National Cancer Institute Oral History Project
Interview with John Ziegler
conducted on August 4, 1998, by Gretchen A. Case
at Dr. Ziegler's home in St. Helena, California

GC: I guess the best way to get started is just to ask you a little bit about your background and your education and what brought you to the NCI.

JZ: I'll be as brief as possible because all this is of course on my c.v. I was educated at Hotchkiss School in Lakeville, Connecticut, and went from there to Amherst College. At Amherst College I was an English major, English literature, specializing in American nineteenth century novels, and I also did a lot of musical activities at Amherst, singing in chorus, directing a men's vocal group, and studying the organ.

From Amherst I went on to Cornell University Medical College in New York City, graduating from Amherst in 1960 and from Cornell in 1964. And from Cornell I went on to the medical division at Bellevue Hospital called the Cornell Second Medical Division and did my internship and residency at Bellevue between 1964 and '66.

As you know, the Vietnam War was heating up considerably during those years, and most of my colleagues were getting drafted. Many of us did not want to go to Vietnam so we looked for alternative ways to continue medical training but not having to go to the rice paddies. So with a very large cohort of colleagues, I applied to the NIH, looking at different institutes and

getting advice from some of my mentors at Bellevue and at Memorial Hospital where I had also trained.

Actually the biggest influence I had during my training was at Memorial Sloan-Kettering. There, I came in contact with Joe Burchenal and Dave Karnofsky and others who were pioneers of chemotherapy. During internship I actually admitted a young girl with Burkitt's lymphoma and discussed this case with the senior staff there because this was a new disease—not previously understood very well—that responded dramatically to chemotherapy.

During my years at Sloan-Kettering, Joe Burchenal and actually Dave Karnofsky suggested that the hospital try and set something up in Africa to pursue this observation, and they actually talked with Gordon Zubrod about the idea. But by that time I had already matriculated into the National Cancer Institute as a "clinical associate" due to start in June of 1966. This was part of the Public Health Service. So while I was interested in the possibility of going to Africa under the auspices of Sloan-Kettering, it didn't work out.

So I appeared at the National Cancer Institute after completing my medical residency in 1966. The original group that I was supposed to work with had shifted into the Endocrine Branch, and they said I could continue to work with them if I wanted to. Mortimer Lipsett and Griff Ross were running the Endocrine Branch at the time. By the time I had arrived there, I was much more interested in Burkitt's lymphoma and in chemotherapy. So they said, "Well, you're perfectly welcome to stay with us, but why don't you go down the hall and talk with

Paul Carbone because as it turns out his group is very interested in Burkitt's lymphoma. He's just returned from Uganda a month ago on an exploratory visit to see if something couldn't be done between NCI and Uganda looking at Burkitt's lymphoma."

So the very next day after arriving, I went to talk with Paul Carbone just literally six doors down the hall on the twelfth floor of the Clinical Center. We had a very fruitful discussion, we hit it off very well, and Paul asked me if I would be interested in joining him to work out a program to continue research in the chemotherapy of Burkitt's lymphoma. I was very enthusiastic about that, so within a week of arriving at NCI I shifted over to Paul's branch, the Medicine Branch. I worked under him as an admitting officer for the Cancer Institute, and we spent the first year getting a program started.

Paul had just returned from a visit to Uganda, which also included Kenya, Uganda, and Nigeria. and he stopped at a number of centers talking to people who had been involved with treatment of Burkitt's lymphoma. In Nairobi he met Peter Clifford, a head and neck surgeon. In Kampala he met Sebastian Kyalwazi, a Ugandan surgeon, and Denis Burkitt who was just preparing to leave at the time. He also spoke with Sir Ian McAdam, the head of surgery where most of these tumors were being treated. Paul also went to Ibadan, Nigeria, and visited with Professor Victor Ngu, who was a surgeon also treating Burkitt's lymphoma.

Paul returned with some ideas about how NCI might collaborate, and the best collaborator seemed to be the Makerere University in Kampala, Uganda.

So when I arrived, Paul had just begun to formulate his thoughts about what to do in Uganda, and it seemed like I would be a very good candidate to work together with him and go off to Africa because I had some chemotherapy training at Memorial, and I was very interested in the subject.

Paul and I worked out a program where I would spend time in the lab, some of the time in the clinic, and together we would go back to Africa in January of that year, which would be 1967, to finalize the program, set up a contract, and get things started. So that's exactly what we did. I was working in the lab on some immunological tests and looking at issues of cell kinetics. In January we went back to Africa for two reasons. One to attend a conference called "Cancer in Africa," which was put on by Denis Burkitt, Peter Clifford, and Linsell, Allen Linsell, who was working, I think, at the International Agency for Research on Cancer.

One of the main issues to be discussed at the conference was Burkitt's lymphoma. So we went to that conference, gave a paper, and spent some time in Kenya. At Makerere University, we met with Professor Kyalwazi, Professor McAdam, and a public health epidemiologist, Richard Morrow. Dick was doing some preliminary work on survival of Burkitt's lymphoma, trying to figure out whether some of these patients might actually be cured by these drugs. So together we formed a team, included some other people such as the Department of Pathology's Michael Hutt, statistician Malcolm Pike, and others, and we moved forward to plan a small cancer research center. I went back to NCI with Paul and

finished up that year doing clinical work, training in the lab, and ordering all of the equipment and supplies we needed to get started in this project in Kampala.

GC: All right. Was this considered then part of the intramural activities because it was Dr. Carbone's lab or was it an extramural—because you mentioned the word "contract." I didn't know if it fell under extramural because of that.

JZ: Good question. It was officially a contract because that was the best mechanism by which to fund the unit, but it was treated as basically an intramural branch in a sense because I remained on staff at the Cancer Institute and remained a senior investigator. The contract was made out to the Ugandan team, Professor Kyalwazi was the principal investigator, but because I was there on site, I was able to help out with most of the paperwork and run the unit. Professor Kyalwazi and the Makerere Ugandan team maintained oversight and I was an on-site investigator and also the intramural connection to the NCI. Paul Carbone was my supervisor, and then I remained on site as the senior investigator.

GC: Okay. But Paul Carbone did not come with you to Uganda?

JZ: No, but he made many visits. He came two, sometimes three times a year, and I would come back to NCI, too, at least once a year so we maintained very close contact.

The objectives were really three-fold. One of the main objectives was to set up a cancer research institute and a cancer research center in Africa, the first of its kind where patients would be brought into a ward that was dedicated to clinical research and kept there while the research was under way and then kept under surveillance

As you probably know, in the Third World the turnover in the wards is very high. It's very hard to keep track of patients. People come in usually in advanced stages of illness and it's often hard to know what happens to them. Very often they discharge themselves when they're near death and go home to the villages. It's extremely hard to sort of keep track of people and to actually monitor their illness because of the great distances that they have to travel. So we worked out a system where we could maintain surveillance on cancer patients.

So our first objective was really just to set up a center and see if we could get the patients to come in from often long, long distances. We worked out a program where they could get on buses and taxis and we would reimburse them so that transport wasn't such a big problem. And then we worked out a situation where they could actually come and stay there in the hospital and the parents, the mother or the father, could be available to help cook and could do other things for the patients.

[Interruption]

JZ: The second objective was to study Burkitt's lymphoma. I haven't described this very much, and there may be others who have also talked about this in your historical review. Burkitt's lymphoma was named after Denis Burkitt who was a surgeon who worked in Uganda for almost forty years.

In the late '50s, early '60s, he noticed children with large jaw tumors. Pathologists at that time, Jack Davies and then later Dennis Wright, started to call these a round cell sarcoma. They had not seen anything like it before. But Dennis Wright correctly identified it as a malignant lymphoma, a very undifferentiated type. Burkitt's lymphoma had a predilection for the jaws and for certain abdominal organs, and this tumor would grow very, very fast. Burkitt quickly recognized that these tumors were not amenable to surgery. They could not be removed. They involved multiple facial bones and often abdominal viscera.

Burkitt himself was quite frustrated by the fact that these children had very rapidly growing tumors and that they were really untreatable as far as surgery was concerned. He made contact with some people at Memorial Hospital, mainly I think Joe Burchenal who suggested he try something called Cytoxan, or cyclophosphamide, a new alkylating agent given in relatively low doses by mouth over a period of fourteen days. When they suggested this, Dennis said, "Well, that would be great, but these children will never stay in the hospital for fourteen days. The turnover and the demand on beds is so great, they're in for one day and out the next." So they said, "Well, there's no reason why you shouldn't try to give this dosage regimen all in one dose." So by sheer fortuitousness, he decided to combine the whole

fourteen-day dose and give it at once in an intravenous injection, which came out to about forty milligrams of drug per kilogram of body weight. Some of these youngsters were getting up to a gram of cyclophosphamide in one dose.

That was a kind of an experiment of necessity because the children just simply didn't stay around. After one large dose to some of these children their tumors just melted away. And in about two to three days they were half the size; within a week they were gone completely. Burkitt was just astonished that this tumor would respond in such a dramatic way. So he got word back to Burchenal and to Gordon Zubrod at NCI, who had become very interested.

This was a tumor that could be potentially cured or certainly brought into dramatic remission. If you give children with acute leukemia vincristine and prednisone, they will go into remission rather promptly as well. But they almost always relapse. Some of the early regimens of chemotherapy to prevent relapse in these leukemic children really made major strides in the history of chemotherapy. The same idea was thought about for Burkitt's lymphoma. One dose of cyclophosphamide could induce a very dramatic remission. What more could be done?

So that's basically the research question that we arrived with when we got there. We knew that cyclophosphamide worked very well, Denis Burkitt had already shown that, and some of his patients never relapsed. Just a handful, maybe 20 percent, would go on to be long-term survivors. But there was a high relapse rate and obviously a couple doses of

cyclophosphamide might not be enough. So we decided to do a chemotherapy trial to see how much cyclophosphamide these youngsters need. We decided to randomize between the one dose that Burkitt had been giving and six doses which we thought would be adequate to completely cure the tumor.

Burkitt had advanced a hypothesis while he was treating these youngsters to suggest that the immune system might be preventing the tumor from coming back, because clearly one dose of drug is not enough to cure the tumor, but in some instances it does. Our research question was, does the immune system help maintain the remission that one dose of cyclophosphamide had produced. He suggested that the immune system might be augmented in these youngsters because many of them had malaria, which is an endemic parasitic disease. Malaria causes splenomegaly and recurrent parasitemias, so children experience a continuous antigenic challenge. Part of the thinking was this stimulation might be a way of augmenting immune response against the tumor.

So that brought us to our third question, what was the immune system like in these youngsters with Burkitt's lymphoma? Was it augmented, and did it have any relationship to remission and regression?

So to summarize the three objectives were one, to set up the unit, two, to ask the question about how much chemotherapy these youngsters needed, and three, to get some idea of what the immune system might be doing and whether it was playing a role in tumor remission.

A whole range of other issues attended this tumor. The obvious one was why is Burkitt's lymphoma so common in Africa and virtually unknown in other parts of the world? Not only was it common in Africa, but it was only seen in certain parts in a belt across the center of the continent, with a concentration in warm, moist areas and rare in the higher, drier areas.

There was originally a viral hypothesis advanced by Burkitt and by Alexander Haddow, head of the Virus Research Institute in Entebbe. When Burkitt showed him his map of Africa with the "lymphoma belt" across the middle of it, Haddow said, "That looks for all the world like the map of yellow fever. Have you thought of a mosquito-vectored virus?" There were a whole range of oncogenic animal viruses—the Moloney virus, the Rous virus, the Rauscher virus. Could there be a mosquito-vectored virus causing the tumor in these youngsters?

Although we were very interested in the etiology from the [US National] Cancer Institute side, our main task was to look at the chemotherapy and the immunology and see what was making these tumors go away. But in the meantime we did collaborate with others. Burkitt had sent off actually a small biopsy of lymphoma to a colleague in Britain, Tony Epstein, and in Epstein's lab along with his colleagues Barr and Achong, wrote a paper in 1964 showing in fact that the cells of these tumors contained a herpes-like virus particle. It had the same anatomy as the herpes virus but it looked different from any of the known herpes viruses and it was given the name Epstein-Barr virus. It should've been called Epstein-Barr-Achong, but unfortunately Achong's name never got attached to it. This discovery raised a great deal of excitement. Here was a lymphoma common in Africa, possibly related to mosquitoes, and

within the tumor is a virus particle, a herpes virus. There were two early groups that started to look at this. One was headed by George Klein of the Karolinska Institute, head of the Tumor Biology Section there, who collaborated mainly with Peter Clifford in Nairobi, and began to look at some of the issues about the Epstein-Barr virus and the antigens that it might express in the Burkitt's lymphoma cells and how these antigens might be involved, in fact, in the genesis of the tumor. The other was headed by Dr. Werner Henle at Children's Hospital in Philadelphia.

[Interruption]

JZ: George Klein was investigating the biology of Burkitt's lymphoma and its relationship with the Epstein-Barr virus. One of the questions he pursued, for example, was whether the virus could induce new antigens on the cell surface that made them more antigenic. The body's immune system might fight this virus-related antigen and assist in eliminating the tumor, and he made much progress in that area.

But one investigator team that really put Epstein-Barr virus on the map was Gertrude and Werner Henle. The most exciting aspect was that here was a brand new virus, linked to a tumor, that was geographically restricted. This could be the first human tumor virus. The first thing the Henles did was to work out a way to look at antibodies to the virus. They did this in very ingenious ways simply by taking the Burkitt's lymphoma cells, which were full of the virus, placing them on little glass slides, putting serum with unknown antibody onto those

slides, washing it off, and then staining it with an antiglobulin to see if any antibodies stuck onto these cells. In doing this, they identified different kinds of antigens which elicited antibody responses, the most common one being one called "virus capsid antigen," the outside coat of the virus. The antibody to the virus capsid antigen became the standard for identifying whether somebody had encountered E-B virus in the past. With the antibody test, they started looking all over the world for who might have this virus, and they found several things. First of all, they found that in Uganda—and we contributed much serum for this analysis—most children by the age of five are infected by the virus up to about 80 percent, all over the country. So if the virus was going to cause Burkitt's lymphoma, it wasn't going to be a unique cause. Because it was so ubiquitous it was going to be the virus plus something else.

Then they looked in America and they found that about in various parts of America 40, 50, 60 percent of youngsters were infected, followed by a lag and then another burst of infection in late adolescence and early adulthood. They couldn't quite explain this biphasic curve. They also tested populations all over the world and found that in poor countries most children and young adults were infected by the time they were ten, fifteen years old. In richer countries, there was a childhood infection, then a little plateau, and then another rise in early adulthood. And while they were puzzling over this, one of Henle's own technicians who had donated blood for the standard test, a negative blood, to use as a negative control, became ill over the Christmas holidays and when she came back to the lab and donated blood again for her control, she had seroconverted to positive. And during that period, she had had a classic

case of what's called "infectious mononucleosis"—swollen glands, sore throat, fever, a little bit of splenomegaly—from which she recovered. But as she recovered, she seroconverted to Epstein-Barr virus. So immediately Henle linked up with a group at Yale University who had a huge serum bank to see if young college students who got infectious mononucleosis-like syndrome had also converted to this Epstein-Barr virus. And the short story, of course, was that most college students with "mono" were seronegative before they got their illness and became seropositive after they got their illness. It was quite clear from this and other studies that E-B virus was in fact *the* cause of infectious mononucleosis. And this explained this late rise of antibodies in late adolescence, early adulthood. Very exciting.

But unfortunately, infectious mononucleosis was not a cancer. It was a self-limited disease, and it went away. So here we were stuck with this ubiquitous virus now known to cause infectious mono and probably minor sore throats in younger children if it caused anything. But what did it have to do with Burkitt's lymphoma?

In the early '70s, the International Agency for Research on Cancer assembled some virologists and immunologists and epidemiologists to do a study up in the West Nile district to learn whether Epstein-Barr virus had more to do with Burkitt's lymphoma. Was it a proximate cause? They set up a large seroepidemiologic survey where they went in and bled somewhere around ten thousand children in many villages up in the West Nile district and stored the blood. A doctor up in the West Nile district, Dr. Ted Williams, saw and treated most of the Burkitt's lymphoma cases. Dr. Williams set up a surveillance system and had

worked with epidemiologists to suggest that there was a "clustering" of Burkitt's lymphoma in certain areas of the West Nile. Time and space clustering analysis is difficult to do in Africa. They set forth a convincing case and suggested that there might be an infectious cause to account for this clustering. In 1970, the West Nile study was started. In the end, they found about twenty-five cases of Burkitt's lymphoma in whom they had previously stored serum and serum collected after the youngsters had developed Burkitt's lymphoma. And they asked the question, was there a difference in E-B virus titres in these two sera? Would they start out negative and become positive or were they positive all the while? It turned out, not too surprisingly, that they were positive all the while. In other words, their very first serum when they were maybe one or two years old was positive for Epstein-Barr virus and when they got Burkitt's lymphoma, of course, they were still positive. The only difference between these with Burkitt's lymphoma and other youngsters was that their blood titres were a good deal higher. They had very high antibody titres, suggesting that they had a rather prolonged or severe infection with viremia and high antibody titres. But I think what they did show at that point was that the virus was not the proximate cause of Burkitt's lymphoma, in other words you didn't get Burkitt's lymphoma from E-B virus in the same way that measles virus causes measles; it was there all the time.

The findings really invited the existence of another co-factor. There had to be something else going on. And Burkitt himself contributed the main hypothesis here, although much credit should go to an NCI pathologist, Greg O'Conor. Greg was working in Uganda in the early years of Burkitt's lymphoma and was the first to suggest that malaria, which was endemic in

the area, might have something to do with the genesis of Burkitt's lymphoma. He thought it might have something to do with stimulating the immune system. Burkitt actually picked up on this idea and did an ecological study to see if the prevalence of Burkitt's lymphoma was consistent with the malaria hypothesis. Burkitt and a Makerere University pathologist, Michael Hutt, did a sort of a classical tumor safari in a Land Rover and about fifty pounds from the Medical Research Council. They just basically drove around to regional hospitals, mostly mission hospitals where records were well kept and where there was a stable catchment area. They observed that those hospitals that reported and reported Burkitt's lymphoma were in fact in hyper- and holoendemic areas of malaria. Those hospitals where they saw very little Burkitt's lymphoma were usually located high up in the mountains, or in arid areas such as in southwest Uganda. There the terrain is mountainous and there's not very much malaria.

Burkitt looked at the island of Zanzibar where Burkitt's lymphoma was very common in the '60s. After the malaria control program had been in place in the late '60s, they could hardly find any cases of Burkitt's lymphoma. The same situation applied in some of the big cities where malaria control had been introduced and Burkitt's lymphoma became quite rare. Kampala was a good example where there was good malaria control in the '60s and were hardly any cases of Burkitt's lymphoma recorded, although there were many in the surrounding countryside. Also there was hardly any Burkitt's lymphoma in the Asian population, which was almost entirely urban. The eighty or ninety thousand Asians who lived in Uganda were traders in urban centers.

GC: The Asian population, was that including the Indian subcontinent?

JZ: All the Asians who lived in Uganda originally came from the Indian subcontinent, brought over to East Africa mainly to build the railroad at the turn of the century. They stayed and raised their families there and became traders and importers.

So in any case, the epidemiology was suggestive that malaria had something to do with the genesis of Burkitt's lymphoma and led to a dual hypothesis: Epstein-Barr virus was ubiquitous and certainly a component of Burkitt's lymphoma in Africa. Virtually every tumor contained the virus in large amounts. But the virus infection was insufficient to cause the tumor. Burkitt posited that malaria was the co-factor. His theory was that both of these diseases are lympho-stimulatory. Epstein-Barr virus mainly infects B lymphocytes and makes them grow and proliferate, and malaria also is an antigenic stimulus to B lymphocytes. So the idea was that these two events coinciding in one geographical location raised the stakes for developing a B-cell [Burkitt] lymphoma. When you have a B lymphocyte population that is augmented maybe three or four fold, or maybe an order of magnitude greater than others, this would raise the stakes of transforming a B cell into a lymphoma. And that's where the theory stayed. It's been that way for two decades. Nobody has ever been able to find a second virus that might be involved, although that hasn't been ruled out either. No one's been able to find another factor that influences the development of Burkitt's lymphoma such as familial clustering or other factors that might suggest a genetic

component. There's obviously nothing that can be implicated in the diet. Most people, I think, believe that it's bad luck, that is, chance. Malaria, Epstein-Barr virus, and a third factor conspire as stochastic events.

The malaria hypothesis might be tested by suppressing malaria in endemic areas and observing the incidence of Burkitt's lymphoma. This experiment was tried at a small mission hospital, Shirati, along the border of Lake Victoria. They gave a population of children chloroquine every week to suppress malaria. There was a suggestion, but not a statistically significant one, that this intervention might have reduced the prevalence of Burkitt's lymphoma, but the problem was that they weren't sure they were getting all the cases, they weren't sure the patients were taking the pills, and there was not a rigorous way to validate the trial.

Anthony Epstein, who discovered the virus, has long been a campaigner of an Epstein-Barr vaccine that might be given to children in areas where Burkitt's lymphoma was highly prevalent to possibly reduce the incidence of Burkitt's lymphoma. This idea has several problems, however. First, there are about a dozen other diseases in Africa which are far more lethal and far more common than Burkitt's lymphoma that need attention first. And second, that the development of a herpes vaccine would be a fairly major undertaking for a pharmaceutical company to develop, treating a disease that was already extremely rare in children. Further, Burkitt's lymphoma was potentially curable with drugs, so it wasn't exactly like liver cancer, for example, which is not curable and very common.

This digression fills out the story of the etiology of Burkitt's lymphoma. We were very interested in the cause, but our primary concern was in chemotherapy.

We'll go back to the chemotherapy story and fill in some of the gaps there. The first study we did, as I said, was to look at the number of doses of cyclophosphamide. We started a randomized controlled clinical trial, probably one of the first controlled clinical trials ever to be done in sub-Saharan Africa. To make this valid and legitimate, we set up a committee in Mulago Hospital that reviewed the science of the protocol to make sure it was safe and effective and that the patients (or their mothers) were able to give informed consent to participate in the trial. The committee also insured that all the safeguards were put in place as far as drug toxicity was concerned, that we were monitoring the white blood counts, and that we were able to follow the patients to properly evaluate the treatment.

The unit actually opened officially in July of 1967 when I arrived there with my family. We were able to start the trial about two months later in September. In August, Dick Morrow and I drove all over the country to every hospital that we could get to that had Burkitt's lymphoma, met with the hospital superintendent and the doctors, and asked them to send us patients. We arranged to reimburse the patients and make sure their travel was taken care of, and their accommodation while they were on the ward. And the patients started to arrive. By September we had already fifteen or twenty Burkitt's lymphoma patients. By the end of the first trial, we had over a hundred patients to evaluate. So it was a common enough tumor to be able to really get good numbers to look at.

The trial started in September, and it was finished in about eighteen months. What we showed was basically a very high rate of remission induced by single doses of cyclophosphamide, exactly what Burkitt had already demonstrated. With this high dose and in these controlled circumstances we were able to confirm that about 90 percent of the children had complete remissions. The tumors just really literally vanished.

We were able to develop a staging scheme as a way of determining the severity of the disease when the patients came in. This had never been done before because of course there weren't any cases of Burkitt's lymphoma studied so systematically. We did x-rays, we did even lymphangiograms, we did all kinds of studies on these youngsters to determine where the tumor was and was the tumor burden. We devised a stage one, two, three, four scheme.

[End Side A, Tape 1]

[Begin Side B, Tape 1]

JZ: We found that the treatment results were related very much to the stage of the disease. That is, youngsters who had small tumors, a low tumor burden, would be treated to remission and remain in remission very easily with one or two doses of chemotherapy, whereas those with larger and more widespread tumors required more extensive chemotherapy. In retrospect, this was an intuitively obvious answer, confirmed from the clinical trial.

We learned two other things that were important. We did bone marrow examinations on all these youngsters. They weren't too keen on it but the procedures were done quickly under local anesthesia. They helped us a lot in learning about tumor spread. And if patients had bone marrow involvement with tumor, that was bad news and we had to be very aggressive with treatment.

The other area where tumors were spread was the central nervous system, and we learned that that was a common site of relapse. That inspired an interesting strategy for chemotherapy. We already knew that acute leukemia will sometimes go to the meninges and that children with leukemia will relapse in what we thought was a protected area. When leukemic cells get into the brain, they are out of reach of the pharmacologic agents, the so-called blood-brain barrier. So you have to give treatment intrathecally, that is, directly into the spinal canal so that the drug reaches the inner linings of the brain. We did the same thing with Burkitt's lymphoma. We found that at least a quarter of the children would have some kind of central nervous system involvement, either at presentation or in relapse. And this complication really necessitated this new strategy of intrathecal treatment. This discovery opened our eyes to the fact that lymphomas in general could go to the central nervous system and that this was something you had to look out for.

So those were the main early discoveries. We also at the same time did studies of immunology. We found that children with Burkitt's lymphoma were immunologically intact. There was no way to say that they were hyper-reactive, but they certainly weren't

immunosuppressed as you might have expected in patients with big tumors. We did feel at the time the immune system might have an important influence on the outcome of the tumors because some youngsters who had long remissions had only one or two doses of drugs, clearly not enough to eliminate the entire tumor cell population according to the kinetics that we understood at the time.

We did make one other discovery in collaboration with a pathologist named Olaf Iverson. We worked together to study the kinetics of the lymphoma cells. His experiments showed that the Burkitt's lymphoma cells divide every single day. That they have a cycle time, a doubling time of about twenty-four hours, making it the most rapidly growing tumor ever known. This observation quite possibly explained why the tumor was so dramatically responsive to treatment. Cyclosphosphamide treatment might affect two or three or four cell-doublings over the period of time that it was active in the body as an alkylating agent. With every cell being drug-sensitive, the tumor burden would rapidly regress with a single dose.

The second chemotherapy study used combinations of drugs. At the time drug combinations were being looked at with great enthusiasm ever since the leukemia experience of Frei and Freireich and their innovative VAMP and POMP combinations, and then Hodgkin's disease with the MOPP combination. We were trying to get effective combinations for Burkitt's lymphoma, and we came up with one that was very useful. When patients relapsed on cyclophosphamide, they generally didn't respond to retreatment with the same drug, suggesting that they had become resistant. So we used other drugs. We used cytarabine,

methotrexate, and vincristine, the same drugs that were effective in leukemia. These were highly effective in Burkitt's lymphoma when used in a combination that was cyclic in nature. That is, we'd give a cycle of cyclophosphamide, a cycle of vincristine and methotrexate, a cycle of cytarabine, and then we'd repeat that. The idea being that each time that you treat, you're treating a new group of susceptible cells so that you don't allow resistance to develop in between treatments. That was a very successful regimen. We achieved about a 90 percent response rate, and by that time we had a good chance to see how many children were relapsing, and how long they lived. After about three years at the unit, the survival rate for Burkitt's lymphoma was about 50 percent. That is, one out of two children would be cured if they stayed in remission for a year or longer. We learned that after a year, the likelihood of relapsing if the patient was in remission for that whole year was extremely small. That gave us some confidence to be talking about a cure. In Burkitt's time, Dick Morrow's study had showed that about 20 percent of children had long-term responses in an open hospital situation. The more controlled environment of the research center and the ability to find children and bring them back and treat them, the long-term remission rate went up to 50 percent.

By the third year in the Lymphoma Treatment Center, we had learned a lot about Burkitt's lymphoma and discussed the results with Gordon Zubrod, Paul Carbone, and Vince DeVita. Actually a number of NCI staff visited the unit over that period of time, and all had input into the studies we did.

As we entered the 1970s I think the message was that this tumor could definitely be cured by drugs alone, that cyclophosphamide resistance did develop but could be overcome with the use of other drug combinations, that intrathecal chemotherapy was extremely important in trying to avert the central nervous system involvement, and that Burkitt's lymphoma was probably the fastest growing tumor of man. Finally, we showed that staging the tumor was very important in predicting outcome and determining the aggressiveness of initial treatment.

Those were, I think, the main lessons that came out of Burkitt's lymphoma research in the early years, which other units subsequently confirmed. The group in Nigeria, which didn't have nearly the resources we had, were still getting very good responses with cyclophosphamide, and Clifford's group in Kenya did as well. Those groups also contributed to knowledge of tumor biology and tumor immunology.

The main features of Burkitt's lymphoma were gradually translated into the evolving field of chemotherapy. Burkitt's lymphoma, Hodgkin's disease, other childhood tumors, and testicular tumors all conspired to say that chemotherapy could cure some cancers.

Over my five years in Uganda, I was joined by three colleagues who were very influential in the work I described. One of them was Dr. Avrum Bluming, who is now in private practice in oncology in Los Angeles. Avrum came for two years and helped a lot with the tumor immunology work. One of the main projects he took on was to take out the tumor and make an antigen from the tumor, that is make a vaccine basically, and inject it back into the skin

and see if the children would react immunologically to their own tumors. He made a very important contribution in that regard. He found that they do react to their own tumors and that there is an immunological reaction to tumor antigens. We never could find out exactly what antigens were eliciting this response, but if you take the tumor and inject it under the skin, a tuberculin-like reaction will appear. Thus, tumors could induce immunity in the natural host, and that this immunity might be tumor-directed.

Another doctor, Leroy Fass, joined us. He's in practice also in Los Angeles. One of the studies he did was to see if the serum from patients who were in remission had any beneficial effect in patients who had active disease. Burkitt himself had taken some serum from a long-term remitter and injected it into the bloodstream of a youngster who had actively growing tumor. He reported that the tumor had regressed a bit. We wanted to take that observation a bit farther and just see if the serum treatment might have an anti-tumor effect. So Leroy set up a double-blind randomized study and in a small number of patients we were able to evaluate whether tumors were being affected by the serum or not. There was no way we could say that the serum from the long-term remitting patient had any beneficial effect in somebody with an actively growing tumor who wasn't on treatment yet. So that was an important negative result because it said probably that if the immune system is important in this disease, the activity does not reside in the serum but more probably in the cellular component.

Another doctor who joined me there was Dr. Ian Magrath, and he launched a very important immunological study. At that time in the early 1970s, a French leukemia doctor named Georges Mathé had reported a very small number of patients with leukemia who received injections of BCG (that's the vaccination that is used for tuberculosis) who sustained longer remissions than youngsters who didn't get the BCG. Unfortunately, his statistics were flawed, but the study raised a great deal of interest in the possibility that BCG might stimulate the immune system.

We decided if any tumor is going to respond to immune stimulation, it should be Burkitt's lymphoma. First of all, patients have intact immunity. Second, there is some evidence that they might be responding immunologically to their own tumor, and third, if BCG could augment this response, we might improve the outlook for the youngsters who don't do so well.

Ian Magrath set up a randomized study of BCG as an adjuvant to the chemotherapy. That study was completed in about 1972, and it failed to show that the BCG was of any clinical benefit. Chemotherapy was probably the strongest component of the therapeutic regimen, and the addition of BCG didn't seem to affect the outcome one way or the other. One thing BCG did do, though, was to augment immunity. BCG augmented tuberculin responses and accelerated skin test recovery after chemotherapy.

During the 1970s many other groups studied immunotherapy. In the '70s immunotherapy was a form of "nonspecific immunostimulation"—a way of generally boosting the immune system with various vaccines. In the end this approach had little or no effect on most tumors.

William Terry and Steve Rosenberg both worked very hard in this area in the '70s and have their own stories to tell about immunotherapy of cancer.

Generally speaking, I would say after a decade of work and many millions of dollars spent, nothing really worked at all of the hundreds of vaccines that were tried. Only two tumors responded to immunotherapy. One was bladder cancer, in which BCG immunotherapy was given locally. Another was melanoma, in which immunotherapy was also given locally. One or two other tumors showed marginal responses, but generally speaking, immunotherapy in the '70s was a lot of promise but not a lot of hope.

Now, with a better understanding of how tumors and the immune system actually interact, I think we'll have a different view of immunotherapy.

GC: Do you think it will be more specific now?

JZ: Yes. First of all, we know which individual molecules are antigenic in a tumor. We have also learned how the growing tumor inhibits the immune response, and there may be ways to alter this. The area of vaccines and adjuvants are now getting another look because of the

discovery of specific tumor antigens and DNA vaccines. But it's going to be a while, I think, before immunotherapy becomes a natural tool of anti-cancer treatment. The antigens are weak and the immune system is limited. The theory that supported immunotherapy—that is, immune surveillance—which posits that the body is always on the lookout for tumor cells and kills them as they appear—probably isn't true. We now understand that cancer arises not as a result of a failed immune system but as a series of genetic accidents, which probably have little to do with the immune response.

In around 1969, the NCI, Dr. Carbone and Dr. Zubrod and others, became interested in some of the other indigenous tumors in Uganda. Stimulated by Professor Kyalwazi, Drs. Templeton, Kiryabwire, Masters, Taylor, and others, we decided to open another ward to deal mainly with the solid tumors of adults. We called it the Solid Tumor Center, and we recruited Dr. Charles Vogel from the NCI. He joined us in '69 and remained for four years as the director of the Solid Tumor Center. And there we saw patients with three or four different tumor types. One of the main ones was Kaposi's sarcoma, as I mentioned earlier. We also saw patients with liver cancer and malignant melanoma. Those three tumors were amongst the commonest tumors of adult men in Uganda, and responsive to chemotherapy. Dr. Vogel started several clinical trials in Kaposi's sarcoma and showed that about a half a dozen drugs worked well in this disease, especially in the more aggressive type. He characterized these tumors and staged them, describing what Kaposi's sarcoma was like in Uganda. This became extremely important work when Kaposi's sarcoma resurfaced recently as a complication of AIDS. The early work that Chuck Vogel did in that Solid Tumor Center

was quite seminal in gaining an understanding of a disease that resurfaced in an epidemic form in the 1980s.

We also learned a lot about malignant melanoma. Nobody really understood about melanoma in people with black skin. It turns out that melanoma is common in blacks, but it hardly ever grows in the pigmented skin. It almost always appears on the palms of the hands and the soles of the feet in unpigmented parts of the body. A pathologist named Martin Lewis did a lot of work on melanoma in the 1960s, when there was much speculation about whether the immune system was operating in patients with melanoma. We did not understand why these tumors didn't grow in pigmented skin and why they appeared at the soles of the foot. And Chuck Vogel again instituted chemotherapy trials and showed that one drug particularly, DTIC, was very active in malignant melanoma. To this day, DTIC is one of the most active drugs ever used.

We also looked at other solid tumors there. Chuck Vogel and another NCI colleague, Aron Primack, studied liver cancer, helping to show what drugs were active and how the tumor was linked to hepatitis B virus. Choriocarcinomas and malignant lymphomas of adults were also seen. And during those years while Chuck was working on the solid tumor side, and Ian Magrath and Av Bluming were working on the lymphoma side, I became interested in a disease called tropical splenomegaly syndrome. This is not a cancer but a form of hyper-reactivity to malaria, and since malaria was very important in Burkitt's lymphoma, it seemed to me that we had something to learn about tropical splenomegaly. I spent a year or two as a

digression to study tropical splenomegaly syndrome. While this had little to do with chemotherapy of cancer, it was important in understanding the pathogenesis of malarial related diseases.

So anyway those were three colleagues who came to Africa and helped with the cancer work.

There are other sidelines to the Africa work which had longer term implications. One of them was that the Lymphoma Treatment Center became known as the childhood cancer center. People didn't often know when they sent a child to the hospital with a lump what it was going to turn out to be, so it turned out that many of the children's lumps were not Burkitt's lymphoma but something else. And rather than send them away, of course, we ended up treating them as well. We accumulated a large series of children with Kaposi's sarcoma, a very rare tumor in children anywhere, but the Kaposi story I'll tell you in a little while that grew out of this. But we treated about twelve children with Kaposi's sarcoma, probably the largest series in the world. We also saw children with retinoblastoma and rhabdomyosarcomas, both of which were responsive to treatment. We saw children with Hodgkin's disease, which in Africa is as common in children as it is in adults. We treated a large number of children with Hodgkin's disease and learned that these youngsters could respond very well to MOPP chemotherapy, the regimen that Vince DeVita and Paul Carbone and others had developed at the National Cancer Institute. With MOPP chemotherapy we were able to get a very high response rate, something like 95 percent, and a long-term survival rate around 75 percent. These rates were similar to those achieved elsewhere in the

world at that time with combination chemotherapy. And a number of those youngsters are still alive today, cured. During my last visit to Uganda, in 1996, I saw one of my very first patients with Hodgkin's disease who's now in his forties. He's a sports medicine doctor on the Olympic Committee. He's a very prominent citizen, and was virtually the first patient I had seen with Hodgkin's disease when he was a schoolboy at age thirteen.

It's a nice story because these tumors are, untreated, completely lethal, and yet with proper management Hodgkin's disease can be cured.

GC: That must be amazing to see one of your patients grow up.

JZ: Yes. He's a lovely person. He became a close personal friend and we still correspond. As a schoolboy, he came in with Hodgkin's disease in the neck and the groin, and we treated him with MOPP chemotherapy. He hated it of course, he was screaming—all the kids screamed; they didn't like to have needles. But he stayed with the program and he got his treatment and his tumors went away. Unfortunately, those early MOPP treatments were sterilizing for men and so that he was never able to have children, but otherwise he was totally fit and healthy and a very happy man.

Treating Hodgkin's disease with chemotherapy taught us something important because there was no radiation therapy in Uganda. Back in the U.S., early stage Hodgkin's disease was treated only with radiation therapy. The controversy in the USA was [at] what stage should

chemotherapy be used? It was almost always relegated to advanced stages, and the radiotherapists treated the early stages. Because we lacked radiotherapy in Uganda, we could show that the treatment results from chemotherapy alone in early stage Hodgkin's disease were just as good as the radiation results.

So that was the story with the childhood tumors, and we were able to really sustain a national unit that still to this day sees children with cancer from all over the country.

Now what happened to the unit was rather sad. In 1972, Idi Amin came to power in a coup and ousted the Socialist-leaning President Milton Obote. Amin was one of his generals and he took over, I think, around February of 1971. He was first greeted with great enthusiasm, especially by the local tribes because he chased out a lot of the northerners who were aligned with Obote. But then he brought in his own swarm of henchmen, and then it soon became quite clear that he was a rather brutal dictator who was both crafty and stupid, and presided over the early demise of the country's economy.

He spent all Uganda's foreign reserves on war materials, and his entire government was corrupt. He instituted systematic genocidal activities against other tribes that he didn't like, and by 1975 it was clear the country was on the slippery slope to economic ruin. Amin literally trashed the country. He chased out all the Asians early in the 1970s. The Asians, who had been the major businessmen in the country, took all their money and their relatives and left the country. And of course quickly it became apparent that no one was prepared to

replace their trading skills. Merchandise was not reordered; spare parts were not available; machinery, buses, and equipment broke down; and pretty soon nothing worked.

Then there was a series of military coups, and a long civil war with renegade groups operating from the bush. In the 1980s the whole country just slowly, slowly imploded.

What happened at the Cancer Institute was that the Ministry of Health took over the Cancer Institute after—I left in 1972, Dr. Magrath and Dr. Vogel left in 1974, and in 1975 or '76 the NCI withdrew its support because it was untenable to continue the contract. Fortunately we had trained some Ugandans who were there to take over the unit as we left. One was named Dr. Charles Olweny, who stayed as long as he could as director. Eventually he had to run away from Amin before he and his family were put into great jeopardy. And he was replaced by Dr. Edward Katongole-Mbidde, who remains, as we speak, the director of the Uganda Cancer Institute.

As I say, I've been back off and on since 1990 and the place is like a museum. It still runs exactly the way it used to run, and everything is still in place. Some of the nursing sisters who were there are still there, and Dr. Mbidde, of course, who was trained by us and then went on to further oncology training in Britain, still runs the center very much in the same way. He's an extremely competent oncologist.

I returned to the NCI in 1972 and headed up the Pediatric Oncology Branch for the next three years. That was originally called the Leukemia Service. And when I came back, because of my interest in childhood tumors and Burkitt's lymphoma and because of the need for more of a pediatric presence at the National Cancer Institute, we converted the Leukemia Service to a Pediatric Oncology Branch.

GC: Oh, so you started that.

JZ: Yes. The Leukemia Service was run very ably by Ed Henderson, and Ed went on to Roswell Park when I arrived in 1972. And in that branch we recruited pediatricians, two of whom, my original recruits, are now real superstars. One of them is Phil Pizzo, who is now at Harvard and he ended up becoming branch chief for quite a while, and the other is David Poplack who is now head of pediatric oncology at M.D. Anderson in Houston. We recruited Ian Magrath back from Africa and he's still in the Pediatric Oncology Branch, working on Burkitt's lymphoma. He made some really major contributions there, and he's maintained a very active interest in international oncology.

Other scientists were already in the branch when I came. Arthur Levine, who is now the director of Child Health, was interested in infectious diseases. The late Brigid Leventhal studied leukemia immunology. She stayed on in the branch for about five years and then went to Johns Hopkins. Dr. Leventhal developed breast cancer and died in the late 1980s. Another scientist, Robert [G.] Graw, was working in the area of stem cell replenishment. He

was interested in harvesting bone marrow cells and stem cells from the bloodstream and transplanting them into people with cancer after giving them super-doses of chemotherapy. The hypothesis was that transplanting hemologically active cells could replenish the bone marrow after toxic doses of chemotherapy.

Now that's an interesting story because it involved Burkitt's lymphoma. When I returned to NCI, my main interest was still in Burkitt's lymphoma so we launched a campaign to recruit American children with Burkitt's lymphoma. They weren't all children; some of them were young adults. But we wanted to learn the similarities and differences between American and African Burkitt's lymphoma. Over the years we were able to accumulate around fifty or sixty patients and we treated them on a series of protocols derived mainly from what we had learned in Africa. Around 1976 I wrote a paper that showed that the American and the African treatment results in Burkitt's lymphoma were exactly the same. We observed the same response rates, the same long-term survival, the same outcome, and really the same natural history using the African staging system. The only difference was that in American Burkitt's lymphoma, the frequency of Epstein-Barr virus involvement was very low—it was about 15 percent—whereas in Africa, as I told you, it was virtually 100 percent. But the tumor cells looked the same under the microscope, and as far as everybody could tell, it was the same disease.

Another interesting study that we did there was with Robert Graw's group, was a protocol to look at how bone marrow autografting could affect the outcome of people who had relapsed.

When patients relapse with Burkitt's lymphoma, the outlook is very poor, largely because they've developed drug resistance, and no matter what treatment you use the tumors just shrink a little bit and always come back.

The most intensive strategy that we could come up with to treat relapse was to give very high doses of drug, enough so that the bone marrow would be completely obliterated. We saved the bone marrow before treatment, cryo-preserving it and holding it frozen. Following a high dose of drugs the bone marrow was infused, replenishing the damaged bone marrow.

We began this experiment in patients with Burkitt's lymphoma because we knew that they would respond to the drug. We just weren't sure how complete and durable a response we'd see. Of the first eight patients we treated in this state of relapse, three of them were cured.

That was rough going for the patients, however. They had very high fevers, had infections, and low blood counts. They required antibodies and blood transfusions; it was touch and go. Five patients died, unfortunately either of relapsing tumor or from toxicity of the treatment.

I remember one of the young fellows at the NCI at that time who had been following these patients, [Dr.] Fred Applebaum, who's now at Hutchison Center in Seattle. He pioneered this marrow autograft procedure. Fred's journal article got a great deal of attention for three reasons. First, it showed that high doses of drugs could be given safely and it induced not only complete but permanent remission. Also, it showed the bone marrow would accelerate

the replenishment of bone marrow after high dose chemotherapy so that the hematologic toxicity was reduced. Third, one dose of these drugs was sufficient to bring about a long-term cure.

The three survivors in this Burkitt's lymphoma series were youngsters in relapse who were really doomed. They had already had many drugs, and their tumors had grown back. Things were really desperate. These three youngsters had not only complete remission and a very stormy course, but they're around today to tell you about it. That initial experience gave people courage to go forward and try this with other responsive tumors. What's now called stem cell replenishment or stem cell transplantation or autografting has become standard therapy in many tumors.

[End Side B, Tape 1]

[Begin Side A, Tape 2]

JZ: Looking back on it, this was a very brave experiment to do because the enormous doses of drug that were given would have been lethal without the support therapy. Robert Graw, Geoffrey Hertzig, Fred Appelbaum, and their team deserve much of the credit.

In 1975 I became Director of the Clinical Oncology Division. Then my duties became more administrative, and I was involved with reorganizing the intramural program with Vince

DeVita. We moved some of the branches around and created new branches. The whole Clinical Center was undergoing major renovation at that time so that many of the laboratories had to be moved and the clinical wards had to be changed. Many administrative tasks occupied my time. But I maintained an interest in Burkitt's lymphoma and continued clinical trials. But toward the end of the 1970s, I became more frustrated with the excessive administrative work and not enough time for clinical work, research, and teaching.

Just in the early 1980s, I got an offer from a colleague at the University of California, San Francisco, as Chief of Staff for Education and Professor of Medicine. In early 1981 I was married to Rue, and we decided to come out here and start a new life in San Francisco.

I left the NCI in August of '81 after a total of fifteen years. One of the curious ironies of my career was that as soon as I arrived out here the AIDS epidemic had struck gay men in San Francisco. We observed gay men were developing Kaposi's sarcoma, and nobody knew much about Kaposi's sarcoma except Chuck Vogel and myself and a handful of other people. So I got involved early on in the AIDS epidemic looking at the malignancies that had resulted. We'd always thought that Kaposi's sarcoma might have an infectious origin because it had a peculiar distribution in Africa and because it didn't behave like many other cancers. It originates in many places in the body simultaneously rather than starting in one location and moving to others. Basically the research issues of Kaposi's sarcoma had to do with why should it be associated with the AIDS epidemic, how could it be treated, and what was its

natural history. Early on in the epidemic we also began to see more and more AIDS-related lymphomas, some resembling the Burkitt-like lymphomas in America.

And again it was mostly gay men developing lymphoma. We first accumulated a small series here in San Francisco and wrote that up in *Lancet* and then a year later collected a larger number of cases from big centers around the country. That was published in the *New England Journal* I think in 1983, just around the time the AIDS virus was discovered. We showed that non-Hodgkin's lymphoma, about half of which were the Burkitt types, accompanied the AIDS epidemic and it quickly became what they call an AIDS-defining illness.

This experience was a postscript for the NCI work that resurfaced as part of the AIDS epidemic. And up to now, there are a number of tumors now that are linked to HIV, but Kaposi's sarcoma and non-Hodgkin's lymphoma are the main ones. Much research is under way now to link immunodeficiency and cancer. There's a new virus, for example, linked to Kaposi's sarcoma. And of course I already discussed the Epstein-Barr virus and its link to lymphoma. There may be other factors that have to do with immuno-regulation or disregulation and HIV infection which puts people at risk for cancer.

Most recently I was able to go back to Africa under the auspices of WHO and do a case control study to study the factors that might link Kaposi's sarcoma to HIV, and also look at

other cancers in collaboration with a group at Oxford and a group at the International Agency for Research on Cancer.

So that's pretty much the whole story of my role in the development of the Institute. Burkitt's lymphoma taught us many lessons: curability of tumors by chemotherapy; better definitions of the clinical features; the importance of staging; the cell kinetics; the immunology; and the relapse patterns in the central nervous system. We learned about the use of intensive chemotherapy and bone marrow rescue to overcome drug resistance in patients who have relapsed. We discovered the relationship of these tumors to ubiquitous viruses, and how these viruses might induce the tumors alone or with co-factors. All of those have been thematic patterns that have woven in and out of my work in Africa and at the NCI.

You must have some questions to fill in some gaps.

GC: I do actually. Going back to when you started doing these clinical trials on Burkitt's in Africa, how established was the idea of having a controlled clinical trial? Would you say that this was groundbreaking or that this was the kind of trial that was being done in other places in the world? Is my question clear enough?

JZ: Yes. Controlled clinical trials were just coming into their own in the early '60s. A lot of chemotherapy was just done anecdotally, or done in series. At St. Jude's Hospital, for example, they'd treat a cohort of patients one way, and then take a new cohort and treat them

a new way and compare the old with the new. There are historical biases and other kinds of biases that creep in using this method. The randomized clinical trials has become the gold standard as far as learning new information about new interventions. These avoid the biases that creep in when you're selecting patients or using historical controls.

I wouldn't say it was groundbreaking, but we performed the first randomized clinical trials to my knowledge ever done in Africa. It was very much the credit of my statistical colleagues who lived and worked there, Dick Morrow, Malcolm Pike, and later, Peter Smith. All of them are now world-class epidemiologists. They designed trials to make sure they were properly randomized and stratified, and that we followed some of the early rules of proper clinical trials. We recognized that we needed hospital committees to oversee the trials, to oversee human rights, and insure that the informed consents were proper.

GC: Actually, that was my next question, is just asking you about the ethics of these trials. You mentioned that these were heroic measures. You were giving huge doses of drugs to people, so it sounds like you went through hospital committees. Did you also go through committees at the NCI or was there discussion among your peers at the NCI about how to ensure human rights, how to decide on the ethics of using a huge [amount of] untreated drug on people. What kind of process did you go through in deciding to go ahead with this trial?

JZ: You're talking about the trials with the high doses of drug, the high-risk trials. During my years at NCI, I was the chairman of the Clinical Research Committee for five years. In the

early '70s was when ethics committees, what they now call IRBs, institutional review boards, were coming into place to safeguard human rights, to look after the appropriateness of patient care, risk, and benefits. Our committee at the NCI was certainly exemplary in that movement. One of the first persons to join our committee was John Fletcher, a Unitarian minister who's now an authority on the bioethics of clinical trials. John Fletcher was a very vocal and helpful layperson in terms of keeping everybody thinking about patient rights and about the ethics of trials. He later joined the whole NIH Clinical Center as bioethicist at the director level.

We had of course scientists on the committee who would judge the rationale and the basis of the trial to make sure that it was a scientifically important question and that the statistics were properly worked out. We didn't have data monitoring boards, but those were soon introduced to follow the progress of a trial and make sure the code was broken at the proper time to learn important early results.

GC: What was a typical day like when you were at—let's start with when you were in Africa. How long were your hours, what would you start out by doing each day?

JZ: Our days were busy. I'd get to the ward about eight or eight-thirty, and immediately we'd have coffee and talk about any problems that occurred during the night. We had medical students from Harvard, Columbia, and Cornell who would do externships with us. We built a small dormitory where they lived and they would take night call and look after things. If they

needed doctors to come in, they'd give us a call and we'd come to the Center. After coffee we'd make our rounds, which took most of the morning because the ward usually was quite full. And then from about eleven-thirty or twelve to one, we'd give out the treatments, review the blood counts that were done for the day, and do any procedures that were necessary, generally bone marrows, lumbar punctures, and biopsies. And then at one o'clock, we'd go and collect the kids from school, go home, have lunch, and come back at two. And generally, from two to four, things were a little quieter. We'd review any other issues that had come up, take on new admissions, paperwork, see patients, and follow up.

We also had a big teaching program so there was almost always some kind of teaching activity going on, a seminar or a journal club or rounds at the main hospital. Then by four to five, the day was over and then we'd play tennis or take a swim. But they were busy times. We worked until one o'clock on Saturdays. When both wards were open, we had to go back and forth between the two. We ended up having forty clinical beds and they were all full most of the time. We were pretty busy.

GC: You were in Africa at the time of the coup. Can you tell me a little bit about that time?

JZ: It was over in a day. Basically, Obote, the president, was in Singapore. Idi Amin marshalled his army and his tanks, there was a little bit of skirmishing between his people and Obote's loyalists, but virtually no bloodshed at all. By the next day, he grabbed the radio and said, "This is General Idi Amin Dada. I am now your new president, and we have formed a new

government and everybody is to remain calm and go back to work, there is no danger." And there was great celebration because most people didn't like Obote. Amin immediately promised to return the king of the local tribe, the King (Kabaka) of Buganda who had been exiled to U.K. He had died in exile, so he [Amin] promised to bring the body back and have him properly buried. Of course the Buganda went wild. They loved it. Amin was very popular in the early days. Hardly anybody was aware that there was a new government, and only as time went by was it clear that he was bloodthirsty and quite stupid. A lot of amusing stories that went around about him, but basically he was a real scoundrel.

GC: Were you ever concerned?

JZ: Yes, I mean, that was a main reason I left Uganda. Amin's regime was getting more and more repressive, he was expelling people right and left. Many of my colleagues had already left the country, and things were beginning to get dangerous. There was a lot of army presence out on the street, roadblocks at odd places, and increasing instability. My five years were up and I was planning to leave anyway. Amin came to power in 1971, and I left in August of '72 so it was just about a year.

GC: You mentioned that as Amin's rule went on, it was harder to get spare parts and equipment and things like that. Was that already beginning to affect the Uganda Cancer Institute while you were there, or did that come much later?

JZ: That came much later. We were fairly well protected. Even after I left, Dr. Vogel stayed on for another two years, and so did Dr. Magrath. The Institute was able to keep operating even during the early years of Amin's regime. Things didn't get really bad until the late '70s.

GC: Did you depend on the National Cancer Institute for supplies, for medicine, for machinery? Did that all come directly from the NCI?

JZ: Yes. We had a very active pipeline to NCI because that's where we got our drugs and most of our equipment. We got a lot of things locally, too. I would say about fifty-fifty. Most of our drugs came locally and we bought our beds and linens and pillows locally.

GC: There was a lot going on in the '60s and '70s, especially with viral research at the NCI, the Special Virus Cancer Program. How connected was your work to that?

JZ: Most of our viral work was related to Epstein-Barr virus and linked up collaboratively with the Henles and with George Klein. The NCI group was mostly lab based. They were looking at animal viruses and they didn't have very much need in the way of clinical materials at that time.

But we were in touch with them. I remember visiting Sarah Stewart and Dick Rauscher and Al Rabson. All those people were very much interested in the Burkitt's lymphoma question and what viruses might come out of it.

GC: Did they ever come to Africa?

JZ: Oh yes. Dick Rauscher came out. We used to take all our visitors out on safari to visit patients, so he had a very memorable experience bouncing around in the Land Rover all the way through the bush to a patient's house. He loved it. Everybody went away with a smile.

GC: So when you came back to the NCI, you mentioned that you moved into more of an administrative role eventually. What were your days like when you came back to Bethesda? Was it the same kind of schedule coming in about eight, eight-thirty, or were they longer or shorter?

JZ: Pretty predictably the same, I guess. I'd just generally get in at eight, there was sometimes a teaching conference that would start at eight or eight-thirty, and then I'd often make rounds on one of the wards. When I was in pediatrics, of course we had our own pediatric ward there, or else I'd be in a clinic for a morning or an afternoon, depending on the scheduling. There were meetings to go to, and then very often there were higher-up meetings that I had to attend, meetings that had to do with drug development, or administration of the division. So

again, as a branch chief and later as a program director, there was just an ever-increasing amount of administrative work having to do with promotions and contracts and contract reviews, and housekeeping chores in the general running of the branch and the program.

GC: Now you mentioned that Dr. Rauscher, you had quite a bit of contact with him, he came out and he came to Africa. Was that while he was Director or was that—

JZ: I think yes, he came out as the Director, yes.

GC: Did the previous [Directors]—did Dr. Endicott or Dr. Baker come out?

JZ: No.

GC: And then by then you were back. So when you were in Bethesda, did you have a lot of contact with Dr. Upton or Dr. DeVita?

JZ: Not so much. DeVita yes, of course, because we shared a lot of interest in the same kind of research. He was head of the Medicine Branch and I was head of the Pediatric Branch. And his son was a patient of ours in the bubble unit for about three or four years.

GC: Did you notice a change in the atmosphere of the Institute as each director came in? Was there a kind of a general shifting?

JZ: Yes, I think so. Ever since the National Cancer Act in 1971, the Institute was politicized to a great degree, and so the Director was always sort of shuttling back and forth to Washington and working with the President and reflecting some of the political issues. There was often some knee-jerk political agenda that found its way down. One year, the President or somebody said, "We need more money in diet and cancer," so they just dumped $10 million on the Cancer Institute and said, "Spend it on diet." And of course everybody was running around, "What do we do with this?" Scientists didn't really enjoy that sort of thing. Dick Rauscher was one of the best people around at getting money in Washington because he was very friendly with the politicians. Even though he wasn't a clinician, he was very articulate about what kind of breakthroughs were being made. But generally speaking, yes, each director would project their own personality up and down the lines.

GC: And I guess with that came some reorganizations. You mentioned that you helped Dr. DeVita with some of his reorganizations?

JZ: Oh yes. DeVita was very concerned with the intramural program. It had grown without any kind of general planning, partly because it belonged to two divisions. One was Biology, Rabson's division, and the other was Treatment, DeVita's division. So there had to be some

negotiating to fit the branches together and make it a little more like an institution. For example, we created a Biostatistics Branch and a new Medicine Branch at the VA Hospital under John [D.] Minna.

DeVita was fairly autocratic in his administrative style, as you've probably heard. He wasn't a consensus builder. So whatever he decided he wanted to do, he went ahead and did it. He pushed a big program in hyperthermia for a while. He was convinced that heating up the body was good for making the drugs get to the tumor. It turned out not to be a very good idea after all.

But that's the way he operated. He liked to promote his ideas. He had some good ones and some not so good ones just like everybody in this business. You can't really fault him for trying to give a shot at things. And he was always trying to reorganize things. He wanted to get a better screen for the drugs. The drugs were going through a mouse screen, which was really kind of antiquated, and he was trying to figure out if he could make it a little more biological. As it turned out, the new screens that they used really didn't work any better than the old ones, but there was no way to know that without trying it.

I think he was a good organizer and he certainly had a lot of good advisors, most of whom he listened to. These were people on his Advisory Board. He did a lot to get the Institute into a better managed machine, planning for growth. I think he did a pretty good job as a director even though nobody really liked his style very much, as you may have heard.

GC: So were you involved in the politics at all? Did you ever have to prepare testimony? Did you ever have to testify before a congressional committee? Go down to the Hill, anything like that?

JZ: No, I tried to avoid that as much as possible. I left that to DeVita and his Division Directors. I don't think I ever did a single testimony.

GC: You came back in '72 which was right after the Act had passed. There was a lot of talk at the time that some of the politicians and some of the public wanted cancer cured by 1976. That that was going to be the goal. Do you remember ever hearing any rhetoric like that, any talk of cancer being cured by '76?

JZ: Not really. Those kind of deadlines didn't make much sense to any of us. Basically even the National Cancer Act was a political directory of every possible thing you think of to do. It was sort of "Well, if we can get a man on the moon, we can cure cancer" agenda, but that was really not possible. The technology wasn't there. The knowledge wasn't there. So it was just basically a way to get Congress to vote more money to cancer. And Mary Lasker was out there pushing interferon. Interferon, I guess, works in a few things now, but you would have thought the way they were pushing it that it was the magic bullet.

GC: Yes, that was the big push for a long time.

JZ: That whole interferon story makes an interesting story for somebody to write sometime.

GC: Were you involved with interferon at all?

JZ: Only just from the sidelines watching it hyped and politicized to the point where people really thought that was going to be the cancer cure. But it wasn't. It works in some tumors, actually, such as kidney cancer and certain leukemias.

GC: Can you tell me a little bit about the working relationships in the Uganda Cancer Institute? How you worked together, how would you come up with ideas? How would you relate to each other in terms of research? Would you throw something out to the group and then other people would talk? Can you just tell me a little bit about how you generated ideas?

JZ: I think our group was exceedingly collegial. We just always worked from consensus, and there were more ideas than ability to carry them out. Although I was sort of the director, I gave everybody free lead to do whatever they felt was good as long as it was humane, sensible, made good scientific sense, and was ethical. So there was a lot of autonomy. The different investigators were free to do whatever they wanted. We had some central protocols, which we had all agreed would be in the main treatment programs, and that was done through Paul Carbone, too, who was our mentor at NCI. Because I haven't mentioned him doesn't mean that he wasn't exceedingly important as a facilitator. Paul really got things going. He's

a wonderful man. He did things very often in such a modest, self-effacing way that you'd never know he was behind it. He's one of those people who worked extremely well behind the scenes, but made things happen and made them happen well. He was always there with support and advice and goodwill. He wasn't treated well by DeVita, as you probably heard, but he is just really a gem of a person. You haven't met him yet, have you?

GC: I haven't.

JZ: You'll really like Paul Carbone. You must put him on your list.

GC: He's on my list.

JZ: Paul is truly a gentleman and really one of the major unsung heroes of the NCI. I think this is mainly because he was so modest in his way and so bright and almost self-effacing. I'm sure he was the one that thought of the MOPP chemotherapy idea. Paul Carbone had a lot to do with some of these major innovations which he would give away to others generously and then step back. But Paul was very good to us at the Uganda Cancer Institute and was supportive right to the very last day. And for that reason we had a lot of autonomy. He just didn't say, "Do this, do that." If somebody had an idea, we'd toss it around and develop a protocol. We hardly had a single disagreement that I can think of, other than the sort of friendly or critical ones that are helpful. And we had very good support from the university

and from our Ugandan collaborators. We brought a lot of Ugandan students to the Institute to help with our research, and they were very productive.

GC: What about the staff and the nursing staff. Were they Ugandans or were they American?

JZ: They were for the most part Ugandans, almost all Ugandans.

GC: Was there a good relationship between the investigators and the nursing staff?

JZ: Excellent. The nurses were really good. They were very well trained and we turned them into oncology nurses in the sense that they would help us keep track of the treatments. We were extremely lucky with our staff.

GC: Did you say that some of the nurses were nursing sisters?

JZ: Yes. In the English system they call nurses "sisters."

GC: I didn't know if they were a religious order?

JZ: No. That's just the English way of referring to nurses.

GC: You were sent to Uganda so soon after you joined the NCI. Was that a surprise to you?

JZ: I was lucky. I was only three years out of medical school when I went there. So yes, it was a surprise. I've always enjoyed a certain amount of autonomy. I like to be on my own. I like challenges starting from scratch and working up to something else, so this was just perfect for me. We walked into an empty room and turned it into a hospital. It was all done in a resource-poor country where you have to hire all the nurses, hire all the floor-keepers, organize the food, organize the pharmacy, organize the lab, bring in beds and bedclothes and pillows, everything. Plus develop a major research lab. We had to build a hematology unit and a clinical chemistry unit, and all of this just sort of came together. It was a lot of fun. I really enjoyed doing that. It was building a hospital from scratch, really.

GC: Did you literally walk into an empty room?

JZ: Yes. Absolutely empty. It was an abandoned hospital. Just bare walls which needed painting and renovating. It used to be a maternity ward but it had been closed for many years. So we just ripped out the windows and put in new windows and built a new roof and cleaned up the floor. Fortunately we had resources to do it, and we had a very good administrator there, a Goan man, who knew everybody in town and got all of the contractors up to do the work. We hired a teacher for the kids because of course they were out of school while they were in the wards. We took the kids on local tours to the zoo and to town. Most of them

were just rural children who had never been out of their compounds before so it was quite an adventure for them.

GC: That's really interesting. So you just opened an in-house school.

JZ: Yes. We had a teacher right there on the spot.

GC: Did people in Uganda and the patients coming in, did they realize the connection to America to the American National Cancer Institute or did they just, do you think they just [thought about] this Ugandan Cancer Institute?

JZ: We had a plaque of course in the front saying who was sponsoring it, but there were a lot of Ugandans on the staff, all the nurses were Ugandan, the medical students were Ugandan and several Ugandan professors from the university who came up and made rounds. Professor Kyalwazi, as I said, was the main Ugandan presence there. Ugandans were aware it was a collaborative project that was both Ugandan and American, jointly.

GC: How was NCI perceived generally at the time when you joined and at the time you were in Uganda? What was the general reputation of the NCI?

JZ: In Uganda or in just generally in U.S.?

GC: Either.

JZ: NCI was certainly the biggest institute at NIH, and in the '60s there was a lot of ferment—a lot of excitement about chemotherapy and about viral etiology of cancer. In the intramural program clinical beds were on one side of the corridor and labs on the other, so you can just go back and forth between the patients and the lab. And there were some world-class scientists who were there rubbing shoulders with you in the corridors. NCI had a very good reputation.

GC: Did you come to the Cancer Institute with—you joined as a part of the doctor draft, it was during the Vietnam era. Did you come in though with certain goals about where you thought you would go with the Institute and what you thought you wanted to do while you were there?

JZ: Well, as I said, I had done some work with Burkitt's lymphoma already in Memorial Hospital, so I was very interested in that. I'd always wanted to go to Africa as a youngster, so when the opportunities came together, I jumped at it right away. It was a perfectly logical thing to do.

[End Side A, Tape 2]

[Begin Side B, Tape 2]

GC: So you said you wanted to keep on [working] with the Burkitt's lymphoma.

JZ: Yes, I think that was probably my main interest when I got there, in lymphomas and chemotherapy of cancer. And as I said, I was influenced a great deal by Joe Burchenal and Dave Kamofsky and others at the Memorial Sloan-Kettering where I trained. That was again a pioneering institution where there were new, exciting things going on in cancer treatment. And now of course it's a major world-class place.

GC: What would you say was the best thing about doing research at the NCI or the biggest benefit of doing research at the NCI?

JZ: Well I would say there were probably three things that were really, really important. One is the collegial atmosphere of the place. You could just go down the corridor and see Al Rabson and talk to him about Burkitt's lymphoma and tissue culture, and you could go see John Fahey and ask him about immunoglobulins and you could go see Tom Waldmann and find out about T cells. Everybody was there with expertise to offer.

GC: And these are people who were top in their fields.

JZ: Top in their fields. And then the other thing of course was resources. You didn't really have to go begging or writing grants. You could just write basically a work order and get what you wanted for your lab. So there was just no obstacle to the resources that were available.

And the third was that there was a very high priority given to clinical research so you could go back and forth between the lab literally and the clinic twelve steps away practically, get your blood specimen, come back to the lab, put it in culture, do what tests you need to do. The ability to do really good basic work on clinical material was totally enhanced. Whoever figured that out in the beginning was very clever to make sure that the wards and the labs were just literally side by side.

GC: And that was rare. That hadn't been done before. That's why the Clinical Center was built.

JZ: Yes, that was my understanding. By bringing in patients with unusual diseases from a long way, putting them on a ward, and then being able to go back and forth from the lab to test their blood and their urine, whatever, was the way to do it.

GC: Did you enjoy the clinical work?

JZ: Oh yes. I think the important thing in those days was that we were all interested in cancer and eventually became oncologists. Oncology wasn't a name in the '60s. It only appeared as

a discipline in the early '70s. I took my first set of boards with DeVita and Chabner and others who were just starting out as newcomers to the field. Now of course oncology is twenty-five years old and doing well.

I loved the clinical work. Paul Carbone ran a very good clinic and he took excellent care of the patients. The number one priority was, of course, making sure these patients were well looked after.

GC: You mentioned that one of your patients, you went back and saw him and he's now in his forties and he's grown up. Were there other patients that you kind of kept in touch with or kept track of?

JZ: I guess I would say that most of them were in Uganda, although there are quite a number of youngsters who had Burkitt's lymphoma at the NCI who we followed for many, many years. Of course, I haven't followed them since I left in 1981, but a colleague of mine, Ian Magrath, is still there following them and they are doing just fine. They're all young adults or older adults, married with families. One of the great rewards of cancer cures is the fact that cancer survivors go on and develop their own lives, and you can think gosh, if they hadn't gotten the right drugs at the right time in the right combination, that might not have happened. So it's very rewarding from that standpoint.

GC: You were talking about there weren't any obstacles to getting resources. Was that as true in Uganda as it was in the United States?

JZ: It was true in Uganda. In the good years of the '60s and early '70s, pretty much everything was available there. Certainly the drugs were available and the reagents and the lab hardware and whatever we couldn't get, we could have quickly air-shipped from the U.S. It worked out fine.

GC: Were there any drawbacks to doing research with the NCI or at the NCI?

JZ: None that I can think of. I think it was probably the richest environment to do research that you could find at that time in the United States. Since then, they've instituted more accountability such as tenure. But it was pretty freewheeling in those days and as long as you had a collegial bunch of people who were like-minded, things went very well.

GC: So if you had an idea you could just run with it, order the supplies you needed, bring together.

JZ: Pretty much, yes, exactly.

GC: Do you think that's the way research should be done?

JZ: Well I think there are a lot of issues there. Good research always comes from clever people who have novel ideas and are supported for them. We have learned in science that you never know where answers may come from. They come from usually sources that you never expected to find. It's really the surprises and the serendipity and the clever minds that are prepared for unexpected events that make the most of scientific discoveries.

GC: So I take it you don't think much of planning like trying to plan programs of research at the Cancer Institute that was going on in the late '60s, early '70s. There was a push to start planning research.

JZ: Yes, I would not be a big fan of detailed planning. I think to have to create a general research context. Generally speaking if somebody has a great interest in a particular area, and then that interest attracts other people who cross-fertilize with ideas, and those ideas develop into experiments and the experiments take you to the next set of ideas, and that's the way research progress is made. But I would not endorse a blueprint to say we're starting at "A" and we're going to get to "Z" by 1975. It just doesn't happen that way, as you well know.

GC: I think that's one of the interesting things about the division between people actually doing the research and the people who were really pushing the War on Cancer in the early '70s, that people really wanted to hear that there was in five years we could get so far, and people

actually doing the research said, "We can't tell you, in a lot of cases, we can't tell you where we're going to be in five years."

JZ: Part of the problem, of course, is the technology. For the space shuttle, the technology was there to create a rocket and build a spaceship and to understand how boosters work and so forth and get man into space. And that was a technological feat that was brought together by the same type of technology that made the atom bomb. But biology is different. We just didn't have enough information about biological systems to be able to make all those predictions. It was really a lot of guesswork. Now I think times are different. Now I think with the genome unraveling and the genetics of human cancer becoming more and more evident each day, there will be a new generation of advances. But living organisms are enormously complex. Reduction of complexity into component parts and then rebuilding them into a system that works is a difficult task. We're now getting to a technological sophistication where gene therapy, for example, can be envisioned.

GC: What are you most proud of of the work you did at the Cancer Institute? Is there any one thing or any one time that you're most proud of, or your favorite? Whichever of those questions you want to answer!

JZ: The Burkitt's lymphoma work speaks for itself because the story unfolded in such a logical way where the lessons just accumulated one after the other. But I have to say one of the most

interesting things I did had nothing to do with lymphoma but was the work I did in tropical splenomegaly syndrome. In this condition people had very large spleens for no obvious reason, and most investigators thought it was due to malaria but nobody could figure out why. I got the idea that this might be due to immune complexes, antibodies and antigens that joined together. So I did an experiment where I took plasma from these patients to look for cryoglobulins which are ways of detecting antigen-antibody complexes. We found that they had very large amounts of cryoglobulins in their plasma. So we took this to the next level and actually looked for cryoglobulin components in the liver using immunofluorescence, which I taught myself how to do. In the end I wrote a paper that showed very clearly that the amount of cryoglobulins was closely related to the size of the spleen and that these cryoglobulins ended up in the reticuloendothelial system of the liver. We hypothesized that the hyperreactive hepatosplenomegaly that you see with malaria could be a result of the particulate stress of these cryoglobulins and their uptake in these organs. And I guess I'm proud of it because I worked it all out myself. I taught myself about cryoglobulin chemistry, immunofluorescence, and I did all the experiments right there on the spot and wrote the paper. So that was a complete solo flight. I had some technical help, but basically that was my own thing.

GC: And that's another example you were talking about you like to build things up from scratch.

JZ: Yes. This was a rare disease, nobody ever heard of it before, and not very much was written about it. It was just a good puzzle to sit down and sort it through.

Another example is during the summer of 1982, I worked in a clinic at a resort in Long Island and saw a lot of cases of Lyme disease. I don't know if you know about Lyme disease. In those days, of course, nobody knew what it was caused by, but it was linked to tick bites. I teamed up with a group at Stonybrook Long Island, headed by Jorge Benach, and together we did a study on some of the blood and tissues from these patients that we were seeing.

Benach found the spirochete, named *Borrelia burgdorfiri*. That was all written up in the *New England Journal of Medicine* and I was one of the co-authors. That kind of serendipity I really enjoyed.

GC: We talked a little bit before I turned on the tape recorder about other people you thought I should talk to. I don't know if any other names had come to mind of other people who I should speak with?

JZ: Well, Steve Rosenberg certainly was a contemporary at NCI and was there for quite a long time. Bill Terry was also around for a long time. Both could tell you the story of tumor immunology. Paul Carbone will give you a wonderful history. I think he came there in the early '60s. But I think you've got most of the main people.

GC: Is there anything else that you'd like to add for the record before I turn off the tape? Is there anything I missed?

JZ: No, I don't think so. I think you got it all.

GC: Okay. This ends the interview then. Thank you.

[End of interview]

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