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Berkeley, California

The San Francisco AIDS Oral History Series

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

Volume VII

Warren Winkelstein, Jr., M.D., M.P.H.

AIDS EPIDEMIOLOGY AT THE SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF CALIFORNIA, BERKELEY

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

Interviews Conducted by
Sally Smith Hughes, Ph.D.
in 1994 and 1995

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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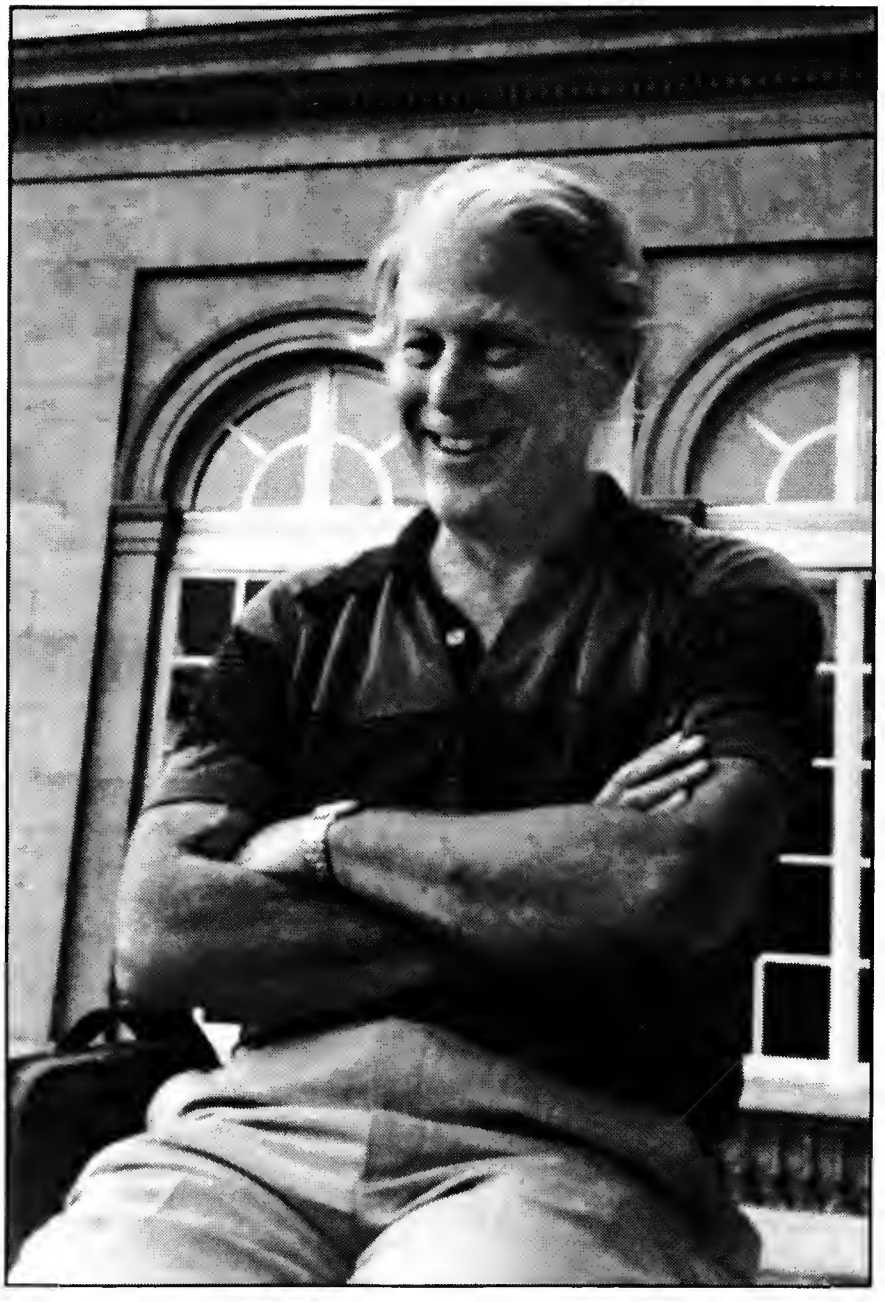

Warren Winkelstein, Jr., M.D., M.P.H., 1983.

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Warren Winkelstein Jr., M.D., M.P.H. (b. 1922), epidemiologist and professor, School of Public Health, UC Berkeley: childhood, education, public health positions in New York state, Salk polio vaccine field trials, and public health service in North Vietnam; history of tension over medical education at UCSF and UC Berkeley; conflicts with National Institute of Allergy and Infectious Disease [NIAID] over direction, contents, and funding of San Francisco Men's Health Study (part of NIAID Multicenter AIDS Cohort Study [MACS]); epidemiological design, collaborations, accomplishments, and publications of San Francisco Men's Health Study; other epidemiological research on AIDS in San Francisco; AIDS vaccine field trial issues, 1994 NIH committee decision against AIDS vaccine field trials; Peter Duesberg and HIV, Winkelstein/Duesberg controversy over HIV.

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

Interviewed 1994 by Sally Smith Hughes, Ph.D, for the San Francisco AIDS Oral History Series. The Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

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Sally Smith Hughes, in memory of John Liebeskind
National Institutes of Health Historical Office
University of California, San Francisco, AIDS Clinical Research Center
Warren Winkelstein

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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
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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 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) is greater than the sum of its parts (the individual oral histories), and

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

should be considered as a totality. To encourage this approach, we decided to bind several oral histories together in each volume.

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.

Furthermore, there is an inherent danger in reaching definitive conclusions on the basis of oral histories with only seventeen individuals.

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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, 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.

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.

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.

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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.

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

THE SAN FRANCISCO AIDS ORAL HISTORY SERIES

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PHASE 2: THE RESPONSE OF THE NURSING PROFESSION, 1981-1984

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Paul O'Malley, M.D., Communicable Diseases
William Owen, Jr., M.D., Primary Care

INTERVIEW HISTORY--Warren Winkelstein, Jr., M.D., M.P.H.

This oral history with Warren Winkelstein documents one aspect of his multifaceted career in epidemiology, namely his contributions to AIDS epidemiology. His greatest interest was to record the history of a long epidemiological study of AIDS from which emerged the San Francisco Men's Health Study. As director of the local group of physicians, epidemiologists, statisticians and others who participated from 1983 into the 1990s, Winkelstein was the primary figure interacting with National Institute of Allergy and Infectious Diseases [NIAID], the federal agency which contracted the work. The relationship was rocky and involved certain fundamental issues, such as freedom of speech, which Winkelstein explains in detail in the oral history. His other interest was to cover his relations with Peter Duesberg, a Berkeley molecular biologist whose argument that HIV is not the causal agent of AIDS has garnered worldwide attention. When the UCSF AIDS Clinical Research Center agreed to contribute to the support of the oral history, it stipulated that we include a discussion of proposed field trials for candidate AIDS vaccines. We readily agreed.

In 1983, Dr. Winkelstein became director of the San Francisco Bay Area segment of an NIAID-sponsored AIDS epidemiology project called the Multicenter AIDS Cohort Study of the National Institute of Allergy and Infectious Diseases. By self-admission, Winkelstein to that point had paid little attention to the new epidemic waxing in the Bay Area, one of its three original centers in the United States. The call out of the blue asking him to direct the study caught him by surprise. But on second thought, he decided that his background in a variety of epidemiological projects, particularly his role in the 1954 trials of the Salk polio vaccine in New York state, made him a natural to lead the study. Politics also played a role. AIDS researchers at San Francisco General Hospital and UCSF had already considered applying to NIAID for a contract to conduct the epidemiological research. But friction within the group worked in Winkelstein's favor. It was decided that he as a neutral and conciliatory figure, unaligned with either faction, was a wise choice to head the San Francisco team.

In the oral history, Winkelstein recounts step by detailed step the stormy progress of the study. Summarizing his problems as project director under five "crises," as he revealingly calls them, we learn of the team's difficulties in regard to achieving freedom to publish, independence of action, rapid public dissemination of study results, and other conditions valued in academia. And much more. Despite myriad problems, the San Franciso team published over 130 papers based on the study, and generated information which fed into further studies, such as the parameters under which AIDS vaccine field trials should be conducted.

It may have been because of the latter application and also because of his role in previous vaccine trials that Winkelstein was asked to serve in the mid-1990s on NIAID's AIDS Research Advisory Committee and its subcommittee, the AIDS Vaccine Working Group. It was this history which the UCSF AIDS Research Center, which partially funded the oral history, was anxious to have recorded. In an interview in this volume recorded a few months after a critical meeting at NIAID in June 1994, he tells how the working group made the difficult and controversial decision to deny approval for two candidate AIDS vaccines to proceed to field trials. To the manufacturers' dismay, the committee decided that neither vaccine promised to be sufficiently efficacious to warrant the expense and in-built risks of a trial.

Winkelstein's interactions with Duesberg were also contentious. (One might at this point consider why the outwardly genial and benign Dr. Winkelstein is involved time and again in contentious events.) As time went on, Duesberg grew more extreme in his stance that HIV is not the cause of AIDS, and consequently more isolated from mainline science. Winkelstein recounts how the initially professorial debate between the two campus colleagues degenerated into accusations of fraud which reached the pages of the widely read journal Nature. Winkelstein of course was far from the only scientist to confront Duesberg and his allies. Yet this account of his interaction with Duesberg can be read as a case study of iconoclasm in science and mainstream reaction to it.

The Oral History Process

Five interviews with Dr. Winkelstein were conducted in his office in an annex of the School of Public Health at Berkeley between August and October 1994. Before each session, he culled his massive personal collection of documents for items relative to the upcoming interviews and lent them to me in advance. Some of the key documents are reproduced in the appendix of this volume; others remain in Winkelstein's possession.

Working from the selected documents, we talked in detail about his personal relationship to the three major topics of the oral history--the AIDS epidemiology study, the AIDS vaccine trial decision, and Duesberg. The tapes were transcribed at no cost to ROHO through arrangements graciously made by Victoria Harden of the NIH Historical Office in Bethesda, Maryland. Dr. Winkelstein made few corrections of the lightly edited transcripts but worked closely with me and editorial assistant Grace Robinson to select the correct documents for citation in footnotes and/or placement in the appendix. As a result, the oral history is a fine example of the interaction of written and oral documentation.

It is more than that. This oral history is also the record of an important phase in Warren Winkelstein's career. It adds important and

heretofore neglected history to this project on the San Francisco AIDS epidemic and also to the work of the NIH Historical Office on the history of NIH contributions to AIDS research. It reveals a man whose wide experience in epidemiology led him in fruitful directions in the course of the AIDS epidemic and on a personal level presented opportunities for displaying his high principles for academic conduct and his skill in interpersonal relationships.

We are grateful to the AIDS Clinical Research Center at UCSF, to Victoria Harden at the NIH Historical Office, and to Dr. Winkelstein for making this oral history possible.

Sally Smith Hughes, Ph.D
Research Historian and Principal Editor

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

Regional Oral History Office
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BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

Your full name Warren Winkelstein, Jr.

Date of birth 1 July 1922 Birthplace Syracuse, N.Y.

Father's full name Warren Winkelstein

Occupation Attorney Birthplace Syracuse, N.Y.

Mother's full name Evelyn Neiman Winkelstein

Occupation Housewife Birthplace McKeesport, PA.

Your spouse Vera Kerrigan Winkelstein

Occupation Retired Univ. Administrator Birthplace San Diego, CA

Your children Rebecca Yunis (1942), Joshua F. Winkelstein (1959), Shoshana Walcott (1962)

Where did you grow up? Syracuse NY and Putney, VT

Present community Point Richmond, CA

Education H.S.: Putney School, Putney VT; BA: University of N. Carolina at Chapel Hill; M.D.: Syracuse University; M.P.H. Columbia Univ

Occupation(s) Public Health Physician, Professor of Epidemiology

Areas of expertise Public health, preventive medicine, epidemiology (infectious diseases, cancer, cardiovascular disease, air pollution effects, violence)

Other interests or activities Music (pipe organ playing), history (public health and epidemiology), biography (author of a series: Vignettes of the History of Epidemiology).

Organizations in which you are active Organ Historical Society, Am. Pub. Health Assoc., Am. Epidemiological Association

INTERVIEW WITH WARREN WINKELSTEIN, JR., M.D.

I UPBRINGING AND EDUCATION

[Interview 1: August 11, 1994] ##[1]
[Dr. Winkelstein's Office in the School of Public Health, UC Berkeley]

Family Background

Hughes: Dr. Winkelstein, would you start please with where you were born, and talk a little about your education and early career prior to your involvement in the AIDS epidemic?

Winkelstein: I was born in Syracuse, New York on the first of July, 1922. My father, Warren Winkelstein, was an attorney, prominent in the Jewish community in social activities, and also a protégé of the dean, William Mosher, of the Maxwell School of Citizenship at Syracuse University, which was one of the first university-based institutes dealing with governmental operations. And my mother, Evelyn Neiman Winkelstein, was from McKeesport, Pennsylvania, and she went to Wellesley College and met my father at a house party in Utica, New York. They were married shortly thereafter. I was the first born.

I grew up, the first years of my life, in a commodious house about ten blocks from Syracuse University. My mother had what I guess you would call almost a salon, in the sense that there were frequent visitors to our house from the university community, musicians, artists, and authors. My mother was famous for giving parties. I met people like Rockwell Kent, and I guess F.P.A. (Franklin P. Adams, a famous literary critic) who came to our house, and other prominent people of the 1920s and early thirties. There were always a lot of things going on.

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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.

As you can see from the picture of the house [which Winkelstein has brought to the interview], it was a pretty large place. Actually, when I was first born, the second floor was two apartments, but when the Depression came along in the 1930s, my parents couldn't rent one of the apartments, so my sister Barbara and I lived in the upstairs apartment. The dining room was my bedroom, and the kitchen I converted into a darkroom. I took this picture myself and developed and printed it.

And then, on the third floor of this house, as you can see, there's a large attic, and originally there were two maids' rooms and bathroom facilities up there. As times got bad, we didn't have live-in maids any longer, so I had one of the rooms as sort of a playroom--it was on this side of the house, which looked westward. The house was on a hill, so I could sit there with my little radio--crystal set, we called them--with my ear phones on. I could look out the window and look across the city, and I could hear the trains whistling in the distance.

I grew up as a somewhat isolated child, except I had a lot of cousins, and it was like an extended family. We ate at my uncles' and aunts' houses. At least twice a week they were in our house, and we were in theirs, and there were three or four uncles and aunts in the community, so it was just kind of an extended community.

The Putney School

Winkelstein: I was also somewhat adventurous, and the story is that my mother decided, when I was about twelve or thirteen, that I should go away to school. She had a friend who was a social worker who knew about a progressive new school in New England. So when I was thirteen, I went off to school.

Hughes: Because you were precocious?

Winkelstein: There were several reasons. What she said, or what people told me, was that my mother had difficulty in coping with my sort of adventurous spirit.

At any rate, I went off, and I guess I was thirteen years old and I had been going to public school up until that time. Then I was sent to camp at this school that was in the process of formation, and it was a work camp. So you

worked on the farm in the mornings, and then you were supposed to do recreational activities in the afternoon, but I got enamored with farm work so I became sort of a farm kid. Then the school opened. It's called the Putney School; you may have heard of it.

Hughes: Oh, yes.

Winkelstein: It's quite well known now. I was admitted into that school. My grandmother, Rachel Neiman, was brought up by my parents to look the place over because she would have to pay for my going away to school. So then I went away to the Putney School which was a progressive school. This is a picture of me with a team of oxen and a wagon that I actually made myself.

Hughes: And that was encouraged at the school?

Winkelstein: Oh, yes. That was a part of the thing. I wasn't a very good student in high school, as you can sort of guess; I was more interested in farm work, and that type of thing, rather than concentrating on studies.

Hughes: But there was an academic component?

Winkelstein: Yes. A major component of the school was to have a strong academic program, and I was weak academically, and the head of the school did everything she could to encourage my academic work. For example, I was elected to be president of the 4-H Club and then also to be on the student council. Mrs. Carmalita Hinton--she was the head of the school--said I couldn't do both. I would have to give up one because it was interfering with all the other things.

Undergraduate, University of North Carolina, 1939-1943

Winkelstein: At any rate, I finished high school and my parents wanted me to go to one of the major universities. I wasn't very interested in going to Harvard, which is where they wanted me to go, but I couldn't go anyway because I did so poorly on the college entrance examinations.

What I did do was to go to the University of North Carolina. And the reason I went there was that I had an uncle who was a lawyer in New York City with a very prominent firm, and the head of the firm was named George

Gordon Battle, a member of a famous family in North Carolina. He said to my uncle that I should go to North Carolina, so I was packed off to the University of North Carolina.

Hughes: Just like that?

Winkelstein: Pretty much just like that. And that's what I wanted to do anyway; I wanted to go to a state university.

And then in college I didn't do very well academically either, and I fell in with a sort of radical group of students.

Hughes: At a southern university?

Winkelstein: Well, North Carolina, Chapel Hill, was a very unique school. It was very progressive. It's the oldest state university in the United States, and it had a tradition of so-called liberalism even though it was a segregated university at that time. But beginning already in 1939--which is when I went away to school--there were already rumblings of integration, and so forth.

The president of the university was Frank Graham, who I think was the first U.S. U.N. representative, and he was very influential on the students. He had open house every Sunday, and the tenor of the university was set by the administration. There were all kinds of visiting lecturers, and there was an atmosphere of openness and liberalism, and Mrs. [Eleanor] Roosevelt came to speak, and things like that.

As I mentioned, I went in with a group of radical students--some were from New York City--because there were a few northern students, and most of them came from New York City.

Hughes: Had you known any of them in New York?

Winkelstein: No. I went there knowing no one.

Marriage, First Child, and a Surveyor's Job

Winkelstein: Then in my third year of college, I got married and left college, and had a baby. That was 1941, I guess. Yes. It

was just after the war had started. I went to Norfolk, Virginia, with my wife Arthur-Rae Marden (she was the eldest of three daughters and her father had wanted a first-born son, so he gave this daughter a boy's name!). That was where they were building huge military installations and anybody could get a job. We came into the bus station and went to the Traveler's Aid. We were very innocent. We didn't know anything, as you can imagine. I was about twenty years old, or so, and my wife was the same age.

And we took a room. In those days, you were lucky if you had a bed. You could rent a bed for eight hours, and then somebody else would have it for the next eight hours, and somebody else would have it for the next eight hours. But anyway, we came to this house--and this has relevance, I think, to my later life--and the lady showed us a room. We said, "Well, we'll think about it." Of course, in those days, that would show that you were totally innocent. You didn't think about it. If you had a room, you grabbed it.

Anyway, we walked around the block, came back and took the room. The lady asked me a few questions, and then she introduced me to an Italian-American man, who lived upstairs with his wife. He was a supervisor in one of the big construction companies. He said, "Come with me on Monday morning and get a job."

He took me on Monday to the Norfolk, Virginia, Engineering Company hiring office. I sat down there and the man called me in and said, "What can you do?" And, having come from this work ethic--this progressive school--I said, "I can do anything. I can dig ditches." Well, in 1942, in Norfolk, Virginia, white people didn't dig ditches, and so he knew he had either a trouble-maker or somebody he didn't want. So, he didn't have a job. Of course there were jobs, but there were no jobs for me.

But since I had to wait for Angelo to take me back to the boarding house, I stationed myself in front of his [the hiring man's] door so every time the door opened he would see me sitting there. Towards the end of the afternoon, he signaled me to come into his office and he said, "I have a job for you. The job is as a rod-man for a surveyor." The rod-man is the fellow who holds the post; you've seen them out on the roads, and so on.

Anyway, when Angelo came for me, he said, "What job did you get?" I said, "I got a job as a rod-man." He said, "Wonderful." By this time he knew a little bit about me.

He knew we were waiting for a baby to come, and all that sort of thing.

So I went to work for this surveyor. It turned out that the man I was to work for was in his mid-seventies. He'd been a land surveyor in Kentucky, and no one could work with him. He was very exacting and a very difficult person. But I had this sort of work ethic and I just did everything I was told to do, and more, you know.

Things went along for a while. One day Angelo saw me in the field working, and he came over and he said, "What are you doing?" I said, "Well, I'm doing my work. I'm a rod-man." He thought I had said I was a rods-man. Rods-men are people who put together the steel reinforcing for cement structures, and he was a supervisor of building cement roofs. Now, the difference was that a rod-man, of the kind I was, made $100 a month working for sixty hours a week, whereas a rods-man made $150 or $200 a week, and so it was a huge difference. But then he stood back and he said, "But you know there's no future in putting together steel reinforcement, and you're going to be an engineer."

Anyway, I worked there for almost a year. And then my parents bailed me out and I went back to the university.

Hughes: What did you major in?

Winkelstein: I majored in sociology, but I was sort of destined to go to medical school.

Oddly enough, at one point, I was rummaging through a box full of documents and there was an old application to college where it said what do you want to be, and I said public health. Probably the reason for that was that we had a very close friend of the family, I.H. Levy, who was a professor of medicine at Syracuse. He was a very forward-thinking person, very socially oriented, like my father. So Dr. Levy had probably somehow influenced me in my formative years to be interested in the social aspects of medicine.

Hughes: Was that also the reason for the sociology major?

Winkelstein: Well, I thought I was going to be a sociologist. I was interested in so-called rural sociology, and that was what North Carolina was famous for as well.

Medical School and Internship

Syracuse University Medical School, 1943-1947

Winkelstein: After graduation from college, of course, the war was on, and I had a baby, Rebecca, so I was of course working as well as going to school. When I finished at the university, I had applied to medical school. My uncle, Ascher Winkelstein, a prominent New York City gastroenterologist, was a physician. In those days, it made a lot of difference. If your uncle, or your father, was a doctor, you almost automatically were admitted to the medical school where he had gone, and people got into medical school not because of their abilities, but because of whom they knew or were related to.

Hughes: Right.

Winkelstein: Then I went into the army, because during the war years, we were in the army or the navy while we were being trained. And then my wife and I were separated, and my daughter was essentially raised by my parents because I was in the army and training in medicine. At any rate, I did pretty well in medical school and graduated with honors.

Internship, 1947-1948, and Second Marriage

Winkelstein: Then I went to New Orleans to Charity Hospital for my internship, because I was interested in going into public health, and I wanted to get an internship. In those days, you got a one-year internship--it's a rotating internship--and then if you went on in specialty training, you did a residency in some field. So I went to New Orleans and Charity Hospital, which was a huge public health hospital where I would get a broad experience, and perhaps extra experience in infectious diseases because at that time public health had an emphasis on infectious diseases. I married again while I was there--a social worker at the hospital, Malce Fittz.

II CAREER IN PUBLIC HEALTH

New York State Public Health Department

Fellowship, 1948-1950

Winkelstein: After I finished my internship, I had a fellowship with the New York State Health Department for two years, a first year of field work, and then one year at the School of Public Health in New York City. I was the only trainee in the state health department in 1948 and '49. So because they were anxious to produce more public health physicians, I was treated as the favored son, if you will.

At that time, the New York State Health Department was a very dynamic and progressive organization, and so I came in contact with a lot of public health people who had considerable influence on me, like Morton Levin, who was deputy commissioner for chronic diseases, and Abraham Lillienfeld, who was only two or three years older than I, who became one of the leading epidemiologists in the country. I was sent around to different health departments throughout the state to get experience in this or that or the other field.

Hughes: Participating in the different programs?

Winkelstein: Yes.

The first place I went to was the headquarters in the capital in Albany. So after I had spent two or three days in Albany getting oriented, I was sent to a place called Hornell, New York. The southern part of New York state is the northern part of Appalachia. So it was a pretty backward area, steep hills and rivers running down through the valleys.

Anyway, Hornell is what's called a division point on the Erie Railroad. A division point is where the train crews were changed and when the New York State Health Department was reorganized in 1918 into districts, the health officers used to travel largely by train. So they put two district offices together at the division point on the Erie Railroad so one district would serve to the west and the other served to the east. By the time that I was a trainee, it was only one district.

My wife and I went there, and I reported for work one Monday morning up over a drugstore on the main street of town. I met the health officer, Dan McMann, and he took me into an office, a small room with a huge desk, a very strange desk, a big, square desk with two knee holes in it. It was a flat-top desk. And on the desk were lying two books: The Sanitary Code, and The New York State Public Health Law. He said, "I want you to study these," and then left me.

Well, you can imagine. Here's this young guy who just finished his internship. The first thing after that's done, he's put in this dank room up over a drugstore, and you can imagine what the reading was like. We had rented a room. I went home that night and--I can't remember it clearly, but I must have been close to tears--and I know I said, "What have I done to my life for this?"

I went back the next day and Dr. McMann came into the room--I'll never forget this--and he said, "I'll bet you've been wondering about this desk?" "Well, yes, it did sort of pique my curiosity."

He said, "This desk belonged to the state health officer before the health department was reorganized in 1918. In the years before that, the state health department consisted of the state health officer and his secretary, and the state health officer sat on one side of this desk and his secretary sat on the other. That was the state health department. Then when they formed these two districts here, they sent this desk out for the district health officers so that one district health officer sat on one side, and the other district health officer sat on the other side, and they couldn't stand each other. They never spoke for twenty years."

He was a very good guy, Dan McMann, and he took me under his wing. I was just sort of in a haze, what we did the

first day. Then he took me everywhere with him and taught me a lot of things.

Hughes: Was it mainly concerning infectious disease?

Winkelstein: No. He was a district health officer, so we would have a staff of public health nurses and sanitarians. We were in charge of farm labor camps, and one of the things I did that summer was to go around with the sanitary engineers inspecting these labor camps which, as you can imagine, were some of the most terrible places possible. We struggled with the farm owners to get them to install privies and reasonable water supplies and so forth.

Then after a couple of months, Dr. McMann one morning told me that he was quitting public health and going to North Carolina and becoming a local physician. So then, after these two months, I was left there as sort of the acting health officer, and the district health officer from the next district would come down every two to three days and tell me what to do.

Anyway, I went on through that year and finished up, and had a lot of experiences, and investigated outbreaks, and wrote my first paper, and delivered it at the New York State Epidemiological Society.

School of Public Health, Columbia, 1949-1950

Winkelstein: Then I went to the School of Public Health. The health department wanted me to go to Johns Hopkins or Harvard, both of which were very prominent schools of public health, but my wife and I wanted to live in New York City, so I went to Columbia, which was not a very good School of Public Health. But, at any rate, I went there.

Meeting Dr. Mort Levin

Winkelstein: During my year in the School of Public Health, the American Public Health Association held their meeting in New York City, and I went as a student. One day I was talking to Dr. Levin, who, as I mentioned, was the deputy health commissioner, a very prominent and important person in the

history of public health. I knew that he came to New York City every month or so. New York City is not a part of the New York State Health Department, but they have a liaison, and he was the deputy in charge of that liaison. I said, "Would you come and have dinner with my wife and me?" Levin said, "Yes. I would like to do that."

We lived in a one-room apartment overlooking an air shaft on West 87th Street. Surprisingly, a month or so later, I got a postcard saying that he was going to be in town and he'd take up our invitation. I thought, Gee whiz, I'll learn all about epidemiology.

Anyway, he came to our little one-room apartment. My wife had fixed the dinner. And Mort and my wife spent the evening talking about the Irish poets in whom they were both interested, and I knew nothing about Irish poets.

Hughes: You never talked about epidemiology?

Winkelstein: They became very good friends for the rest of their lives.

District Health Officer, Erie County Health Department, Buffalo, New York, 1950-1951

Winkelstein: I had spent one of my training periods in Buffalo where they were forming a new health department, which was to be a model health department. So after I finished my field training, and my M.P.H [Master of Public Health] I went to Buffalo as a district health officer and I stayed there for about six months, at which time I was called back into the army for the Korean War.

The state health department had done all kinds of things to try to get me assigned to New York state rather than to be sent overseas. They tried to get me in the army, the navy, and so forth. Eventually, I went into the Public Health Service with the understanding that they would only call me up if they needed my special talents, of which there were none at that time.

The ink was no more than dry on my commission than I was called up. And the state health department thought I would be called to the Centers for Disease Control--what was called the Communicable Disease Center at that time--to join

the Epidemic Intelligence Service, which was being formed at that time.

I've always said that Alex Langmuir lost my papers because I didn't get sent to the Centers for Disease Control.

Public Health Division, Special Technical and Economic Mission, North Vietnam, 1950-1951

Winkelstein: There was a group of about fifty nurses, physicians, and sanitarians whom the Public Health Service called to Washington to be trained to be sent overseas in what was then called the Mutual Security Agency--MSA. It was the successor to the Marshall Plan and the forerunner of the present Agency for International Development.

Anyway, the plan was that this group of physicians, nurses, sanitarians, and so forth, would be trained in languages, social issues, political background, and so forth, at Harvard, Yale, and the Centers for Disease Control, over a period of three or four months. We went to Washington and everybody was told what the plan was: three months of training and all wives and family would be sent along.

But there were two people who were called up--myself and one other guy, Clifford Jope--and they said, "We're sending you overseas immediately because you already have training." We were the only ones who had had prior training. That was on, I don't know, a Friday, or Monday, or something like that. A week later, we were in Saigon. We stayed there for a month or so, being oriented into the programs that they had.

And then--there were three of us--we were given our choice of where we would be sent: North, Central, or South Vietnam. Fortunately, each of the three chose a different place, and I chose to be sent to North Vietnam. Cliff Jope was sent to Central Vietnam. He came from a missionary family, and that was an area where there were a lot of missionaries. The third guy was not terribly interested in anything; he wanted to stay with the nightlife in Saigon. I went to Hanoi and lived there for the next two and a half years.

Hughes: Doing what?

Winkelstein: Well, I was directing the United States Aid Program in Public Health. We had a two-pronged program. One part was called Impact Programs, which were designed to provide various public health services directly to the population; the other part of the program was development of infrastructure. We worked with the Vietnamese government, which was a puppet government set up by the French, because this was still during the period of French-dominated war. The war was going on, of course, in Hanoi, and, as you can imagine, that was a pretty intensive experience for those two and a half years. I was there by myself the first year, and then my wife joined me the second year.

At the end of that time, the Foreign Service wanted me to stay in the Foreign Service, but I felt that that was not for me--how can I describe the life of the Foreign Service? It wasn't what I envisioned as my career. You had servants, and you had a substantial income, and so forth.

Director, Division of Communicable Disease Control, Erie County Health Department, Buffalo, 1953-1956

Winkelstein: Instead of that, I went back to Buffalo and rejoined the health department and resumed my career development. I went back not as a district health officer but as the Director of Communicable Disease Control.

The Polio Vaccine Field Trial

Winkelstein: Shortly after I returned to Buffalo, the polio vaccine field trial was implemented and our health department was one of the largest units in the field trial. I was put in charge of running that program.

Hughes: For any particular reason?

Winkelstein: Well, I was Director of Communicable Disease Control.

Hughes: That makes sense.

Winkelstein: Besides which I was the young, vigorous person who would run it. I mean, I was directed by my bosses. Anyway, we had 30,000 children in the trial. It was one of the largest parts of the 1954 vaccine field trial. I came in contact with people like Dr. Thomas Francis, who was the director, and Jonas Salk, and many others.

As my career developed in the health department, my contacts with people both locally and nationally grew through activities like the vaccine field trials. And then, because of our experience in vaccine field trials, we became sort of a focus for vaccine trials, and so when measles vaccine came along our health department was drawn in immediately.

One thing led to another. I stayed in the health department for three or four years, and then there were political problems in the health department. We were being pushed to contribute to the Republican party, and substantial amounts of money, and that wasn't very nice.

Fellowship, Roswell Park Memorial Institute, Buffalo, 1956-1957

Winkelstein: So I left the health department and took a fellowship at Roswell Park Memorial Institute. I think that was 1957 or so, and that was with Abe Lillienfeld. I stayed there for a year.

State University of New York at Buffalo

Establishing an Epidemiology Program at the Chronic Disease Research Institute, State University of New York at Buffalo, 1958-1968

Winkelstein: Then, the State University of New York at Buffalo had formed something called the Chronic Disease Research Institute, and Dr. Lillienfeld, who was a prominent epidemiologist, located me in that unit to establish a research program in epidemiology, which I did. It was then that I began really to do epidemiological research.

What happened in Buffalo was quite interesting. It, too, was sort of a progressive medical school, under a man by the name of Stockton Kimball, who was a very far-sighted educator. He was the dean. Unfortunately, he died prematurely of bacterial endocarditis, and so then there was a series of two or three deans in the medical school. The medical school became very politicized.

Under Stockton Kimball, they had drawn in a group of very bright, young people, contemporaries of mine--David Karzon, myself, and then there was a fellow by the name of Ken Nyswander. There were about six or eight of us who were probably in our mid-thirties who were very, very good. And when the school became politicized, we all started getting interested in the offers that we were constantly getting. We all left Buffalo. Everybody left. Nyswander went to Davis; I went to Berkeley; Karzon went to Vanderbilt, and one went to the University of Pennsylvania, and so everything kind of blew up.

First Deputy Commissioner, Erie County Health Department, Buffalo, 1959-1962

Winkelstein: At the same time--the health department had been cleaned up --the new health officer asked me to come and be the first deputy health officer, so I became the deputy health officer [1959-1962] for Erie County. At the same time I continued to develop the epidemiology program in the university.

Then I got a Career Development Award from the National Heart Institute in 1962, and I left the health department and went full-time to the university. That I did for five or six years, and then I came to California. During those years, I did research in air pollution, I conducted a population-based study of blood pressure, helped teach medical students, and so developed my research career.

Hughes: Here?

Winkelstein: No. This was in Buffalo.

III PROFESSOR OF EPIDEMIOLOGY, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF CALIFORNIA, BERKELEY, 1968-PRESENT

Appointment

Winkelstein: Then in 1968, I was invited to come here to be a professor of epidemiology.

Hughes: How did that come about?

Winkelstein: Well, by that time, I had done research in infectious and chronic diseases, and had substantial experience as a public health administrator; I had done these vaccine field trials. I had worked closely with a very prominent local pediatrician/virologist, David Karzon. He and I were together for a number of years.

Hughes: What was the reputation of Berkeley's school in 1968?

Winkelstein: Well, you know, I had been in a medical school. I didn't think very much of schools of public health when I was working in a medical school. I thought we didn't need schools of public health; we had strong departments of preventive medicine in medical schools.

But, of course, Berkeley is another matter. If you get offered to be a full professor at Berkeley, you go. When the call comes, you take it. But actually, I had been coming here for about three or four years and giving lectures.

The person, Ruell Stallones, known far and wide as "Stony", that I would have worked with was a terrific guy, and he and I were very good friends. But I knew that I couldn't work with him. He was too strong a personality. And so as long as Dr. Stallones was here, I didn't want to join the faculty. I'm sure that Bill Reeves has talked a

lot about Stony,[1] and Stony was a terrific person. He left to become the first dean at the School of Public Health at the University of Texas. When he left, I was recruited to be his replacement, and after he had left, then I felt I could come. We were very good friends and good colleagues. I just felt that we would lose that if we were in the same department. I already knew Dr. Reeves and had great respect for him.

Hughes: How had you met him?

Winkelstein: There were fewer people in the field then, and you got to know all the major players. You just knew everybody. I used to always go to American Public Health Association meetings, and the epidemiology section was the epidemiology focus for everybody, so we would go there and see Dr. Francis, and Alex Langmuir, and Abe Lillienfeld, and we'd all drink beer together and have parties and see each other. It was a lot of give and take, so you got to know almost everybody.

When I came on the faculty here, I probably knew more of the faculty than many of the faculty knew each other because I was very active in the American Public Health Association, and by then I was on the council and all kinds of things like that. So that's how I got to know people.

Hughes: What research did you do right after you came?

Winkelstein: Well, they were involved in a big Japanese-American study of heart disease, and we were studying people at Hiroshima, in Honolulu, and here in the Bay Area. Stallones and [S. Leonard] Syme had really set this study up, and so I joined that study group.

Acting Dean and Dean, 1971-1981

Winkelstein: In the 1970s, I was dean, and I had a lot of difficulty getting research funding. In fact, even though one of my grant applications had been used by the National Institutes

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[1] See the oral history with William C. Reeves, "Arbovirologist and Professor, UC Berkeley School of Public Health," an oral history conducted in 1990 and 1991 by Sally Smith Hughes, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 1993.

of Health as a model--they used to send it out to people to show them how to write--I had seven grants [applications] turned down in a row, for a variety of reasons.

One time, one of the people at NIH said, "You know, if you would just do a nice case-control study, we would fund you." Well, I wanted to do some rather innovative different kinds of study designs and approaches and they weren't acceptable to people. And then also, as dean, people thought that I couldn't do both jobs. I frequently told students I kept writing things and doing things while I was dean because I had to use my head instead of being all bogged down with administrating grants. I was writing things sort of creatively. So my research output really sort of lagged during those years, but I did do some things, and I published some reasonably well-accepted papers.

Introduction to the AIDS Epidemic, 1983

Girish Vyas

Winkelstein: When I ceased being dean, which was December 1981, I was dabbling in various things. I didn't really have anything very pressing that I was doing or teaching. I can't remember exactly what I was doing in the way of research--nothing very important.

Then one day I got this telephone call from a professor at UCSF, and he said he'd like to come and see me. Well, I don't know if you know anything about the relations between medical schools and schools of public health, but for a professor of the school of medicine to ask to come and see somebody in the School of Public Health was a little bit unheard of. More likely he would have said, "I'd like you to come over and see me."

A Request for Proposals from the National Institute of Allergy and Infectious Disease, 1983

Wnkelstein: Well, anyway, this Professor Vyas, Girish Vyas, came over to see me one afternoon. He was putting together a team to respond to a request for a proposal from the National

Institute of Allergy and Infectious Disease [NIAID] to study the new epidemic of AIDS, and he wanted me to be on his advisory committee. Andrew Moss had suggested that because Andrew had been a Ph.D. student with us. I said, "Well, I don't know anything about AIDS." I hadn't paid much attention to it, and at that time--it was 1983--it wasn't a big deal. I thought about it and I said, "Well, I'll let you know."

The next day I called him up and I said, "All right. I'll be on your committee." So we had some meetings and they were trying to put together this response [to NIAID]. I went to the meetings and put my two cents in. Then one day, he called me up again and he said, "I want to come and see you again." It turns out he lives in Orinda so he could stop on the way home.

Vyas came, and he said, "I want you to take over the project and be the principal investigator." I said, "What do you mean?" He said, "Well, my colleagues at UCSF are very upset, and they don't want us to apply for this project, and they don't want me to be involved in it."

As you probably know, at the beginning of the epidemic, the lead at NIH was in the [National] Cancer Institute because a prominent expression of AIDS was Kaposi's sarcoma, so that fell in the purview of the National Cancer Institute. The National Cancer Institute had put money into San Francisco and had funded Paul Volberding and Jay Levy and Marcus Conant and several others to do research on this new epidemic. They were involved in that.

And then the NIAID put out this request for proposal, which these guys interpreted as an effort by another institute to get into the act, if you will, and squeeze the others out, or it was the mechanism by which NIAID would obtain specimens and so forth from San Francisco.

Hughes: Yes, I see.

Tensions within the UCSF AIDS Group

Winkelstein: So there was a jurisdictional kind of disagreement and at that time it was very bitter. I mean, these people were not very nice, to say the least.

Hughes: This was the group that's primarily centered at San Francisco General?

Winkelstein: That's right. And at Parnassus,[1] as well. There was a meeting which I did not go to, which was apparently a very, very bitter shouting match, and not at all nice, in which they told Vyas in no uncertain terms that he shouldn't get in bed--if you'll pardon the expression--with the National Institute of Allergy and Infectious Diseases.

Hughes: Because they were going through the National Cancer Institute?

Winkelstein: Because they were in the Cancer Institute, and Andrew Moss was associated with the Cancer Institute people and he felt that he couldn't join Vyas's effort. He was, in a sense, advising him.

Decision to Initiate a Proposal to NIAID

Winkelstein: So Vyas came to me and said, "They'll accept you. You're an outsider.[2]" I said, "Well, gee, I don't know anything about this. I'll think it over." Again, the same answer. I went home, thought it over, talked it over with my wife, and decided I would do it.

Hughes: Why did you decide that you would do it?

Winkelstein: Well, because I felt that I was the person to do it. I had a background in infectious diseases. I had conducted large-scale field work. In the discussions that I had been to already with the advisory committee, we had decided to do the project based on a population sample, which was, it turns out to be, the unique aspect of our study. I had experience; I had done sample surveying in blood pressure research in Buffalo.

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[1] Parnassus Avenue is the location of the main UCSF campus.

[2] See appendix correspondence dated June 10, 1983. Dr. Winkelstein made the correspondence referenced in this oral history available to the interviewer in preparation for the interviews. Unless otherwise noted, references in the oral history are to documents in the appendix to this volume and/or in Dr. Winkelstein's personal collection.

I had a background in cancer epidemiology, which I had done here. I had a background in infectious disease epidemiology. I had a background in survey research. I had worked for the federal government overseas and had had a lot of experience with grants and so forth. I thought I could do it, and I didn't have anything else pressing to do. Besides which, it looked like it was going to be a very serious problem--epidemic.

Hughes: By then?

Winkelstein: Yes.

Hughes: What made you think that?

Winkelstein: Because it was increasing exponentially. Every month, the cases were essentially doubling. So even though at that time there were only 100 cases in San Francisco, it already began to look like a serious epidemic.

Hughes: Can you remember exactly when Vyas approached you?

Winkelstein: Yes. It would be April or May 1983, because the deadline for the submission of the RFP [request for proposal] was something like July 1, or even June 15. I can't remember.

The first thing I had to do, of course, was get in touch with these key players--Paul Volberding, Marcus Conant, Jay Levy--and talk with them and indicate that this was not going to be competitive but was going to be collaborative.

Hughes: How did they react?

Winkelstein: Well, as I recall, Marcus Conant was very supportive and the others were, by then, willing to accept our effort. Already Vyas had brought in several people--Bob Anderson, who was a very prominent gay physician himself and was a very interesting guy. So there was a small team that had been put together. And Jim Wiley from the Survey Research Center of UC Berkeley.

There were about six--maybe five--weeks left to put together the proposal. Nothing had been put on paper. So I started coming into the office at five or six in the morning, working until nine or ten on the project, and then doing other things. We put together the proposal, and we submitted it, and we were one of five grantees or contractors.

Continuing Tension with UCSF over Medical Education at Berkeley

Efforts to Establish a Medical School at Berkeley

Hughes: Now, you spoke about the tension between the medical school and the School of Public Health. Were you meaning in general, or was it magnified in this particular instance?

Winkelstein: In general. Nothing to do with the AIDS epidemic.

Hughes: What was the basis?

Winkelstein: I don't know. We have a small sort of experimental medical school on the campus at Berkeley. And originally that was to be a full-scale four-year medical school in the East Bay. Historically, what had happened was that the medical school originally was split between Berkeley and San Francisco, with the clinical aspects in San Francisco and the preclinical here on the Berkeley campus. In the 1950s or so, the preclinical was all moved over to San Francisco.

The East Bay doctors wanted a medical school in the East Bay, so they formed committees jointly with the University of California, which were operative when I came here in 1968. I became involved in that, and particularly with a guy by the name of Professor Bob Biller, who was in the School of Public Policy. He and I, and Henrik Blum, and Ned Rogers until his retirement, and several others in the local medical society were the key people in forming a plan for a medical school based at Berkeley.

Basically, the plan was to have a medical school without walls; that is, to utilize the courses that were already in place on the Berkeley campus for the preclinical work, and to develop clinical affiliations with practitioners, have a practitioner-based medical school, very much on an old model that had been abandoned for the full-time academic centers.

Anyway, there's a long history. To make a long story short, the medical school was, of course, threatened by the prospect of a medical school without walls, which would cost a tiny fraction of the cost of the academic medical center. They didn't like that concept, and so we went through some huge battles over that.

I wouldn't say that was the basis necessarily of the tension between medical schools and schools of public health, but there's always been a tension everywhere between the two because schools of public health have a totally different approach from the medical approach.

Hughes: You mean in terms of prevention rather than prophylaxis?

Winkelstein: Yes. When I was dean and Lester Breslow was dean at UCLA, we had a committee to review the organization of public health education in the university. We were trying to get more money for the schools of public health. Schools of public health receive something like 3 percent of the health sciences budget of the University of California--3 percent--and yet they play a major role in the health of the state. What we were arguing was to increase us from 3 to 5 percent; the rest of the health sciences will go down from 94 percent to 92 percent, and you'll never notice it. But, no, it could never happen.

The Health and Medical Science Program at Berkeley

Hughes: What happened in the end to the medical school without walls?

Winkelstein: What happened was that the concept was nixed. What we have now is a preclinical program here on the Berkeley campus, and then the students go to San Francisco for their clinical work.

But at one point, Alberta Parker and I had gone to Chicago and had really gotten a commitment from the Association of American Medical Colleges to give us provisional accreditation, and when Julie [Julius] Krevans heard about that--he was the dean of the [UCSF] medical school and he was very prominent in medical politics--he managed to get the whole nixed.

Then the director of the Health and Medical Science Program on this campus gave an interview to The Berkeley Gazette--which has gone out of existence--on the whole history of the thing, and the role of San Francisco in putting the damper on the Berkeley experiment. One of the regents saw this article, and he called up the president of the university, Charles Hitch, and the president was pretty upset, and he called a meeting for Monday morning at 8 AM.

I'll never forget it. The Berkeley Gazette used to come out--I think--on a Friday. It was a weekly.

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Winkelstein: Attending the meeting were the chancellors of UCSF and UCB, the deans of UCSF medical school [Krevans] and UCB School of Public Health [Winkelstein], the director of the Health and Medical Science Program and vice president for Health Sciences, Cornelius Hopper. The President, Charles Hitch, worked himself up into an absolute lather. He opened the meeting by pointing his finger at this guy who was running the program on the Berkeley campus, and he said, "I don't know what you had in mind; I don't know what you were thinking; I don't know what your intention was."

At that point, Chancellor [Albert H.] Bowker, who was a very quiet, unassuming guy said, "Charlie Hitch, if you don't know what he was thinking, and you don't know what he said, and you don't know what he intended, how can you be against him?" Anyway, the meeting went downhill from there.

Finally, I said something like, "You know, everything was going along fine, and then Dean Krevans intervened and managed to get it all canceled, at the Association of American Medical Colleges."

The president of the university started shaking his finger at me and said, "How can you make such claims?" Then at that point, Krevans got up and said, "Well, Warren is absolutely correct. That's just exactly what I did."

Well, the upshot of the whole meeting was that the president said, "You guys will have to put these things in order and divide up the responsibility. We just can't have two medical schools." So that was the end of an independent medical school on this side of the bay, and from then on it was a question of working out how it would be arranged between the two schools.

Hughes: I remember when Ernest Lawrence and his group were producing radioisotopes for clinical use, there was talk about affiliating with or establishing a medical school, because Berkeley was suffering from a lack of clinical material.

Winkelstein: Exactly.

IV THE SAN FRANCISCO MEN'S HEALTH STUDY

[Interview 2: August 17, 1994] ##

More on Tensions within the UCSF AIDS Group

Hughes: Dr. Winkelstein, last time you got us up to your first involvement with the AIDS epidemic, which revolved around Dr. Vyas' withdrawal from the RFP. My first question is, why did he decide to withdraw?

Winkelstein: Well, he withdrew because of pressure from his colleagues at the University of California, San Francisco, who were being funded and essentially sponsored by the National Cancer Institute. The RFP that Dr. Vyas was proposing to respond to came from the National Institute of Allergy and Infectious Diseases. And the UCSF research team felt that this was essentially a battle over turf; that the NIAID was trying to horn in on, if you will, the territory of the National Cancer Institute, so the UCSF team put pressure on Dr. Vyas not to respond to the RFP.

The way out of that which Vyas saw was to have someone not on the UCSF faculty head up the team, because he would still be involved as a co-investigator--as a research worker--in the project if it were approved. So, that's why he came to see me and ask me to head it up. As I have mentioned, I was on his advisory committee and was helping him design the response.

Hughes: Did you have any reservations?

Winkelstein: Well, at the beginning, as I think I also mentioned, I didn't have any knowledge of what was going on. I hadn't kept up on the AIDS epidemic. I had only read a few articles in the newspaper, so I didn't feel that I was very knowledgeable.

On the other hand, after I thought about it for a while, I felt that my background was probably just exactly what they needed for a person to direct this. I had had infectious disease experience. I had had chronic disease and cancer epidemiology research experience. I had been involved in large-scale activities with the government, both in my overseas work earlier and in the vaccine field trials. And as I looked into the issue, it became apparent to me that AIDS was going to be a major problem, and so I decided to do it.

The NIH Request for Proposals

Hughes: When you looked carefully at the RFP, did anything leap out at you?

Winkelstein: Well, the main thing that the RFP asked for was a population-based study, and it included a clause which turns out to be government boilerplate, but which at the time I really believed. It said, "Independently and not as an agent of the government, the contractor shall..." and then it gave the scope of the work. Well, it didn't mean that at all, as became apparent later on. It didn't mean that the contractor was going to be independent and not an agent of the government; it meant exactly the opposite. It meant, dependent and as an agent of the government, you're expected to do the following... But I, in my naivete, believed that clause, and I kept using it in my subsequent disagreements with the NIH and, of course, I was laughed at. But there it was and I can show it to you if you want to see it. And it's in italics to emphasize it.

Government Contracts vs. Grants

Hughes: Tony Fauci, considerably later, made the point that this was a contract as opposed to a grant. Now, how does that apply?

Winkelstein: Well, contracts are the mechanism by which the government gets things done that it wants to do, like building fighter planes, or war tanks, or bridges, or hospitals, or whatever. So, when you sign a contract, you agree to do precisely certain things and to deliver certain items.

A government-supported research project has a great deal more flexibility. You propose to conduct research, you lay out the research plan, and it is reviewed, as is a contract, and once approved, you conduct the research pretty much as you want. You're afforded complete flexibility, whereas under contract, you're expected to have every deviation approved, no matter how minor. You have to have specific approval for each piece of equipment that you buy, and so forth and so on. So, there are a lot more restrictions in a contract.

Hughes: Which you appreciated?

Winkelstein: Which I understood.

Hughes: From the very start?

Winkelstein: Yes. But I also thought that it was the intention of the government that we should act independently, and not as an agent of the government. In other words, that we would have a certain amount of flexibility. As subsequently turned out, eventually we were given a considerable amount of flexibility because of the nature of the situation, and because eventually we showed that we were able to provide the government with a lot more than had been contracted for.

Crisis #2: Freedom to Publish

Hughes: It was the nature of government contracts to require review of publications?

Winkelstein: In the RFP--the request for proposal--there are, of course, a whole series of specifications for the contract, and there was a clause, numbered 19, which provided for the government to approve every document, every publication, every presentation. When we were discussing and responding to the RFP, we indicated that we could not sign a contract with Clause 19 in it.

Actually, I should mention to you how these things are done. You respond to the RFP indicating how you're going to conduct the research that they want you to do. And then they decide whether they're going to approve--award you--the contract. After they make that decision, then the contract is actually negotiated. In other words, there are several

levels; you get accepted for--as it were--technical content, and then details are negotiated.

During the negotiation phase, after we had been approved, we raised the issue of Clause 19, and we said that we would not be able to sign a contract containing Clause 19.

Hughes: What does Clause 19 state?

Winkelstein: It says specifically that the project officer shall approve all publications and presentations. And so the government came back to us and said, "Well, if you don't like Clause 19, suggest the wording for Clause 19." So we did. We suggested alternate wording, which the government accepted. The alternate wording said essentially that the project officer shall review all publications and presentations, and so forth, and within thirty days give his opinion. The contractor--that's us--agree to consider his opinions, but they're not binding. And with that revision, we were able to accept Clause 19.

Hughes: Well, that's crisis #2, right?

Winkelstein: That is crisis #2.

Proposing the Study

Design

Hughes: What did you propose to do?

Winkelstein: Well, we proposed to do a population-based study. By "population-based," I mean we proposed to take a random sample of single men living in the nineteen census tracts of San Francisco where the epidemic, up to that point, had been most severe. Andrew Moss had written a paper, published in The Lancet, which had outlined those areas of San Francisco where the cases were occurring. At the time that we wrote our plan, there were only 150 AIDS cases in San Francisco.

Hughes: That was in mid-1983?

Winkelstein: It was mid-1983 when we made our proposal. So the study was to be based on a sample of men. The proposal was that they

would come in, be examined, specimens would be obtained on a six-month basis for a period of three years, because the contract was only for four years. And, at that time, we expected that within that brief period of time, we would be able to figure the whole thing out because that's the way things normally are.

Hughes: You had no idea about the latency period at that point?

Winkelstein: No.

Hughes: Or how complicated the disease is?

Winkelstein: We had no idea about a lot of things.

We proposed to study a series of hypotheses which were based on our knowledge of both infectious disease epidemiology and cancer epidemiology because, at the time we were responding, the principal expression of this disease was these opportunistic infections and Kaposi's sarcoma. Kaposi's sarcoma, at the early part of the epidemic, was such a prominent part of the epidemic; that's why the Cancer Institute was involved.

Hughes: Right.

Winkelstein: So, we proposed to look at issues like aggregation in households, exposure to toxic chemicals, smoking, drug use, nutritional factors, occupation--a whole series of items that epidemiologists generally look at when they're trying to figure out an epidemic. And we also proposed to do these clinical studies and laboratory studies.

Institutions Involved

Winkelstein: So, at the beginning, we brought together a group of investigators from the Irwin Memorial Blood Bank, from the Children's Hospital of San Francisco, from the University of California at San Francisco, from the Survey Research Center in Berkeley, as well as one of the pharmaceutical companies that, at that time, was doing certain biological tests which couldn't be done anywhere else.

Hughes: Which one?

Winkelstein: I think it was Lederle.

Hughes: Why was Children's included?

Winkelstein: Well, Children's was included because, when we were looking around for a site at which to locate the project, somehow Dr. William Lang was approached. I don't remember exactly how that occurred. He's an internist at the Children's Hospital. Children's Hospital is a misnomer because it wasn't a children's hospital; it was a general hospital. And recently, as you know, it's been combined with the Presbyterian Medical Center, as California Pacific Medical Center.

Anyway, Lang was a young internist working with a large AIDS clientele and was very much interested in getting into clinical research, and so he arranged for the Children's Hospital to be the locus of our clinical activities. We had to have a place. And I don't remember why we didn't choose the medical center--I can't think of the name of it--which is down closer to the Castro District.

Hughes: Davies.

Winkelstein: Davies Medical Center. There was some reason. Either they were not anxious to have us or they distrusted our objectivity

Hughes: Why not San Francisco General which was already engaged in AIDS activities?

Winkelstein: Well, we couldn't go to San Francisco General because the investigators there didn't want us. They were the people supported by the National Cancer Institute.

Hughes: That's right.

Winkelstein: We had to develop working relationships with them, but nevertheless we weren't about to get into their territory. That would have been very difficult.

Hughes: Were there tensions around that?

Winkelstein: No. The first thing I had to do, after I took over from Dr. Vyas, was to mend fences with all the people at UCSF, which I did. I visited some, talked with them, and I think their opposition then dissolved. Over time, they became very supportive, and we had no problems after that.

Other AIDS Epidemiologists

Hughes: Well, one of the people in that San Francisco General group is Andrew Moss who, as you mentioned, had done the census tract study that was published in The Lancet in 1983.

Winkelstein: Well, Andrew was really the logical person to take over the project but there were several reasons why they didn't want to do that. At that time, he was working very closely with these National Cancer Institute people, so he couldn't very well separate himself from that. And he was probably a bit junior at that time to take over a project of this dimension.

Hughes: There was yet another epidemiologist who was early involved, and that's Selma Dritz from the San Francisco health department, and the epidemiologists from the CDC were involved.

Winkelstein: Well, you see, the CDC was already on the ground, if you will. They had their population, which was derived from the hepatitis vaccine trial of the 1970s. And our plan called for a population-based sample. We did have conversations with them and we agreed that if our sample happened to pick the people from their study, we wouldn't take them.

Hughes: I see.

Winkelstein: Calculations indicated that there would only be a small overlap. It turned out there was a small overlap, maybe ten or fifteen or twenty people, most of whom I think continued in both studies.

Hughes: And that didn't cause any tensions?

Winkelstein: No. We had good relations. We met with all the concerned players, and so I don't think there was any strong feeling. We met with Andrew, and Andrew was part of Vyas' group, and I don't recall any tensions there. Epidemiologists, by and large, get along together. Eventually, as you know, Andrew Moss brought his group in and merged it with the San Francisco Men's Health Study.

Hughes: What year was that?

Winkelstein: 1989 or '88.

The Contract Review System

Hughes: You mentioned that there were several steps in firming up a contract. One of them is the review process itself. Is it a peer review system?

Winkelstein: It's usually a peer review system with outside reviewers, along with internal reviewers. The ordinary project research grant usually gets reviewed by almost 100 percent external reviewers. Contracts usually have a mixture of agency staff plus outside reviewers. We eventually found out who one of the reviewers was. Other than that, I don't know who they were.

Hughes: Did they present questions that had to be resolved?

Winkelstein: No. We did not have any site visits. We submitted the response at the end of June, early July [1983], and we got an answer in August, I believe.

The Budget[1]

Winkelstein: Now, in the negotiations, there were two major issues, after it was approved. The first, I've already discussed, was Clause 19. The second was the budget. We didn't learn until considerably later that originally the NIH had planned to have two projects. They apparently obtained additional funding and decided to have five instead of two, but they didn't get five times as much money. They got maybe three times as much money.

We had submitted a budget and, when the negotiations came around, we were told we would have to cut our budget by approximately 25 percent. And we argued that we couldn't do the work for the money they were offering us. But they stuck to their guns, and we wanted to do this project. By this time, we were totally committed to doing it.

Actually, I was on vacation. My wife and I had exchanged our house with a family in Paris, so I was in Paris. I was on the telephone two or three times a week with Jim Wiley, and eventually we accepted a very substantial cut in our budget.

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[1] On this subject, see the letter in the appendix dated 12/6/83.

A Multicenter Study

Opposition

Winkelstein: Now, the other problem was that the NIAID staff saw this as a multicenter study, even though it had been advertised and awarded as an independent study.

Hughes: Implying much greater collaboration?

Winkelstein: Yes. Between the projects. Also, the fact that we were the only ones that were doing a population-based study meant that our costs were very substantially higher than the other submissions, because, when you're doing a probability sample, for example, you have to survey. We had to survey something like 4,000 houses, or maybe it was 5,000, to get the 1,000 people that we ended up with. Whereas, if you did a grab sample, you either used a clinic population which was already present, as they did in Chicago, or you put ads in the paper, as they did in Baltimore and Pittsburgh and Los Angeles, and people come in. There's no recruitment process.

Whereas we were going through a new-lab- or population-based proposal. So, on the day that everything began, we began to have money problems, and that's what leads to Crisis Number 1--the money problems. So, anyway, that was that.

Hughes: Well, according to the correspondence, the end of September of 1983 was the original start date, which I assume did not happen.

Winkelstein: Well, the contract went into effect on the first of October.

Hughes: In later publications, you talk about the recruitment of the sample.

Winkelstein: Here's what happened. When October 1st came, we had a plan. We had to recruit staff, and we had to make the questionnaire, we had to do all these things. And we had a time schedule. I can't recall precisely what it was, but it's somewhere in the documents.

The ink was no sooner dry than all five groups were called to Bethesda--that's two or three individuals from each center--and we were told that it was not to be five

independent projects, as advertised and as awarded, but a multicenter study with coordination. And that's what prompted my letter, which I gave you.[1] I argued, as you know, very vigorously about what the consequences of a coordinated multicenter study would be, and why I thought it was not a good idea.

Hughes: Why don't you repeat them for the benefit of the tape.

Winkelstein: Let me repeat them without looking at the letter, because I think I know what they were. The overriding argument that I made was that when you don't know very much about a situation such as this epidemic, you're better off with a diversity of approaches. And the ingenuity or the creativity of the investigators in the five different centers was likely to yield more information and resolve more issues than if we all did things together. Now, that argument was not accepted, nor were any of the other arguments, but that was my core argument.

The second point was that if we were going to have total uniformity, then that would require a great deal of negotiation between the five centers. We would have to develop the questionnaire. It would have to be a common questionnaire, which would mean it would be a questionnaire with the lowest common denominator, and that doing all those things would delay the onset of field work by a long time. And I thought that was undesirable. I thought it would probably double the lead time until we could get in the field. Every week that went by the epidemic got worse, and I felt that it was imperative that we get into the field as quickly as possible. Those were the two major points at issue.

There were several others, all pretty much interrelated. I argued that we had a different study design than everybody else because we were population-based, and that's what the RFP had asked for. None of the others were population-based. And that there would be difficulties in merging the data because of the diversity of recruitment procedures that the different centers were using. I felt that was a third major argument against merging the projects together.

Hughes: This argument that you and your group were putting forward was interpreted by NIAID as simply a means to facilitate priority in publication; that competition was the basis of your argument.

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[1] Winkelstein to Kaslow, Nov 11, 1983. See appendix.

Winkelstein: That was later on. The NIAID, unbeknownst to us, had convened a workshop in the spring of 1983. At that workshop, they had discussed their plans for--at that time, I think--two field studies, and they had been urged by the people at their workshop to have a multicenter study rather than separate studies. I wasn't involved in that workshop.

It's true that we were very quickly seen as being obstructionists and stubborn, and I don't know what else, because we didn't buy into this idea right away. On the other hand, we did cooperate. We took the lead in organizing the development of the questionnaire because we were with the Survey Research Center. We were the only group that had real expertise in survey research which, in a way, this [entire study] was. So, our people went to Chicago and helped train people, and organized meetings to develop the questionnaire, and we did a great deal. I think we cooperated. I think we went the extra mile in cooperation, even though we were opposed to this, and we were constantly objecting that--

Hughes: "This" being the collaborative approach?

Winkelstein: That's right. But, of course, the arguments had no impact.

The Questionnaires

Hughes: Well, let's turn to the questionnaires. There already were some questionnaires out there concerned with AIDS. The KS Clinic at UCSF also had an intake questionnaire. Was your questionnaire developed independently?

Winkelstein: No. We looked at all the questionnaires that were available, but there were considerable differences of approach between the five different groups. I think it's fair to say that two of the groups had relatively little epidemiological background.

Possible Reasons for Choosing the Five Participating Groups

Hughes: Why were two groups that weren't particularly strong in epidemiology funded to do epidemiology?

Winkelstein: Well, I can't answer you. I don't know the exact number of responses to the RFP. At one time, I was told that there were twenty-seven responses, and there were five chosen. Now, it's always difficult to know why the five were chosen.

One clearly had a very strong laboratory component, and that laboratory component was, I think, already working on the problem. Whether that threw the balance in their direction or not, I don't know. Ours was, as I say, population-based. I don't know what the other twenty-two looked like. I suppose I could find out if I was interested. I've got many more important things to do than go through the Freedom of Information Act.

It's very hard to say how these things happen. Sometimes there are very prominent investigators who may not be epidemiologists, but who are established clinical researchers.

Hughes: In AIDS research?

Winkelstein: Well, in infectious disease. It was already known in 1983 that this was a homosexual men's disease, primarily. The extent of drug-related cases was just being recognized. And one group had a very strong connection with gay men's clinical programs, and so forth. So, there could have been a variety of reasons for picking the various places.

I don't know anything about what the reviewers were told. The reviewers might have also believed that these were to be independent free-standing investigations, in which case they might have emphasized differences between the groups, or they might have been told, before we were told, that it was to be a multicenter study. I don't know.

Data Analysis

Hughes: What about the analysis of data? Some of that, I presume, was to be done by each of the five centers, but wasn't there some also to be analyzed by NIAID?

Winkelstein: Well, everything had to evolve because, when the projects were submitted--and, as far as I know, this is the case for the other four that were approved--we planned to do all of our own analyses. That was the original plan.

Now, when the projects were put together--and, of course, the questionnaire was standardized--it meant that the data would have to be standardized. So part of the development of the Multicenter AIDS Cohort Study [MACS] was to develop the procedures. And Crisis Number 2 partially hinges on this whole problem of how the data were going to be analyzed and presented. Another argument in the beginning for not doing it collaboratively was the delays that would be necessitated getting the information out.

Not at the beginning, but eventually, there was a data center established at Johns Hopkins. We still send our data to that data center, and it is available there to be used in any way that the National Institutes want to use it.

Hughes: There was some correspondence--perhaps it was later--that indicated that there was an analysis going on at NIAID. I believe it was [Robert] Kelley who made the point, in response to an argument that you had put forward, about the analysis being slowed down; that he didn't anticipate that NIAID would be a problem in terms of analysis of data. Do you know what he was talking about?

Winkelstein: Well, there have been a succession of project officers. The project officer is the technical person at NIAID who oversees the contract. And the contract officer is the person who has the authority to have things done, as it were.

The first project officer--Richard Kaslow--was very much interested. He's an epidemiologist. I think he was head of the epidemiology group in NIAID at that time. He was very much interested in the research as such, being a participant really in the research. But there was no mechanism at the beginning by which anything could be done, because in the first place it would take six months to do the first round of examinations. Then it would take time to get all the data together and, at the beginning, there was no repository, there was no mechanism, so all that had to be created.

Each center transmitted its data at the beginning in readable form, but each was differently readable so it would all have to be re-read onto some kind of a master database. I can't tell you much about what went on centrally. But, eventually, actually after we were separated, they began to publish collaborative data from the four other centers.

Hughes: It doesn't sound to me as though it was much of a problem.

Winkelstein: Right. Well, it also should be understood that, by 1983, the NIH had a great deal of experience in multicenter studies. A lot of cancer studies had been multicenter studies. A number of heart disease studies had been multicenter. They knew how to organize a multicenter study.

Had the RFP indicated it was to be a multicenter study, and had that been anticipated, there would have been a data center, perhaps a central laboratory or whatever, but there wasn't because that was not the original plan. And so retrofitting was a monstrous task.

Including A Heterosexual Population

Hughes: You mentioned that one of the unique features of the San Francisco study was the population-based aspect of this study. The other one, which I believe you brought up, was the inclusion of 200 heterosexual--

Winkelstein: That was a consequence of the design.

Hughes: --controls.

Winkelstein: Well, they weren't controls. It was a consequence of the design. The sample was of single men, so the criteria for being in the sample were age 25-54, which at that time was the age range of [AIDS] cases, and single status. So, that meant that the probability sample would reflect the sexual preference because, when the men were recruited, they were not interviewed. They were just invited to be in the study. They were told what the study was, and then invited to participate.

When they came to the clinic, then they were given this so-called informed consent form, and it was only after informed consent that they could be interviewed and their sexual preference determined, along with everything else. So, it turned out that there were 200 heterosexuals in the study.

Hughes: Why was that a stumbling block?

Winkelstein: Because it cost money. None of the other centers had any heterosexuals. They didn't recruit heterosexuals. So the argument was, why should we pay for 200 heterosexuals? That's one-fifth; that's 20 percent of all your activity

that is being directed toward people we're not interested in.

Hughes: And how did you reply?

Winkelstein: We said, "One of the valuable aspects of the San Francisco Men's Health Study is that we can now compare people who have AIDS, people who don't have AIDS, people who are not in the risk group, with all kinds of things, behavioral characteristics, biochemical characteristics, and so forth," which we, of course, did. Eventually we were one of the few places in the country which could give any information on sexual practices of heterosexual men because we had all this information equally from heterosexuals and from homosexuals.

Hughes: Well, Kaslow was one of the critics, and he called the inclusion of the heterosexuals "an unnecessary luxury."[1]

Winkelstein: That's right.

Hughes: But as an epidemiologist, could he see your argument?

Winkelstein: He didn't buy it.

Hughes: I guess you could have dropped the heterosexuals--

Winkelstein: We eventually did, but after eight years, because there was nothing being found. We had examined, and examined, and examined. I thought that was a very valuable part of our study, especially when so little was known about AIDS. When we were actually able to do a test for the AIDS-related virus, we found there were no infections in heterosexuals. That was terribly important. We didn't know how this disease was being transmitted. I mean, we had some ideas, but we didn't know.

Maybe there would have been 20 percent infected in the heterosexuals. How would we know? It was critically important, in my opinion, to have this random sample of population. And I think it turned out to be very valuable.

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[1]November 10, 1983 meeting of the co-investigators of the MACS.

Proposed Etiology

Hughes: You mentioned these diverse approaches that epidemiologists usually take--the nutritional, the biochemical, et cetera. Was there an etiology that you and the rest of the group were favoring by 1983?

Winkelstein: Oh, I think most of us thought this was an infectious disease, sexually transmitted. All the characteristics were there.

Hughes: But it was still important to keep those other parameters?

Winkelstein: Right.

Taking a Conciliatory Approach with NIAID

Hughes: In a letter to Kaslow, in November of 1983--so in the very early period of negotiation--you said you had been warned that if you contracted with NIAID that you "would becomes tools of the Institute."[1]

Winkelstein: That's right.

Hughes: Do you care to say who said that?

Winkelstein: That was all part of the original concern that the faculty at UCSF had with Girish Vyas. That was essentially what they said: "You'll be a tool of the institute."

Hughes: Then you say in that same letter that, after careful review of the RFP, you're not as concerned. In retrospect, should you have been?

Winkelstein: Well, I don't recall the full context of that letter, why I was writing it. I suppose I was trying to mend fences because my letter of November 11, 1983[2] in which I had given all these reasons for opposing the multicenter concept had essentially left the situation rather negative. I mean, if

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[1] Winkelstein to Richard A. Kaslow, M.D., November 11, 1983. See appendix to this volume.

[2] See previous footnote this page.

all you had in hand was that letter you might say, "Well, these people [in the San Francisco Bay Area] are not prepared to go along." But, in fact, we didn't ask to hand back the money. We had put forward our argument and we had lost, and the only choice for us was to participate or to quit, and we were participating.

So, I undoubtedly would have written a letter that would have been somewhat conciliatory.[1] It's so many years now. But my guess is that I was writing a letter which would indicate that we were going to go along. We weren't giving up our ideas, but we were going to cooperate, which we did. And there was a hope for collegiality. As you see, as you review all of the material, it eventually broke down, but we tried.

More on Crisis #2: Freedom to Publish

Hughes: Deborah Kiest wrote a letter dated August 29, 1983--[2]

Winkelstein: Deborah was the contract officer [at NIAID].

Hughes: She's reflecting one of your concerns, I believe, and passing it on to [Gregory J.] Pryor, who was the contract officer at NIAID.

Winkelstein: I think that reflects, again, our feeling that we did not want someone in Washington deciding what we could and could not say; that we were the better judges of that, if there was to be any selection. There was no way we would agree to the original Clause 19.

Hughes: And some of that was--I'm reading into what you're saying--that you felt that it was necessary to tailor any publications somewhat so that--

Winkelstein: I don't know if that's a good word for it. I guess it would be that we would be more concerned about, for example, delays in transmitting information.

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[1] Warren Winkelstein to Robert Kelly, NIAID Contracting Officer, December 6, 1983. See appendix this volume.

[2] Deborah Y. Kiest, NIAID Research Coordinator, to Gregory J. Pryor, NIAID Contracting Management Branch, August 29, 1983.

Hughes: So, you wanted anything that had public health significance to get out quickly?

Winkelstein: Yes. I think that would be it.

Sensitivity to Gay Community Concerns

Hughes: Were you sensitive as well to what you perceived to be the needs of the local gay community?

Winkelstein: One of the key co-investigators, Bob Anderson, was a gay physician, and so he had a lot of insight. In fact, Vyas was really involved in this because he wanted to get Bob involved. Bob is a rather brilliant--a very brilliant--guy who has had a funny career in and out of research and with private drug companies, and so forth. And so he was very sensitive to the gay community. And several other members of our initial and subsequent staff were members of the gay community. So, there was a considerable sensitivity about these issues in our research group.

I, myself, had had no contacts with the gay community. I had no homosexual friends. It was a totally new world for me. I just approached it as I approach anything else in life, and I've had no problems or issues, but I think we--everybody--appreciated the sensitivity of this.

Well, so did the NIH. In the prologue of Clause 19, I think it says, "Recognizing the sensitivity of the issues surrounding the epidemic," or something like that.

The Stop Work Order, April 20, 1984

Funding Problems

Hughes: There's quite a bit of correspondence between you and various officials at NIAID, beginning I'd say in 1983--

Winkelstein: Yes, it does.

Hughes: --and continuing through 1984. You were trying to explain why you had to keep delaying one aspect of the project after

another which, in a nutshell, was because of lack of sufficient funding, was it not?

Winkelstein: Well, that's right. There were several problems. One problem had to do with the delays caused by developing the multicenter collaborative effort, and the other came about because of financial problems which reached a crisis in less than a year. That was Crisis Number 1.

I think there's a considerable amount of correspondence about budgets. We would submit a budget; it was too big; they'd send it back. And the problem was that, as the NIH developed this collaborative study, they also changed the scope of the work, and the scope of the work also changed almost monthly because other information began to come in.

Hughes: So, the scope was expanding?

Winkelstein: So, the scope was expanding; the money had been cut by 25 percent. We were required to notify them, within some period of time--I think it was sixty days--of when we were going to run out of money. So we were not more than two-thirds through the first funding year when we could foresee running out of money. So, that's when we were negotiating with them and they were getting angry with us, as I think the tenor of the letters indicate.

Then one Friday night--I don't know what the date was--when the university here was actually in recess, a telephone call came. Somebody was working in Sponsored Projects Office. They took it, and it was noticed that termination proceedings were being initiated. So, I was notified on this Friday afternoon. You've probably got it down in your notes somewhere.

Hughes: Yes, I do. This was the Stop Work Order?

Winkelstein: Yes. That was April 20, 1984. That was just before we were to go into the field. And so I spent the weekend mobilizing my advisory committee and my colleagues, and then, on Monday morning, I was in the office at six o'clock so I could talk to Dr. Krause, who was then-director of NIAID. I called him directly and told him what had happened, and by eleven o'clock that morning the Stop Work Order had been rescinded. And then we were authorized to negotiate for supplementary funding to carry us through the first year.

Hughes: Was there ever an explanation of why that Stop Work Order was issued?

Winkelstein: No. You can only make inferences. Well, it was issued because we were spending too much money, and we were being uncooperative about reducing our expenditures. We kept sending them budgets that were too big. And so someone there-- We always called him the "Gray Eminence" because we thought it was somebody behind the contract officer--not the contract officer himself--who was making these decisions. I know there was a man by the name of Pollock who was in charge of these things. I didn't learn until more than a year later that it was he who made the decision to issue the Stop Work Order.

But clearly by this time we were a thorn in the side of the project officer because we had a project that was quite different from all the other four. Although we were cooperating, we were making waves; we weren't being "yes" persons.

Delays in Launching the Field Study

Hughes: What about the delays?

Winkelstein: We wanted to go as fast as possible. We felt that we would have been in the field months earlier but we couldn't get freezers. We couldn't buy freezers because there were delays in authorization, and we had all kinds of problems. Yes, we were delayed.

Hughes: Now, when NIAID decided that your budgets were too high, were they putting them in the context of what the other four centers asked for?

Winkelstein: I don't know. My guess is it was a combination of factors. The problem was that we signed a contract. That meant that we were supposed to deliver. Now, it's like a court case; there are two sides to every question. Putting ourselves in the NIAID position, they said, "These guys signed a contract to do the work at a certain price and now they're saying they can't do it, and they're over-spending." On our side, we would say, "Yes, we signed a contract under duress, but we did sign a contract. But then you required us to do more work." And so I wouldn't want to place blame. I'm sure that we were partially to blame for these problems, especially looking back. On the other hand, eventually they did supplement our funds.

Now, if they were going to issue a Stop Work Order, they should have said, "Look. If you can't resolve this by such and such a date, we're going to issue a Stop Work Order," in which case I would have written a letter to the director and said, "We're being threatened with a Stop Work Order." And we would have worked it out. The government always has the option to cancel the contract, and so do we. That's in the contract.

But they just precipitously issued a Stop Work Order. Anybody who had a modicum of intelligence would know that we were going to appeal, and that we were going to appeal right up to the director. And you'd think they would have gone to the director first and said, "Look. We're going to issue a Stop Work Order to these people." You know, you would warn your boss. I can only infer that by that time they had had their fill of us and they would have liked to get rid of us.

Consulting the Research Team

Hughes: You were the spokesman for the epidemiology group. How much were you consulting with your research colleagues and trying to represent them in your correspondence with NIAID?

Winkelstein: I never do anything alone. I practically never even write an important letter without bouncing it off one or more of my colleagues. Everything that you see--not everything, not every letter, but the major actions are all taken after consultation with the whole group. On the other hand I think they took--

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Winkelstein: --a very strong leadership position, you know. And, generally speaking, my colleagues supported me, but not always. But I think I represented them responsibly.

The Four Other Research Centers and Population Recruitment Policies

Hughes: You've mentioned in passing the names or the locations of the four other centers. Would it be pertinent to give just a thumbnail sketch of what they did?

Winkelstein: The four other centers are Los Angeles (UCLA), Chicago--Northwestern Medical Center, University of Pittsburgh, Johns Hopkins University School of Hygiene and Public Health.

In Baltimore, they originally tried to assemble a cohort from volunteers. They advertised and they used various methods for recruiting their population. They were unable to get sufficient population in Baltimore and they went to Washington, D.C. and they recruited there.

Hughes: You mean, because there weren't sufficient numbers of AIDS cases in Baltimore?

Winkelstein: No. Because they couldn't get enough volunteers. And then they went to Washington and used the same techniques--advertising through organized groups and so forth--to recruit people. They got additional participants from Washington and then they went to Wilmington, Delaware. So, they finally drew their cohort from Washington, D.C., Baltimore, and Wilmington, Delaware.

Communities were partially selected as two communities that would have high rates, one that would have very low rates, and two that would have intermediates rates. The Pittsburgh cohort had difficulties in recruitment primarily because it didn't have much AIDS. They recruited by advertising and they sent recruiters out to gay bars and dance halls.

In Chicago, the program was based largely on clinic populations that were already attending gay medical clinics. And in Los Angeles, they recruited largely by advertisement for volunteers.

Hughes: Was that the other high incidence location?

Winkelstein: Yes. Chicago and Baltimore were intermediate.

Hughes: Well, that's Crisis Number 1, unless you want to say something more about it.

Winkelstein: There's very little more to say. As I say, the Stop Work Order came a week or two before we were scheduled to begin our field trial, and we went ahead with it. As I recall, we got some supplementary funds to carry us through that year. And that was that. At the time, we had our hands full doing our pretrial, and then we started our major program of recruitment, I guess, in June or July of 1984. But, I think it is reasonable to assume that having gone "over the heads"

of contract and project staff to the director and having their decision reversed, that we had generated considerable bitterness among the [NIAID] staff.

More on Crisis #2: Freedom to Publish

Hughes: Well, let's move to Crisis Number 2 which we've talked about a little. In a nutshell, it was the problems over publication policies.

Winkelstein: And also the virus research.

Hughes: One of the concerns that was directly expressed was that publication by one center would preclude later publication by each one of the other centers--or as a collaborative publication.[1] Was that indeed an issue?

Winkelstein: Well, it was an issue for Dr. Kaslow.

A Paper on AIDS Prevalence, 1984

Winkelstein: I don't remember the exact date, but at the end of 1984, about two-thirds of the way through our first cycle of examinations, we already had a test for virus. The announcement of the isolation of the virus was made in 1984, I think in May[2], which was just about the time the studies were getting in the field. And one of the laboratories which had isolated the virus originally was Jay Levy's lab in San Francisco. We had brought Jay Levy into our group to do the laboratory work.

And so in late 1984 for the first time we had a population-based estimate of the prevalence of HIV infection. The AIDS virus then was called HTLV-III or ARV, AIDS-associated retrovirus or whatever. So, we followed our contract procedures and sent a copy of our manuscript to

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[1] Winkelstein to Richard A. Kaslow, M.D., Ph.D., 11/26/84.

[2] Margaret Heckler, the head of the Department of Health and Human Services, made the announcement of the isolation of the AIDS virus, not till later named HIV, in April 1984.

Kaslow, and he didn't do anything about it. And so we published a letter in The New England Journal of Medicine on the prevalence of HIV infection in San Francisco.[1] And that was the first population-based estimate of the prevalence of the AIDS virus in a defined population of U.S. homosexual men.

Hughes: That paper was based on an early antibody test?

Winkelstein: That was based on an antibody test that Levy had developed in his lab. There had been a previous publication from the City Clinic, from the CDC group, using another test. And they had reported, I think, 68 percent prevalence of infection among homosexual men. However, this population had been recruited from specialized (sexually transmitted disease) clinics. We reported 36 or 40 percent [infected], or something like that.

Criticism of Publication by the Other Centers

Winkelstein: Well, we used to have monthly meetings of the investigators for the five multicenter AIDS studies, and the other investigators were quite angry that we had published, for two reasons. They argued they couldn't publish. I said, "That's nonsense. Of course we can publish. When we have important information we'll publish and you should to."

They also argued that we had done this clandestinely. And I showed them the letters that show that we had notified the project officer strictly in accordance with the requirements of revised Clause 19.

Changes in the Contract's Publication Policy

Hughes: The project officer, Kaslow, had approved publication?

Winkelstein: Oh, he couldn't approve. He was entitled only to comment, remember? That was the revision of Clause 19. And he

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[1] For this and other references to Dr. Winkelstein's publications, see his bibliography in the appendix. The reference referred to above is #144.

hadn't bothered to comment, so he had remained passive. He could have said, "You shouldn't do it," or he could have said anything. We were obligated to consider whatever he said, but we weren't bound by it, and he said nothing!

So, then he proposed that we have a publication policy. And the only difference between the proposed publication policy and the original Clause 19 was that, instead of the project officer reviewing and approving, a committee of the five investigators would. And I objected to that. Then there was an exchange of letters, and finally the project officer wrote me a letter--I put it in your collection--in which he wrote down the unbelievable statement that, "Your arguments based on contract provisions and academic freedom are not compelling."[1]

That's when our sponsored project officer, Nancy Caputo, wrote back to the NIH saying, "Academic freedom and contractual clauses are all we have." So, that was that part of the controversy. That was in December [1984] when she wrote that letter.

In 1985, early in January, Kaslow wrote again and said, "Only one group objects to the policy." And then he essentially said he expected me to conform. It is true that I did not consult with my colleagues before I wrote. Well, no, I did. I don't know if you remember: There's a little note.

Hughes: Yes, I remember.

Winkelstein: I sent that out to all the colleagues and the advisory committee; I said I would not agree to that.

Hughes: In your handwriting. In fact, you signed your initials.

Winkelstein: So, that was part of Crisis Number 2.

The Contract Modification Regarding Virology

Winkelstein: The other part had to do with, at the end of '84 or the beginning of '85, the NIAID sent out a proposed modification--it had five or seven points that we were to

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[1] Kaslow to Winkelstein, December 6, 1984.

do, and there would be funding for it--that had to do with virology, because now the virus had been isolated and tests were now available. We already had our own test, which was different from the one NIAID wanted.

So, we sent in a protocol to do three very special things. I can't remember, but they're in the correspondence. In other words, we laid out our plan, which, strictly under the rules of the game, we were not entitled to do; we were supposed to do what NIH told us to do.

Hughes: It was more than just who was going to do what because I know you wrote about the virus isolation work going on in Levy's lab.

Winkelstein: Right.

Hughes: And Vyas was doing DNA hybridization.

Winkelstein: Right. Immune complexes.

Hughes: Yes.

Winkelstein: So, we proposed to do these other things and NIAID proceeded to approve funding for the other four centers, even though the other four centers were not going to produce anything like what we were able to produce. We were hounding NIAID to fund us, and they were saying, "We won't fund you because you're not responding to the modification--number 16 or whatever--to the contract."

Anthony S. Fauci, M.D. Takes Action: The Studies Are Separated

Winkelstein: So, then we were notified, clandestinely, by someone at NIAID--on a Wednesday, or something--that on Friday they were going to commence termination of our contract. That's when I wrote the letter to Dr. Fauci, and that letter was carefully crafted with my colleagues' agreement. You'll notice there's a letter to Fauci, which is one page long and a couple of lines on the next page.[1] Then there's an attachment which has all of the grievances, if you will, the

[1] Winkelstein to Anthony S. Fauci, M.D., February 6, 1985.

delays in funding the virus work, and the disagreements over publications policy.

Then, what he did with that, which we knew he would do--he gave it to his deputy Jim Hill, who is an old-line [U.S.] Public Health Service guy--very, very good--who I fortunately have known for many, many years. And Jim Hill's job was to get to the bottom of this whole thing.

Hughes: Resolve it?

Winkelstein: And resolve it. So, apparently that's what Jim Hill did.

At the end of February--whenever it was--Fauci wrote to us--

Hughes: February 22, 1985.

Winkelstein: Yes. On the first page he reiterates the company line, "This is a contract," and all that. And then, he proceeds to cut the Gordian knot and he says, "We will have two studies: the Multicenter AIDS Cohort Study, and the San Francisco Men's Health Study." And then he proceeded to authorize everything that we asked for--the exact budget that we asked for and so forth. I couldn't believe it when I saw it. I mean, the world had just changed its color. We had come out from under a cloud into bright sunshine.

Hughes: Was that Jim Hill's work?

Winkelstein: Well, he looked into the matter. I don't know exactly what he did. You'd have to ask him. But they wouldn't take such drastic action if they hadn't carefully evaluated it.

As you can see from what happened subsequently, we won a very bitter struggle over publications, over funding of virus studies, over autonomy. I mean, we were not supposed to have so much autonomy, but we were convinced that we were right. This was an important issue. It was important in many ways: one, because we thought we could make substantial progress in the direction of controlling the epidemic and, secondly, we knew that we were right in our insistence on the freedom to publish.

We weren't against a publications policy. In fact, I think I wrote a letter saying, I think a publications policy is fine, but it must not abrogate the clauses in the contract, nor should it interfere with academic freedom.

And we just felt those were too important; we couldn't compromise them.

Hughes: There's a philosophical argument going on that relates to freedom of inquiry, freedom of the press, freedom of expression. Then there's the argument that the science you are doing is absolutely critical to stopping this frightful epidemic. Which, or a tangle of both, is winning the day?

Winkelstein: Oh, I think it's both. The situation had come to a critical point. There were three things that could happen. One is the contract could be terminated. The second thing is that we could agree to become good little boys and girls. (By that time we even had a woman in our group.) And the third thing was that we could be separated, which I think was the wise thing to do. I'm sure that Dr. Fauci made that decision.

Hughes: It would have to come at that level?

Winkelstein: Oh, no question. So, I think it was the right decision. I think that the issue of funding is sort of secondary. We were perhaps being arrogant to think that we knew better than NIAID as to what should be done in terms of the laboratory investigations at that point, but sometimes you have to be arrogant. We thought we were right.

Hughes: By February of 1985, it was quite clear that San Francisco had a real role to play in the characterization of the virus because Levy's paper had been published in Science in August of 1984.

Winkelstein: Yes. I didn't mention that at that point the MACS--Multicenter AIDS Cohort Study--did not have a laboratory that could do virus isolation. They would have to set it up with Chuck Rinaldo in Pittsburgh. And we were working with one of the world's three or four leading virologists in the field, so we felt pretty strongly that we were on the right track.

Hughes: Well, there was an interesting article in The Chronicle that appeared right at this time, which I thought must have played into your hands. It was an editorial dated December 24, 1984.[1] The editorial was about a report that had originated at Harvard which was, in a nutshell, complaining

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[1] Unwise meddling in research. San Francisco Chronicle, December 24, 1984.

about government interference in scientific research. Was it gratuitous that the editorial landed in your lap at that particular juncture?

Winkelstein: It was absolutely gratuitous.

Hughes: Well, Crisis Number 2?

Winkelstein: Crisis Number 2 was resolved. Shortly thereafter, Dr. Kaslow returned to his original post as director of the epidemiology branch, I guess. We got a new project officer, Hal Ginsberg. His boss was [John R.] LaMontagne.

Things went along pretty well in '85 and into '86. Then came time to renew the contract because it was a four-year contract originally. There were some serious problems. There were some budgetary problems. There were budget cuts and we had to fiddle around and curtail certain activities and stretch out examination cycles, and all kinds of things. But nothing of a crisis or confrontational nature. It was just serious administrative problems.

The Contract Renewal, 1987

Winkelstein: Then came the renewal, and everything seemed to go along fine. We had what's called a noncompetitive renewal, which means that you apply for renewal but you're not in competition with anybody; you're in competition with yourself.

Hughes: Is that usual with contracts?

Winkelstein: It can be done, yes.

Now, interestingly, we didn't apply as a multicenter contract. Of course, we were outside [contractors]. I don't know what the others did. But we, of course, by that time were by ourselves again. So we applied, and we were approved--provisionally approved--subject to answering twenty-one questions.

Hughes: Now, this was May of 1987?

Winkelstein: Yes.

Request for Neuropsychiatric Examinations

Winkelstein: Now, the twenty-one questions were straightforward but, in the renewal RFP, we were asked to do neuropsychiatric examinations. And we spent a lot of time and effort working up the neuropsychiatric stuff. We responded with a neuropsychiatric component of our project.

Hughes: Was that a reflection of growing realizations that AIDS dementia--

Winkelstein: AIDS dementia had been discovered and was of interest.

After our project had been approved and the twenty-one questions were submitted, we decided in consultation with our project officer that we did not want to do the neuropsychiatric component. We had a number of reasons. The principal reason was that we felt that it was just impractical to do in the situation that we were involved in. It was too complex, the examinations were not well enough established and validated, and we were just uncomfortable with it. We didn't think it would contribute. And so, with the agreement of our project officer, we removed it from the proposal.

Then one morning, our sponsored project officer was talking with her counterpart in Bethesda who accidently dropped the bombshell that we were not going to be approved. I immediately called up our project officer and he was very upset because that decision was not supposed to be revealed at that time. Nevertheless, he confirmed that we were not going to be approved.

Hughes: Did he give you reasons at that point?

Winkelstein: Oh, yes. Because we dropped the neuropsychiatric component. A source selection group had met the previous day and recommended against renewal. I remember saying to Hal Ginsberg, "Didn't you tell them you had approved the deletion?" He answered that he was not supposed to participate in committee deliberations, which I thought was ridiculous.

Hughes: What does that mean?

Winkelstein: It's a review committee of some kind. They had reviewed our twenty-one questions and our neuropsychiatric proposal. That was probably in the twenty-one questions.

Hughes: Yes, it was.

Winkelstein: And our decision not to do it. They had decided that we shouldn't be awarded the contract because we weren't responding to it. Our sponsored projects office said, "You cannot appeal this." And I said, "I cannot not appeal it. I'm going to appeal this." And so that's when I wrote that long memorandum that starts out, "At 8:01..." or something in the morning, to document all this stuff.[1]

Then I mobilized all my investigators and I sent letters out--tons of letters--to [CDC Director] Bill Foege, to all kinds of people all over. And sent them a copy of my memo. We talked to congressional people, and so forth. That's why I wrote you the note that said, "By this time, we knew we had to have some enemies,"[2] because they made the decision to not renew the contract within twelve hours of the source selection committee, and I knew that they couldn't have taken it up to Fauci. It had all been done at some lower level.

Hughes: Was it your "Gray Eminence"?

Winkelstein: Yes, I'm sure. Plus, by this time Ginsberg now had a guilty conscience because he should have told the source selection committee. He said that he was not allowed to speak at a meeting with the source selection committee. I never believed that on an issue of this importance, a $14 million dollar project contract--that's what it would be for the next four years--that a person could be silent in the room and let people say, "These people are nonresponsive," when the project officer had approved the decision not to include a neuropsychiatric component.

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[1] Memo, Warren Winkelstein, Jr. to whom it may concern, July 23, 1987, Termination of NIAID contract support of the San Francisco Men's Health Study (SFMHS).

[2] Dr. Winkelstein's note to the interviewer, dated 12/8/94, accompanying documents related to crisis number three read: "You can infer that by 20 July 1987 we had some powerful and thirsty enemies!"

Other Concerns

Hughes: There's a letter from Mary Anne Glick and Harold Ginsberg written to you, and the date is August 11, 1987, so just after the termination.[1] They list all the criticisms. Glick and Ginsberg point out two criticisms which they say were of most concern to the review committee, and they do not designate the NP exam. What they designate as a main concern is the fact that only 59 percent of the 1,750 men eligible for inclusion actually participated in the study.

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Hughes: They were worried about bias introduced by the low sampling rate. And the other point that they brought up was that only 700-800 were attending the six-monthly examination cycles.

The point I'm trying to make is that you were told that it was the NP examination, or your failure to respond to it, that was the major concern. Well, according to the review committee, that may have been one of the concerns, but it was not a major one.

Winkelstein: Well, do you remember, in one of the documents I reviewed the twenty-one questions? [2]

Hughes: Right.

Winkelstein: I think it was in my first evaluation of the situation that I pointed out the questions I thought were problematical and the ones that weren't. And it turned out in the end that I had pretty much spotted the right ones. Those are trivial issues which could have been straightened out by a telephone call. You don't cancel a contract after you've approved it, and after you have assured the investigators you're going to do a site visit. That was another thing, you remember, in the May letter, they said, "Well, there will be a site visit, if necessary."

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[1] Mary Anne Glick and Harold M. Ginsberg, M.D., J.D., M.P.H. to Warren Winkelstein, Jr., August 11, 1987.

[2] See correspondence in appendix dated May 26, 1977; June 26, 1977; July 21, 1977; July 23, 1977; July 30, 1977; August 7, 1977; August 11, 1977.

Hughes: Then what was the reason?

Winkelstein: Oh, the reason, I'm sure, was that as soon as they found a chink, namely failure to respond to the neuropsychiatric requirement, that would be an excuse to cancel the contract.

Enemies

Hughes: Because they just wanted you out of their hair?

Winkelstein: Well, it's clear that we had powerful enemies.

Hughes: Yes, but why?

Winkelstein: Oh, because we had gone over their heads twice already. Now, that's only my inference. I can't tell you for certain. All I can tell you is that people in bureaucracies don't like it when the contractors go over their head and reverse their decisions. That's what had happened twice, now. And I'm sure the same person was still there. When he saw the name "Winkelstein," he probably started gnashing his teeth.

Compromise

Winkelstein: And so we appealed to Dr. Fauci, and he sent Jim Hill and LaMontagne and Ginsberg, and a bunch of other people, back here in August 1987. In the correspondence, I say, "We finally came to a compromise." And the compromise was that they would reissue the RFP and we would respond to the reissued RFP, which is unheard of. I mean, we were out.

So, they reissued the RFP, which meant that we had to respond. As I said in my letter to the investigators, "It's a lot of work, but it will all come out okay in the end." So, we did respond. And, of course, we put back in the neuropsychiatric component.

A Site Visit

Winkelstein: The irony of the whole thing is that then they had a site visit. And they put together a blue ribbon committee with Nancy Mueller from Harvard as the chair, and Lincoln Moses as a statistician from Stanford, and we had Carolyn Britton the top neuropsychiatrist in the county on AIDS from Columbia University. I mean, you never saw such a roster of distinguished people to come and site-visit us.

Of course, I had mobilized our team and had all these people assembled. Some of the things that the NIAID people didn't know was that Nick Jewel, our statistician, had been a fellow of Lincoln Moses, and Nick is fabulously brilliant. We had all these people, and my group made presentations. The quality of all my colleagues in the room speaking on their work, and Jay Levy, and John Greenspan, and all these people, and then some young recent postdocs who were working with Mary Claire King, I mean, it was just fabulously impressive, at least it was to me.

The site visit team recommended that we be given the contract minus the neuropsychiatric component. So, Ginsberg departed shortly after that. That was that crisis, and we got over that one. I don't want to sound paranoid, especially on these tapes, but there's no way to interpret this except to say we had enemies. But we also had supporters and friends, and the supporter and friend was Dr. Fauci, the director. He had supported us all along. And the only reason that we get support is that our group has done good work. There's no reason to spend millions of dollars and go against your staff, and to do all these other things, unless our group was worth supporting. So, that's who I think is responsible. (Incidentally, when all was said and done by 1996, our group had produced approximately 150 peer reviewed articles on many aspects of the HIV/AIDS epidemic.)

Crisis #4

Improved Relations with NIAID

Hughes: Now, the last crisis, Crisis Number 4?

Winkelstein: Yes. The last crisis was a mini-crisis.

After Dr. Ginsberg left, NIAID brought in Sten Vermund as the director of the AIDS epidemiology program, and Lew Schrager became our project officer, a young, bright, able guy. Our relations absolutely changed and we became closely collaborative with these people. I mean, they were very, very good, sound people. Vermund has recently left NIH to go to the faculty at Alabama, and Schrager is still with NIAID. He has taken Vermund's job.

At any rate, we were now working with our supporters and colleagues. It put us in a funny position because, if we were having trouble, we could no longer go over their heads. And we did have a problem.

Proposing a Survey of Young Homosexual Men

Winkelstein: We had proposed in our renewal to do a survey of heterosexuals in San Francisco, a serological survey to determine if HIV was spreading from the homosexual to the heterosexual population. We had made some projections based on prevalence of HIV infections in bisexual men, and their reported contacts with heterosexual females, which indicated the relevance of such a survey on sexual behavior. And that had not been approved in our renewal. So then we had proposed to do a study of young homosexual men because all of the cohorts in the United States had aged since they had been recruited in 1984, so nobody knew anything about what was going on in men under the age of thirty. So, we proposed to do another sample survey of under-thirty men.

Also by this time, people were thinking about vaccines, so we wanted to do this survey partially to get us information on what was going on, and partially to begin to lay the basis for learning something about doing vaccine field trials. So we made a proposal to NIH to do such a survey, and we happened to have $350,000 of available money within our contract that we could free up for this project.

Delayed Approval

Winkelstein: So, in March of 1990, I went to Bethesda and made a presentation to the group about the Young Men's Health Study, and it was very favorably received. We had worked it out with Schrager in advance. The contract people were in the room, and everybody agreed this was a high priority, very important, and we should do it right away. The contract people said, "We can clear this because you've already got the money. No new funds are involved. We can get this cleared in a matter of weeks." It took close to eighteen months before we were able to get this project in the field. All kinds of bureaucratic road blocks were placed in the way. Dr. Schrager worked very hard to get this project in the field, and he was just blocked in every way by bureaucracy.

Hughes: What was going on?

Winkelstein: Well, one of the bureaucratic problems is that, if you do a survey under contract with the government, the Office of Management and Budget has to approve the survey instrument. That's like throwing it into a black hole, to try to get any kind of a survey instrument, especially one on sexual practices, out of Management and Budget in the Bush Administration, as you can imagine. We had to try to stay out of that procedure.

So, to stay out of that, you have to get something called a clinical waiver. And we were blocked in getting our clinical waiver for a long time by people who didn't want us to do it.

Hughes: Why?

Winkelstein: Well, I don't know. I don't want to accuse anybody, because this is another group of people. But it was bureaucratic--and I kept trying to get Vermund and Schrager to go to Fauci, but they wouldn't--because we knew that sooner or later they were going to approve this thing, so why not sooner? I mean, we had the money. It was just absolutely ridiculous.

Hughes: You were hamstrung?

Winkelstein: Oh, I wanted to write a letter to The New York Times, but wiser heads said, "No, that's not the way to go."

Hughes: I meant in terms of research. You really were stalled?

Winkelstein: Eventually, we did it, and of course got a lot of interest and it was very important. I mean, NIAID is using the data. All kinds of people are using the data.

Hughes: That data has become one of the bases for the vaccine evaluation?

Winkelstein: Well, it certainly provided some important information.

Phasing Down the San Francisco Men's Health Study

Winkelstein: In 1991 or '92, NIAID got some mandates from Congress having to do with studying AIDS in women and in children, but they didn't get any extra money. So, the Division of AIDS had to cut back on some of its ongoing projects, and we knew that. We were in discussions with our project officer, Schrager, and we knew there were serious funding problems.

We had invited him to come to San Francisco and visit us for ongoing discussions on budget and other matters. So, he came. I don't know when it was. I think it was February of 1992.[1] Jim Wiley and I had breakfast with Lew Schrager, and he didn't say anything about what he was going to say at our meeting.

So, then we had our meeting. We met every two weeks, that is, the investigators, the participant advisory committee chairman or representative participant advisory committee, our research assistants, and so forth, so we had all of our team there--maybe ten or fifteen people.

Lew got up and said, "This is the last round of examinations of the San Francisco Men's Health Study. We're phasing out at the end of this current cycle of examinations. There will be no more exams." Closing down the project essentially. Well, that caused consternation, as you can well imagine, and we unloaded on him.

So at lunchtime, he called up Sten Vermund, and they had a long conversation, and he came back and said, "Well, we'll negotiate this." That's when I prepared the phase-down

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[1] Winkelstein to Schrager, March 23, 1992.

proposal, and then I went to Washington, I guess in March, to present the phase-down. I had already sent it ahead. And the phase-down was agreed to and that's the basis of our current operations.

At the same time, we made proposals for vaccine preparation studies. So what they decided to do was to continue our contract to its termination, which is October 1995--next year--and to phase down the San Francisco Men's Health Study so that we're now just following the slow progressors and the seroconverters, and a few other control people. And we're conducting an annual surveillance of everybody, so we call them up and find out what their status is. And then we've done these Young Men's Health Study and vaccine preparatory studies. So, that's what was decided and agreed upon.

Hughes: What was the reaction of the scientific community when the full thrust of the project was terminated?

Winkelstein: Do you mean Crisis 3, or Crisis 4?

Hughes: Both.

Winkelstein: It's been very unfavorable to NIH for both. One of the arguments that I put forward is that, after following these people for ten years, and bleeding them white and punching them and probing them and questioning them about the innermost secrets of their sex life, to abandon them just seemed to be unfair to them.

On the other side, there's still a lot to be learned from following these people all the way out, as long as may be. And so, from a scientific point of view, I think it's been a very unwise decision. But I'm sure that the decision has been driven, in this case, by budgetary considerations. NIAID can't do everything, and I appreciate that. I mean, that's a problem.

I happen to think that more money should be made available. I think the priorities are wrong; that the parts of the so-called women's initiative are draining money where it shouldn't go. On the other hand, there are areas of research at NIH which are being under-funded, and that may include some women's research as well. I'm not against a fair and equitable division of research funding, but I think some of the doctrine and formula solutions have been costly to the country from a scientific point of view.

Various AIDS Epidemiological Studies

The San Francisco City Clinic Study

Hughes: Is the Men's Health Study the longest-standing longitudinal epidemiological study on AIDS?

Winkelstein: No.

The studies have all been very productive. I would not argue that the MACS has not, although I think for the money spent ours has provided perhaps as much as any other study. But the longest study is the City Clinic Study. That takes advantage of the fact that they have blood from these men in 1978, and it's just fantastic what they've been able to do with it now. They've had consistently good people working there, at the San Francisco Health Department, and they've done very, very good work over the years.

Andrew Moss and the Merger

Winkelstein: We combined with Andrew Moss, who's a brilliant investigator, in--what?--1989, and I think that's been a fruitful merger.

Hughes: What was the story behind the merger?

Winkelstein: Andrew ran out of money. Universitywide AIDS [Research Program], I think, had been supporting him, and they decided to cut back on their support. So Andrew came to us and we went to NIH and said this was an opportunity to join these cohorts. Andrew has a component that was probability sample based. It's not his whole cohort, but it's part of his cohort. And it was on that basis that we were able to argue that it was appropriate to bring his group into our group.

Hughes: Were there compatibility problems, or any kind of problems?

Winkelstein: There were some problems, but nothing serious, nothing we couldn't get over. His questionnaires had been different, and we had to do some work to get them together, but we did it, and I think it's been fruitful.

Accomplishments of the San Francisco Men's Health Study

Hughes: Why don't we conclude with your singling out what you consider to be the major accomplishments of the San Francisco Men's Health Study.

Winkelstein: Wow. Number one, I think that we were able to replicate--but establish in a more definitive way--the mode of transmission in homosexual men, namely, receptive anal intercourse for the acquisition of infection. I think we were able to do this more definitively than other studies because of the design; we were dealing with a probability sample rather than selected samples which could always be questioned with respect to certain selection biases.[1] So, that was the first thing.

The second thing was that, I think for the first time, we were able to accurately evaluate the prevalence of infection in a defined population of homosexual men. Again, the other studies all had selected samples and, therefore, you didn't know exactly what the real prevalence and incidence of infection was in the population. So we were able to do not only prevalence but, because of the repeated surveys, we were able to estimate the incidence and to show that it was declining. We reported that work in Paris at the third international meeting, the first time anything favorable about the epidemic had been reported; namely, that the transmission rates were down.[2]

This also gave us the opportunity to estimate the infectivity of the virus because we had a probability sample which gave us estimates of what the risk of contact in infection was in the population, and we had rates of seroconversion. From those two things, we were able to estimate infectivity. And we made the first estimate of infectivity, and that was that it was about 10 percent, about 1:10 partners, or about 1:30 contacts. And that's very important. That was fundamental for understanding the dynamics of the epidemic.[3]

Then there were a number of other things that were done that essentially replicated other studies, but I think the

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[1] Winkelstein bibliography #121.

[2] Winkelstein bibliography #123.

[3] Winkelstein bibliography #124.

most important thing in the biophysiology area was the development, by Mike Ascher and Haynes "Chip" Sheppard of our group, of a new model for the pathogenesis of AIDS, a model based on the interaction of lymphocyte activation and immune response. And their work on that came out of the San Francisco Men's Health Study.

There are 135, 140 papers based on the study. There are papers on psychosocial issues, including a recent paper in The Journal of American Medical Association on depression and progression. And then there are papers--I think the first papers--on nutrition from the San Francisco Men's Health Study showing a protective effect of multivitamins.

And then there are some other studies. There's the study that Dennis Osmund reported in Amsterdam that the favorable effect of AZT is attributable to the treatment of opportunistic infections. I think that came out of the merged study. So, I think there have been a number of firsts and important breakthroughs.

Hughes: Well, I think you got the major ones because, as part of your scramble to revitalize the project, you outlined the accomplishments thus far.[1] I think the only one that maybe could be added is the first accurate modeling of the latency period.

Winkelstein: That was done by Peter Bacchetti in Andrew Moss' group before he was joined to the San Francisco Men's Health Study.

Hughes: So, you can't strictly claim it.

Winkelstein: That was Bacchetti and Moss. We can't claim it. We claim them, though. When we can use them, we claim them. As I've said before, we have managed to get some awfully good people to work on this project.

Hughes: Yes. Well, thank you, Dr. Winkelstein.

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[1] See, for example, "Summary" prepared for NIAID site visit, January 14, 1988.

AIDS Epidemiology

[Interview 3: September 6, 1994] ##

Hughes: Dr. Winkelstein, last time we talked about the institutional relationships in your AIDS studies. Today, I'd like to talk in more detail about the actual epidemiology, particularly of the San Francisco Men's Health Study.

In the grant application in 1983, although the study itself didn't begin until 1984, there were three specific objectives:
"1. The investigation of behavioral risk factors associated with AIDS incidence;
2. The investigation of biomedical risk factors associated with AIDS incidence;
3. Establishment of a repository for preservation of biomedical specimens..."[1]

Is this standard epidemiological procedure?

Winkelstein: Well, I suppose it translates the request for proposal that NIAID issued because those objectives are part of the RFP, rephrased perhaps, except for the repository, which is required by the federal government. A researcher would establish their own repository anyway.

Recognizing Immune Deficiency in AIDS

Winkelstein: But, at the time, as I think we've already discussed, very little was known. I mean, a little bit was known because, right at the beginning, the nature of the disease was recognized, namely, the immune deficiency and the consequences of immune deficiency. They had been known for a long time with respect to other causes for immune deficiency, so immune deficiency disease was not a new thing in 1981. It was just that this was not typical or a known immune deficiency.

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[1] The Natural History of Acquired Immune Deficiency Syndrome (AIDS) in Homosexual Mean, RFP-NIH-NIAID-MIDP-83-11, Principal Investigator Warren Winkelstein, Jr. [n.d.] (Irwin Memorial Blood Bank documents, San Francisco, CBBL 02453, binder 1a #2405-2605.)

Recognizing AIDS as an Infectious Disease

Hughes: How about an association with a virus?

Winkelstein: By February, 1983, 1,000 cases of AIDS had been reported in the U.S. It had now been named, because it didn't have a name up until 1982, and it was increasing rapidly, and it was appearing in limited populations, particularly homosexual men.

In other words, by 1983, it had been shown that AIDS was occurring in people who were sharing needles--recreational drug users. It had been shown in infants of people at risk for AIDS. It was a little early for transmission by blood transfusion, although that was beginning to be known. And there were certain other aspects of it which made it look like an infectious disease.

There were also some case-control studies which had shown very early in the first year, among maybe the first one hundred cases, that they were associated with promiscuous sexual activity among homosexual men. So, it looked, at that time, like it was probably an infectious disease, or it could have been some kind of a common exposure. So people were looking at whether it was related to perhaps some kind of toxic drug exposure or an infectious agent.

Now, people like Don Francis recognized quite early that it looked like other diseases of a retroviral nature which also are associated with immune deficiency, so that's why they were looking for a retrovirus. I'm sure you've already interviewed some virologists, so you know that you have to have some idea of what it is you're looking for because there are various different ways of looking for things.[1]

It's always amazed me that in a disease like aseptic meningitis due to Coxsackie virus, you can only grow the virus in suckling mice. I mean, who would have thought to use that model. You know, it doesn't grow in adult mice; it only grows in suckling mice.

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[1] See the oral history with Donald Francis, M.D. San Francisco AIDS Oral History Project: The Medical Response, 1981-1984. An oral history by Sally Smith Hughes, PhD, recorded in 1993 and 1994, Regional Oral History Office, The Bancroft Library, University of California, Berkeley. Hereafter, UCB AIDS physicians series.

Designing the Study

Hughes: When it came to the actual design of the study, did you rely on your previous experience, or did you consult others?

Winkelstein: Well, we had a group that was composed of Jim Wiley from the [UCB] Survey Research Center, and Andrew Moss, who's an epidemiologist who had actually gotten his Ph.D. with us here, and Bob Anderson, who was a clinical pathologist, and Girish Vyas, and Herb Perkins from the blood banks, now called the blood centers--Irwin Memorial Blood Centers--and Bill Lang, who was a clinician, who had considerable experience with treating AIDS patients working at what was then called Presbyterian Hospital, now the California Pacific Medical Center, and Tom Coates, who's a psychiatrist at UC San Francisco. Those were the principal organizers of the study. There was a lot of interaction among that group. I think the basic design of the study came about because of discussions between Jim Wiley, Andrew Moss, and myself.

Using a Population-based Sample

Winkelstein: The really unique aspect of this study is the population-based sample which no other study has used since.

Hughes: Well, explain why that is important.

Winkelstein: Well, it's important because, in the first place, when you have a population that is self-selected, or selected through some mechanism like a clinic, you don't know what this population represents.

If you get your study population from, let's say, a sexually transmitted disease clinic, well, then everybody who goes to that clinic has at least a suspicion that he or she has a sexually transmitted disease, and people like that are different from other people. They have a sexually transmitted disease because they have more sexual partners or what have you. So, that population will not be representative of any population that you can define.

We felt that it was important, since we knew so little, to have a population that was representative of those people at risk for this particular disease so that whatever our observations in our study population would be could be

extrapolated to the population in general, and you had a rigorous scientific rationale for that extrapolation. Whereas if you have a selected population, you have to make statements like, "We assume that this population is representative, at least with respect to its biological behavior."

If you want to find out things, like we subsequently did, such as what is the frequency of particular behaviors associated with transmission, you can't get that from a selected population; you have to have a representative population. I remember that at one of the early meetings of the group Jim Wiley said, "I don't want to be associated with this project unless we do it in a first-rate proper way." And I felt the same way about it.

The RFP had asked for a population-based study, and we were the only responders to come back with a proposal for a population-based sample.

Hughes: Why is it that others avoid a population-based study?

Winkelstein: It's very difficult to do. For example, we had decided to do our study in the area of San Francisco [the Castro District] which, when we wrote our proposal in 1983, had the most AIDS cases. Well, at the time we wrote the proposal, there had only been 125 cases in San Francisco. So, we chose to do our project on nineteen census tracts. And, in order to get a probability sample, you have to do things such as-- Well, first, let me tell you how the study was designed.

Using San Francisco Census Tracts

Winkelstein: The reason we selected nineteen census tracts was because Andrew Moss, in collaboration with the city health department, had published a paper in early 1983 showing the distribution of AIDS cases in San Francisco. He published that in The Lancet. And we used that to designate the areas. So, each census tract became what we called a stratum for the project.

Then, within each census tract, we chose at random a group of blocks. And the number of blocks that were chosen was inversely proportional to the population of the census tract. It's just a technique that samplers use. So, now,

let us say, we had nineteen census tracts and maybe we had ten blocks in each census tract. So, that means we would have approximately 190 blocks.

Now, in order to get the sample, each of those blocks had to be in a sense enumerated to know how many households were on each block, so that meant we had to send people out. Having enumerated the households, we could take a random sample of houses on each block that would, in our estimation, provide the number of people we wanted. Now, that's a very labor-intensive technical problem. Nobody undertakes that unless, in the first place, they've had survey experience.

But we were working with the Survey Research Center which is among the best survey centers in the world. I mean, they do very rigorous work. So, when they go out and do any kind of an opinion survey or medical survey or whatever, they want to be able to tell whoever has commissioned the survey that they have an accurate estimate of whatever it is they want to measure in that population. So, that's what we did. Eventually we had over 4,000 households.

Then we had to go and visit each household and take a census of who lived in that household to see if there were eligible men. Eligibility was defined as a single man between the ages of 25 and 54. At that time, that was the age-range of AIDS. Later on, we knew that that was unreasonably restrictive, but in 1983 we didn't know that. So, then we had to knock on 4,000-plus households, take the census, and invite the eligible men living in those households to join our study.

Right after we had begun--we began doing this in June of 1984--there was a huge furor because the test for HIV--it wasn't known as HIV then--but the test for the virus was announced, and there was a rumor that the CDC was going to have everyone who tested positive put in quarantine. This caused a huge furor across the country in the gay communities. And we were just at the process of knocking on people's doors and inviting them to join the study, in which, obviously, they would be tested for HIV.

So, in addition to the technical problems that I've just outlined, we were then faced with the adverse publicity and hostility--if you will--so we had to mobilize leaders in the community, from the mayor on down through neighborhood leaders. We had letters, and we published ads in the gay

newspapers, and did all kinds of things. Eventually, we ended up with about a 70 percent--a little under 70 percent --participation rate in our study.

Hughes: How does that compare to other surveys?

Winkelstein: Well, it's pretty good. I also had done sample surveys in Buffalo where I worked for some years. We used to think that if we got under 90 percent we were doing very poorly. But nowadays the populations have been sampled and sampled and sampled, and times have changed, and people have different views, and have a different trust of governments and organizations, and so forth. So it's much more difficult to get very high participation rates on field surveys than it was, say, twenty-five years ago. So, I think we did pretty well.

We have ways of testing the representativeness of our sample by comparing it to population characteristics published by the census, and our sample looks very similar to the characteristics of the census.

Hughes: You made that comparison?

Winkelstein: Well, yes.

[tape interruption]

Collaborating Institutions

The UCB Survey Research Center

Hughes: We've mentioned some of the institutions that were involved in the study, but I thought it might be good to go down the list. You've mentioned Children's Hospital where the actual physical exams and specimens were taken. Is that not true?

Winkelstein: Right.

Hughes: You just mentioned the Survey Research Center. Is that a center that's available to any university researcher?

Winkelstein: Well, you obviously have to obtain funding for your research. It is an organized research unit of the University of California so it receives some core funding

from the university, but the bulk of its funds come in relation to specific projects. So, they're able to maintain a small core staff on state money, but it's very small. The rest has to be obtained by individual projects.

Hughes: I see.

Winkelstein: But it is available to faculty to help them conduct appropriate field research. For example, Dr. Syme in our school and others have utilized the Survey Research Center to conduct their field research.

Hughes: Had you used it before?

Winkelstein: No.

Hughes: It didn't involve any particular coordination problems?

Winkelstein: Everything that one does requires some negotiation and coordination. But since Jim Wiley was the associate director, [coordination was easier]. You could call him the technical director, because he's an adjunct faculty member and not a regular faculty member. There's always a regular faculty member who's the director of an organized research unit. But in a research unit that does as much field research as this Survey Research Center does, then you have to have a very high quality technical staff, and the center has that.

Jim Wiley is a very well-known survey research person. His Ph.D. is in sociology and he's internationally recognized. He was a co-principal investigator, although NIH doesn't recognize co-principal investigators. But, for practical purposes, he and I shared direction of the project, and we still do.

Hughes: So the survey aspect you could pretty much turn over to him and his people?

Winkelstein: Well, we all work together, of course. But yes. They helped develop the questionnaire. At the beginning, when we were in the Multicenter AIDS Cohort Study, the Survey Research Center played a major role in developing the questionnaires for the entire five-center project. And they also played a major role in training personnel. So, yes, the Survey Research Center was and is critical to the conduct of this project.

The California State Department of Health and Human Services

Hughes: Well, another institution was the Viral and Rickettsial Disease Laboratory at the state department of health.

Winkelstein: Right. They actually didn't come in until later. I don't think the state health department came in until about two years into the project [ca. 1986].

Jay Levy at the UCSF Cancer Research Institute

Winkelstein: Jay Levy was not with us at the time we submitted the proposal. And we later worked with him because he was the first one to have a test. He had a test for the AIDS virus before a test was available from any other source. The work that we published early on was based on immunofluorescence, which is a different technique than the ELISA test, which is what's more commonly used now.

Because Levy's lab was more oriented toward basic research, it became more and more difficult for him to satisfy the large-scale needs of our project, and so his role became gradually changed from the servicing of our project to specialized studies, which he continues to do in relation to our study. And the routine virology and serology moved over to the state laboratory. Then Dr. Haynes "Chip" Sheppard, particularly, and Michael Ascher played an increasing role in our project. But they were not in it at the beginning.

Hughes: How was Levy brought into the project?

Winkelstein: I don't remember the exact way, but probably by my going to see him and talk with him. He was a very enthusiastic participant at quite an early stage. I would have to look up the records to see just exactly when we began to involve him.

Hughes: I'd be interested to know whether it was before or after he published [August 1984] the isolation of his virus, ARV, AIDS-related virus.

Winkelstein: AIDS-related retrovirus. It was probably after, but I'm not sure. It was he and Bob Anderson who published the first

paper from our study. The date of that is 1985, so it doesn't really tell us very much. But you can tell because this study was done mid way in the first cycle of examinations, which means that Jay Levy was working with us in 1984. By the time we began to do field work, he was involved with us. But I don't think he was involved in the preparation of the response [to the RFP].

Hughes: I understand the actual repository for your specimens was at San Francisco General?

Winkelstein: Not originally. Originally, we stored the serum specimens at the Children's Hospital and half of everything that we collected was sent to the National Institutes of Health. That was part of the contract.

Irwin Memorial Blood Bank

Winkelstein: But the lymphocyte subsets were all done at the Irwin Memorial Blood Banks now Irwin Memorial Blood Centers. And that meant, because the technology was less advanced than it is today, and the clinics where we drew blood were in the evening, that we had to have night shifts at the blood bank. So the blood that was collected in the clinics, which were held at night, was then processed in a laboratory at the Children's Hospital, and transferred to Irwin Memorial for lymphocyte separation and storage.

So the storage of the cells--all the cell materials--was, and still is, at the Irwin Memorial Blood Centers, whereas the serum and semen and throat washings were all stored at the Children's Hospital. But it didn't take too many years--again, I'd have to look at the records--before the Children's Hospital could no longer accommodate things.

The UCSF AIDS Specimen Bank

Winkelstein: In the meantime, Dr. John Greenspan at the [UCSF] dental school had developed a repository for the university task

force program on AIDS[1]. So we then negotiated with him to transfer our entire serum repository to the university, which we did, and where it remains at present, because he had more facilities, and more flexibility. They had a computer system, and so forth, so that was all done. That was part of the evolution of the project.

Hughes: The specimens were stored on the Parnassus campus?

Winkelstein: Well, I don't know where they are now. They've been moved, I think, to wherever John's repository is. They were stored at Parnassus for a long time, but then they ran into problems, as well, with respect to space. You see, we now have hundreds of thousands of specimens because we had, say, roughly 1,000 men to start with. We were seeing them twice a year. We were drawing a large amount of specimens.

So, if we had 2,000 visits a year, and probably we drew 30 cc's, cubic centimeters of blood each time, so that would be 60,000. It's an astronomical amount of material that was collected. And then, especially at the beginning, there were special groups, people who seroconverted, that is, who became infected while in our study. They came in four times a year instead of twice a year. So, there were specimens for them at each occasion. So, the volume of material was very large.

Hughes: Now, were the conditions for the use of such specimens the same as for any other specimens?

Winkelstein: Part of the incompatibility between the Multicenter AIDS Cohort Study and our study had to do with the philosophy of specimens and particularly data. The MACS always maintained a much more possessive approach to specimens and data, and we always adopted a more flexible and open access policy. So, we very early set up a system by which people could get access to our data. And so there are people who have used data from the San Francisco Men's Health Study all over the world.

To my knowledge, we have only refused access to our data once. And that was when we received a request from ACT UP in New York City, and they wanted us to do some particular analyses of the data, which would have taken us about a person-month to do, and we said we would do it only if they

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[1] The University of California Task Force on AIDS, now Universitywide AIDS Research Program, distributes state funds for AIDS research.

paid for it and, of course, they weren't interested in paying for it.

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Winkelstein: The specimens which are of most interest to people are, for example, specimens on people who seroconverted and, since the number of seroconversions is relatively small, we've been pretty stingy about letting those specimens out.

We have forms which bona fide research people who are associated with established institutions can fill out and send in. And we have a little subcommittee that reviews and then approves them. And that includes both specimens and data.

Now, there have been some people who began as sort of outside investigators and then became co-investigators, such as, Mary Claire King, who's a genetic epidemiologist, who was not a part of the original team, but who later became associated with us to do genetic studies. And there have been other examples of people who began by making requests for materials or specimens and then were incorporated as members of the team.

Hughes: My understanding is that a committee of UCSF's AIDS specimen bank establishes who actually will get the material, and its policy is less liberal than the policy that you are describing.

Winkelstein: Well, I don't know about whether it is with respect to specimens. Data are not quite as precious as the specimens are because a specimen is lost once it's examined, and the data remain there forever. So you tend to be more restrictive on the specimens, and we are.

Now, there's another aspect to the specimens which we've been utilizing more recently, and that is that specimens that we send to the federal government are put into a governmental bank and they're available to anybody anywhere in the world. Again, they have to submit protocols and go through a committee. So, occasionally someone will obtain specimens from the federal repository and then they come back to us to get information on the characteristics of the donors.

Biohazard Precautions

Hughes: This, of course, is a lethal virus. Were you forced to set up P2 facilities in all these areas, or did they preexist the epidemic?

Winkelstein: Well, I don't think we were authorized to be a P2 laboratory, but we did take very extensive precautions.

Hughes: So P2 safeguards aren't mandatory?

Winkelstein: No. I don't recall it. Bob Anderson, who was with us for the first three or four years of the project, was a clinical pathologist and very knowledgeable. He was sort of in charge of the clinical pathology, so that the original drawing of the blood and so forth was under his supervision, as was the small laboratory which processed them. By the time they got to Irwin Memorial, I assume they had a P2 laboratory and, of course, with Levy's lab, or the state lab, they are controlled by all the necessary requirements.

The California Public Health Foundation

Hughes: Well, I think the only institution that we've left out is the California Public Health Foundation.

Winkelstein: They're nothing but a conduit for contract monies to the state laboratory.

Hughes: Dr. Michael Ascher is identified with it.

Winkelstein: Yes. That's right. Well, both "Chip" Sheppard and Ascher are. Well, at any rate, that's the formal way we channel money to the Viral and Rickettsial Disease Laboratory.

The UCB School of Public Health

Hughes: Do we now have all the components of this complicated system?

Winkelstein: Well, except the School of Public Health. Well, the School of Public Health is where I sit and the graduate research

assistants work, as well as Nick Jewel, the professor of biostatistics, and Mary Claire King, genetic epidemiologist, who are associated with the project. But all of these things, from a working point of view, we work together.

Now all the outside organizations you spoke about have to have subcontracts with Berkeley, that is, UCSF, Irwin Memorial Blood Center, Children's Hospital, and the state health department. But, of course, we don't have to have a subcontract. We can move monies.

Hughes: Was this a more complicated project than you were used to in epidemiology?

Winkelstein: Well, yes, to some extent. But I had had experience in multicenter studies, and I had worked with vaccine field trials.

One of the first big things I was involved in, in my career, was the polio vaccine field trial, and that had very complicated logistics because I was in charge of one of the largest segments of the vaccine field trial, which was in Erie County, New York. We had 30,000 children, 15,000 receiving placebo and 15,000 receiving vaccine, and a complex schedule, involving fifty schools, and thousands of volunteers, and hundreds of health department personnel, and hundreds and hundreds of clinics. So, my background in working in the health department in various activities had given me some experience with complicated operations.

Now, every operation is different. And this one with the four or five institutions had a group of separate problems. But our problems were relatively minor with respect to the interaction of the institutions. I think these institutions had pretty competent administrative personnel who made it fairly easy. Our problems were with the federal government, not with each other.

Resolving Tensions and Turf Battles

Hughes: I talked over the weekend with Andrew Moss[1] about the origins of the project and, as you know, there were some tensions which explain why the group at UCSF did not respond to the

[1] Telephone conversation with Andrew Moss, September 3, 1994.

RFP. Was there resentment that your group, which hadn't been involved in the epidemiology of AIDS, was now in it, and with an enormous project?

Winkelstein: There was tension and concern over turf at the beginning between and among all the partners. As time went on, I think a number of things happened. One is that there was enough for everybody to do, and also people began to work in different areas and become sort of expert in those areas. We had very, very good people here in San Francisco, whether you're looking at the clinical activities, or the laboratory activities, or the field epidemiology. And I think it became fairly apparent to most people that we knew what we were doing, and that we were doing things that they didn't know how to do, and that we were colleagues and were not trying to impose on somebody else's area of expertise or interest.

I never felt anything but support from all of the people that had originally opposed responding to the RFP. When we were having difficulties that I described last time, they were extremely supportive to the extent of writing letters to Dr. Fauci and speaking in support of the project and making themselves available.

Andrew himself was a bit aloof at the beginning, but he was very enthusiastic and a major supporter and, as you know, eventually brought his group into our group, and we melded them together and now we work as one group.[1] So, I don't think there was any residue of resentment from that. I think once it was over, it was over. And I have felt, in the past few years, that everybody has been more collegial and more concerned about the projects than they are about turf.

Hughes: Well, Andrew was very complimentary of your conciliatory role, and he talked about how you fostered cooperation and smoothed over rough waters.

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[1] In the September 3, 1994 telephone call, Moss said that he had done for Winkelstein's group what an epidemiologist should never do, namely, give an opportunity for a competing epidemiological study. One should instead use, he maintained, a "scorched earth policy". But he conceded that it had worked out well for him in the end when he joined the San Francisco Men's Health Study.

The Questionnaire

Hughes: You said last time that the questionnaire was not totally original, that you pulled some of it from other sources. By that, did you mean from some of the existing AIDS questionnaires?

Winkelstein: Well, I don't remember exactly how the questionnaire came about. I remember certain intense battles over parts of it. Almost all field questionnaires draw on whatever has been done in the past, and clearly we wanted to get the information that CDC was collecting, and we wanted to get additional information.

As you recall, we were part of the Multicenter AIDS Cohort Study, and the questionnaire was the product of discussions among the various investigators, and there were considerable differences of opinion.

The actual construction of the questionnaire fell more to people like Selma Monski at the Survey Research Center, and some other personnel, both at this Survey Research Center and at some of the other centers.

Issues that would be discussed by the principal investigators would be things like, for example, the extent of the sexual practices questionnaire and the extent of the drug questionnaire, and what would be included amongst the diseases--past diseases--and what would be included under other factors.

So, for example, I wanted to get information on smoking because, in the first place, I had been interested in smoking-related diseases for a long time, but I also argued that, since we didn't know what we were dealing with, and cancer was a major component--Kaposi's sarcoma--that it didn't make any sense not to ask cigarette questions. Because we had had some battles over other things, I remember somebody saying, "Well, give him his smoking information." So, I got smoking in.

But we didn't want nearly as much drug information because we were working with a probability sample. We had no particular reason to believe that every recreational drug was likely to be a candidate for being a risk factor. So our group argued for limited information on drugs, maybe drug information on nitrite use. Others argued for very extensive drug information. We were concerned about what

this would mean in terms of participation, in terms of accuracy, and so forth. Eventually, our group's views did not prevail and the drug questionnaire was a lot longer than I would have wanted.

I wanted a short questionnaire because I don't believe in long questionnaires. I believe that you should ask questions about issues about which you have a research question; others believe you should collect as much information as possible on the off-chance that it may be useful. Those are two different philosophies. And I also argue that long questionnaires frequently lead to inaccurate, lazy responses.

So, there were a lot of arguments around what to put in the questionnaire. I wanted the sexual practices to be limited to those which were thought to be common among homosexual men, or known to be. We had gay men in our research group and, of course, we could call on them for consultation, but we ended up with every kind of sexual practice imaginable. I just felt that we would never look at it, and it had no relevance, and you had to have a rationale. I lost that argument.

So, the questionnaire ended up as a committee product, and a committee product was not the best way to go, but there perhaps wiser heads prevailed, so that's the way we went.

Hughes: Didn't the population, which was intended for study in the five different areas, also color the sort of questions that each given group would want to ask? For example, your study was in an extremely high AIDS incidence and heavily homosexual area, which I'm assuming was not true of some of the other centers. Wouldn't that slant your questions a certain way?

Winkelstein: Possibly. Yes. But don't forget it was a common questionnaire.

Now, there were a couple of things that were also of some interest. We wanted to put in nutritional questions, and I don't remember why that was not done, but it wasn't. So, we did a nutritional questionnaire that was self-administered that was not funded by the NIAID. We added it as a supplementary instrument. We also administered a supplementary sociopsychiatric questionnaire, which some of the other groups did not.

We tried to obtain funding for our nutritional study from the National Cancer Institute, and we were unable to get funded. The reason we went to the National Cancer Institute was because we used the National Cancer Institute's standard nutritional survey that they do for cancer-related studies. And that's always been a sore point for us because we gathered some of the earliest information and we're just now beginning to publish. Barbara Abrams, who's a professor of nutrition and epidemiology here in the School of Public Health, has had a graduate student working on this, so we've recently begun publishing some information from our early studies, which others did not get.

Hughes: What was the rationale for postulating that nutritional factors might be involved?

Winkelstein: Well, because anybody who's studying chronic disease ought to be interested in nutritional issues. I mean, there's plenty of evidence that nutrition is related in some way to immunity and has an effect, and certainly, if you're dealing with a cancer, you're interested in some nutritional factors as well.

The hypotheses might not be quite as specific as some of the others, but certainly we had some nutritional hypotheses having to do with vitamin C and antioxidants, and so forth. So, that's what we wanted to do but we failed to obtain funding for that.

[tape interruption]

Poliomyelitis: The Wrong Model

Hughes: I was wondering about the terminology "chronic" as opposed to "acute" disease, because I'm imagining that in 1983 and 1984, as the study was getting off the ground, it was conceived of as an acute disease, was it not?

Winkelstein: When we started out, I really thought that in four years, which was the term of the contract, we would have worked this thing out. I thought that the disease was going to follow the model of poliomyelitis, that is, that there would be a lot of infections, because I really thought it was an infectious disease, and only a few cases of disease. You see, in polio for every 100 infections, you only have about

three or four cases of poliomyelitis. And I thought that would be the model here.

Well, of course, that's totally wrong. It's turned out to be exactly the opposite, that is, that a high proportion of infections result in disease. We don't know yet what that's going to be because we had no idea when we started out that the incubation period would be ten years long.

Now, every month that went by, and the more we studied, the more we realized what we were dealing with what would be a long-term progressive illness leading up in most cases to death. So, I can't tell you when that became more and more apparent, but it did, because the constant proportion of infections that came down with AIDS and died kept increasing in our study. So that now more than 50 percent of those who were infected when they entered in 1984 are dead.

But certainly by the end of the first three years of field study and four years of the contract, it was clear that we were dealing with a long-term disease.

Hughes: And did that have an effect on the study design?

Winkelstein: No. I think it was a very solid design. The first thing we didn't know was what proportion of the gay population in the Castro was infected. That had been estimated in the Centers for Disease Control study--that is, the [San Francisco] City Clinic--at 68 percent. That was early when they first had a test [1985]. When we published our first paper in the New England Journal of Medicine we got 36 percent. Well, in our study, when the sample was completed, it was 48 percent. All these things are important to know, and I think that having taken a representative sample gave us a lot more information that we would not otherwise have had.

Specimen and Data Collection

Hughes: Well, let's talk about the actual collection of information and specimens, which occurred twice a year in most cases. Although you said that some of the seroconverters came four times a year?

Winkelstein: Yes.

Hughes: It was the team at Children's that was conducting the interviews and the physicals?

Winkelstein: No. The interviews were under the supervision of the Survey Research Center. So, they recruited and supervised the interviewers. Bill Lang was in charge of the physical examinations and the collection of the specimens in the clinic. Bob Anderson was in charge of the hospital laboratory, that is, the processing of the specimens, and then their disbursement to their various repositories. The actual examinations were done by physicians' assistants, under Bill Lang's supervision.

Hughes: Was there anything that cropped up in the course of the study that had to be changed in reference to either the physical exams or the tests?

Winkelstein: Nothing major.

Hughes: I noticed in the 1983 grant application that you list the lab studies that you intend to do, and then you say that you plan to do additional lab studies not at NIAID expense. They involved tests for α-1-thymosin, β2-microglobulin, and the total hemolytic complement. Did that indeed happen?

Winkelstein: Well, some of those happened. Some of the work that Dr. Vyas did was funded by other funding sources. Then there were studies on cytomegalovirus that were projected to be done by another investigator at UCSF. Again, I'm not very good at recalling names.

Hughes: Larry Drew?

Winkelstein: Yes, Larry Drew also did some work. He took some bloods and worked on them. So, there was some other work to be done.

Hughes: These people had grants?

Winkelstein: They had their own funding. We also have the [un?]enviable record of having the smallest grant ever awarded by the university task force on AIDS--I think it was $400--to do sedimentation rates.

Hughes: A singular honor. Were there problems that arose that hadn't been anticipated in collecting bloods?

Winkelstein: It was difficult because at first we collected samples of semen and feces, and handling those samples really is a tough assignment.

Hughes: I can imagine.

AIDS Epidemiology in San Francisco

Early Studies

Hughes: We've alluded to the fact that there were three AIDS cohort studies going on simultaneously in the same city: one is the City Clinic Cohort; there's Andrew Moss's, which I guess is technically the San Francisco General Hospital cohort--

Winkelstein: That's correct.

Hughes: --and then, of course, there's the San Francisco Men's Health Study cohort. Were these all going along independently, or was there interaction?

Winkelstein: Originally, they were all going along in their separate ways. Somewhere in our proposal, we recognized--at least with the City Clinic project--and indicated that people who are in the City Clinic project will not be included in our project. We estimated how many that would be. It turned out to be a small number. So, that overlap never came up.

The Northern California AIDS Epidemiology Consortium

Winkelstein: When we began, there was so much going on that there was really not very much chance of getting together. However, at some point we formed a Northern California AIDS Epidemiology Consortium, and that was open to anybody who wanted to join it. So we invited the people at the University of California at Davis who were doing some work on AIDS, and of course Dr. Nancy S. Padian was beginning her studies of heterosexuals, and the three studies that you've just mentioned.

So, we established this consortium, which was designed to meet--I can't remember--monthly, when we began, and we met monthly for quite a while. We discussed various issues and talked about different things and presented and reported from conferences we'd attended and presented ideas for studies. That was quite active for maybe a year or more.

Like so many of those things, people get so busy they just don't attend anymore, and so that consortium gradually disappeared.

Andrew Moss Joins the Study

Winkelstein: In the meantime, informal relations intensified, particularly between Andrew Moss' group and ours. Andrew eventually ran into some funding problems and came to see me. And we talked about joining forces.

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Winkelstein: As I mentioned before, NIAID eventually approved the merger and provided modest funding, about $120,000/year. It must have been $20,000 he needed the first year. And so that led sort of inexorably to the merging of our study and Andrew's study.

The Three San Francisco Cohorts

Winkelstein: In the meantime, we were very close to San Francisco Department of Health Director George Rutherford and then, after George--who was it? Sandra Hernandez. And now we work very closely. The City Clinic Cohort continued on its own. Then we started having annual meetings for study participants. The first year we had a meeting for study participants in Andrew's study and ours, and the next year, and the year following, we had it with all three cohorts. So, gradually we began to be more interactive, if you will.

AIDS Vaccine Studies

Winkelstein: And when we came to the vaccine stuff, we were very much interactive. Susan Bookbinder and us, and Paul O'Malley--Paul O'Malley came here from the Centers for Disease Control to help run the City Clinic program and he's been here since, I guess, 1983. He's been very helpful to us in many situations. He's a member of the gay community and has many connections and insights and we turn to him for advice, and

he's been most supportive. So, our relations have never been strained, but have, I think, grown better.

When the RFA was issued for vaccine studies last February [1994], the decision as to whom would respond was discussed extensively, and we all agreed that it should be the city health department and that we would support their application. So, in their application, there's a letter from me indicating that all of the information we've gathered in the Men's Health Study was available to them, as well as access to our lists of people for recruitment purposes for vaccine field trials, and so forth. So, I would say that, at the present time, we work very closely together.

Publications Stemming from The San Francisco Men's Health Study

Hughes: Well, the first publication from the San Francisco Men's Health Study came out in 1985, and I think we probably talked enough about that because that's what precipitated Crisis Number 2. Are you happy to move on?

Winkelstein: I'm very happy to move on.

The Two 1987 Papers in JAMA

Hughes: There were two papers that came out in--

Winkelstein: Right. There were two papers that came out in The Journal of American Medical Association.

Hughes: --1987.[1]

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[1] W. Winkelstein, Jr. et al. Sexual practices and risk of infection by the human immunodeficiency virus: The San Francisco Men's Health Study. JAMA 1987, 257:321-326; W. Lang et al. Clinical, immunologic, and serologic findings in men at risk for AIDS: The San Francisco Men's Health Study. JAMA 1987, 257:326-330.

Winkelstein: And those papers were reprinted in, oh, at least four of the AMA's Journal of the American Medical Association's international issues.

Hughes: How was that decision made?

Winkelstein: I don't know. It was made by the editors of The Journal. The editors of journals, as you know, have the copyrights, so they don't even ask you; they send you a copy of your paper in Japanese, or whatever, and that's always fun. When we got separated from the MACS, one of our colleagues at a research meeting said, "That's Warren when he got the letter from Dr. Fauci."

Hughes: Dr. Winkelstein is pointing to a grinning face on the cover of JAMA.

Winkelstein: So, those two papers, which were given lead positions in that particular issue of JAMA, were among the most important publications from our study. They didn't really forge any new ground, but they were the first based on random samples.

For example, in the clinical paper, there's a graph showing the CD4 T-lymphocyte distributions. What it shows is that, for seronegative--that is uninfected--homosexual men and, of course, uninfected heterosexual men, those curves are exactly the same. In other words, they are superimposed one on another; you can't tell the difference. A lot of people thought that gay men had different T-cell distributions because they had many more--were thought to have many more--sexually transmitted diseases, and particularly would have different T-cell distributions, but they didn't.

And the fact that these two papers reported on probability samples--population-based--gave a lot of credibility to the observations. So, the observations there regarding transmission--that is acquisition of infection--by receptive anal intercourse among homosexual men, which had been sort of accepted before our paper, solidified.

There is an index of citations. You'll find literally thousands of citations of those two papers, so they provided a great deal of solid information on clinical laboratory and epidemiological factors, which had been available but really hadn't been, as it were, solidified. So, I think those papers were quite important from that point of view.

Hughes: Where did the earlier work on receptive anal intercourse come from?

Winkelstein: Oh, it was from several places. I can't remember exactly the reference in the paper.

The Paper on Declining Rates of HIV Transmission

Winkelstein: Then there were two subsequent papers that came out that were very important. The first one was the paper on declining rates of transmission in San Francisco that was given at the third international conference in Paris.[1] That was--as I think Time magazine put it--the first good news in the epidemic. It wasn't terribly good news because the rates were still pretty high, but it was favorable. And that could not be done other than through a probability sample. So, I think that was important.

Hughes: Do you credit your study as having an influence on those declines?

Winkelstein: You'd like to say that the information that was in those original articles had been part of the basis for a lot of health educational materials, but who can say? The STD rates among homosexual men had started to go down in 1983 in San Francisco. There was a lot of information available in the community about risk factors.

Hughes: Health department literature stressed the dangers of multiple partners. Your study was not the only one saying that.

Winkelstein: No. Just as I said, there was nothing new in those first studies of ours, but it was replication and on a very solid basis.

The 1987 Paper on Infectivity

Winkelstein: Now, the second subsequent article which was important was not as important from a public prevention point of view but

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[1] Winkelstein bibliography #123.

was from epidemiological, modeling, and understanding of the disease. That was the paper on infectivity, which came out I guess in 1987.[1]

And that, of course, was only possible because of the design of the study because, in order to estimate the infectivity, you had to have an estimate of exposures, and the only way you could get an estimate of exposures in the community was to have a sample, otherwise you wouldn't know what the risk of exposure was in the community. So, with the information on seroconversions in the SFMS and the estimate of exposures, it was possible to estimate infectivity. And, as far as I know, that estimate has remained pretty constant since.

The Gay Community

The Promiscuity Issue

Hughes: The social implications seem particularly striking in this disease. I've read that certain members of the gay community felt scapegoated. There were objections to the wording of certain reports, such as use of the word "promiscuity".

Winkelstein: Is it used in our publications?

Hughes: I'd have to look. Certainly the idea of multiple partners was highlighted--

Winkelstein: Certainly.

Hughes: --as a real risk factor. Were there problems with the gay community feeling that it was being put in a bad light?

Winkelstein: I don't think so.

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[1] Winkelstein bibliography #124.

The Participant Advisory Committee

Winkelstein: Maybe four or five years ago at one of our annual meetings, one of the participants got up and lambasted the investigators for a variety of sins, the most important being that we had not adequately informed the participants in the study of our findings. And he was very aggressive and very articulate. I said that he was probably right, and it seemed to me that we had not involved the participants adequately. And so I suggested that we form a participant advisory committee, which we did. And this person, John Caldwell, became the chairman.

Now, one of the problems was, of course, how are you going to get a representative group? You couldn't very well have an election because the identity of the participants was basically confidential. So, it was a self-appointed participant advisory group. We sent out a letter suggesting anybody interested get in touch with John. We invited representatives of the participant advisory committee to come to our research meetings, which were held every other week. And they began doing that.

They also had a monthly meeting and passed various resolutions, and we, I think, generally acceded to those. For example, they asked us to let them see any communications, such as letters, between us and the study participants prior to sending them out. And we did that. Occasionally we slipped up on that, and then they would slap our hands.

Three years ago I was asked to give a lecture at the University of Michigan, at the summer school, the Schuman Memorial Lecture. My lecture was a discussion of the ethical issues surrounding notification of participants and of the public of findings. I gave credit to John, and I asked if I could use his name, and he allowed me to. I gave my paper, and a lot of people said it should be published, but I've never gotten around to revising it and publishing it.

I have a letter from John, which I'll show you, in which he tells how his mistrust of the investigators has changed by his participating in the research meetings. And it's from a very cynical position to an understanding of the complexities and appreciation of the concerns of the investigators.

I do think that this participant advisory committee is very important. It's not easy to organize, and it's not easy to work, but we have had excellent suggestions from them, and things to investigate as well. So, when we had our workshop last spring, we had John on one of the panels.

Organizing Conferences for the Media

Winkelstein: Then Nancy Padian and the guy from The San Francisco Chronicle--

Hughes: [Charles] Petit?

Winkelstein: Yes. I think it's Petit. --organized a meeting three or four years ago of media people and AIDS researchers. And we had a little three-quarters-of-a-day workshop. It was quite well attended. I'd say twenty-five people came to discuss media relations.

Then this last year, we got a grant from the university task force and in conjunction with the school of journalism, the media people in San Francisco, and the AIDS research group, we organized a day-long workshop on media-science relations. We held it at the state health [California State Department of Health Services in Berkeley] department and we had about 100-150 people come.

So, we have moved from a rather isolationist--if you will--position of scientists doing our thing and publishing our papers, to at least a concern about relations with the community and with the participants. We haven't accomplished everything that we should.

Handling Community Inquiries

Winkelstein: We haven't had community relations problems. Maybe it is because when confronted, we have not been overly defensive. Obviously, everybody is defensive when you get attacked. But we've--I've--tried to be as reasonable and understanding as I can and I think, well, it's a way of trying to do it.

You never know [the full implication of] what you do. A small thing may have a big implication. So, if I get a

telephone call from a study participant, I remind myself not to be rushed, and even if I am in a position of stress, I listen and I try never to cut people off and I try to answer their questions. And I don't try to pass the buck. If I don't know the answer, I either say, "I'll get it for you," or, "This person will be able to give you that information. Give me five minutes to call him up ahead of time and tell him you're going to call," or something like that.

You never know. I mean, the telephone can ring and you can talk to a person. You don't know who that person is, or what that person's motive is in calling, so I just try to do the best I can. That's the only way I can see to do it. To the extent that that has helped our relations, I guess it has. It probably hasn't been terribly important.

Targeted Prevention

Hughes: Well, in February of 1986, you, Dr. Levy, and others wrote a letter to the editor of JAMA, in which you said that concern about heterosexual transmission had risen in recent months.[1] Do you remember why there was particular concern at that time about heterosexuals?

Winkelstein: Oh, I supposed somebody had written a book, or somebody had made a pronouncement. The [U.S.] Public Health Service was making a big fuss. This has been a big issue from very early in the epidemic.

In fact, Dr. Don Des Jarlais from New York, who is an expert in the field of drug-related AIDS, and Nancy Padian and I have just had a manuscript accepted for publication as a "Sounding Board" article in The New England Journal of Medicine on targeted control efforts, targeted prevention.[2]

The thesis of our argument is that much of the prevention, which has been based on this concept of

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[1] W. Winkelstein, Jr., J.A. Wiley, N.S. Padian, and J.A. Levy. Potential for transmission of AIDS-associated retrovirus from bisexual men in San Francisco to their sexual contacts. JAMA 1986, 255:901.

[2] Des Jarlais, D.C., N.S. Padian, and W. Winkelstein, Jr. Targeted HIV prevention program (Sounding Board). New England Journal of Medicine 1994, 331(21):1451-1453.

universality of risk, is misplaced; that the funding of things like the Alternate Test Site Program, which has never been evaluated, is not as efficient or effective as would be targeted research, or targeted prevention, in those groups--communities--that are really at risk. And the general heterosexual population in the United States is not at risk --I mean, there's basically no transmission going on. There is among a small targeted--targetable--group of women.

We wrote a little piece for JAMA, which I think was published as a letter, in which what we did was to take data from our study and estimate the potential for transmission through bisexual men to women in San Francisco.

[Scanning publication] Since we didn't have any information on the actual distribution--the actual infectivity--we made some estimates. In fact, we used this little analysis to support our request for money to do a serological survey in San Francisco in women in the Marina District, where it's thought that there are a lot of single women. We wanted to investigate that potential transmission at that time, and we couldn't get the money.

Hughes: Oh, really? But you did do a study--

Winkelstein: Oh, much later, 1992 or something. It took us years to get the Men's Health Study funded. You know, we're not talking big money. But the reasons why-- Well, part of the reasons are bureaucratic. The contracts are restricted to what you're contracted to do, and to expand the scope of a contract is a bureaucratic nightmare.

So, basically, it was bureaucratic restrictions which prevented us from doing something that everybody whom we talked to at NIH, or anywhere else, thought should be done. That's a whole other story.

Letters to the Editor

Pros and Cons

Hughes: You've written a lot of letters to the editor--

Winkelstein: Yes. We've been criticized for that--

Hughes: Why?

Winkelstein: Letters to the editor are not generally peer reviewed; they're judged by the editors, generally speaking--not always--sometimes they have peer review. I think this one was peer reviewed. But they're considered to be less rigorous--if you will--than articles. On the other hand, letters can get published in a matter of a month or two, and articles frequently take a year or more, not only to write but to get processed. So, the letter is a vehicle for quick transmission of information.

So, for example, this was a big issue at that moment in time--

Hughes: Heterosexual transmission?

Winkelstein: The heterosexual business. We could put this analysis together in a matter of a couple of days, and write this letter, and get it out in maybe a couple of weeks, and get it published in a month or two, whereas, if we had gone the route of a paper, it would have been at least a year.

Hughes: Right.

Winkelstein: The same thing when CDC announced the change in the diagnostic criteria for AIDS[1]. We did an analysis and we put it out in the form of a letter because we thought it was important to get this information before the scientific community quickly, and that's how we did it.

JAMA, which is, of course, a widely read journal, has sometimes turned down our letters, but very frequently has agreed with us that it's important to get the information out. So, that's why you find quite a few letters.

Hughes: Well, others of those I've interviewed have also used the letter as a means of communication. Andrew Moss, for example, in 1983 used a letter in The Lancet to communicate his census tract information for the same reason: he wanted to get the information out.[2] The letter to the editor long

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[1] H.W. Sheppard, Warren Winkelstein, Jr., D. Osmond, A.R. Moss. Effect of new AIDS case definition on a number of cases among homosexual and bisexual men in San Francisco (letter) JAMA 1991; 266; 2221.

[2] A.R. Moss et al. AIDS in the "gay" areas of San Francisco (letter). Lancet, April 1983:923-924.

predates the AIDS epidemic, but do you think, because of the urgency of the AIDS situation, that perhaps the epidemic did have a role in maybe not legitimizing, because you're saying that you were criticized, but in pointing to the letter as a means of quick dissemination of information?

Winkelstein: I don't know. It's hard for me to say.

Hughes: You haven't been aware of a greater tendency to use letters to the editor to communicate AIDS information?

Winkelstein: Well, traditionally letters have been used to create dialogue and, in the British literature, they've sometimes become pretty vitriolic, and there's sort of a tradition for that. It's like in the Senate [Parliament]: "The Honorable Gentleman from Bristol doesn't know his--"

The Effect of the New AIDS Definition

Hughes: Well, one of your letters to the editor is entitled "The Effect of the New AIDS Case Definition on Numbers of Cases Among Homosexual and Bisexual Men in San Francisco."[1] You wrote that, with this new case definition of January 1993--

Winkelstein: Well, it was proposed two years before that.

Hughes: Yes. Because the letter is dated 1991. It look that long--

Winkelstein: Well, part of the delay was because of the reaction. Our letter was--I think--the first reaction.

Now, there were several things involved here. One was that we had been telling people for a long time that HIV infection was not synonymous with AIDS. The proposal was to make 200 T cells, CD4 lymphocytes, a criterion for diagnosis of AIDS. What we estimated in our letter was the number of people who are asymptomatic with 200 cells, of which there are a substantial number. And there are also a substantial number of people who get AIDS before they have 200 cells.

So, we felt that this would make people a case of AIDS who weren't a case of AIDS before. And we had all been

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[1] H.W. Sheppard, W. Winkelstein, Jr., D. Osmond, and A.R. Moss. JAMA 1991, 266(16):2221.

preaching for a long time this issue because, by this time--1990s--if you have AIDS, that's terrible, whereas, if you were just HIV-infected, well, that's not very good, but it isn't as bad as having AIDS.

Hughes: Right.

Winkelstein: Now we were going to automatically give a lot of people AIDS who hadn't had it the day before. And then there are all kinds of problems having to do with monitoring the epidemic, and so forth. Now, there are those who argue that HIV should be reportable. Don Francis is one. And he believes, I think--but you'd have to ask him--that mandatory reporting would be favorable in terms of prevention.

So, that's what that letter is about. And we just felt that this was a bad idea at that particular point in time, but we wanted to provide information on which people could make judgements. As you know, CDC had proposed to put that revised AIDS definition into effect months after they proposed it, and they didn't actually implement it for two or three years.

Hughes: Because of objections such as yours?

Winkelstein: From us and others as well. The Europeans have never accepted it, so in other countries it is not a criterion.

Hughes: Well, it seems to me another problem with changing the disease definition--it's rather an obvious problem, particularly to an epidemiologist--is you lose continuity. Did that concern you as well?

Winkelstein: Oh, yes. I think that's mentioned in the letter. I can show you from a recent report in the Morbidity and Mortality Weekly Report just how confusing the whole thing is. I think the reported cases are no longer very useful because the diagnostic criteria have become so diverse.

Hughes: What was the underlying logic, if there was one?

Winkelstein: Well, among other things, they wanted to make certain people eligible for the funding, what is called the Ryan White Act. And one of the things that we argued, although I'm not sure it's in the letter, is that all that would happen is that the Ryan White Funds would be divided up into smaller pieces rather than any more funding becoming available. So, that was one reason. And I guess another reason-- Well, I can't remember.

Papers Stemming From the San Francisco Men's Health Study

Hughes: There are lots of papers that came out of the San Francisco Men's Health Study, papers with your name as co-author, and papers without it. Just to give people an idea, there were papers on staging systems for HIV disease.[1]

Winkelstein: Right.

Hughes: There was your favorite on the relationship of smoking and the elevation of CD4 counts.

Winkelstein: Right.

Hughes: And CD8 cells in progression to AIDS, et cetera.

Winkelstein: I try to keep my name off papers that I didn't really have something to do with, so if you look at the full list of papers related to the San Francisco Men's Health Study, I'm sure that there's a lot of papers there where I'm not listed among the authors.

The Flap Over Infected Seronegative People

Hughes: Yes. There are just so many papers that came out of this study. One that interested me particularly was a subject of the international AIDS conference two years ago, 1992: the cases in which the virus didn't seem to be present, and yet there were low CD4 counts.[2] Do you want to say anything about that debate?

Winkelstein: Well, at one of the international meetings, a scientist, I think from Los Angeles, David T. Imagawa[3], reported that 25 percent of seronegative people were infected. He actually

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[1] For references, see Winkelstein's bibliography in the appendix.

[2] Sheppard, H., W. Winkelstein, Jr., W. Lang, and E. Charlebois. CD4 + T-lymphocytopenia without HIV infection (letter). New England Journal of Medicine 1993, 328(25):1847-1848.

[3] David T. Imagawa, H.L Moon, S.M. Wolinsky et al (10 additional authors), "Human immunodeficiency virus type 1 infection in homosexual men who remain seronegative for prolonged periods," New England Journal of Medicine, 1989; 320; 1458-62.

gave data on four individuals, and they used the polymerase chain reaction [PCR] to make a diagnosis of infection. I examined that paper carefully and felt that the data did not support that conclusion. Furthermore, saying that there were a large number of infected people who were not seropositive has huge preventive and epidemiological implications.

So, we immediately began looking in our studies--I think Dr. Li-Zhen Pan[1] with Dr. Levy were the first to publish on it; I'm not sure--to see if we could find such people, and we couldn't find them.

Hughes: Now, were they using PCR as well?

Winkelstein: Yes. From the MACS--I think Imagawa is part of the MACS, too--Wolinsky and a bunch of others published a paper in which they said that the average interval between infection and seroconversion was eighteen months. We examined the data that were given in that paper, and it was even less convincing.

So then not only we but people at CDC and the several other investigators tried to confirm this work and couldn't. We undertook a whole series of studies culminating in the one which I put in there[2] in which we did every specimen on a seroconverter that we had. We had forty-eight seroconverters. We did all of their specimens. We could find no virus longer than six months before. Maybe one was twelve months. So, we could not confirm either Imagawa's or Wolinsky's work.

Furthermore, in the discussion, there was one case--I think either at twelve months, or something--and our investigators, Mike Busch and Chip Sheppard, went back to the actual clinic in which these specimens were drawn, and they did genetic studies of everybody in the clinic. They found that there had been a specimen mix-up.

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[1] Li-Zhen Pan, H.W. Sheppard, W. Winkelstein, J.A. Levy, "Lack of detection of human immunodeficiency virus in persistently seronegative homosexual men with high or medium risks for infection," Journal of Infectious Diseases, 1996; 164; 962-64.

[2] H.W. Sheppard, M.P. Busch, P.H. Louie, R. Madej, G.C. Rodgers, "HIV-1 PCR and isolation in seroconverting and seronegative homosexual men: absence of long-term immunosilent infection," Journal of Acquired Immune Deficiency Syndromes, 1993; 6; 1339-46.

And then we did a huge study of polymerase chain reaction. We did a quality control study in which we had five laboratories examining 200 specimens--identical specimens--roughly half, not exactly half, of which were seropositive, and roughly half which were seronegative. We knew which were infected with virus. So, we've done a great deal of work and probably spent a million dollars--I don't know how much--just to prove this.

Hughes: The conclusion of that study was that PCR was a fallible test, right?

Winkelstein: Well, it was a pretty good test. But you really have to be careful.

Hughes: Well, that's what I mean: it's easy to contaminate, right?

Winkelstein: Exactly.

Epidemiological Contributions to the Epidemic

[Interview 4: September 23, 1994] ##

Hughes: Dr. Winkelstein, last time we talked in some detail about the epidemiology, specifically about the San Francisco Men's Health Study. Please summarize what you feel to be epidemiology's contributions to the AIDS epidemic? What specifically was it contributing that other lines of research were not?

Winkelstein: Well, I think that epidemiology has played a central role in what we know about the epidemic. In the first place, it identified those subgroups in the population who were getting AIDS, so it described the epidemic in terms of risk groups. It monitored the course of the epidemic and the spread of the epidemic, not only the spread among the initially identified homosexual/bisexual population, but then among the drug-using population, in addition to other segments such as blood transfusion recipients, hemophiliacs, women contacts of largely drug needle-sharers, and then from mothers to infants. All of that can be called epidemiological.

And then, of course, it was epidemiologists who first identified the epidemic in Africa, and also who described it in Europe, and eventually in Asia. So, the epidemiologists

have played a major role in monitoring and surveillance. Building on that, they have made predictions and modeled the course of the epidemic, so that not very long after the epidemic began, projections were being made which have turned out to be reasonably accurate. A purist would argue that they weren't good, but they were really quite good in terms of predicting the huge, disastrous nature of this epidemic.

Secondly, I think that epidemiologists have, very early, identified the modes of transmission in precise detail so that preventive strategies could be adopted. Now, people will argue that prevention has not been very effective. But I would argue that there is good evidence that changed behavior based on epidemiological knowledge has produced a damping of the epidemic, certainly among homosexual/bisexual men.

So, I think the epidemiologists have played a central role, and they've also mounted the studies on which the more biologically-based scientists have been able to identify markers of progression and other biological factors which they have been better able to study because of the existence of epidemiological cohort studies.

Epidemiologists have played some role in the development of clinical drug trials, although that has not been a major activity of epidemiologists.

Hughes: Is that traditionally the case?

Winkelstein: Yes. If and when vaccine trials are actually implemented, the epidemiologists will play a major role in organizing those efforts.

Decline in Epidemiological Findings

Hughes: Once the virus was isolated, was there a diminishing of the importance of the epidemiological approach, and bench science took on more importance?

Winkelstein: It's very hard to say. My own feeling is that, as the epidemic has progressed, the epidemiologists have had less to find. The epidemic is well understood at this point. Its epidemiology is well understood, so we're not constantly discovering new things. For example, early in the epidemic,

because of the nature of our samples, which I've described before, we had information on bisexual men and the numbers of female contacts they had, and what proportion was infected.

So, very early on, we could make estimates of what kind of spread there would be from males to females in San Francisco, under certain assumptions of infectivity and mixing patterns of the population. Those are pretty much epidemiological issues. Well, having done that, then you at least understand dynamics. The next thing to do would be to do surveys to see how well the model of spread predicted what actually happened. For that, we were unable to get funding, as I think I mentioned before.

The understanding is there, and what's left for epidemiologists is sort of a public health function, less of an epidemiological research function and more of a monitoring and surveillance function, which is what the epidemiologists are doing now.

Well, they can do some other things. They can begin to study behavioral interventions, for example, and things of that nature. But if you thought of it in terms of the slope of discovery, it's flattened out. There's not a lot of new epidemiology and not so many exciting new things.

At the same time, you could almost say the same thing for the bench scientists. They've learned a huge amount about retroviruses, and this particular retrovirus as well, over the past ten years, probably more advance in understanding of retroviruses than in any other decade. But, in a sense, it too is plateauing because we haven't gotten any recent breakthroughs.

I know there's intensive work going on with an effort to expand things, but at the beginning, obviously, the curve of knowledge is explosive as you discover new things about this virus, and then it all necessarily slows down.

Hughes: This would be true, more or less, of any epidemic?

Winkelstein: Well, this is a very peculiar epidemic. It's a unique epidemic. I guess every epidemic is. But this is unique because of the chronicity of this disease, the long incubation period. Now we're looking, for example, from an epidemiological point of view at the various characteristics of people who progress rapidly to AIDS versus people who progress slowly, and we're trying to find out if there are

any biological markers or behavioral or environmental factors which influence progression. That's what our group is currently doing. That was what our research meeting yesterday was looking at, and not finding very much.

Hughes: Is that a study separate from the Men's Health Study?

Winkelstein: It's part of the regular San Francisco Men's Health Study which involves the San Francisco General Hospital cohort as well. No, it's not a part of the Men's Health Study.

Focus on the Gay Population

Hughes: Well, you just touched upon one unique facet of the epidemic, namely its chronicity. Is there anything else that is specific to the AIDS epidemic that has required you to tailor your methodology to this particular epidemic?

Winkelstein: I don't think so. It seems to me that we have used standard approaches. I mean, our approach, as I talked about earlier, was to take a sample of the population that was affected. As a result of the way the epidemic developed in San Francisco, our group has not studied, for example, the epidemic among drug users, so we don't know very much about that. Andrew Moss did some work in that area, but not a lot.

Because the epidemic is so different in different populations, the results of our studies apply to the homosexual/bisexual population. And I'm sure that our findings are fairly generalizable among those people. Now, when we study natural history of disease, that is the biological characteristics of the infection, it may be slightly different, but we don't think it's going to be fundamentally different among people who acquire infection by drugs, or people who acquire infections by sexual contact.

But, at the same time, we recognize and we are puzzled, by the fact that Kaposi's sarcoma occurs largely in homosexual men and not very much in men whose infections are acquired by sharing of needles. And that's an enigma which, as far as I'm concerned, nobody has solved. People have made proposals--hypotheses--but, as far as I know, all of them have pretty much come to naught. Every once in a while we examine our own data to see if there's anything that

would shed light on that, or we get some bright idea to look at this, or that, or the other thing, but up until now neither we, nor anyone else, seems to have solved that enigmatic aspect of the epidemic.

Epidemic Modeling

Hughes: In predicting how the epidemic is going to spread, have the standard formulas held true?

Winkelstein: Well, I should say that the field of epidemic modeling has moved very rapidly during the past ten years as a result of this epidemic, so all kinds of new ideas have been introduced, and new applications of older ideas.

We have working with us Dr. Sally Blower, who came from working with Roy M. Anderson and Robert M. May at Oxford, who are the leading modelers--if you want to call it that--of infectious diseases in the world. She's been doing a lot of work here on our data, and has published a number of papers including estimates of how vaccines would work in populations.

Hughes: I saw her paper in Science.

Winkelstein: When was that? I haven't seen it.

Hughes: It was in the September 3, 1995 issue. The focus of the issue is vaccines, so you'd be interested in it.

Winkelstein: Yes.

Hughes: So, the epidemic has had an impact on epidemiology itself. Are there other ways it has made an impact?

Winkelstein: Well, I never thought about it that way. Even though you read about epidemiologists and epidemiological studies, and the Centers for Disease Control has announced this, or that, or the other thing, it's amazing how many educated lay people still don't know what epidemiology is. You go to a party or something, and say, "I'm an epidemiologist," and people say, "You mean, you're studying skin diseases?" It's just amazing to me.

So, to some extent, the prominent role that epidemiologists have played has perhaps provided some public

education, but it's still the laboratory scientist who gets the attention, as you just noted by this last flurry about the breast cancer gene, which made everybody all excited.

The methods of epidemiology are fairly straightforward, but some of the applications, like the modeling, are very technical and have been emphasized in this epidemic. There was a lot of interest in epidemic modeling in the period from 1910 to about 1925, and that was largely around understanding what was going on with malaria and trying to figure out how to control it by modeling the epidemic--mathematical models. Then, in the 1920s, there was a considerable interest in studying epidemics in animal models, so there was quite a lot of work, both in England and the United States, on epidemics in animals.

Hughes: Naturally occurring--

Winkelstein: No. Experimentally produced epidemics. They used agents like a mouse typhoid bacterium, and they looked at things like crowding and diet and genetics in animals, to see whether they could get a better understanding of human epidemics. And interest in that pretty much disappeared by about 1930.

While animal epidemics are not currently studied--I know of no one who is doing epidemiology in experimental animal models--the mathematical model has had a real resurgence as a result of the HIV epidemic.

Hughes: Why are animals no longer considered?

Winkelstein: It didn't work very well. I mean, it worked, but it didn't provide any information that probably isn't better obtained by studying human populations, whereas the mathematical modeling has produced new information. Now, there would be arguments. Some would argue mathematical modeling is a big waste of time, but others would say no.

Stigma

Hughes: The risk groups for AIDS consisted of socially marginal groups. If a person is a member of a population that is already socially stigmatized, placing him or her in a risk group just exacerbates the problem.

Winkelstein: Well, you said it. That's right. I think, to some extent, of course, it has complicated the study of the epidemic. It certainly has complicated the control of the epidemic. And it has required a lot of sensitivity on the part of investigators to get the confidence of these groups. And I think the last time I spoke about our-- Didn't I talk about our participant advisory committee?

Hughes: Yes, you did.

Winkelstein: I think that it would be a very interesting study to see how the activist groups have interacted with the epidemiology world. But there's no question that this epidemic, perhaps more than any, has had this additional problem of stigmatized populations to deal with.

On the other hand, people have been stigmatized since the earliest epidemics. In the plague epidemics, the movement of Jews from southern Europe into northeastern Europe was accelerated by the plague because Jews had moved through Africa and into Spain and were spreading into southern France, and the plague in many places was blamed on them. They were subjected to tremendous discrimination and violence, and so they fled northeastward into what's now the Ukraine and Russia.

And then, of course, the treatment of lepers in the Middle Ages was another aspect of what you're talking about. I'm sure there are other examples. I'm not an expert in that history.

Hughes: That's a good start.

Multidisciplinary Collaborations

Hughes: Several different disciplines have worked together from the start of the epidemic. As a result, do you think some bonds have been established amongst the disciplines?

Winkelstein: I don't really know. My training and experience from the beginning has emphasized collaboration. My mentor, Abe Lillienfeld, was a convener, so I followed in his footsteps. We've always felt that epidemiology required a broad approach, and essentially a team approach.

For me, it's never been an issue. In our study, we have an extremely wide range of expertise, from internal medicine, pathology, sociology, psychology; we have different people whose specialty is virology, immunology, and so forth representing all of us. To do effective research, it was necessary to bring these people together, and so you could say that the epidemic required that, or stimulated that, and I guess it did. But I never thought about it that way; I just did it.

Hughes: It's a common approach for an epidemiologist?

Winkelstein: Well, I don't know. I'm sure there are epidemiologists who prefer to work alone, or there are epidemiologists who wouldn't.

If you read the article one or two days ago in The New York Times about this breast gene investigation, in the group that found the gene, there were forty or fifty-some collaborators. There were collaborators all over. And then the article describes other groups that did not collaborate, that worked alone and in isolation. So some people work that way and other people don't.

I think that the breast gene story, if it's ever told from a history of science perspective, will probably point that out. The group that found the gene was open, collaborative, and drawing on a whole group of scientists. The competitive groups that failed were those which worked alone. And I think it's that way in epidemiology.

In this particular epidemic, you can't be very effective working alone. It's just too big.

Hughes: Too big in all senses. I'm thinking of more than geography.

Winkelstein: That's what I mean. You can't be a good virologist and be a good epidemiologist. You can be an amateur epidemiologist and a good virologist, but it's very hard to do everything.

More on the San Francisco Men's Health Study

Funding Problems

Hughes: As I understand it, the funding from NIAID began in 1992, specifically for the San Francisco Men's Health Study?

Winkelstein: Well, as you recall, sometime in the late eighties, we had proposed to do a study of women, and that had received no support. And then we proposed to include a study of young men when our contract was renewed and that was not approved. The bureaucrats felt that that was an extension of the contract which wasn't proper. But the need to do a study of young men to find out what was going on was obvious, and became more and more obvious as time went on, as there was no information.

Then, we discovered that we had some unspent money--namely $350,000--and so I went to Washington and proposed that we use the money to do a study--survey--of young men.

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Winkelstein: Everybody who attended the meeting was very enthusiastic, including the fiscal people--the contract people--but nothing got done. It took a year and a half to get clearance to use the money that we had for this project. We probably had that meeting in 1991 because I think we began field work in early 1993.

The holdup was actually over something called a clinical exemption. I don't know the exact terminology. But under contracts with the NIH, if you do a survey of any kind, the questionnaire has to be approved by the Office of Management and Budget, and that usually is a morass, especially when you get into sensitive issues like sexual practices. You can get into endless negotiations or blockage of your project.

The way to get around it is to get something called a clinical exemption, which allows you to ask questions that the Office of Management and Budget doesn't get to review. There were people in the NIH who didn't want us to do this survey, for the same reason that there would be people in the Office of Management and Budget. So it took a long time to get around the internal bureaucratic difficulties.

Actually, we didn't get the clinical exemption. We funded the serological survey from NIAID, and we got the money to do the interviews from the Center for AIDS Prevention Studies, which works with the National Institute of Mental Health. And so they paid for the questionnaire, and they had apparently already gotten around the problems of review. So we had to use subterfuge, if you will, to get our project done. The Center for AIDS Prevention Studies at UCSF gave us a small amount of money--not enough. We cheated a little on the money.

Purposes

Winkelstein: There were two basic purposes. One was that nowhere in the country was there any information on what was happening with respect to the epidemic among homosexual/bisexual men under the age of thirty, because all of the studies had been set up ten years before, and everybody was over thirty. So our study was aimed at ascertaining what the HIV infection rates were, what the prevalence of infection was, what the behavioral patterns of these younger men were. And that was important for the same reasons it was important ten years before: to know what was going to happen in the epidemic, to predict the course of the epidemic, to understand what was happening and perhaps to get information that would be useful in prevention.

The second purpose of the study was to find out what homosexual and bisexual men knew about vaccination, immunization, about their willingness to participate in field trials, because if the incidence of infection was as high as 3 percent per year, then it would be feasible to do vaccine trials in San Francisco. As I indicated in a couple of those memorandums that I wrote, I felt quite strongly that the appropriate place to do trials of vaccine efficacy was here, rather than in the Third World.

AIDS Vaccine Issues

Favoring San Francisco for Trials

Hughes: For the record, say why you felt that.

Winkelstein: Well, there are several reasons. Number one is that there's some indication the viruses may vary so you may have to have different vaccines in different places. So testing a vaccine in San Francisco, which is based largely on a San Francisco isolate, would have been the appropriate population in which to test the vaccine.

Secondly, I felt that doing vaccine trials in Third World countries would introduce a whole series of problems because, generally speaking, they would be conducted by outsiders, and there would be, perhaps, difficulty in people understanding the process of a placebo-controlled vaccine. Populations are generally less educated in the Third World, and so the vaccine trial could be misinterpreted as protective and make matters worse. There were a series of considerations of those kinds which made me feel that it would be better--if we could--to do it in this country, which I still feel is the best thing.

Hughes: Has it been decided?

Winkelstein: Well, it's been decided that the candidate vaccines, which have been prepared by two companies [Chiron and GenVax], will not be tested in Phase III trials at the present time.

Government vs. Industry Vaccine Programs

Winkelstein: I felt all along that we've made a strategic error in essentially putting vaccine development in the hands of private companies, and then letting the testing of the vaccines be done by the National Institutes of Health. It seems to me that the National Institutes of Health should play a more dominant role in vaccine development and testing, and then license the private companies to produce a vaccine.

Hughes: In order to emphasize the science and the humanitarian aspects, rather than the business?

Winkelstein: Yes. After all, the drug companies are for-profit organizations. And so their investment, their research, is based on the prospects for profit.

Considering AIDS Vaccine Field Trials

Inadequate Data

Winkelstein: I'm not an expert in this field, so I don't know how that influences their research. But one of the theories is this: I was on the AIDS Research Advisory Committee, which made the final recommendation to the National Institutes of Health not to go forward with the vaccine field trials. And one of the main reasons was that I felt that the data that was presented to us was inadequate to merit a field trial because it was done on, I think, seven chimpanzees; the total studies were in seven chimpanzees. Now, I thought that was just ridiculous, inadequate.

It turns out that the U.S. government has literally hundreds of chimpanzees living in quarters better than most prisoners, and if you want to get one of these chimpanzees for medical research purposes, you have to pay essentially the lifetime maintenance costs. So for a drug company to get a chimpanzee may cost several hundred thousand dollars. I'm not an expert in it; it's what I've heard.

Apparently, those costs played a role in limiting the number of chimpanzees that were used by the drug companies in testing and challenging their vaccines. Now, that seems to me just ridiculous, absolutely ridiculous. They should be given--or made available--whatever number is a proper number. But I can tell you that seven is not. It's just inadequate. Three controls got infected on challenge. Four were vaccinated, three were protected. Something like that. I've probably got it wrong.

The scientists from the vaccine companies indicated that we should do a field trial in humans. And I said, "We just have to have more data." And there were many other reasons as well.

Hughes: I thought there were some human data; that there had been some trials at San Francisco General Hospital.

Winkelstein: Well, there had been. You see, vaccine trials are thought of in three phases. The first phase is very preliminary, in which you really are concerned about whether the vaccine will cause untoward reactions. The second phase is where you expand the trial to see whether it will produce evidence of whatever it is you're trying to produce; in this case,

antibodies against part of the genome you'd be imprinting. And Phase III is a trial in large populations where you're testing the efficacy of the vaccine to prevent infection in the population.

Phase I and Phase II trials have been going on with these vaccines, so they have been giving them to humans and producing antibody to gp120. Of course, nobody knows what the mechanism of prevention would be because we don't know the correlates of infection or of noninfection.

Hughes: Why did the committee make its decision based on only the data from the seven chimpanzees?

Winkelstein: Because that was the critical information. That's the critical test: could you protect against challenge by the virus? Phase I and II don't say anything about the challenge of the virus; they just are trying to determine whether the vaccine produces some kind of a biological reaction, which had been demonstrated.

The AIDS Research Advisory Committee and the Vaccine Working Group

Hughes: There is evidence that, in addition to an antibody response, you would also wish to have a cellular immune response. Was that a point of discussion?

Winkelstein: Oh, yes. Don't forget, there were about twenty-seven members of the committee, and the expertise ranged all the way from lay people to molecular biologists--statisticians, epidemiologists, pathologists, chemists, biochemists, and so forth. There were some very interesting things about this process.

The AIDS Research Advisory Committee was mandated by Congress to advise the director of NIAID on the programs of the institute. And so that committee meets about three times a year.

I rotated off it after the decisive June 17, 1994 meeting. In addition to that, there's something called the Vaccine Working Group, which is made up of a smaller number of NIAID scientists, along with some outside scientists, including members of the AIDS Research Advisory Committee.

That committee met in April [1994] and listened to presentations by the drug companies which had produced the vaccine, and actually took a vote and recommended that there should be field trials. That was made public in a newsletter from NIAID. Some of us--well, I won't speak about others; I'll speak only about myself, but I know that others have the same feeling--were rather disturbed by this because it was known that on June 17th we were supposed to review everything and make a recommendation. But the Vaccine Working Group had already made a recommendation, so we felt in a rather awkward position.

Hughes: Was that a subtle--or not too subtle--form of persuasion?

Winkelstein: I don't know. I can't say what that was. Personally, I think it was inept. I think that they might have come to some conclusion, but that recommendation should then have been given to the AIDS Research Advisory Committee and not to the public.

Hughes: What was the recommendation?

Winkelstein: Their recommendation was to go forward.

The discussion at the Vaccine Working Group was, should they go ahead and test a vaccine for less than 50 percent efficacy, which would require a large trial, or should they test the vaccine for a very high level of efficacy? Drug companies wanted to test for a low level of efficacy; scientists wanted to test for a high level of efficacy because there were many people, like Sally Blower, for example, who would argue that a low-efficacy vaccine would do more harm than good, for a variety of technical reasons.

The June 17, 1994 Meeting

Winkelstein: So, shortly before the June 17th meeting, all the members of the AIDS Research Advisory Committee received, from the two drug companies, a large packet of informational material which many of us thought was not exactly appropriate, but, on the other hand, maybe it was appropriate.

Hughes: Why inappropriate?

Winkelstein: Well, we were being essentially lobbied. They would have argued that it was providing us with the latest information. So I'm not really upset about that.

Anyway, about a week before the June meeting, I called up people in NIAID and said, "We should have a two-day meeting, not a one-day meeting; we can't make such a momentous decision in one day." They said, "No, we can't do that. There's no way we could extend the meeting." Of course, there's always a way you can extend a meeting if you want to. Obviously, they didn't want to.

Everybody knew that this meeting was to be very important. So, when we got there, there were three television teams on an elevated platform. There were perhaps fifty or more journalists. It was a large crowd of people because these meetings are public.

Hughes: Were there activists there as well?

Winkelstein: Activists were there as well. All kinds of people.

Dr. Fauci, who was NIAID director, usually comes to the AIDS Research Advisory Committee meetings for an hour, where he reports on budget, answers questions and so forth, essentially initiates the meeting. He said at the June meeting that he was going to be there all day long and listen to the entire discussion, which he did. He stayed for the entire meeting and took notes, but he didn't participate in any way.

And then the meeting began. First there were presentations from staff, which there always are, on various aspects of the science. Then there were presentations from the two drug companies. And, of course, the committee members asked questions. And then there was an opportunity for statements from the public, and I think two activist groups and a former NIH scientist, Sten Vermund, spoke. I couldn't figure out whether he was for vaccine trials, or not. The activists were against the trials.

Hughes: Why?

Winkelstein: Well, activists were against it because, like many of us, they felt that the evidence was not good enough that we had a good vaccine, and they felt that the communities which had been affected by HIV had been disappointed so many times that it would be very bad to again involve them in something which the scientists were so ambivalent about.

Hughes: Martin Delaney, who previously pushed for accelerated drug approval, is now taking a different stance.

Winkelstein: Well, Martin is a member of the AIDS Research Advisory Committee. I don't know if he still is, but he was very articulate and very opposed in that June 17th meeting.

Hughes: Saying that the trial should not go forward?

Winkelstein: That's correct.

Sometimes a committee like that is rambling, and people make speeches and it's not very productive. But I thought that the discussion was extremely thoughtful and serious that day. In fact, you can tell how serious it was because one of the television crews packed up and left. That showed it wasn't very interesting. There wasn't enough fire for them.

There were some very interesting things. For example, we have one member of the committee, a biochemist from, I think, Washington University in St. Louis--a very brilliant man who always takes a very active role in discussions. On that day, he didn't say anything until about three o'clock in the afternoon, at which point he gave about a fifteen-minute analysis of the situation.

Decision Against Vaccine Trials

Winkelstein: Anyway, at the end of the day, the chairman of our committee, Dr. Ashley Hall, said, "Okay. Now, we'll go around and each person on the committee should give their opinion and briefly the justification for their position." So he went around, and I would say three or four people excused themselves for one reason or another. One of them had done some consulting for one company, and other people couldn't make up their mind, or whatever. But the rest, maybe twenty-one or twenty-two, were all against.

So, Dr. Fauci then got up and said he was taking the advice of the committee, and in fact he was making the decision that the field trials would not go forward at this time.

So then there was a press conference with Dr. Fauci and the chairman of our committee. And, because I had to stay

overnight anyway, I decided to listen to the press conference. And it was fascinating.

I don't know if you've ever heard or met or seen Dr. Fauci. He's very much like President Clinton. He's an extremely bright, articulate, responsive person. He answered questions for about forty-five minutes. And he knew a lot of the reporters. A reporter from Science magazine asked a lot of questions, and of course there were reporters from all the major news media and the local television, as well. So, all in all, I thought it was a fascinating meeting.

Every single one of the people at the meeting took problem seriously; it was like being on a jury. Everybody realized that this was really extremely important. I think essentially everybody had done their homework and had read the materials they'd been given, and studied them, and had come to some informed conclusion.

Now, naturally, the scientists from the drug companies were pretty unhappy. I think my friend Don Francis will never speak to me again, but maybe time will soften things.

A Setback to Vaccine Development

Hughes: In a certain sense, it was a setback to vaccine development. Well, yes and no. That could be argued either way.

Winkelstein: Well, it may be. I know a lot of people felt that the drug companies were almost putting pressure to do field trials, although nobody ever said it. There was sort of the implication: we have hundreds of thousands of doses of vaccine on the shelf ready to go in field trials, and we've spent millions and millions of dollars developing this vaccine, and now you're not going to test it. Why should we spend millions of dollars developing vaccines?

I know the government has put a lot of money into the development of vaccines--

Hughes: And so has the state.

Winkelstein: And so has the state. But, nevertheless, they don't, in a sense, take the lead.

Hughes: It's the companies that take the lead.

Winkelstein: That's right. So, there was that sort of implied threat. Once a scientist is working for a company, no matter how independent, eminent, ethical and moral they are, when they take their first paycheck, they're signed up with the company. I'm sure Dr. Francis realizes that.

Hughes: Is this decision going to have stultifying effects on the development of vaccines in industrial settings?

Winkelstein: Well, I think it may very well. I don't know enough about it to really speak to it, but I would think that the government would have to take a more active leadership role in vaccine development.

Hughes: By what criteria was the committee supposed to judge whether the trial should go forward or not?

Winkelstein: On the basis of data presented to us regarding the Phase I/Phase II trials, plus the experimental evidence that the vaccine was protective in chimpanzees. And we just don't have that information.

Dani Bolognesi's Changing Opinions

Winkelstein: Now, a couple of years ago, three years ago, we had a meeting at UCSF on vaccines, and Dr. Bolognesi, who is a very prominent investigator, was here from Duke. He's also a member of the AIDS Research Advisory Committee. He and I got into quite a little hassle. The argument that he put forward was that we had to do vaccine trials in order to obtain the information that was needed to move vaccine research forward.

And I said, "We can't do that. We epidemiologists who have to go in the field with these field trials are not going to test a vaccine that you lab scientists can't say to us, 'There's reason to believe that this will work.' You're saying you want us to go in the field and do some research on human beings. We don't want to do that." He was, at that time, very strongly in favor of going forward with field trials.

He changed his tune totally. By the time of the April meeting--the Vaccine Working Group--he was opposed to it,

and at the June 17th meeting he spoke very eloquently against going forward at this time with vaccine field trials.

Hughes: What changed his mind?

Winkelstein: The data. He's a good scientist. And then there's a lot of data that I don't fully understand.

More on the Possibility of a Government Vaccine Program

Hughes: Was the committee trying its best to make the decision based strictly on scientific data? You were not thinking, "If we decide against allowing these field trials to go forward, what then will be the effect on vaccine development in biotech or pharmaceutical companies?"

Winkelstein: Well, we weren't really asked to give that consideration.

Hughes: I know you weren't.

Winkelstein: Well, like I said before, there was an implied threat that if we didn't approve the field trials, the companies would stop developing vaccines. There was that implied threat. And I gave that some thought, and maybe that influenced me to vote against it because, as I've expressed myself several times, I think the strategy is wrong. I think that the government should take the lead in promoting and paying for the development of the vaccines. So, maybe, in a way, it's a step forward, from my point of view, [to have voted against AIDS vaccine trials.] But I don't know if it's going to work that way.

Hughes: Was there any talk of turning over vaccine development to the government?

Winkelstein: No. I didn't hear that.

Low-efficacy Vaccines

Hughes: The other argument that I've heard is, when you're dealing with a fatal disease, almost any vaccine, even one of 10 percent efficacy, should be given a chance.

Winkelstein: Well, there are many aspects to that. Number one is that, as Sally Blower has shown, in a low-efficacy vaccine, you may be doing more harm than good for a variety of reasons. So, setting that aside, let's say you test the vaccine and it's 30 percent effective, and you've done a very large trial and so you are confidence that that efficacy is the efficacy of the vaccine. Then you're obligated to start using that vaccine. So, that may stop development of a more efficacious vaccine.

Now, you're going to test your next vaccine against your previous vaccine, and there are very deft arguments against using low-efficacy vaccines. They may encourage new risk behavior which may result in an increase of occurrence of disease. So, it's a very, very tricky problem.

I guess I was not terribly opposed to maybe a trial to test the vaccine at 90 percent efficacy, but the drug companies weren't interested in that because they didn't think their vaccine was that effective. So, there were many considerations going into everybody's vote. But, anyway, that's the way I look at it.

Hughes: It's a very interesting story, and the sequel we don't know yet.

Winkelstein: The dynamics are terrific. I don't know what's going to happen.

I just received a packet from Genentech with a letter from Don Francis and a copy of his presentation at Yokohama on the vaccines, so he still thinks they should be tested.

Dr. Winkelstein's AIDS Committee Memberships

Hughes: I read that you have, since 1987, been a member of the city of Berkeley's AIDS Advisory Committee.

Winkelstein: That's been totally inactive. It's never done anything.

Hughes: Why?

Winkelstein: I don't know.

Hughes: What about the Advisory Committee on HIV Vaccine for the California Department of Health Sciences?

Winkelstein: I think we had one meeting some years ago in Sacramento. I remember going to the meeting. I remember the building which was their AIDS office. I remember George Rutherford was there. I don't remember what we discussed.

Problems of Committee Membership

Winkelstein: I was surprised, on the 17th of June [1994], to find that I had rotated off the AIDS Research Advisory Committee.

There's one very frustrating thing about committees like this, where you would go to the meeting for one day--sometimes the meetings are two days--and it's just not often enough to go two or, at the most, three times a year. And you very quickly feel as though you're some sort of a tool of the staff because it's very difficult to object to something. The staff have worked up a proposal, and they've done a lot of work on it, and so you're in an awkward position. You sort of feel as though you're a rubber stamp to what the NIH wants to do.

Now, we did actually turn back some proposals that were brought before us for advice, but over the several years that I was on the committee that was really a rare event. Most of the time you rubber stamp what you're given.

Hughes: Is that particularly true of government committees?

Winkelstein: I think it's true of a lot of committees. Now, it depends on what the committee is. If you're in a study section at NIH, most of the time you're turning things down. I've never been on a council. Those are the advisory committees to the whole institute. I think they're somewhat similar to the kind of committee I was on--a broad range of expertise, and sometimes people are on the committee for political reasons.

Hughes: Do you know specifically why you were appointed?

Winkelstein: I don't know specifically.

Hughes: What would be your guess?

Winkelstein: Well, I'm an epidemiologist. They need a certain number of epidemiologists on the committee. A group here that I head up had done good work, and had been very supportive. We

provided a lot of data to the NIH and to other investigators. I don't know why. I guess somebody thought I could contribute to the committee. I must have had friends and whatever.

NIH Committees in General and as Related to AIDS

Hughes: In the case of a congressionally appointed committee--

Winkelstein: It's not congressionally appointed; congressionally mandated, appointed by the NIH.

Hughes: What is the difference?

Winkelstein: The advisory committees, I think, are appointments made by the director of NIH, or the President--I'm not even sure. A congressionally mandated committee means that Congress tells NIH, "You must have a committee to advise AIDS research." So they mandate that you have to have that committee made up of wide representatives.

Hughes: But they don't pick the membership?

Winkelstein: No. I think, in this case, it would be picked by the director of NIH, obviously under the recommendation of the director of the NIAID, who would have recommendations from his staff on various people.

Hughes: So, it was probably Fauci who had the largest say.

Winkelstein: That's correct. The Vaccine Working Group is not a congressionally mandated committee, nor are many other committees. So the NIH, or any other agency, can create an advisory committee whenever it wants.

Hughes: The June 17th meeting was composed of two committees, namely, the congressionally mandated AIDS Advisory Committee, and Fauci and I think six other members of the Vaccine Working Group?

Winkelstein: Well, no. I think that the AIDS Research Advisory Committee has on it members of the Advisory Council to the NIAID. Each institute has a council, and that council is like a board of directors and they advise the director of the institute. They have subcommittees. And I was a member of

a subcommittee on vaccines and a member of the AIDS Research Advisory Committee at the same time.

The mandate was, "You shall have a committee to advise you on AIDS research." I don't know whether the resolution said, "It shall have representation from...," or what. All I know is the committee had wide representation from science, from local government, from the lay public, and so forth.

Hughes: On the other hand, you can't get around the fact that NIAID, in the person of Fauci, had the determining decision in who was going to be on the committee.

Winkelstein: That's correct.

Hughes: Even if it was congressionally mandated, in effect, in practicality, the committee was composed by Fauci?

Winkelstein: Oh, yes.

Hughes: With some advice.

Winkelstein: Sure.

Hughes: The initial institute to be involved in the AIDS epidemic was NCI [National Cancer Institute].

Winkelstein: Right.

Hughes: Was there a representative from NCI on the committee?

Winkelstein: I think there was. Now, I don't think they were on the AIDS Research Advisory Committee because none of the members of the committee were government people. Now, the Vaccine Working Group has government people working on it. But there were certainly staff from NCI and from CDC [Centers for Disease Control]. The CDC was represented at the meeting.

Hughes: I suppose this is the way things usually work? I mean, one institute more or less takes ownership of a disease?

Winkelstein: Yes. Well, as I mentioned in our first discussion, there was a turf battle here between the NCI-supported investigators and the proposed NIAID investigators and the CDC investigators at the City Clinic.

Dr. Winkelstein's Vaccine Trial Experience

Hughes: Did your experience with the polio vaccine field trial in 1954 and other things that you have done in epidemiology give you a perspective that other people on this committee could not have had?

Winkelstein: Well, I think it probably did. I was involved in measles vaccine field trials as well as polio vaccine field trials. One thing that I think I appreciated, perhaps more than some other people, was the difficulties involved in these things. People who have never done these trials don't know what it means to have a placebo double-blinded field trial with hundreds--if not thousands--of participants, and what that means from a logistical point of view and from a public relations point of view.

We argued that one of the reasons why we should be funded to do vaccine preparatory studies was because I had experience. I was the only one in the whole bunch who had experience.

I wanted to do field trials. I'm very anxious that we get a vaccine. At the moment, I think that the prospects of a vaccine are not very good, but eventually I think that we must find a vaccine, because I just don't think [without an effective vaccine] we're going to lick it [AIDS], even though I'm involved in setting up a behavioral practices intervention trial. But I was very anxious that, if a vaccine were available, that we test it in San Francisco.

If we had a good vaccine, I think we could control the epidemic. There are people who say, "Well, even if you had a good vaccine, you can't control it." I don't buy that. I think if we had a really good vaccine, with 80 percent efficacy, or something like that, I think we could lick this disease.

Hughes: But not with one that's lower than that?

Winkelstein: Well, I have my doubts.

Hughes: And you'd choose San Francisco because this is a high-incidence area?

Winkelstein: This is a high-incidence area.

V PETER DUESBERG AND THE AIDS EPIDEMIC

[Interview 5: October 26, 1994] ##

Duesberg's Science Background and First Publication on AIDS

Hughes: I understand that Peter Duesberg's first paper on AIDS was published in 1987, and in a very reputable journal, namely the Proceedings of The National Academy of Sciences.

Winkelstein: Well, any member of the National Academy can publish anything they wish in The Proceedings, without peer review. In fact, if you look at the footnote to each of those papers, it will make clear that they consider this to be an advertisement. The footnote says, "These articles conform to the definition of an advertisement," because they're not peer reviewed. That's neither here nor there.

Are you sure the first paper was published in The Proceedings of the National Academy? I think the first paper was published in Cancer Research, or something like that.[1]

Hughes: Oh, you could be right.

Winkelstein: But some of the subsequent papers were published in The Proceedings.

Clearly, the 1987 paper was very important because Duesberg himself is a very important person. He was one of the younger elected persons to the National Academy of Science and did very important work in the development of the theory of oncogenes and was internationally known and a very prominent investigator, so that paper attracted considerable interest and attention. I had known Peter

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[1] Peter H. Duesberg, Cancer Research 1987, 47:1199.

Duesberg since shortly after I joined the faculty here because I had served on at least one committee with Peter, and that would have been in the early seventies.

An Early Duesberg Seminar on AIDS

Winkelstein: At any rate, I saw his paper, and then I saw an announcement that he was going to give a seminar in the department of zoology here on campus in the Life Sciences Building. This would have been in 1987 or 1988. I don't remember. So, I went to the seminar and I was appalled by what he had to say. In particular, at that seminar, he made clear his opinion that AIDS was not an infectious disease and was not sexually transmitted, and that there was no danger from transmission by sexual activity.

Well, this seminar, while it was attended by some faculty, was largely attended by students, mostly graduate students. I felt that the evidence was overwhelming that this was an infectious disease; the evidence was overwhelming at that time that it was a deadly disease, and I felt that this message was very, very irresponsible at the very least.

Hughes: What was he basing those statements on?

Winkelstein: Oh, basically the same arguments he's giving today--drug use, homosexual behavior, and so forth, were what was causing the disease, not an infectious agent. He, at that time, was still saying, "I would be willing to be infected. In fact, being HIV-positive is favorable, not unfavorable, because of its antibodies," which, of course, reveals a profound misunderstanding of the concept of immunology. I think he's learned a little immunology since.

So, I got up--I was pretty upset, to say the least--and made an impassioned speech regarding the infectious nature of the disease and the consequences of infection, which were pretty clear by that time. So, that was the beginning of my involvement with Dr. Duesberg on this issue.

Hughes: Was his involvement just through the oncogene retroviral connection?

Winkelstein: Well, I don't think that I can say how he got interested. My understanding is that he was on sabbatical leave at the

National Cancer Institute, and that during that period, he wrote that initial paper giving his ideas. So, I don't really know what led him to then begin to put forward those ideas in various places.

Hughes: Had he a track record of having an iconoclastic approach to science?

Winkelstein: He may have. I don't know anything about his career because his field of research is totally outside of my field. I've frequently discussed this with him: while he feels totally free to pontificate about epidemiology, I don't feel free at all to pontificate, or even to speculate, on virology. So really our scientific paths have not been parallel.

Donald Francis[1] and Winkelstein Meet with Duesberg

Winkelstein: Well, shortly after this seminar--I was really very upset by this--Donald Francis and I--Don Francis, at that time, was consultant for the California state health department on assignment from the Centers for Disease Control--took Peter Duesberg to lunch at the Faculty Club to discuss this with him as scientists, because we were so appalled by what we felt was an anti-scientific position. We discussed this for an hour and a half, I paid for the lunch, and then we left.

Oh, we picked him up at his laboratory, and when we did, he was gleefully making jokes about Dr. Robert Gallo, with whom he had had exchanges, and making all kinds of depreciatory comments about Dr. Gallo.

Anyway, after the lunch was over and Dr. Duesberg had gone back to his laboratory, Don Francis and I were walking through the campus and I said to Don, "You know, he never heard a word. He never heard a word we said." That was my assessment of the meeting, that when we were talking he was not listening. And I believe that's been sort of the pattern ever since. He doesn't listen to the rationale. But he is a brilliant man, and I guess he's read a lot, and I don't understand how he can take the position he's taken, but there you have it.

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[1] See the oral history with Donald P. Francis, M.D., in the UCB AIDS physicians series.

Duesberg's Contentions

Hughes: Well, shall we go into what I understand to be the main points of contention, as far as the dissenters are concerned? It's of course, not just Peter Duesberg, although he's the most visible representative. There's a certain consistency in their arguments.

One of their prime arguments is that scientists in general cannot really explain how HIV damages the immune system. A second argument is that HIV is associated with AIDS only through correlation. The third is that predictions based on the theory that HIV is the cause of AIDS have failed. They're thinking there of the early predictions that the epidemic would spread into the heterosexual population.[1]

Failure to Explain the Immunopathology of AIDS

Winkelstein: Well, let's take those up one at a time. The first one: Of course, I'm not competent to discuss the problems and the enigmas which remain with respect to the immunopathology of the disease. But Duesberg and his colleagues argue that, because it isn't understood, HIV is not the cause. But I find that that's the case for essentially every disease. Let's take a couple of examples.

In infection by the polio virus, which affects the nervous system, motor neurons, and then sometimes ascends into the central nervous system, why does polio virus attack only motor neurons and not sensory neurons? We don't know the answer to that. Why is the polio virus specific for nervous tissue? Why doesn't it attack the muscles? Why doesn't it attack the liver? Why doesn't it attack some other part of the body? We don't understand that. And you can say the same for essentially every disease.

For example, Dr. Duesberg and those who think as he does argue that infection by the HIV doesn't always cause AIDS. Well, in fact, it does for a large proportion of cases. But

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[1] See, for example: Peter Duesberg, "HIV is Not the Cause of AIDS," Science 1988, 241: 514-517; and a response: W. Blattner, R.C. Gallo, and H.M. Temin, "HIV Causes AIDS," Science 1988, 241:515-516.

many infectious agents do not have a total penetrance, in a sense. Polio virus, for every 100 persons it infects, produces disease in maybe one, or two, or three. Syphilis, if untreated, produces disease in 50 percent of its infections. And every disease has its own characteristic penetrance, if you want to call it that. Some infections, like measles, almost invariably produce disease whereas, as I said, polio very rarely produces disease. And why, or who is chosen, is not known.

So, the fact that we're ignorant of part of the pathoimmunology, or whatever you want to call it--the natural history of HIV infection--seems to me irrelevant to the question of whether HIV is the cause of AIDS. That question is answered by a different set of data, if you will. So, on that score, I would say that that is not an effective argument.

Failure to Prove HIV as the Cause of AIDS

Winkelstein: Now, let's see the second question was?

Hughes: The association of HIV with AIDS is through correlation only.

Winkelstein: Well, that, of course, is ridiculous. That's constantly given as a reason for when you don't want to accept a causal association. There are a whole series of criteria that we use to evaluate whether an association is a causal one. For example, the increase in the sales of certain kinds of automobiles--let's say Honda Accords--is associated with the increase in AIDS because, over the last decade, these cars have become very common. But that association is clearly ridiculous, and is obviously spurious, and can be shown to be spurious.

When we come down to the question of whether HIV--whether a virus--is associated with the outcome of AIDS, then we have a whole series of criteria, such as: isolation of the virus from cases and not from non-cases, the fact that AIDS only occurs in people who are HIV-infected. Then there are a whole series of strengths: consistency, plausibility, time sequence is very important; the infection takes place before the occurrence of the disease; the disease is not occurring before the infection, and so forth. So, we have a series of criteria by which we can evaluate

strength of association, or correlation. Practically everything is decided that way.

The evidence for HIV and AIDS is as strong, or stronger, than the evidence for diphtheria toxin causing diphtheria, or measles virus causing measles, or smallpox virus causing smallpox. They're all correlational. On the other hand, there's a lot of additional supportive evidence.

So, the argument that it's only correlational, which we hear mostly in connection with cigarette smoking and lung cancer--well, it is only a correlation--it's just a terribly powerful, strong correlation. And, well, that's what I have to say about that.

Failure of Predictions Based on the HIV Theory

Hughes: The third argument is that predictions based on the HIV theory of AIDS causation have failed.

Winkelstein: That's blatantly not true. Shortly after this epidemic began, we began to see cases of AIDS in people who had received blood transfusions and who did not belong in the groups that had already been demonstrated to be at risk, particularly homosexual men and needle sharers in recreational drug abuse.

It was very quickly--well, not very quickly--but it was shown in a matter of a few years that the people who got AIDS subsequent to blood transfusion had received blood containing the HIV. This was strong evidence favoring the causal relationship between HIV and AIDS, because people who were transfused and did not belong to risk groups and who had received uncontaminated blood did not get AIDS. And we're talking of many hundreds, if not thousands, of cases of transfusion-related AIDS.

Now, when the HIV was identified, a serological test for blood was developed and, even before the serological test, blood banks like the Irwin Memorial Blood Centers in San Francisco were screening out high-risk people and not allowing them to donate blood.[1] And then with the

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[1] See the oral history with Herbert A. Perkins, M.D., in the UCB AIDS physicians series.

introduction of a test, the occurrence of transfusion-related cases of AIDS dropped down to essentially zero. So, I think that Duesberg's argument seems to me to have no validity at all.

And then they have claimed that hemophiliacs don't get AIDS. That's not true. Hundreds and hundreds of hemophiliacs who have been infected by Factor VIII, before it was heat-treated, have developed AIDS and have died. So, the argument is spurious. They keep repeating this. They've been shown the data, and the data are readily available on blood transfusion, and the prevention of transfusion-related AIDS by screening the blood. If that is not evidence of an effectiveness of the HIV theory--if you want to call it that--I don't know what is.

In the first place, every properly run blood bank in the entire world screens its blood for HIV, and no one in his right mind would accept blood that had not been screened for HIV, just as we screen blood for hepatitis B, we screen it for syphilis--the organism that causes syphilis, as well. So, I don't understand. I've never quite understood that claim that is made by Duesberg and his associates. It makes no sense.

Hughes: Have you and others challenged him specifically on that point?

Winkelstein: Countless times.

Hughes: And how does he respond?

Winkelstein: I don't know. He just repeats--

The American Foundation for AIDS Research sponsored a meeting at the National Academy of Sciences in Washington to discuss Duesberg's thesis, and to that meeting they invited science writers, and there were maybe fifty or a hundred at that meeting. The scientists who were invited to participate and who did included Dr. Fauci, Director of National Institute of Allergy and Infectious Diseases, William Haseltine, a Harvard professor prominent in molecular biology; Murray Gardner, from UC Davis, who's a prominent investigator in the field of simian immunodeficiencies; myself; the meeting was chaired by Dr. Ginsberg from Columbia--I can't remember his first name; Dr. Duesberg, and his mentor, Dr. Harry Rubin.

Throughout that meeting, whenever anyone was presenting, like Fauci, or Haseltine, or Gardner, or me, or whoever, frequently Peter would get up and wander around the room and chat with this or that reporter. He wasn't listening to what was being said. Occasionally he would look back at the presenter and maybe toss out a question, or something. Interacting with Duesberg has been a very strange phenomenon.

Duesberg Supporters

Hughes: Well, what about the other dissenters?

Winkelstein: Well, who are some of the others?

Hughes: Well, some of the others are prominent scientists. I saw a reference, for example, to Wally Gilbert, who is a prominent molecular biologist at Harvard and, as far as I know, still maintains a high reputation in the field, Kary Mullis, who received the Nobel Prize for PCR [polymerase chain reaction],[1] Richard Strohman[2] and Harry Rubin on this campus. These are reputable scientists, not fringe people, as some of the people associated with Duesberg are. Some of the people associated with Duesberg aren't even scientists.

Winkelstein: That's right. Phillip Johnson [of UC School of Law] is a good example.[3]

Hughes: Exactly.

Winkelstein: Well, let's take Kary Mullis as an example. Mullis received the Nobel Prize for what can only be considered a brilliant discovery. I don't know how he made the discovery. Some say it was an accident. But, whether it was an accident or

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[1] Charles A. Thomas, Jr., Kary B. Mullis, and Phillip E. Johnson, "What Causes AIDS?", Reason, June 1994, 18-23.

[2] Richard C. Strohman, "An open letter on the HIV-AIDS hypothesis: Scientific Community has shut out dissenting AIDS theories," The Daily Californian, April 1, 1993, p. 4. Also see Winkelstein's response: "Dissenting Scientists: Earth is not flat", The Daily Californian, April 13, 1993, p. 4.

[3] Phillip E. Johnson to Warren Winkelstein, March 31, 1993. (Winkelstein personal correspondence.)

not, he recognized the importance of the discovery and, quite properly I think, received the Nobel Prize, although this is not a field that I know anything about.

And I think that's the key. He a biochemist. He's not a virologist. He's not an immunologist. He's not an epidemiologist. Does receiving the Nobel Prize for the discovery of the polymerase chain reaction qualify him to be an expert in other fields? I don't think so.

I've read Mullis's article, which was published in Reason magazine, in collaboration with Phillip Johnson and another person, and it's just full of misstatements, misrepresentations. I would never go into Peter Duesberg's or Kary Mullis' laboratory and start playing around with test tubes. It's beyond my comprehension that an expert in one field would meddle in another. The fact that a person has achieved prominence in one field does not quality that person to prominence in another field.

Hughes: I'm playing the devil's advocate.

Winkelstein: I understand. That's your job.

Hughes: What about Richard Strohman and Harry Rubin? They are basic biological scientists on the Berkeley campus. They have a certain credibility in speaking on the subject of AIDS because it is related to their field of expertise.

Winkelstein: Maybe. I don't know enough about Dr. Rubin's field of work, nor do I know that much about Richard Strohman's field, to evaluate their competence to judge the etiology of AIDS.

Now, there are clearly major problems in understanding the full, natural history of this disease, and no one who works in the field denies that. We've come a long way in the ten years that the epidemic has been recognized--it's now thirteen years--but we don't know all the answers. And I don't know any scientist that I've encountered working on HIV who says that we know all the answers, or now thinks that we have a comprehensive understanding of the natural history. Otherwise, why are they working on it? If we knew the answers, we wouldn't have to work on it. I don't understand the position that Duesberg and these other people take; of course, there are unanswered questions.

As I said earlier, there are unanswered questions about every disease. Do we know all the answers about lung cancer? Of course not. We've been studying it for decades,

we know a great deal, but we don't know all the answers. You can't tell me any disease for which we know everything.

Now, to pick out the fact that there are gaps in knowledge and argue that, because there are gaps in knowledge, we don't know anything is not very understandable to me.

Hughes: If your argument is widely understood--that knowledge in any field has lacunae--why do these people choose AIDS as their target of continuing criticism?

Winkelstein: You'll have to ask them that question. One can speculate as to why they might choose this disease. Certainly, it has given notoriety to Dr. Duesberg beyond anything he ever could have achieved through his scientific work. His name is known basically throughout the world by people who never would have heard of him otherwise.

Duesberg's Scientific Productivity

Hughes: His scientific career has been hurt. From what I understand, his funding from NIH has been cut off, and I would think that his research effort would be severely hampered.

Winkelstein: Well, I suggest that the answer to that question might come if you did a literature search to see what kind of scientific work, other than his pontifications and polemics on HIV, has been published in the past five or six years. I did such a research recently, and didn't find very much. My thesis would be that he's lost his grants because he stopped working.

Hughes: Not because of his stand on AIDS?

Winkelstein: Well, he claims it's because of his stand. Do a MEDLAR search and find out what he's done other than this work--well, I won't call it work--other than his publications on HIV and AIDS, and I don't think you'll find very much.

Hughes: When you did that search, did you discover that he had done actual laboratory work on AIDS?

Winkelstein: As far as I know, he has done no laboratory work on AIDS. Now, I think he'll claim that he may have put in an application and it was turned down.

HIV and Koch's Postulates

Hughes: One of Duesberg's major points is that HIV as a cause of AIDS does not fulfill Koch's postulates.[1] Do you want to address that?

Winkelstein: Well, first, Koch's postulates were first enunciated by Jacob Henle in 1840, and Robert Koch was a student of Jacob Henle. Henle was an early pathologist and wrote a theory of infectious disease in his first pathology book. In that chapter, he laid down a theory of infectious disease which subsequently proved to be extremely perceptive and accurate.

Koch proposed the postulates, which are based on Henle's theories, in his classic paper on the cause of tuberculosis. The tubercle bacillus did not satisfy fully the postulates. The postulates were enunciated in 1880 at a time when the science of microbiology was in its infancy. It would be highly unlikely that Koch's postulates would continue to be applicable in the 1980s because we've moved far beyond that. There are a whole series of microbiological agents which were not even dreamed of at the time--the virus, for example. And some of the other aspects of infection were unknown at the time the postulates were advanced, such as infection without disease, chronic carrier states, and many other things. So the fact that HIV doesn't satisfy the classical postulates is not, to me, a sufficient argument, because neither does tuberculosis, neither does poliomyelitis, neither do many other agents which we accept as causal agents for disease. On the other hand, HIV does satisfy, to a considerable extent, Koch's postulates, and so I think that's not a very strong argument.

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[1] Peter Duesberg, "HIV is Not the Cause of AIDS," Science 1988, 241: 514.

AIDS and Drug Use

Hughes: What Duesberg puts forward, as you are probably too fully aware, is the hypothesis that AIDS is caused by continuous and cumulative drug use. I suppose one reason that you and he have become the spokesmen for opposite camps is because he has turned to the data from your San Francisco Men's Health Study. Am I right in that assessment?

Winkelstein: Well, he's misused the data, but that's correct. For a long time we said to Dr. Duesberg, "Why don't you join the research effort?" And he did not choose to do that. And then two or three years ago, he finally sent a graduate student to fill out the forms that we require to get access to our data. He had another faculty member countersign, because the graduate student, Bryan Ellison, had to have a faculty sponsor--he had one from the statistics department--and so we did give him access to our data.

Now, we also published a commentary in Nature called "Do Drugs Cause AIDS,"[1] in which, using data from our study, we, I think demonstrated to everyone's satisfaction that drugs do not cause AIDS.

Peter never invokes Koch's postulates with respect to drugs, and he uses the weakest of analyses in his arguments in favor of drugs as a cause of AIDS. The 200 HIV seronegative heterosexual men in our study had the same pattern of drug use as the homosexual study subjects except for the use of poppers and yet only one became HIV positive in eight years. So, with the exception of that drug, the use of drugs was about equal between heterosexuals and homosexuals. And, of course, there was no AIDS in the heterosexuals and, of course, there was no AIDS in the seronegatives either.

But just for the moment, for the argument about drugs, let's compare the heterosexuals with the homosexuals. So, except for the issue of nitrites, you could say that drug use was equal in the two groups. If drug use had been the cause of AIDS--excluding nitrites--then you would have seen at least some cases in the heterosexuals. We saw none.

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[1] M.S. Ascher, H.W. Sheppard, W. Winkelstein, Jr., E. Vittinghoff. Does drug use cause AIDS? Nature 1993, 362(6416):103-104.

Now let's take the homosexual men, half of whom were seronegative on entry to the study, and the other half were seropositive. It is true that the seropositives had higher use of drugs, because that is a risky kind of behavior; people who are likely to have multiple sexual partners, which is a risk factor for sexually transmitted disease, are likely to do a lot of other things--they're more likely to take drugs, they're more likely to be promiscuous, risk-takers, what-have-you. But, when you control for the use of drugs, then the difference is solely in the HIV positivity.

In other words, if you take light users of poppers and heavy users of the drugs among seronegatives, there is no difference in AIDS occurrence. And so if you use the data from the San Francisco Men's Health Study properly, you will find that the relationship is entirely explained by HIV positivity, not by drug use.

Furthermore, there are seropositive men--although Duesberg denies it--who, over eight years, didn't use any of these drugs and who developed AIDS. And there are no HIV-negative heavy drug users who developed AIDS. So, his arguments do not stand up in the face of critical analysis of the data. He accused us of fabricating our data. I'll speak to that when we come to that.

Winkelstein Claims Duesberg Misused Data

Hughes: You said that Duesberg misused your data. Could you tell me exactly how he did?

Winkelstein: Well, in a paper that Bryan Ellison and Peter Duesberg jointly authored, which, as far as I know, has not been published--and I gave you the reviews to that paper--they claimed that there were cases of AIDS among the HIV-negatives, because they claimed that HIV-negatives had AIDS-defining conditions. Well, that is not true.

If there had been AIDS cases among the HIV-negatives, then the death rate among HIV-negatives would have been elevated. The death rate among HIV-negatives was essentially the same as among heterosexual negatives; it was very, very low. The death rate--forget about AIDS--the death rate among the HIV-positives was close to 50 percent in eight years. Now, in young men--I don't care whether they're drug users or not--the death rate of 50 percent is

just very, very excessive. So, if you look at the end points only, HIV positivity was the key factor in the high death rates.

As I say, if AIDS were occurring in the HIV-negatives, as Bryan Ellison and Peter Duesberg claim, there would have been excess deaths. I calculated the numbers, and I gave them in the paper[1] I gave at the AAAS [American Association for the Advancement of Science] meeting in San Francisco in June 1994. It would have been forty-three, or something like that. There were actually seven deaths, or something like that, over the eight-year span I followed. So, I don't think their arguments hold up any way you cut it.

Hughes: Did they respond to your counter-arguments?

Winkelstein: I didn't hear them respond.

Duesberg Charges the Winkelstein Group with Data Fabrication

The Commentary in Nature, 1993

Hughes: Well, let's discuss Duesberg's charge that you fabricated data in your commentary in Nature.[2]

Winkelstein: Let me tell you the story. I don't know in what year, but a so-called op-ed article appeared in the San Francisco Chronicle, authored by a senior fellow at Stanford, advancing the Duesberg theory. My colleagues Mike Ascher and Chip Sheppard and I responded with a letter to the San Francisco Chronicle[3].

I don't know how that letter came to the attention of the editor of Nature--an English-based medical journal--but it did, and we were invited by the editor of Nature to write

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[1] W. Winkelstein, "Some remarks on causal inference based on data from the San Francisco Men's Health Study" (unpublished). Presented at the 75th annual meeting of the Pacific Division of the AHAS, June 21, 1994, San Francisco.

[2] Duesberg letter to Nature, April 10, 1993.

[3] W. Winkelstein, Letter to the Editor, San Francisco Chronicle, September 14, 1992, p. A20.

a commentary on Duesberg's position. So, we authored this commentary.[1] My understanding is that our commentary was peer reviewed, which is not necessary for an editorial-type publication, but it's my understanding that the editor of Nature sent it to several reviewers. It was published.

Unfortunately, in the table, we had categorized the study population as heavy users of drugs and light users. In the text, however, it was very clearly stated that light users included non-users. I mean, that's crystal clear. It's right there. But Duesberg argued that we had fabricated the data; that there were no "nones" in the table.

Let me back up just a bit. In accordance with the custom, the editor of Nature sent the commentary to Duesberg for comment before publication. Duesberg sent back a letter, and then--it's my understanding because we were told by the assistant editor of Nature that this happened--every two or three days he sent a revised letter, finally changing some words--I can't remember what they were--to "fabrication of data."

In the meantime, while he was negotiating, if you will, with Nature, he sent a copy of his letter that he had sent to Nature for publication to one hundred people around the world--scientists, newspaper people, and so forth. That's highly unethical to do. And the editor, John Maddox, of Nature decided not to publish Duesberg's response.

Hughes: Why?

Winkelstein: Well, you'd have to ask the editor precisely why he made that decision. Eventually, he wrote another editorial titled, "Does Duesberg have the right of reply?" in which he explained his position because failing to publish Duesberg's letter caused, as you can imagine, a considerable amount of furor.

In the meantime, Marty Schechter and his colleagues in Vancouver published an article in Lancet on drug use and AIDS. Their findings, based on their Vancouver study, were precisely the same as ours, except that their data were even better than ours because they had drug use from the time of infection to seroconversion, so they had a very good paper.

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[1] Ascher et al. Does drug use cause AIDS? Nature 1993, 362(6416):103-104.

Duesberg wrote a letter to Lancet criticizing their paper--rejecting their findings--and repeating charges of fabrication of the San Francisco data, and also his criticism of our paper, to which, of course, we responded in Lancet, as did several other people.

Winkelstein's Reaction to the Fraud Charge

Winkelstein: I was, naturally, very upset at being accused of scientific fraud because there was no fraud; there was no fabrication. And we were being accused of that widely by Duesberg. He was repeating the charge every time he appeared on a platform anywhere.

Hughes: Now, in terms of the profession of science, is there any charge that could be more damaging than scientific fraud?

Winkelstein: I suppose rape, murder, or something like that.

Hughes: I meant in terms of your profession.

Winkelstein: To a scientist, I don't know much worse than being accused of scientific fraud. The only thing worse is to have committed scientific fraud. But Duesberg didn't raise this charge in the usual channels. I mean, he didn't go to the officials of the university and say, "This professor is committing scientific fraud." He just repeated it.

Hughes: Yes.

Winkelstein: Well, the NIH has rules about charges of scientific fraud, so even though Duesberg didn't bring charges of scientific fraud, I went to the UCB vice chancellor, Ian Carmichael, and said, "I want you to investigate his charges. He's making charges and I want to be investigated." The university at first was a big reluctant. I mean, who wants to get involved in this? And no charge had been formally made to them.

So then I wrote to the vice chancellor and provost in charge of research, asking for an investigation. And I sent with it all the documents I had, which included the letter that Duesberg had written and circulated, the commentary article, and then a series of memoranda in which I had endeavored to get Duesberg to retract the fabrication charge.

I asked Phillip Johnson, a prominent professor of law who was a supporter of Duesberg, to intercede on the basis of fairness and propriety. He wrote me and indicated that he agreed that the charge of fabrication was ill-chosen and that he had spoken to Duesberg and that Duesberg had refused to budge on that. I also wrote to Richard Strohman and asked him to intervene. As far as I know, he did not. He wrote an editorial in The Daily Cal.

Hughes: He never responded directly to you?

Winkelstein: He never responded directly.

Then I wrote directly to Peter Duesberg and said, "I just don't understand how you can accuse me and my colleagues of scientific fraud." And he never responded.

UC's Investigation

Winkelstein: Those documents accompanied my request for an investigation and, in accordance with NIH procedures, then the university conducted an investigation.

The investigation consists of two stages. The first stage is to decide whether there is a case, and the second stage is to investigate if there is a case. So, in the first stage, they appointed a committee--of one, actually--a distinguished professor. He interviewed Dr. Duesberg and he interviewed me and he examined the data. I wrote him a letter saying that of course we would make all of our data available to anyone he wanted. He could look at it. They could have a data run. They could do anything they wanted. I welcomed that. And he conducted his investigation and then he concluded that there was no basis for the charge. He said a generous interpretation is that Dr. Duesberg misinterpreted. Something like that. I can't remember the exact wording. So, that was that.

I don't know whether Duesberg is repeating that charge. I think he has on occasion. That's the story. It took a lot of time, a lot of energy, a lot of wasted emotions, and so forth and so on. It doesn't seem to bother him in the slightest.

More Criticisms from Duesberg

Hughes: Well, Duesberg also criticized the content of your Nature commentary, calling it "worthless for a scientific appraisal of the drug-AIDS hypothesis because it fails:
1. To study the AIDS risk of HIV-positive, drug-free controls,
2. To quantify recreational drug use,
3. To observe drug use long enough to detect toxicity, and,
4. To report AZT use altogether."[1]

Winkelstein's Rebuttals

AIDS Risk in the Control Population

Hughes: He claims that your commentary fails to study the AIDS risk of HIV-positive drug-free controls.

Winkelstein: Wrong. Our study, which he has repeatedly criticized, is based on a probability sample of men. It's the only study in the world that starts out by taking a scientific sample. So, in the sample are represented single men between the ages of 25-54, which was the age range of AIDS at the time the study was designed, regardless of their sexual preference and regardless of their HIV status. Those factors were unknown when the sample was drawn.

After the men were admitted into the study and had received informed consent form and signed them, then they were interviewed, and they were examined, and they were bled, and so forth and so on. And it turned out that, of the 1,034 men in the study, approximately 800 were gay, homosexual, bisexual--whatever you want to call it--and 200 were heterosexuals. At the time of entry into the study, half of the homosexual men--48 percent--were infected, and none of the heterosexual men were infected.

The men have been followed over a period of ten years. At the time the commentary was published, I believe they had been followed for 86 months, I believe. I can't remember

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[1] Letter, from Peter Duesberg to Maxine Clarke, Executive Editor of Nature, March 23, 1992. Private papers of Warren Winkelstein.

the exact number. Of the heterosexual men, during the follow-up period, one became infected. Of the homosexual men seronegative on entry, something like forty-five became infected. Of the 400 men who were positive on entry, approximately half died in the eight-year follow-up, and so that would be roughly 200 men died. Among the seronegative homosexual men, something like eight died. I can't remember the exact number. Among the heterosexual men, something like four died. So, I think right there you have an indication of the strength of the association.

Assessment of Drug Use

Winkelstein: Now, how about the drug use? The drug use was determined at each interview. There were basically two interviews a year. Not everybody attended every session. But most men were followed. Over the eight-year period, we lost less than 10 percent to follow-up, so we knew what happened to them. Drug use was ascertained at each time.

The analysis of drug use was both simple and complicated. The complicated analysis was just referenced in the Nature commentary, in which it said "analysis using each follow-up session gave the same results."

What the analysis showed was what I said before: this study did not pick drug users, non-drug users; it picked a random sample, which then was classified according to drug use. And there was no relationship between drug use and the outcome AIDS when HIV serological status was taken into account. That's what we call a controlled study. The study was controlled for HIV status, as well as for drug use. So, as I mentioned before, there were AIDS cases among non-drug users, or among light drug users, as long as they were HIV-positive. There were no AIDS cases among HIV-negative heavy drug users. So, his claim is not borne out by the data, and anyone is welcome to read the commentary and come to their own conclusions.

AZT and Toxicity

Hughes: His third point is that the study failed to observe drug use long enough to detect toxicity.

Winkelstein: Well, it's true that we didn't analyze for AZT. That's a different issue. For most of the time, AZT was only administered after people got AIDS. I mean, the initial studies of AZT were as a treatment for people who had AIDS, to prolong their life, which, if you recall in the famous O-19 Study which was terminated prematurely, there was a favorable survival.

Now, prophylactic use of AZT was not instituted until 1988 or '89. It was not relevant to the study that we were doing on recreational drugs. And so the study of AZT in our population as a toxic--because Duesberg believes it's toxic --is really not very possible. It just doesn't work that way because most of AZT is given after you have AIDS. How can it cause AIDS when it's given after AIDS has started? So, it doesn't make any sense.

Recreational Drug Use

Winkelstein: Now, what was the other part?

Hughes: His third point is your failure to observe drug use long enough to detect toxicity.

Winkelstein: We did observe recreational drug use throughout the course of the eight-year follow-up, as I mentioned. That's in the commentary. In fact, we published two papers from the San Francisco Men's Health Study, the first two papers, I think, published anywhere in the world on use of AZT by HIV-infected men.[1] In other words, we wanted to know if men were using AZT and other antivirals and other drugs? And our data were used by the National Cancer Institute.

Nature's Decision Not to Publish Duesberg's Response

Hughes: John Maddox, the editor of Nature, chose not to publish a response from Duesberg. In retrospect, do you think that that was an unfortunate decision from the standpoint of providing fuel for Duesberg's and his colleagues' argument

[1] Winkelstein bibliography #153 and #167.

that they were shut out of the normal channels of scientific discourse?

Winkelstein: Well, obviously, Maddox made his position clear in his editorial. My own feeling about it is this: if I were an editor and I received the kind of letter that Duesberg wrote, in which he charged another scientist with fabrication of data, I think I would send it back to him and say, "If you're going to make charges of scientific fraud in my journal, you'd better be prepared to back them up, and I want more evidence than is in this letter."

Secondly, most scientists are supposed to know the ethics of publication. While it may be ethical to show a friend or a colleague some publication--prepublication--like a letter or something, or ask for an opinion, the wide distribution of his letter I believe was unethical and would raise questions about whether it should indeed be published.

So, I think that most of us--and I would include myself, and I think I can speak for my colleagues as well--would have welcomed a response from Duesberg. We would have had an opportunity to rebut. But if you're accused of scientific fraud, we don't welcome that unless you can come forward and give some real evidence. There was no evidence of it.

I've published over 130--maybe 150 now--articles, probably two-thirds of them at least, and probably more, have been peer reviewed, and there have been many times when people have written letters. Very frequently, they've raised points that I missed, or pointed out things that were questionable, or added something to what had been said. I mean, that's part of science. We welcome dialogue. That's important. But in the way he did it, I don't know if it would have contributed anything or would have changed anything.

Further Charges from Duesberg Supporters

Hughes: Well, the Duesberg camp also charged that page proofs of your commentary were sent out prior to publication by NIH. Is that true?

Winkelstein: Not that I know of. I never heard it. That would be very, very unusual. I couldn't imagine that would have been done. Duesberg would have to substantiate that claim.

Hughes: In fact, now that I think about it, I know that at least two offices within NIH were contacted and they denied having sent anything out like that.

Winkelstein: That would be so unusual, I can't imagine it happening.

Hughes: What would be the point of concocting a story which could be easily disproved?

Winkelstein: Well, because by this time Bryan Ellison was involved, and he puts a new dimension on many of the things that have happened. I don't know. That would be my explanation. He's an extremist.

Hughes: You're saying that he carries things further than even Duesberg would carry them?

Winkelstein: That's correct.

Hughes: Well, then there was a letter written on March 20, 1993 from Serge Lang, a mathematician from Yale, to the council of the National Academy of Sciences.[1] He criticized the scientific establishment for handling "purported scientific results concerning AIDS" by press conference. And he gave two examples. The first was Gallo's press conference in April of 1984 in which the AIDS virus--it was not yet called HIV--was announced. Indeed, I believe he is correct there; that conference did precede Gallo's publications in Science.

His second example was your commentary in Nature.

Winkelstein: I responded to him.

Hughes: Do you want to repeat it for the record?

Winkelstein: I can't remember the details.

Hughes: In reference to the Nature commentary, apparently even after the controversy had become public, Duesberg continued to make public addresses repeating this charge.

Winkelstein: Right.

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[1] Serge Lange to the Council, NAS, April 29, 1993.

Michael Ascher Contacts David Perlman

Hughes: Apparently you and Dr. Ascher were understandably concerned, and Dr. Ascher contacted David Perlman.[1]

Winkelstein: Correct.

Hughes: David Perlman is a science reporter for the San Francisco Chronicle.[2] Why did Ascher contact him?

Winkelstein: Well, I guess because Perlman had been sort of monitoring Duesberg over time. I don't know. You'd have to ask Mike exactly why he kept informing Perlman. The Chronicle had published, as I said, the op-ed article and our letter. Over the years, David Perlman had occasionally written articles on Duesberg. I don't know. I guess that was just it.

Hughes: I don't have evidence for this in your papers, but I think it is fairly well known that Perlman supports the HIV hypothesis, and I think from that standpoint has been criticized by the Duesberg camp as presenting slanted reporting on this very issue.

Winkelstein: Well, I don't know. David Perlman is, I think, widely considered to be a very prominent, ethical and good science reporter. I suppose Perlman believes in the infectious disease theory and probably doesn't believe the world is flat either.

American Association for the Advancement of Science Panel on AIDS, June 1994

Hughes: In June of 1994, the western section of the AAAS held a day-long conference on AIDS. There was considerable contention when the program was published because it was heavily weighted in favor of the Duesberg faction. Do you want to comment on what happened at that point?

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[1] FAX, Michael S. Ascher to David Perlman, March 23, 1994.

[2] For Perlman's stories on the AAAS AIDS panel, see: "AIDS Rebels Try to Steal Show," San Fancisco Chronicle, May 26, 1994, and "AIDS Symposium Changes Lineup," Ibid., June 7, 1994.

Winkelstein: Well, here's what happened. Most of us who belong to the AAAS--I sort of hesitate to say what I'm going to say, but it's the truth--when we receive an announcement of a regional meeting, flip it into the waste basket. I mean, I didn't pay any attention to it.

Someone--I think it was Mike Ascher--thumbing through the announcement noticed this session on AIDS. Then he called me and of course I then looked at it. We realized that this was very peculiar and that the entire panel of speakers was basically supporters of the Duesberg position, although later they denied it, but they were. They didn't necessarily support the Duesberg position because Charles Geshekter, who organized the panel-- Oh, wait a minute. There is a little bit of background.

There had been a meeting up in Marysville, or somewhere like that, a few months before, at which Duesberg spoke and the Duesberg position was put forward at--I think--the state college up there. We learned about it because Mike Ascher is in the state health department. He had been contacted by somebody up in that neighborhood in the Central Valley who asked, "What's going on? Who are these people? They're giving these strange views." So, Mike, when he saw the AAAS program announcement, recognized Geshekter's name as being involved in that previous business up there.

So we wrote a letter to Science about this, objecting to it as one-sided. That was again somehow picked up by the United States representative for Nature magazine, which had become involved in a sort of an anti-Duesberg crusade because the Times of London had been publishing articles on Duesberg on the front page of the Sunday Times. And so there was a lot of furor in England over the Duesberg thing.

Hughes: Were the Times articles slanted?

Winkelstein: Oh, yes, They were pro-Duesberg, radically pro-Duesberg. I understand that the guy who wrote the articles has since been fired, and the editor has been moved to a remote office; I think New York City.

Anyway, to come back to the AAAS meeting--I don't remember the exact sequence--but we got in contact with the local organizers, drawing to their attention what was going on, and then of course there was quite a fuss. There was a question as to whether to cancel the meeting, or what to do. And so, finally, the AAAS decided to invite people with alternate views to present so it wouldn't be so one-sided.

They called me and I said, well, I would participate providing Warner Greene, or some other reputable virologist, immunologist, and so forth, would participate. Eventually, they organized this panel which included people from the other side.

Naturally, the organizers of the meeting were rather upset because they had their meeting all organized, and they thought it was unfair and unethical and everything else that they would be interfered with in the full expression of their position. Then the meeting was held, and I thought it deteriorated into a pretty ugly scene at the end.

Representatives of the orthodox position, which would be the alternate position from the original program, made presentations in the morning, along with the original presenters.

At the end of the presentations, Geshekter invited everybody to come up and sit on a panel, even though it was the understanding, I believe, that there was to be no questioning and panel discussion. So, we were all invited up onto the stage, and I guess everybody went.

Hughes: So, that was the first time you had heard of the panel?

Winkelstein: I believe so. I'm a little bit vague on that. Because my wife was ill at that time and in the hospital, I wasn't my complete self, so I'm a little bit confused as to what may have happened.

At any rate, the discussion was sort of rambling, and they received questions from the audience, and then there were interactions between the members of the panel. Kary Mullis asked me to define what an epidemic was, and I started to define an epidemic, and Geshekter said, "We don't want any academic descriptions here." And then Mullis said something like, "There is no epidemic." I can't remember the details.

So, questions were raised to me and to other members of the panel. It wasn't very nice. There was a little shouting going on between, I think, Mullis and me. I'm not quite sure who.

Hughes: What was your motive in participating?

Winkelstein: Well, it was exactly the same as it's been all along. It isn't the fact that those views are unorthodox. That does

not at all bother me. What bothers me is that I think that Duesberg and his supporters are dangerously irresponsible. We're not arguing or discussing a scientific issue, does the sun go around the Earth or the Earth go around the sun? What they are putting forward here is a theory that this is not an infectious disease, that it is not transmitted by sharing of needles and promiscuous sexual activity, and that those activities are unrelated to the transmission of this disease.

This is a deadly disease. It isn't a disease like gonorrhea, which is uncomfortable but can be treated and is usually not life threatening. It's not a disease like herpes, which is uncomfortable and unpleasant, and so forth, but usually not life threatening. This is a disease that kills, and not only does it kill but it kills in a horrible way. It isn't even like lung cancer. Lung cancer is a terrible disease, but after the cancer is giving you symptoms, you die in a month or two.

Here with AIDS, you have a prolonged period of miserable suffering. I mean, this is a horrible, terrible disease. And it's transmissible and it's preventable. So, that's why I find it very difficult to step aside and allow these people to go unresponded to. So, that's my motivation.

Skeptics of the HIV Hypothesis

Phillip Johnson

Hughes: There are two spokesmen in the Duesberg camp who--I guess this is a value judgment on my part--have backgrounds that one could surmise might color their philosophy. One of them is Phillip Johnson, who is known to be a creationist and has published a book on Darwin and evolutionary theory, which I understand debunks the concept of evolution. And then you've just told me that Ellison is an extremist. This leads me to wonder, is there a political agenda, as well as a scientific agenda, in this controversy?

Winkelstein: To argue that drug users get AIDS because they take too many drugs, and that homosexuals get AIDS because they engage in homosexual sexual activities, which is the basic theorem behind that, is whatever you want to call it--racist, or

what? I don't know. I mean, I'm not prepared to get into that kind of thing. I don't know what their motivation is.

My first knowledge of Phil Johnson's involvement was when I was invited to a seminar which he gave over in the [UCB] law school, which I went to, and he sat in an armchair and pontificated that all he wanted to do was get the facts straight. I said that this was not a legal advocacy situation and that the issue should be dealt with by people who were experts. How can a lawyer evaluate the immunological/virological/epidemiological data? I wouldn't pretend to evaluate the torts, or the law, or the legal aspects of the case. As I said before, you wouldn't hire an electrician to repair your toilet: I mean, you hire a plumber. I don't think you would hire a lawyer to evaluate the validity of an infectious disease hypothesis.

Hughes: Have you challenged him?

Winkelstein: Oh, of course. He doesn't agree with me, obviously. But we have a correspondence. There are letters back and forth.

A lot of my friends say, "Oh, he's horrible." Well, he's a human being. I mean, at least you can talk or interact with him. He's just got ideas that I think are terrible.

Richard Strohman

Hughes: You received a handwritten note from Richard Strohman in March of 1993, which said simply, "How can one best begin to sort out those factors other than HIV--in addition to HIV--that do damage to the immune system?"[1]

Winkelstein: I don't know what's gotten into Richard Strohman. The whole purpose of our research, and of most others' research, is to get at the truth as we can find it, so we do the best we can. We're constantly looking for other risk factors for AIDS and we haven't found them. I mean, smoking has a small effect; age has a small effect, a few other things.

We have fourteen scientists. We have virologists, immunologists, internists, clinical pathologists,

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[1] Richard Strohman to Winkelstein, March 26, 1993.

psychologists, epidemiologists, biostatisticians, dentists, pathologists, all these people working on the San Francisco Men's Health Study, looking at all aspects of the data, conducting elaborate laboratory studies, publishing papers. If we found something, do you think we would hide it? No. We would leap forward. If we found, hidden in our data, another cause of AIDS, we would be the first to shout it from the housetops. After all, that would make us even more famous than Peter Duesberg. These arguments make no sense.

We have been working our tails off for years. We've been struggling with NIH to maintain the continuity of our funding. We've worked with our participant advisory committee. We've joined in community efforts. We've written and we've talked and we've done everything we could.

Peter has accused HIV investigators of getting rich. Well, maybe some have, but I can assure you that Dennis Osmond and Jim Wiley and Warren Winkelstein have not made anything except their regular university salaries off of this. We have no hidden agendas, and I don't think we're evil persons.

I've said this before today, and that is that we're profoundly concerned with this terrible epidemic. I'm an epidemiologist, and my life's work is to try to do the best I can for the public health. So, that's where I stand on that issue.

Dissenting AIDS Theories and the Peer Review System

Hughes: Well, this may be flogging a dead horse, but I think Duesberg and his group do play upon fears that are expressed both within and without the scientific community. Harold Varmus, who is head of NIH, has called for a review of the peer review system; there has been some talk that it is, to put it loosely, an old boys network; that what you have is people of like views judging the merit of research.

With this in the background, is there any justification in the claim that--

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Hughes: --the scientific community is shutting out dissenting AIDS theories?[1]

Winkelstein: Well, the simple answer is I don't think so. But I do believe that there is, in general, some difficulty in getting funding for unorthodox and new things.

My own experience over the years is rather interesting. I did very well with my grants in the late fifties and sixties when I was doing my work in Buffalo. In fact, one of my grant applications was used by the National Heart Institute as a model. They used to send it out to people to show them how to do a grant application.

After I came to California, I had seven applications in a row turned down because they did not fit the paradigm that was popular at the time. In fact, one of the NIH staff one day said to me, "If you would just put in a nice case-control study, we've love to fund you." Which I interpreted to mean, "If you'd just put in a nice study to study the relationship between cholesterol and heart disease, we'd love to fund you," a subject which has been studied over and over so many times it's hardly worth repeating.

So, it is true that under the peer review system there is some reluctance to fund studies for which the reviewers are not very sure that there will be a positive result, and that to some extent may be a deterrence to new ideas. On the other hand, it seems to me that the record of NIH since the Second World War is pretty fantastic.

The same thing on publishing articles. Sometimes we miss something that's quite important but, overall, it seems to me that things work very well. And I say that having been turned down as often as I've been approved for grants over the years.

Hughes: You're not aware of any organized effort to keep dissenting viewpoints in regards to the AIDS issue out of circulation?

Winkelstein: Absolutely not. In fact, my colleagues Mike Ascher and Chip Sheppard have advanced an unorthodox view about the natural history of the infection, and they've argued back and forth and presented in meetings. They get invited all around the world because they have a different point of view. Tony

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[1] Richard Strohman. Scientific community has shut out dissenting AIDS theories. The Daily Californian, April 13, 1993, p. 4

Fauci has encouraged them even though for a long time their views were quite opposed to his views.

In fact, despite what I said about new ideas, new ideas also are attractive for funding, and so both things are happening at the same time. One is that perhaps review committees are sometimes reluctant to approve new studies, or new directions, or new questions, and so forth. On the other hand, if new ideas come forward, under other circumstances they're very attractive, and people jump on them and want to investigate them.

Duesberg's Failure to Focus on His Area of Scientific Expertise

Hughes: Do you think that's been true consistently through the history of the AIDS epidemic?

Winkelstein: Let me say one thing about Duesberg. There were aspects of Duesberg's original criticism that many scientists thought were extremely valid. I think that Duesberg did himself a lot of damage by getting into areas where he was clearly inept, like epidemiology. If he had stuck to the virological problems and tried to solve them, got involved in the research, I think that we might be in an entirely different situation.

I think if you read his first article on AIDS--I think it was in Cancer Research--you'll find it divided essentially into two sections: one in which he criticizes the molecular biology, and the second one where he evokes a whole lot of spurious epidemiology. I've heard my colleagues who are virologists and immunologists and pathologists talking about this: if he had stuck to that part of his criticism concerning molecular biology and developed it and gotten involved in research, I think that the whole story would have been different.

Hughes: Have you noticed an evolution of his argument?

Winkelstein: No.

Hughes: It's stayed pretty constant?

Winkelstein: As far as I can see. He still makes statements like, "Infectious diseases are randomly distributed." That makes

no sense at all. The characteristic of all diseases are that they're nonrandomly distributed in populations. He says, "The fact that there's an unequal sex distribution [of AIDS infection] in the United States argues against an infectious disease interpretation." That's wrong. It argues in favor of it.

Hughes: Also, he argues that not only is HIV not a sufficient cause of AIDS, but it's not even a necessary cause. Harry Rubin said at the June 1994 AAAS meeting that he considered the possibility that HIV was not in itself sufficient to cause HIV disease, that there may be cofactors. The establishment is now pretty much coming around to that view.

Winkelstein: That's a standard view. All of us believe that there are only a few infectious agents--measles is one--which require no cofactors. Take tuberculosis, a classic example of a disease which is influenced by cofactors. Tuberculosis is caused by the tubercle bacillus. I don't think even Peter would deny that. But whether you get tuberculosis--the disease--is going to be conditioned by your nutrition, your activities, your stress, your sex, your genes. Most diseases are influenced by cofactors.

These people who throw this word "cofactors" around--Richard Strohman is one of the prominent ones--all it does to me is to demonstrate their ignorance of epidemiology. Epidemiology is partially based on the concept of multifactorial causation. Whether it be infectious diseases or chronic diseases, I don't believe, with very few exceptions, that a disease is caused by a single factor; lots of factors are necessary.

Hughes: Well, what more would you like to say on the subject?

Winkelstein: I don't know. As one of our graduate students once said in the Ph.D. qualifying exam, "If you ain't got no more questions, I ain't got no more answers."

General Remarks on the AIDS Epidemic

Hughes: Is there anything you want to say about AIDS in general?

Winkelstein: If we didn't know it before, we now know what most thoughtful epidemiologists have known for a long time, and that is that infectious diseases remain a major problem for

the human population. It's unlikely that AIDS will be the last new epidemic. There will emerge other epidemics. Whether they are going to be as drastic as this one, who knows?

There was an epidemic of optic neuralgia in Cuba last year, with 50,000 cases. People are generally unaware of that. Epidemics are constantly occurring. I don't know if HIV and AIDS teach us that; it just reaffirms that. So don't be surprised if something else crops up.

Hughes: Are there lessons that the AIDS epidemic has taught us that are perhaps unique?

Winkelstein: Well, I don't know if they're unique, but clearly we were slow to react to this epidemic. It's always so easy to say in retrospect, "We should have reacted stronger earlier." Whether it would have made any difference or not, I have no idea. But the epidemic was slow in developing. It was over a year before we got a name for this thing that was happening. Actually, they isolated the causal agent fairly fast. The first recognized cases were in the early eighties, and the French had the virus in 1983, and I guess we had it in '83, and it was announced in '84. And that's probably pretty good because of the obscure nature of this agent.

Hughes: Do you think it made a difference--I'm talking about the slow response--that the early cases were largely in the homosexual population?

Winkelstein: It probably did. Yes. We know that the CDC was asking for money; the administration was resisting giving the money. CDC recognized the severity much faster than the Reagan administration was willing to recognize it. So, I'm sure that that was a factor.

Hughes: Well, I thank you very much.

Winkelstein: Well, I thank you. It's been a pleasant experience.

Final Typed by Grace Robinson

TAPE GUIDE--THE SAN FRANCISCO AIDS EPIDEMIC: THE MEDICAL RESPONSE, 1981-1984, VOLUME VII

Interview with Warren Winkelstein

APPENDIX

O "Controversial AIDS Theories Debated at Forum in S.F.," San Francisco Chronicle, June 22, 1994, p. A 7 238

P "Some Remarks on Causal Inference Based on Data from the San Francisco Men's Health Study", Warren Winkelstein, Jr., June 21, 1994. (Winkelstein personal collection) 239

APPENDIX A: AIDS CHRONOLOGY[1]--by Sally Smith Hughes

1968-1970 David Baltimore and Howard Temin independently discover reverse transcriptase, a marker for retroviruses.

1974 Charles Garfield founds Shanti Project to provide free volunteer counseling to people with life-threatening illnesses.

1976 Robert Gallo isolates T-cell growth factor (interleukin-2), allowing T-cells to be cultured in vitro.

1978 San Francisco Mayor George Moscone assassinated; Dianne Feinstein becomes mayor.

1980 Gallo demonstrates that retroviruses (HTLV-I and HTLV-II) can infect humans.

1981:

February Michael Gottlieb, UCLA, diagnoses Pneumocystis carinii pneumonia [PCP] in two homosexuals.

March Gottlieb diagnoses another case of PCP in a homosexual.

Sandra Ford, drug technician for Centers for Disease Control [CDC], officially notes increase in requests for pentamidine, for treatment of PCP.

Constance Wofsy diagnoses CNS toxoplasmosis in gay patient at San Francisco General Hospital [SFGH].

April Gottlieb diagnoses two more cases of PCP in homosexuals.

Two Kaposi's sarcoma [KS] cases in San Francisco and Stanford announced at UCSF dermatology grand rounds.

May/June Donald Abrams and others see cases of PCP in gay men at SFGH.

June 6 CDC's Morbidity and Mortality Weekly Report [MMWR] publishes Gottlieb and Wayne Sandera's report on PCP in 5 gay men.

June 8 First meeting of CDC Kaposi's Sarcoma/Opportunistic Infection [KSOI] Task Force, headed by James Curran. Purpose to characterize syndrome and determine frequency, risk, and etiology. Surveillance and case file for KS and PCP initiated.

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[1] This chronology is an ongoing working draft created to assist the oral history project; its focus is San Francisco and its accuracy contingent upon the many sources from which it was derived. Revised February 1998.

June (late) First case of KS diagnosed in gay man at SFGH.

July City of San Francisco establishes reporting and case registry system for KSOI.

July 3 First press report of syndrome appears in New York Times.

MMWR reports Kaposi's sarcoma in 26 gay men.

July 13 First article on KS in New York Native.

August CDC requires health departments to notify CDC of all KSOI cases.

Aug. 28 MMWR reports first heterosexuals, including first female, with KSOI.

September CDC begins case-control study with 50 gay KSOI patients and 120 "healthy" gay ccontrols to determine factors in homosexual environment possibly causing KSOI.

Sept. 15 CDC and National Cancer Institute sponsor workshop on KS and opportunistic infections. CMV leading candidate for cause.

Sept. 21 First KS Clinic and Study Group held at UCSF.

October Friedman-Kien et al. begin study of clinical course of KS in gay men.

November Shanti begins to focus on psychosocial problems of people with KSOI.

December First clinical descriptions of immunosuppression in IV drug users.

John Ziegler, Conant and Paul Volberding receive $50,000 from American Cancer Society to support KS Clinic at UCSF; first grant awarded for AIDS.

CDC investigators suspect that causal agent of AIDS is infectious but cannot provide irrefutable evidence. Others support "lifestyle" hypothesis.

Reagan proposes massive cuts in CDC budget.

Dec. 9 Marcus Conant passes out flyers on KS at American Academy of Dermatology meeting in San Francisco.

Dec. 10 Durack at Duke suggests amyl nitrites ("poppers") might cause immune dysfunction.

New England Journal of Medicine article links immune deficiency to T4 helper cell/T8 suppressor cell ratio.

1982:

Early 1982	Syndrome is named gay-related immunodeficiency disease--GRID.
January	First case of immune deficiency linked to blood products is reported in a hemophiliac.
	Helen Schietinger becomes nurse-coordinator of KS Clinic at UCSF.
	San Francisco health department makes first request for tax funds to support AIDS prevention and community services; Board of Supervisors appropriates $180,000 for AIDS programs.
April	Congressional subcommittee hearing in Los Angeles on AIDS, Henry Waxman (D-CA), chairman.
May	(Mother's Day) Conant, Frank Jacobson, and Richard Keller write articles of incorporation for Kaposi's Sarcoma Research and Education Foundation, predecessor of San Francisco AIDS Foundation.
May 15	Friedman-Kien et al. publish study showing promiscuity greatest risk factor for KS. Authors support immune overload theory of AIDS causation.
June 18	CDC reports cluster of PCP and KS cases in LA and Orange County, suggesting infectious agent is cause of AIDS.
June 26	UCSF Nursing Services sponsors conference, Kaposi's Sarcoma and Pneumocystis Pneumonia: New Phenomena among Gay Men.
July	CDC, FDA, and National Hemophilia Foundation representatives meet to plan risk evaluation of blood products for hemophiliacs.
July 9	CDC publishes first report of 31 cases of opportunisitic infections in Haitians.
July 13	First international symposium on AIDS, at Mt. Sinai Medical Center, New York, sponsored by Mt. Sinai and New York University schools of medicine.
July 16	MMWR reports first three cases of PCP in hemophiliacs, representing first cases of KSOI caused by blood or blood products.
July 21	KS Foundation operates hotline for advice and referrals regarding AIDS, KS, and opportunistic infections [OIs].
July 27	CDC adopts "acquired immune deficiency syndrome--AIDS" as the official name of the new disease.

Aug. 13 National Cancer Institute [NCI] issues RFA for research on AIDS.

Sept. 24 CDC publishes first official definition of AIDS: a disease due to defect in cell-mediated immunity occurring in people with no known cause for immune deficiency.

First? published use of term "AIDS", in MMWR. Rapid adoption of term thereafter.

October KS Research and Education Foundation contracts with San Francisco Department of Public Health [SFDPH] to provide AIDS education services in San Francisco.

Oct. 29 UCSF Departments of Medicine and Dermatology and Cancer Research Institute sponsor program in medical education, Acquired Immunodeficiency Syndrome and Kaposi's Sarcoma. Almost 200 physicians and scientists attend.

November MMWR suggests that hospital staffs caring for AIDS patients use hepatitis B precautionary measures.

December Shanti makes first in series of contracts with SFDPH to provide counseling services and a housing program for people with AIDS [PWAs].

Dec. 1 House of Representatives votes $2.6 million to CDC for AIDS research.

Dec. 4 CDC presents Blood Products Advisory Committee with evidence of AIDS transmission through blood supply; no official action taken.

Dec. 10 Ammann, Cowan, Wara et al. report first case of possible transfusion AIDS, in MMWR.

Dec. 17 MMWR reports four cases of unexplained immune deficiency in infants.

Late 1982 Most investigators convinced that AIDS is caused by an infectious agent.

Nation's first AIDS specimen bank established in UCSF School of Dentistry, coordinated by KS Clinic.

1983:

Early — New York City health department establishes formal AIDS surveillance program.

Beginning of bathhouse crisis. Formal AIDS infection control guidelines instituted at San Francisco General Hospital.

January — Montagnier, Barré-Sinoussi, and Chermann at Pasteur Institute, seeking to isolate an AIDS virus, begin to grow cells from lymphadenopathy patient.

President of New York Blood Center denies evidence of transfusion AIDS.

Orphan Drug Act becomes law, giving exclusive marketing rights, tax breaks, and other incentives to companies developing drugs for rare diseases.

Jan. 1 — First outpatient clinic dedicated to AIDS (Ward 86) opens, at San Francisco General Hospital.

Jan. 4 — CDC national conference to determine blood bank policy re blood screening for AIDS; no consensus.

Jan. 7 — CDC adds heterosexual partners of AIDS patients as fifth risk group for AIDS.

Montagnier et al. find traces of reverse transcriptase in lymphadenopathy cell cultures.

San Francisco's Irwin Memorial Blood Bank [IMBB] adds medical history questions designed to screen out donors from high-risk groups.

Jan. 14 — National Hemophilia Foundation asks blood and plasma collectors to screen out high-risk donors.

Jan. 19 — Irwin Memorial Blood Bank adds more questions about medical history of potential donors.

February — At Cold Spring Harbor Workshop on AIDS, Robert Gallo suggests that a retrovirus probably causes AIDS and presumes a variant of HTLV-I or HTLV-II.

Feb. 3 — Physicians from UCSF KS Study Group urge IMBB to use hepatitis B core antibody test to screen out blood donors with AIDS.

Feb. 7 — IMBB launches confidential questionnaire designed to detect potential blood donors with AIDS. Bay Area Physicians for Human

Rights urges potential donors to refrain from donating if they have AIDS symptoms.

March — CDC establishes clinical definition of AIDS in attempt to standardize epidemiological surveillance.

UCSF Task Force on AIDS created, mainly to establish infection control policy.

California requires reporting of AIDS cases, but not AIDS -Related Complex [ARC].

Public Health Service [PHS] recommends members of high risk groups reduce number of sex partners.

Mervyn Silverman, SFDH director, forms Medical Advisory Committee on AIDS.

Mar. 4 — MMWR first refers to "high risk" groups: gays with multiple sex partners, IVDUs, Haitians, and hemophiliacs.

CDC states that "available data suggests that AIDS is caused by a transmissible agent."

Mar. 17-19 — New York University sponsors AIDS symposium.

Mar. 24 — FDA issues blood donor screening guidelines.

April — Congressman Phillip Burton dies; Sala Burton eventually elected to his seat.

City of San Francisco and Shanti open hospice-type care center for neediest AIDS patients.

Conant, Volberding, John Greenspan, Frank Jacobson, and others persuade Willie Brown to ask for $2.9 million in state funding for AIDS research.

April 11 — Date NCI officials later cite as when NCI became committed to finding AIDS etiology.

April 14 — Irwin Memorial Blood Bank [IMBB] adds donor sheet designed to screen out donors at high risk for AIDS.

April 26 — Recall of San Francisco Mayor Feinstein, supported by White Panthers and some gay groups, fails.

May — NIH announce $2.5 million for AIDS research. NCI and NIAID issue RFA [Request For Applications] for research on an infectious agent.

Heat treatment to reduce infectious agents in transfused blood approved by FDA.

San Francisco health department issues first brochure on AIDS.

Feinstein declares first week in May AIDS Awareness Week.

May 2 "Fighting for our Lives" candlelight march in San Francisco to bring attention to AIDS; similar march in NYC.

May 6 Journal of the American Medical Association [JAMA] press release: "Evidence suggests household contact may transmit AIDS."

May 12 UCSF announces receipt of $1.2 million for AIDS research; Paul Volberding, principal investigator

May 20 Montagnier publishes discovery of "T-cell lymphotrophic retrovirus," later called lymphadenopathy-associated virus (LAV).

May 23 San Francisco Board of Supervisors votes $2.1 million for AIDS programs, $1 million of which is for out- and inpatient wards at SFGH.

May 24 Edward Brandt, Assistant Secretary of Health, declares AIDS research #1 priority.

May 31 Health department director Mervyn Silverman, backed by Feinstein and San Francisco Board of Supervisors, requires city bathhouses to post public health warnings about contracting AIDS.

June UC issues guidelines to protect AIDS patients and health workers.

San Francisco Men's Health Study begins to recruit participants.

Feinstein chairs first U.S. Conference of Mayors Task Force on AIDS.

July California legislature approves $2.9 million for AIDS research.

Donald Abrams begins work at SFGH AIDS Clinic, bringing 200+ lymphadenopathy patients from UCSF.

July 26 12-bed inpatient Special Care Unit (Ward 5B) opens at SFGH--first dedicated AIDS hospital unit in U.S.

July 28 Universitywide Task Force on AIDS created to advise UC president on guidelines for and coordination of state-supported AIDS research at UC.

August — Willie Brown, Rudi Schmid, Conant and other AIDS researchers criticize UC for delays in releasing state funds for AIDS research.

September — At Cold Spring Harbor NCI meeting on human T-cell leukemia retroviruses, Montagnier et al. report LAV-like viruses in 5 lymphadenopathy patients and 3 AIDS patients, selective affinity of LAV for CD4 helper lymphocytes, and evidence of similarities between LAV and lentivirus causing equine infectious anemia. Gallo presents findings of HTLV-I in 10% of AIDS patients; doubts LAV is retrovirus.

UC states that there is no scientific reason for healthy medical personnel to be excused from caring for AIDS patients.

Bureau of Infectious Disease Control, SFDPH, begins active surveillance of AIDS cases in San Francisco.

Sept. 13 — Montagnier sends Gallo sample of lymphadenopathy-associated virus [LAV].

Sept. 21 — UCSF Task Force on AIDS publishes infection control guidelines for health care workers caring for AIDS patients.

November — KS Research and Education Foundation contracts with State of California Department of Health Services to provide information and referral services on AIDS to other counties.

Mika Popovic in Gallo's lab discovers method for growing AIDS virus in T-cells.

San Francisco Department of Public Health asks for legal option to make baths off-limits to PWAs. Lawyers decide that medical uncertainties about AIDS prevent such action.

Jay Levy obtains six viral isolates from AIDS patients but decides not to publish until further proof.

December — Pasteur Institute applies for U.S. patent on diagnostic kit based on ELISA test for LAV antibodies.

Feinstein votes against live-in lover legislation, angering gay community.

AIDS Clinical Research Centers established with state funding at UCSF and UCLA to collect clinical and laboratory data.

National Association of People with AIDS formed.

Entry "AIDS" added to Cumulated Index Medicus.

Council of State and Territorial Epidemiologists passes resolution making AIDS a reportable condition.

Hospice of San Francisco contracts with SFDPH to include AIDS patients in its care of terminally ill.

1984:

January — Annals of Internal Medicine reports case of heterosexual transmission of AIDS before overt manifestation of disease (hemophiliac to wife).

American Red Cross, American Association of Blood Banks, and Council of Community Blood Centers oppose proposal to screen out high-risk groups from blood donor pool.

Jan. 6 — CDC updates its definition of AIDS.

Jan. 12 — NEJM publishes CDC documentation of first 18 transfusion-associated AIDS cases.

February — Chermann in talks in U.S. states that French have discovered AIDS virus.

March — President of New York Blood Center continues to deny HIV transmission by blood.

Larry Littlejohn, gay activist, sponsors San Francisco ballot initiative to close baths.

Mar. 2-4 — 19th Annual San Francisco Cancer Symposium, "Cancer and AIDS". Conant, Abrams, Wofsy, Ziegler, Volberding speak.

March 26 — Government allots $1.1 million to develop AIDS antibody test to seven institutions, including Irwin Memorial and Stanford blood banks.

April — Feinstein issues first formal statement that Silverman should close baths. Silverman responds that he will formulate guidelines banning sex activity in baths that spreads AIDS.

NIH applies for patents on Gallo's AIDS antibody test, a diagnostic kit based on Western blot technique.

April 9 — Silverman and state and San Francisco health officials outlaw sex in bathhouses, rather than close them.

April 24 — Margaret Heckler, Secretary of Health and Human Services, announces discovery by Gallo et al. of AIDS virus, that an AIDS test will be available soon, and that a vaccine will be available in 18-24 months. Gallo had not yet published his results.

May	Gallo publishes four reports and Montagnier one, in Science, linking AIDS with a new retrovirus which Gallo calls HTLV-III and Montagnier calls LAV.
	Board of Supervisor's president Wendy Nelder chides Silverstein for "shameful" delays in proposing sex guidelines for baths. Silverman replies that he is waiting for board to transfer authority to regulate baths from police to health department.
	Rock Hudson diagnosed with AIDS.
May 1	IMBB and other Bay Area blood banks begin testing blood for hepatitis B core antigen.
Summer	Silverman orders bathhouse surveillance for unsafe sex.
June	Board of Supervisors committee delays action on giving health department authority to regulate baths until after Democratic National Convention in San Francisco.
	IMBB adopts directed blood donation program.
July	Democratic National Convention in San Francisco.
August	After gay lobbying, Board of Supervisors tables move to give Silverman regulatory power over baths, killing his idea to promulgate sex guidelines for baths.
	Levy et al. isolate virus, ARV, which they claim to cause AIDS.
September	Chiron Corp. announces cloning and sequencing of ARV genome.
	Giovanni Battista Rossi in Italy isolates AIDS virus.
October	Feinstein forms Mayors Advisory Committee on AIDS.
	FDA approves Lyphomed's injectable pentamidine for PCP and gives it orphan drug status.
	Bureau of Communicable Disease Control, SFDPH, begins surveillance of average monthly AIDS bed census.
Oct. 9	Silverman closes baths and private sex clubs as "menace" to public health. Baths reopen hours later.
November	Gallo et al. clone HTLV-III.
Nov. 28	San Franciso Superior Court Judge Roy Wonder rules baths can remain open if monitored for safe sex practices every 10 minutes.

December — Montagnier et al. report cloning of LAV; they also report CD4 molecule as LAV receptor.

Silverman resigns as director of SFDPH.

90 reported cases of transfusion AIDS; 49 reported cases of Factor VIII hemophilia cases.

CDC recommends use of heat-treated blood products for hemophiliacs; other specialists differ. Heat-treated blood products become commercially available.

National Kaposi's Sarcoma Reasearch and Foundation renamed San Francisco AIDS Foundation.

Dec. 26 — Simon Wain-Hobson, Pierre Sonigo, Olivier Danos, Stewart Cole, and Marc Alizon at Pasteur Institute publish LAV nucleic acid sequence in Cell.

1985:

January — Gallo et al. publish full nucleic acid sequence of HTLV-III.

Jan. 14 — Irwin Memorial Blood Bank prohibits males having more than one male sex partner to donate blood.

February — FDA approves Gallo's AIDS diagnostic kit based on Western blot technique.

Feb. 1 — Paul Luciw, Jay Levy, Ray Sanchez-Pescador et al. at Chiron publish ARV nucleic acid sequence.

Feb. 7 — Dan Capon, M.A. Muesing et al. at Genentech publish ARV nucleic acid sequence.

March — San Francisco County Community Consortium founded for community-based AIDS drug testing.

March 2 — FDA approves Abbott Laboratory's commercial test for AIDS. Red Cross contracts with Abbott, one of five companies supplying test, and in days phases in test. Britain and France delay testing six months to introduce their own antibody tests.

March 3 — IMBB introduces genetically engineered hepatitis B antibody core test.

March 4 — First International Conference on AIDS, Atlanta

March 6 — IMBB institutes anti-AIDS virus antibody test, the first blood bank in U.S. to do so.

March 14 — San Francisco Chronicle reports army study showing AIDS transmission through heterosexual contact.

Spring — California legislature and Gov. Deukmejian approve bill banning HIV antibody testing without subject's written informed consent, except at test sites where testing is anonymous. Bill also bars employer and insurance company discrimination on basis of AIDS status. $5 million appropriated to establish HIV community test sites. Disclosure of test results to third party must be improved in writing by test taker.

April — CDC drops Haitians from high risk groups for AIDS.

May — US Patent Office awards patent on Gallo's antibody test.

Summer — AIDS diagnostic kits using ELISA become commercially available. California law mandates every county to offer AIDS test at public health centers; guidelines for preserving confidentiality.

June — American Association of Blood Banks, American Red Cross, Council of Community Blood Centers agree not to begin "look back" program to identify people who have received AIDS-infected blood.

National Institute of Allergy and Infectious Diseases [NIAID] creates first AIDS Treatment Evaluation Units, predecessor to AIDS Clinical Trial Groups (ACTGs).

California public health clinics begin testing for AIDS.

June 24 — IMBB adds bar codes for confidential exclusion of blood units.

September — Mathilde Krim and Michael Gottlieb found American Foundation for AIDS Research [AmFAR], merging AIDS Medical Foundation of New York and National AIDS Research Foundation of Los Angeles.

Martin Delaney and others found Project Inform.

October — Public's awareness of AIDS rises with Rock Hudson's death.

Congress allots $70 million to AIDS research day after Hudson's death.

December — Pasteur Institute sues for share of royalties on AIDS antibody test.

CDC first considers vertical transmission of AIDS virus; advises infected women to "consider" delaying pregnancy until more known about perinatal transmission.

CDC contracts with San Francisco AIDS Foundation to develop materials for anonymous AIDS testing sites.

Late in year Department of Defense announces that new recruits will be screened for AIDS and rejected if positive.

Third UC AIDS Clinical Research Center founded at UCSD. Goals of three centers broaden to include rapid evaluation of new therapeutic agents.

13-year-old Ryan White, a hemophiliac with AIDS, is barred from school in Indiana.

CDC expands surveillance definition, in light of HIV antibody test.

KEY PARTICIPANTS
in San Francisco AIDS History, 1981-1984

Appendix B

*[1]Donald A. Abrams, M.D., AIDS clinician and member of original AIDS physician team at San Francisco General Hospital (SFGH); early research on AIDS-associated lymphadenopathy (swollen lymph glands); organizer of County Community Consortium.

*Arthur J. Ammann, M.D., pediatric immunologist at University of California, San Francisco (UCSF); conducted early studies of AIDS-associated immune deficiency in adults and children; reported first case of transfusion AIDS; currently head of a pediatric AIDS foundation.

Francoise Barré-Sinoussi, retrovirologist at Pasteur Institute and member of team which isolated AIDS virus.

Edward N. Brandt, Jr., M.D., Ph.D., Assistant Secretary for Health, U.S. Department of Health and Human Services, 1981-1984.

Conrad Casavant, immunologist in Department of Laboratory Medicine and associate director of Clinical Immunology Laboratory at UCSF; died of AIDS in 1987.

Jean-Claude Chermann, retrovirologist at Pasteur Institute and member of team which isolated AIDS virus.

*Marcus A. Conant, M.D., clinical professor at UCSF, and dermatologist with private AIDS practice; diagnosed first case of Kaposi's sarcoma in San Francisco; founder of first AIDS clinic (at UCSF); medical activist at local, state, and federal levels.

James W. Curran, M.D., M.P.H., epidemiologist and director of AIDS research at Centers for Disease Control (CDC), Atlanta, Georgia.

William Darrow, CDC sociologist.

Larry Drew, virologist at Mt. Zion Hospital, San Francisco.

*Selma K. Dritz, M.D., M.P.H., epidemiologist at San Francisco Department of Public Health (SFDPH); tracked early AIDS cases in San Francisco; addressed medical and community groups on AIDS recognition and prevention.

Gaetan Dugas, French-Canadian airline steward who was among first to be diagnosed with AIDS; sometimes mistakenly referred to as "Patient Zero" and held responsible for early dissemination of AIDS.

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[1] The asterisk indicates that the individual has been interviewed for the AIDS Medical Response oral history series.

Edgar Engleman, M.D., medical director of Stanford University Hospital blood bank.

Anthony S. Fauci, M.D., director of AIDS activities at National Institute of Allergy and Infectious Diseases, later director of Office of AIDS Research, currently director of NIAID, National Institutes of Health (NIH).

*Donald P. Francis, M.D., D.Sc., epidemiologist and virologist at CDC in Phoenix and Atlanta; conducted early epidemiological and virological studies of AIDS; later became CDC advisor on AIDS to California Department of Health Services; current director of research on AIDS vaccines at a biotechnology company.

Robert Gallo, M.D., retrovirologist at National Cancer Institute, NIH, involved in controversy with Pasteur Institute over isolation of AIDS virus and patent rights to HIV test.

*Deborah Greenspan, D.D.S., D.Sc., clinical professor of oral medicine at UCSF; identified AIDS-associated hairy leukoplakia; instrumental in establishing infection control procedures in dentistry.

*John S. Greenspan, D.D.S., Ph.D., professor of oral biology and oral pathology at UCSF; organized and directs UCSF AIDS specimen bank; current director of UCSF AIDS Clinical Research Center.

Margaret Heckler, Secretary of U.S. Department of Health and Human Services, 1983-1985.

Harold Jaffe, epidemiologist with the AIDS program at CDC.

*Jay A. Levy, M.D., virologist and professor of medicine at UCSF; second to isolate AIDS virus; devised early AIDS diagnostic test and heat treatment to rid blood of HIV.

Luc Montagnier, virologist and member of Pasteur Institute team which isolated AIDS virus.

*Andrew R. Moss, Ph.D., M.P.H., epidemiologist at SFGH; conducted early epidemiological studies of AIDS in San Francisco showing high incidence in gay community; later work focused on AIDS incidence in drug users and homeless.

*Herbert A. Perkins, M.D., scientific director (later president) of San Francisco's Irwin Memorial Blood Bank; involved in formulating national blood bank policy regarding blood screening for HIV; currently represents blood bank in legal cases associated with transfusion AIDS.

*Merle A. Sande, M.D., professor of medicine and chief of medical services, SFGH; chairman of AIDS advisory committees at university, health department, and state levels.

Randy Shilts, journalist who covered AIDS for San Francisco Chronicle; author of And the Band Played On: Politics, People, and the AIDS Epidemic; died of AIDS in 1994.

*Mervyn F. Silverman, M.D., M.P.H., director, San Francisco Department of Public Health; center of controversy over closure of San Francisco bathhouses; current director of American Foundation for AIDS Research.

*Paul A. Volberding, M.D., oncologist and chief of AIDS Services, SFGH; member of original AIDS physician team at SFGH; prominent AIDS clinician.

Girish Vyas, Ph.D., professor of laboratory medicine, UCSF.

*Warren Winkelstein, M.D., M.P.H., epidemiologist at University of California School of Public Health; director of early on-going epidemiological study of AIDS (San Francisco Men's Health Study); member of panel deciding in June 1994 to disprove expanded clinical trial of two AIDS vaccines.

*Constance B. Wofsy, M.D., infectious disease specialist at SFGH; member of original AIDS physician team at SFGH; authority on Pneumocystis carinii pneumonia and women with AIDS.

*John L. Ziegler, M.D., oncologist at Veterans Administration Medical Center, San Francisco; authority on AIDS-associated lymphoma and Kaposi's sarcoma.

Biographical Sketch - Warren Winkelstein, Jr.

Dr. Warren Winkelstein Jr. received his undergraduate degree from the University of North Carolina at Chapel Hill in 1947. He received his medical education while serving in the U.S. Army, graduating from Syracuse University in 1947. After an internship at the Charity Hospital in New Orleans, he became an apprentice epidemiologist in the New York State Department of Health and received the Master of Public Health degree from Columbia University in 1950. During the Korean War, 1951-1953, he served in the Public Health Service on assignment to the U.S. Technical and Economic Mission to Cambodia, Laos, and Viet Nam, where he directed a public health assistance program based in Hanoi. He had joined the Erie County Health Department in Buffalo in 1950, and except for his overseas service, served in that Department in various capacities (district health officer to first deputy commissioner) until 1962. In that year he received a Career Development Award from the N.I.H. and became a full-time faculty member of the Medical School of the State University of New York at Buffalo. In 1968 he left Buffalo to join the faculty of the School of Public Health of the University of California at Berkeley where he continues his professional activities. He served as Dean of that School from 1972 to 1981.

His research interests have spanned a wide spectrum of issues. He participated in the 1954 Poliomyelitis Vaccine Field Trial and, subsequently, carried out early field trials of both inactivated and live-attenuated measles vaccines. With colleagues from the Department of Pediatrics in Buffalo, he was among the first to describe the epidemiology of outbreaks of enteric cytopathic human orphan virus infection. In the early 1960's, he turned his attention to non-infectious diseases, carrying out pioneering studies of the disease effects of air pollution and the determinants of blood pressure levels. After moving to California, he conducted epidemiological studies of various cancers and was among the first to point out a causal association between smoking and cancer of the uterine cervix. In 1983, he joined with a multi-disciplinary team from various Bay Area medical institutions, to study the HIV/AIDS epidemic. In recent years, he has completed biographical studies of Abraham M. Lilienfeld, Edward Jenner, and John Snow. He has published more than 150 articles and chapters, and one book.

Dr. Winkelstein has received many awards and honors. Among them are: M.D., cum laude (1947), Career Development Award from the National Heart Institute (1962), election to the Institute of Medicine of the National Academy of Sciences (1989), the Abraham Lilienfeld Award of the American Public Health Association (1992), and election to fellowship in the American Association for the Advancement of Science (1993). He received "distinguished alumnus" awards in 1989 from both the University of North Carolina at Chapel Hill and Syracuse University. In 1991, he received the Berkeley Citation, the highest honor conferred by the campus on its faculty. In 1997, he was elected an Honorary Fellow of the American College of Epidemiology.

Dr. Winkelstein, and wife Veva, live in Point Richmond, Cal.

CURRICULUM VITAE
(Revised: 2 March 1998)

Warren Winkelstein, Jr., M.D., M.P.H.

BIRTHPLACE & DATE: Syracuse, New York, 1 July 1922

CITIZENSHIP: United States of America

FAMILY STATUS: Married, three children (Wife: Veva Kerrigan Winkelstein)

RESIDENCE: 560 Washington Avenue
Point Richmond, CA 94801
Tel: (510) 236-7393

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University of California
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International Environmental Epidemiology Institute
560 Washington Ave.
Point Richmend CA 94801
Telephone: (510) 236-7393
FAX: (510) 235-1195

EDUCATION:

B.A.: University of North Carolina 1943

M.D.: (cum laude): Syracuse University 1947

M.P.H.: Columbia University 1950

POSTGRADUATE TRAINING:

Internship: Charity Hospital of Louisiana at New Orleans 1947-194

Apprentice Epidemiologist: N.Y.S. Dept. of Health 1948-1949

Research Fellow, Department of Epidemiology, Roswell Park Memorial Cancer Institute, Buffalo, N.Y. 195
1957

PROFESSIONAL QUALIFICATIONS:

Medical Licensure: New York, Louisiana

Diplomate: American Board of Preventive Medicine

MILITARY SERVICE:

U.S. Army 1944-1945
U.S. Public Health Service 1951-1953
U.S. Public Health Service (Inactive Reserve;
Permanent Grade: Medical Director) 1953-1982

POSITIONS:

County District Health Officer, Erie County Health Department, Buffalo, N.Y. 1950-1951

Regional Representative, Public Health Division, Special Technical and Economic Mission to Cambodia, Laos, and Viet Nam (Mutual Security Agency), Hanoi, Viet Nam 1950-1951

Director, Division of Communicable Disease Control, Erie County Health Department, Buffalo, N.Y. 1953-1956

Chief, Dept. of Epidemiology, Chronic Disease Research Institute of the University of Buffalo, N.Y. 1957-1963

First Deputy Commissioner, Erie County Health Dept., Buffalo, N.Y. 1959-1962

Associate Professor (Epidemiology), Dept. of Preventive Medicine, State University of New York at Buffalo, School of Medicine 1962-1964

Professor, (Epidemiology) Dept. of Preventive Medicine, State University of New York at Buffalo, School of Medicine 1964-July 1968

Assistant Managing Editor American Journal of Epidemiology 1965-1975

Professor of Epidemiology, Department of Biomedical and Environmental Health Sciences, School of Public Health, University of California, Berkeley July 1968-Present

Associate Dean for Student and Academic Affairs, School of Public Health, University of California, Berkeley May 1970-June 1971

Acting Dean, School of Public Health, University of California, Berkeley July 1971-July 1972

Dean, School of Public Health, University of California, Berkeley Sept 1972-Dec 1981

Program Head, Epidemiology Program, School of Public Health, University of California, Berkeley July 1987-1990

Acting Director, International Environmental Epidemiology Institute	1994-Present

TEACHING:

Assistant (Part-time) State University of N.Y. at Buffalo	1953-1954
Instructor (Part-time) " " " "	1954-1955
Associate (Part-time) " " " "	1955-1956
Assistant Professor (Part-time) " " "	1956-1962
Associate Professor (Full-time) " " "	1962-1964
Professor (Full-time) " " "	1964-July 1968
Visiting Professor, Dept. of Clinical Epidemiology and Social Medicine, St. Thomas' Hospital Medical School, London	April 1967
Professor, (Full-time) School of Public Health, University of California, Berkeley	July 1968-June 1991
Professor (Emeritus), U.C. Berkeley	July 1991-Present
Adjunct Professor, Department of Epidemiology School of Public Health, University of Michigan	July 1993-1997
Professor in the Graduate School, U.C. Berkeley	Sept. 1995-Present

HONORS AND AWARDS:

M.D. (Cum Laude) Syracuse University	1947
Special Research Fellow, National Heart Institute (PHS)	1956-1957
Buswell Research Fellow, University of Buffalo	1958-1959
Research Career (Development) Program Award HE-K3-6566 National Heart Institute (PHS)	1962-1968
Gold Medal, National University of Ascuncion, Ascuncion, Paraguay	May 1963
Citation, New York State Air Pollution Control Board	1968
Delta Omega	1968
Distinguished Alumnus Award (Gold Headed Cane), Syracuse Medical Alumni Association	1987
Institute of Medicine	1989
Distinguished Alumnus, University of North Carolina at Chapel Hill	1989
Berkeley Citation	1991
Abraham Lilienfeld Award, American Public Health Association	1992

Fellow of the American Association for the Advancement of Science 1994
Honorary Fellow of the American College of Epidemiology 1997

PROFESSIONAL ORGANIZATIONS: (current)

American Public Health Association (Fellow)
American Association for Advancement of Science
American College of Preventive Medicine (Fellow)
American Epidemiologic Society
Society For Epidemiological Research
International Epidemiological Association
International Environmental Epidemiology Society

MAJOR OFFICES IN PROFESSIONAL ORGANIZATIONS:

Secretary, Epidemiology Section, APHA	1967-1970
Member Governing Council, APHA	1967-1970
Executive Committee, Council on Epidemiology, AHA	1968-1971
President, N.Y.S. Academy of Preventive Medicine	1966-1967
Chairman, Executive Committee, Continuing Education Program, Western Branch, APHA	1971-1973
President, American Epidemiological Society	1976-1977

MAJOR COMMITTEE APPOINTMENTS:

Air Pollution Training Committee; Division of Air Pollution, Bureau of State Services, Public Health Service	1962-1965
Heart Disease Control Program Advisory Committee; Division of Chronic Diseases; Bureau of State Services, Public Health Service	1963-1966
Committee on Cardiovascular Disease Epidemiology; Epidemiology Section, American Public Health Association	1963-1967
Scientific Advisory Committee for Mass Mammography Study; Health Insurance Plan of New York (HIP)	1962-1968
Committee for the 1980 Census (Chairman) Epidemiology Section, A.P.H.A.	1965
Subcommittee on Epidemiologic use of Hospital Data, U.S. National Committee on Vital and Health Statistics	1965-1968
Research Committee, American Heart Association	1966-1971
Preventive Medicine Research Study Committee (Chairman), American Heart Association	1968-1971

Consulting Committee on Epidemiology of the Inter-

Society Commission for Heart Disease Resources	1969-1972
National Air Quality Criteria Advisory Committee	1969-1972
Executive Committee, Association of Teachers of Preventive Medicine	1969-1972
APHA Environmental Health Hazard Project: Panel on Arsenic Studies (Chairman)	1975-1976
California Air Resources Board - Research Screening Committee	1974-1976
National Research Council - Commission on Natural Resources: Panel on Effects of Ambient Environmental Quality	1975-1977
National Cancer Institute Ad Hoc Working Group (Epidemiology) on Mammograph Screening for Breast Cancer	1975-1977
American Board of Preventive Medicine, Inc. (Member and Trustee of the Corporation)	1970-78
Panel of Experts on the Archives of Public Health Service Documents Relating to Effects of Nuclear Weapons Testing on Health (Chairman)	1979
Advisory Committee for Epidemiology Los Alamos National Laboratory	1977-1986
Board of Scientific Advisors National Institute of Occupational Safety and Health	1983-1987
Advisory Committee, III International Conference on AIDS	1986-1987
City of Berkeley, AIDS Advisory Committee	1987-1993
Institute of Medicine - Committee to Advise the American Red Cross	1989-1991
California Medical Association - Scientific Advisory Panel on Preventive Medicine and Public Health	1991-1996
California Department of Health Services - Advisory Committee on HIV Vaccine	1992-Present
AIDS Subcommittee of the National Advisory Allergy and Infectious Diseases Council	1993-1994
AIDS Research Advisory Committee, National	

Institute of Allergy and Infectious Diseases 1993-1994

Scientific Advisory Panel, The Gulf War Research Team, Naval Research Center, San Diego CA 1995

Chairman, Scientific Advisory Panel, Electric & Magnetic Fields Program, California Department of Health Services 1997-Present

MAJOR CONSULTANT APPOINTMENTS:

International Cooperation Administration
Surveyed public health problems and health resources in Ivory Coast, Upper Volta, Niger, Dahomey, and Togo. Recommended programs for U.S. Aid. Dec 1960-March 1961

University of Buffalo
Reviewed accomplishments of U.B.-U.S. Agency International Development Contract for assistance to Medical School, National University of Ascuncion, Paraguay. Renegotiated Project Agreement & Contract National University, USAID and University of Buffalo. Jan-Feb 1962

Epidemiology Branch, Communicable Disease Center (PHS)
Assisted in planning and announcing U.S. assistance for smallpox eradication and measles control in 18 countries of West Africa. Visited Upper Volta, Liberia, Fed. Rep. of Cameroon, and Guinea in this connection. Nov-Dec 1965

University of Southern California and National Cancer Institute
Advised on study design for epidemiological study of the etiology of cancer in man and household pets. 1968-1972

World Health Organization
Attended meeting on Research and Reporting Programme of the project, Epidemiology of Drug Dependence, Geneva, Switzerland and assisted with preparatory work in this connection. Served as chairman of of the meeting. 13-17 Sept 1976

State of New York, Department of Health
Development of criteria for rehabilitation of Love Canal Emergency Declaration Area. 1984

National Academy of Sciences
Workshop on the Epidemiology of AIDS. Mar 1986

U.S. Public Health Service, Cool Font Report
A Public Health Service plan for the prevention and control of the AIDS virus. June 1986

WHO Special Program on AIDS

Preparation of standardized methodology
for HIV serosurveys in developing countries. June-July 1987

National Academy of Sciences
Advisory committee workshop on modelling the spread
of HIV infection and incidence and prevalence. Aug 1987

New York State Health Department
Planning for statewide HIV seroprevalence
surveys. Sept 1987

Consultant to the House of Lords Subcommittee on Medical
Research Sept 1987

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G/L Arch AIDS 8-12/83
Winkelstein

UC Joins National Study on AIDS

10/1/83

By David Perlman
Science Editor

The University of California is joining a $15.3 million national study involving thousands of healthy homosexual men in a long-term effort to discover the causes of AIDS and to detect its earliest signs, federal authorities announced yesterday.

Researchers at UC's Berkeley and Los Angeles campuses have been awarded a total of nearly $6 million. Each group will follow the lives of about 1000 gay men over the next four years and to ferret out clues to the deadly acquired immune deficiency syndrome.

The scientists will study the men's lifestyles and psychological makeup, and collect samples of blood, semen and urine for detailed

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UC STUDY OF AIDS

From Page 1

studies of their chemistry, their virus levels and the status of their bodies' immune systems.

The other institutions that will be conducting similar research are Johns Hopkins University in Baltimore, the University of Pittsburgh and Northwestern University Medical School in Chicago. The project is being conducted nationwide by the federal government's National Institute for Allergy and Infectious Diseases.

The range of cities was deliberately chosen because the incidence of AIDS is extremely high in San Francisco and Los Angeles, low in Pittsburgh and Baltimore, and low but rising in Chicago, according to federal health officials.

The study group at Berkeley is headed by James Wiley, assistant director of the Survey Research Center, and Dr. Warren Winkelstein Jr., professor of epidemiology in the UC School of Public Health.

Their $2.9 million government research contract calls for teams of field workers to visit more than 4000 San Francisco households and recruit more than 1000 volunteer participants between the ages of 18 and 54. The participants will come from the 19 census tract areas of San Francisco with the heaviest concentrations of gay men, where most of the city's 271 AIDS cases have been reported so far.

Similar detailed studies will also follow 200 non-gay men from the same areas of the city. They will volunteer to serve as control subjects for the project.

Participants in the study will report to a clinic at Children's Hospital in San Francisco twice a year for the next three years to undergo physical examinations and to donate specimens for analysis.

Altogether the researchers in the Berkeley program will collect a total of 100,000 body specimens that will be studied by scientists and technicians at the Irwin Memorial Blood Bank and UC San Francisco. Half the body samples will remain for long-term scientific study by the UC researchers, while the other half will be allocated to AIDS investigators all over the world.

The volunteer participants will also be questioned closely about their diet, drug and alcohol use, smoking, exposure to toxic chemicals and radiation — as well as their psychological status, their sexual activity and history of contacts with known AIDS patients.

If current statistics are correct, up to 60 of the San Francisco participants in the study would be expected to contract AIDS during the project. So by comparing the massive data acquired on the men who develop AIDS with identical information on those who remain healthy, the scientists hope to discover the major risk factors and identify the early markers that may signal the most vulnerable men.

Because the study will focus on randomly selected research subjects who are healthy, and will follow them for several years, scientists consider the project far more likely to yield reliable results than other research techniques that analyze data retrospectively after subjects have contracted the disease.

The UC Berkeley project will start with a small pilot study in January, and the massive effort will begin in March.

AIDS has stricken more than 2300 Americans in less than three years, and 80 percent of its victims have died within two years of contracting one or more of its many resulting infections such as Kaposi's sarcoma and pneumocystis pneumonia.

The cause of the syndrome is unknown, but it is believed to be spread by repeated sexual contact or contaminated blood — never by merely casual contact. Scientists believe an unidentified virus is responsible, although repeated assaults on the immune system by diseases and parasite infections may also play a role.

The majority of AIDS victims are gay men with multiple sexual partners and disease-promoting patterns of sexual behavior.

THE BAPHRON

Bay Area Physicians for Human Rights Official Newsletter
Vol. 5, No. 11 November, 1983

UC Berkeley Funded

The National Institute of Allergy and Infectious Disease (NIH) has contracted with the Department of Biomedical and Environmental Health Sciences, School of Public Health, UC Berkeley to do a prospective study of gay and straight men in order to trace the "natural history" of AIDS in our community. Under the direction of Warren Winkelstein, MD, MPH, Professor of Epidemiology, the study will focus on residents of the famous 19 "census tracts" of San Francisco which have been found to yield a very high percentage of AIDS patients. A pilot study will begin in January to check out the "study instruments", and the definitive effort is scheduled to begin in April, 1984.

The study will recruit at least 1000 gay men and 200 "straight" men by trained social workers using door to door techniques under the direction of James Wiley, Ph.D., of UC's Survey Research Center. It is estimated that up to 60 new cases of AIDS will be discovered in this sample over a three-year period. The study will be explained to the participants, and they will be asked to present themselves to a special facility at Children's Hospital for completing a questionnaire, donating samples of blood, urine, stool, and semen, and undergoing complete histories and physicals at six month intervals. The serum samples will be utilized for chemical and serological studies; urine will be frozen for chemical analysis and viral studies; semen and rectal swabs will be preserved for viral studies and ova and parasite examinations. Half the samples will be stored frozen for use by NIH at a later time, or when biological markers are identified. Behavioral risk factors will also be sought, including occupational exposures, alcohol, tobacco, nutrition, and psychosocial factors in addition to sexual patterns.

Sub-contractors include Irwin Memorial Blood Bank (Dr. Herbert Perkins) for analysis of total T-cells, helper T-cells, suppressor T-cells, killer T-cells, monocytes, and total B-cells; Girish Vyas, Ph.D. at UCSF for studies of immune complexes; Thomas Coates, Ph.D., UCSF, for psychological studies; and Dobri Kiprov, MD of Children's Hospital for studies of anti-lymphocyte antibodies. Roche Biomedical Laboratories will analyze serum for beta 2 microglobulin, thymosin alpha-1, and total hemolytic complement assays. Drs. Robert Anderson and William Lang will be responsible for the clinical and laboratory studies respectively at Children's Hospital. There is also an Advisory Committee which will review progress regularly and advise on scientific issues; BAPHR's Will Warner is on this committee.

At the Executive Board meeting Oct. 2, BAPHR voted its wholehearted support and will furnish a letter of endorsement to Dr. Winkelstein for use in recruiting volunteers for this important study. Similar studies are also planned in Baltimore, Pittsburgh, Chicago, and Los Angeles.

AIDS Update

Modlin, RL, Hofman, FM, Meyer, RR, Vaccaro, SA, Ammann, AJ, Conant, MA, Rea, TH, Taylor, CR. "Altered Distribution of B and T lymphocytes in Lymph nodes from homosexual men with Kaposi's Sarcoma" (UCSF and UCLA) *Lancet* 8353, Oct. 1, 1983 pp 768-771. Immunostaining was performed on lymph nodes from 10 homosexual men with Kaposi's Sarcoma and compared to 40 other reactive lymph nodes and tonsils in presumably healthy persons. In normal reactive nodes B cells were confined in follicular centers, whereas in Kaposi's, B cells were found invading the interfollicular area, normally inhabited only by T cells. This same interfollicular area contained an abnormally low ratio of helper:suppressor T cells in Kaposi's Sarcoma. The authors conclude that B lymphocyte proliferation may be the cause of altered immune state in Kaposi's and the abnormal subsets of T lymphocytes may be merely a response to this.

Black, PH, Levy, EM. "The Human T-Cell Leukemia Virus and AIDS". (Boston Univ) *New Engl Journ of Med* 309:14, Oct. 6, 1983 pp 856. The authors disagree with the hypothesis that Human T Cell Leukemia (HTLV) is the causative agent of AIDS for the following reasons: 1)HTLV is T-cell-tropic and stimulates production of cells with T4 (helper) markers; in AIDS there is depletion of this cell population. 2) Lymphomas in AIDS patients contain B cell markers. 3) Antibodies to HTLV detected in 25 percent of AIDS patients may be explained by non-specific polyclonal B-Cell activation independent of current antigenic stimulus.

Golubjatnikov, R et al. "Homosexual Promiscuity and the Fear of AIDS" *Lancet* 8351, Sep 17, 1983 pp 680. A survey of 488 homosexual males from Madison, Wisconsin reveals that the median number of sex partners was 6.8 per month in early 1982 and 3.2 per month in early 1983. AIDS has not yet become prevalent in Madison.

Ketterer, WA, Albert, TJ, Cline, F, Feigen, GM, Owen, WF. "Medical problems of homosexuals" *Medical Aspects of Human Sexuality*. October 1983 pp 55-81. This is an excellent roundtable discussion concerning the approach to the gay patient including history taking, diagnosis and treatment of certain infectious diseases.

James Campbell

NOVEMBER GENERAL MEETING

Some most interesting aspects on charitable donations and estate planning will be presented at the November 13, 1983 BAPHR meeting. On hand to lead the seminar will be Mr. Richard Nelson, attorney, financial planner and estate adviser, as well as our own general counsel Mr. Matthew Coles, attorney. Enough detail to stimulate further enquiry will be given, and the question and answer period should be most provocative.

ALL members will benefit by what they learn, for themselves, and also the ever needful good causes of BAPHR. Please have your questions ready!

November 13, 7 p.m., Franklin Hospital, Duboce and Castro, Auditorium, B Level.

Ted Winn, Jr., M.D.
Finance Committee

11 November 1983

Richard A. Kaslow, MD
Chief, Epidemiology and Biometry Section
National Institutes of Allergy and
Infectious Diseases
Bethesda, Maryland 20205

Dear Dick:

The meeting of the five contractors with staff of NIAID on 20-21 October was welcomed by us. We looked forward to the meeting as an opportunity to learn what other research groups planned to do, to identify common objectives, and to explore the possibility of developing a small core of common data collection procedures. During the meeting it became apparent that the various contractors had proposed, and the Institute had approved, widely disparate study designs. Implementation of these designs will require quite different procedures and efforts. Since we are investigating a disease of unknown etiology whose natural history has not yet been clearly elucidated, useful results are more likely to come from such a varied approach, representing the best efforts of highly competent investigators, than from a uniform and regimented investigation.

It is important at this point to re-emphasize the unique character of the San Francisco study and the special problems it presents. Because it is based on a probability sample, whereas the other projects are not, we have a unique opportunity to measure the prevalence of putative risk factors in a geographically defined population. In addition, our design gives us a better opportunity to elucidate the natural history of AIDS as currently defined, and to measure the prevalence of conditions which many of us think are precursors or end results of the same disease process. In order to realize these scientific goals, our field procedures must produce a high level of participation and a sample that is free of selection bias.

As you know, my colleagues and I have been concerned about the quality of the working relationship between staff of the NIAID and ourselves in the conduct of the AIDS research upon which we are embarked. When we began our preparation of a response to the RFP, colleagues at the University of California in San Francisco urged us to abort the effort suggesting that if we obtained the contract we would become tools of the Institute. Careful re-examination of the RFP convinced us that this would not be the case. To a large extent, we were influenced by the first paragraph of the statement of work which begins, "Independently, and not as an agent for the government, the contractor shall exert his best efforts to furnish services, qualified professional and technical personnel, material, equipment and facilities not otherwise provided by the government under the terms of the contract as needed to perform the work set forth below." We did, of course, take note of the sentence concluding the state of work that, "the nature of the work requires

that the government maintain close control over the use and publication of results generated from work done under this contract". However, after we had negotiated a revision of Clause 19 of Article XIV of the special provisions, allowing us to publish results of the study without permission of the Institute after a 45-day review period, we felt that we could proceed without jeopardizing our scientific integrity.

When our technical proposal was approved and accepted, we assumed that it satisfied the statement of work laid out in the RFP and that its realization would be supported by the contract. Of course, the substantial cuts in the budget which were imposed upon us were of great concern. Nevertheless, we were reassured by the wording of Article I of the actual contract which reaffirmed the desire of the Institute that our research should be conducted "Independently...", that our technical proposal was incorporated into the statement of work by reference, and by the telephone conversation between Debra Keist and Gregory Pryor in which he assured her that the technical proposal had been approved and that adjustments to the budget could be considered after the contract had gone into effect.

As the meeting of 20-21 October went on, and as indicated in your letter of October 26, it became evident that increasing efforts are being made by NIAID to standardize data content and collection procedures as well as laboratory operations. We think that this will have serious adverse effects on our study as well as on those of the other contractors. These are some foreseeable problems:

1. Adoption of a centralized questionnaire will represent the "least common denominator" approach. That is, the items will be limited to those on which everyone agrees and the domains of investigation will be those which are most obvious at the moment. Because such domains are already extensive, the common questionnaire will be so large that time and effort constraints will limit the ability of the individual investigators to follow up their own hypotheses. We believe that the administration of a long, omnibus questionnaire on the first clinic visit, combined with the physical examination and collection of specimens, might result in diminished cooperaton of eligible men and tend to select men whose dispositions and circumstances tolerate the burden of participation, thus sacrificing the very purposes that probability sampling is designed to achieve.

   Furthermore, since the various investigators will be limited in their ability to pursue their own individual interests and hypotheses, there may be a subtle tendency to implement the questionnaire less rigorously than might otherwise be the case. Of course, inhibiting the exploration of new hypotheses also means limiting the ability to explore new etiological possibilities which is, after all, the major purpose of the endeavor. Indeed, we feel that the effort to retrofit the several projects into a uniform data collection format has already diverted our group from consideration of fundamental research issues. Such diversion of the various investigators could jeopardize the entire project.

2. Standardization of questionnaires and laboratory procedures as presently planned is bound to slow up the research and possibly dissipate the energies of the investigators in long procedural negotiations. Our own time table has already been set back at least two months because we have been prohibited from initiating negotiations for acquisition of necessary laboratory equipment until after the scheduled meeting of laboratory investigators on 20-21 November. We were prepared to begin our organizational efforts and equipment procurement procedures as soon as the contract was approved. This would have given us a full two months more than is now possible. In fact, we anticipate additional delays subsequent to the meeting of the laboratory investigators.

3. The proposal requiring additional standard laboratory procedures at each of the study sites which was advanced on 21 October, will necessitate both contract and subcontract modifications that will require additional time and result in further delays. If NIAID wishes to have these procedures done, perhaps they should carry them out in their own laboratories utilizing materials from their share of the repository. It had been our understanding and intention that additional laboratory studies would be funded through grants obtained from NIH under the R01 procedures or from other funding agencies. In fact, one of our investigators is currently applying for support of of additional laboratory studies under this mechanism and we are planning to fund our psychosocial studies with grant support obtained from the National Institute of Mental Health.

4. As suggested above, standardization of procedures will probably not work anyway. With respect to laboratory procedures, extensive experience indicates the difficulties of standardizing procedures among laboratories. Such an objective is not necessarily undesirable, but it would require a very serious and major effort not already foreseen. As we have indicated to you, we are committed to certain procedures already since the laboratory which will do the lymphocyte studies is engaged in AIDS research with UCSF investigators and cannot change its procedures. Established investigators of the calibre of Herbert Perkins, Girish Vyas, and James Geyer are unlikely to be amenable to post hoc standardization.

Clearly, my colleagues and I are not happy with the way things are developing. We feel that if the Institute had planned to conduct the research under strong centralized control, the RFP should have been more explicit in this regard. There are certainly precedents for such an approach. However, if, indeed, the Institute had intended the research to be conducted "Independently...", Institute staff should bend their efforts toward coordination instead of integration. We believe that this would facilitate rather than obstruct the optimal realization of the reseach objectives laid out in the RFP.

The Key Investigators and Advisory Committee for the University of California, Berkeley project agree that this issue requires early resolution. In the meantime, we are doing our very best to move the project forward.

With warm personal regards, we remain

Sincerely,

Warren Winkelstein, Jr., M.D., M.P.H.
Professor of Epidemiology

James A. Wiley, Ph.D.
Assistant Director
Survey Research Institute

cc: Mr. Gregory Pryor
Mr. Robert Kelley
Ms. Debra Keist

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SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF BIOMEDICAL AND
ENVIRONMENTAL HEALTH SCIENCES

EARL WARREN HALL
BERKELEY, CALIFORNIA 94720

December 6, 1983

Robert Kelly, Contracting Officer
Contract Management Branch
National Institute of Allergy
and Infectious Diseases
Westwood Building, Room 707
5333 Westbard Avenue
Bethesda, MD 20816

Re: Contract NO1 Al 32519. The Natural History of Acquired Immune Deficiency Syndrome (AIDS) In Homosexual Men

Dear Bob:

I thought the meeting last week went very well and I am pleased by the progress which is being made to achieve a mutually acceptable core questionnaire. I still hope that such a questionnaire can be sufficiently concise to allow the individual investigators some flexibility in adding areas of interest which each wishes to pursue independently.

We have carefully reviewed the scope of work statement in our contract and remain convinced that it is specific with respect to the laboratory tests which we are obligated to perform. These are identified in A.4.d. and by reference in our technical proposal. If we are to perform additional tests, we believe that the scope of work must be amended. While we still question your authority to make amendments unilaterally, we are prepared to consider renegotiation of the technical specifications of the contract. However, if amendments are made, rebudgeting either by internal rearrangement or by provision of additional funds will be required. In order to proceed in an orderly manner with both amendment of the scope of work and budget modification, we need a letter from you or Dr. Kaslow with specific proposals. While the information which Bob Anderson brought back from the laboratory meeting is helpful in a general way, it is not specific enough to serve as a basis for contract modification.

I look forward to an early resolution of this issue.

Sincerely,

W

Warren Winkelstein, Jr., M.D., M.P.H.
Professor of Epidemiology

J

James Wiley, Ph.D.
Assistant Director, SPC

cc: R.A. Kaslow
D. Keist
J. Lashof
P. Tannenbaum

3/27/92

A 26 San Francisco Chronicle ★★★★★

Budget Cuts Threaten 8-Year S.F. AIDS Study

By Sabin Russell
Chronicle Staff Writer

In a surprise move, the Bush administration is proposing to sharply curtail an 8-year-old study of AIDS in the gay population of San Francisco, prompting a vigorous attempt by researchers to salvage the program.

The Men's Health Study began looking at the health and behavior of 1,035 men living in San Francisco's Castro district in 1984 and since then has given scientists a vital window on the extent and progression of the AIDS epidemic.

"I think we need more research, not less," said Warren Winkelstein, a Berkeley epidemiologist and the project's director, who is meeting with federal officials this week to negotiate the future of the program.

Designed before researchers even knew that AIDS was caused by a virus, the study has yielded a wealth of information and was the first to reach the conclusion that about half of San Francisco's gay population had already been infected. The study's findings have been used to track the changing nature of the epidemic and to set the direction of AIDS prevention efforts.

Managers of the study, which is financed with a $1.5 million annual grant from the National Institute of Allergies and Infectious Diseases, learned in late February that the Bethesda-based federal agency wanted to virtually end the project by the end of September. The institute is facing an $8 million cut in its AIDS contract research budget and also wanted to refocus the San Francisco study on preparations for vaccine trials in 1994.

Winkelstein's negotiations this week appear to have saved the program from the ax, and discussions are now under way to retain a scaled down version.

Anthony Fauci, director of the National Institute of Allergies and Infectious Diseases, yesterday said the issue is still being negotiated. "The only decision that has been made is that we will not terminate the project," he said. "We have no intention at all of abandoning San Francisco."

APPENDIX I

UNITED MEN'S HEALTH STUDY
BERKELEY: SURVEY RESEARCH CENTER
FAX: (510) 643-8292
PH: (510) 642-3086

United Men's Health Study Publications
September 20, 1993

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APPENDIX J

2 doc's giving my views in gen'l. on proph & therapeut. c trials. W.

MEMORANDUM

To: Dr. Schrager
From: Dr. Winkelstein W
Subject: Preliminary Remarks Regarding HIV Vaccine Field Trials
Date: 4 February 1992

Lew,

Some local issues have sidetracked me so this may be less than I had promised. First, some thoughts on where trials cuuld be carried out. Obviously, trials of so-called therapeutic vaccines, which would be administered to already infected persons, could be carried out wherever substantial numbers of HIV seropositive persons are located. Locations such as San Francisco, New York, and other large cities are obvious possibilities. Existing cohorts have some characteristics which make them particularly attractive for trials of therapeutic vaccines. The variability in host response to HIV infection as well as the effects of chemotherapy almost mandates long term follow-up of persons in such trials. Because of the necessity for elaborate clinical, immunological, biochemical, and virological follow-up of these study subjects, tests of therapeutic vaccines should be carried out only be highly qualified investigators with extensive resources and facilities. Groups like our's would be well qualified to organize such trials. Incidentally, our group is currently preparing some material for Dr. Jeremy Graden, of your division, which will be relevant to evaluating trials of therapeutic vaccines. Specifically, we will be evaluating various biological and clinical markers for use as "end points" for such trials.

There is widespread belief that prophylactic vaccines will be more effectively tested in developing countries, where attack rates are high, rather than in developed countries where attack rates have been generally lower. I disagree with this approach. As I will show later in this communication, attack rates do not have to be very high to make field trials feasible. Furthermore, vaccine field trials require a high degree of methodological sophistication and rigorous implementation. In developing countries, this frequently means that foreigners are required to manage the research. This can lead to resentment and the perception of exploitation even if the foreign personnel are under the auspices of an international organization like W.H.O.. In addition, there may be more fundamental arguments in favor of developing vaccines from virus strains isolated from populations which are to be the eventual targets for immunization. Finally, there are strong reasons why vaccine field trials of an HIV vaccine should be double-blinded and placebo controlled. This approach may be even more difficult to implement in developing countries than in developed countries.

In order to effectively plan a HIV prophylactic vaccine field trial, certain information is needed. First, we need to know the incidence of HIV infection in potential target populations. Second, it would be desirable to be able to identify groups at relatively high risk of infection. Among homosexual men, this means determing the patterns of sexual practices among them. Third, we need to know what proportions of potential study populations would be willing to participate in a placebo controlled prophylactic vaccine field trial. As you know, all of this information will be obtained in the San Francisco Young Men's Health Study (SFYMHS), scheduled to begin data collection in early March. (Household enumeration has already been completed. This is a major part of the work.)

Ordinarily, and ideally, determining the incidence of infection in the random sample of young men requires a second cycle of examinations carried out after an appropriate time interval. However, we believe that by combining information regarding duration of high risk sexual activity (which we will obtain) and HIV seroprevalence at the time of the survey, we can estimate the annual incidence of infection before carrying out a second cycle of examinations.

With the information described above, it will be possible to design an appropriate sampling scheme to obtain a study population. We believe that obtaining a study population broadly representative of the homosexual population will be preferable to a specialized high risk population for a phase 2 trial. I will be glad to amplify this point in a separate communication. I would like now, however, to consider the issue of sample size requirements. In discussions with various local epidemiologists, the consensus regarding current annual incidence rates among homosexual men, under the age of 30, is between one and three percent. Without any knowledge of the current status of phase 1 trials, I have estimated sample sizes for vaccines of 66% effectiveness, 90 percent effectiveness, and unknown efficacy. These estimates are shown on the first attachment, entitled, "Sample Size Estimates". All of the estimates are minimal and have rather wide confidence intervals (not shown). The precision of the estimates could be improved by increasing the sample sizes. The gist of the exercise is that modest sized samples can provide usable estimates of vaccine efficacy.

You will note that I have used a sample size of 3,000 (1,500 vaccinees, 1,500 placebo controls) as the maximum sample size in the examples presented. The reason for this is that I assumed a minimum desirable effectiveness for a vaccine of 66 percent and a minimum practical annual incidence rate for a study population of one percent. (Of course, attack rates of some diseases for which vaccines have been field tested have been much lower. But then, sample sizes have been huge, e.g., the Poliomyelitis Vaccine Field Trial of 1954 had more than 200,000 subjects in each of the

vaccinated and placebo groups.) We believe that it would be feasible to recruit a study population of 3,000 or more young homosexual men in San Francisco (assuming a fairly positive response to our survey questions regarding willingness to participate).

Consideration will also have to be given to the possibility of a multicenter vaccine field trial. This will depend to some extent on the HIV infection rate estimated in the SFYMHS. In my opinion, it may be better to have separate trials in different communities, using comparable protocols, than to have a single large study with pooled data.

In considering a vaccine for the control of an epidemic, it is informative to consider the necessary level of effectiveness of the vaccine as well as the proportion of the population required to be immunized in order to control the epidemic. In a second attachment, entitled, "Epidemic Stabilization Threshold", I have touched on this issue. The formulation is based on the work of Anderson and May. The idea represented by the attachment is that the proportion of the population which must be immunized in some period of time in order to stabilize an epidemic is a function of the efficacy of the vaccine and the average number of secondary infections produced by each infected persons. To bring the epidemic under control, a larger proportion of the population must be immunized. In the first example, the combination of a vaccine which has an efficacy of 66 percent with an average number of secondary infections per primary case of three, produces a required proportion of population immunized which is greater than 100 percent. This means that under these circumstances the epidemic could not be controlled although, of course, it would be "damped". The other examples are a little more optimistic, although they require very high levels of population coverage to produce epidemic control. The underlying concept here was provided by Wade Hampton Frost in his classic paper, entitled, "How Much Control of Tuberculosis" (AJPH 1937; 27:759-66). I think that careful thought must go into deciding what level of vaccine effectiveness is sufficient to merit mass immunization efforts.

I hope that these few remarks will be of use to you. I must caution you, however, that I have not had an opportunity to discuss this material with my colleagues, which is my usual practice before sending out such a communication. The numbers haven't even been checked!

cc: Dr. Moss
Dr. Wiley
Dr. Sheppard

Sample Size Estimates
(Double-Blind Placebo Controlled Field Trial)

xample 1: Vaccine Efficacy 66%:

ncidence 1% P.A.: N=3,000; 15 Pl. Cases, 5 Vacc. Cases (p=.02)
2% P.A.: N=2,000; 20 Pl. Cases, 7 Vacc. Cases (p=.01)
3% P.A.: N=1,400; 21 Pl. Cases, 7 Vacc. Cases (p=<.01)

xample 2: Vaccine Efficacy 90%:

ncidence 1% P.A.: N=2,000; 10 Pl. Cases, 1 Vacc. Case (p=<.01)
2% P.A.: N=1,000; 10 Pl. Cases, 1 Vacc. Case (p=<.01)
3% P.A.: N=600; 9 Pl. Cases, 1 Vacc. Case (p=.01)

xample 3: Vaccine Efficacy (VE) Unknown:

ncidence 1% P.A.: N=3,000; 15 Pl. Cases, 6 Vacc. Cases: VE=60%
15 Pl. Cases, 7 Vacc. Cases: VE=53%
15 Pl. Cases, 8 Vacc. Cases: VE=47%

2% P.A.: N=3,000; 30 Pl. Cases, 5 Vacc. Cases: VE=93
30 Pl. Cases, 10 Vacc. Cases: VE=67
30 Pl. Cases, 15 Vacc. Cases: VE=50

3% P.A.: N=3,000; 45 Pl. Cases, 5 Vacc. Cases: VE=89
45 Pl. Cases, 10 Vacc. Cases: VE=78
45 Pl. Cases, 15 Vacc. Cases: VE=67

)idemic Stabilization Threshold:

$E = 100(1 - 1/R_0)$

Where:
P = Proportion of Population Immunized
E = Vaccine Effectiveness
R_0 = Average Number Secondary Infections Produced by Each Infected Person

:ample 1: E = 66%, R_0 = 3:

$P = 100[(1 - 1/R_0)/E]$
$P = 100[(1 - 1/3)/.66]$
$P = 100(.67/.66) = >100\%$

Note: Under these conditions, and given the assumption of random sexual mixing, this combination of E and R_0 would not stem the epidemic. Any combination of lower E or greater R_0 would not stem the epidemic

:ample 2: E = 66%, R_0 = 2:

$P = 100[(1 - 1/2)/.66]$
$P = 100(.5/.66) = 76\%$

Note: Under these conditions, the epidemic could be controlled If more than 76% of the susceptible population were immunized.

:ample 3: E = 90%, R_0 = 3:

$P = 100[(1 - 1/3)/.90]$
$P = 100(.67/.90) = 74\%$

Note: Under these conditions, the epidemic could be controlled if more than 74% of the susceptible Population were immunized.

$$PE = 1 - 1/R_0$$

Where:

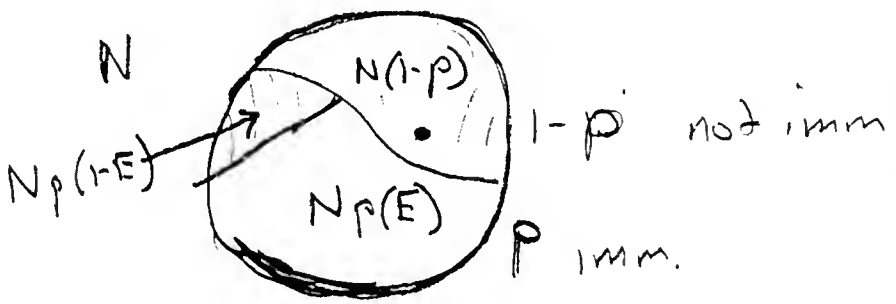
P = Proportion of Population Immunized

E = Vaccine Effectiveness (expressed as a proportion)

R = Rate of Growth of Epidemic
(Average Number Secondary Infections Produced by Each Infected Person per unit time.)

Vaccine Effectiveness & $1/R_0$

.95
.85
.66
.50



$$P \cdot E = 1 - \frac{1}{R}$$

$$R \cdot P \cdot E = \frac{R-1}{R} \times R$$

$$R \cdot P \cdot E = R - 1$$

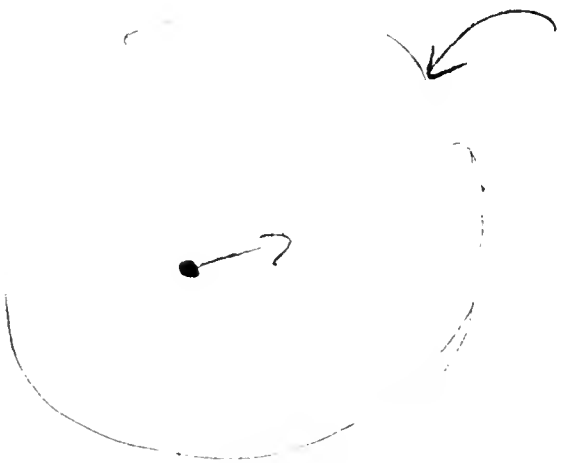
$$1 = R - R \cdot P \cdot E$$

$$= R(1 - P \cdot E)$$

$$\frac{1}{1 - P \cdot E} = R$$

C = # of (random) contacts per person per unit time

I = infectivity

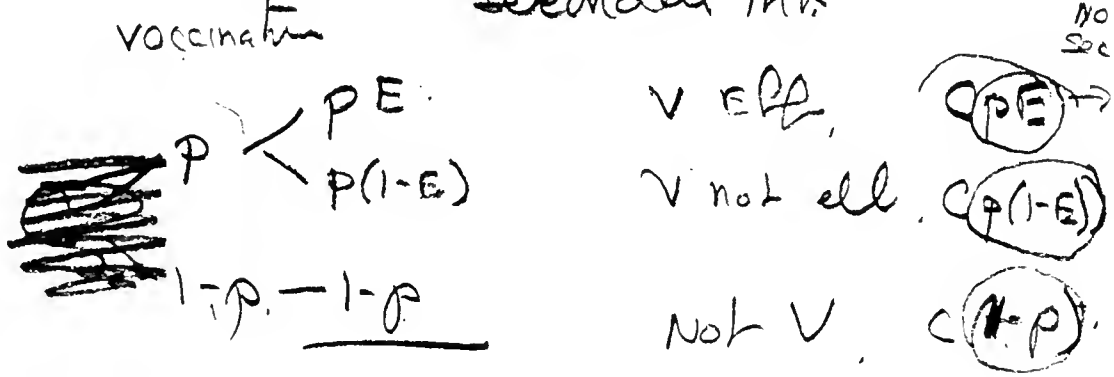


N = total size of pop.

NC = # contacts / unit time

NCI = total number of infections / unit time

$R_0 = C \cdot I$ ← per individual generation of secondary inf.



$CI\,p(1-E) + CI(1-p) =$ # of second inf. $= R$ after intervention

(CI under R_0; CI under R_0)

$$R_0\left(p(1-E) + (1-p)\right) = R$$

$$R - pE + 1 - p$$

$1 - PE = R/R_0$ ← input.

$1 - R/R_0 = PE$

set $R = 1$ to get the stabilization threshold

$1 - 1/R_0 = PE$

$100 \cdot .95\% = .95$

$.50 \times .50 = .125$

R_0	PE IF E=.66
2	$1 - 1/2 = .5$
5	$1 - 1/5 = .8$
10	$1 - 1/10 = .9$ ←

206 0945

(415)

Sample Size Estimates
(Double-Blind Placebo Controlled Field Trial)

Example 1: Vaccine Efficacy 66% (Incidence Reduction: 50%):

Incidence 1% P.A.: N=3,000; 15 Pl. Cases, 5 Vacc. Cases (p=.02)
2% P.A.: N=2,000; 20 Pl. Cases, 7 Vacc. Cases (p=.01)
3% P.A.: N=1,400; 21 Pl. Cases, 7 Vacc. Cases (p=<.01)

Example 2: Vaccine Efficacy 90% (Incidence Reduction: 89%):

Incidence 1% P.A.: N=2,000; 10 Pl. Cases, 1 Vacc. Case (p=<.01)
2% P.A.: N=1,000; 10 Pl. Cases, 1 Vacc. Case (p=<.01)
3% P.A.: N=600; 9 Pl. Cases, 1 Vacc. Case (p=.01)

Example 3: Vaccine Efficacy (VE) Unknown:

Incidence 1% P.A.: N=3,000; 15 Pl. Cases, 6 Vacc. Cases: VE=60%
15 Pl. Cases, 7 Vacc. Cases: VE=53%
15 Pl. Cases, 8 Vacc. Cases: VE=47%

2% P.A.: N=3,000; 30 Pl. Cases, 5 Vacc. Cases: VE=93%
30 Pl. Cases, 10 Vacc. Cases: VE=67%
30 Pl. Cases, 15 Vacc. Cases: VE=50%

3% P.A.: N=3,000; 45 Pl. Cases, 5 Vacc. Cases: VE=89%
45 Pl. Cases, 10 Vacc. Cases: VE=78%
45 Pl. Cases, 15 Vacc. Cases: VE=67%

Text: (Show first transparency entitled, "Some Preliminary Observations, etc.") This brief presentation was prepared at the request of Dr. Jeremy Gradon of the Medical Branch of the AIDS Division of ~~the~~ NIAID. It addresses four issues which the listed authors consider important in the planning of the evaluation of HIV component vaccines for HIV seropositive individuals. These issues are shown on the screen:

1. The problem of confounding by antiretroviral therapy.
2. The incidence and timing of clinical end-points. (The specific request of Dr. Graden.)
3. The problem of confounding by hosts' natural immune and activation responses.
4. A preferred measure of vaccine efficacy.

1. The problem of confounding by antiretroviral therapy:

Table 1 shows data obtained in a recent telephone survey of HIV seropositive subjects without AIDS who were participating in the San Francisco Men's Health Study and the San Francisco General Hospital Cohort. The data show the use of antiretroviral chemotherapy according to CD4 cell count. Among the surveyed subjects with less than 200 CD4 cells/ul or 200-500 cells/ul, current or ever use of AZT (zidovudine) varied between 54 and 90 percent. For use of any retroviral, the range was 62-92 percent. More importantly, two-thirds of all subjects with CD4 cell counts less than 500/ul were currently receiving antiretroviral therapy. While it may be argued that a therapeutic vaccine can be evaluated in persons undergoing chemotherapy because they are randomly distributed to vaccinated and placebo groups, to the extent that the chemotherapy is effective in delaying or arresting the progress of immune system deterioration, the effects of the vaccine will be more difficult to assess. Furthermore, evaluating a vaccine in persons undergoing concurrent chemotherapy will almost certainly extend the required observation time or substantially increase the required sample size. Seventy-nine percent (134/169) of all seropositive subjects with CD4 cell counts less than 500/ul had used antiretroviral chemotherapy at one time or another. Because of the frequency of intermittant use, we think that most infected persons in this cell count category will be using chemotherapy during the course of a trial, particularly if the trial extends for more than a year's duration.

Among subects with CD4 cell counts greater than 500/ul, approximately one-quarter had ever or were currently using antiretroviral chemotherapy. Clearly, it would be much easier to recruit a study population who are not on chemotherapy in this cell count category. Whether sufficient end-points for evaluating a vaccine will occur within a reasonable time frame in subjects in this cell count category will now be addressed.

*Winkelstein presentation, Division of
1 AIDS, NIAID, NIH, February 12, 1992.

2. The incidence and timing of clinical (non-AIDS defining) conditions:

Figure 1, shows the cumulative incidence of hairy leukoplakia in the San Francisco Men's Health Study among HIV seropositive study subjects who did not have this condition on entry. This is an example of the analyses we have prepared for the five specific clinical end-points specified by Dr. Graden, i.e., oral thrush, hairy leukoplakia, persistant fever, diarrhea, and weight loss. The data shown in Figure 1 are for subjects with CD4 cell counts of 200-500/ul and greater than 500 cells/ul on entry. The analyses utilize standard life-table survival methods (more appropriate for these types of data than the currently popular Kaplan-Meier approach). In Figure 1 it is apparent that among HIV seropositive subjects with 200-500 CD4 lymphocytes on entry, the cumulative incidence (shown by the dotted line) is about 20 percent after 12 months, 30 percent after 24 months, 45 percent after 36 months, and 55 percent after four years. The corresponding cumulative incidence proportions (shown by the solid line) for subjects with greater than 500 CD4 cells/ul on entry are; 10 percent at 12 months, 20 percent at 24 months, 30 percent at 36 months, and about 40 percent after four years. Analogous graphs for the other four designated end-points have been provided to Dr. Gradon.

In Table 2 the cumulative incidence over 24 months according to CD4 cell count on entry are shown for each of the five designated clinical end-points and certain combinations of them. It is apparent that thrush and hairy leukoplakia have substantial incidence in both cell count categories, 41 percent for one or the other in the 200-500/ul cell count category, and 24 percent in the over 500 cell/ul category. The other single end-points have substantially lower incidence and are unlikely to be useful in the evaluation of therapeutic vaccines. Grouping the clinical end-points into a composite of any two or more, increases the incidence somewhat over the composite for oral lesions only.

(Take off the overhead transparency until Table 3 is called up.)

3. The problem of confounding by hosts' natural immune and activation responses:

A number of studies have demonstrated strong predictive values for the development of AIDS in HIV seropositive men by immune markers such as P24 antibody and activation markers such as beta-2-microglobulin and neopterin. High levels of P24 antibody are associated with slow progression to AIDS and high levels of activation markers are associated with rapid progression. The opposite result with respect to progression has been observed for both low P24 antibody level and low activation markers. Furthermore, it has also been shown that the level of immune response to HIV infection is highly variable and is

established shortly after infection. Similarly, the level of lymphocyte activation by infected persons is highly variable and appears to be established early in the natural history of infection. When both immune and activation responses of infected persons are taken into account, progression follows a predictable pattern. This is shown in data from the San Francisco Men's Health Study as displayed in Table 3. Two hundred thirty-eight men, almost all of whom had entry level CD4 T lymphocyte counts greater than 500 cells/ul, were divided into four groups using the geometric means of the initial P24 antibody titers and neopterin levels. Progression to AIDS was then observed over 54 months. Among 73 subjects with low activation markers and high P24 antibody titers on entry, about 10 percent developed AIDS during the observation period. Among 68 subjects with high activation markers and low P24 antibody titers on entry, about 60 percent developed AIDS (relative risk of 6.3). Among the 97 subjects with low activation and low antibody, and high activation and high antibody, progression was intermediate at about 35 percent. We have not yet examined the predictive value of immune titers and activation markers for the oral lesions associated with HIV infection but we suspect that these will also show the same kinds of patterns as they are strongly associated with CD4 T lymphocyte cell counts.

These observations indicate that, in order to avoid a risk of serious confounding, vaccine evaluation study subjects should be stratified according to immune and activation response before random allocation to vaccinated and placebo controlled groups. Furthermore, it may be hypothesized that subjects who show a poor immune response to natural infection may also be resistant to artificial immunization. ~~This phenomenon would be easier to identify in a stratified model than by post hoc analysis.~~

(Take off the overhead transparency until Figure 2 is called up.)

4. A preferred measure of efficacy:

Because of the long and variable incubation period of AIDS, the defining criteria promulgated in 1987 by CDC would not seem suitable as end-points for evaluating a "therapeutic" vaccine. Also, if a vaccine were administered late in the natural history of the infection, within a year or two of the onset of defined AIDS, the likelihood of an effective immune response seems questionable. Using non-AIDS defining clinical conditions associated with HIV infection, such as thrush and hairy leukoplakia, has the disadvantage that a substantial proportion of HIV infected persons do not develop these conditions over relatively long periods of time. According to the previously shown Figure 1, 45 percent of persons with CD4 cell counts of 200-500/ul did not develop hairy leukoplakia in four years. On the other hand, almost everyone who is infected with the HIV suffers a decline in CD4 T lymphocyte counts which begins very

shortly after infection and continues until death. In the San Francisco Men's Health Study and the San Francisco General Hospital Cohort, less than 15 percent of infected men have maintained stable CD4 counts over seven years of observation.

Figure 2 shows the declines in mean CD4 cell counts over a 48 month period for the 238 seropositive men who provided the data for Table 3. They have again been divided into four groups according to initial antibody and activation response as described previously. Among those with low neopterin levels and high P24 antibody titers, the annual mean decline over four years of observation was 64 cells/ul. Among those with low neopterin levels and low P24 antibody titers, and high neopterin levels and high P24 antibody titers, the annual mean decline was 70 cells/ul. Among those with high neopterin levels and low P24 antibody titers, the annual mean decline was 108 cells/ul.

In view of these observations, and the central role of the CD4 T lymphocyte in immune system regulation, we believe that serious consideration should be given to the use of CD4 T lymphocyte cell count declines in subgoups defined by antibody response and immune system activation for component vaccines for HIV seropositive persons. Whether any of the non-AIDS defining clinical end-points, discussed previously, can be usefully combined with observation of CD4 T lymphocyte declines depends on their relationship to immune and activation markers as described here for CD4 T lymphocytes. We are performing such analyses currently as a consequence of Dr. Gradon's 24 January request.

Some Preliminary Observations on Measures Efficacy for Trials of "Therapeutic" HIV Vaccines

. Winkelstein, A.R. Moss, M.C. Samuel, D. Osmond,
H.W. Sheppard, M.S. Ascher, W. Lang

Issues for Consideration

The problem of confounding by antiretroviral therapy.

Incidence and timing of clinical end-points.

The problem of confounding by hosts' natural immune and activation responses.

A preferred measure of efficacy.

e data presented here were derived from the San ancisco Men's Health Study and the San Francisco neral Hospital Cohort, supported by Contract 1-AI-82515 fron the Natioal Institute of Allergy d Infectious Diseases.

12 Feb 1992
NIAID/FDA

Table 1

Antiretroviral Use by Clinical Status and CD4 Count

on-AIDS Subjects	AZT				Any Antiretrovira			
CD4 Cells/ul	Ever		Current		Ever		Current	
	%	(N)	%	(N)	%	(N)	%	(N)
=<200 (N=52)	90	(47)	54	(28)	92	(48)	67	(35)
1-499 (N=117)	73	(85)	60	(70)	74	(86)	62	(73)
=>500 (N=120)	27	(32)	23	(28)	27	(32)	23	(28)

Figure 1

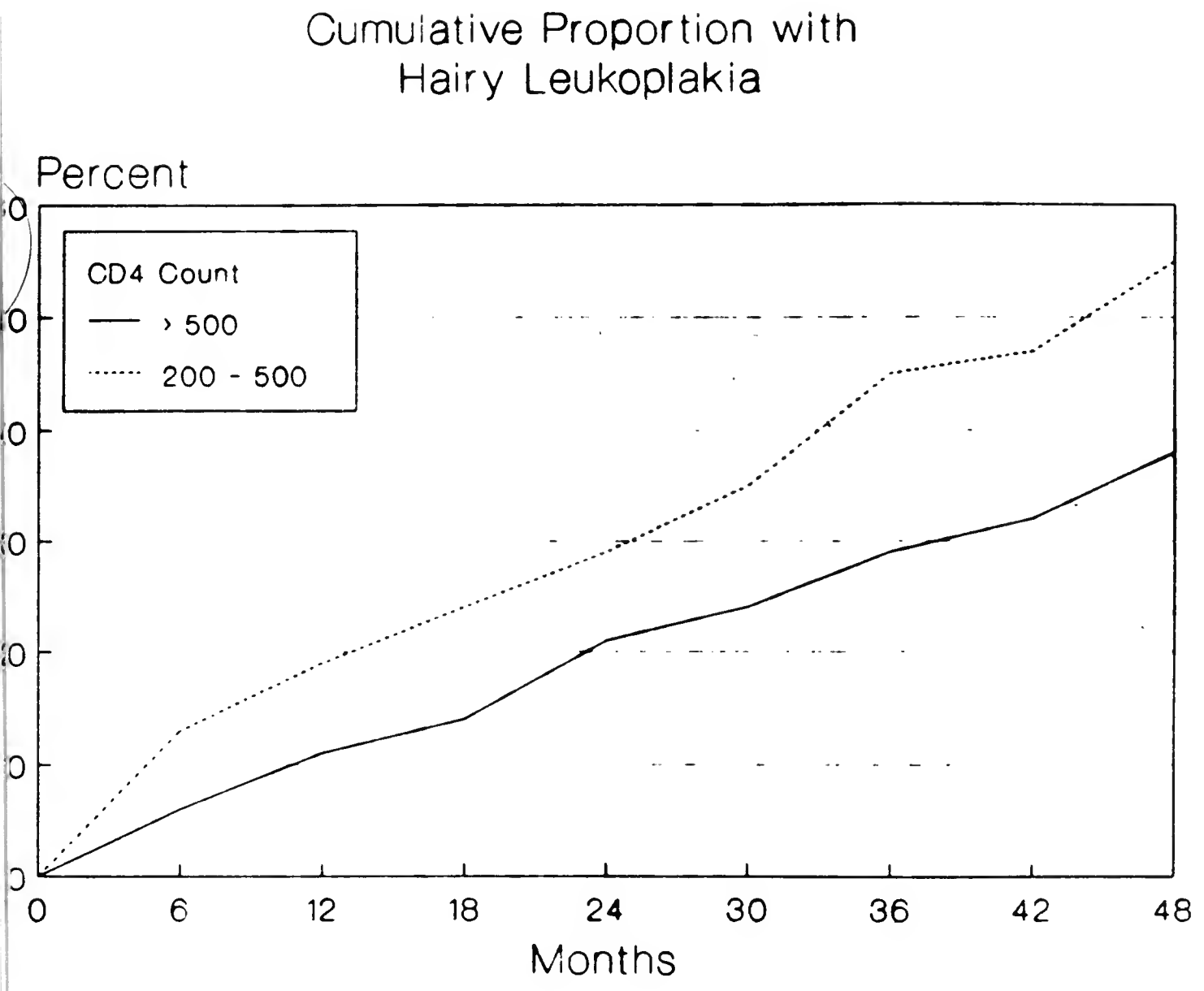

Cumulative Proportion with
Hairy Leukoplakia
Percent
CD4 Count
› 500
200 - 500
0
6
12
18
24
30
36
42
48
Months

Table 2

Incidence of Clinical Manifestations of HIV Infection in 24 Months According to CD4 Cells/ul on Entry (SFMHS)

Clinical Manifestation	24 Month Incidence 200-500 CD4 Cells %	(N)	>500 CD4 Cells %	(N)
Thrush	35%	(130)	20%	(180)
Hairy Leukoplakia (HL)	29%	(136)	21%	(182)
Thrush and/or HL	41%	(126)	24%	(174)
Persistant Fever	13%	(141)	5%	(193)
Diarrhea	14%	(137)	11%	(184)
Weight Loss	13%	(139)	6%	(194)
2 or More of Above	65%	(77)	52%	(77)

Notes:

1. N's vary because of exclusions due to presence of clinical manifestation on entry.
2. History of thrush in preceeding 6 months or present on examination.
3. Persistant fever: persistant and or recurring temp. higher than 38^{0}C for at least 2 weeks.
4. Diarrhea for at least 2 weeks.
5. Weight loss: an unintentional weight loss of at least 4.5 kg. in previous 6 months.

Table 3

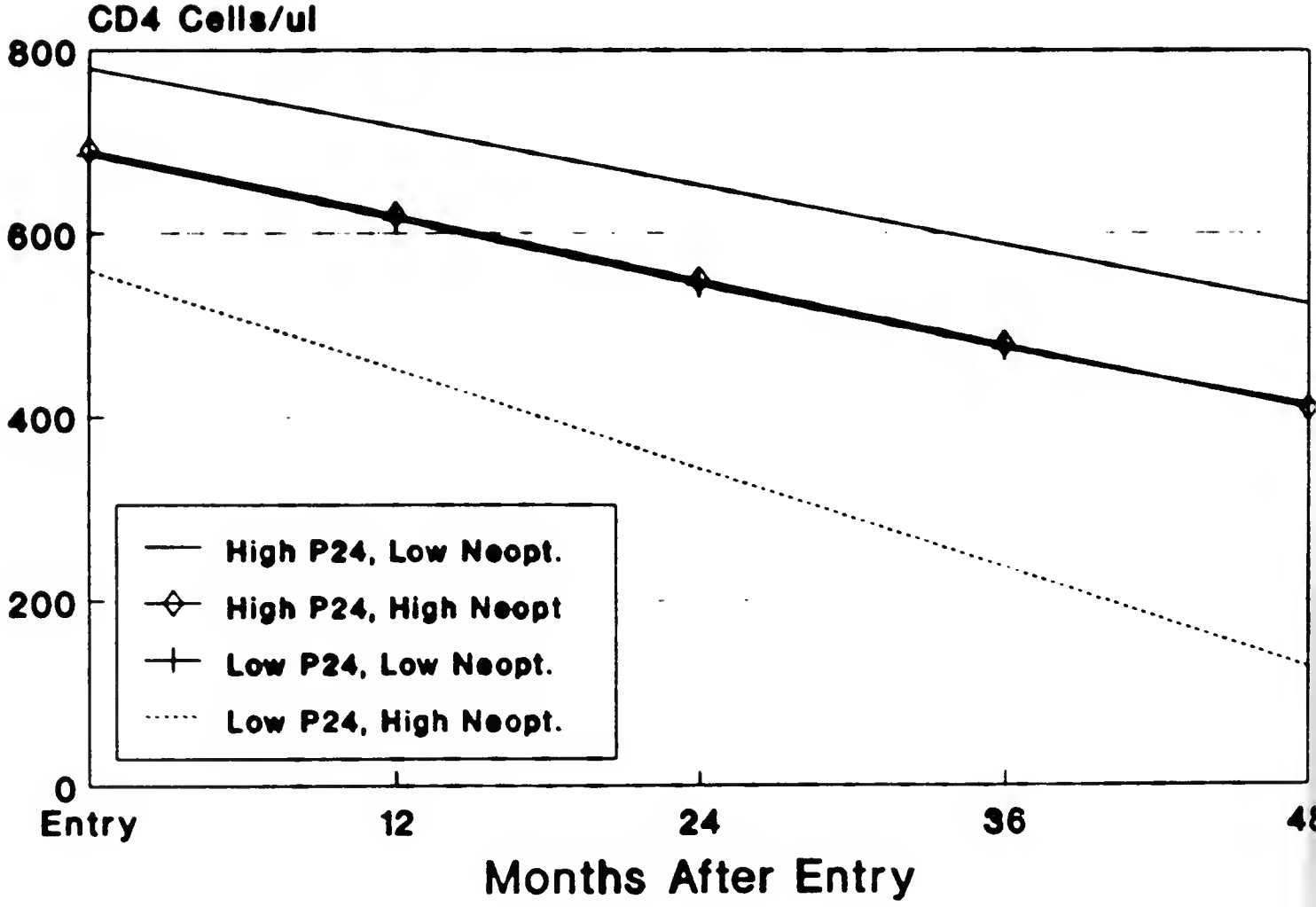
The Bivariate Predictive Value of P24 And Serum Neopterin at Cohort Entry

Neopterin Level	P24 Antibody Titer	N	AIDS in 54 Months	Relative Risk
Low	High	73	7 (9.6%)	1.0
Low	Low	49	17 (34.7%)	3.6
High	Low	48	16 (33.3%)	3.5
High	Low	68	41 (60.3%)	6.3

Note: The study population was divided into four groups using the geometric means of the initial neopterin levels and P24 antibody titers (2.4 ng/ml and 1:245, respectively).

Adopted from: Sheppard HW, et al. The initial immune response to HIV and immune system activation determine the outcome of HIV Disease. JAIDS 1991;4:704-712.

CD4 T Lymphocyte Declines:
By Immune and Activation Status



Biologist disputes AIDS theory

Professor threatens to inject himself with HIV as proof

By Stephen Yeh
Contributing Writer

In 1987 UC Berkeley molecular biologist Peter Duesberg threatened to inject himself with HIV, the Human Immunodeficiency Virus, to dispute the prevailing theory that HIV causes AIDS.

Although Duesberg did not follow through on his threat at the time, he says he is still willing to carry it out in order to call attention to his controversial AIDS research.

"AIDS research is misguided. It is largely HIV research," Duesberg said. "The only catch is, HIV doesn't cause AIDS. HIV is a pussycat. It is a retrovirus, and retroviruses have not been shown to cause any human diseases, nor even to kill cells in laboratory tests."

The flamboyant Duesberg, who has taught on the Berkeley campus for more than 20 years, has been heavily criticized by the scientific community for his views on AIDS, which are contrary to widely held beliefs about the cause of the disease.

Warren Winkelstein, a UC Berkeley epidemiologist, agreed that the understanding of how HIV causes AIDS is incomplete, but said the theory that HIV is the cause of the disease is well established.

"The evidence for HIV is overwhelming. Literally thousands of studies support HIV as a cause of AIDS," Winkelstein said.

Joan McKenna, director of research at TBM Associates, a research company in Berkeley, said, "I think Peter has done a service. He has thrown his body to the media to open up the door to real investigative science."

Duesberg argues that there is no proof that HIV causes AIDS, and said the HIV hypothesis has not been tested in a well-controlled study.

Researchers just assume it is true and then collect clinical anecdotes that agree with their hypothesis, Duesberg said.

"In the last 10 years, AIDS-defining diseases have increased, particularly among homosexuals," Duesberg said. "In the last 20 years, drug use has exploded among male homosexuals. Meanwhile, contrary to media propaganda, HIV infection in the population has remained

SEE PAGE 2

Prof questions AIDS theory

FROM FRONT PAGE

at a stable 0.4 percent since 1985. If the percentage does not change, this implies that HIV is not a new virus."

Duesberg said according to his alternate hypothesis on the cause of AIDS, an increase in the consumption of drugs such as alcohol, heroin or cocaine, combined with prolonged malnutrition and antibiotics for venereal diseases, leads to a collapse of the immune system and accounts for the steady growth of AIDS diseases.

Duesberg noted that not one controlled study has been done to prove that the incidence of AIDS diseases in these risk groups depends on HIV. A controlled study would show once and for all whether HIV, or conventional health risks (such as drugs or diet), or some other microbe, causes AIDS, he said.

But most scientists are wary of accepting, or altogether disregard Duesberg's hypothesis.

"I cannot respond without shrieking," said Robert Gallo, from the National Cancer Institute, in *Science*. "Too ridiculous to waste precious time answering."

But Duesberg may be gaining support: In the past year about 50 scientists have banded together to form the Group for the Scientific Reappraisal of the HIV/AIDS Hypothesis.

Even John Maddox, editor of *Nature*, a leading science journal, said in *Science*, "I feel sorry that *Nature* has not done more to give his view prominence. . . . The scientific community is coming around to the view that AIDS is more complicated than the baby talk stories we were all given a few years ago."

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SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF BIOMEDICAL AND
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EARL WARREN HALL
BERKELEY, CALIFORNIA 94720

2 April 1993

John Maddox, Editor
Nature
4 Little Essex Street
London WC2R 3 LF
United Kingdom

Dear Dr. Maddox:

Professor Richard Strohman has provided me with a copy of a letter addressed to you regarding the commentary by Ascher et al. which appeared in the 11 March issue of Nature regarding the drug etiology causal hypothesis for AIDS. As one of the authors of the commentary, I would like to briefly comment on some of Professor Strohmans assertions. However, if you decide to publish Strohman's letter, it would, perhaps, be more appropriate to obtain a response over Dr. Ascher's signature.

Here are my comments:

1. Strohman misinterpreted our study as being retrospective when it is clear from the text of the commentary, as well as from the tables and figure, that it was prospective. Thus, we did evaluate, "...extent and duration of drug use...".

2. Strohman asserts that Duesberg, "...always also includes AZT as a drug of suspicion for AIDS...". However, in the statement of his hypothesis which we quoted and referenced (no.4), Duesberg did not include specific reference to AZT. Furthermore, cohort data are not the best test of a causal hypothesis for AZT. Nevertheless, we have since supplied data on AZT use to Executive Editor Clarke.

3. For your information, we have repeatedly urged Peter Duisberg to turn his considerable talents to research on AIDS, if only to test his own hypotheses. He has chosen, instead, to advocate his drug etiology hypothesis based largely on ecological data and his knowledge and interpretation of immunology and retrovirology. To my knowledge he has conducted no research on the subject himself. However, over two years after our original offer, he recently asked for access to our research data and it was provided in accordance with our general policies regarding such requests.

To the Editor: Duesberg has asserted (1) that the study on which we based our commentary (2) of his drug etiology theory of AIDS is, in his words, "worthless". His evaluation is based on claims that we did not evaluate, "HIV-positive, drug free controls", failed to, "quantify recreational drug use", did not, "observe drug use long enough to detect toxicity", and failed to, "report AZT use altogether". the last claim is correct and we hasten to remedy this omission.

Fifty-eight (27%) of our 215 AIDS cases were diagnosed prior to the introduction of Zidovidine (AZT) therapy in 1987 and, therefore, could not be attributed to AZT. Subsequent to the introduction of AZT therapy for AIDS and its recommended use for prophylaxis of certain HIV infected persons, it was extensively used. Thus, it is not unexpected that of 157 cases diagnosed after the introduction of AZT, 132 (84%) reported ever using AZT. All of these cases were also HIV seropositive. However, it is interesting to note that 110 HIV seronegative study subjects reported some use of AZT (presumably as a prophylactic). None of these persons became infected by the HIV or developed AIDS.

With respect to Duesberg's claim that HIV seropositive drug free controls were not used and that drug use was not quantified, we would draw your readers' attention to the figure and its legend which clearly spells out the structure of our drug use score which includes and quantitates use of the four most commonly reported recreational drugs viz., marijuana, nitrite inhalants, cocaine, and amphetamines. The claim that the "seropositive-no drug" users group is a "fabrication" is based on a misreading of the text describing Table 2. The number of HIV seropositive study subjects in Table 2 with no nitrite inhalant use in the previous two years is 66 and the number of seropositive subjects with a composite drug use score of zero in the figure is 20.

The claim that we failed to observe drug use long enough to detect toxicity is also based on a misreading of the text. It is clearly indicated, therein, that drug use data were routinely collected at the twice-yearly examinations and that a logistic analysis of the longitudinal drug use data showed no positive association between long-term or continued drug use and the development of AIDS.

In a New York Times newspaper discussion of our Commentary (3), Dr. Jerome Groopman, a distinguished AIDS researcher, is quoted as follows, "Science keeps an open mind at all times, but there comes a time when you have to declare that the earth is not flat. It is incumbent on those who rejected H.I.V. to come to terms with this."

M.S. Ascher
W. Winkelstein, Jr.
H.W. Sheppard
E. Vittinghoff

1. Duesberg PH. Unpublished letter
2. Ascher MS, Sheppard HW, Winkelstein W Jr, Vittinghoff E. Does drug use cause AIDS? (Commentary) Nature 1993;362:103-4.
3. Kolata G. Debunking doubts that H.I.V. causes AIDS. New York Times, Thursday, March 11, 1993.

Submitted 10/6/94

APPENDIX N

UNIVERSITY OF CALIFORNIA, BERKELEY

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SCHOOL OF PUBLIC HEALTH
EPIDEMIOLOGY

140 WARREN HALL
BERKELEY, CALIFORNIA 94720 -7360

10 June 1994

Editor, Reason Magazine
3415 S. Sepulveda Blvd.
Suite 400
Los Angeles CA 90034

Madam;

The article, "What Causes AIDS?" contains misleading and incorrect information questioning the contagious nature of HIV infection and its causal role for AIDS. This has serious consequences, as this infection almost invariably results in long, painful, terminal illnesses and death. The authors are distinguished in fields far removed from the epidemiology of HIV and AIDS about which they pontificate. Would any of your readers hire an electrician to repair a faulty toilet?

The authors assert, "the only evidence that HIV *does* cause AIDS is correlation.". Correlation has established the causes of many diseases: smoking and lung cancer, Staphylococcus aureus infection and toxic shock syndrome, and ionizing radiation and leukemia, to name a few. They state, "There are many cases of persons with all the symptoms of AIDS who do not have any HIV infection.". This is not surprising as immune suppression, the underlying cause of AIDS, may result from defective genetic mechanisms, toxic chemical exposures, medicinal treatments, and infections other than HIV. They also assert, "There are also many cases of persons who have been infected by HIV...and show no signs of illness.". About half of all HIV infected persons develop AIDS within 10 years and of these, 90% are dead within two years. In studies observing HIV infected persons for more than 10 years, over 85% have developed AIDS.

The authors claim that the San Francisco Men's Health Study, for which the undersigned is "principal investigator", was "...designed not to test the HIV theory but to measure the rate at which HIV positive gay men develop AIDS. They did not compare otherwise similar persons who differ only in HIV status, did not control effectively for drug use, and did not fully report the incidence of AIDS-defining conditions in the HIV negative men..." These assertions are misleading or just plain false.

The San Francisco Men's Health Study is an epidemiological investigation of the cause or causes of AIDS, its transmission, and the natural history of the disease. Participants were a random sample of 1,000 single men living in AIDS affected areas

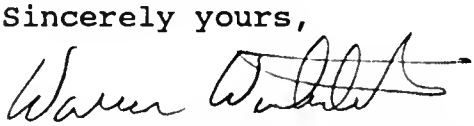
of San Francisco in 1984. When a serological test for HIV infection became available in late 1984, the participants were tested to determine HIV infection status. This allowed the investigators to conduct a large number of important analytic studies of causal factors, modes of transmission, and the natural history of HIV infection and AIDS.

An analysis of drug use, AIDS incidence, and progressive immune deficiency, using appropriate statistical techniques and proper controls, was published in 1993. No relationship between drug use and AIDS incidence or immune deficiency progression was found. The advocates of the drug etiology of AIDS have never accepted these findings, nor, the findings from several other rigorous studies of the drug hypothesis.

Because an AIDS diagnosis is almost invariably followed by death within two years, deaths may be substituted for AIDS diagnoses to evaluate the occurrence of cases among the uninfected. In the San Francisco Men's Health Study, 581 participants, who were uninfected by the HIV on entry, remained uninfected for over eight years. Among them, eight deaths ocurred, for a cumulative rate of 1.4%. Of the 400 men infected by the HIV, 169 deaths occurred, for a cumulative rate of 42.3%. These data are inconsistent with the contention that there were AIDS cases among the uninfected.

Space precludes a complete refutation of the other misstatements which burden the article, "What Causes AIDS?". More importantly, the readers of Reason Magazine should not be misled about the consequences of HIV infection. As indicated above, these consequences are very serious. Regardless of whether or not HIV infection causes AIDS, it is a strong predictor of premature death.

Sincerely yours,



Warren Winkelstein, Jr., M.D., M.P.H.
Professor of Epidemiology (Emeritus)

cc: C.A. Thomas, Jr.
K.B. Mullis
P.E. Johnson

Controversial AIDS Theories Debated at Forum in S.F.

By David Perlman
Chronicle Science Writer

At a scientific forum unique in the history of the AIDS epidemic, advocates of theories long dismissed or ignored by most of their colleagues found an establishment platform yesterday to contend that the HIV virus is not the cause of AIDS.

Peter Duesberg, a molecular biologist at the University of California at Berkeley, offered mountains of data to support his claim that AIDS is not an infectious disease. In the United States and Europe, he insisted, it is caused primarily among homosexual men by use of aphrodisiacs called "poppers" that are based on amyl nitrite compounds, other drugs ranging from cocaine to marijuana and AZT, an anti-viral drug used to treat AIDS.

In Africa, Duesberg said, the diseases called AIDS are caused by the same immunity-destroying social problems that have afflicted Africans for centuries — malnutrition, bad sanitation and inadequate health care.

Duesberg and his colleagues spoke yesterday at the annual meeting of the Pacific Division of the American Association for the Advancement of Science at San Francisco State University. The AAAS is the nation's largest scientific organization. In the past, its AIDS sessions have featured leading researchers presenting evidence that the unusual virus is the basic cause of the epidemic.

Flawed Evidence

To Duesberg, however, that evidence is flawed.

"AIDS does not fit any definition of an infectious disease," he said. The virus called HIV is "typically extremely rare and inactive and frequently not even present" in people who have AIDS, he said.

Cocaine and many other drugs have long been known to cause the same diseases that are now called AIDS, he said.

The audience of more than 100 appeared by their applause to be Duesberg allies. There was more muted applause for Duesberg's opponents, one of whom is Dr. Jerold Lowenstein, a nuclear medicine specialist at UCSF who treats scores of AIDS patients and conducts AIDS research in San Francisco and Africa.

Lowenstein offered research showing that HIV is present in virtually everyone with any of the AIDS-related diseases. Wherever HIV infections have surged — in Africa and more recently in such Asian nations as Thailand — AIDS cases and deaths have also increased, he said.

Risk Factors

The major risk factors that permit HIV infection also lead to the disease, he said. The presence of genital ulcers, where the virus can enter the bloodstream, means a five-fold increase in AIDS risk, his data shows, and sexual intercourse without a condom increases the AIDS risk 50-fold.

Another Duesberg opponent is Dr. Michael Asher of the California Department of Health virus laboratory in Berkeley. He countered Duesberg's indictment of "poppers" as a cause of AIDS with figures from a San Francisco study of several hundred gay men showing that none of those uninfected by HIV got Kaposi's sarcoma, one of the major AIDS diseases, even though they were heavy users of the drug. Nearly half of the men who used the drug and were infected with the virus developed the disease, the study showed.

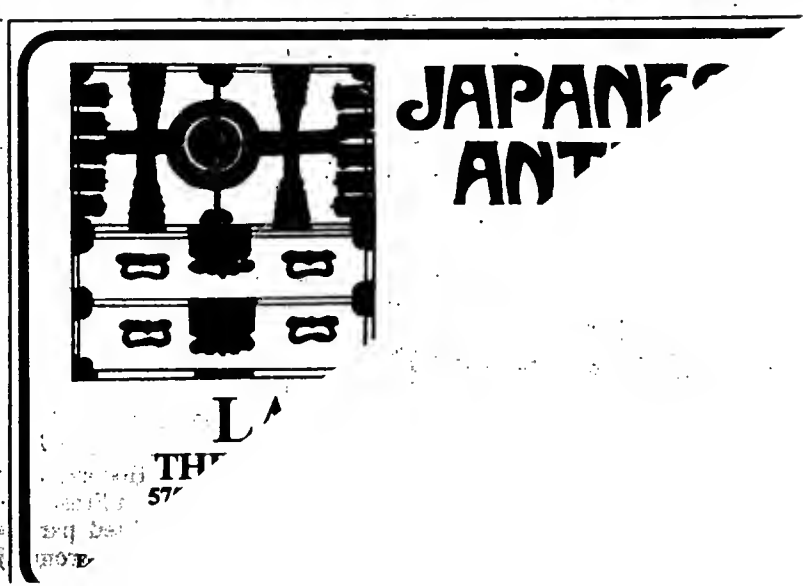
As to Duesberg's claim that AZT causes AIDS, Asher noted that in a recent study of 233 men who developed AIDS, 90 acquired the disease before AZT was developed. Asher agreed that the drug is toxic and has failed to live up to its early promise. But he said that calling AZT the cause of AIDS is like saying insulin causes diabetes.

'Catastrophic Error'

In support of Duesberg's claims, Phillip E. Johnson, a Boalt Hall School of Law professor, maintained that there is strong evidence showing that top AIDS scientists — including Robert Gallo of the National Cancer Institute and Anthony Fauci of the National Institute of Allergy and Infectious Disease — have committed a "catastrophic error" by insisting that their focus on HIV must bar all other theories about the causes of the disease.

"Official story tellers," Johnson said, have caused Americans to accept a single unproven theory as fact, while making outcasts of serious researchers such as Duesberg.

"Official explanations of how an ordinary retrovirus can kill cells it never infects have grown more complicated as the prospect of a cure or a vaccine has grown ever more distant," he argued.



Some Remarks on Causal Inference Based on Data from the San Francisco Men's Health Study

Warren Winkelstein. Jr.
Professor of Epidemiology (Emeritus)
University of California at Berkeley

For Presentation at the 75th Annual Meeting of the Pacific Division of the American Association for the Advancement of Science, 21 June 1994, San Francisco

When, in 1983, under the auspices of the National Institute of Allergy and Infectious Diseases, my colleagues and I decided, ~~in 1983~~, to study the epidemiology and natural history of AIDS, ~~relatively~~ little was known about the disease. Its cause was suspected to be an infectious agent, possibly a retrovirus. The intense clustering of the disease in gay men, ~~at that time~~, strongly suggested a sexually transmitted disease but other hypotheses seemed plausible, including exposure to toxic chemicals, and excessive use of recreational drugs. The natural history of the disease was pretty much limited to the observation of profound depression of CD4+ T lymphocytes. We decided that the most effective strategy for unravelling the epidemiology and natural history of this newly emerging disease was to study it in a random sample of men drawn from the area of San Francisco where the epidemic was most severe at that time ~~In 1983~~. Thus, in 1984, we sampled 19 census tracts within a five kilometer radius of the corner of Castro and Market Streets, the epicenter of the epidemic, obtaining a study population of over 1,000 AIDS free men. These men have been followed twice yearly with examinations and detailed questionnaires since recruitment. When the AIDS related retrovirus, subsequently named human immunodeficiency virus (HIV), was isolated in late 1984 and a serological test for infection became available, the study population was characterized with respect to infection status.

The first slide shows the eight year follow-up experience of

Insert A: Earlier today, and on other occasions in other venues, Duesberg and Ellison have asserted that there were ~~some number, usually~~ 45, AIDS cases among HIV seronegatives in the San Francisco Men's Health Study. My colleagues and I, and others who have seen or heard these assertions, have repeatedly ~~shown~~ pointed out to Duesberg and Ellison why these are false positive diagnoses. They have chosen to disregard these critiques. We can use the data before you to test their assertion.

Line three of the table indicates the high eight year case-fatality ~~percentage for~~ AIDS diagnoses. The actual rate is approximately 80 percent. Therefore, if there had actually been 45 AIDS cases among the HIV seronegatives, one would expect that deaths from AIDS in this group would number approximately 36 (.80 X 45) and the total deaths among HIV seronegatives would have been approximately 43 instead of the observed seven. You may judge for yourselves whether the observed deaths among HIV seronegatives is consistant with the claimed 45 AIDS cases among them.

Note: Calculation of the case-fatality rate:

Expected deaths from non-AIDS causes in the HIV seropositives is the death rate in HIV seronegatives multiplied by the number of seropositives: .019 X 400 = 7.6

Subtract eight cases from the deaths among HIV seropositives to get the estimated number of AIDS deaths: 169 - 8 = 161

Divide AIDS deaths by AIDS cases and multiply by 100 to get the eight year case-fatality percentage: 169/204 X 100 = 82.8 (80 percent used in the text to simplify audience comprehension)

application of two of these criteria to the evaluation of a causal inference from the data shown in the first slide. I will present an analysis of confounding and data replicating San Francisco Men's Health Study findings.

Early in the epidemic, it was hypothesized that AIDS was caused by excessive use of amyl nitrite inhalants by gay men to enhance sexual gratification. More recently, it has been suggested by Duesberg that the HIV - AIDS causal association is spurious because of confounding by amyl nitrite use, i.e., amyl nitrite causes AIDS and is associated with high risk behavior leading to infection by a non-pathogenic HIV. The next slide shows that, indeed, use of amyl nitrite weekly or more frequently is associated with having 10 or more sexual partners in two years, a strong risk factor for acquiring HIV infection. Forty-nine percent of gay men were in this category as compared to 33 percent in the heavy use, lesser number of partners category. The association is quite unlikely to be due to sampling variation. Also shown on the slide are data indicating an association between amyl nitrite use and AIDS, albeit the association is not as strong as the HIV - AIDS association shown earlier. To evaluate which association is spurious, i.e., caused by confounding, the data need to be stratified as shown in the next slide.

In this slide the gay study population has been divided into four groups according to HIV serostatus and amyl nitrite use on entry. As already shown, no AIDS cases occurred among the HIV

seronegatives. Among the HIV seropositives, 51 percent of the heavy users of amyl nitrite developed AIDS and 47 percent of the light or non-users of amyl nitrite developed AIDS for an insignificant difference of four percent. Clearly, the amyl nitrite association with AIDS shown on the previous slide is completely explained by the confounding effect of the strong association between both HIV infection and AIDS and HIV infection and amyl nitrite use. More complex regression analyses using drug use data from each of the 16 examination cycles confirm a lack of association shown on the slide before you. (Slide off)

We also examined the relationship between HIV infection, drug use, and CD4+ T lymphocyte loss in the San Francisco Men's Health study. We showed that CD4+ T lymphocyte loss, the pathognomonic characteristic of HIV infection, is limited to HIV seropositive study subjects and that there was no discernible difference between the time trend of cell loss among HIV seropositive men classified according to a composite drug-use score. This finding was replicated by a similar analysis carried out by Schechter et al. on data from the Vancouver cohort study as shown on the next slide. The data show trajectories for CD4+ T lumphocyte cell counts over time. The two upper lines show the trajectories in HIV seronegative subjects who were users and non-users of nitrite inhalants, and the two lower lines show the counts over time for HIV seroconverters who were users and non-users, As in the San Francisco Men's Health Study, CD4+ T lymphocyte cell declines were limited to HIV seropositive study

subjects and the trajectories were indistinguishable between the drug users and non-users.

The foregoing provides strong epidemiological support for a causal inference for the association between HIV and AIDS and no support for the hypothesis that the AIDS epidemic is due to excessive drug use. In the time remaining to me, I would like to say a few words about the HIV/AIDS epidemic in San Francisco. (Slide off)

Key factors in the propagation of an infectious disease are, first, the infectivity of the agent, epidemiologists call this the transmission probability. It is the probability that an exposure results in infection and varies with each infectious agent and its mode of transmission. Thus, HIV has a low infectivity for sexual contact but a high infectivity for direct blood transmission. Second, the number of exposures in a given period of time which provide the opportunity for infection. And, third the duration of infectiousness which is usually very short for most acute infections and very long for slow acting viruses like HIV. By combining these factors, epidemiologists compute a parameter called the basic reproductive rate, R_0. If this parameter exceeds one, it means that each infected person will generate more than one additional case and the epidemic will be propagated. If R_0 is less than one, the epidemic will die out. Using data from the San Francisco Men's Health Study, the basic reproductive rate for HIV infection in San Francisco gay men in 1984 can be calculate to be 12 as shown in the next slide.

The interpretation of an R_0 of 12 is straightforward. It is the average number of new infections produced in San Francisco by one infected individual who remained infectious during the 10 year incubation period of AIDS. (Slide off)

From 1984 onward, extensive educational efforts were mounted in San Francisco by various agencies to alert the gay population to the dangers of HIV infection and the available methods for preventing infection, viz., limitation of numbers of partners and use of condoms during sexual intercourse. A number of surveys indicated substantial behavioral changes during the late 80's which would favor a lowered rate of transmission. In order to more objectively measure the effectiveness of prevention, we conducted another population based serological survey in 1993. This yielded the necessary data for calculating the basic reproductive rate for HIV infection in gay men in 1993. R_0 in 1993 was 2.2 compared to 12 in 1984. The conclusion to be drawn from these observations are that while the spread of the epidemic in San Francisco gay men has been considerably reduced, HIV infection continues to be propagated. It is also important to note that the lowered basic reproductive rate is consistant with the recently announced "peaking" of AIDS incidence in San Francisco and the prediction that, unless infection rates are further reduced among gay men, the local epidemic in the gay community will continue through the 1990's, albeit at a considerably reduced level.

The epidemiological data which I have presented from the San Francisco Men's Health Study, along with data from many studies

in this country and abroad, cannot support an alternative to a causal role for HIV and AIDS. The late Abraham Lilienfeld, one of the leading epidemiologists of the 20th century, taught that a major consideration in evaluating an observed association for cause was that the incidence of the disease should decrease with elimination or modification of the hypothesized causal factor. This is exactly what has happened in San Francisco where a decline in HIV infection rates has been followed by a decline in AIDS after an interval equivalent to the incubation period.

Thank you very much.

the study population with respect to AIDS and mortality according to sexual orientation and HIV serostatus. Among 367 gay men who were uninfected by the HIV on entry, ~~i.e., HIV seronegative~~, throughout the eight year follow-up, none developed AIDS and seven died for a cumulative mortality of 1.9 percent. Among 45 gay men who were HIV seronegative on entry but who became infected during the eight year follow-up, 11 developed AIDS and eight died for a cumulative mortality of 11.1 percent. Among 400 gay men who were HIV seropositive on entry, ~~i.e., infected by the HIV,~~ 204 developed AIDS and 169 died for a cumulative mortality of 42.3 percent. Among 214 heterosexual men, all of whom were HIV seronegative on entry, one became infected during the eight year follow-up, no AIDS cases occurred and one death was recorded for a cumulative mortality of 0.5 percent. These data would appear to support a causal inference for HIV and AIDS. ~~(Slide off)~~

~~However~~, Epidemiologists apply ~~additional~~ criteria to evaluate the validity of such inferences. These criteria include the strength of the association, the presence of a dose-response effect, i.e., increased occurrence of disease with increased exposure to the suspected causal agent, control of confounding variables, i.e., accounting for extraneous factors associated with both exposure and disease which produce spurious associations, independent replication of findings, and biological plausibility. Although only strength of association ~~was shown~~ on the ~~previous~~ slide, the HIV association with AIDS can be shown to satisfy all of these criteria. Let me now demonstrate the

Incidence of AIDS and Deaths According to Sexual Preference and HIV Serostatus, SFMHS, 1984-'92

Sexual Preference	HIV Serostatus	N	AIDS Cases n	AIDS Cases %	Deaths n	Deaths %
Homosexual:						
	Negative	367	0	0	7	1.9
	Converted	45	11	24.4	5	11.1
	Positive	400	204	51.0	169	42.3
Heterosexual:						
	Negative	214	0	0	1	0.5
	Converted	1	0	0	0	0
	Positive	0	0	0	0	0

Numbers of Male Sexual Partners and Amyl Nitrite Use, SFMHS, 1982-'84

Male Sexual Partners	Amyl Nitrite Use[1] Heavy[2]	Light or None[3]
=>10	404 (49%)	113 (14%)
0-9	264 (33%)	31 (4%)

X^2=16.58, d.f.=1, p=<.0001

1. During 24 months before entry.
2. Heavy = weekly or more frequent use.
3. Light or None = Less than weekly or no use.

AIDS and Amyl Nitrite Use, SFMHS, 1984-'92

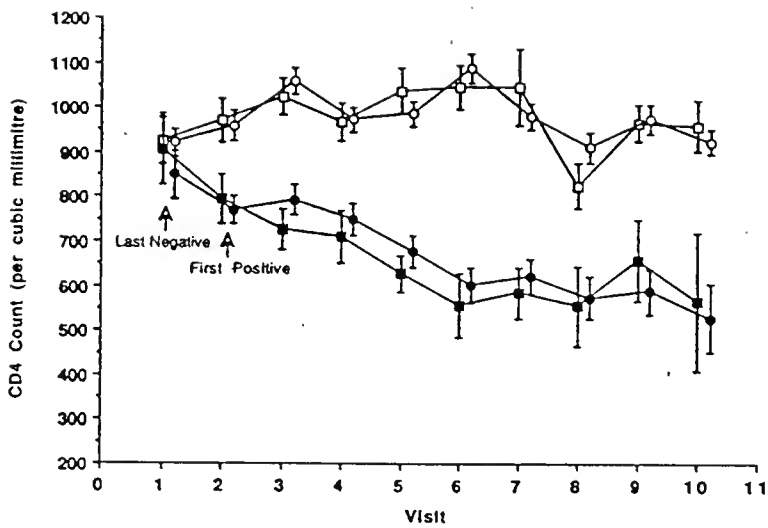
Amyl Nitrite Use	AIDS Cases	Incidence
Heavy (N=144)	54	37.5%
Light (N=668)	161	24.1%

O.R.=1.89, (95% C.I.=1.27-2.81), P <.001

AIDS Incidence, Amyl Nitrite Use, and HIV Infection: SFMHS, 1984-'92

HIV Serostatus & Aids Incidence	Amyl Nitrite Use[1] Heavy[2]	Light or None[3]
HIV Positive:		
Number Observed:	105	340
AIDS Cases:	54	161
Cumulative Incidence;	51.4%	47.4%
HIV Negative:		
Number Observed:	39	328
AIDS Cases:	0	0
Cumulative Incidence:	0	0

1. During 24 months before entry.
2. Heavy = weekly or more frequent use.
3. Light or none = less than weekly or no use.



CD4 counts for seronegative and seroincident groups stratified by use of nitrite inhalants.

$$R_0 = BCD$$

Where: R_0 = Basic Reproductive Rate
B = Transmission Probability (0.1)
C = Mean Annual Number of Partners (12)
D = Duration of Infectiousness (10 yrs.)

Thus: $R_0 = 0.1 \times 12 \times 10 = 12.0$

INDEX--The AIDS Epidemic in San Francisco: The Medical Response, 1981-1984: Volume VII, Warren Winkelstein

Sally Smith Hughes

Graduated from the University of California, Berkeley, in 1963 with an A.B. degree in zoology, and from the University of California, San Francisco, in 1966 with an M.A. degree in anatomy. She received a Ph.D. degree in the history of science and medicine from the Royal Postgraduate Medical School, University of London, in 1972.

Postgraduate Research Histologist, the Cardiovascular Research Institute, University of California, San Francisco, 1966-1969; science historian for the History of Science and Technology Program, The Bancroft Library, 1978-1980.

Presently Research Historian and Principal Editor on medical and scientific topics for the Regional Oral History Office, University of California, Berkeley. Author of *The Virus: A History of the Concept*, Sally Smith Hughes is currently interviewing and writing in the fields of AIDS and molecular biology/biotechnology.