to say that in some ways I didn't think that the European labs were as well-equipped to have gotten a foot in the door in this disease. And I was pleased for them to have been in the forefront of looking for the AIDS virus. They always had been trying so much to make a name for themselves, Jean-Claude particularly, and Françoise too. So I was really proud of them. I wrote them a letter before I came, saying congratulations and expressing my pleasure to see them involved. But, I felt they were wrong. They published in *Science* in April 1983 that they had isolated an HTLV [human T cell leukemia virus]-like virus.[2] And Gallo also published that he had isolated an HTLV-like virus.[3]

I got some nasty comments from Bob Gallo: "Jay Levy, who does he think he is, talking against this retrovirus?" Because I put together the fact that HTLV is cell-associated, and so you would never get enough to make plasma infectious as we knew it

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[1]For comment on this and other events associated with blood transmission of HIV, see the oral history in this series with Herbert Perkins.

[2]F. Barré-Sinoussi, J.-C. Chermann, et al., "Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS)," *Science* 1983, 220:868-871.

[3]R. C. Gallo, P. S. Sarin, et al., "Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS)," *Science* 1983, 220:865-868.

could be. Moreover, HTLV is not cytopathic; it transforms cells. So it didn't fit the AIDS picture. I said, "It's impossible that this be the virus. If HTLV's there, it's a passenger; the patients are immunosuppressed. We're going after the real virus."

Hughes: The realization that Gallo was on the wrong track prompted you to go after what you're calling the real virus?

Levy: Not at all. Because from '82 I was looking for the virus, right? So what difference did Gallo's publication make? No, if anything, I was pleased to see they were completely off on the wrong track by sticking to HTLV. I was going to take the right track, but with a hell of a lot less money than they had.

So then I went to Paris, and I wrote to the Pasteur Institute group saying, "I'm coming," and they invited me to Luc Montagnier's Saturday morning lab meeting to hear more about LAV [lymphadenopathy-associated virus]. Well, I was very impressed that he got the whole lab in on Saturday morning, and was pleased to be able to go to the meeting as well.

Hughes: He had started those Saturday sessions because of AIDS?

Levy: I guess. Perhaps it was a usual session for his lab.

Immunology Meeting, Japan, July, 1983

Levy: But I have to backtrack a bit to say that in July of '83, I went to the international immunology meeting in Kyoto, Japan. At that meeting, I spoke on nutrition and autoimmunity--totally unrelated to AIDS. But there was the uproar: "What about this new disease?" Japan was asking, "What is AIDS? What is AIDS?" There was so much commotion over it that Susan Zolla-Pazner, who was an immunologist in New York and now a good friend of mine, organized a press conference there to discuss where we were in general to finding a cause, and I went to it. She did a sensational job. I didn't know her then; I wrote to tell her that she did such a good job handling the questions. She is very bright.

There was a young French guy--I think it was Marc Alizon--who got up and talked about the HTLV that they had isolated. He didn't speak English that well, but I didn't recognize that. What I did recognize was that he said that the one thing clear in his studies was that antibodies to this virus were found only in French people. Everyone took that statement as exclusive, and thus few took him seriously.

So in October 1983, when I met with Luc, Jean-Claude, and Françoise and they described their virus, I was surprised they had something that potentially could be the AIDS virus. As John Crewdson correctly reported, I came back to the hotel and I said to my wife, "Sharon, I think they may have it."[1] I've got to say, I felt they had a good head start. I didn't even have my equipment, and I felt bitter that I wasn't given the opportunity to really go after the virus. I couldn't do reverse transcriptase assays in my lab to look for this virus because no one would let me use an ultracentrifuge to spin down material from AIDS patients.

I said to the French group at the time, "Well, you know, this is a big surprise to me because when your young fellow [Alizon] got up to speak in Japan in July, it sounded like you just had a French virus." And they all laughed and said that was because of his [poor English] language, and he got a little embarrassed. I said, "Well, look, if this is so, I'm going to be the first group to confirm you, because I don't think that the NIH, which is Gallo and Essex, is onto it." And they said, "You're absolutely right; they think it's HTLV. We've been telling them they're wrong; they don't believe us." The French group told me how LAV grows preferentially in CD4 cells, and it kills the cells. And they had an immunofluorescent test to look for antibodies in the blood. It showed the virus in the cultured peripheral white cells. But the problem was, the white cells kept dying.

More on the Levy Lab's Search for the Virus

Levy: So when I came back to the lab in October, we had gotten the ultracentrifuge, because Rudi Schmid allowed us $50,000 from the State of California grant. So we began doing our RT [reverse transcriptase] assays. It was the undergraduate student Tony Hoffman, a chemistry major at USF [University of San Francisco], who did the reverse transcriptase assays. He was one of the few I could keep in my lab since he was not paid.

Hughes: He knew the assay when he arrived?

Levy: No, I had learned it, and the method was part of our lab protocol, and we perfected it. In fact, after working on the initial

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[1]John Crewdson, "The great AIDS quest," *Chicago Tribune*, November 19, 1989, section 5.

procedure, Tony improved the technique and, in October 1983, we found some RT positives, but we also found some controls that looked kind of positive. We had to work out the parameters that would give us really accurate results. At the same time, in the back of my head was the question, "Is this a retrovirus? Would a retrovirus be in Factor VIII products?" I was waiting for the data from Cutter Labs.

By the end of November [1983], we had some real positives; but we also had some negatives (from AIDS patients); we didn't have a virus that was growing like crazy. We could only say: We have a virus candidate, but we can't say it's the cause of AIDS, because we aren't finding it in all the AIDS cases. It was a situation where I had so many patients coming in; we had so few people to work; we were doing so much; there was only a certain amount of things we could get to.

Hughes: Where were the patients coming from?

Levy: Many from Paul Volberding, but to tell you frankly, several of them came right to this door because Harry Banghardt, one of my classmates from Wesleyan University where I went to college, was a doctor, and he had a lot of friends who were gay, and they were infected. I have to say that Harry, who later died from suramin treatment of HIV infection, brought me some of the most interesting cases, including the one that gave me high virus replicative activity in November-December [1983]. Then we knew we had something. We also thought the virus was similar to what the French had.

Hughes: Why did you think so?

Levy: Because it was killing lymphocytes. I then called Françoise, and I said, "Send me some serum and fixed infected cells on slides, so we can see if it's the same virus." She sent the serum, and we did the immunofluorescence assay, and we found that the serum recognized some of the viruses we isolated but not all. So we felt maybe our virus was different from that of the French. Then I began thinking, We have a different one. They have a different one. This may be just a passenger virus in an AIDS patient, and we haven't found the real cause. So we continued to isolate viruses, checked the sera for antibodies to our agent and to slides fixed with the BRU (the French) agent. I called Françoise and told her, "We've got some cross-reactivity, but not with all [viral] isolates."

And then in March 1984 when I found that the mouse retrovirus survived Factor VIII purification, I realized that we'd better concentrate on this human agent with RT activity. We'd

done all this animal work--guinea pigs, mice, rats, hamsters--inoculating in the brain, in the gut, bleeding them, checking them. I had a UCSF medical student looking at peripheral blood to see if there was any depression in white cells in the blood. It took an incredible amount of energy, something that I just don't think I could do again. We attacked the problems from many sides and again with very few people to help.

We had to travel ten miles to the animal facilities, because for safety precautions they had to be in a lab separate from the campus. I had to get separate biohazard hoods in which to work. Fortunately, the state funds paid for this. I was right next to Stan Prusiner's prion experiments with animals; that's where they put us with the AIDS work. And despite using many animals we didn't have any results that looked good.

I also called Sy Kalter in San Antonio at the Southwest Texas Foundation. I looked on this as being an opportunity to call on all my friends, everybody I knew from earlier virology days. He had a primate colony. I said, "Look, I want to send you blood to put into primates. I would like a chimpanzee." He got permission at the last minute, and then it was taken away. So the best we could do was to put it into baboons.

Hughes: Why was permission taken away?

Levy: The institute didn't want to give up the chimps. Sy was getting near retirement, and they took control away from him.

Carlton Gajdusek

Levy: I also got a call from Paul Brown, who worked at NIH with Carlton Gajdusek, the Nobel Prize-winner for slow viruses. Brown asked would I be willing to work with Gajdusek to isolate the AIDS virus in chimpanzees? I took him down to meet Ed Cadman, our new director of the Cancer Research Institute, who I thought was supportive. I wanted Ed to hear it, because I was nervous that I would be doing all this work and then I would lose control of the project.

Hughes: Lose control to whom?

Levy: To Gajdusek. I would send all the bloods to him and then never hear from him again. It would be tough.

I called Werner Henle as well, who was one of my mentors, and he said, "Jay, you have to be very careful because you will lose control." So I wrote a letter to Gajdusek saying that I'd be happy to collaborate, but that I expected that we would be very forthright about it, and that it would be my project working with him; we would work together on it. I never received another letter from him, and never heard from Paul Brown again. Apparently he went to Gallo and to Montagnier, and he did work with them. They published an article in which Gajdusek was the first author, so I thought my concern was reasonable.

Hughes: Why were you moving into primates?

Levy: Because I wanted to see if I could find the AIDS virus in a chimpanzee, which is the closest relative to man, and get a disease; then I might isolate the virus that way. That's the only way you can get hepatitis B virus. I knew this was the only method that led to isolation of some human viruses.

Hepatitis B as a Model for AIDS

Hughes: Hepatitis B keeps cropping up in people's conversations. Why was it picked as a model for AIDS?

Levy: Because it was transmitted at a high rate among homosexual men; it's passed sexually; it affects the immune system, and it certainly would survive Factor VIII purification.

Hughes: Were there any ways in which that model misled you?

Levy: Yes. It misled you in that it was soon found that some people, like children, got AIDS and they didn't have hepatitis B antibodies. The hepatitis B model just didn't hold up. The CMV model held up longer than any of the others. Nevertheless, many investigators thought antibodies to hepatitis B core antigen might be a surrogate marker for AIDS virus infection.

Levy Misses A Key Meeting

Levy: In February of '84, there was a meeting, organized by Bob Gallo, at Park City, Utah in which they were to discuss AIDS. As was usual for Gallo meetings, I wasn't invited and did not have any funds to go on my own. At that meeting, Jean-Claude Chermann

presented the data on what he now called LAV. Susan Landau was working with me part-time on the project. She's a co-author on the ARV paper. She said, "I'm going to Park City with my husband to ski; I'll look in on the meeting." I said, "Okay, great. At least I'll have somebody to report on the meeting." Susan came back from the meeting, and this was my big mistake: I should have gotten her to take notes. She said, "Jay, it's no big deal. They were talking about HTLVs and -Is and -IIs and -IIIs, and everything that we have talked about. There was nothing new." Apparently, every time Jean-Claude Chermann started talking about his virus [LAV], Gallo got up and said, "It's a contaminant; you don't know what you're talking about," and really downplayed the French results that he did not believe.

Suddenly in March [1984], there was a big turnabout, and then Gallo rushed four papers into publication. In fact, one thing Abe Karpas from England showed, which I was amazed at, was that Gallo had submitted a paper in January to *Science*, which appeared with the other papers in May, in which words had been changed! In January, the virus was HTLV-I. In May, it suddenly became HTLV-III. In other words, he completely did a turnabout, and changed everything around, and put the four papers together for *Science*.

Now, you can ask why he had four papers in *Science*: Because Bob Gallo had incredible power. You can then see why he was so feared; nothing could touch him. He did whatever he wanted. Anyone that did him bad, you were out of the picture. He ran it like an autocrat, tyrant--whatever you could call him. It was a dangerous situation for science; he controlled it all. And that's why he could do what he did and almost get away with what he did.

How could I fight him in a university that doesn't even want to have a press conference to draw attention on our work? I published in *Science*[1] [on the isolation of the AIDS virus] and did get some publicity,[2] but not to the point of saying, "Jay Levy's group found the AIDS virus." Forget it! Gallo's announcement had already been in every newspaper and magazine around the world! It wasn't as if I could have a press conference

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[1]J. A. Levy, A. D. Hoffman, S. M. Kramer, et al., "Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS," *Science* 1984, 225:840-842.

[2]"UC-San Francisco studies confirm French finding of retrovirus in AIDS and demonstrate a retrovirus could be passed through blood clotting factor," UCSF News/Public Information Services, May 9, 1984.

in May and say, "Yes, but we have the virus as well." He published before we did.[1]

So if I had been there in Park City, I think I would have heard the French data a little bit better, and I would have taken our results more seriously and gotten the paper out faster--before the Factor VIII data came through. However, I still think that not having the Factor VIII data would have made me reluctant to write it up as the AIDS virus.

Hughes: So the effect would have been the same?

Levy: It might have been the same, except I think by March [1984], I would have quickly put the paper together, and I probably would have published in the same issue with Gallo.

Hughes: Now, this is pure speculation, of course, but what if you had had the filter for the hood and the ultracentrifuge earlier than you did?

Levy: We would have had the virus a year earlier. There's no question in my mind. It was so easy to find. We were a lab dedicated to finding viruses. We still are. There weren't very many left; everyone was put out of business by Reagan's economic program in '80. There's no question in my mind about that. And more the ultracentrifuge than the hood; the hood was important, but that was only $1,500. The ultracentrifuge was $50,000, and I had to wait much longer for that money. Even if I had had the centrifuge in June as planned by the state legislature, I would have isolated the virus earlier.

Gallo Reverses His Stand on the AIDS Virus

Levy: I've got to backtrack: in April of '83, just before the *Science* papers from the French and from Gallo came out, I was invited to a meeting at NIH to discuss AIDS. Richard Krause, then head of NIAID [National Institute of Allergy and Infectious Disease], organized it. At that meeting, there were many people who were involved in AIDS research, including Tony Fauci. And I remember never having met Tony before, and they said, "Oh, this is one of the new young immunologists coming up the ranks at NIH; very bright guy." He and I hit it off very well from the beginning.

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[1]Gallo's papers on the AIDS virus were published in *Science* in May 1984; Levy's paper was published in *Science* in August 1984.

I talked quite openly about the types of viruses which might cause AIDS. They had people talking about the epidemic of canine parvovirus that occurred in '77. Could this be the canine parvovirus causing AIDS? There was some evidence that perhaps it was a parvovirus, which of course I was looking at.

Hush was around that Gallo had found an HTLV in association with AIDS--it didn't bother me at all--but there was a big hush about it. So they demanded that his associate [Edward] Gelman talk about it. I think he said that he had evidence of the virus in the white cells. Frankly, I didn't believe it.

Hughes: Who is Gelman?

Levy: He worked with Bob Gallo.

It was clear that NIH looked to Bob Gallo to solve this [AIDS] problem. He was their leading virologist, and he had the resources--$11 million or more a year. So from all over the world, people were sending specimens to his lab.

Hughes: Since the AIDS agent is cytopathic, why did Gallo link it to HTLV?

Levy: Exactly my question. They said, "Well, it might not be HTLV, but it's HTLV-like; it may be a cytopathic counterpart." And when they isolated HTLV-III, they said it cross-reacts with HTLV-I, but that is false. The viruses Gallo isolated in 1983 were HTLV, so their role in AIDS did not make any sense. Bob Gallo has this way of being able to make an observation and draw public attention to it. It actually has some positives, because he can put forward an issue, even if the data aren't that great. So he got all this attention on HTLV, and it was wrong. So did Max Essex. And it misled a lot of people. That was the bad part of it.

The French Group's Conclusion: A New Virus Causing AIDS

Hughes: One difference between what Gallo was doing and what you and the French were doing is that you and the French had a more open-ended view of what the AIDS agent might be?

Levy: Yes. I think that Gallo was convinced that it had to be a retrovirus, because he wanted to put more attention on retroviruses, since he found one (HTLV) and it wasn't getting much attention.

The French wanted anything, and they were retrovirologists, so when they found this retrovirus, they thought it was brand new. They didn't approach it like I did, which was to ask, "Could it possibly be just another contaminant?" It was a new retrovirus; at least it looked that way. But I didn't know that.

Hughes: Why did the French assume that it was a new virus?

Levy: Because they knew it kills lymphocytes. They told me it did not cross-react with HTLV, although that was inferred in the *Science* paper. There were differences between the AIDS virus and HTLV. Now we know that the cross reactivity was written in by Bob Gallo when he was the reviewer on that paper. Luc Montagnier didn't have the courage, apparently, to say it was wrong. I have the feeling Montagnier was uncertain as to what was the truth, and maybe it was Françoise and Jean-Claude who really knew they were onto something important. But anyway, for some reason, there was a "greying" of what was really true.

Hughes: I read that the first electron micrographs of LAV were difficult to interpret.[1] Do you remember that?

Levy: Well, I didn't see any of the electron micrographs--oh, yes, when I went to the Pasteur Institute I saw them, and they looked okay but it was difficult to know if the agent was new. But I know that Bob Gallo thought, and others thought as well, that this virus [LAV] was a contaminant, that the French were famous for contaminating cultures with viruses from other sources.

They said there was some cross-reaction with the horse lentivirus, equine infectious anemia virus, which was I must say dear to my heart. I had done a lot of sleuthing about the equine infectious anemia virus years ago when I first suggested it could be a retrovirus. And Gallo thought it was a contaminant. I think he even said so at one point. I think he said it to me. I did wonder about whether equine infectious anemia was a possibility as a cause of AIDS. That's why I thought, Well, if we don't find something like this in our patients, it could be a contaminant.

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[1]John Crewdson, "The great AIDS quest," *Chicago Tribune*, November 19, 1989, section 5, p. 4.

Levy's First Reverse Transcriptase-positive Viral Isolates, Late 1983

Levy: When, at the end of '83, I did get the first isolate that I thought was right, I found out that the guy from whom the virus was cultured had been traveling in France. I suddenly thought, Uh-oh, maybe he picked up this virus, and it's not the AIDS virus. And I couldn't find him, because he was on vacation for a couple of weeks. Well, what unfolded was isolations, RT positives, but also many negatives. Now I know why we had many negatives. We were attempting to isolate virus like other people were doing, which is far from being the ideal.

Hughes: Please explain.

Levy: Well, because we were not putting fresh, normal white cells into the cultures. We would just take a person's white cells, put them in culture with a mitogen, and wait for the virus to come out.

Hughes: You mean white cells from infected people?

Levy: Yes.

Hughes: So the people were already unhealthy?

Levy: Well, yes, they were feeling some symptoms. And what we now know is that there are in many infected individuals lymphocytes that can suppress HIV, so you wouldn't find it in a culture alone. But we only learned that by chance in '84 when we asked why some blood cultures did not release virus.

Also, from October of '83, when I came back from France and had my ultracentrifuge, to March of '84, which is six months later, I had with me just a student, a technician, and a secretary doing this work. We had about twenty positive cultures. We were confident. We concentrated on one culture, which happened to be from a patient whom I actually saw through Harry Banghardt. I had seven milliliters of the patient's blood; that's all. And this virus came out with such activity that it was just unbelievable.

Hughes: Was it just luck that you had concentrated on that particular specimen?

Levy: No. It was just that, when cultured with the white cells, the virus grew like crazy, and we found antibodies to it in peripheral white cells. I said, "Well, this is a really good prototype," and that became our ARV-2. We had an earlier one we called ARV-1, and there were other cultures that might have been positive. We

didn't count them, because we didn't grow them for a long time. That one [ARV-2] we concentrated on.

Announcing Levy's AIDS-Associated Retrovirus

Levy: So Gallo has his press conference [April 23, 1984], and he didn't mention the French. "Live at Five" [a television news program] asked me if I'd comment. This was in April, I think. I went down and said, "We have similar viruses too." So that was my first announcement that we had the virus.

In early May, Gallo's four papers came out. I was to give a lecture at a joint meeting of the American Society for Clinical Oncology and the American Association for Cancer Research [AACR] on viruses and autoimmunity and immune disorders, and I chose that moment (May 9, 1984) to show all our data on our AIDS virus, which we called AIDS-associated retrovirus, ARV. And these were beautiful data. We had EM [electron microscope] pictures, and everything was there. I remember Marty Hirsch coming up to me after the meeting--he was a co-speaker--and saying, "Jay, I can't get over all the data you have. Why haven't you spoken about it?" Though it was written up in a Canadian newspaper, and the *San Francisco Examiner* (Richard Harris, May 9, 1984) and *San Francisco Chronicle* (May 10, 1984), I said, "If I did, I wouldn't have the paper accepted for publication." Journals do not like publicity before a paper is published. I wanted to get it published in *Science*.

So I wrote the paper up in May, and sent it to *Science*, and it got reviewed, and it got accepted within a month.[1] There was one point during the review when I was afraid it wouldn't be accepted. One editor had said, "Well, why do we need another paper on the isolation of the AIDS virus?" And I said, "This is in San Francisco, and the isolation is totally independent." And the paper then sailed through the review process.

Hughes: Did it make a difference that yours was a different isolate?

Levy: Well, the reviewers didn't know that.

Hughes: Oh, because nothing had been sequenced.

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[1]J. A. Levy, A. D. Hoffman, et al., "Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS," *Science* 1984, 225:840-842.

Levy: Right. So Gallo's papers came out, and of course the news was all over the world. I asked the university whether we should have a press conference. Oh, no, they didn't want any press about this. This isn't the way we do things.

Hughes: What was the thinking there?

Levy: Well, it was Rudi Schmid. He didn't like any publicity on AIDS; it's not the way you do it. Also I think the school was afraid to have any attention given to this disease for fear it would compromise chances of getting good housestaff. Many young people might avoid an AIDS medical school. Also in general, a scientist should wait until the paper is published. So I waited until August; the paper did not come out quickly like the Gallo papers.

Hughes: Was his reviewed faster than yours?

Levy: Yes. It was submitted in March, accepted in April, and published in May. Mine was submitted in May, accepted in June, and published at the end of August. So I lost out in being considered in the same group of discoverers. But deep down, I felt that eventually my contribution would be understood and that the scientific community would see that I worked independently. The room I worked in you can see is a tiny little room. I was able to do it with very limited funds and staff. I actually grew the cells myself. And there is something to say for that.

I did say in my paper that I never had the advantage of having the French virus in my lab. I had heard from Luc Montagnier that he had sent the virus to Gallo, and in the back of my mind I thought, Well, once you have their virus, you know how to grow it, you can get it much faster. I had to work completely independently. So I say in my *Science* paper that this is the first <u>independent</u> confirmation. I also realized that in the Gallo paper, they made no mention of having the French virus.

I also wrote Bob Gallo and asked him for his rabbit serum against his HTLV-III, to see if that cross-reacted with mine, and I never heard from him. Later he actually told me that when he got the letter, he was so angry that I was involved in this research, he decided he wasn't going to answer me.

Hughes: You make quite a point of the fact that ARV could not have been contaminated by LAV--

Levy: That's right.

Hughes: --because you deliberately didn't receive any virus samples from the French.

Levy: Exactly. If you're going to confirm somebody, don't bring their virus into your lab because how would you know the difference? That's very important.

Hughes: Did you foresee that having LAV in the lab was going to be a problem for Gallo?

Levy: No. I knew that my problem would be to just stay on top and let others know, "Look, I was there also."

When Gallo started calling himself a co-discoverer of the virus, that really got me upset. If he was a co-discoverer, then I was a co-discoverer. Gallo says he isolated his virus at the end of '83. There's no evidence that he did. Yet, in my lab we have it documented in our lab books that the viruses were isolated in late 1983.

After my lecture at AACR in May [1984] where I presented the data on ARV, I was invited to a meeting in Denver by Marvin Rich to talk about the virus. They had invited Gallo, Montagnier, and me. That June, I was to go to southwest Texas to inject my viruses into a chimpanzee, and I decided, "I'm not going to that meeting; I'm going to inject my chimpanzees." In retrospect, it was interesting that someone back then actually did try to bring us together. I don't think it would have made any difference if I had gone. Historically, I think I would have still been treated as, "Oh, you too?"

Hughes: Is that the way it really has been?

Levy: Yes. They will say, "You're one of the three," or they'll say, "You're the third person to isolate the virus. When really, I was probably the second. In fact, I know I was the second. Because I'm the only one who had a different virus.

The UCSF AIDS Specimen Bank

[Interview 3: July 25, 1993] ##

Hughes: Dr. Levy, please comment on the AIDS specimen bank.

Levy: It was decided, probably by Marc Conant, that we had a rich source of material from AIDS patients for people worldwide, or at least nationwide, and that we should organize a specimen bank that would take care of storing the specimens. We had to figure out who could take care of it. The only one who had space, who had a

freezer available and was willing to do it or could be coaxed into doing it, was John Greenspan. He set up the specimen bank, and I don't know who was on his committee. We did discuss how much plasma to collect, what tissue to collect, how should it be handled, and so on--John should really fill in those details.[1]

Hughes: How did that tie in with what you were doing? You started out with the Kaposi's sarcoma problem.

Levy: We did not rely on John's tissue bank, because I had fresh specimens from Marc Conant or from Paul Volberding. Where it became more important to us was some years later when we began doing work with John on oral manifestations of AIDS, when the tissue from hairy leukoplakia patients and so forth was sent up to us through that facility.

Hughes: How actively was the tissue bank used?

Levy: John knows that. The bank is expensive to run, and he has had to justify it for a long time. He's been successful. There was very, very active use of it in the first years of the epidemic. Now, as the disease has spread, I don't know if people have as many demands on it.

I can recall that if we wanted specimens or sera from patients with *Pneumocystis*, we could just call John and he would send us 0.1 milliliters of it quickly--very easy to get the samples. It was of great benefit in those early days when you wanted to have well-characterized material. But I think others who didn't have as much access as we did to fresh material from patients took advantage of the bank more than we did.

Research on Kaposi's Sarcoma

Hughes: You mentioned last time that Dr. Conant gave you some biopsy material from Dan Turner in February 1982. What did you do with it?

Levy: Marc called me and he said, "Jay, I have a KS patient in my office. Do you want to come on over?" So I went over and met Dan. Marc removed a Kaposi lesion from the leg of Dan Turner and I took it back to the lab. Since I was so limited in staff, I did all the work, which was essentially wash the tissue, cut off all

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[1]See Greenspan's oral history in this series.

the material that I thought was not the tumor but was adventitious tissue, connective tissue. Then I decided on my own that the only way to get the cells to grow in culture was to try to create a micro-environment so that if the cells produced any factors that would help it grow, they would be produced locally and might stay if I didn't have them diluted out by the medium.

So I decided I would cut it up, mince it with scissors and forceps--this was only a one-millimeter biopsy; it really required micro-procedures--and then I put it all under a very thin cover slip. I pushed the cover slip down on the tumor tissue, then added the growth medium. The growth medium finds its way underneath the cover slip and it's kept there. The cells after two weeks grew out from the biopsy. We developed thirty-three different cell lines by that technique. After a lot of work to try to find the agent for Kaposi's, which was not successful, we were sidetracked to the finding of the AIDS virus, so we froze those [KS] cells away. We still have them frozen. They never formed tumors when inoculated in nude mice, so we weren't sure they were malignant.

One of the reasons I was looking at the growth factors for KS was that I published a paper with John Ziegler in '83 in *Lancet*[1], saying that Kaposi was probably like a hormone-dependent tumor and needed factors to get it to grow. Well, two weeks ago we again cultured a Kaposi's sarcoma tumor. I want to revitalize that project. I still want to look for an agent. The cells have grown. It really is fun, ten or eleven years later, to redo the research and have it work so nicely. I now have a few people helping me.

Hughes: In 1982, were you looking for an infectious agent in Kaposi's?

Levy: Yes, I was.

Hughes: Why?

Levy: In those days, I didn't know that Kaposi's was caused by something that killed the immune system. I thought it was an agent that was spreading around, causing malignant tumors. So I concentrated on Kaposi's sarcoma. Once we realized that it was an epi-phenomenon, a result of immune deficiency, then we started looking for the agent of the immune deficiency.

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[1]J. A. Levy, J. L. Ziegler, "Acquired immunodeficiency syndrome is an opportunistic infection and Kaposi's sarcoma results from secondary immune stimulation," *The Lancet* 1983, ii, 78-81.

Hughes: At some point, you switched from tissue to blood.

Levy: Yes. That came about when we were able to get a good filter in our hood, because we could then bring HIV-infected blood in here. We also needed an ultracentrifuge as well as other equipment to work on blood, and none of that came through until the Willie Brown initiative that gave us the money in June of '83. And then, as you know, Rudi Schmid seized the money, wouldn't let us have it, so I didn't have any money until September to purchase the ultracentrifuge. And then when I got the ultracentrifuge, I had to negotiate to get a room to put it in, which was that tiny closet across the hall there. We put the ultracentrifuge in there, because no one would let me bring AIDS material into any other lab. Subsequently we found the reverse transcriptase in the cultured blood cells and were able to isolate the virus we called AIDS-associated retrovirus.

Hughes: Do I understand that you limited yourself to the KS problem mainly because of difficulties in getting the equipment you needed to do virus isolation?

Levy: There were two reasons. One was, first we thought that Kaposi's held the answer to this disease in young men, because we first thought it was an epidemic of Kaposi's sarcoma. And then later, because we didn't have any equipment nor place to do the work on blood, we couldn't approach the culturing of white cells to look for an agent.

Hughes: If it was an epidemic of Kaposi's sarcoma, how did you explain *Pneumocystis*?

Levy: *Pneumocystis* was not very prominent on this campus. And while it was seen, it wasn't emphasized as much as Kaposi's. At first, it didn't enter into the thought process, frankly.

Hughes: So to you, in those early days, AIDS was Kaposi's?

Levy: Yes. It wasn't even called AIDS, as of course you know. It was epidemic KS and then gay-related immune deficiency. We're talking early '82.

To recapitulate, in August of '81 I see my first U.S. Kaposi's sarcoma patient, with Paul. Now I'm waiting to work on it. I have no money, no hoods, nothing to do it, and finally we get some help. And I immediately go to the Kaposi's. It must have been a few months later that it became clear, or more evident, that this syndrome comprised not just a tumor, but an infectious disease causing immune deficiency. But then we couldn't do anything at first except to concentrate on Kaposi's.

Immune Deficiency

Hughes: When did immune deficiency enter into your thinking?

Levy: At the end of 1982, I put together this hypothesis in *Lancet* that said that AIDS was an opportunistic infection which took advantage of a compromised immune system. A lot of people have been trying to see if that's true, but it isn't true.

I originally thought that in individuals whose immune system was somewhat altered--i.e., babies, gay men who have used drugs, IV-drug people--the AIDS agent in most cases would be fought off, but there would be a group of people that would succumb. My thought was that the immune deficiency created an imbalance in the immune system, causing some elements of the immune system to overreact and produce cytokines that worked on increasing growth of endothelial cells, which are the origin of Kaposi's sarcoma. So I called AIDS a disease of hypo- and hyper-immune response. I still believe that. It's just that the hyper-response which keeps emerging as an idea--autoimmune-type--isn't as prominent a problem as we might have expected. But Kaposi's sarcoma could be a result of a hyperactive immune system trying to respond to a deficit that has occurred because other elements of the immune system don't work.

Hughes: You suggested in this paper that the immune deficiency preceded what we now call AIDS.

Levy: Right. I thought that we would see lots of infected people that had fought off this agent because I came from a background of virology where that is true for most virus infections. Epstein-Barr virus causes mononucleosis in only a small percentage of people who get EBV. Paralytic polio is observed in only 1 percent infected. I discussed this point at the AACR [American Association of Cancer Research] annual meeting in Canada on May 9, 1984, where I also announced our virus, ARV. I said that we expected that this agent might be found without disease, and we in fact were the first group to show healthy people had the virus but no symptoms.

Seropositivity Without AIDS

Levy: Interestingly enough, that was a small part of my 1984 *Science* paper. And then Marty Hirsch's group went on to publish an article on just one person who was clinically healthy who had the

virus. In other words, I learned sometimes you put so much into one article that the readers can't keep track of what you have covered. So in this case we said it in our paper, and then later other people came in and said, "Well, do you know seropositive people can be healthy?" Well, we knew that in the beginning. My only disappointment was and still is that there are not many infected people who do not get ill. It's interesting as I relate that to you that the long-term survivors of HIV infection have now become the major focus of my research.[1]

In 1984, I started studying healthy individuals who we felt were infected for two years. It had by 1984 almost become the dogma that everyone infected got AIDS. That concept is so naive. In those early days, we thought two or three years was long-term survival. Who would have thought of a disease--and this is the problem with Peter Duesberg--that would take a long time to kill or to cause symptoms? There are very few, very few diseases that take as long as AIDS does to manifest themselves. Perhaps cancer could be another example.

Puzzling over Etiology

Hughes: Explain how that observation relates to Peter Duesberg.

Levy: Peter Duesberg says he's never heard of an agent that takes so long to cause disease, so HIV can't be the cause of AIDS. He thinks that he knows so much about viruses that he's right, but he has to accept the fact that there are models in animals that show a slow development of disease. Many of these viruses are known as lentiviruses, "lenti" for "slow". But Peter doesn't want to move from the animal model to humans.

Well, I'm not as blocked in that thinking. I'm a medical person; I know about pathogenesis. I know it takes ten or twenty years for cancer to develop. Some of those cancers are caused by viruses. So we shouldn't be surprised, except that this [HIV] has a different aspect; it is a lytic virus, not one that transforms, and it is an agent that attacks the immune system.

I think what's very important in research is that you have to be able to change your concept when it looks like it's different. I've already told you, my concept was AIDS was

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[1]Jay A. Levy, *AIDS*, 1993 7: 1401-1410.

Kaposi's sarcoma. And you said, "Why not *Pneumocystis*?" We see *Pneumocystis* in cancer, so I chose to think of that as, oh, sort of an epiphenomenon of a cancer virus.

CD4/CD8 ratios were brand new. I mean, no one was doing the CD4 analysis regularly. If we had, we might have been able to say, "Wait a second, the immune systems are abnormal." But I might have then responded, "Of course, a cancer virus is causing this immune problem," and stuck to KS. It was something I had been working on; I had lot of clinical material.

What I cannot remember is when I suddenly made the switch to say, "The causal agent is in the blood." I think it had to have been the end of '82 because in 1983, when I read of Montagnier's finding virus in the blood, I already knew that's where you should be looking. But we couldn't get the virus assays going because of our lack of equipment and funds. We were already growing some white cells in culture. We could just grow them and look for changes in them, which we did. But most of our subjects were not so sick.

Hughes: Weren't you also aware of AIDS in hemophiliacs?

Levy: Yes.

Hughes: Didn't those cases indicate that the virus had to be in the blood?

Levy: Well, by that time, I already knew. End of '82, early '83, I knew it was in the blood, and that this disease [Kaposi's sarcoma] was an epiphenomenon.

Hughes: When did you get state funds?

Levy: May '83. So we said already in that grant that we would look in blood. So we had to have known in January of '83 that this virus was in the blood. And I could not work on it, because I didn't have the equipment nor funds.

Hughes: Were you involved with lab studies in connection with the patients who presented at the KS Clinic?

Levy: I know occasionally we were asked to do the antibodies for ARV, but that would be the beginning of '84.

Hughes: You mean once you had the HIV antibody test?

Levy: Yes, right.

The Immunofluorescence Assay for HIV

Hughes: What about your immunofluorescence test?

Levy: That was developed for the first time in '84, after the agent was isolated. We found the agent, and then developed the assay.

Hughes: What is to be said about how it was based scientifically?

Levy: Well, first, we had to find the agent in the blood. Once we had the equipment to do reverse transcriptase assays to look for the virus, we were at the time separating white cells by Ficoll/Hypaque separation, which was the classic way of doing it based on density. The granulocytes go to the bottom of the tube and the lymphocytes are at the interface of the material. Red cells go down to the bottom as well. After you remove them, you have all your lymphocytes, macrophages, free of red cells.

You put the white cells in culture with interleukin-2 [IL-2]. Interleukin-2 is a growth factor that had been discovered at NIH as being important for growth of white cells. We began to study what occurs over time. Now, in those early studies, we worked with Dan Stites, Conrad Casavant, and Tom McHugh, because we did not have our own machine to look at CD4 and CD8 cell ratios. So they were doing that for us, and many of our early publications were done because they helped us.

Hughes: Was the machine a cell sorter?

Levy: It's not a cell sorter; it's a flow cytometer that shows you what types of cells are there.

Hughes: How recent was that technology?

Levy: That was a brand-new technology. It was developed by Len Hertzenberg and his wife Lee, and it revolutionized the ability to quickly look at subsets of white cells. What happens is the antibody attaches to its antigen on the surface of the cell. It's either fluorescinated or has rodamine or one of the other fluorescent dyes. In some cases you use another antibody to pick up the attached antibody. And then you put the cells through a machine with laser beams, and it tells you what percentages of the cells are of a particular type. It was expensive to do that procedure then. The antibodies were expensive.

Hughes: Was there just one machine at UCSF?

Levy: I think there were two. There was also a separate one in a core facility. We worked with Dan Stites, and that was a big help to us, to be able to watch over time what happens to the white cells in a subject.

Hughes: Is flow cytometry the only way of obtaining numbers of CD4 and CD8 cells?

Levy: You could do it with a microscope by immune fluorescence. That's what they do in third world countries. You find how many cells show fluorescence with specific antibodies. We didn't do that. I know we tested it, though, because we did some fluorescent testing. I remember going back to Steve Shohet's lab where Margaret Clark was, and we looked at labeling of the cells with fluorescent antibodies versus the flow cytometer method.

More on RT-positive Viral Cultures, Fall 1983

Levy: You put cells in culture with IL-2, then you watch them over time. You remove fluids and assay for reverse transcriptase. At first, we didn't start taking fluids out as early as three days since it's expensive to do reverse transcriptase [RT] assays. So we took them out at about nine, twelve, and fifteen days. This was probably October or early November [1983] that we were getting some RT-positive cultures. But we couldn't be sure that this wasn't a cellular factor, because the reverse transcriptase assay is a most sensitive technique, and it can also pick up cellular enzymes. So we had to put the virus back into culture and check on its infectivity.

Hughes: Cellular enzymes can be confused with the RT?

Levy: Right. Any DNA polymerase can use the template that we used. I had already worked in that area when we were looking for an endogenous human retrovirus, and we kept coming up with cellular polymerases. So I knew that I'd better not jump to a conclusion on one assay. So we had to isolate and grow an agent. That took us about a month. So by December, I guess, we began thinking more along the lines that we had the AIDS agent.

Visit to the Pasteur Institute, October 1984

Levy: Now, as you remember, I was in Paris in October of 1984, and, as I said, I went to see my friends at the Institute Pasteur because Jean-Claude Chermann and Françoise Barré-Sinoussi had been associates of mine in 1979 when I did a sabbatical in Paris with François Jacob. All the virus studies had to be done in their lab for safety reasons. I have known Jean-Claude since the early seventies. He was under Montagnier. I only saw Montagnier once during that period, near the end of my sabbatical stay, when I went and described my research, which was on embryocarcinoma cells and virus infection.

Hughes: You mean that Montagnier wasn't really deeply involved with the lab work?

Levy: He wasn't deeply involved with Chermann's work, because Montagnier was not working on retroviruses; he was working on interferon.

I know we went through this, but I went to Paris to congratulate them for the isolation of the AIDS virus, because it was not a major lab in retroviruses--in the world. In France, they were okay. And I was pretty proud of the fact that they had a paper in *Science* in April [1984], and that they were showing Bob Gallo that they could also find viruses like Bob Gallo was finding viruses. But Bob Gallo's virus was HTLV, which I was adamantly convinced was not the cause--

Hughes: At what stage?

Levy: Oh, at the very beginning. I was interviewed, and Bob Gallo was furious with me for saying it wasn't the cause.

Hughes: Go over the reasons.

Levy: It couldn't be a cause of this disease, because HTLV is not produced by the cells in sufficient quantity that you could have sufficient virus in blood products to infect hemophiliacs. Hemophiliacs become very important for my way of thinking.

Hughes: Whom Gallo never paid attention to?

Levy: I don't know, but he never seemed to pay attention to them. He was somewhat lucky, because he could have missed the agent even more, because he didn't consider the fact that some hemophiliacs never got a blood transfusion, that they had platelet transfusions and Factor VIII and Factor IX and got this disease. Thus if HTLV is so cell-associated, it could never be the cause. Now we find

out, he changed the abstract of the French to sound like their virus was HTLV.[1] So it misled a lot of us, which is one of the things the country's concerned about.

Hughes: Including you?

Levy: Absolutely. I talked to you about going to the meeting in Japan, and hearing about the French agent, and kind of laughing because Alizon said antibodies to it were only found in French patients. Which was really due to his language problem. He didn't mean to say it. Then later, the more I heard, the more I realized that I had been misled by everything I had read in our press, that indeed this [LAV] looked different from HTLV.

Hughes: I pulled you away from telling the other reasons why you thought the causal agent couldn't be HTLV.

Levy: HTLV is highly associated with T cells; it does not kill T cells; it transforms them. So how could you explain the CD4 cell loss? And the virus would have to have been produced in very, very high amounts to have been recognized as being transferred among homosexual men by sexual routes. It can be passed from women. But most of the time, HTLV is passed by milk. So when I told the French, "Your agent is HTLV and could not be involved," they responded, "No, that's not the case," and they started telling me how LAV grows in high titer, how it kills CD4 cells, and has a preference for growth in CD4 cells.

I said to the French, "Look, if you're right, once we get set up, we should be able to confirm you right away." They said, "Oh, you can have our agent." I said, "Oh, no. If I confirm your finding, it will be totally independently. Otherwise, no one will believe it."

So I came back to UCSF; we finally got an ultracentrifuge; we started doing it, and we isolated a retrovirus. But we didn't recover this virus lots of times. We only got it out, oh, maybe 10 percent, 15 percent. We weren't yet capable of isolating the virus in an efficient manner. We now know why.

That lack of consistent recovery is the initial basis of Peter Duesberg's theory. I had lunch with Peter during those early periods, and I said, "You know, we can't get the virus out of a lot of people." He still holds on to that information. I

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[1]F. Barré-Sinoussi, J.-C. Chermann, F. Rey, et al., "Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS)," *Science* 1983, 220:868-871.

strongly felt the data indicated that we just weren't good enough technique-wise to get out the virus; Peter read it as, it's because the virus is not there.

Research on Blood-clotting Factors

Levy: But I also was concerned that this retrovirus might not be the cause. Maybe it was a passenger in an immune deficiency state. And what threw me was the Factor VIII. How could a retrovirus survive all that purification procedure for clotting factors?

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Levy: I believed the method for obtaining and lyophilizing Factor VIII would destroy the [viral] envelope and kill the virus. I asked: Cytomegalovirus? Herpes viruses? They're not passed by Factor VIII or Factor IX; they're enveloped viruses. A retrovirus would also be affected.

Hughes: Retroviruses are killed in the purification process.

Levy: Yes. But I also realize now there's nowhere near the quantity of these viruses in the blood as is true of HIV. I actually wrote up a little paper, which was not published, in which I said, "Is a retrovirus involved? If it is, it's got to go through all these purification procedures, and it seems logical that it might not be the cause, and we should be looking for another agent."

I had learned that a researcher can come up with ideas but has got to prove them. So I decided to see if a retrovirus could be the cause of AIDS by doing experiments in which plasma specimens would be spiked with the murine retroviruses. That one has the same chemical properties of the AIDS virus but would be easier to work with in large quantities. As I told you, I called around to five companies purifying Factor VIII. Only one--Cutter --agreed to do it with me; the others said because of patent rights, they didn't want to get involved, and they should have big regrets now.

Hughes: I don't understand how patent rights fit in.

Levy: They didn't want me to know how they purify. Actually I didn't care what they did to purify the factor.

Well, Cutter said, "We're happy to do it." Cutter came over and I gave them the murine virus. They spiked the plasma and did

the separation studies. This experiment was set up at the end of '83. We began studying it in January and February of '84. It was a lot of work. In March of '84, there was evidence that virus was surviving the purification. I was very surprised. It didn't survive 100 percent, but if there were a lot of virus in blood, you knew it could survive. So it fulfilled my view of Koch's postulates; everybody with AIDS could have gotten this type of virus.

More on Isolating AIDS-associated Retrovirus

Levy: So we really then began emphasizing research on HIV or ARV--the AIDS-associated retrovirus, as we called it. We concentrated on this one agent. I had EM [electron microscope] pictures taken and antibody studies extended. March [1984] was quite an active month.

Hughes: Was there an electron microscope here?

Levy: No, I took it to Lyndon Oshiro, who for years had been working with me on EM studies. I view AIDS as being that one opportunity to call in all the people that were here working with me in the early days of virology. I had actually organized a group in the San Francisco area when I first arrived in the seventies to interact on a regular basis. We called the group the Tumor and Virus Group of the West. Walter Nelson-Rees came up with the name so we'd have the acronym TuViGrouWe. That group met every two months at different places--Berkeley, Stanford, and here--and it combined people in many different areas of virology, including tumor virology.

Hughes: Isn't Oshiro over at--?

Levy: Berkeley, State Labs [State of California Department of Health and Human Services].

Lyndon and Paul Arnstein were part of this group. Paul later was the one doing all my inoculations of Kaposi's sarcoma tumors into nude mice to see if they'd grow. And Lyndon collaborated on EM studies. Interestingly, the lyophilization work on retroviruses that I did later with Factor VIII and ARV was actually done earlier with mouse retroviruses with Howard Fieldsteel who was at the Stanford Research Institute. Then we

studied this means of preserving retroviruses.[1] So what you're really seeing, Sally, is that suddenly many things I'd done before came together for this challenge. And I found myself turning to papers that were seemingly unrelated to AIDS. Even when we were trying to prove that HIV was not associated with any other diseases, I called my former colleagues and mentors. For example, the Henles helped me on some antibody studies.

Gallo has had papers that were wrong and I think misled scientists. For example, he had a paper in *Science* that said that the origin of HTLV-III, as he chose to call it, was located in Uganda around the Lake Victoria basin, because he found these antibodies to the virus in children there but curiously not in adults. Now, how could the virus be in children and not in adults? It didn't make any sense. It seemed like the Gallo group didn't consider a mechanism; they just reported the data, and the results were later proven wrong.

We evaluated 300 serum specimens from all over Africa that the Henles had stored. We used the immunofluorescence assay [IFA], not the ELISA [enzyme-linked immunosorbent assay] technique. The Henles actually were at a meeting and presented those data, and Bob Gallo said, "Well, Jay Levy probably didn't do the assay correctly." The Henles responded, "Well, no. He's done a lot of IFA assays and knows how to do them. We taught him." Well, the reason for Gallo's claim of HTLV-III in children was nonspecific sticking of antibody to the ELISA plates. It was all wrong. A *Science* paper!

So we return to my earlier comments: As I mentioned, I worked in Africa on Burkitt's lymphoma. Now, that experience came into my research on AIDS. I knew Africa; I knew the problems in Africa, and I had sera from Africa to use for these studies. Thus, when I returned to Africa in 1987, I wasn't surprised at the living conditions in the hospitals. My colleagues who had never been there before said, "Oh, this is terrible." I was not surprised as I had already seen this. So many things in my past came together with the present.

If I had been more like a Bob Gallo and jumped rapidly to a conclusion, I probably would have published in December of '83 that we had a retrovirus similar to that of the French. At the present state of my career with no tenure position, I couldn't be that quick to a conclusion. If wrong, it could hurt my

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[1]J. A. Levy, A. H. Fieldsteel, "Freeze-drying is an effective method for preserving infectious type C retroviruses," *Journal of Virological Methods* 1982, 5:165-171.

credibility. I must tell you as well that we got slides of infected cells from the French, and we weren't getting positive immunofluorescence assays regularly with their reagents nor our sera. That was why we developed our own IFA. So we couldn't be 100 percent sure that our agent and their agent were the same. We therefore continued to keep ARV as a separate name.

Press Conference on the Isolation of ARV, August 16, 1984

Hughes: If you follow scientific etiquette, the press conference or the publicity should follow publication in a peer-reviewed journal.

Levy: That's right, and we did have a press conference. My paper came out in *Science*, and there were a lot of calls. So I said to Marc Conant, "I think there probably should be a press conference, and I want you there." Because he had been so helpful to me. So they had one.

Hughes: The university?

Levy: The university public relations group organized the event. I remember, I used the blackboard, and [*San Francisco Chronicle* reporter] Randy Shilts covered it here. Because the virus had already been found, they didn't emphasize that this was an independent discovery but rather that the virus was in an area in California where there are many cases. The articles emphasized healthy people being infected.

Hughes: Was that the emphasis the press chose to take from your presentation?

Levy: I'd have to read the article again. I remember being somewhat disappointed that they didn't pick up on the fact that we really had been among the first to find the virus.

What makes it important is that we were a small group. When I first started work on isolating the virus, there were only four of us. Then later we had six or eight. Our paper has almost everything that Gallo's four papers had; we put it into one. We had better serology. We had almost 100 percent people with AIDS showing antibodies, once we had our immunofluorescent assay working.

Infecting Cell Lines

Levy: So now after we got the virus out, we started to look at peripheral white blood cells using immunofluorescence, but they died off, and not a lot of them got infected. So as I had known from all my work in viruses before, I started to try to infect cell lines. I couldn't get any cell lines infected.

Hughes: What were you using for cell lines?

Levy: Oh, there were a lot of them around--MOLT4, CEM. They were tumor cells lines, T-cell lines, B-cell lines, macrophage cell lines. I couldn't get it to work until we tried HUT78 cells that I got sometime before this from Adi Gazdar who developed the cell line.

Hughes: Was it easy to get HUT78?

Levy: Adi Gazdar was a friend of mine. We had worked together at NIH. I didn't have the money to get it from ATCC [American Tissue Culture Collection]. It would have cost me $80, so I thought, Why don't we just get it from the source--Gazdar? In the long run it was better, because then I knew what I got. At least I knew this was HUT78.

Hughes: What do you mean?

Levy: If I got it from the American Tissue Culture Collection, it should be right. But I wasn't getting lines from them because of the cost. Instead of asking someone else, I chose to get the cells from the researcher who derived the line, so I did not think there could be any mix-up.

Hughes: Was there any hesitation to give them to you?

Levy: No. I wrote, Adi sent the cell line to me, and we called it $HUT78_{AG}$, for Adi Gazdar, so everyone knew the source.

Hughes: Crewdson made quite a point of the fact that Gallo was using a subgroup of the cell line, H9.[1] What difference did that make?

Levy: I'll tell you this story. Much of the work on AIDS, I was doing in the lab myself.

Hughes: You mean instead of--

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[1]John Crewdson, "The great AIDS quest," *Chicago Tribune*, November 19, 1989, section 5, p. 13.

Levy: Instead of a technician. I like being in the lab. But in those days, I had to do a lot of the work. So I went in the back room, and I inoculated our virus, ARV-2, which was the one that was growing really well in cell lines. Ends up this isolate is not our best grower, but it was the one that did best then. ARV-2 did not replicate well in most cell lines. Our ARV-1 strain didn't grow well in any cells, and so we froze it away.

When I put ARV-2 in the HUT78 cells, it grew. So drawing from my days with the Henles, I quickly developed an immunofluorescent assay using these cells. We called it the E line since it was the fifth cell line I had tried in that experiment.

Hughes: Why does the virus grow in one cell line rather than another?

Levy: Well, that has now become a major area of research. The viral envelope has to interact with the cell surface to get inside the cell, and some cell lines have a cell surface that permits it to enter and some do not. So this virus grows well in HUT78. By the way, we had other viruses that did not go into HUT78 but enter other cells. That question has formed one of the major avenues of study in my laboratory.

Because you're interested in how an investigator reaches decisions on research, let me repeat that I worked on murine viruses, xenotropic viruses. They grow in a variety of different cell lines, and these viruses can be distinguished by what cells they grow in. So it was a natural for me to think, ARV, what does it grow in? Therefore I tried lots of cell lines. I also asked whether we could get it to grow in a variety of different animal cells. I tried all sorts of animal cells as well as human cells.

More on the Immunofluorescence Assay for HIV

Levy: The assay is conducted as follows: you fix the cells on a slide with cold methane/acetone. Then you add the human serum in different dilutions, and the antiviral antibodies if present attach to the viral proteins associated with the cells. Then you use an antibody that detects human antibodies. This second antibody is fluoresceinated and therefore can be detected with a fluorescent microscope. If antibodies in the serum reacted nonspecifically to human cells, every cell in the assay would stain. So specificity would be lost.

So I devised a simple approach: mix 50 percent infected cells with 50 percent uninfected cells, then perform the IFA. Any sera giving 50 percent or less staining and in a particular manner would be considered positive. With that technique, Larry Kaminsky, who was a dermatology fellow in my lab, did the immunofluorescent assays. To this day, every serum under analysis is given an LK number in continuing this process. I taught Larry as I was taught, and he worked out the pH conditions and the system needed for best results. We found out we could do the IFA in twenty minutes, making it later helpful for kidney transplant surgery. At first Larry did all the sera for San Francisco--for the blood bank, for everyone in the community.

Then we taught the IFA to Judy Wilbur at the [San Francisco Health Department] city clinic, and she used it. We sent cells to Chip Sheppard at the state lab [State of California Department of Health Services], and he set up the assay over there. Evelyne Lennette received the cells and began doing the test at her company, Virolab in Berkeley. They did immunofluorescence assay [IFA], so then after awhile, we stopped doing it routinely for everybody. I couldn't afford it. So I'm very pleased that we were able to farm out this technology long before ELISAs were commercially available.

Hughes: Over what period?

Levy: That was from April of '84 until March of '85, when the commercial ELISA came out. Herb Perkins from the Irwin Memorial Blood Bank in the early days, for example, would call on me: "Jay, can you do a serum?" Many of my early publications, like with Herb on hemophilia,[1] with Marion Kuerper and the others, were IFA-based. Lots of work.

Hughes: Were you doing this testing gratis?

Levy: Oh, yes. But IFA wasn't sophisticated enough for other researchers, so many did not accept this approach for looking at anti-HIV antibodies. Yet you could use this assay in a developing country. Also, we didn't have an ELISA plate reader nor could we afford one. We also did not have immunoblot assays developed for extracting and placing proteins on gels, which is what Bob Gallo's group had done. These are techniques that required equipment that we did not have. In the end, many were saying you had to do immunoblot in order to really know the result on an antibody test.

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[1]H. A. Perkins, S. Samsen, J. Garner, et al., "Risk of AIDS for recipients of blood components from donors who subsequently developed AIDS," *Blood* 1987, 70:1604-1610.

We kept arguing for immunofluorescence, and I had to publish a couple of papers to prove it.[1] I wanted the developing countries to know that they could test for HIV in their own laboratories with just a slide containing fixed cells.

Hughes: And IFA was picked up as the technique?

Levy: No, IFA was considered too subjective.

Hughes: They wanted ELISA?

Levy: They wanted ELISA or immunoblot. A simple serologic assay did not seem to appeal to investigators studying what appeared to be a difficult agent to find. I found an unreasonably tremendous resistance to IFA. It was a cheap test, and anyone could do it.

Hughes: What about sensitivity?

Levy: Sensitivity was very good with IFA. The problem was, one could argue, and it's true, that you had to be fairly experienced to read it. You had to have practice in reading for a few days to be certain. Several individuals came to our lab to learn IFA. We actually published how you would detect a positive [reaction] by various distributions of the antigen, with the criteria that were needed;[2] it was not hard.

Hughes: Describe exactly how you read the test.

Levy: You put cells that have been reacted with serum and fluoresceinated anti-human antibodies under a fluorescent microscope. The laser beam picks up the anti-human antibodies that fluoresce. When you look inside the cell, you see fluorescence in a characteristic pattern. Moreover, we mixed

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[1]L. S. Kaminsky, T. McHugh, D. Stites, P. Volberding, G. Henle, W. Henle, J. A. Levy, "High prevalence of antibodies to AIDS-associated retroviruses (ARV) in acquired immune deficiency syndrome and related conditions and not in other disease states," *Proceedings National Academy of Sciences (USA)* 1985, 82:5535-5539.

E. T. Lennette, S. Karpatkin, J. A. Levy, "Indirect immunofluorescence assay for antibodies to the human immunodeficiency virus (HIV)," *Journal of Clinical Microbiology* 1987, 25:199-202.

[2]L. S. Kaminsky, T. McHugh, D. Stites, et al., "High prevalence of antibodies to AIDS-associated retroviruses (ARV) in acquired immune deficiency syndrome and related conditions and not in other disease states," *Proceedings National Academy of Sciences* 1985, 82:5535-5539.

positive infected cells with uninfected cells to rule out nonspecific staining.

Hughes: So if you get one fluorescent cell, the assay is positive?

Levy: No, on these assays you'd have to have 50 percent or a little less, depending on the level of antibodies present. At least 40 percent had to be positive. Alternatively, if you had 80 percent positive, you had to do it again, since antibodies to normal cells must be involved. Or you need to absorb out the antibodies to human cells. The procedures were not difficult.

One day, when I'm able to tell the story, all these barricades to getting issues resolved faster, because we were not given the attention, will be surprising. The focus was on the East Coast.

Hughes: Now, was the focus on the East Coast because Gallo had the prestige and the money and the government behind him? Or was it because until recently West Coast medicine was in the shadow of what was going on on the East Coast?

Levy: I think it was both. I think that if it had been anyone else competing with me on this topic, I still would have problems getting our message accepted, because this school was not a strong advocate on AIDS, never has been, and other schools would have picked up the momentum and gone with it.

Changing Research Foci

Hughes: From 1983 on you focussed exclusively on AIDS?

Levy: I continued to do some work on the murine xenotropic viruses through '85. Then I combined that work with a study on using those animal viruses to mix with the human virus [HIV] to show that you could get HIV into animal cells if they carried the envelope coat of a different retrovirus. But the studies in the 1980s were mainly aimed at AIDS. Kaposi's sarcoma at first had been the issue. Kaposi's is getting new focus now in my lab.[1]

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[1]J. A. Ambroziak, D. J. Blackbourn, B. Herndier, et al., "Herpes-like sequences in HIV-infected and uninfected Kaposi's sarcoma patients," *Science* 1995, 268:582-583.

I had to give up work on endogenous human retroviruses that we were finding in placentas[1]; there was no money, yet it's a fascinating area which unfortunately no one has picked up on yet. I hope one day I can go back to it. I had to give up all the work on xenotropic viruses: Why are they inherited in the animals? What do they do? What about the anti-xenotropic virus factor that I described? It's a lipoprotein that neutralizes the virus. I've had phone calls recently, "What's being done on it?" "Nothing." "Why?" "There's no one to fund it." Now there is practically no person outside of the NIH working on xenotropic viruses, to my knowledge. It is unbelievable for such an important field. We have money really only for human disease.

In March 1984, when I came from that meeting on HTLV where Gallo gave me a hard time, I had lunch with the Henles, and I said to them, "You know, we have the AIDS virus, but I hate giving up xenotropic viruses. They said, "Don't think twice. Move to human systems. That's where you'll make your mark."

Hughes: Were they thinking of funding too?

Levy: Funding, respect, prominence. In retrospect, of course that was the answer, but I was still disdainful of people who jump into opportunities and don't continue in basic, fundamental work. I have really learned the realities, because it has changed everything in my career. My whole existence here at UCSF was down the tubes, so to speak, while I was working in the murine systems. The minute HIV and AIDS came and I began to work in that field, I was much more protected. I don't know if I still have the base, but I'm still respected for what we are trying to do. People meet me in the elevators and they say, "Jay, you're doing such good work now." And I say, "That would be fine if they'd leave the damn 'now' out." [laughter] Because really I am doing the same thing I did before. Everything I learned in the animal system, I moved to the human system, and since there were very few biologists doing it in the 1980s, we were able to advance the HIV field quite quickly and have many publications.

Hughes: Is it working on human systems, or AIDS per se, that makes you acceptable?

Levy: It's human systems and AIDS. I don't know if I worked on AIDS in cats, if I would get this acceptance. It's the human aspect, yes.

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[1]J. Nelson, J. Leong, J. A. Levy, "Normal human placentas contain virus-like RNA-directed DNA polymerase activity," *Proceedings National Academy of Sciences* (USA) 1978, 75:6263-6267.

I think you hit on something very interesting. If it were human arteriosclerosis caused by a virus, that would be fantastic. If it were human diabetes caused by a virus, that would also be better. But AIDS--we had a dean [Rudi Schmid] here who didn't want to mention the word; you had a head of medicine [Lloyd Hollingsworth "Holly" Smith] who didn't want to mention it. They thought it would reduce the number of residents and interns who came to work here. It was a financial and political issue. AIDS research was not a popular area but had to be worked on. So how do you get a base from which you can really influence policy? My laboratory until recently has not been the place people come and say, "What do you think? Where is AIDS research going?" We had many of the right answers, but we were never asked.

Discovering the Importance of CD8 Cells

Hughes: One of the technical breakthroughs was the realization that, to keep the cultures going, you had to keep adding fresh white blood cells. Would you talk about technical breakthroughs?

Levy: "Fresh cells" may be confusing. What you need is enough target cells for the virus to keep replicating. You also need to stimulate those cells so they're activated and thus susceptible to infection.

Hughes: You mean, so that they're dividing?

Levy: They're dividing. So you've got to take the white cells out and add a mitogen, like phytohemagglutinin, PHA, and then three days later, wash it out and add your virus. You also need to do that to activate the viruses inside an infected person's white cells to come out and grow.

Hughes: These are all techniques that existed before AIDS?

Levy: Those techniques were around. I have to say that Françoise Barré-Sinoussi in her article went through the technique for growing the virus in very good detail and most are still used today.

Hughes: In 1983?

Levy: Eighty-three. But what she didn't say, as I recall, was you had to keep adding in fresh normal white cells. In fact, because we are purists, when we were trying to isolate the virus, we never added in normal lymphocytes as fresh targets. We took the white cells from a patient, put them into culture, added PHA, and virus

came out or it didn't come out. By this method, we didn't isolate a lot of viruses. It wasn't until '86 that we figured out why. It was because the CD8 cells that are in the blood sample as well, when activated by the PHA, work against the virus; they suppress the virus.

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Levy: When we discovered this effect of CD8 cells, I was as excited as I've ever been in HIV research. I think I was even more excited than finding the virus, because the virus came about by culturing. With CD8-cell function, we had to figure it out and then devise the experiments to prove it.

Hughes: How did you happen to work that out?

Levy: Because we couldn't get the virus out of the blood of so many people, many of them healthy. Why? Was the virus not there? I remembered work with the Henles on Epstein-Barr virus: I knew that it was the CD8 cells which suppress the Epstein-Barr virus. So I said, "Let's take out the CD8 cells." There was at that time a technique to remove CD8 cells from a blood sample. You need monoclonal antibodies to the CD8 molecule. You attach them on a plate; you add the blood sample to the plate; the CD8 cells attach to the antibodies in the plate. Then you remove the non-adherent cells that lack CD8 cells and put them in the culture. In one week, by using this procedure, the virus came out. Then we collected the CD8 cells and added them back to the culture. The virus went away. We could repeat this process. The results were just dramatic.

Chris Walker, my postdoc, made that observation with me and did beautiful work.[1] The finding was cited by Channel 5 as the most important science story of '86. We had TV people (Dave McElhatton) here in December 1986 to film the lab and give the report. It deserved it, and it still deserves it. We're still trying to figure out the mechanism. I think that's what really put us on the map in terms of discoveries in AIDS research.

Collaborating with Chiron Corporation

Levy: We also benefitted from the fact that our virus, ARV-2, was cloned very soon after its isolation. When I had the virus and I saw all

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[1]C. M. Walker, D. J. Moody, D. P. Stites, J. A. Levy, "CD8+ lymphocytes can control HIV infection in vitro by suppressing virus replication," *Science* 1986, 234:1563-1566.

the competition, I only had a small group, and I didn't have anyone who did molecular biology. I went down to see Bill Rutter at our university.[1] Now, there again, talk about my family of past contacts: Bill Rutter was in biochemistry, and his personality and my personality match very well. He's a very outgoing person, very bright, very accomplished, but likes fun like I like fun. We joke around a lot and I have great respect for him.

So I called and later met Bill one day in his office, and I said, "We have this AIDS virus that we need to clone." He said, "Jay, we can do it in my lab [in the Department of Biochemistry and Biophysics, UCSF], but you should really go and see my company [Chiron Corporation] since there we can do it faster." I got nervous; I said, "Company, you know, that's new for me." I had been told not to work with companies. Well, that's why Herb Boyer got burned, and I just was not ready to do it.

Bill said, "Just go over and talk to the group." So I went over to Chiron, and I was overwhelmed by all the equipment, organization. I knew that if I wanted to be in this competition to clone and sequence HIV and find a solution for this problem, I needed the help of a company. Bill said to me, "We could clone this virus in two or three years in my lab at UCSF. We can do it in two months at my company."

So we began working with Chiron. And there again the Gallo publication, his comments, and his manipulation of the media and the stories led us astray. He kept saying the AIDS virus was HTLV-III. It offends me so much the way he manipulated the interpretation of his EM [electron microscope] pictures, all his data, to make it sound like the virus he found was related to HTLV. It was a totally different family, totally different. Like apples and oranges.

So when Chiron went to clone our virus, they said, "We'll use an HTLV probe to find the viral DNA." I said, "Don't! It's totally different. Do an acute infection and take the DNA from the acute infection." But for one month they did it using an HTLV probe, and then they came back and said, "Jay, you were right.

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[1]For more on Rutter and his contributions, see: William J. Rutter, *The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco*, volume 1, an oral history conducted in 1992 by Sally Smith Hughes, Ph.D., Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 1998. Also available online at: http://www.lib.berkeley.edu/BANC/Biotech/

It's not HTLV." We lost a month. But for that delay, we could have been ahead of the competition. As it was, we were the first but by only a few days [to clone and sequence the AIDS virus].

Cloning and Sequencing the Virus

Hughes: Grmek mentions four groups that were cloning and sequencing the virus.[1]

Levy: That is right. We worked with Paul Luciw and Dino Dina at Chiron and cloned and sequenced our prototype virus with their group. Luciw is now at Davis, but he was at Chiron then. It is perhaps interesting to note that when we described our virus, Murray Gardner asked if he could have it. He had gotten Gallo's virus, and he had gotten Montagnier's virus. Murray was one of those individuals that everyone trusted. He was really friendly, a communicative and cooperative person, so no one minded giving him the virus. Well, he set one of his students, Marty Bryant, to compare them. Now, this work was going on in '84. He presented the data at a meeting in Colorado. The results showed that HTLV-IIIB and LAV looked exactly alike in terms of restriction enzyme analyses of the viral genome, but ARV-2 was very different.

Hughes: Did this set off alarms immediately?

Levy: It didn't. Many thought, Oh, the group in California has something strange.

Hughes: [laughs] Maverick.

Levy: Yes, it's a maverick, exactly the word.

In fact, I was back at NIH in November 1984, and Mal Martin and Janet Hartley asked me to give an informal talk on my research, and I did. At the end of the talk, Mal Martin said, "But Jay, I just came from a meeting in Colorado where Murray Gardner presented his data, and I think you'd better be very

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[1]The virus was cloned virtually simultaneously by groups at NIH and the Pasteur Institute. The nucleotide sequence was established, again almost simultaneously, by groups at the Pasteur Institute, NIH, UCSF-Chiron, and Genentech. For details, see: Mirko D. Grmek, *History of AIDS: Emergence and Origin of a Modern Pandemic*, Princeton, N.J.: Princeton University Press, 1990, pp. 74-75.

careful, because your virus is really a maverick. It's quite different from the Gallo virus and the Montagnier virus."

I said, "Malcolm, we have two other virus isolates, and they're totally different from the first one I got." And that's when he went, "Oh, my God." Absolute quote: "Oh, my God." And he knew, and I knew--but I don't know if I realized the ramifications of that finding at the moment. When he challenged me with, "You have a maverick," and then I said, "But wait a second," to defend it, suddenly it all came through. From then on, Malcolm went on a campaign to show that what Gallo had was really the French virus, and Gallo was saying, "I never received the French virus," and all the lies continued. Malcolm is most courageous, because he's continued to provide the truth all the way up to the courts.

Hughes: Is there anything to be said about the other cloning teams? There was the NIH-Harvard team, which of course was using HTLV-III; and then there was the group at the Pasteur with LAV, which included the Englishman, [Simon] Wain-Hobson.

Levy: He did the molecular work with Montagnier.

Hughes: I'm talking about the sequencing.

Levy: Oh, sequencing. Okay, fine.

Hughes: And then Paul Luciw--

Levy: At Chiron.

Hughes: Right. And then what about Genentech?

Levy: They took the Gallo virus.

Hughes: What did these groups find?

Levy: The results showed that IIIB and LAV were very similar in nucleotide sequence. But people wanted to know, couldn't that be by chance?

Hughes: When this sequencing was going on, was everybody very aware that this was a real race, that there were four teams competing?

Levy: Absolutely. I joined up with Chiron because they came to me, and they really wanted to work with me to develop the AIDS virus story. I said, "Look, if you want to work with me, I can't work under the conditions I have. I have nothing in this tiny little room at UCSF. Can you help me out? Can you give some money to the lab to renovate a room, and we can work better?"

"Absolutely," and they gave us some funds for a part-time technician, and we really got going.

Genentech called and said, "Give us the virus and we'll clone it." I said, "Well, I would like you to help me out." They said, "Oh, we'll do this for free for you." So I said, "Thank you very much but no." To this day, there are people over there that don't forgive me for not giving them the virus. But they were not willing to help me with my lab. Chiron was and really helped us make progress.

Hughes: I thought Genentech did work with ARV.

Levy: No. Never. They may now, because Phil Berman is more active, and there are others there at Genentech who would like to use ARV-SF2.

So we were in a race, and we got it cloned first. I can remember that Chiron wanted to announce it to the press, and I was very uncomfortable. Our [UCSF] public relations person, Michele Reichman, didn't approve of press conferences before publication. But I had no control: Chiron was going to do it if we joined them or not. So they did it; they made an announcement.

Hughes: Now, this is just the cloning, not the sequencing.

Levy: The cloning. However, that was a big step towards a vaccine. The virus has an RNA genome that makes a DNA copy of itself through its reverse transcriptase enzymes. This DNA integrates into the chromosome of the cell. That DNA is captured by selective probes for eventual cloning. By this time, I was deriving an infectious DNA copy of the virus--one that gives rise to infectious virus once introduced into a cell. So when Chiron was probing with HTLV, they never found ARV because the AIDS virus differs from HTLV. What we did was take the early viral DNA products in the cytoplasm as the virus is replicating and pulled out the clone. We looked at its restriction mapping, and those results formed the first paper.[1] The data were important in showing the differences between ARV and HTLV-III/LAV.

Hughes: So right away, you were getting a clue--

Levy: That the restriction maps of IIIB and LAV as compared to ARV were different. But LAV and IIIB were exactly the same. In fact, each of them had a second virus variant in the analyzed preparation, a small amount of a related virus variant. Now, can you see how

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[1]P. A. Luciw, S. J. Potter, K. Steimer, et al., "Molecular cloning of AIDS-associated retrovirus," *Nature* 1984, 312:760-763.

crazy it would be to think that this finding is by chance? Gallo did say it was probably the same person, or a contact--the subjects giving IIIB and LAV both came from New York and could have known each other. I found these explanations highly unlikely.

So there was a big race to clone the virus first, and Chiron made the announcement. I was somewhat accused of wanting publicity, but really it was Chiron that handled the press conference. Nothing was linked to the university. But truthfully it wasn't the right thing to do. A scientist should have a publication before a press announcement. And in fact, when we later called *Science*, they said, "No, we're not taking your paper because you already made a press release." But *Nature* took it. And then Gallo published in *Science*. He had two papers. I heard, Luc Montagnier's paper went to *Nature*, and it was held up because Gallo has all these connections at *Nature*, and they decided not to publish it. Quickly it went to *Cell*,[1] and *Cell* published it within a few days.

Hughes: Is that the clone, or is that the sequence?

Levy: Clone. So that got everybody's paper out about the same time.

Hughes: And then you were racing to sequence?

Levy: Then we were racing to sequence, and we got there at around the same time. We published it in *Science*,[2] and it's a beautiful paper--a really comprehensive article.

Hughes: With no press announcement?

Levy: No, that time, we published before any press announcement.

Hughes: After the cloning, did people think that the vaccine was right around the corner?

Levy: Yes. Around the corner. Many thought once you express the proteins, you've got the vaccine. They didn't know that all the viruses [HIV isolates] were different. We did, but I think we were still optimistic.

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[1]S. Wain-Hobson, P. Sonigo, O. Danos, et al., "Nucleotide sequence of the AIDS virus, LAV," *Cell* 1985, 40:9-17.

[2]R. Sanchez-Pescador, M.D. Power, P.J. Barr, et al., "Nucleotide sequence and expression of an AIDS-associated retrovirus (ARV-2)," *Science* 1985, 227:484-492.

Controversy over the Virtual Identity of HTLV-III and LAV

Hughes: You and the others who were working on sequencing the virus almost immediately recognized the significance of having, for all intents and purposes, identical sequences for LAV and HTLV-III. But how long did it take the press and the scientific community to recognize the implications of this work?

Levy: When the truth emerges, you'll find that it was known but made a cover-up by the government.

Hughes: How?

Levy: In the government, researchers were not allowed to call the AIDS virus anything but HTLV-IIIB. That was a directive from the government, and any connection to LAV was essentially hidden. Moreover, the French apparently were not totally convinced IIIB was LAV--here I don't understand the French.

Hughes: But it's more than finding the virus. One of the things that was motivating this battle for credit was the tremendous monetary prize.

Levy: Well, the U.S. government wanted it, I suppose for royalties from the patent. They're getting it.

Hughes: Yes, but the Pasteur Institute needed it too.

Levy: They're getting 50 percent. But the Pasteur Institute left the patent fight; they couldn't afford fighting the U.S. government. So they dropped it. They said, "Okay, we'll do 50-50." Now they're starting up the legal battle again. I can't understand it, and I will never be quite privy to it. Crewdson probably will be one day. Perhaps in his book. There are all sorts of stories that we can't approach here, because they're not documented. I can only talk from my viewpoint, from conversations with Gallo and things that I know from events back then.

But this story was a real cover-up, and every bit of effort was made to hush up everyone. The most famous story was Murray Gardner's. After he proved in Colorado, through the work of Marty Bryant, that IIIB and LAV were identical, they decided to write a paper. He sent the manuscript to me, and I said it was okay. He sent it to Montagnier; he said it was okay. And Gallo squelched it. Gallo's group said, "No, you can't publish it."

In fact, he did more than that. The story that one day will be published after all these issues are discovered is that Peter

Fischinger went from the NCI to visit Murray Gardner about building a primate facility to increase the primate colony. And in that conversation, Peter Fischinger either said it directly or inferred, "If you want this facility, you'd better not publish your paper."

Hughes: How do you know that?

Levy: Because Murray Gardner told me that. I was furious and said, "Murray, you're being blackmailed." He said, "Jay, what can I do? I need the facility, and they have a lot of power, and I'll be left picking up the pieces." Which is true. Marty Bryant, who is now talking openly about it, called me and asked me, could I do something to convince Murray otherwise. I couldn't. And Marty Bryant left research. He is now a pediatrician. So that's one of the worst stories from this history. I can assure you that the lawyers are trying to get the documentation but it will be difficult to get the real letters, et cetera.

Hughes: Pasteur's lawyers?

Levy: No, the U.S. government investigating the case, because Gallo has appealed his misdemeanor charge, and now the OSI [Office of Scientific Integrity, NIH] is trying to really get him, to show what a dishonest person he is. They needed all the correspondence from me and Murray but I cannot find copies of all this. Unfortunately, I didn't even have a copy of my 1984 letter to Bob Gallo asking for his rabbit antibody, but John Crewdson had it.

Hughes: Because he got it from Gallo?

Levy: Yes. Freedom of Information Act. So he's faxed me--now I have a copy in my file. Amazing. I'm very disappointed that I do not have the documents to reveal these important events in history.

Mikula Popovic's Use of Pooled AIDS Virus

Hughes: Crewdson also makes the point that Popovic used pooled virus in his attempts to isolate the virus.[1] Would you comment?

Levy: That is the worst technique, and when I read it, I didn't believe it.

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[1]John Crewdson. "The great AIDS quest," p.11.

Hughes: When you read it at the time?

Levy: I read it at the time in *Science*. I said, "Who would ever do that?"

Hughes: Why did he?

Levy: Because he thought that the viruses were all defective, and they would help one another, and then he would get out a real infectious virus. It is a technique used by a person who's not a well-trained virologist. Now, Mal Martin just told me at the Berlin meeting [Ninth International Conference on AIDS, 1990] he doesn't even think Popovic ever used a pool. There's no record in any of his notebooks. All of a sudden, out comes this virus, and it's IIIB.

Hughes: You mean LAV?

Levy: LAV, yes. Well, they called it HTLV-III.

Hughes: Yes. But it's one and the same virus. Crewdson claims that there's no possible way of tracing the genealogy of these viruses that were supposedly being grown at the same time as LAV.[1]

Levy: Yes, that's right. None at all. They don't have them frozen away and the notebooks are incomplete.

Hughes: What?

Levy: They never kept the records.

Hughes: But what about records?

Levy: Many records disappeared. There were no records of the cell cultures from which the viruses came. Now, some of this is understandable. We just cleaned out my freezer. I'm a little more sensitive now to saving samples, but in the old days, I would have thrown out a lot of that stuff. Why do I need to keep the first isolate of ARV? I have it now in culture anyway. So it's admirable the NIH was able to go back to the freezer and find the original IIIB strain. Only at NIH where they've got lots of money and freezers could you do this. And who wants to clean them out? I think that's probably a good explanation for the story. But they had no records of these other virus isolates. The most recent paper in *Nature* where they said they took all the earliest

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[1]Crewdson. "The great AIDS quest," p.11.

ones and compared them, they found exactly the same results. The virus was LAV.

I think what's also so fascinating is, even the French virus was a contaminant.

Hughes: So we'll never know?

Levy: What do you mean?

Hughes: We'll never know what Gallo was growing?

Levy: Yes. If they were ever growing it. My point is, they were never growing anything. They said they had RF in culture at the end of '83. They didn't; it appeared in '84. They got it in '83, but they never had it growing, as far as I can tell.

Hughes: What's RF?

Levy: It's a Haitian isolate. My feeling is that they never had anything growing; they couldn't get anything to grow. They got LAV; it grew; they got it into HUT78 so they had an assay system for the virus.

Controversy over the Cell Line, HUT78

Levy: Now, we didn't talk about HUT78. That's a very important point in this history. It's probably the only one, like getting Al Capone on income tax, that they may get Gallo on. Because Popovic wrote that he went into his incubator and took out a T cell leukemia line and subcloned it. I read the paper; I thought that it was a line that he had established and was growing. It ends up being HUT78, but they didn't say that. They gave it a new name, H9.

Hughes: Implying that it was a new cell line?

Levy: I think so. A new cell line, absolutely. They tried to deny that, in fact. Popovic says, "I wasn't sure what line I had when I opened the incubator; we had so many lines." Is that an argument of a good scientist?

Hughes: Why was he trying to cover up the cell line identity?

Levy: Because again, he was following his boss. I think that they knew all along it was HUT78. HUT78 is easily available at ATCC, so anyone who wanted to work with HIV could get it there. Instead,

these scientists had to write to Bob Gallo, and what he did was create an incredible collaboration with everyone around the world. From what I gather--I never got anything--you had to ask his permission to publish, and his name was on many of the papers. It was a way of maintaining control.

Hughes: Is there any difference between H9 and HUT78?

Levy: None! They did chromosome checks and cell surface markers. They're exactly the same. One wonders if Popovic even cloned the cells. But he probably did.

Scientific Controversy and AIDS Research

Hughes: Well, what implications does this episode have for AIDS research and for science as a whole?

Levy: Well, I'll tell you it has turned lots of people away from AIDS research. To me, it reflects the Reagan years, where dishonesty reigned, and it just dribbled down to science. My only hope is that Clinton is going to clean things up. Although Harold Varmus and I have our differences, I think Harold's going to NIH as director will bring integrity back to the institution. He won't put up with these shenanigans. I think Gallo is worried, although he's at NCI, which is a little independent from NIH. The incident has been very destructive, terribly destructive for science.

Hughes: Well, it's been destructive for science as a whole, wouldn't you say, because this is one of a number of instances where the public perception is that scientists can't be trusted.

Levy: That's exactly right, and Gallo should have been disciplined long ago. Hopefully Gallo will have his day in court this month. The lawyer from OSI asked me to testify against Gallo. I just couldn't do that.

Hughes: Why?

Levy: Because I don't have anything concrete from letters or other documents. I have conversations; I have hearsay. It's better yet to get the Marty Bryants and the Murray Gardners to testify. And it's very uncomfortable to testify against a fellow scientist. It's very difficult--it's scary. I have little money now; I have no ongoing grants, and it is very political there at NIH. I mean, if they wanted to help me out, they could help me out. They're not helping me out with financial problems. The system is very

bad, in terms of protection. If you really want to be an honest person and do the right thing, you better have tremendous security--financial and political.

Giving the Virus an Official Name ##

Hughes: Dr. Levy, as you well know, you were on a subcommittee of the International Committee on the Taxonomy of Viruses, which was empowered to name the AIDS virus. Why was it considered necessary to convene a subcommittee to name this virus? Isn't that a little out of the ordinary? Normally, the discoverer names the virus.

Levy: Exactly right. But since the discoverer was being challenged by another "discoverer," the issue was not settled. Luc Montagnier's group had called it LAV; Gallo was calling it HTLV-IIIB; and we of course were calling it ARV. I would not have been uncomfortable calling it LAV; I didn't like the term, but I agree, the first person to get there should name it. If Gallo wasn't at NIH, he would never have gotten away with this, but he did. So U.S. researchers were saying, "We've got to call it IIIB." And since that was so confusing, and most people were uncertain as to what to call it, they decided they'd better form a committee and at least get one universal name for the virus.

Each of us put in our own suggestions for names. It was quite clear that if any of the three major discoverers put in a name, it would never make it. I personally liked human immunodeficiency virus, but I didn't put it in. Of course, I put ARV in, as well as others.

Hughes: Why didn't you suggest HIV?

Levy: Because if they said, "Jay Levy wants HIV," I can assure you that Bob Gallo and Luc Montagnier would have said, "We're not voting for it." It had to be a neutral person. I know Bob Gallo would have said that; I don't know about Luc. When we came up with HIV, which Harold Varmus handled as committee chair, I congratulated Harold. He did a terrific job. It would have been very tough to bring us all together in the same room. These are pretty high-powered, opinionated people. He did it strictly by fax and phones.

Hughes: The committee never met?

Levy: We never met. Harold had the prestige and the respect to get people like Gallo to at least listen. Even in the end, when everything was done, Gallo and Essex refused to sign.

Hughes: Well, I understand this process went on for quite some time. What actually occurred?

Levy: First we were asked to turn in names. We wanted every name possible. And then we all voted, and we narrowed it down. We each gave reasons why we liked or we didn't like a suggestion. We narrowed it down to, I don't know, a handful, and then we voted, and HIV won.

Hughes: Why?

Levy: Because it was the best name of all of them. There was human retrovirus, HRV; there was human lentivirus. We knew it had to have an H--that we all agreed on--and it should have only three letters.

Hughes: Why would it have to have an H?

Levy: For human, in case there were other AIDS viruses that came along, and of course we knew there were. The committee didn't want to call it human retrovirus, because there are other retroviruses. Now, there were lots of complaints about HIV, because many people said, "Maybe they don't have immune deficiency." But we quickly said--I was one of the ones--"Polio virus is polio virus, but not everybody who is infected with the virus gets polio." So HIV is the best that you can do.

Hughes: Why didn't Essex and Gallo endorse HIV?

Levy: Because they wanted it to be HTLV-IIIB.

Hughes: Harold Varmus has written a paper on this subject.

Levy: On naming it?

Hughes: Yes. Let me quote Harold Varmus. He said, "Some perceive, wrongly in my view, that our final recommendation," which of course was to name the virus HIV, "will form a verdict upon contested issues of priority of discovery, issues that could influence patent rights, the awarding of major prizes, patriotic

sentiments, and financial gain."[1] Was this background on your mind as you were choosing a name for the virus?

Levy: No, that never came into my mind. But then again, I wasn't in the running for a patent, although we have a patent on our virus. We were not in the running for the big patent with Montagnier and Gallo. But obviously neither Gallo nor Montagnier was going to allow IIIB or LAV to be accepted as official names for the virus.

Patenting the Virus

Hughes: You can patent a virus?

Levy: This was a surprise. Yes, you can patent a virus, but you should patent the virus for its use in some kind of diagnostic test or approach. So what the French did is they patented the virus as grown in peripheral white cells. Gallo took the same virus and put it into the H9 cell line, which of course is HUT78, and he said, "Well, I not only discovered the virus," which now we know is the French virus, "but I showed that it can be used in this diagnostic test for antiviral antibodies." And then Adi Gazdar said, "Yes, but you took my cell line, HUT78." So Gallo had to give Adi Gazdar some financial compensation. I don't know the details but it was interesting.

Hughes: So you can patent a virus to be used for a specific purpose.

Levy: Yes, for a purpose.

Hughes: Was there precedent for this?

Levy: I think it originated with the AIDS problem. Now, it's routine. Any time they find a new virus, they rush to patent it. With all due respects, Jonas Salk said, "To patent polio is like patenting the sun."[2]

Hughes: Thank you very much, Dr. Levy.

Transcribed and Final Typed by Shannon Page

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[1]Harold Varmus, "Naming the AIDS virus," In: E. Juengst and B. Koenig, eds., *The Meaning of AIDS*, New York: Praeger, 1989, p.3.

[2]Salk made the comment in response to a question by Edward R. Murrow, who asked on national television who owned the patent on Salk's polio vaccine. Salk replied: "Well, the people I would say. There is no patent. Could you patent the sun?" (Jane S. Smith, *Patenting the Sun: Polio and the Salk Vaccine*. New York: William Morrow and Company, 1990, p. 338.)

TAPE GUIDE--Jay A. Levy

University of California San Francisco
NEWS/PUBLIC INFORMATION SERVICES
532 Parnassus Avenue San Francisco, CA 94143 (415) 666-255

Michela Reichman, Assistant Chancellor
Source: Andy Evangelista (415) 666-2557

EMBARGOED FOR RELEASE:
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UC-SAN FRANCISCO STUDIES CONFIRM FRENCH FINDING OF RETROVIRUS IN AIDS AND DEMONSTRATE A RETROVIRUS COULD BE PASSED THROUGH BLOOD CLOTTING FACTOR

TORONTO -- A UC-San Francisco virologist today reported results of two studies that add further support to the theory that a retrovirus plays a major role in acquired immune deficiency syndrome.

A study by Jay Levy, MD, UCSF associate professor of medicine and an investigator in the Cancer Research Institute, confirms findings by French scientists that a retrovirus -- lymphadenopathy associated virus (LAV) -- could be the primary cause of AIDS. So far, Levy has found evidence of LAV or a LAV-like agent in blood cells of 28 of 50 AIDS patients in San Francisco. In three of the 28, Levy's laboratory has direct proof of the similarity to LAV.

The study was reported here today at a joint meeting of the American Society of Clinical Oncology and the American Association for Cancer Research.

Last year, researchers (F. Barre-Sinoussi, L. Montagnier, J.C. Chermann) at the Pasteur Institute in Paris discovered LAV in blood of AIDS and pre-AIDS patients in France. The suspected virus grows preferentially in certain lymphocytes (white blood cells), which become damaged or diminished in AIDS patients. The loss of these cells appears to be responsible for their inability to fight off opportunistic infections and cancer. Levy's research group found retroviral enzymes and proteins in white blood cells, as well as antibodies to LAV, which indicate infection, in over 50 percent of the patients studied. Evidence of the virus was not detected in any of 21 healthy controls. For the study, Levy used reagents supplied by the Pasteur Institute researchers to compare his isolates with theirs. Electron micrographs also have confirmed the similarities, Levy reported.

The relationship of the UCSF LAV-like agent and LAV to the HTLV-III retrovirus, recently described by Robert Gallo of the National Cancer Institute, is not yet known, says Levy. Recent reports, however, indicate strong

(more)

similarities between LAV and HTLV-III. Although they are major steps in AIDS research, Levy cautioned that these new findings do not yet establish absolute proof that either virus or a similar one is ~~the~~ cause of AIDS. He is conducting experiments, infecting animals with the UCSF isolates, in an attempt to determine whether or not they are responsible for AIDS.

In a separate presentation at the ASCO and AACR meetings, Levy today reported results showing retroviruses can survive procedures previously used to produce the clotting factor (Factor VIII) used by hemophiliacs. Levy, working with researchers from Cutter Laboratories in Berkeley (Milton M. Mozen, PhD, and George Mitra, PhD), tested the stability of a mouse retrovirus, resembling LAV, through the clotting factor production process. The process did not substantially inactivate the retrovirus, Levy reported.

This is counter to previous beliefs that a retrovirus could not survive such a process, and the study possibly explains why some 30 hemophiliacs in the United States have developed AIDS. The factor, used by hemophiliacs to prevent uncontrollable bleeding, is usually prepared from blood contributed by thousands of donors. The study by Levy and his coworkers did indicate that the heating procedure used now by Cutter eliminates the retrovirus effectively.

The process is now being used by maufacturers of Factor VIII to further minimize the chances of hemophiliacs contracting AIDS, says Levy.

Taken together, Levy's studies -- indicating presence of LAV or a LAV-like agent in the blood of AIDS patients in San Francisco and demonstration that a retrovirus can be transmitted in blood clotting factors -- lend further support to the theory that a retrovirus is involved in AIDS.

Levy's research is supported by grants from the state of California and the National Institutes of Health. His UCSF research team includes Susan Kramer, PhD, Lyndon Oshiro, PhD, Anthony Hoffman, Jill Landis and Joni Shimabukoro.

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AE

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f: letters to PV Ap-June '84

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BERKELEY, CALIFORNIA 94720

June 27, 1984

Professor Jay A. Levy
Cancer Research Institute
Department of Medicine
1282 Medical Science Building
University of California
SAN FRANCISCO CAMPUS 94143

Dear Professor Levy:

Re: ISOLATION OF A RETROVIRUS FROM A PATIENT WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME
NIH Grant Number 34980
STATE OF CALIFORNIA Contract Number 83-00060
UC Case: 84-118-1

Thank you for disclosing your invention pursuant to University policy.

Your disclosure will be reviewed to determine patentability, patent obligations to parties outside the University, and whether the University will undertake formal patent action.

We will keep you advised relative to our evaluation and may ask you for additional information. Normally, about ninety days are required for this procedure.

In the interim, please let us know if you intend to publish or present a paper or need to disclose this invention in any other manner to others outside the University (other than as noted in the Record of Invention). Such a disclosure could result in a loss of patent rights in most foreign countries, to the extent that foreign rights are still available. It is our intent to act as promptly as necessary in patent matters, such as not to intefere with your desire to publish research results promptly through the usual academic channels.

Rights to file patent applications abroad have been most probably lost due to your presentation in Toronto, Canada. I would

appreciate information as to the exact date of this presentation.

If you have any questions concerning these procedures, please do not hesitate to call me at 8-582-5000 (ATSS) or 415-642-5000.

Sincerely,

Valentin Fikovsky
Patent Manager

cc: Professor Paul A. Volberding
L. Mardie Petrakis, Contract and Grant Office, UCSF
Roger G. Ditzel, Director
Patent, Trademark, and Copyright Office

Virus outpaces AIDS here, study finds

By Richard F. Harris
Examiner science writer

Exposure to the virus suspected of causing AIDS is far more widespread among gay men in San Francisco than the disease itself, according to results of experimental blood tests.

A survey of blood products from gay San Francisco men, tested by the federal Centers for Disease Control in Atlanta, documents the rapid spread of the suspected AIDS virus in The City.

A positive test result does not mean the person will become ill, but the consequences are uncertain.

Samples collected in a hepatitis study in 1978 show 1 percent of this sexually active population had been exposed to the AIDS virus. By 1982, 24 percent of that group had been exposed, according to Dr. Harold Jaffe, co-director of the CDC's AIDS Task Force.

More recent samples reportedly show 50 percent of that population had been exposed to the virus, according to widely circulating reports about the CDC research. Jaffe, however, declined to confirm the last figure.

Because the ability to detect the suspect AIDS virus has proceeded much faster than an interpretation of that test, the findings present a tough dilemma: Should the test be made widely available to homosexuals and others potentially exposed to the virus before the results are understood?

The question is agonizing for homosexuals who would like to know whether they have been exposed, even though the test doesn't reveal whether they are contagious and does not predict whether they will develop the disease.

It is also a worry for health officials, who fear widespread testing will lead gay men to abandon healthy changes in lifestyle. Health experts say those habits are still the most important protection against AIDS, even among people who may harbor the virus.

Part of the problem is that the so-called AIDS tests do not detect the disease, but rather determine whether individuals have at any time come in contact with the virus.

People exposed to the virus build disease-fighting antibodies, which linger in the bloodstream and can be detected years after initial contact by the new test.

Dr. Jay Levy, a virologist at UC-San Francisco who has conducted his own tests of more than 300 blood samples from gays in The City, would say only that his findings show the virus is "prevalent" among gay men who have been sexually active.

The precise figures from his study and that done by CDC are not important, he said, because neither represents a cross-section of San Francisco's gay community.

The federal study is of a group of men at high risk for hepatitis, which is spread like AIDS through exchange of body fluids, and Levy's studies are of men who consider themselves at risk for the disease.

Both studies support an expectation among health officials that exposure rates to the virus will vastly overshadow the 550-plus cases diagnosed to date in The City.

Levy's laboratory is far too small to conduct exposure tests except in specific research projects, but a test could be mass-produced by the

—See back page, col. 4

San Francisco Examiner
July 1, 1984

Big increase in AIDS virus exposure

—From Page A1

end of the year by any of five biotechnology firms now working to develop one.

There is as yet no absolute scientific proof that the suspected virus causes the often fatal immune system disorders of the acquired immune deficiency syndrome, although many AIDS researchers believe the virus, discovered last year in France, is at the root of the problem.

The chief suspect is called lymphadenopathy associated virus, human T-cell leukemia virus or AIDS-associated retrovirus, depending on the laboratory where it was isolated.

Although scientists expect the three suspects to be one and the same virus, that has yet to be proven.

Like people once exposed to the hepatitis B virus, many of the men who show signs of exposure to the AIDS virus appear to be in good health.

The vast majority of people carrying hepatitis antibodies live a healthful life without ever being sickened by the virus.

So far, AIDS has apparently followed the hepatitis pattern: A minority of people exposed to the virus get the full-blown disease; some get only a milder form of infection called lymphadenopathy; and some have so far shown no signs of illness.

The epidemic is too young for scientists to know whether that pattern will hold.

Until that question, among many others, is resolved, prominent AIDS researchers suggest the test for AIDS should be confined to research labs and blood banks, rather than made available for general testing.

"I'm not sure I want to be tested," said Dr. Paul Volberding, who as head of the AIDS clinic at San Francisco General Hospital may have been exposed to blood from AIDS patients or other disease materials.

No health worker has contracted the disease from his or her work, he said, but there is no telling how people might interpret a positive exposure test.

"Does it mean (exposed people) are not insurable? Will they lose their jobs? Are they going to get AIDS? There are a lot of important issues I don't think have been very well thought out," Volberding said.

Noting that 10 AIDS patients died last week at S.F. General, Volberding said, "People don't know how horrible this disease is."

Until more is known about interpreting the test, AIDS researchers are concerned it will spur unwarranted fear about the results.

The question is compounded by the fact that so many people are likely to be identified as potential AIDS victims by the antibody test.

Health officials are also concerned that some at-risk men will conclude from the test results that the disease has already done its maximum damage. That could lead some people to abandon the low-risk lifestyles that have made remarkable inroads among gay men.

Ironically, as far as scientists can tell, those healthful habits are even more critical for men who have been exposed to the virus.

If virus is lying dormant in those people, a strong immune system would be more likely to keep it at bay, Volberding said.

"Not only is it important to avoid exposure to other (sexually transmitted) agents, but to keep your head in good shape and find ways of coping with (disease-linked) emotions such as depression," said Rob Roy Woodman, a psychologist with the city-funded AIDS Health Project.

Until its significance is known, the test itself could provoke depression, Volberding said.

"We don't want a test like that to become routinely available until some of these questions are answered," said Dr. James Chin, a leading AIDS researcher in the state's Office of Health Services.

Despite these considerable drawbacks for individuals, scientists note the test will be an indispensable tool for research and a long-sought method of assuring that blood bank supplies are free of AIDS.

Otherwise, Chin said, "The whole medical, legal and ethical ramifications have to be worked out. I don't think we have any good answers to them right now."

SCIENCE

HIV Survivors Who Have Beaten Disease

By David Perlman
Chronicle Science Editor

Yokohama

Hundreds of healthy men and women whose immune systems remain undamaged years after they were infected by the AIDS virus may offer promising clues to new treatments and vaccines to combat the epidemic, one of America's outstanding young AIDS researchers reported here today.

Dr. David Ho of New York City's Aaron Diamond AIDS Research Center is studying a small contingent of volunteers known among themselves as "long-term survivors" to learn why they seem to resist every attack by the viruses that invaded their bodies, and he has found significant keys to the puzzle.

More than 500 of the survivors are being followed by AIDS specialists at the San Francisco Health Department, but Ho is concentrating on a group of 10 — nine men and one woman — who volunteered to be research subjects in New York. All have been infected for at least a dozen years, all are totally free of disease symptoms, and none shows any decrease in the functioning CD-4 cells of their immune systems.

CD-8 Cells

In addition, all continue to show healthy numbers of CD-8 cells, which many scientists consider to be extremely important in protecting immunity to the ravages of HIV, the AIDS virus.

The subjects continue to show healthy numbers of CD-8 cells

The CD-8 cells apparently decline in number as HIV-infected people begin to show signs of AIDS.

Scientist after scientist at this 10th International Conference on AIDS has called for more research into the unknown factors triggered by the CD-8 cells whose importance was first recognized years ago by Dr. Jay Levy of the University of California at San Francisco.

"We have no clue at all as to what factor in the CD-8 cells is working to suppress the virus," Ho said. "It remains an unanswered question."

One answer, however, may lie in the basic nature of Levy's protective CD-8 cells, Ho suggested. They may belong to a cell class called cytotoxic T lymphocytes, or CTLs, which are known to destroy all kinds of cells that are infected by viruses.

Volunteer Group

In the volunteer group Ho is studying, seven of the long-term survivors are gay, two are intravenous drug users and one is a heterosexual woman. None appears to be linked by any unique genetic pattern, he said, and neither Ho nor his colleagues have been able to discover a "unique lifestyle" that makes them different from others who typically progress to disease after HIV infection.

In most of the group, Ho said, even the most meticulous analysis has failed to find any trace of virus now, while in the others the virus count is at least a thousand times lower than in infected men and women who have already been hit by one or more of the AIDS diseases.

All members of the group that Ho is studying have mounted a strong antibody response that can neutralize the virus, Ho reported, and the evidence suggests that when the survivors were first infected the viruses stopped reproducing after only a few days.

"We know these are pretty wimpy viruses," Ho said, but just how their host humans have weakened them to the point of impotence remains a mystery, he said.

Whatever characteristics account for their survival, the findings should provide valuable guideposts and research targets "to lead us toward new vaccines or therapeutics," Ho said. "And that may at least provide a ray of hope to patients."

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August 9, 1994

UCSF Newsbreak, February 25-March 10, 1995

AIDS research focuses on CD8s and the immune system

Jay Levy still forging ahead despite years of being ignored by peers

By ALLEN J. BALDERSON

Jay Levy is one of UCSF's many AIDS heroes. He was one of the first researchers in the world to identify the mysterious HIV virus as the cause of AIDS more than a decade ago.

But his studies on long-term survivors of the disease, and how CD8 cells may play an important role, have basically been ignored for years by much of the research community. Yet, he has forged ahead, never wavering from his commitment to his original findings.

Now, though, many of these same researchers are rediscovering Levy's seminal work and in a rash of new journal articles,

Jay Levy

giving the UCSF researcher some long overdue acclaim.

To understand Levy's research, a few basics on HIV infection are in order. This diabolical virus mutates each time it multiplies, and is thus able to escape the immune system's ability to destroy it. HIV can infect as many as 100 billion cells in the body, without seemingly affecting a person's health. HIV's main targets are CD4 lymphocytes, a group of white blood cells that help the immune system function. The number of CD4 cells in the blood has been an important parameter for researchers and clinicians alike in measuring the immune system's function. In people not infected with HIV, CD4s measure anywhere from 600 to 1200 cells/ul. When CD4 cell levels drop below 500, there is concern that the disease may be advancing.

CD8 lymphocytes, another component of the immune system, are present in uninfected people at about half the number of CD4 cells. In many diseases, these cells are responsible for attacking and killing virus-infected cells or cancer cells. Levy's work indicates that some CD8 cells, in very low numbers, can block HIV replication in CD4 cells without killing the CD4 cells. This novel antiviral activity can be observed in healthy infected people, especially in those living with HIV for many years.

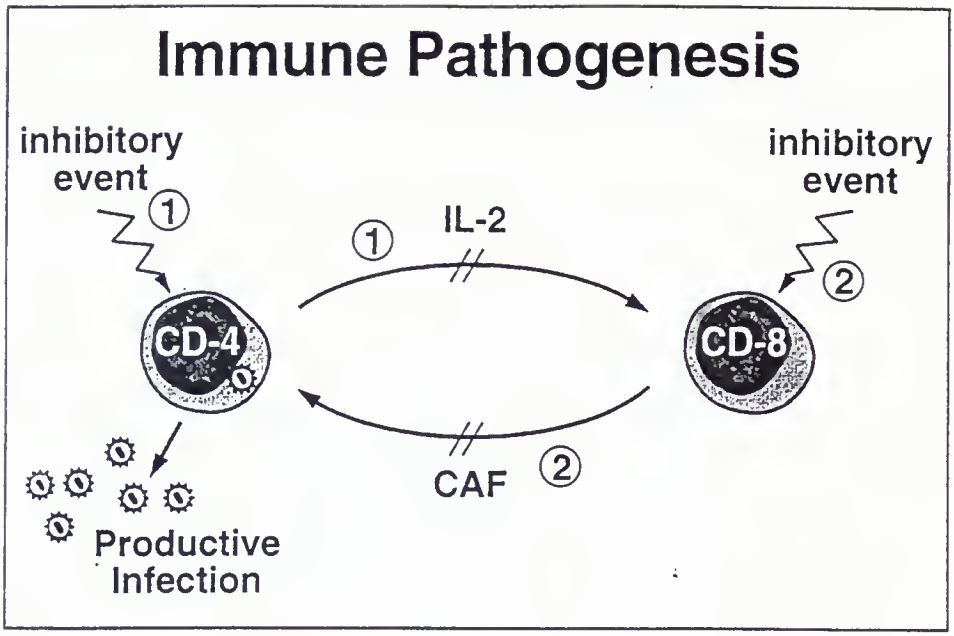
These observations, first made by Levy in 1986, led to the discovery of a substance secreted by CD8s now known as the CD8+ cell antiviral factor or CAF. This protein is a cellular factor or "cytokine" unlike any of the previous cellular products identified. Levy's lab now is undertaking a more complete study of this protein. His group recently noted that certain cellular factors produced by other immune cells can affect the ability of the CD8 cells in HIV-infected people to suppress virus replication. These findings could explain why there is a loss in the antiviral activity of CD8 cells over time, even before the reduction in CD4 cells. "It may be that the cytokines produced by CD4 cells are decreased sufficiently to compromise CD8 cell function," explains Levy. "The virus no longer is held in check by the CD8 cells and then advancement to AIDS takes place."

People with HIV who have lived longer than 10 years with a normal CD4 count (over 500 cells/ul) have several characteristics associated with their strong CD8 antiviral response. These long-term survivors have limited amounts of virus in their blood, the virus is not very virulent, and it does not infect a wide variety of cell types. The CD8 cells appear to be responsible for these features because they can limit the replication and mutation in HIV over time, says Levy. Strong CD8 activation seems to keep the HIV from wreaking havoc on a person's system.

HIV patients and physicians should know that while a blood test can show a CD8 cell count, it will not indicate the number of cells producing cell antiviral factor or CAF. "You need to have laboratory experiments examine the function of the CD8 cells — how well they will suppress virus replication in the CD4 lymphocyte," says Levy. In one study, Levy's group found that if the virus is readily recovered from cultured white cells, then the CD8 cells are not functioning effectively. "This is a very quick method of determining whether or not one's immune system is losing its ability to control HIV," says Levy.

To develop a marker for diagnosis and clinical follow-up, CAF needs to be identified, according to Levy. "We then can make an antibody that can be used to detect this CD8 factor in the blood and on the surface of cells. Then we can count the cells that are producing this protein and look at changes in this important antiviral response over time."

"Quite frankly, I'd rather see a cellular immune activity that could kill the virus-infected cells, but it's apparent that the major factor



Source: "HIV and the Pathogenesis of AIDS"

observed in healthy HIV-infected people and long-term survivors is this anti-HIV suppressing response," says Levy. "This CD8 cell activity can keep the virus from replicating and allows the body to maintain a healthy state. We surmise that if the virus is unable to replicate, eventually the infected cells will die as a normal matter of course. The number of infected cells in the body will be reduced, as we previously observed in infected chimpanzees."

"This CD8 cell activity can keep the virus from replicating and allows the body to maintain a healthy state."

— AIDS researcher Jay Levy

At present, there are no practical ways to stimulate CD8 antiviral activity. Nevertheless, learning how long-term survivors maintain AIDS as a result. The persistent HIV infection and disease progression in baboons will enable Levy and his colleagues to study new therapies and vaccines. Baboons, which have immune systems similar to humans, also are substantially cheaper than other animal models such as Rhesus monkeys or chimpanzees. A baboon costs around $1,800 (up from $500 just a few months ago); the price tag on a Rhesus monkey is $2,500 and jumps to $30,000 for a chimpanzee.

While Levy is gratified that his research finally is gaining attention, he must continue to wage his bureaucratic funding battles because he says research money is going elsewhere and not into basic science. "There is not enough attention being paid to research that can find an effective treatment for AIDS," he says. "And they [people in charge of funding] just don't see the ramification AIDS research has to other disciplines, for example cancer."

Meanwhile, AIDS continues its relentless march into our lives, making it today the number one killer of Americans between the

Proven Connection — HIV Causes AIDS

Differences between U.S. and African epidemics don't disprove cause of both

By Jay Levy, Nancy Padian and Jeff Sheehy

San Francisco Chronicle
May 30, 2000

THE VIEW PUBLISHED in Open Forum last week during South African President Thado Mbeki's visit to San Francisco gives the impression that the association between HIV and AIDS is still questionable. The contrary is true.

The overwhelming evidence indicates that HIV causes AIDS.

The HIV deniers have pointed to President Mbeki's recognition that HIV in Africa has been transmitted predominately by heterosexual contact, as opposed to the United States and other developed countries where HIV has been transmitted predominately by homosexual contact. The belief has been stated that this discrepancy somehow proves that HIV does not cause AIDS.

It is important not to confuse the epidemiology of HIV transmission in the United States with what is occurring in Africa. In this county, the studies used to determine the odds of transmitting HIV in a single act of unprotected vaginal sex between an infected man and an uninfected woman, which stand at about 1,000 to 1, excluded risk factors known to increase HIV transmission. These low odds do not hold in the presence of other well-established risk factors, prominent in Africa, such as other sexually transmitted diseases, which can increase the risk. Thus warnings, based on science about heterosexual transmission that lead people to change their behaviors to save their own lives and the lives of others, have been a critical component of our prevention strategies.

Indeed, successful HIV prevention programs have actually been responsible for maintaining low infection rates among heterosexuals in this country.

Notwithstanding this country's success in limiting heterosexual transmission of HIV, there are many factors that could account for the widespread heterosexual epidemic in Africa that differ from what we have observed here. As is the case with virtually all illnesses and infections, patterns of disease distribution and transmission differ depending on location.

Some of these factors are biological, and some are behavioral and social. Biological factors include the high prevalence of other sexually transmitted diseases, which facilitate transmission, and the high rates of bacterial vaginosis among women, known to increase susceptibility. Also, in Africa a predominant virus (clade C) may be more easily transmitted through mucosal contact. Further, the presence of many tropical diseases, as well as nutritional and other factors among people in developing countries, may compromise their general immune competence and thus increase susceptibility to HIV infection.

Behavioral and social factors that could facilitate the heterosexual spread of HIV in Africa include a greater power imbalance between genders that makes it much more difficult for women to avoid sexual contact with an infected husband or to negotiate condom use. Importantly, there is less access to health care, which greatly contributes to high rates of sexually transmitted diseases and other health problems that might increase susceptibility to HIV.

Finally, far fewer resources have been available for successful prevention programs when such resources are urgently needed in Africa and the developing world to fight this disease.

There is an abundance of evidence proving that HIV causes AIDS. A fact sheet (found at *http://hivinsite.ucsf.edu/*) prepared by the Office of Communications and Public Liaison at the National Institute of Allergy and Infectious Diseases clearly shows the link:

Koch's postulates, developed in the late 19th century, are the most cited criteria used over the years to prove the connection between disease-causing agents and disease. These tenets have served as the litmus test for determining the cause of any epidemic disease.

To restate:

1. Epidemiological association: The suspected cause must be strongly associated with the disease.

2. Isolation: The suspected pathogen can be isolated — and propagated — outside the host.

3. Transmission pathogenesis: Transfer of the suspected pathogen to an uninfected host, man or animal, produces the disease in that host.

MARGARET SCOTT / *Special to The Chronicle*

With regard to postulate 1, numerous studies from around the world show that virtually all AIDS patients carry antibodies that indicate HIV infection.

With regard to postulate 2, modern laboratory techniques have allowed the isolation of HIV in virtually all AIDS patients, as well as in almost all HIV-positive individuals with both early- and late-stage disease. In addition, the polymerase chain reaction procedure and other sophisticated molecular techniques have enabled researchers to document the presence of HIV genes in virtually all patients with AIDS, as well as in individuals in earlier stages of HIV disease.

HIV infection always precedes AIDS. Postulate 3 has been fulfilled in tragic incidents such as those involving three laboratory workers with no other risk factors who have developed AIDS or severe immune deficiency after accidental exposure to concentrated, pure HIV in the laboratory. In all three cases, HIV was isolated from the infected individual, sequenced and shown to be identical to the infectious virus from the laboratory.

In addition, through June 1999, the Centers for Disease Control received reports of 55 health care workers in the United States with documented, occupationally acquired HIV infection, of whom 25 have developed AIDS in the absence of other risk factors. The development of AIDS following infection with HIV also has been repeatedly observed in pediatric and adult blood-transfusion cases, in mother-to-child transmission, and in studies of hemophilia, injection-drug use and sexual transmission in which antibodies to HIV can be documented using serial blood samples. Indeed, young children free of any risk factors that might be associated with immune disorders (e.g., illicit drug use, malnutrition, therapy for other diseases) have developed AIDS. HIV was the only infectious agent associated with their disease.

We know that HIV causes AIDS. We know how HIV is transmitted. We know that advising people to avoid contact with HIV is the best way to avoid infection. We can only hope that the public is aware that encouraging even one person to stop practicing safe sex, to believe that HIV is no longer something to be feared, can have tragic consequences.

The reality underlying this divisive controversy is that so much remains to be done. In several communities here in the United States, HIV is spreading. In Africa and in much of the developing world, the spread of the disease is catastrophic. If left unchallenged, HIV will continue to infect and sicken the populations of the world. Instead of continuing to question the overwhelming evidence that HIV causes AIDS, let us join together to fight this infectious agent before it can create even more devastating damage in the world.

Dr. Jay Levy is professor of medicine at UCSF, and director of the Laboratory for Tumor and AIDS Virus Research. Dr. Nancy Padian is professor of obstetrics, gynecology, and reproductive science at UCSF, and director of international research at UCSF's AIDS Research Institute. Jeff Sheehy is the communications deputy director for UCSF's AIDS Research Institute.

CURRICULUM VITAE

Date and Place of Birth:	November 21, 1938; Wilmington, Delaware
Present Address:	Cancer Research Institute, University of California, School of Medicine, San Francisco, CA 94143-1270
Home:	1111 Lake Street, San Francisco, CA 94118
Marital Status:	Married
Education and Degrees:	
1960	B.A. – Wesleyan University, Middletown, CT
1961	Research Fellow, Université de Paris, Paris, France
1965	M.D. – Columbia University, College of Physicians and Surgeons, New York, NY
Present Positions:	Professor, Department of Medicine; Research Associate, Cancer Research Institute; Director, Laboratory for Tumor and AIDS Virus Research University of California, School of Medicine, San Francisco, CA
Awards & Honors:	Phi Beta Kappa, Sigma Xi, Wesleyan Memorial Award, 1959-60 Fulbright and French Government Awards, 1960-61 Research Career Development Award, 1972-77 American Cancer Society-Eleanor Roosevelt International Cancer Fellowship, 1978-79 Safani Lectureship on Leukemia, Dartmouth-Hitchcock Medical School, 1979 ICRETT Fellowship, 1982 Wallace P. Rowe Memorial Lectureship, Lerici, Italy, 1984 Murray Thelin Award, National Hemophilia Foundation, 1986 B. Frank Polk Memorial Lectureship, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, 1986 Patricia R. Woodard Lectureship, 1987 American Medical Association Distinguished Lecturer, Chicago, 1987 Nathalie Schmidt Memorial Lectureship, Northern California/American Society of Microbiology, 1987 Certificate of Appreciation, American Cancer Society National Board of Directors, 1987 Miles–Yale Lectureship, Yale University, 1988 Harry M. Rose Memorial Lectureship, Columbia University, College of Physicians and Surgeons, 1988 Maxwell L. Rosten Memorial Lectureship, University of California, Irvine, 1989 Distinguished Visiting Lecturer, San Francisco State University, 1990

Distinguished Lecturer, Creighton University, 1991
Distinguished Lecturer, Washington State University, 1991
Maurice R. Hilleman Lecture, Children's Hospital, Philadelphia, 1993
Courage Award, Chronic Fatigue Immune Dysfunction Syndrome Foundation, 1993
The Miles, Inc. Distinguished Lectureship, Washington State University, 1993
Fellow, American Association for the Advancement of Science, 1993
University Lecturer, The University of Texas, Southwestern Medical Center, 1993
Divisional Lecturer, American Society of Microbiology, 1994
Award of Distinction, American Foundation for AIDS Research (AmFAR), 1994
Henry T. Finch Jr. Lecturer, Regional HIV AIDS Consortium, Charlotte, NC, 1995
Armine T. Wilson Lecturer, Delaware Medical Society, 1995
Distinguished Alumnus Award, Wesleyan University, 1995
Fellow, Molecular Medicine Society, 1995
Fellow, Infectious Diseases Society of America, 1996
Fessinger-Springer Memorial Lecturer, University of Texas at El Paso, TX, 1996
Doctor of Science Honorary Degree, Wesleyan University, Middletown, CT, 1996
Distinguished Speaker, Biology Department and the Center for Genetics and Molecular Medicine Seminar Series, University of Louisville, Louisville, KY
Distinguished Lecturer, Distinguished Lecture Series, University of Kentucky, Lexington, KY, 1996
Distinguished Lecturer, Distinguished Lecture Series, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, 1996
Special Recognition Award for Outstanding Leadership as Chair of the Finance Committee, American Association for Cancer Research, 1997
One of the Ten Most Influential People of the Bay Area, San Francisco Sunday Chronicle Examiner, 1998
Wellcome Visiting Professorship Award, University of Puerto Rico, 1999
George Sarlo Award for Mentorship in AIDS, AIDS Research Institute, UCSF, 1999
Heroes in Medicine Award, International Association of Physicians in AIDS Care, 2000
Leon G. Smith Infectious Disease Institute Hall of Fame, St. Michael's Medical Center, Newark, NJ, 2000.

Editor (1988-2000);
Editor in Chief (2000-): *AIDS*

Editorial Boards:

Cancer Research
Virology
Journal of Clinical Immunology
Clinical and Diagnostic Laboratory Immunology
Molecular Aspects of Medicine, -2001
AIDS Research and Human Retroviruses
AIDS Abstracts
International Journal of Oncology
Microbiologica
AIDS '91 Summary
AIDS '92 Summary
AIDS Information
AIDS Patient Care and STDs
International Journal of Oncology

Committees:

Cell and Developmental Biology Study Section, American Cancer Society, 1983-87
International Advisory Committee, International Conference on AIDS, 1986-1996
Scientific Program Committee, International Conference on AIDS, 1987, 1990, 1992
Chair, Scientific Program Committee, 6th International Conference on AIDS, San Francisco, 1990
Program Committee, American Association for Cancer Research, 1983-84; 1986-87
Scientific Advisory Board, American Association for Cancer Research, 1984-87
Long-Range Planning Committee, American Association for Cancer Research, 1987-90, 1990-93
Board of Directors, American Association for Cancer Research, 1988-91
Special Conferences Committee, American Association for Cancer Research, 1989-92
Chair, Local Committee for Annual Meeting, American Association for Cancer Research, 1989
Local Committee for Annual Meeting, American Association for Cancer Research, 1994
Minority Issues Committee, American Association for Cancer Research, 1990-93; 1996-2000
Clowes Award Committee, American Association for Cancer Research, 1992
Representative, Physicians for Human Rights, American Association for Cancer Research, 1992-
Legislative Committee, American Association for Cancer Research, 1992-
Chair, By-Laws Committee, American Association for Cancer Research, 1992-93

Chair, Finance Committee, American Association for Cancer Research, 1993-96
Scientific Advisory Board, American Foundation for AIDS Research, 1986-
Chair, Science Policy Committee, American Foundation for AIDS Research, 1994-
Executive Committee, American Foundation for AIDS Research, 1994-
Board of Directors, American Foundation for AIDS Research, 1993-
Executive Board, American Committee for the Weizmann Institute of Science, 1987-
Board of Trustees, Wesleyan University, Middletown, CT, 1988-91
Advisory Board, International Alliance for Haiti, 1989-
Chair, Basic Science Section, 2nd Annual Conference on "Neurological and Neuropsychological Complications of AIDS Infections," Monterey, CA, 1990
Chair, Basic Science Section, 3rd Annual Conference on "Neurological and Neuropsychological Complications of AIDS Infections," Padua, Italy, 1991
Co-chair, Basic Science Section, 4th Annual Conference on "Neuroscience of HIV Infection: Basic and Clinical Frontiers," Vienna, Austria, 1993
Advisory Board, Chronic Fatigue Immune Dysfunction Syndrome (CFIDS) Foundation, 1990-1996
Advisory Board, International AIDS Society, 1993-1996
Scientific Advisory Board, Oregon Regional Primate Research Center, 1994-96
Scientific Committee, 5th Annual Conference on "Neuroscience of HIV Infection: Basic and Clinical Frontiers," Vancouver, B.C., 1994
Scientific Committee, 6th Annual Conference on "Neuroscience of HIV Infection: Basic and Clinical Frontiers," Paris, 1996
Friend, Xth International Congress of Virology, Jerusalem, Israel, 1996
International Scientific Committee, XI International Conference on AIDS, Vancouver, B.C., 1996
Program Committee, Annual Meeting of the American Association for Cancer Research, 1996
Membership Development Committee, American Association for Cancer Research, 1996-99
Program Committee, Annual Meeting of the American Association for Cancer Research, 1997
Mayor Willie Brown's AIDS Scientific Advisory Council, 1997-
International Scientific Advisory Board, Rhone-Poulenc-Rorer, 1997
Scientific Advisory Committee, Brown University/Tufts University Center for AIDS Research, 1997-

International Review Committee, 12th World AIDS Conference, Geneva, Switzerland, 1998
American Foundation for AIDS Research, Opportunity Fund Committee, New York, NY, 1998-
Board of Directors, People to People Ethiopian/American AIDS Association, 1999-
Agence Nationale de Recherches sur le Sida, Government of France, Scientific Advisory Board, 1999-
Chair, Local Arrangements Committee, 91st AACR Annual Meeting, 1999-2000
Chair, Molecular Biology Subcommittee: Cancer Genetics III: Human and Retroviral Oncogenes- Structure and Function/Viral Oncogenesis, 91st AACR Annual Meeting, 1999-2000
International Scientific Review Committee, XIII International AIDS Conference, 2000
Advisory Committee, United Religious Initiative Foundation, 2000-
Organizing Committee, 3rd International Symposium on NeuroVirology, 2000
Scientific Advisory Board, NIH HIV Vaccine Design and Development Team, Chiron Corp., 2001
International Scientific Board, 10th Conference on Neuroscience of HIV Infection, 2001
Scientific Review Committee, 1st IAS Conference on HIV Pathogenesis and Treatment, 2001
Scientific Advisory Committee, Deutsches Krebsforschungszentrum, Heidelberg Germany, 2001

Committees – UCSF:

Committee for Human Research, 1974-77
Vice Chairman, Committee for Human Research, 1976-77
Representative to Academic Senate, Dept. of Medicine, 1980-81
Student Research Committee, 1987-94
Chancellor's AIDS Coordinating Council, 1989-95
Executive Committee, Center for AIDS Research, 1988-
AIDS Research Council, 1988-1990
Organizer, AIDS Research Workshop, 1985-90
Faculty, Graduate Group in Oral Biology, 1989-
Chair, Track A Basic Science Committee, 6th International AIDS Conference, 1990
Faculty, Center for AIDS Prevention Studies, 1990-
Faculty, Fogarty International Fellowship Program, 1990-
Promotion Committee, Department of Medicine, 1990-
Ad Hoc Committee on Aerosol Transmission of HIV Infection, 1991
Ad Hoc Committee on HIV and Health Care Providers, 1991
United Way Faculty Representative, Cancer Research Institute, 1991
Faculty, Molecular Medicine, 1993-

Biosafety Committee, 1993-1998
Minority Affairs Committee, American Association for Cancer Research, 1996-2000
Chancellor's Advisory Board on AIDS, 1996-97
Dean's Task Force on AIDS Program Planning, 1996
UCSF AIDS Research Institute, Executive Committee, 1996-
UCSF AIDS Research Institute, Steering Committee, 1997-
Medical Network Group for UCSF Medical Students, 1997-
Preceptor, Course IDS 131/132 Foundations of Patient Care, 1997-
UCSF Chancellor's Advisory Board on AIDS and Emerging Infections, 1997-
Chair, ARI TAG for HIV vaccines, 1997-
Organizer, HIV Vaccine Workshop, 1997
Organizer, Anti-Bacteria Vaccine Workshop, 1998
General Clinical Research Center (GCRC) Advisory Committee, 1998-
UCSF California AIDS Research Center, Advisory Committee, *ex officio*, 1999-
Scientific Advisory Group, Institute for Global Health, 2000 -
HIV Basic Science Executive Steering Committee, 2000 -

Memberships:

American Association for the Advancement of Science
American Association for Immunologists
American Association for Cancer Research
American Society for Clinical Investigation
American Society for Microbiology
American Society for Tropical Medicine and Hygiene
American Society for Virology
Association of American Physicians
Association of IUCC Fellows
International AIDS Society
International Union Against Cancer
Western Association of Physicians
Western Society for Clinical Research
Infectious Diseases Society of America
HIV Medical Association of the Infectious Diseases Society of America

Patents:

"Purifed AIDS-associated virus ARV-2" (Patent No. 4,716,102)
"HIV-2 strains capable of infecting humans and non-human primates, and infected non-human primates with immune system disease" (Patent No. 5,543,131)
"CD8+ cell antiviral factor" (Patent No. 5,565,549)
"Hybridization assays for detecting the presence of an AIDS-associated virus" (Patent No. 5,736,328)

Training and Experience:

1959-1960	Teaching Assistant in Biology, Wesleyan University, Middletown, Connecticut. Biochemical research conducted on fungi in the laboratory of Dr. V. Cochrane.
1960-1961	Fulbright and French Government Fellowships. Laboratoire de Biologie Animal, Université de Paris, Paris, France. Under the direction of Professor Th. Lender and Professor E. Wolff. Studies on regeneration of planaria.
1961-1965	College of Physicians and Surgeons, Columbia University. Research conducted with Drs. H. Rose and H. Rosenkranz on lysogenic bacteria, and Dr. E.C. Curnen on viruses in Burkitt's lymphoma.
Summer 1962	USPHS Summer Fellowship, Jerusalem, Israel; Work at the Kiryat Hayovel Health Clinic, Department of Public Health and Social Medicine, Hebrew University. Under Professor S. Kark.
Summer 1963	Lederle Medical Fellowship, Karolinska Institutet, Stockholm, Sweden. Conducted research with Professors E. and G. Bertani on lysogenic bacteria.
Summer 1964	Louisiana State University Medical Fellowship. Makerere University College, Kampala, Uganda. Training in tropical medicine under the direction of Dr. Lawrence (England) and Dr. D.J. Jelliffe (USA). Research conducted on viral etiology of Burkitt's lymphoma, in collaboration with Drs. T.M. Bell and A. Haddow, East African Virus Research Institute, Entebbe, Uganda.
1965-1966	Intern in Medicine, Hospital of the University of Pennsylvania. Under Dr. J.B. Wyngaarden. Research conducted in the laboratory of Drs. Werner and Gertrude Henle, Philadelphia, on Epstein-Barr virus (EBV) in Burkitt's lymphoma.
1966-1967	First-year Resident in Medicine, Hospital of the University of Pennsylvania. Under Dr. J.B. Wyngaarden. Research on EBV continued in the laboratories of Drs. Henle and Dr. Robert Austrian. Research on human lymphocytes conducted in Dr. Vittorio Defendi's laboratory, Wistar Institute, Philadelphia, Pennsylvania.
1967-1970	Staff Associate, National Cancer Institute, National Institutes of Health, Bethesda, Maryland. Studies of DNA and RNA oncogenic viruses in the laboratory of Drs. Robert J. Huebner, Wallace P. Rowe and Janet W. Hartley.
May 1970	Collaborated with Dr. Alfred Prince, New York Blood Center and Dr. George Kafuko, Director of the East African Virus Research

	Institute, Entebbe, Uganda. Search for EBV and infectious hepatitis virus in wild chimpanzees in forests of Uganda.
1970-1971	Second-year Resident in Medicine, University of California, School of Medicine, San Francisco, California. Under Dr. L.H. Smith, Jr. Research conducted on epithelial cell transformation with Dr. T. Crocker in the Cancer Research Institute (Director, David A. Wood, M.D.).
1971-1972	Visiting Scientist CNRS, INSERM. NATO Fellowships, Paris, France. (1) Studies on human cell transformation by murine RNA tumor viruses were conducted in the laboratory of Dr. M. Boiron, Hôpital St. Louis, Paris. (2) Work on infection of mammalian cells with DNA from RNA virus-transformed rodent cells was performed in collaboration with Drs. M. Hill and J. Hillova, Villejuif. (3) Further characterization of the anti-viral inhibitor associated with NZB cells was done in collaboration with Drs. C. Jasmin and J.-C. Chermann in the laboratory of Dr. G. Mathé, Villejuif.
1972-1977	Assistant Clinical Professor, Department of Medicine; Research Associate, Cancer Research Institute, University of California, School of Medicine, San Francisco, CA. Established laboratory for the study of endogenous type C viruses.
1978-1982	Associate Professor in Residence, Department of Medicine; Research Associate, Cancer Research Institute, University of California, School of Medicine, San Francisco, CA.
1978-1979	Eleanor Roosevelt Fellowship. Visiting Scientist. 7/1/78-1/1/79, with Dr. Nechama Haran-Ghera, Department of Chemical Immunology, Weizmann Institute of Science, Rehovot, Israel. Research on T-cell differentiation and radiation-induced tumors. 1/1/79-8/1/79, with Professor François Jacob, Institut Pasteur, Paris, France. Studies on type C virus interaction with murine embryonal carcinoma cells.
1982 (April)	ICRETT (International Cancer Technology Transfer) Fellowship. Visiting Scientist, Weizmann Institute of Science, Rehovot, Israel. With Professor Nechama Haran-Ghera. Research on dual-tropic type C viruses in mouse T-cell leukemias.
1982-1985	Associate Professor in Residence, Departments of Medicine, Microbiology and Immunology; Research Associate, Cancer Research Institute, University of California, School of Medicine, San Francisco, CA.

1985-1996	Professor in Residence, Department of Medicine, Research Associate, Cancer Research Institute, University of California, School of Medicine, San Francisco, CA.
1996-present	Professor in Residence, Department of Medicine, Division of Hematology/Oncology; Research Associate, Cancer Research Institute, University of California, School of Medicine, San Francisco, CA.

PUBLICATIONS

Original Articles

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