National Cancer Institute
Oral History Interview Project
Interview with Joseph Burchenal
Conducted on January 26, 2001
by Peggy Dillon
Darien, Connecticut

PD: Good morning. This is Peggy Dillon of History Associates Incorporated. I am speaking with Dr. Joseph Burchenal for the NCI oral history interview series. We are at his home in Darien, Connecticut. Today is January 26, 2001.

JB: Good morning.

PD: I would like to talk with you today about your work in cancer chemotherapy in general and also your involvement with the National Cancer Institute in particular. Before we get into your career overall and NCI, I'd like to ask you about your background. If you could just tell me a little bit about your upbringing and education . . . I understand that you were interested in chemistry from a very early age.

JB: I was born in Milford, Delaware, but I lived in Wilmington, Delaware, for the first part of my life. My mother died when I was three, in childbirth. So I lived with my father in Wilmington. He was a lawyer. I went to school at Tower Hill School. The majority of my friends in the school had fathers or mothers–fathers mainly–who worked for Dupont. They were very likely to, so that there was a lot of interest in chemistry there. In fact, it was the same way on the street where we lived, where the fathers were mostly chemists. But my interest in chemistry, I guess, started when I was eight years old and I had a cousin who was eleven who was given a Chemcraft set and he used to show us all of the interesting things that he could do with it. And then, of course, after a couple of years, I

graduated to a Chemcraft set of my own and made all sorts of interesting things. But mostly, I was more interested in making gunpowder, which is what Dupont was making at that time. And so we used to make handfuls of gunpowder. But gunpowder, to go off, must be very well mixed. And so we used to . . . we couldn't really get it mixed . . . I mean, this was charcoal from match sticks and saltpeter, which we bought at the drug store, and sulphur . . . flowers of sulphur which we would get someplace else. But, in order to do it, we would put it in water and swish it around and get it a little bit better mixed there. And I remember once having quite a pile of this stuff and it was still wet and I made a cake out of it in a little pan and put it in the oven . . . in the coal stove. And I left it there until it dried. Fortunately it didn't go off or anything. But actually, when we set it off in the pan this way, in the open air, it would just flare up tremendously. It would not explode.

PD: It would just swoosh?

JB: Yes. It would just swoosh up like a flash or something. So I was interested in it there. Then I went on the Phillips Exeter Academy in New Hampshire for my work before college, and there, I was very interested in chemistry. I mean, I took chemistry I and then I took chemistry II. There weren't many people in chemistry II . . . maybe about ten of us. But the professor there was very interesting, and so I got more interested in it there. And then I went to Princeton. And at Princeton, I majored in chemistry. But after three years . . . well, earlier in that . . . during my time at Princeton, my mother came down with an osteogenic sarcoma of the leg. After the operation the surgeon told me, "We took off the leg and we think we got all of the tumor, but if it comes back it will come back in the lungs. If it comes back in the lungs there's nothing we can do about it."

PD: There was no chemotherapy treatment at that time?

JB: No, there was not even chemotherapy for infectious disease at that time. And radiation therapy wouldn't do anything for the pulmonary metastases. So, she went on and, for a couple of years she was fine, and then she came down with metastases and gradually got worse. So, my third year at Princeton, I decided . . . since I wanted to go to medical school anyway, that I would probably better do it after my third year at Princeton, before my mother died, or if my mother died, because I had a nine-year-old sister who would have been–at least I thought would have been–as we had moved up to Swarthmore then, for about three years. I thought I had to be in Philadelphia so I applied to Penn and to Temple. Penn immediately turned me down, and so I paid my fee at Temple and everything else. Then two weeks before time to start school, the dean wrote me and said, "There happens to be an opening here now. We can take you if you want to come." So I said, "Sure." I don't know whether somebody died or what happened, but at any rate . . . so, I got into Penn. I had fun with this. I was given an award by the University of Pennsylvania just this last spring as an outstanding alumnus. So I started off the talk by saying that when I did decide to go to medical school, I applied to Penn and Temple, but Penn turned me down so I signed up to go to Temple–and only went to Penn after they had a last-minute opening. And I got gentleman's marks there. I did not get . . . didn't make AOA [Alpha Omega Alpha, the Phi beta Kappa of medical school] or anything like that, the way my sons have done. But I got by, and I was interested in chemotherapy. And then I was interning in Baltimore and I started out in pediatrics. And I had three or four cases of acute leukemia in children. And I was very impressed that it went as fast as an infectious disease. This was just the beginning of the antibiotic era. In fact, sulfanilamide was the only thing we had when started my internship.

PD: What year was this?

JB: That was in 1937, just after I graduated. But at any rate, and since you could do something with acute diseases with sulfanilamide . . . I mean, strep infections or staph infections, sulfanilamide worked pretty well then. There was no resistance to it. So I

thought, well, acute leukemia acts almost as it if were an infectious disease . . . it goes so much faster. Maybe it would be worthwhile hitting it with chemotherapy. Well, I knew that sulfanilamide didn't work, because we were treating these patients who were obviously frequently infected with strep and stuff and, although it would take care of the strep, it wouldn't have any effect on the leukemia. So, I did think that the acute leukemias which I saw in children, compared to the cancers of lung and all sorts of abdominal cancers and so on, that I saw when I was on the adult service . . . I thought it would be much better to work in pediatrics than in adults, if I wanted to do chemotherapy of cancer. So I took a year of training in pediatrics at Cornell at the New York Hospital at Cornell, and a very fortunate thing for me, which they don't have anymore, I'm afraid, is that in those early days, they had an elegant dining room on the eighteenth floor, with chairs. We [a mixture of interns, resident staff, and faculty] were sitting at tables with linen napkins and we were waited on and everything else. This has never happened to me since in a hospital, but at any rate, the result was that the interns and residents were there and the attending physicians as well. And I remember one time I was fortunate to sit at a table where, on my right hand was Dr. Jacob Furth, who was an outstanding man in mouse leukemias. He was professor of pathology there. And on the other side was Dr. Claude Forkner who had just finished writing the great, outstanding, tome on leukemia. They started asking about what I wanted to do, and I said I was interested in leukemia. So Forkner said, "Well, anytime you get a leukemic slide and you want to go over it, I'd be glad to go over it with you, and I'm in my office right . . . not far from the pediatric ward and I'm usually there until at least ten o'clock at night. So if you come off duty, bring them in and we'll look at them together." So we did that. And I had mentioned to Furth that I was interested in animal tumors and leukemias. He was the outstanding authority on mouse leukemia at the time. He said, "Well, you can come over to my lab at work." So, in the long run, I did come over to his lab on my nights off and worked and set up an experiment on the relation of pregnancy to leukemia, and worked with the mice and learned how to inject mice and so on. So he got me well started on

things. And then I was married and we decided to take a year of Wanderjahr in Europe to visit the important clinics.

PD: What?

JB: The old apprentices . . . when they had had all their training as apprentices, and before they took their exams, would take a Wanderjahr and they'd go and work for various masters in various places. A travel year, in other words. So I decided we'd go over the Europe and take a Wanderjahr there, and I would work in Germany with Aschoff and then at various places that I thought were outstanding in pathology and leukemia. So we went by boat and we got to Paris and we found that the place was full of raw recruits . . . French Army recruits who were just coming in. So it made us think that there was probably going to be trouble. But I went on the assumption that in the year before, there had been Munich and there had been a high pitch and then it calmed down for a year. And I thought, "Well, this is probably going to blow over too." But, rather than go to Germany, we decided to go to Switzerland. So we went to Switzerland and started to hike from Lucerne, over the mountains, or the Furka Pass and the Rhone Glacier to Geneva, which is about two hundred miles. And we got about halfway there and every day as we got closer and closer, we could read in the papers that things were happening and that Ribbentrop and Franz Von Papen [two high-level German foreign officials] were shuttling between Berlin and Moscow to settle things. At any rate, things looked worse and worse all the time. Well, we got up to the pass and we were staying at a little hotel, which was also the post office, and when we got down in the morning, there was a notice on the wall there, "Attention, grenzemobilmachung," which means "the frontier mobilization" in Switzerland. And it only takes Switzerland about six hours to mobilize their frontiers, so we knew that they must think it was pretty serious. So we walked over the pass and got down to the hotel on the other side and decided maybe we'd better abandon this long downhill trip to Geneva, and start up over the Grimsel pass to get to Interlochen and get someplace where we could get more news, instead of being way in the

back woods there. So, we started to walk up the pass and we got about halfway up, and it was raining and we had all our clothes on our backs, and it was miserable . . . and a couple of guys came along in a car and they apparently turned out to be jewelers who had come to Switzerland to, I guess, to buy watches and jewelry. They were from Argentina. But they gave us a ride to Interlochen. We got there and that was a more central place. So we got in the post hotel there and went to bed. And before we went to bed, I said, "You know they had been fooling around with this business of threats and counter-threats for a week now. If they wanted war, they'd have had it already. I don't think it's going to do anything." The next morning, we were awakened by the little paper boy, "Extra, Extra," "Kreig, Kreig, Kreig," *"Zurich Ziti" –Zurich Zeitung* was the Zurich paper. And so I got up and went down to the boy and got the paper and there it was, the Germans had marched into Poland. So we knew there was trouble there and it looked as though the rest of our Wanderjahr was going to go by the board.

PD: So you came back?

JB: No. There were an awful lot of Americans over there, and of course this being about the first of September, they all had to get back fairly soon for school and college. And so they would call up the consulate and say, "Well, now what should we do?" And they'd say, "Well, get out. Get out in a hurry. Go by way of Paris." And, so, the people would get all packed up and all set to go and then they'd make the mistake of calling the consulate again just to make sure, the next day, and the consulate would say, "Oh no. Don't go by way of Paris. Go by way of Rome. And, so, everything was all higgly-piggly there . . . nobody knew what was going on. And since we had no particular commitment, there was no reason for us to go back then. So we decided to stay put. So we collected all our goods, our suitcases, which we parked at Lucerne before taking this hike across the mountains. And we went up to Zurich and found a little pension there, and stayed there and I found that I could work in the Kinderspital, the children's hospital, under Professor Franconi, where they had a lot of children's tumors. And I found I could

work in the blood and bone marrow laboratory at the university hospital, under Professor Karl Rohr, who was doing sternal punctures. I had never done sternal punctures before. In fact, they weren't being done in the United States at that time. So I learned how to do these, and how to read them. So, it was a very useful thing.

Well, it went on, and it was quiet and the Swiss were . . . you just had to be careful where you went. You'd go up in the woods and they'd say, in German, "If you're deaf, don't go here. We challenge once and then we shoot." (The Swiss are very good shots.) There were frontier guards all over the place, and guards up in the mountains too, and not necessarily on the frontiers. So I had good training in sternal punctures and I saw a lot of children's tumors in the Kinderspital, the children's hospital. So, we purposely stayed away from the U.S. embassy and the consulate. We figured that if they saw us, they'd say, "Get the hell out. Get out. Get out." So we waited about six weeks and then we sheepishly walked in, expecting to catch hell and they said, "Oh no. We're glad to see you." "What? What should we do?" "No hurry, just get out before the first of April . . . perhaps that would be a good idea." But nothing more than that. So, we were going to stay there until then. And then, just before Christmas, I got a cable from George Minot at Harvard. I had already applied for a residency at the Thorndike Laboratories. I had applied for it for the following July. And he wrote and said that he suddenly found that he had a half a residency and that if I was interested in coming, I could split that half of a residency with Henry Brewster, who also wanted it, and we could stay until July 1. He said, "Now, if you're here, it doesn't mean that we're going to keep you on for another year or two." But I figured, well, if I was there, I'd be a lot better off than if I didn't take it.

PD: Right.

JB: So, we came home and we moved to Boston and I went down there. And there, I worked on leukemia and I worked with Castle and Minot on pernicious anemia and on polycythemia vera and leukemia.

PD: And this is before your Army tour of duty?

JB: Yes [this happened in January 1940]. And while I was there, it was decided to put together the 5th General Hospital, just as they had had in World War I, which would be made up of Harvard people. So I joined that and things were quiet until, of course the seventh of December [in 1941] when Pearl Harbor was attacked . . . and shortly after that, we got a notice to get all our affairs in order because we were going to meet at South Station on the tenth of January and we were just going to go out of the world. We would essentially disappear. So, make all your arrangements for everything . . . your wills and arrange all your currency. Put your checking accounts in your wife's name and all that sort of stuff. And, so, we duly arrived at South Station [in Boston] on the tenth, and we got into a train. And none of us knew where we were going or anything. Well, it turned out we turned up in Fort Dix. And they immediately got us in and started equipping us with underwear which was so darn hard it was impregnated with sulphur gas, for gas warfare . . . and they got us all sorts of equipment and gave us shots and we got three or four hours of sleep and they'd get us up the next day and do the same thing and get . . . you know, they were in a tremendous hurry for about, oh, three or four days, I guess. And then . . . whether it had anything to do with it or not, I don't know . . . the Normandie burned at its pier in New York. This was all very mysterious. The Normandie was a very fast French ocean liner, which was used for moving troops. So, we think we were going to go on that, but, at any rate, we then slacked off a bit and it wasn't until sometime in February, I guess . . . maybe the end of January. Anyway, we started off for someplace in Europe . . . we didn't know exactly where . . . in a big convoy, with one battleship, some cruisers, and many destroyers, as well as some troop ships and many supply ships. And about halfway to Halifax, which we were going to stop at first, our ship suddenly stopped. So there we were, lying dead in the water, and the convoy couldn't wait around for us because it was a submarine area, “torpedo junction,” as they used to call it. And all of the convoy sailed on past us, and they left us with one little DE, Destroyer Escort. And we stayed there all night, dead in the water, and every once

in a while the DE would go scooting out someplace and drop a couple of depth charges and then come back again. It didn't make you feel any better. But at any rate, I guess the DE would hear something that might be a submarine, so they'd go out and chase it. But, at any rate, then the next day we got the thing fixed so that we could limp along about six knots, I guess, or something like that. And we did make it to Halifax.

There, a big convoy was forming up, which we were supposed to be on, but that convoy traveled a lot faster than the six knots, and we couldn't seem to get the propeller shaft fixed, to make it any better. So, the end result was that the convoy steamed off without us, and we came back again with one DE escort back to Boston. I remember reaching the submarine gates at Boston. I was just so happy to see them . . . really thought they were beautiful. But, at any rate, we got home and then about a month later, I guess, another convoy formed up and they put us on a different ship. And we got over to North Ireland.

I was interested in infectious disease. And, I mean, I figured there was no cancer, but I wanted to get something that was like that, where chemotherapy could be used. So we were in North Ireland for a while. And then I was sent down to Salisbury, England, to spend six weeks with a group that was made up of the American Red Cross, British Ministry of Health and Harvard University, which was made up to study infectious disease. They were . . . they had the assumption that, with everyone going to the underground in the bombing raids in London, that there would be tremendous epidemics and meningitis and all sorts of things that come from people being in close contact. And so this was an infectious disease research hospital, and we saw a lot of interesting things, including meningitis, although the severe epidemics never developed as expected. But there were a smattering of them. We saw a fair amount of meningitis and the usual measles and mumps and stuff like that. But at any rate, then I went back to my unit. Back in Belfast, we were there in November of 1942 when the troops came in. The 34th division was there and they took that out. More troops came in and would stop and

offload their sick people to us and take on replacements and then form a convoy for the North African invasion. I was picked to organize a truck convoy down to the place where we were going to set up a new hospital. It turned out to be Salisbury again. We took over a hospital which was said to be built originally for the Canadians. They didn't take it so we moved in. And we had the job of outfitting the whole hospital, which we did. And we stayed there until the spring of 1944 when, as they were building up for the invasion, they made us leave our hospital and go out on the Salisbury plain in tents to be ready for the invasion. That was for D-Day. So, we did that and then after D-Day we moved down closer to the port. And we went across on D-plus 30 . . . July 6, I think it was . . . 1944. And we were to set up a hospital . . . it shows you the problems of doing things in the Army and when you're fighting a war . . . the Army had picked two good sites for us . . . nice high ground where there would be no marsh, no mosquitoes, no nothing. Well, the Germans hadn't gotten out of that one and the second one was . . . still, they hadn't gotten out of that either. So they dumped all our stuff down on a marsh near the town of Carenton. Mosquitoes . . . I've never seen so many mosquitoes. We were in tents, and we built up a tent hospital there that eventually took care of as many as 1700 patients at a time.

PD: And were you doing any kind of chemotherapy training during the war? You mentioned infectious diseases.

JB: I was Chief of Infectious Diseases, yes. We had, essentially, sulfanilamide, we started out with, then we got sulfadiazine. Sulfanilamide didn't work in pneumonias. It worked in strep infections. Sulfathiazole and sulfapyridine worked in the pneumonias, but they were pretty nasty to take. Then sulfadiazine, which was the final compound that came out, worked very well in that type of disease and also was pretty well tolerated by patients. So, we were using that entirely. We had not had a chance before we went to Normandy to use penicillin.

PD: Okay.

JB: Penicillin, as you know, was discovered by Fleming in 1928. He found that a Petri dish plated with staphylococci had a clear zone in it. And it happened that a little piece of fungus had gotten in, and there was a large clear zone around where something in the fungus had killed the bacteria. But that was a discovery way before its time, you see. He wrote a paper on it, but nobody did anything about it because this was before sulfanilamide had come out, and people didn't believe chemotherapy was possible.

PD: By at least a decade, right?

JB: Well, not quite a decade, but almost . . . in 1928 to 1934, when Prontosil, the precursor of sulfanilomide, was discovered. I remember when I was in medical school, I asked an instructor, if you've got mercurochrome and got iodine and stuff like that, that you paint on the skin, it's good for infection there . . . it prevents infection. Why couldn't you take some of those dyes and inject them intravenously and take care of a patient with septicemia? Because we had one girl who was a year ahead of us who had gotten herself stuck by a needle that she was trying to put into a rabbit, and she had hemolytic streptococcal infection and a septicemia for about a month or two, hovering between life and death, and there was nothing they could do about it. Well, it was just about that time that the original sulfonamide studies were done in Germany. And, as far as I was concerned, I first saw the red dye Prontosil Soluble being given to a patient with a meningococcal infection, in my junior year there. But that's about all I remember of seeing it then. And then the . . . it was very experimental at that time. But, then the . . . my first year in Baltimore, we then had sulfanilamide in tablets, which we could give to patients. So, that's when we started out.

PD: So, after the war, you came back here and you joined Memorial Sloan-Kettering right away? How did that come about?

JB: No. I came back to the states a little bit early, because my wife had died in 1943 and I wanted to see how my daughter was doing with her grandparents, because she was four and I didn't want her growing up with just her grandparents alone. I wanted her to be where other children were. So I came home in March of 1945, and I got her squared away and everything, and then I came back to the Army headquarters in Washington, and said, "I want to get back to my unit." "No. Can't do it. Nothing is going that way. It's all coming back." Because, by this time, the war in Europe had stopped. This was probably in May, I guess. So, "What do you want to do?" "Well," I said, "I'd like to go to the southwest Pacific then, where there still was war going on." They said, "Fine. We'll fix that." But, I said, "First, I want a course in tropical medicine." They said, "Fine. We'll arrange that."

I took the course in tropical medicine and had a wonderful time at Walter Reed, and enjoyed it very much. I didn't study very much. I had a good time and enjoyed it and Washington. When I got through, they said, "Do you still want to go to the southwest Pacific?" I said, "Hell no. The war is over there. Why would I want to go there?" They said, "Well, how would you like to go to Walter Reed as chief of tropical medicine there?" I thought, "Gee. That's wonderful." I don't know why they said it, but later on, I found out that, despite the fact that I hadn't studied particularly much in my course of tropical medicine . . . I just enjoyed it, and so on. But when it came to the final exam, which we had, they were only allowed to give out one mark. And that was to the one person that did the best. And it happened to be me. So, that was very important.

By the 10th of January, 1946, I had four years in the Army. They asked me to stay, but I thanked them and said, "No. I'll take my terminal leave." And, so, I took my terminal leave. In the meantime, I had gone to the Surgeon General's office and asked them what was available in civilian life, and fortunately, a friend of mine from Thorndike, Dr. Hale Ham, was down there in there in the Surgeon General's office, and he said, "Well, we'd be

delighted to have you in the Chemical Warfare Service if you want. But if I were you, I'd go up to New York and see what [Cornelius] "Dusty" Rhoads is doing. He's the director of Memorial Hospital and he's trying to build a Sloan-Kettering Institute, which will be very close to the patient so that the questions at the bedside can be taken to the bench right away . . . to the investigator . . . and the discoveries of the investigator can be taken to the patient right away." And I said, "Well, that sure sounds like what I want." And, so, I went up there and talked with him and I said I wanted to do work on mouse leukemia and the chemotherapy of leukemia and cancer in patients. And he said, "Well, I think that's a good idea." He said, "I have a colony of mice of my own . . . or, I had before the war, and I think it would be fine." At any rate, I only mentioned that business of the tropical medicine exam because the rest of my marks were very much gentleman's marks at Exeter and Princeton and Penn. But, I mean, they were perfectly good, but they weren't outstanding marks. But, I think the fact that I got first in that tropical medicine made him think, "Maybe he's got something there." So, at any rate, I did get in there.

PD: With Dr. Rhoads?

JB: Yes. With Dr. Rhoads. And I started there . . . I finished my leave on the sixth of March 1946, and that same day I came into Memorial, and I was there for my whole career. And I set up immediately getting a mouse colony and starting to do chemotherapy of mouse leukemia. And we were using, of course, the compounds from the chemical warfare service at first, and the nitrogen mustard derivatives. There were a tremendous number of those derivatives, and we used to test them all in mouse leukemia. And none of them were much much better than the original ones.

PD: So, I'm interested in how you went from that stage to working on the drugs that became the basis for the combination chemotherapy, and that led you to work on projects with, at the same time with Dr. [Lloyd] Law. How did that come about?

JB: Well, I was doing work with the nitrogen mustards at first, and then I heard by the grapevine that Sidney Farber was working on folic acid antagonists and he had something very exciting up there. I didn't know Farber, but I did know a man who was working in his lab, Dr. Louis Diamond, who had lived close to me when I was in Brookline before, at Harvard. And I called him up and I said, "Is this true, that Farber has really got remissions there?" Because we had been treating acute leukemia with nitrogen mustards. And, in acute leukemia, the count comes down and all, but the hemoglobin doesn't come up and the platelets don't come up. So, in other words, it's just a general suppression of cells.

PD: So, the patient still would die?

JB: Yes. So, he said, "Yes, Joe, it's true." And so, I thanked him. And so, I called up Sidney Farber and I said, "I hear you've got remissions in acute leukemia." He said, "Yes. Would you like to come up and see them?" I said, "Sure." So, I came up to see them and there was no question in my mind. I went over the charts and saw the patients and everything else, and there was no question in my mind that these were true remissions. I mean, both the leukemic cells had come down, but then the normal cells had come back and the marrows had come back. So, I went down to Memorial and reported it and we started treating children. He said, "Here is some aminopterin, if you want it," and he said, "I'll introduce you to Dr. Subbarow, who was the head of the project at Lederle . . . S-U-B-B-A-R-O-W.

PD: Okay.

JB: . . . and he'll give you some derivatives. So, we got not only aminopterin, but we got what we call amethopterin, now called methotrexate, and lots of other derivatives which we tested in mice. Well, in patients, . . . the first five or six patients I treated, we didn't

get anything that was useful. I mean, the counts came down, but the patients didn't go into remission.

PD: With single doses, or what . . .

JB: Yes. With daily doses of aminopterin. And, I remember Dr. Rhoads and Dr. Kornofsky were all for writing a paper and saying that Farber was wrong. But I said, "No. I saw those remissions. I know they were remissions and they were real ones. Just wait." And so we waited, and sure enough, eventually we began to get remissions too. That just shows the danger of small numbers, because Dr. Guest, a hematologist out in Cincinnati or somewhere, his first seven patients all responded to it. And he wasn't treating it any different than we were. Whereas our first five or seven didn't respond at all. But, you know, you get about a third, or maybe, at most, a half of the patients responding.

PD: Okay.

JB: Well, so we used a lot of different folic acid antagonists . . . most of which produced remissions in children with acute leukemia. But none seemed any better than methotrexate. Methotrexate was a shade easier to use, for some reason or another, than aminopterin. Whether it's because we knew how to use the antifolics or not, I'm not certain why it was. The dose with methotrexate was about, I think, five or ten times as large. But the toxicity was somewhat similar. Maybe there was a little bit more of a spread between effectiveness and toxicity. I don't know. Or maybe we just got better at the whole thing.

So, we settled on methotrexate, as most people did. And we got good remissions. And we got remissions with some of the other derivatives that Subbarow had given us. I guess we didn't study them sufficiently to feel that they had any great advantage over methotrexate. Then we worked on that, and at the same time, I knew Lloyd Law got it

and he showed that his leukemia would respond to methotrexate also. I knew that, in our patients, they would respond for six months or a year, and then the disease would seem to become resistant to it. And I knew that resistance to antibiotics occurred, certainly, in bacteria. So, I decided I'd try leukemic cells. I had two sets of cells . . . I'd inject a group of, say, ten mice, with leukemia. And then I would treat them all.

And then at the end, I would take the leukemia and put it into one set of mice that were not treated and another set that were treated. And, at any rate, after about four or five generations, the leukemic cells which had been through the treated mice were totally resistant to treatment, whereas the other cells that hadn't been treated at all still could be treated just as well. So, it was just typical resistance as you'd get in bacteria. There was nothing very striking about it. At the AACR [the American Association for Cancer Research] meetings, I told Lloyd about it and he started working on resistance too, and he published, about six months or maybe a year later, on the same thing in his L1210 leukemia line.

PD: And again, were you two formally collaborating, or did you just happen to be working on the same thing at the same time?

JB: No. We just happened to be working on the same thing.

PD: Okay. But you stayed in touch with him about what your respective findings were?

JB: Yes. There were a lot of meetings where we would go there at the same time, and we'd always talk it over then.

PD: Okay.

JB: No, we didn't have any . . . nothing formal at all. And he was working at, in Bar Harbor, for a while, until about 1948, I guess. And then he moved down, I think, down to the NIH from then on.

PD: Right. That's when he came to . . .

JB: So, we would see each other at meetings, but we never actively collaborated other than that. He was using a leukemia L-1210 in C-58 mice and I was using the AK-4 leukemia in white AK mice. Then, of course, at the same time that I was working on methotrexate, I was also working on a large number of compounds because Chester Stock and Dusty Rhoads in our group had made patent agreements with some seventy-odd industrial, chemical and biological groups to send their compounds to us for screening against tumors. Dr. Stock was testing them against sarcoma-180. Dave Karnofsky was trying them against mouse tumors in eggs. I was testing them against leukemia in mice. And so we got many compounds. The first compound that I can think of that came from the group of George Hitchings and Gertrude Elion at Burroughs Wellcome. We got a 2-6-diamino purine, which we thought might be a nucleic acid precursor. We tried that on mice and it worked very well. And it worked not only on the ordinary AK-4 mouse leukemia, but also on the line that was resistant to methotrexate.

PD: Okay.

JB: Now, this was with our AK-4 leukemia. And so we thought that this compound would be worthwhile trying in patients. We had one patient who did extremely well and went into remission for about three years, a young woman, who, despite all our advice, said she was going to have a baby. She knew she had leukemia.

PD: Hold on one second. I just need to change the tape.

PD: Okay, so go ahead and tell me about the woman who wanted to have a baby

JB: We said, "You can't have a baby. If you have a baby with leukemia, you are certainly going to have tremendous hemorrhages and you are surely going to die." She said, "I don't care. I'm going to have a baby." She and her husband had just recently been married, and she was very religious. He was a pastor, I think. So, she did go on and become pregnant. And the leukemia stayed away. And she had her baby. And then, when he was about two years old, she relapsed with leukemia again . . . I mean a recurrence, and nothing we tried did any good. And she went downhill and died. But that was about all we saw with 2-6 diamino purine. Lloyd Law had tried the compound in his L-1210 leukemia and seen nothing. So then we went on studying other purine derivatives. A lot of water went under the bridge between that and the next good compound that Trudy Elion and George Hitchings synthesized, a 6-mercaptopurine. Parenthetically, Lloyd tried it later in his L-1210 leukemia and it worked well. It did nothing with our AK-4 mouse leukemia, but in Dr. Stock's work on sarcoma 180 it worked very well. It sort of sterilized the tumors. It made them so that they could not be transplanted. So, we decided this was very hot stuff. And we rushed it through Fred Phillips in Pharmacology. He was an excellent pharmacologist. And he did the toxicity in mice, rats, and dogs. On the basis of that, we took it in to patients right away. And it worked beautifully in patients, and produced remissions in patients sensitive to and resistant to methotrexate. So as far as Lloyd and I were concerned, he had a leukemia which picked it up. My leukemia didn't pick it up. Fortunately, Stock picked it up in his sarcoma 180, so we had a chance to use it. But then I realized that, maybe, our AK-4 was not the leukemia to use for screening. So, I made arrangements with Lloyd and switched over to his L-1210 strain and from then on used L-1210 all of the time.

PD: And then you picked it up?

JB: Yes. But, by that time, we knew it was active in patients too. And so we put it in the patients and it was beautiful seeing the patients because, when it worked, you'd see the leukemic cell coming down and the platelets start to creep up and the hemoglobin and red cells start to come up, and the patients would do very well. So, we continued it in patients, and I remember it was done very quickly. Trudy sent it to us in 1951. It had gotten through all of Pharmacology and all animal testing and everything that we needed, still by 1951, and in the spring of 1952, we put it into patients. And we knew in six months that it was a very active compound. So by January 1953, I had at least ten patients who had done well on it.

PD: When you say well, what do you mean, in terms of . . .

JB: Went into complete remission.

PD: For good? Or for a certain amount of time?

JB: Oh no. Well, at that time, nothing went into it for good. They just went into it for a period of time . . . six months to a year, or something like that.

PD: Okay.

JB: There were a lot of hematologists we had been talking with during the time that we were working on this. So I called them up and said, "We've got this new compound, 6-mercaptopurine which seems to work even in methotrexate-resistant cases, and if you'd be interested in treating it, I'll get the data together and we'll present it. If you come here in the first week of January, I'll show you. So, we got six or eight hematologists coming in and we showed them the evidence. George Hitchings was there, and I mentioned that fact that if you really think you like it, George Hitchings will give you some. Well, those were the days before the FDA. So, George gave it not only to people in New York who

were working with it but also people who were in other states working with leukemia. Burroughs Wellcome was in New York state. And, so, we had quite a few people working on it. So, when we presented it at the American Association for Cancer Research in May of 1953, by that time, the other groups I had given it to could get up afterwards and say, "Yes. This is, indeed, true. We've tried it and it works for us too." So, that worked out very well. And that got real interest in chemotherapy because now we had two compounds which were working in chemotherapy . . . I mean chemotherapy in acute leukemia. Of course, we also had the nitrogen mustards for Hodgkin's disease and stuff like that.

We had this big set up at Sloan-Kettering with all these different institutions, and, I mean, both chemical and biological groups out there, university chemistry departments and industry. And we had a big screening set up. Dr. Chester Stock had good relations with these, and they would send compounds in to us. I think there were seventy odd groups that we had relations with, saying that we would test all of their compounds. If they had something that they wanted kept confidential, we would treat it confidentially. And we would send the results back to them, but to nobody else, and so on. The other ones, why, of course, we would broadcast. So, at any rate, that worked very well.

And we were getting a tremendous number of compounds in. I would try a few of them in mouse leukemia, because I couldn't handle the tremendous number of compounds that were coming in. So, I think that Ken Endicott and Gordon Zubrod and the people down at NCI felt that what we were doing was interesting, but the Congress and Mary Lasker . . . of course, Mary Lasker was pushing all of this . . . gave them five million dollars to set up the Cancer Chemotherapy National Service Center (CCNSC), which I think Ken Endicott was head of then. And they set up a whole screening set up very similar to ours at Memorial, only much bigger. And then, about that time . . . I'm a little bit vague about this, because I'm only sure this was after Dusty died . . . but, at any rate, NCI said, "You've got a large number of grants at Sloan-Kettering from us, and what we're going to

. . . we're going to consolidate them all." I think there were about four million dollars worth of grants. And they said, "We're going to consolidate them and that will be 40 percent of your budget," or something like that, and "We'll expect you to report all the things to us."

Well, since we had to report them to NCI, then we had to abrogate all the agreements we had that were confidential with all the producing groups. So that sort of wrecked our program. And then the NCI, with Mary Lasker's help, got money from Congress and Congress offered five million dollars to set up a mouse screening program. I'm not sure, but I think this was the time when we were called in with Gordon Zubrod to discuss how we were going to handle it. And, in the end, we set up various types of screenings at NCI and there were also various people who wanted to do the screening, such as Howard Skipper at Southern Research Institute. But, they all did it without the confidentiality that we did, but they still were able to get most of the compounds. So, since they were doing that, Sloan-Kettering had a pretty hard job raising money to do ours.

So our program gradually died . . . or, it didn't die, but it got very much smaller, whereas the NCI screening program was the big one. So I guess Ken Endicott or Gordon Zubrod . . . I'm not sure which . . . decided we ought to have a group that would decide what was done, particularly with the chemotherapy . . . the use of the drugs clinically, and evaluate the use of the drugs for clinical trial. So, that's when Jim [Holland] and I were asked to form two groups . . . the leukemia group A and leukemia group B. So he had the leukemia group B, which later on became Cancer and Leukemia Group B (CALGB), whereas I had leukemia group A, which stuck pretty much to acute leukemias and children's tumors. And now leukemia group A has grown so that it treats about half of the acute leukemias in children in the country.

PD: Today?

JB: Yes.

PD: So, it's very much like throwing the stone in the pond and watching it ripple . . .

JB: That's right. Yes.

PD: And you chaired that from the start?

JB: What?

PD: You chaired leukemia group A . . .

JB: I chaired leukemia group A for a few years and then I asked Lois Murphy to take it over. The group was a pretty coherent group of pediatricians who were all interested in leukemia. After Lois, Denny Hammond came on as chairman and greatly expanded the group. So, then, when Denny Hammond got it, he increased it markedly in size. And so, it ends up by now having . . . or at least the last time I checked, having about 140 different groups of pediatricians. Not 140 pediatricians, but 140 separate groups working on the acute leukemia. They treat about half of all the acute leukemia in children in the country. Denny Hammond had it for eighteen years, I think, and then, various other people have taken it over.

PD: How long were you a part of that group?

JB: Well, I have been a part of the group all along, but I was the head of it only five years, I guess, to get it started. Because I wasn't really interested in large-scale testing. I was more interested in finding new compounds in patients. Once I felt that they were effective, I let somebody else prove that they were effective on a large-scale basis.

PD: Had you, at any point, wanted to be more of a hands-on clinician rather than a researcher? I mean, how . . .

JB: Oh, I was doing . . . yes, I was doing that all the time. I was seeing all these children with acute leukemia.

PD: Okay. So, you would always split that?

JB: Well, I'll say I always did it up until 1964 or 1965. And Lois Murphy and Charlotte Tan worked with me on that in the children, and Norma Wollner. These are all people that I had picked as pediatricians to come to Memorial to work. Then, in 1964, I became Vice President for Clinical Affairs, I guess, at Memorial. So, then, I was less hands on. I mean, with Lois Murphy and Charlotte Tan, I took care of little Robin Bush, the present President's sister. That was long ago. We treated her with mercaptopurine and, unfortunately, she had a very fulminating acute leukemia. We would treat her and she'd go into remission but then she'd come back a month later or something and her white count would be up to 600,000 or something. And then we'd treat her again and bring it down slowly and things would be in good shape for a while and then she would relapse again, so that, even today, we probably would have had a good deal of trouble holding it . . . a very aggressive leukemia.

PD: Even though I want to keep talking in terms of the chronology of your career, I was wondering if you could talk a little bit about the juxtaposition of the medical community's approach to what you and other chemotherapy researchers were doing. I mean, on the one hand, there was this profound skepticism to . . .

JB: Yeah.

PD: . . . combination chemotherapy, and then, on the other hand, there was all this intellectual excitement about what was going . . . I was just wondering if you could sort of describe, or speak to the intellectual and emotional atmosphere within the medical community at the time.

JB: Well, when we started, the usual thing was, "Oh, this beautiful little child has leukemia. Don't bedevil her with all these treatments and make her sick," and everything else . . . "Let her die in peace. Don't do anything to it." And that was the general practitioner's or pediatrician's idea. A lot of them said that. Then, as we gradually began to get better results, then they fed patients to us . . . and we had more patients as things worked out better. But at first, there was a great skepticism. And, of course, with solid tumors, leaving out Hodgkin's and lymphosarcoma . . . but for the carcinomas, well, that skepticism lasted a lot longer, and rightfully so, because we weren't really doing a hell of a lot for them. But, of course, I was, at least, in the leukemic side, where we did demonstrate effects.

PD: You were seeing results faster than the people in other fields?

JB: Yes. That's right. Certainly in children's leukemia compared to adults.

PD: So, and what was the intellectual excitement like? I mean, would you just go to conferences and be beside yourself over the gains you were making with this real sense of being excited. [telephone interruption] We were talking about, kind of, the intellectual excitement of the era . . .

JB: Oh, yes.

PD: . . . and whether you had the sense that you were part of this big pioneering effort. And what was it like talking with your colleagues?

JB: Well, at first we weren't part of any big effort. I mean, it was just a few of us doing it. And then, we got more and more, and that was fine. But actually, the stuff that was done by the cooperative groups, often times it was phase three stuff, proving that it's slightly better than something else that is known to be good, and proving it's a little bit better, or that the combination is somewhat better. But I was never as interested in that as I was in getting new compounds to start out with and maybe trying with one combination or another.

I remember, my first study, I had a patient who was treated with 6-mercaptopurine and a glutamine antagonist called azaserine. And the child went into . . . this was 1954 . . . the child went into remission and stayed in remission. And, at the end of a year, we thought maybe she might be getting ready to relapse, but it doesn't look as though she really did relapse, but anyway, we gave her a little methotrexate for a short while, a month or so. And then, after that, she had nothing and she kept doing very well. So I thought, well, the first thing we did in leukemia group A was to try 6-mercaptopurine and azaserine in a randomized trial. Well, it was our first phase three trial and it didn't show anything . . . it didn't show any greater beneficial effects. So, I guess that her case was just an aberrant effect from, maybe, 6-mercaptopurine alone. But, at any rate . . .

PD: All right. You were talking about working in the sixties. One of the things you did then was you got together a body of evidence about five-year cure rates, didn't you?

JB: What? About what?

PD: During the 1960s, wasn't it you who accumulated a lot of information about various cure rates of leukemia patients around . . .

JB: No. What I did was, in 1959, we had a meeting out at Madison on fluorouracil and its derivatives. And we found that fluorouracil and fluorodeoxyuridine seemed to work

better, at least according to one report that showed up . . . seemed to work well in patients with liver tumors. And liver tumors are pretty rare here. They aren't so rare in Africa. In fact, they're very common in some parts of Africa.

So, then we were, at that same conference, trying to get the synthesis of 5-fluorodeoxycytidine, And that was extremely difficult to make. It would have been very expensive. And so I got up at that time and said, "Well, it's terribly expensive and all, but it looks as though fluorouracil does work in patients with liver tumors, and maybe this would be the place to try it. Now, liver tumors are fairly uncommon here, but it would seem to me that maybe we should take a small amount of it down to Africa and see if we could do better with it there.

So, I sat down at the end of the conference with the person who handed out money for cancer work at the American Cancer Society. He said, "Joe, you know, if you're serious about that, I think the ACS would be willing to foot a bill of, perhaps, a thousand dollars, to get you down there and back and check it. So I came home and I told Dusty Rhoads about this, and at the same time he had just seen a bunch of head and neck tumors . . . tremendous things that grew in Nairobi and Kenya.

And we had one of our men who was doing intra-arterial chemotherapy with these drugs, and the idea was to squirt the concentration right into the tumor and maybe you would get better effects than if you gave it systemically to the body at large, through intravenous . . . So, he thought that this would be a great idea. So, he was an extremely busy man because he was trying to run SKI and trying to a dozen different things. So, he said, "I'll go down to Kenya and look at this, and see if these tumors are really the sort we could use. And then I'll come back and we'll see what we want to do with it."

So, he got his tickets and he went out to the airport and started to get aboard the plane to London, and they said, "Well, this flight is flying to London, but you're only wait-listed

from London to Nairobi. He said, "I can't be wait-listed. I've got to go then, because I've only got twenty-four hours to spend down there. I've got to be back for a meeting of the Board of Governors . . . so he came back in high dudgeon and said to hell with that . . . and unfortunately, about a week or so later, he died of a coronary. So, later on, Art Denues, who had taken his place as head of Sloan-Kettering, came up to me and said, "Joe," you know, "if you're still interested in going down there and looking things over, I think it would be a good idea for you to do just that. And you can take Kay Rhoads along with you." That was Dusty's wife. He said, "She's an excellent secretary. She can take shorthand when you're driving fifty miles an hour over bumpy roads. And it will get her mind off Dusty."

So, at any rate, we arranged that. And we went down there about the first of January, I think. And there we met with Tom Umboya and all the powers that be down there, and it looked as though we had a pretty good chance of doing it. In the meantime, we had met with the young Aga Khan, who happened to be in New York. He was going to Harvard at the time. And he was an interesting . . . well, he came in, dressed in his usual gray suit and everything, and he sat down at the conference with us, and we explained all of the things that we were doing with the new compounds, and so on, and we thought, "Well, it's just going over his head. He's not paying much attention to it," and so on. Well, it turned out that when we got through, he started asking questions, and he really had absorbed the whole thing, even though he wasn't a medical man. But he had the important stuff.

And so he said, "Well, if you people go down there, we've got a hospital there that was just built a couple of years ago for my uncle, the Aga Khan, and we'll give you a couple of beds where you can take patients in and keep them there as long as you want, and take them out." So, this was fine. When Kay Rhoads and I went down there, we found that we could get beds at the King George VI hospital and also at the Aga Khan hospital.

And, so, we arranged to have a team go down there and try treating them. Well, in the meantime, we found a lot of jaw tumors.

Then we went to Kampala, where we ran across Mr. Burkitt, or he came over for a meeting or something, and we talked with him and he said, "I've got more damned tumors of the jaw and of the abdomen," and so on, of children that he wanted to treat, and so we went to see them, and decided that this was something that really was a great gold mine of tumors. So we started him working on these tumors using the high-dose methotrexate used by Min Chiu Li and Roy Hertz in the treatment of choriocarcinoma at the National Cancer Institute. We found that we did have a few of those tumors in Nairobi, but they were the only ones that came into Nairobi from outside, not the ones that came originally from Nairobi, but they came from the lowlands and came up to Nairobi. And it turned out, with Burkitt's study, parenthetically, he went all over from Uganda all the way down to South Africa and back, in an old secondhand station wagon with one pathologist, who was a friend of his. And the two of them made this tour through all South Africa. It must have cost them $500 at most, or maybe only $100, that’s how cheaply great things can be done sometimes.

But, at any rate, he just did that and he would ask the people, "Have you ever seen any jaw tumors here?" and he would explain what it was, and "No, we haven't seen it." Well, he'd pull out a picture on a paper and say, "Have you seen anything like this?" "Oh yes. We have seen those." And so, he found out . . . and did a very nice job. He plotted it and he found that down in South Africa, it only occurred in areas below 1500 feet high. When you went up to the Rhodesias, you might see it up as high as 3000 feet. When you came up to . . . well, Uganda and Nairobi, it could be anywhere under 4000 feet. And he thought it probably was due to an insect transmission or something like that. But, at any rate, he did a very nice job. But the upshot of it was that there was lots of it over there and we started treating it at the same time.

And the doctor who came over with us to treat, using intraarterial treatment of the tumors, did his study on tumors, but it didn't seem to do much better than intravenous. So what we really did was to switch to Burkitt's tumor. And, then, he was only treating the patients for two or three months. Then we sent a young German who had been with us for two years, Herbert Oettgen, we sent him down. He had been with us for two years and decided he wanted to stay with us. But at that time, someone who came over on whatever his card was had to go out of the country for two years before they could reapply. So we sent him down to Nairobi for two years and he worked on Burkitt's tumor down there and did a very nice job, and found out that it was extremely responsive to chemotherapy and that, not only nitrogen mustard, like Cytoxan, and things like that, but other drugs would work. At first we tried large doses of methotrexate, and that worked well. But still, Cytoxan seemed to be the best treatment.

PD: So, you were applying very directly the techniques you had learned studying leukemia?

JB: Yes. That's right. And he had worked with me in leukemia for two years before he went down there.

PD: Okay.

JB: And so I went down there about every six to twelve months, to see how things were going. And, of course, he'd send case histories back to me, and, so we knew what was going on. And that worked very well and we found that this tumor was so sensitive, I mean, almost all of them responded to it and you'd see these great tumors of the jaw or the abdomen, and they'd just melt away. And some of them wouldn't come back. And Burkitt was treating them, and then after two or three months, if they were all cured up apparently, he would send them out into the bush, telling them to come back if they had any trouble. Well, of course, they didn't come back. And he marked them off as having died of the disease. And then one day he happened to be out in the bush, and found one

of them he had discharged a year ago, and he was still fine. And, so, he realized that something like that could happen.

PD: It was working.

JB: What?

PD: It was working.

JB: Yes. It was working. And, so we originally suggested to Burkitt that he use high doses of methotrexate, just as Hertz had used for choriocarcinoma. Hertz and . . .

PD: Min Chiu Li?

JB: Yeah, Hertz . . . Li and Hertz had used that. And so we used those large doses, and that worked. And then when Cytoxan came along, it worked even better. But it is an interesting sideline on these tumors . . . almost all of them seemed to be in males. But the reason for it is simple. In the first place, a tumor on the face shows up much quicker than a tumor in the abdomen. They all had tumors in the abdomen too, but it was not as obvious as in the face. And the second place, when it happened in a male . . . if it's a male, that's something. You rush them to the hospital right away. If it's a female, they would pay attention to it. I mean, that was the African tribal feeling, that, you know . . .

PD: So, the women were allowed to die?

JB: No, but to them the girls were not as important as the boys.

PD: Wow. Around this time, or late sixties, early seventies, you got . . . I'm switching gears here because I wanted to ask you a bunch of unrelated questions . . . how did you become

a member of the National Panel for the Conquest of Cancer? You became a member of the Yarborough Commission.

JB: Oh yes. Well, that wasn't . . . Yarborough Commission wasn't until the late sixties . . . 1968, 1969 or 1970.

PD: Okay. How did that come to pass?

JB: Well, because I was in charge of clinical chemotherapy at Memorial Sloan-Kettering, and Sloan-Kettering was the biggest institute outside of the National Cancer Institute, in cancer, so I was the one that was picked to do that.

PD: And how did you contribute to that commission?

JB: Well, we had all these compounds and combinations which we had worked with, and that's where I helped out.

PD: So you said, "Here are the drugs that are working for cancer and here are the drugs that are not."

JB: That's right . . . so far, that we haven't found that work. And since I was working on acute leukemia and all the rest of my group A were acute leukemia, why, it was pretty much the same thing. And we had worked on compounds together before. We worked on mercaptopurine, methotrexate, and azaserine, so we knew how each one worked.

PD: Were you a pivotal person in terms of crafting the language of the report, or were you a more behind-the-scenes participant?

JB: To a certain extent, I guess, but, I mean, there wasn't much crafting. You either got effects or you didn't, or you got an occasional effect.

PD: So you just . . . you submitted straight scientific results?

JB: Mostly, yes.

PD: And you were not really involved in the politics.

JB: Oh yes, yes, sure. I was too . . . acute leukemia group A. Yes, we all talked together and decided how it should be done, and so on.

PD: Dr. Holland was also on that panel.

JB: Yes. He was on the cancer and acute leukemia group B.

PD: Did you get to know Mrs. Lasker very well?

JB: Very well. Oh, she was at Sloan-Kettering all of the time . . . Mary Lasker was probably the most important person behind the scenes in cancer research.

PD: What was she like?

JB: Oh, a wonderful person, beautiful woman . . . Wellesley graduate, I think. And a beautiful woman, but also, she really knew how to work things. She had lots of money, but she would use her money to get people interested in it and then get somebody else to put the money in. I mean, she put in plenty of money, but her big thing was in getting the NCI and various other people to put money in.

PD: What activities did she have going at Memorial Sloan-Kettering? I mean, you said she was there a lot.

JB: Oh, well, she was interested in chemotherapy and the stuff that we were doing.

PD: Okay. What would you say was her role, in terms of the importance of cancer research and this passage of the National Cancer Act?

JB: Oh, her role was . . . she was a damned spark plug. She was great. For instance, it was she that got [Senator] Ralph Yarborough interested in doing it and forming the Yarborough Commission. And she would be behind the scenes, sort of, egging people on, but you wouldn't know it. She did it very nicely and carefully. Oh yes, she was the one who really started the Yarborough Commission, which led to the National Cancer Act.

PD: Okay. And did you get to know Mr. Schmidt as well, Benno Schmidt?

JB: Oh, Benno Schmidt, I worked with very closely, yes. Yes, because we went down to Washington together, usually with Laurance Rockefeller, and they were both on our board of trustees. Actually, Benno was the chairman of the board for quite a while.

PD: Part of that effort, while you were on that panel . . . did you and James Holland and Mathilde Krim write a small green book about the state of cancer research? Dr. Holland mentioned this yesterday. Did you . . . is there some document . . .

JB: I don't know. Mathilde . . well, I didn't think she was . . . did too much in this business. She sort of came in from the side. But, I don't know about what she wrote, in the way of a small book.

PD: Did you and Dr. Holland work on this book? He described it as a little green book that talked about the state of cancer research at the time.

JB: I don't know what it was, you know.

PD: Okay.

JB: It may have been something that was different from what you say about the little green book. But, at any rate, that doesn't provoke any ideas with me.

PD: Okay. Well, then, along these same lines, were you present at the signing of the National Cancer Act?

JB: Oh yes, naturally.

PD: What was that like?

JB: It was very nice. We went down into the White House through the back door, and Nixon signed the thing, and I think he gave us a pen apiece, but . . .

PD: What did you think of the idea that cancer could be cured by a certain date, or that the war on cancer could be won?

JB: Well, I was delighted to see the money for cancer research and the push. I never felt that cancer would be cured by any particular time. I mean, I thought that something would be nibbled off and something else, and something else, and so on, as has happened, actually. There wasn't anything . . . no remarkable discovery which just finished cancer off. I mean, we got rid of the acute leukemias and then the lymphosarcomas and . . . at least the lymphosarcomas in children, and then the osteogenic sarcoma, and various things like

that . . . but, and choriocarcinoma. But I never thought that there would be any single drug that would do it.

PD: So, pretty much, the successes evolved about as you expected . . .

JB: Yes.

PD: . . . in stages, and certain ways . . .

JB: I think so, yes. I mean, they went in a very, what turned out, at least in retrospect, to have been a very orderly result.

PD: After the Cancer Act was passed, Memorial Sloan-Kettering became a comprehensive cancer center. Did that change things there, that relationship between Sloan-Kettering and NCI?

JB: No.

PD: Around the same time that the cancer act was passed, you chaired an NCI committee on cancer chemotherapy. What was . . .

JB: Well, the NCI committee . . . also, the World Health Organization.

PD: Okay.

JB: Yeah, WHO.

PD: How did that committee get formed, and what was your role in it?

JB: Well, let me go into the World Health Organization first. I was on the World Health Organization . . . I can get my CV and find out exactly when. But, on that, I was on the committee on cancer chemotherapy, on cancer in general. And then we decided to make it a cancer chemotherapy committee and I was chairman of that. And while I was chairman, I knew I had a couple of grants that I could pass out, so I decided that the two hottest places to work were Burkitt's tumor, and I would organize a conference on that, and Jim Holland, who was working on choriocarcinoma, we would give him thirty thousand to organize that conference. So that we did that business and we each had conferences. Burkitt and I had one in Kampala in 1966, and Jim Holland had one in Bagio in the Philippines the next year, on choriocarcinoma. The idea was to get all the people together who were interested in that area and see what new could come of it.

PD: That's what the committee was about?

JB: Yes.

PD: Were there specific accomplishments or decisions that came out of that?

JB: Well, they got better ways to use chemotherapy for Burkitt’s tumor, leukemia, and choriocarcinoma. I mean, more people started working on combinations.

PD: Hold on one second. I'm just going to put a new tape on.

PD: Okay, we were talking about the NCI committee on chemotherapy that you had chaired. Is there anything that you wanted to add beyond what you just told me, in terms of the kind of collaborative meetings you had and some of the advancements in different kinds of cancers?

JB: No, we had the ones on, as I say, on Burkitt's tumor and on choriocarcinoma. And those were the only big meetings that we arranged, or that I, at least, had anything to do with. After that, I think that the acute leukemia group A would occasionally have meetings. But, by that time, I had passed the chairmanship on to Lois Murphy or someone else, so that I was no longer chairman of it.

PD: Okay.

JB: And then, it was just a question of deciding what the best compounds to pick out of the ones that had been working in mice and so on.

PD: So, you were always looking for new compounds, correct. That was sort of the backbone of your interests.

JB: That's correct. Because there was nothing that was really good. I mean, that worked perfectly, so we could always do better.

PD: So, what were some of the inroads you made? I mean, after you started working with leukemia and had successes with those compounds, what other kinds of cancers did you make inroads, generally speaking . . .

JB: Jim Holland went into the choriocarcinomas particularly. I was interested in the acute leukemias and Burkitt's tumor in Africa. Dave Karnofsky was working with me closely and was doing the solid tumors and, of course, the lymphosarcomas and Hodgkin's disease. So, of course, lymphosarcoma and Hodgkin's disease, primarily, responded well, so we would treat those. Then all the other tumors were fairly rare in children, but there are tumors that do surprisingly well with chemotherapy. I think that's about all I can think of that we did there.

PD: How did the advancements you made with leukemia translate into other kinds of successes . . . the knowledge that you gained from using different combinations, or doses.

JB: Well, yes, the stuff that we used in acute leukemia, for instance, and the combination that we used with the addition of Cytoxan in solid tumors in children, such as lymphoma, lymphosarcoma and Hodgkin's disease. We managed to get good result there working, just as Jim Holland at Roswell Park and Tom Frei and Emil Freireich at NCI were doing.

PD: And so, again, you were proceeding in parallel sequence in keeping each other posted, but not formal collaboration?

JB: Yes. That's right. No formal collaboration among these three groups.

PD: Did you continue to do the same kind of research that Dr. Law was doing after those initial . . .

JB: No. Frankly, I don't know exactly what Dr. Law was doing after that time, but, as I say, when it turned out that his L-1210 picked up 6-mercaptopurine whereas our AK-4 did not pick it up so well, then it was sarcoma 180 in our group that really got us started on that, and because of that, I changed and used his line of L-1210 instead of AK-4 and changed from AK to C-58 mice. But other than that, I don't think we cooperated too much. I mean, we developed resistance to methotrexate at much the same time, and he developed resistance to other compounds, but I didn't work, really, with him very, too much, except to start.

PD: Tell me about some of the other colleagues you've worked with over the years, either, at NCI or elsewhere, in your research . . . mentors, proteges, peers. Who are the names? Who are the people that stand out and why?

JB: Well, I don't think we had any mentors, Dave Karnofsky and I, because we were the ones who started it, and Jim Holland, the same way. We all were coequals and we did get help from each other and borrowed ideas from each other. But Gordon Zubrod was very good. I believe he had been in charge of the malarial program during the war, finding new drugs for malaria. So he really knew how to go about getting compounds and getting them from the various people and various companies. And he was very good, but he was not really doing clinical work. His forte was getting the drugs in and testing them in animal tumors.

PD: And, by getting, do you mean working in collaboration with a drug company, or just physically obtaining them?

JB: Well, physically obtaining them, yes. Yes. The drug companies didn't have the big screening set up that he had, so they would send them in to him, as they used to send them in to us. But when the NCI really developed their program, then there was no point in our keeping a large program going.

PD: Okay. Does anybody else come to mind besides Dr. Zubrod?

JB: Well, Ken Endicott was in charge of the whole thing, as I remember then. No, one little thing I remember . . . when we first started up and there was a lot of hoopla about it, and Congress gave us five million dollars [to NCI's Cancer Chemotherapy Committee] to set up the mouse screening program at the NCI . . . this called for a lot of mice. And you don't just don't get mice overnight. . . these are all inbred mice, so you have to grow them up. I remember, we said, "Here's your five million back. We can't use it this year. It takes time to breed mice. We can't do much with it now, but we would like five or maybe ten million next year when we have more mice." So, they had to grow the mouse colonies because you can't do large-scale screening unless you have the right type of

mouse. And the right type of mouse takes time to breed. So we did have that little problem. But, I can't think of any others.

PD: Any other directors of NCI with whom you collaborated in any way?

JB: I'm trying to think. Ken Endicott went on from the chemotherapy screening program to be head of NCI. I would have to see who the directors of NCI were after that time, to refresh my memory.

PD: Did you work with Vincent DeVita at all? He later came to Memorial Sloan-Kettering.

JB: Yes, in a way. He was working on the lymphomas down at NCI, but after I had given up working closely with them. And that was the area that Dave Karnofsky had been working in, but Dave died in 1969, and so we didn't have a strong voice in the lymphoma side of things.

PD: Any other colleagues who stand out in your mind?

JB: Well, of course, Dave Karnofsky was the great one. And he was truly a great man in chemotherapy and in internal medicine and in teaching. He was very good at teaching our residents and fellows. And we had a lot of fellows in chemotherapy who would come to us. And then they would go out and, in due turn, they would train their own fellows. And so, all the training that Karnofsky gave them, really, passed on to whole generations of chemotherapists. So, whereas the work I was doing was mainly on acute leukemia and was not as broad-spread as the cancer at large . . . I mean, I was going to say large animals . . . large people, which is much more common.

PD: Were you in the position to mentor people yourself?

JB: Yes. I had fellows coming to work with me. For instance, Herbert Oettgen came to work with me originally, and, well, most of them came to work in, with us. And, but the particular ones I was working with most closely were Lois Murphy first, then Charlotte Tan and then Norma Wolner and they all stayed. So we didn't need to many other fellows in pediatrics after that.

PD: They were long-term people?

JB: Yeah. They stayed right until they retired.

PD: What would you describe as the greatest accomplishment of your career in studying cancer?

JB: Oh, I don't know. I guess, generally, stirring the pot, getting people interested in Burkitt's tumor, because it was such an aggressive tumor and it really was a large collection of lymphosarcoma or almost leukemic cells. And to see it melt down with chemotherapy and just disappear and sometimes not recur made me realize that you could really do wonders with chemotherapy, and if you could give chemotherapy for that, with as good results, then you ought to be able to do it in leukemia.

So, I boosted the stuff on Burkitt's tumor very much and, as I mentioned, I was able to get a conference with Burkitt under WHO auspices [World Health Organization] in Kampala, which brought in a whole range of disciplines to bear on it. I mean, immunologists who had never worked on any kind of cancer before. I brought them down to have them look at it. Virologists would look to see if there was a virus. And chemotherapists who had never been to Africa and knew nothing about Burkitt’s tumor. I got a lot of different disciplines interested in Burkitt's tumor. And then I think they, in turn, went over to leukemia and to the big doses of treatment that Frei and Freireich developed.

PD: Did you work with Dr's. Frei and Freireich?

JB: Not specifically, because at that time, they were down at the NCI, and they were using these whopping doses of combination chemotherapy, and doing it very successfully. And we began using the same thing. They were the ones who started with the really big doses in combination chemotherapy. It was better than one drug alone, and nothing had been done as aggressively as they did. And as they did that, leukemia group A and leukemia group B started doing more and more with combination chemotherapy, deciding where certain drugs worked really well in the induction of leukemia and were not particularly toxic, such as steroids and vincristine.

And those could get treatment started and take the edge off leukemia and get the count down a bit and get the patient in a bit better shape, and then you could hit them with mercaptopurine and methotrexate, and with anything else that you wanted to use. I mean, they did it, really, by putting four drugs together and really hitting the leukemia and lymphomas with the forms of therapy that they used. We would know what they did every time there was a meeting. We would always talk with them and they'd present papers and so on, so we followed them very closely, but we didn't collaborate specifically with them.

PD: Okay. You were talking about being proud of the work you did to advance treatment for Burkitt's tumor. Are there any other accomplishments that you think really . . .

JB: Well, one other thing that I did, which, to me, was exciting, I decided that we ought to see how many acute leukemias really survived, with the present poor methods of treatment. This was before the big combination therapy. So I sent out a flyer to all the people whom I knew were working on leukemia and found out that Farber had six or seven cases that had gone into remission for over five years, and somebody else two cases, and somebody else had one case and so on.

We circulated a questionnaire to all the members of the Society of Hematology, or the Society for the Study of Blood, or whatever it is . . . and that's where we began to get a few cases that had survived quite a while. I think Farber had seven or eight of them. And then I went to Europe, and had my secretary send out the same memo to all the members of the International Society of Hematology and I got back reports from them. And when we had finished up with that study, we had about 107 patients who had survived five years or more in good health without recurrence.

PD: This was in the sixties?

JB: Yes. This was in the sixties. Some of them had had other ones who had gone four and a half or five years, and then had relapsed, and I think, maybe, a few, a couple, who had gone five years and relapsed after that. But not many. So that indicated to me that, since there were 107 cases that had survived five years or more without relapse, it was obvious that in all these cases, the treatment was doing remarkable things. And I broke the data down, and one patients was treated with just steroids alone, and another was treated with methotrexate alone and another was treated with mercaptopurine alone.

But a combination of mercaptopurine and methotrexate was better than anything else, and methotrexate and steroids was just behind it, and so on. So it began to look as though combination therapy was really important. Originally, I had thought, mistakenly, that you had three classes of drugs . . . the steroids, methotrexate and mercaptopurine, that all worked and they worked in patients who were resistant to the other two. But I had the idea that you could get six months out of steroids, and you could get six months out of methotrexate and six months out of mercaptopurine. But if you put them all together, they might relapse in the six months and then you'd get resistant cases to all three drugs. So, I was a little bit against it. But then Jean Bernard, in Paris, started using combination therapy, and he got better results. Not tremendously better, but definitely better. I think

he was using steroids and methotrexate. So then, gradually we all began using combination therapy.

PD: With that call you put out, for reports of patients still in remission, was that the first of its kind?

JB: I think so. It was just a narrative account of where these leukemias were. I mean, some people would have large numbers of tumors and, maybe, very few that survived. And then there would be others that had only twenty patients and three of them might have survived. So, there was nothing statistical about it, or anything like that. It was just to give an indication that some patients with acute leukemia with some treatments did apparently survive. But I remember that there was a case in 1927 that was reported by Minot and Castle, of a young girl who had acute leukemia, and all the signs were perfect for it. And I'm not sure she was treated with anything except transfusions, but at any rate, eventually the leukemia disappeared. And she had gone two years with no sign of recurrence. And they published it. And all the well-known, and thought-they-were-well-known hematologists got up and said, "Oh, this is not right. It must not have been leukemia to start out with." But when they sent the marrows slidesout to these people, there was no question it was acute leukemia. But, at any rate, even the hematologists were not believing it at that time. But it did turn out that you could get occasional remissions.

PD: That was rare.

JB: Yes. It was extremely rare. Yes. That was without treatment at all, of any importance.

PD: Who else would you say we should interview for this history of cancer research, and especially as it concerns the National Cancer Institute?

JB: Well, Howard Skipper and Abe Goldin did a tremendous amount in the mouse leukemias, at the Southern Research Institute and at the NCI. Now, I don't know whether Howard or Abe are still extant or not. I haven't heard to the contrary, but I haven't seen them at a meeting in quite a while. I had a letter from Howard, I think, about a year ago, saying he was still going over the files to see what he could find out from them. He was great on combination therapy, and he would look over the files as to what had been tried, and so on, and suggest different things that should be done. Farber, of course, was extremely important. You can't interview him, though. He was important because he showed the first acute leukemia patients with good remissions on aminopterin and then he kept on working with it and he worked with mercaptopurine and all sorts of other drugs that we supplied him with, as well as him supplying us with drugs. So, that was very good, and the group up there were excellent.

PD: He was the pioneer.

JB: Yes. He certainly was with aminopterin.

PD: That was the first effective drug.

JB: Yes. Exactly. And he got into it by working with what was really a folic acid derivative. And someone in New York . . . I can't remember her name now . . . felt that she had gotten remissions with it. So he thought of using that. He tried it and didn't get any remissions. In fact, he felt it was making patients worse. And then, I guess Lederle came up with aminopterin, this first strong folic acid antagonist. Now, whether he got Lederle to do it or whether Lederle happened to be making these folic acid antagonists, I don't know. They were studying folic acid, and they made one that seemed to work the opposite way in the test tube.

So he tried that. And found that he got remissions. And after those five remissions, he was in business. He was the top man in the area, and he did very well. He was a good organizer . . . he was like Mary Lasker. He could push people to do things. But Mary Lasker, you cannot overestimate what she did for cancer research. She did a tremendous amount because she knew how to do it. She had money of her own, but she would only put it in places where it was important to stimulate bigger things. And she certainly got it done.

PD: And she was planning to move on to other areas besides cancer, wasn't she?

JB: I don't know. I wouldn't doubt it.

PD: Any other people who would be good to interview?

JB: Well, of course, Chester Stock was extremely important in setting up our program, which, in turn, was the prototype for the National Cancer Institute and he did a very good job with that. Dave Karnofsky was extremely important until he died. He was a great man. There's Jim Holland and Tom Frei and J Freireich.

PD: We have spoken with them.

JB: And, of course, the ones who worked on the solid tumors, who did a very good job. And I'm not sure I can think of any others. They'll probably come to me later on.

PD: You can let me know. You were saying that Don Pinkel would be another good candidate to interview.

JB: Yes. Well, for instance, here in the beginnings, they have Don Pinkel, and Hitchings and Elion. And Hitchings and Elion did a tremendous amount at Burroughs Wellcome.

Because after we had found 6-mercaptopurine was active and we were using it all the time, they made all sorts of other derivatives that might work, and things that would help. For instance, if you treated patients too hard and got too much uric acid in the blood, they would get gout or the uric acid would plug up the kidneys. And Hitchings and Elion had various drugs for stopping hyperuricemia as well, and which are useful now in treating gout also.

And then, for the hub of people at NCI, he's got down Gordon Zubrod, Tom Frei and Freireich. And then, in the periphery, he's got Howard Skipper, Jim Holland, Don Pinkel.

PD: This is from the [John] Laszlo book . . . *The Cure of Childhood Leukemia*?

JB: Yes. And, so, having Don Pinkel was extremely important in this because he had St. Jude's Hospital and he got really interested in chemotherapy. And they had a lot of children with acute leukemia there.

PD: That was out in Memphis, right?

JB: Memphis. Yes.

PD: Okay. Have you donated your papers to any particular institution?

JB: Not exactly. I mean, the papers are all published, so they can get them that way if they want them. I've got a bibliography list so researchers could get them out if they wanted to. But, other than that, I haven't done anything. I have probably got a lot of them here, but not all.

PD: Are you still going into the city every day, or do you have a position?

JB: No. I had the unfortunate situation that, when I was at Sloan-Kettering, they had a mandatory retirement age of seventy. So, when I came up to June 1983, I was seventy, and they said, "You have to retire." So I duly retired. Then, about a year or two later, the New York state legislature voted that this was not legal, that you could not have these mandatory retirement times. So, from then on, everyone else who came along, the people I had worked with, and so on, who were a little bit younger, didn't have to retire. And some of them are staying on. Marty Sonnenberg, for instance, is having a party on his eightieth birthday now, and he had been working at Sloan-Kettering up to that time. So, I could have worked much longer, but it turned out that they were very strict at that time. They said, you know, "Everyone retires at seventy," and so on.

PD: So, did you pursue research at any other institutions?

JB: Well, no. I worked at Sloan-Kettering, at the Rye Laboratories, where I had my mice, anyway, until 1989. And they were gradually getting rid of the Rye Labs, or getting rid of the people in there. They were bringing them into the city or they were letting them go, or what not. And finally, the only ones that were left were Jack Fox's group, which synthesized organic chemical compounds for us and for other groups. And I worked close to them and stayed there until they finished in December 1989. Sloan-Kettering decided to close up the laboratories, which they did, and left them closed for a while, and then gradually sold them.

PD: So since 1989, you have been completely retired.

JB: Yes. And so they stopped that whole set up and moved them all into the city, thinking that everyone wants to live in New York. They'd much rather live in New York. Whereas I was here commuting back and forth. I figured out I did more than a million miles commuting.

PD: It's not a bad commute though, by D.C. standards, not at all.

JB: No. It isn't. No, it's not nearly as bad. Although, at rush hour, it can be, sometimes, real bad.

PD: Well, are there other issues you wanted to talk about that I did not ask you about?

JB: Well, let's see what else there is here. This is . . . see who he cited here . . .

PD: What is that book you have? It's called Cancer . . . ?

JB: It's called *Cancer of Progress, 1960*. It's a British book. It's Progress . . . edited by Ronald Raven. Let's see who it has here . . . tobacco smoking is the cause of cancer . . . Ernest Wynder and Detrick Hoffman . . . these are mostly surgeons in England. Larionov . . . was from Moscow, and he was in charge of cancer chemotherapy there. And I went over to see him a couple of times. But he was working on most of the same compounds that we were working with, except that they were particularly interested in the nitrogen mustard derivatives, which we had long before decided, as far as acute leukemia was concerned, were not too interesting. And actually, Jim Holland went over and worked with him for a year.

PD: In Russia?

JB: Yes, in Moscow.

PD: That's right. He spent eight months over there on behalf of NCI?

JB: Yes. That's right. And, as I say, Herb Oettgen, who worked with us very closely and did the work on Burkitt's tumor in East Africa. Oh, and of course, Ernie Wynder did a tremendous amount to show that tobacco caused cancer.

PD: Something else occurred to me, which is to ask you how many compounds you have come up with in the course of your career? Did you ever add it all up?

JB: No. We tested, of course, thousands and thousands of compounds. Well, let's start at the beginning. We tested a lot of different nitrogen mustard compounds. None were better than HN-2. None of them worked in acute leukemia in children. They did work in some of the solid tumors and lymphomas in man. The best one, probably, was Cytoxan, or cyclophosphamide. But, with nitrogen mustards, once they were shown to be effective, and we were working with some new derivatives, there is a valence in the nitrogen mustards which anything can be put on.

So, all of these people who had been working on the antimalarial study, during World War II, took their compounds and hitched them on to nitrogen mustard. So we had mustards and mustards going and coming out our ears that they wanted tested. And NCI had it too. I don't know whether it was Jim Holland or who it was who said, "A mustard is a mustard, is a mustard." And, so, we did have a lot of compounds that way. And Larry Onhoff worked, as I say, almost entirely with the mustard derivatives. But Cytoxan seemed to be a cut above the general run of the mustard derivatives that we tested. It was better tolerated and could be given by mouth or intravenously and it just was a . . . generally seemed to be more effective and less toxic to people.

Then, when we got to the purine derivatives, 6-mercaptopurine and thioguanine act similarly, and neither one seems to be much better than the other. So they are very useful. Azaserine . . . that didn't do anything by itself, but in combination, Chester Stock showed that it was definitely active in the sarcoma-180 and we felt that it was slightly

active in mouse leukemia. And, as I say, we had one patient where it seemed to work very well, but generally, it was not very effective.

There was one compound that the Banning lab in Canada . . . Banning and Best came up with insulin for diabetes . . . People had sent them teas from the East Indies and the West Indies and all sorts of herbal things that might work. So, one of the guys was working up there and they got into cancer work and he said, "I'll try this particular compound." So he tried the compound and he gave it to rats with a tumor, and the tumor disappeared and so did most everything else . . . I mean, the bone marrow and everything.

JB: And, so, he called this lympholeukoblastin and it . . . I think that was the name . . . but, at any rate, he gave it a name . . . one that reflected what the compound probably was . . . I mean, its general root. And it had a very marked effect on normal animals. And they tried it in Hodgkin's disease and it did have some effect there. And we used it. And gradually they got the compounds that were better for mouse leukemia from that. I'm not sure whether vincristine was one of them or not. But, at any rate . . . oh, we had . . . we worked with asparaginase.

And that was a big effort, but didn't prove a great deal. Long ago, someone had shown that guinea pig serum caused a particular odd tumor in mice or rats to disappear, temporarily, at least. And when that was sort of resurrected and brought back as a possible clinical thing, they . . . the people got worried, well, the amount of guinea pig serum you'd use would require untold numbers of guinea pigs, because the amount that was extracted from the serum was tiny. And then they figured that maybe you could go down to Brazil, I think it is, and there's a capybara or some much larger relative of the guinea pigs whose serum also could be used. And they were figuring all sorts of ways of doing that. And then finally, someone came up with asparaginase that could be synthesized. And we made a big study of that. And that did produce remissions in acute leukemia. But again, not very remarkable. But there was a big push on that at one

time and it was quite a job to synthesize, but fortunately, I think, the people at Merck found that they could develop this stuff from the bodies of the e-coli that they had used for developing one of the antibiotics, so that they were able to recycle some of the waste material that they already had. But, at any rate, they made enough of it so that we could try it clinically. And it did work, clinically, in some patients with acute leukemia . . . not very well. And it worked on our mouse leukemia P-815, I remember. And that got quite a big push for solid tumors and leukemias and lymphomas. And it was moderately effective in leukemias, but not very much. But it, at least, was a big study and people got excited about it because it was discovered in this odd way, that the guinea pig serum would have an effect on tumors.

PD: But it must have been hard to know, going into any of these studies, which was going to pan out.

JB: Oh yes. You didn't know. You had to go ahead with it. Let's see what else there was . . . of course there were a lot of steroids that were tested, but none of them were better than cortisone or prednisone. Some of them may have had fewer side effects . . . I mean, a little more effect on the leukemia and a little less, causing big bellies and spindly legs and so on. ACTH was tried, which stimulated the pituitary. But that, although it would produce remissions in acute leukemia and in chronic lymphocytic leukemia, was not any better than lots of other things. I don't know what else . . . I'm sure there are a lot of other compounds I just don't happen to think of at the moment.

PD: Okay. Any other thoughts?

JB: No, except that the work that Jean Bernard first did and then Holland and, particularly Frei and Freireich did, of using these big doses of compounds and damn near killing the patient. It turned out to be very useful in both acute leukemia and in particularly the lymphomas and Hodgkin's disease. And they did a great job with that. And Jim did a

lot more work with just high doses of methotrexate in choriocarcinoma and found that is effective. That's why we had the conference in the Philippines, because choriocarcinoma occurs here only as a rare occurrence. But in the Far East, it's quite common, and so he was able to treat it over there and it turned out that he could cure it too. So, that was an important milestone.

But combination chemotherapy . . . and gradually coming to realize what compounds could be given to an acute leukemia went it was first started . . . when it first appeared . . . when there was danger of bleeding and all that, you'd give compounds which would cause the white count of the leukemic cells to go down, and have various effects without too bad an effect on the platelets, so that it was safer to start off with those gentle compounds and then, once you got them into a little bit of remission, then you'd hit them with the more active compounds . . . say, more dangerous compounds.

And if you pushed it hard enough, then you began to get results that the leukemia stayed away. And then all the groups developed their own protocols, but, more or less, with that idea in mind. Norma Wollner did very good work on carcinomas in the . . . or, a lot of children's tumors where she used a combination like that . . . but particularly relying heavily on the mustard-type derivatives. And then one thing that I was particularly interested in . . . well, Jim Holland . . . and I can't remember who else . . . were working on osteogenic sarcoma, and they found that actinomycin and various other things . . . adriamycin worked very well to produce remissions in these patients, so that occasionally one remained cured. So they pushed that very hard. And Jerry Rosen used large doses of methotrexate in patients with osteogenic sarcoma. And that's sort of where I came in, so I was very interested in this. He gave very large doses which would be fatal if they were left alone. But he let them go for twenty-four hours and then he would give lots of leucovorin (citrovorum factor), which would inactivate the methotrexate. And in that way, he began to get long-term remissions and cures. And, so, that was, I think, particularly interesting. And Jim Holland did it with slightly different compounds and

did a very good job. So, that was another tumor that came under control. And that was one that I originally was most interested in, because that's how I got into medicine and chemotherapy.

PD: Well, thank you very much for your recollection.

JB: Yeah. I'm sure there are a lot of other things I should have told you, but I can't think of them now.

PD: Well, if you do, you can let me know.

JB: Yeah. I should have prepared it more. I should have gone over some of my stuff.

PD: Well, thank you.

[End of Interview]