

*This is an interview with Dr. William A. Blattner, Chief, Viral Epidemiology Section of the National Cancer Institute (NCI), National Institutes of Health (NIH), at his office in the Executive Plaza North Office Building, Bethesda, Maryland. The interview was conducted by Dr. Victoria A. Harden, Director of the NIH Historical Office, and Dennis Rodrigues, program analyst, NIH Historical Office, on 2 March 1990.*

Rodrigues: Would you tell us about your training and your professional background before you came to the NIH, how you came to the NIH, and how you became involved with HIV disease?

Blattner: I did my undergraduate medical school training at Washington University in St. Louis. I had my first experience in epidemiology during summer rotation through [Dr.] Lou Allen Sale, who was the head of preventive medicine at Washington University. He arranged for me to go to Mexico as a COSTEP [Commissioned Officers Student Training and Extern Program], which is a PHS-sponsored [Public Health Service] activity. I spent three months in Mexico City working at a children's hospital, trying to assist in some studies of nutritional determinations, particularly measuring red cell enzyme assays in children with malnutrition. It was not scientifically productive, because we spent most of the summer trying to get reagents shipped down to Mexico to run the assays. The problems we experienced in trying to get a fairly routine substrate for an enzyme assay taught me a lot about the prolonged delays that can occur in international research programs. If I had been in St. Louis, I could have gotten the substrate in twenty-four hours. It took me two months to get it in Mexico City. There were the problems of transportation, customs, and living and working in the Third World environment. I think that often we do not appreciate what our overseas colleagues have to put up with--they do not have things we take for granted. It has helped me, subsequently, in my efforts in the international arena, to be a little more sympathetic about why things do not happen pronto.

After graduating from Washington University, I went to Rochester, to the Strong Memorial Hospital at the University of Rochester in New York. I did two years in internal medicine, and from there I went to Cornell [University] to do my third year as assistant chief resident at Cornell and the [Memorial] Sloan-Kettering [Cancer Center] in New York. During my time in Rochester, I can remember getting a call from Joe [Dr. Joseph] Fraumeni. He had done some archaeologic work in the Commissioned Corps Office over in Building 10, looking for potential applicants for the epidemiology program. He had come across my folder, and for whatever reasons, invited me to the NIH for an interview. That set the stage for my coming to the NIH in 1973, after my year at Cornell. At Cornell, I had the good fortune of working frequently at Sloan-Kettering, which provided me with my first experience in oncology as it should be practiced. I think it focused my attention on the idea that cancer is an important disease, and it poses a challenge similar to that of AIDS, because it is a multi-system disease that involves the totality of the patient. To be a good oncologist, you have to be a complete

physician, because cancer has so many complications.

Harden: Is this what you mean by "oncology as it should be practiced?"

Blattner: Yes. At Sloan-Kettering there was an attitude of optimism and a belief that cancer was a treatable, potentially curable disease. When I first arrived, because of my previous experience, I did not have such an optimistic and hopeful attitude. I am basically an optimistic person; in the face of adversity, I look for the positive potential in the situation rather than the "down" side. The Sloan-Kettering experience thus oriented me toward a career in cancer.

Cornell also introduced me to a very strong infectious disease community. Tony [Dr. Anthony] Fauci had come to the NIH from Cornell a year or so before, and Henry Masur interned, I think, under me. I made a lot of contacts that would subsequently be important in my interactions here at the NIH. Dr. Warren Johnson was the director of the International Health Care Services at Cornell, and working with him was a very positive experience.

The years at Rochester and Cornell provided balancing experiences in the development of my career. Rochester was more of the city-hospital type of environment. There I learned to treat a lot of common diseases in my sleep--so to speak. Cornell was much more of a referral center, and the staff saw a lot of unusual diseases. It also has a large international clientele, which enabled me to see some disease problems that are common in overseas countries but rare here--for example, parasitic infestations. There are various diseases you usually do not see in a lifetime, unless you work in a place like Cornell. These two experiences, I think, laid the foundations for my career.

I came to the NIH without any real training in epidemiology. In 1973, I planned to spend two years at the NIH, after which I would go back to New York and do sub-specialty training in infectious diseases, or whatever I might end up doing. When I came to the NIH, I spent a lot of time on the cancer wards and also on the infectious diseases wards on rounds with Tony Fauci. I was interested in the interrelationships of the immune system with cancer. I had an interest in an interdisciplinary approach to research, and I was brought by Joe Fraumeni and Bob [Dr. Robert] Miller into the study of families at high risk for cancer. I had a strong interest in developing the application of laboratory approaches to cancer etiology, which has now become popular as the field of biochemical epidemiology and is the "approach du jour" in epidemiology. But I was taking a lot of courses through the FAES [Foundation for Advanced Education in the Sciences, Inc.] evening graduate school at the NIH. I took subjects beyond those that one might expect someone in epidemiology to take, particularly courses focusing on the immune system. My basic approach was to study families at high risk for cancer, believing that an interdisciplinary method bringing laboratory and epidemiological

techniques together would uncover the pathogenic and etiologic mechanisms that underlie the process of development of cancer.

In 1974, Joe [Fraumeni] had a call from Bob [Dr. Robert] Gallo, who, at that time, was over on Pearl Street, where the Air Rights Building is now--the old Bionetics facility. Gallo's laboratory was working with the HL23 virus which was then thought to represent the first human retrovirus but subsequently was shown to be an animal contaminant. This circumstance was the source for a lot of grief for Bob, but it was a useful time for me from a certain perspective. I established a close relationship with Bob that has gone on since then. I think that in dealing with Bob Gallo an important aspect of the relationship is trust. We developed a trusting relationship at that point despite the adversity of the time for Bob. My role in this Gallo laboratory project basically was to interview and to collect information on the patient from whom the leukemia bone marrow containing the HL23 virus had been obtained by Gallo. In January 1975, I made a trip to visit the woman and her relatives in her home town in Kansas to get additional material. That material was used in subsequent attempts to isolate the virus. We never succeeded. We still have material from this woman and her family members in the freezer. In 1974 I had gotten married, and on this trip to Kansas in 1975, I took along my bride. We planned to visit some of my relatives in the area after completing my work. My wife is a nurse, so she drew the blood and collected information from the patient's family.

During this time I recognized the need to establish a repository of biologic materials. The specimen from the woman in Kansas was added to that repository. I had a little table top centrifuge in my office in which I would spin the specimens down. In retrospect, with all that we now know about biosafety, many of the things that we did in those days as house officers, blood smears, for example, were done without much concern for biosafety. I got tired of spending my evenings labeling tubes, so later we developed a more formal repository which now houses thousands of samples.

To return to my early work with Gallo, when we became interested in the relationship of the Gibbon ape leukemia virus to the woman from Kansas's virus, I tried to track down the apes that had been the source of the animal virus isolate. That led me subsequently to Sacramento and the Bay area, where there was an "ape lady" who was famous for keeping primates in her home. In fact, she was on the cover of the local Sunday magazine from a Sacramento newspaper, holding up her Gibbon ape. Interestingly, another species of monkey was also in the picture. This Sacramento woman had all these apes and monkeys living together in her backyard. The importance of this was that one of her animals was the source, as I understand it, of the Simian sarcoma virus discovered at Davis [University of California, Davis]. One of her animals was probably cross-infected from a different species. That led to a different type of malignancy in a different species

of monkey. These were the interesting background things that Gallo really appreciated. I did not get anything scientifically out of this work except Bob's friendship and good will.

After the blow-up over acceptance of HL23 [as a retrovirus], for reasons that are recorded--presumably contamination--I returned to my studies of families, focusing primarily in the area of immunology. I made my first contacts with Sam [Dr. Samuel] Broder. He and I were clinical associates together in 1975 on 12 West [in the NIH Clinical Center]. Subsequently, I worked with him in the immunologic evaluations of some families in collaboration with colleagues from Tom [Dr. Thomas] Waldmann's group. After I arrived at the NIH, I can remember [Dr. Costan] Berard's first lecture on the concept of T- and B-cells. I would go every year to hear the update on the progress made in understanding the relationship between the immunopathology that was going on and the immunology that was being characterized. It was a very exciting time. I learned a lot about fundamental biology and immunology, which proved useful later on. Also, I established an association with [Dr.] Dean Mann, whose future work was very important in defining immunogenetic aspects of cancer and familial cancer. I also met [Dr. H.] Uchiyama, who was from [Dr. Kiyoshi] Takatsuki's group in Japan and who had come over to Sam Broder's laboratory. At that time they were working with HUT102 and had established B-cell lines from one of the patients who was the source of the first isolate of HTLV [Human T-cell Leukemia Virus]. Uchiyama was critical to Dr. Waldmann's and Sam's development of anti-*tac* antibody, which was the monoclonal to the interleukin-2 receptor. There was a lot of networking and interaction going on at this time. This was when I first heard about T-cell leukemia.

At the beginning of 1980, Bob Gallo brought me back into the fold, so to speak, with the question of a new virus that they were in the process of characterizing. They were focusing on the relationship of this HTLV virus to mycosis fungoides, which was the clinical diagnosis on the patient, CR, from whom the virus was isolated. Bob told me about his work and I helped him get samples from cases of mycosis fungoides. We ran a lot of tests, but none of the cases were positive.

Mr. Gordon Piller, who runs the Leukemia Research Fund in the U.K., had come over to the NIH a few times in the preceding years. Bob Gallo had brought me over to his laboratory a few times to meet Mr. Piller, because Piller was trying to develop in the U.K. a front-line, field-oriented approach to epidemiology modeled after the approach I was pursuing. At that time, most of the epidemiology in the U.K. was being run out of armchairs in Oxford, by looking at statistics, and not really "pressing the flesh" in a certain sense. Mr. Piller was an important contact, because in May 1981, the Leukemia Research Fund sponsored a one-day meeting in London, and I was invited to it. That was really, for me, a watershed event. I was fairly successful at what I was doing in family studies and had a lot of ideas

and many projects going on. I had not given the HTLV story as much attention as perhaps I should have.

I went to this meeting in London, which had a rather interesting format. Sir John Dacie, a famous hematologist from the U.K., had developed an approach to such meetings in which he got rid of all the props that scientists use, such as slides, blackboards, and charts. He put us into a fairly barren, quite old amphitheater in the Royal College of Pathology, which was established around 1853. The scientists sat around a table--a few French, a few from the U.K., myself and Bob Gallo, talking about leukemia research without any slides or any other props.

The night before this meeting, Bob had given a talk, which was one of his usual whirlwind tours of the field looking at where things stood with HTLV. The talk was inspirational. Dr. Gallo has a beautiful way of synthesizing things. He came down from the lectern after his talk. I was standing there with him when a dermatologist from one of the local hospitals came up to him afterwards, and said that he did not think that the patient, CR, had the diagnosis he was said to have. He did not think the patient had mycosis fungoides. For me, that was a real red flag. We had been looking at mycosis fungoides but had not been finding anything. So, I was primed somehow, with that little comment, to start thinking about the HTLV problem again.

As a consequence, the next day Gallo revealed a little more of the unpublished data, in which he had a few positive cases from Japan with this ATL [adult T-cell leukemia/lymphoma] syndrome that he had gotten from Professor [Yohei] Ito. He revealed that all of several hundred mycosis fungoides cases were negative. Danny [Dr. Daniel] Catovsky presented some cases of West Indians, three or four, who had an unusual form of clinical lymphosarcoma cell leukemia of T-cells. This information jelled in my head. I went back to my hotel room and I wrote a four-page letter, of which I still have a copy, outlining my next three years of research. It was really extraordinary for me, because I had not done that sort of thing before. I had a series of hypotheses: (1) HTLV-1 caused the ATL disease in Japan; (2) it was causing this disease in the West Indies; and (3) it also caused other unrecognized immunologic aberrations.

We started a collaboration with Catovsky, who sent over some serum from these West Indian cases. This was the first time that Gallo's people started getting clear positives. In the meantime, they made a second isolate from a black woman from New York. I went up to New York and spent the day in the record room at SUNY [State University of New York] Downstate State Hospital, where I reviewed a huge chart. There was not very much there. I flipped over the nursing notes and there was the information I was looking for. This woman was from the Caribbean. She was from Saint Lucia, and that provided another confirmation of a Caribbean connection.

I was doing some work on genetics of families and had visited an investigator in the Auburn Building in Bethesda. The Red Cross used to have a laboratory in the building. I went into this doctor's office to see if he would run some sort of red cell genetic markers on some families. Although I did not know it, he had been doing a study with Dr. Michael Crawford of Kansas University Medical Center, who is an anthropologist, on sera from the Caribbean. I told him about my idea of a link between the Caribbean and cases of leukemia and lymphoma. He said, "Isn't that an interesting coincidence? I'm studying sera from people in the Caribbean Islands." Our conversation led to a collaboration and subsequently the first epidemiologic paper linking the virus to the Caribbean and ATL. Most people focus on the Catovsky paper, which is in the *Lancet*. It did not present any HTLV testing data, however. Catovsky had written a pathology paper, and I had added some things to the discussion about the link of HTLV to these cases--to scoop myself, in a sense. But Catovsky had the paper almost written and it was important to get the information out.

At that time, there were some fairly unpleasant things going on with Professor [Yorio] Hinuma in Japan, who was really giving Bob Gallo a hard time. Bob had gone to Japan in 1981 at the invitation of Professor Yohei Ito to speak and to try to set up a collaboration. Bob had gone with the idea that he was going to give reagents to the Japanese and that there was going to be an exchange. Greg [Dr. Gregory O'Connor] was involved in this. Bob told me that Dr. Hinuma was in the audience for his talk, and that Hinuma was scheduled to talk about EBV [Epstein Barr Virus] and the related work he was doing. Gallo presented his paper and according to Dr. Gallo, Dr. Hinuma went ashen because he had gotten these cell lines from Dr. Kyoshi and had been doing immunofluorescence with these ATL sera while Gallo had already discovered the virus. It created a very unpleasant and nasty interaction.

The Catovsky paper turned the focus away from Japan and provided another venue, so to speak, for this virus. I published the first paper later that year [1981] describing the Caribbean as a viral endemic area and I reported the first sera on the ATL cases from the Caribbean, as well as from the normal population. That was an important first chapter for me. One of the jokes I made at the time of the London meeting's close was: "Maybe, we should have a meeting about this in Jamaica next year."

In the fall of 1981, we met with Greg O'Connor, and we went down to PAHO [Pan American Health Organization], where Bob Gallo and I met with Dr. Allayne and some other people. Dr. Allayne gave me the name of the head of the pathology department at the University of the West Indies, [Dr.] Nigel Gibbs, who is now at WHO [World Health Organization]. I was aware that the department had published in the cancer research area, and I hoped there were people on the faculty

with whom we could work. I wrote to Dr. Gibbs, essentially inviting ourselves to his campus. I said, "We are interested in this syndrome; here are some features of it." He wrote back politely and said, "You're welcome to come. We don't have any of that kind of problem down here, but I would be glad to meet with you." Bob and I went to Jamaica in January 1982 and established contact in what became an ongoing research project with the University of the West Indies, supported since 1983 under a contract mechanism. Lo and behold, as we went on clinical rounds, we found two ATL patients. I took some serum from them back with me to the NIH. Within a year, we accumulated sixteen to twenty cases of ATL and showed that over half of the newly diagnosed lymphoma patients there had ATL.

Harden: You were able to identify Japan and the Caribbean as sites for this virus. Does it exist in other places, too?

Blattner: Oh, it is in a lot of places. We were also surveying other populations at this time. Some of our data were false positives and some were true positives. The assays were tough. It was also a critical time in terms of developing assays for retroviruses. We started out with insensitive and nonspecific assays, but we were able, through the availability of reagents and sera, to work with [Dr.] Carl W. Saxinger and [Dr.] Marjorie Robert-Guroff to purify the antigens and develop assays. Carl Saxinger had a contract with BioTech and Dr. Ann Bodner. That group worked to develop an ELISA [Enzyme-Linked Immunosorbent Assay] assay. In the course of this, we developed a close relationship. We developed computer links to allow us access to the data to promote analyses of results and so on. These are some of the important little details.

Later on in the HIV [Human Immunodeficiency Virus] story, these links were really key, because we had the direct ability to do testing quickly and get results back directly once the AIDS virus was identified. I think the key thing about this period was summarized in an *Annals of Internal Medicine Clinical Conference* on ATL and HTLV. It was published in 1982 or 1983. Sam Broder was the editor. It was Vince [Dr. Vincent] DeVita who introduced that program and said, "This discovery was really the culmination of one of the eight original objectives of the Cancer Institute when it was established in 1937: define human retroviruses associated with cancer." In many respects, however, this major discovery was overshadowed by AIDS. Retroviruses, of course, had first been recognized at the turn of the century.

Harden: Except for one thing. At the turn of the century, there was no way to differentiate viruses into groups as there is today.

Blattner: Yes. I do not think viral differences were appreciated until the work of Dr. Ludwik Gross in the 1950s, when he was able to start actually characterizing

different types. When you go back to the turn of the century, there were filterable agents with the ability to cause leukemias, which later served as reagents in the virus-cancer program.

Harden: Have DNA or RNA non-retroviruses been linked with cancer?

Blattner: Some have, but they are ubiquitous. The thing that distinguishes HTLV from EBV and some others is that the retroviruses are very restrictive. It just shows the diversity of how viruses cause trouble. This was a major discovery. Gallo had invested much time and effort in this issue, and in some respects, I think it is a tribute to him that he even got into AIDS. You have to recognize that he has made a major discovery, a tremendous breakthrough, after all these years of negative data. There were very lonely days for Bob, when he was searching alone for cancer-causing retroviruses in humans. He was the laughing stock of science at one point, but he persisted in looking for these retroviruses. I was there for some of that, and I know that people have very selective memories for these things. During this time, he was very successful in characterizing this virus and its genes. I think it is important to realize the background--where were all the Nobel laureates when AIDS came along? They were off doing whatever they wanted to do.

Bob Gallo was one of a very small handful of people who had any competence to look at the AIDS problem, and he got involved without having to be pushed into it. All the things that are going on related to this [John] Crewdson's claims are tremendous distortions. That article [John Crewdson, "The Great AIDS Quest," *Chicago Tribune*, November 19, 1989, Section 5, pp. 1-16] and the Shilts book [Randy Shilts, *And the Band Played On: Politics, People, and the AIDS Epidemic*, 1987] are the sources of all the nasty stuff going on. There is a total lack of appreciation for the fact that this man could have spent the rest of his career focusing on HTLV and could have made contributions of a tremendous caliber by themselves.

Anyway, while all of this work was getting started in the HTLV area, I was the head of the Family Studies Section at NCI; Jim [Dr. James] Goedert was in my section and Bob [Dr. Robert] Biggar was coming in at this point, having returned from Ghana. Jim was basically doing clinical epidemiology; he made important observations about the relationship of certain congenital anomalies to the risk for testicular cancer and about familial cancer. We would go on ward rounds at Georgetown [Hospital], I think, where he had recently come from. Goedert is a very gifted guy. He is one of these people with no formal training in epidemiology who nevertheless has a "green thumb" for etiologic research. [Dr.] Elizabeth McKeen introduced me to him.

He was at Georgetown going on ward rounds; this was in December 1980, as I



remember. Jim was alerted to the case of a young medical student with Kaposi's sarcoma, which was an oddity. We did not see Kaposi's in that age group and so were drawn to studies of people with unusual ages of onset of cancer and so forth. In May and June of 1981, we went to the ASCO [American Society of Clinical Oncology] meetings, and I think there was some discussion of unusual occurrences of Kaposi's. The CDC [Centers for Disease Control] was working with people in Los Angeles. During that time, I was personally embarking on the HTLV path. There was a convergence and coincidence of events taking place, with Jim Goedert recognizing one of the first patients with AIDS. In fact, Jim is a co-author of the *MMWR [Morbidity and Mortality Weekly Report]* report of the first cluster of Kaposi's sarcoma. The memo that you may have seen from Joe Fraumeni--I do not know what the date of it was--was a reflection of the people within my branch stirring to address intertwining sets of issues. In some respects Joe helped us all begin pulling in the same direction.

Bob [Biggar] was not in the section at that point. He was newly back from Ghana when he said that he wanted to fly to Denmark. Contrary to the portrayal in the Shilts book, it is difficult when you have someone new come into your program. Biggar was new; he had come from the Viral Cancer Program. Foreign travel in the Cancer Institute at the NIH is not something that you take lightly. There has to be a lot of justification for it. Bob's request was not turned down, as Shilts suggested, because AIDS was of no interest for NCI. Rather it was because of bureaucratic requirements to justify overseas trips, which are a politically sensitive issue given all the talk about government "junkets" etc.

Another piece of the puzzle was discovered during our collaboration with Dean Mann. We had set up a fairly high powered immunologic capability through an interagency agreement with the Uniformed Services University [for the Health Sciences] with Mike [Dr. Douglas Michael] Strong, who ran a transplantation service. One of the things that we were able to do through this mechanism was to develop a lot of immunologic assays. We also bought a FACS [Fluorescence Activated Cell Sorter] machine. A FACS machine is used for identifying T-cell subsets and, in retrospect, was one of the key instruments that helped us recognize the extent of the problem caused by AIDS.

Harden: When did you first start thinking of AIDS as a separate disease--something that was not just a curious phenomenon?

Blattner: By the fall of 1981 we had a pretty good idea from work that Jim [Dr. James] Curran reported at that infamous meeting in 1981 when he came up here to the NIH. I cannot remember whom he was briefing. It was September 1981, as I remember it, when everyone was talking about the ground work that the CDC had been doing. There were many potential grantees at the meeting. There was a fellow--a Kaposi's sarcoma researcher from New York. I cannot remember his

name right now.

Rodrigues: Dr. Alvin Friedman-Kien?

Blattner: Yes, Friedman-Kien was there. He had lunch with Curran. I was very gung-ho on getting the wheels going on this thing, because it seemed pretty important, especially from a cancer research point of view. Kaposi's sarcoma seemed like a very important lead to pursue. During this period, Bob Biggar made his trip to Denmark. Through [Dr.] Peter Ebbesen, he began collecting materials from one cohort of gay men in Denmark. The concept behind that project was that in order to understand the dynamics of an epidemic, it would be best to be at the leading edge. If you are in the middle of the epidemic, you are swimming in a sea of information.

Inspired by Bob's concept, Jim Goedert went to New York and laid the groundwork for studying cohorts of New York and, subsequently, Washington, D.C., gay men. The first eleven patients of the fifteen studied for our February 1982 *Lancet* paper provided a lot of information. They were, as far as I know, the first group of clinically normal gay men that were immunologically evaluated. We wrote a somewhat misdirected paper on these people, however. It had the right information but some conclusions were misinterpreted. Maybe we overstated the association between a significant level of immune suppression in these people and their exposure to amyl nitrite. That information was available because of the FACS machine. Jim Goedert can tell you more details about his trip to Atlanta in the course of these cohort follow-ups. He was the first person to provide a population estimate of the severity of the AIDS epidemic. My recollection is that 30 to 40 percent of the hundred or so gay men evaluated had substantial immune deficiency.

We went wrong in our analysis in that paper because we were looking at the various behaviors, and one of the behaviors associated with immune deficiency was the use of amyl nitrite inhalants. In retrospect, we can think about this differently. It was a mark of a high risk behavior for HIV infection. You have to understand that when you are going through this kind of process and living it, as opposed to looking back on it, things were not that clear. There were very few of us who were living it, because there were not very many people working in the area. It is very clear to people in retrospect how "stupid" we were, but ultimately the problem got solved through the process of scientific research.

Harden: One of the things in which we are very interested is your thought process as you approached a totally new disease problem and worked it out.

Blattner: Well, it was not easy and it was not clear. An example of one wrong turn on our part was our first AIDS paper published in the *Lancet* in 1982. Unfortunately as a

by-product of this paper, we were labeled as the group that thought that amyl nitrite caused AIDS. In retrospect, it is easy to see how our analysis was confounded. People who had the most severe immune deficiency had the strongest history of amyl nitrite use. What this really reflected was the fact that people who had the heaviest nitrite use were the people who had the largest amount of anal receptive sex. As a result they probably got the virus earliest.

The other thing that was somewhat astonishing about these data was the insight they provided into the gay life style. Many of these men had a large number of partners. People had sixty to a hundred partners in a year with the bath-house sex and all the other things that were going on. Many investigators were people who were not involved in STD [Sexually Transmitted Disease] research and certainly not very aware of the gay life style. This was all a little overwhelming in some respects. A positive aspect of this study was to show the extent of CD4 damage in non-AIDS high-risk persons. This was one of the first publications to show the extent of CD4 abnormalities in gay men at risk for AIDS.

Harden: Was there opposition among the scientists to looking into this disease because it was a disease of the gay population?

Blattner: I did not sense that. I wrote a review of Randy Shilt's book *And the Band Played On* for *Scientific American*. It gives some insights into my thinking. Basically, the NIH has a system that is excellent for promoting research, but this was not research as usual. It took a while to appreciate the extent of the AIDS problem. There just have not been any other pandemics recently. There was a lot of sentiment in the early eighties that pandemics were not possible in this day and age. The NIH has an approach that works for solving problems, but it may take several years to get money into the pipeline in the extramural program. I think one of the advantages and the strengths of the intramural research environment is that you really do not have to justify your research in advance. You are given money and an ounce of faith to go out and do good research, and in five years an outside site visit team comes back to tell you if you still have a job. The scientist must make choices, but it does create an opportunity to take somewhat higher risks than people are able to do who have to apply for grant money.

I have not gone through the grants process, so I do not know, but it is my understanding that key people on the study sections make the decisions as to what research gets supported. These people also tend to be fairly conservative in the review process. There were a lot of applications at the time of the early epidemic coming from researchers like Friedman-Kien and some of his people, for example. These applications were getting shot down in the study sections because people did not appreciate the nature of AIDS. It is hard to put forward hypotheses and have the study section deal with them. There was one episode in 1982, when the first money for the MACS [Multi-Center AIDS Cohort Studies] was released.

This actually was a significant NCI initiative that was not appreciated. We had dry runs in which we tried to justify why we were requesting money. I was not directly involved in that, because it is an extramural activity, but I can remember advocating that the first million dollars should go towards AIDS epidemiology research. In the extramural program, it is more of a process. The grants getting process was not prepared to deal with the realities of a new pandemic that was totally unexpected and totally undefined at the beginning. There has never been a disease like AIDS. I hope to God there is not another one. At this time, AIDS was really the proverbial elephant--everybody had his or her hands on the elephant but could understand only a portion of its components.

Rodrigues: What were some of the events or findings that turned your thinking away from the lifestyle theories, like the amyl nitrite theory, as causes of AIDS? Was it the epidemiological findings that finally pushed those other theories off to the side or were there other laboratory findings?

Blattner: The work of the CDC and the expanding number of persons like hemophiliacs identified as at risk for this syndrome were two things. Our own studies of the epidemiology of CD4 cells, which showed that levels were associated with certain sexual transmission behaviors, also influenced our thoughts. Some alternative theories remained until the day of the press conference in which Gallo got dragged out on stage by Secretary [Margaret] Heckler for the announcement that the AIDS virus had been discovered. You can go back and look at publications talking about all the theories. Some of the early issues of *AIDS Research*, for example, summarize some of these theories. There were charts showing too much semen and too much blood--suggesting immune overload and collapse. Here was a virus that kicks in EBV [Epstein Barr Virus], so on and so forth. There were some publications on the work that Jim Goedert did looking at the cohorts. He started to get things right in terms of using T-cell subsets as an exposure marker, to use epidemiologic parlance. There was evidence that people who had lower T-cell subsets were infected. In fact, that was one of the conclusions, but these papers got overlooked because other papers came along. We were analyzing the subset data.

It was in late 1983 that we were beginning to formulate a pattern of transmission of the disease. One of the key aspects of this is that when you do data analysis, much time is spent on cleaning-up of data and file organization, so that you can actually manipulate the data and get the parameters condensed into something that is meaningful. There is a lot of leg work that can take months. All this was going on, when in early 1984, one Sunday morning, we were invited to breakfast with Bob Gallo at the Bethesda Marriott. He told us that he had the cause of AIDS in a continuous cell line. We were able to move quickly and get samples that had been retained from the cohort studies. There were many people who had ideas on how to use our serum. There was a famous CDC case control study. By the time the

cause of AIDS was discovered, as far as I know, all the sera from that case control study had been used to look at just about everything. Bob Biggar and Jim Goedert stuck to their guns and held it in reserve until a likely cause was found. There was a lot of pressure to look at HTLV-1 as one of the possible causes.

We had links with Bob Gallo's laboratory and a direct computer link to the BioTech laboratory where some of the first plates for the ELISA were developed. The technology that had been hard won between 1981 and 1984 for HTLV was used quickly in the HIV issue. Even with the fairly imprecise test, we were able to prove epidemiologically that HTLV-III was etiologically the cause of AIDS. These papers came out in the fall of 1984, within a few months of Gallo's papers. They are hardly ever cited; people often cite the next wave of papers that show the same thing, but those came out at least a year later.

Harden: You were involved with the rebuttal to [Dr.] Peter Duesburg's assertions that HIV does not cause AIDS. Your paper in *Science* arguing for HIV as the etiological agent was based on epidemiologic criteria, but your response to his arguments was based more on laboratory findings--fulfilling Koch's postulates. What you have been describing to us is a confluence of laboratory research and epidemiological studies. Could you explain further what evidence convinced you that the retrovirus HIV was the cause of AIDS?

Blattner: Going back to 1984, it was a gut level intuition that led to this insight at the time of the publication of the Gallo papers. The situation at that time was one where we had spent several years thinking very intensely about the problem and gaining insight through epidemiological study of CD4 subsets in high risk groups. This was not a time when we got much sleep. We worked on these problems and went up a lot of blind alleys. All of a sudden, in the summer of 1984, we ran a test, the one discovered and reported by Gallo for HTLV-III, and everything fell into place. What we were dealing with was suddenly crystal clear. We did not need a lot of semantics to know that we were home. In some respects, it is like pushing a button, and all of a sudden a door opens. You start to understand things.

Harden: You are convinced that it is not a fluke.

Blattner: Yes. One hundred or 99 percent of all the signs that we had anticipated should be associated with AIDS and its etiological agent were right. People who had intact T-cell subsets were not antibody positive; people who had severely depressed T-cell subsets had antibodies. People who had a lifestyle that put them at greatest risk for infection were infected; people who engaged in safe sex and did not abuse drugs were not as likely to be infected. Of people for whom we had serological samples, those who sero-converted developed AIDS. People who did not sero-convert did not develop AIDS. These findings did not answer every question that Peter Duesberg has raised. But, at that time, after the frustration of fighting this

problem, this was a big step.

We had done some experiments--Dean Mann, Jim and Bob, in our laboratory, where we reproduced AIDS in the test tube by monitoring CD4 counts. We never published this research because we were never able to isolate the virus, but we reproduced the disease in the test tube. When we co-cultured umbilical cord blood, the T-4 cells disappeared, so we knew that there was something going on in the test tube that was killing T-4 cells. It may have been one of the first demonstrations of this phenomenon; I do not know. There are a lot of firsts, but many people make these discoveries.

Harden: Why do you think that Duesberg persists in his criticism?

Blattner: I think that he must be very sincere in his belief. I think that it has to do with the fact that the AIDS virus is so different from any other virus that we have seen. We are used to viruses causing diseases in a short period of time. The HTLV virus has taught me otherwise. Duesberg does not believe that HTLV causes ATL either. It has to do with how you think as a scientist. He is a very brilliant guy and an excellent scientist, but we think differently. When I see something like the HTLV virus that can be transmitted from a mother to her offspring, and then some thirty or forty years later, show up as a leukemia, I see a great opportunity to understand the fundamental biology of cancer. It gives us a hook on what is going on in the process of cancer. I cannot satisfy Duesberg's criteria that HTLV causes ATL. I believe it to be so. I am not going to live long enough to be able to prove it because of the long latency period. But I can try to understand it from the biology that is emerging from the study of this virus. HTLV seems to have the ability to select clones of cells that multiply. Those cells burn out, and then these little mini-tumors disappear. I think that is a pretty good analogy to a lot of cancer. There are many smokers walking around who have had spontaneous cures of their lung cancer. Who knows why? We do not know. I look at these as opportunities to expand our horizons.

I guess that Duesberg is legitimately concerned that we might be barking up the wrong tree because this virus behaves so differently. The major concern, just like our misinterpreted paper about amyl nitrite, is that there are so many opportunities for coincidental agents being present in the AIDS setting. That was the whole problem. There was a man from NIAID who held a press conference only weeks before Gallo's one claiming that a fungus caused AIDS, because it created a substance analogous to the immunosuppressive material used in kidney transplants. You are probably aware that there were a lot of opportunities to discover all kinds of opportunistic agents in AIDS. You come to something like HIV and then you are really stuck. Is HIV a pathogen, or is it a passenger? I think Duesberg is on the fence on that issue. I personally think that the evidence is overwhelming that HIV is the cause. We will see in a paper to be published this

month from Mitch [Dr. Mitchell] Gail, a statistician, that treatment is impacting the AIDS epidemic and that AZT [3'-Azido-2', 3'-dideoxythymidine] probably has changed the course of the epidemic, at least among gay men.

So, in time, all of Peter's concerns will to be answered. Transfusion intervention will be recognized as preventing AIDS. Treatment targeted at the virus will be shown to be of benefit. Ultimately Peter has made the mistake of confusing cause with understanding pathogenesis. We know the cause of AIDS is HIV. However, we do not know how it brings about the actual AIDS illness. This is an important issue that will take time to solve. Many pathogenic organisms are known to cause disease, but the way they cause disease is not yet known.

Harden: Historically, it has happened both ways, of course. A new agent that does not fit the paradigm is eventually shown to be the cause in one disease scenario. In contrast, there have been many, many times when people have erroneously declared an agent to be the cause of a disease.

Blattner: That is absolutely true. If we did not have Peter Duesberg, it would be bad, because we need people to raise these kinds of questions. There is a potential for harm when there is a lack of attention to detail, which I felt in Peter's response to us on the transfusion issue. He did not acknowledge, or study well enough, the complexity of the statistics that were being examined to be able to dismiss them. But the real potential for harm in that situation is that it may reinforce the denial of people that AIDS is a sexually-transmissible disease, allowing people to place themselves in unfortunate circumstances where they may become infected. Denial is a very strong human emotion. It is very strong in any serious illness or disease. Here we have a situation in which we cannot afford denial, because to deny is potentially to give someone a death sentence. To avoid therapy for something treatable because there is a lingering doubt about its cause is also not good. That is where I see the danger.

Rodrigues: There was serious concern about the risk of infection for health care workers in epidemiological work, and you were involved in reviewing the needle-stick injuries. Could you comment on that?

Blattner: I think that early on we were not as smart as we could have been in our own precautions. Thank God, nobody in our laboratory got the infection through that route. But early on, I do not remember us wearing gloves very often. If you had a blood spill, you would wipe it up. Not being concerned about things like that was stupid. Gallo's laboratory was overcrowded, and his staff was overworked. There was a lot of tension; fortunately, nobody got infected. As we began to gain insight from the work with our cohorts of gay men, we expanded our activities. We had actually started our surveillance of laboratory workers in the HTLV era, because it was an infectious agent. They actually became a study cohort.

The health care worker surveillance in AIDS was an extension of that. Stan [Dr. Stanley] Weiss, another person to whom you might be interested in talking, is active in this field. He is at the University of New Jersey Medical College in Newark. He is very energetic and expansive. He was involved through Hal [Dr. Harold] Ginzburg, who was at NIDA [National Institute on Drug Abuse] at that time, in some drug abuse cohorts. He also set up the surveillance mechanism for laboratory workers and worked on a case that is in the courts of New York, about this unfortunate woman doctor who became infected. It was obvious that health care workers--if there was any analogy to patterns of transmission of hepatitis--were at risk. There was also a tremendous problem of confidentiality and risk of disclosure. It forced us to stretch ourselves beyond what we had ever done before, in terms of setting up mechanisms to maintain the confidentiality and protect the privacy of the individual. When a woman doctor turned up positive in our initial screening, there was a great concern that NCI should be aware of the potential dangers. [Dr. Robert] Yarchoan and others were beginning to develop therapies. When people had their blood drawn, they were given an ID card with a number on it. No identifiers were maintained. It was just good fortune when a person called in for his or her results. Then there was the whole problem of the source of infections. Did the people who tested positive have pre-existing infections or had they sero-converted after a hospital exposure? The burden of proof was always on the side of proving that infection was not by sexual transmission.

We were the first to identify a hospital doctor who had become infected through an occupational exposure. However, when we reported this at the Interscience Conference on Antimicrobial Agents and Chemotherapy meeting, that particular presentation got laughed off the stage. It has been one of the themes that I stick to, however, and I have a very strong political philosophy in addressing this epidemic. I think that denial is a major component of our response to the epidemic. The Public Health Service and many other people are involved in that denial. One of my missions is to make the only contribution that I can legitimately make, which is that as a scientist. Thus, my contribution has been to make sure that good science blows bad policy out of the water and makes people confront the issues by discoveries which cannot be ignored by policy makers.

The health care worker was one such case, the laboratory worker was another. Until it happens, it is not real. That laboratory worker episode was one of the most trying and complex things in which I have ever been involved. There was a long lag between the time that we first recognized that the individual was infected and when we were in a position to report the finding publicly. Of course we immediately informed the laboratory workers and the biosafety office about this case, since we could not prove that the infection was acquired in the laboratory. The person was positive at the time of enrolment--weakly positive, so we could not rule out another source of exposure. We could not go and tell a bunch of



laboratory scientists that AIDS was a laboratory infection without proof. We were working against technology. The technology for isolating this virus, despite Randy Shilts's statements in *And the Band Played On*, is very complex.

It was not until the spring of 1986-87, that a new technology came along that allowed the virus to be isolated. This is because in the early stages of infection, the virus may go into adherent cells more than into circulating cells. We could not get an isolate until "Mika" [Dr. Mikulas Popovic] developed his culture system for monocytes and Dr. Dave Waters, Ph.D., of Program Resources Inc. at our Frederick, Maryland [Cancer Research Facility] developed a whole blood co-culture assay that allowed one to pull out the adherent cells containing the virus. Once isolated, we were able to have different laboratories characterize that the virus was indeed the laboratory strain being grown by the infected individual. This finding was immediately announced by the NIA safety people to alert people to the risks. There was a lot of resistance to that conclusion, however. It was dismissed as a contamination problem. Fortunately, we had two different laboratories that were independently isolating the virus and thus we were able to disprove the contamination theory.

The most unpleasant part of this work for me has been dealing with the media. Basically, I do not like to get out in front of the cameras. It causes me a lot of anxiety to talk to the press, because they invariably use what you say for the point they are trying to make rather than the one you are trying to make. I have never felt comfortable with that. I am much more comfortable with the role of a scientist who is in the laboratory trying to do good science. I would rather enforce policy by science than by getting up and saying something. It is much different from anything else in science, because of the profile that is involved and the potential for missteps. For example, the case of the second infected laboratory worker, who was identified by another investigator, was mishandled. Of course, I was the one who got the nasty calls: "How could you be so stupid and not tell that person for so long"? I said: "Hey, wait a minute; I didn't know anything about this." In contrast, in the case of the first infected laboratory worker, everybody was informed from day one. We went to great lengths to prove that this person had been infected with the laboratory strain with which the person had been working; to identify with the safety people what the possible exposures were; to make sure that the person knew what the implications were, in order to prevent spread to a sexual partner, and so forth. It is very stressful. Working in the AIDS arena has been a very stressful experience.

Harden: Thank you, Dr. Blattner.

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