NCI ORAL HISTORY PROJECT

INTERVIEW WITH

Emil Frei, M.D.

June 3, 1997

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National Cancer Institute Oral History Project
Interview with Emil Frei, M.D.
conducted on June 3, 1997, by Gretchen A. Case
at the Dana-Farber Cancer Institute in Boston, Massachusetts

GC: Today is June 3, 1997. It's about 11:00, and this is Gretchen Case talking with Dr. Emil Frei. I'd like to start out by just talking a little bit about your education and what you did before you came to the National Cancer Institute.

EF: I went to St. Louis University, pre-med, starting in 1942. I was there for a year, and in 1943 I was subject to the draft, so I went into the service, into the Navy and into the Navy college training program which became the V-12 program. They sent me to Colgate for a year, so after two calendar years, which were three academic years because of the accelerated program, I applied to medical school. I applied to Yale and got in, and in 1944 I started at Yale and graduated M.D. 1948. Then after that, I interned back in St. Louis.

Having been in the service for the V-12 program, we were obligated to go into the service for active duty, that is we were in the ready reserve. So when Truman sent the troops into South Korea, I got a telegram fairly shortly after that. So I was in the service for two years, fifteen months of which was in the Far East and the Korean theater, and then came back and finished my residency first at Washington and then at St. Louis University.

Dr. Zubrod was my professor in St. Louis. He was associate professor, I believe, then and I did some research under him during my residency there. He was offered and took the

job as clinical director back at the National Cancer Institute, and he asked me to join him, which I did in April 1955.

GC: Did you come to the National Cancer Institute specifically knowing what you were going to work on?

EF: Well I knew of course I was going to work on cancer, it was the National Cancer Institute, and I knew that I wanted to do a clinical-type research. What I had hoped to do was to continue the work that I was doing with Dr. Zubrod which had to do with using laboratory models for our clinical treatment regimens. I had developed a model for PPLO infection, i.e. mycoplasma infection. It involved infecting the rats' external auditory canal. It sounds complex but it was quite reproducible. We demonstrated that the new antibiotic, new at the time, tetracycline, was highly effective in our model. So that got me into microbiology, and therapeutics, if you will.

At the same time, I did a study in patients with pneumonia, a comparative study of tetracycline versus penicillin, and they came out to be about the same, which was important because it meant that tetracycline was a very good drug. That was published in the *New England Journal of Medicine*. It required a lot of clinical trial, and experimental design and statistical know-how. So I really went to the National Cancer Institute with the idea of applying science to a cancer problem, a clinical cancer problem.

We were in the right place, NIH, at the right time, 1955, because they had just finished the clinical center. A lot of the beds were empty, a lot of the laboratory space was empty. Dr. Zubrod was very supportive. We decided to focus the clinical activities on

acute lymphocytic leukemia in children. So for the first four or five years there, I worked primarily on kids with acute lymphocytic leukemia under Dr. Zubrod's umbrella of vision and administration and inspiration. My closest associate during that period was Dr. Freireich.

GC: You say that you chose leukemia. Why leukemia?

EF: There were several reasons. One is that Dr. Jim Holland, who had been there before us, who left before we came, had started the program on leukemia, so there were some patients that we inherited, if you will, from him. But mainly because the leads at the time, in terms of therapeutic research in cancer, were limited. Those leads that we had were primarily in acute lymphocytic leukemia (*ALL*), and particularly in children because we had models of lymphocytic leukemia in laboratory animals, particularly in inbred strains of mice. So we could study the biology and treatment of ALL in the mouse leukemia models.

Also, *ALL* was the only disease wherein chemotherapy was significantly effective. There were two drugs, methotrexate which was discovered here, and 6-mercaptopurine, which was discovered at Sloan-Kettering. So it was a disease that we had the tools to study in the laboratory. It was a disease for which there was already some effective treatment that we could build on.

And the third reason was that most cancers occur in elderly patients, and there you have competing illnesses and so forth which can complicate clinical research, whereas pediatric patients are generally healthy. That reduces the complications and increases

the effectiveness of the investigative treatment. But the real reason was that there was an expectation that we could make progress there, whereas for certain other common tumors like lung cancer, et cetera, there was not that expectation at the time. There were no really good leads.

GC: In this decision-making process to choose leukemia, were you part of the decision-making process or was it that it was already established and you came in?

EF: No, we made the decision. What was established was that there were some six or seven patients with acute lymphocytic leukemia at NCI in 1955 which drew our interest to that disease. Children are a challenge and also a joy to work with. And the fact that there were a couple of agents, 6-mercaptopurine and methotrexate, that could cause the disease to go away, that is the patients could go into complete remission. Unfortunately, they didn't stay there with one drug, but you had the sense that yes, here we can do something. If we do a little more, maybe we can make a major impact. So there was at least a foot in the door.

GC: So you began studying leukemia. Can you tell me about how that research process went? Eventually you came up with a very successful drug regimen.

EF: The first thing we had to do was sort out the chaos in the field at the time. Dr. Zubrod was the major inspiration for that. Reports of *ALL* and its treatment prior to 1955 were largely compilations of anecdotes; that is, prospective experimental designs were lacking. The collection of data was sporadic. Criteria for response weren't expressed, so that when somebody said they had a 50 percent response rate, you had no idea what that

meant. It might mean in one patient disappearance of leukemia cells from the peripheral blood and another decrease in spleen size, et cetera. There was no systematic approach to treatment, that is, where you start with a given dose and adjust the doses in accordance with some prospective schema. People think of leukemia as a disease of the blood. It's not. It's primarily a disease of the bone marrow. And yet, aside from the initial marrow which established the diagnosis, doctors prior to 1955 didn't look at the bone marrow. So what we set about to do was to systematically look at organ function, at leukemia infiltration, particularly leukemia infiltration of the marrow, to try to decide what is important, what correlates with survival and with complications, what can we use to tell us that our treatment is really doing something fundamental. We found a lot. A major finding was that the thing that correlated best with a significant increase in survival was the attainment of a complete remission, that is, where the leukemia cells actually disappear from the marrow. So that gave us criteria for response. This is all by way of saying that from 1955 going forward, at the insistence of Dr. Zubrod, we wrote protocols, we defined what complete remission was in advance, we defined how treatment would proceed in the more broad tactical way, if you will. And that was really a watershed, because in science you can make limited advances with qualitative observations, but to really advance you need to have a quantitative fix. If you don't know what drug A and drug B do separately, it's hard to study them in combination. You've got to know individually how active they are in terms of progress, such as combination chemotherapy. I lump all of the above under the rubric of experimental design.

GC: Now was this true that you say that before you did this work, there really wasn't experimental design. Was this true of all cancer research? People did not generally write protocols or define their terms?

EF: Yes.

GC: So this had an impact on cancer research in general, as well as just leukemia.

EF: Yes. Absolutely. It was a watershed for the treatment of cancer really. For the research treatment of cancer. And it was controversial. A lot of people said you've got to treat every patient as an individual, which of course is true. But you have to have certain common denominators that you deal with. You have to be able to cross-talk with other investigators that are doing research.

GC: Was it controversial within the scientific community? Was it controversial to the public?

EF: Both. It was controversial to the clinical community, if you will, and this would be physicians and patients and so forth, because it was felt that you were making patients fit a protocol whereas what you should do is fit the protocol to the patient. Now that sounds like a very compelling argument, but if you don't really know what you're doing, you need to have a prospective protocol that asks that question that gets an answer. And it turns out that patients do best in that setting in any event.

Obviously the protocol has got to be such that the doctor has an out if clearly the patient isn't doing well and it may be because of the protocol. Then the doctor can withdraw the patient or the patient can at any time withdraw from the protocol just by expressing the

desire to do that. The application of scientific experimental designs was probably the most important single thing we did, mainly because without it, we would have been lost.

The questions we asked in the form of protocols that led to increased complete remission rate, increased duration of remission, increased control of meningeal leukemia, and finally improved survival and cure were made possible by getting quantitative experimental designs in place.

GC: And you say that all came down from Dr. Zubrod.

EF: Well, Dr. Zubrod had very broad responsibilities. We saw him frequently during maybe the first year or two, not very often thereafter. But his spirit permeated our work. He supported and defended our program. The view that we could make progress towards the cure of any form of cancer was not viewed as very likely. There was a fair amount of skepticism and cynicism about that. A lot of people felt that the money might be better spent, say, on basic research.

And that's where Zubrod played a very key role. He was in a high administrative position within the National Cancer Institute, and the people that wanted to curtail the clinical program had to deal with him, and he was totally in favor of it in many ways because he had created it, but he was strongly supportive of us, myself, particularly, J Freireich, and some of the others as well. So in terms of the specific scientific questions asked, the specific directions we took, Dr. Zubrod didn't play a big role in that. His role was really one of inspiration, administrative cover, broad brush influence, and so forth. Very important.

GC: What about the directors of the National Cancer Institute that you worked with or worked under. Did you have contact with them frequently?

EF: Well, I was a young buck when we started. In 1955 I was thirty years old and I was low on the totem pole so . . . . The director of the Cancer Institute at the time was Rod Heller. He was a senior fellow—very good and supportive. I saw him at social affairs and occasionally at professional interactions and so forth. Then there was Ken Endicott, and let's see, during that period . . . Carl Baker after Endicott. They were the main directors while I was there, and then, of course, I've known the directors since then as well since I've left.

GC: Were they involved in your day-to-day work at all? Did they come and talk to you about it? Check on you?

EF: No. The director of the National Cancer Institute had very broad responsibilities. They were very supportive, particularly Ken Endicott who was director of the National Cancer Institute during much of the time that I was there. He was very friendly, very supportive. He would say very nice things about what we were doing on the Medicine Branch, et cetera. And the others were as well.

GC: I know some of the work you did inspired controversy. How did they respond to that kind of controversy?

EF: The controversy of course was the platelet transfusions, combination chemotherapy, supportive care, all of that. We'll get to that. But the way they responded to it was generally supportive. Let me just give you an example. One time after I had started the MOPP program in Hodgkin's disease with DeVita in 1962 or 1963, we had treated about eight or nine patients and they had done very well instead of with the four-drug combination, they went into complete remission very quickly and they stayed there. Now the study wasn't that old, so how long they were going to stay there we didn't know. But a high proportion of patients went into complete remission and they went into complete remission very quickly. We constructed that program out of some of the principles that we'd established in acute lymphocytic leukemia where we'd made major progress—we thought maybe curative progress. We didn't know at the time because we didn't have adequate follow-up.

Dr. Endicott asked that I present that to the National Cancer Advisory Board. I did so, and a very prestigious hematologist, who I probably should not name, said at the end of my presentation something to this effect: That when he had patients with disseminated Hodgkin's disease, he'd send them to Florida for whatever vacation they could have. If they were really sick, he'd cool them off with say one drug. But, the idea of using four toxic drugs at once, in his view, had no chance of curing the patients and was unconscionable. He used that word, "unconscionable."

You know, that's pretty hard on a young physician, especially when you're trying to help patients, to have that kind of thing happen. Given that kind of criticism from somebody of prestige on an advisory board would have caused an investigation. Dr. Endicott did set up an internal review committee to review the program on Hodgkin's disease. By

that time, we had a lot of support and a lot of credibility, and it was a perfunctory investigation. And Endicott supported it all the way through, that is, he supported us all the way through.

GC: So he set up the investigation . . . .

EF: He had to set up the investigation.

GC: He had to do it. But in a real sense, he wasn't investigating you because he believed in you.

EF: Yes. That's an example. I don't want to make it sound as though it was hostility all the way, it was not. We had a lot of support, from the directors, from Zubrod, from other people in the clinical and basic sciences, at the clinical center and the National Cancer Institute and other institutes and so forth. It was a great place to work. The kind of thing we did there would have been very difficult and probably impossible to do at the time in any general hospital and probably in a university hospital.

GC: Why's that?

EF: In the first place, the purpose of NCI was to do research. If you're in practice, the purpose is to deliver the best of established care. If you're in an academic center, you've got teaching, you've got committees, you've got all kinds of other things to do. The purpose of NCI was to do research. Zubrod used to say, "If you have no effective treatment for this for a given situation, do something different. Do something new."

And that's the kind of support we had. There was the expectation that we would do something different. We were in research, we were supposed to do that. Medicine is very tradition bound and very deductive oriented; that is, you see a patient and you make observations, and you deduce a diagnosis and treatment. That's deduction. That's good. But that doesn't allow you to treat with something new. That just allows you to find the best of what is established. The doctor who criticized us at the NCAB was saying is that we were defying tradition. He didn't say it that way, but he was representing tradition. These patients are going to die anyway, why torture them with four drugs, et cetera.

And while we said, "Look. We think that this might be curative of Hodgkin's disease because our basic studies said that it might be, and our clinical extrapolations from *ALL*, from acute lymphocytic leukemia, said that it might be." That didn't have any impact on him at all. I would say about half the NCAB supported him, and the other half supported the camp of Dr. Endicott and myself.

GC: Because they knew of your work or they knew of your reputation?

EF: Well, they heard the presentation. It was still very early. After another five years when we had patients with acute lymphocytic leukemia and Hodgkin's living for years without treatment, we thought they were probably cured then, and it turned out that many of them were. So that vindicated the whole field. So that by 1970 we were secure—but in 1963 it was still problematic-controversial. Things could still be tough.

GC: So at the NCI, you had kind of a freedom to be creative and forward thinking.

EF: The purpose of the institution was to do research.

GC: What about other resources there? What else helped you do your research in terms of people or money or equipment? Were any of those things major factors?

EF: Again, the policy of the institution, the purpose of the institution, the raison d'être of the institution was to do research. It was to take acute lymphocytic leukemia in children and move them towards a better response and ultimately hopefully to a cure. For example, the patients didn't pay for travel, expenses, everything was covered so that helped. We could keep them in the hospital for lengthy periods of time for study. There was no limitation of money in that era, strangely enough, at least for the interim. If I needed an expensive instrument, it was forthcoming.

EF: So we had a lot of support from the patients, a lot of support from some, but not all, of the staff. As I've indicated, some were concerned about it. Again, we were in the right place at the right time.

GC: Okay. You said Dr. Freireich arrived just a few months after you arrived. Did you immediately become a team?

EF: Well, we became friends almost immediately. His wife was pregnant, Deanie, and we had five kids at home. The evening of their arrival they came over to the house. The wives got to know each other. The kids got to know each other. We became fast friends. The thing that happened immediately, of course, when he came up to my office labeled "Emil Frei." J said, "Well, they've forgotten to put my full name up there." I'd

never met anybody with a name as close to mine as his was, and when you think of it, that's an extraordinary .

GC: It's amazing.

EF: Yes, it is amazing. And we had a lot of fun with the names. Later on in our careers, I would introduce him as being perfect in all ways save for the fact that his name was overly long.

EF: So we had a lot of fun together. A lot of the progress in the treatment of leukemia came from the two of us because we were doing the on-line work, certainly at the National Cancer Institute. Zubrod played an important role, Paul Carbone played an important role, Myron Karon, who died some years later, was the first pediatrician at the National Cancer Institute, and he played an important role. You can't do that kind of research as a loner, you've got to have a team. We had a very effective team.

GC: What were the dynamics of your team? Would one person come up with the idea and then throw it out and have other people bounce ideas around off of that, or how did things usually go?

EF: Well, that's a very important question, and the answer is there was a lot of heterogeneity as to how that happens. Some of it is organized. For example, we had a meeting every Friday at three o'clock of all the investigators. We discussed ongoing projects, new projects, observations that people made from the patients, from the laboratory, from their reading that might impact on what we were doing or what we might do better or

something new. Creativity was emphasized and that was a formal meeting. But of course there were a lot of informal meetings, there were rounds with the patients, J Freireich and I used to talk, I'm sure, an hour, an hour-and-a-half a day generally late in the afternoon every day for seventeen years. Freireich is a very creative guy, Zubrod in his way was creative, and so were the others. As a matter of fact, there are some ideas, such as polychemotherapy, the combination chemotherapy for acute leukemia or Hodgkin's, platelet and WBC transfusions, that came primarily from myself and Freireich, and I'm not sure even to this day…

GC: I think we lost a little bit at the end of that. We were just talking about the inspiration generally came from you and Dr. Freireich for?

EF: For the polychemotherapy, then there was the platelets. There were a lot of individual projects. We worked as a team. We took care of the patients as a team, we did a lot of the work as a team. Generally, individuals had responsibility for specific projects within the framework of the team. Freireich might be involved, let's say for the combination chemotherapy of the children. Carbone and DeVita were involved primarily in the combination chemotherapy of the Hodgkin's disease which started a little bit later. It wasn't that we didn't all pitch in and work in all of those areas, but it was that certain people had certain responsibilities. The branch was never large in terms of the number of people.

GC: How many people?

EF: Well, there were myself, Freireich, Brindley, who left after about five years, Carbone, who was very important. He came in around 1960 and was with us till '65. He stayed on at the National Cancer Institute; we left in '65. There was Sy Perry who came on in '62, sort of late in the game, there was Myron Karon who came on around 1956, '57, a pediatrician, very important.

GC: So a small group.

EF: Very important were the fellows who rotated through. These were a highly selective, good group of trainees who came to the National Institutes of Health for two years. They were training with us in medical oncology. They helped with the patient care and became involved with the research as well.

GC: Do any of those fellows stand out in your mind? Do you remember anyone in particular?

EF: Oh sure. DeVita was one of them, for example. DeVita, Canellos—I don't know if you have his name on your list but he is one. Who do you have on your list? Probably a lot of them are fellows.

GC: Probably a lot of them I don't have on my list.

EF: Well let's see. DeVita, Moxley, Silver, Richard Silver. Len Gold, Lewin, Hersh, Bodey. There were as many as six to eight new fellows a year, and they stayed on for two years. The fellows were really very important to our operation.

GC: What kind of projects would you give them when they came in?

EF: For example, DeVita got the project of the combination chemotherapy MOPP for Hodgkin's disease. That was his clinical project for his first year.

GC: These meetings, the three to five-thirty every Friday meetings, were they open to people outside of your group doing the research on leukemia? Did others from other parts of the Institute come and listen or was this really a closed kind of brainstorming session?

EF: It was the latter for the most part, but if we were going to discuss a given subject and we wanted people there who knew about that subject who were not part of our group, I'd invite them to come to that meeting. So you had the core group of people who came every time, and then ad hoc people who would come depending upon the subject matter, and they would help with that. They weren't really closed. Anyone could join. We may have been boisterous but never secretive. But it was Friday afternoon, and it was a time when you had to be a zealot to participate in the conference, so that the people who came, by and large, were the working group. And that's nice because then you don't, you know, with the questions and the contributions which somebody who's actually working on the problem, not somebody who is sort of free-floating, if you will. I would say at those meetings that we would average maybe fifteen people.

GC: So fairly small.

EF: Fairly small, but it included the clinicians. The clinical investigators, some of whom I haven't mentioned, included the laboratory investigators, particularly people like Abraham Goldin, Lloyd Law, you should have those names.

GC: Yes.

EF: Some of their younger people. Zubrod came sometimes, Dave Rall was there almost all the time. Dave Rall was our pharmacologist, made major contributions.

GC: What about the nursing staff? Did they ever attend for any reason?

EF: Yes, they attended off and on as a rotational basis. I told the chief nurse that we would like since it is a research institution for the nurses to feel involved in the research and to see it sort of in its generic ambiance, if you will. So they would rotate the nurses. There were usually one or two nurses there on a rotational basis and there were some nurses who became very interested in the research and the science and came regularly.

GC: Were they involved in other ways?

EF: Well, for example, they might be involved in giving the drugs. That was important to the protocol. They might be involved in certain lines of analyses of the protocols or analyses of, say, a group of five or ten patients who had been treated in a certain way. They'd put it all together and present it. In the first place, we had very good nurses who were interested in research.

GC: Let's go back a minute to the leukemia, the combination chemotherapy. Why did you choose this combination of drugs? What brought you there?

EF: That was probably the first scientific decision we made. Lloyd Law, who was a basic scientist, discovered L-1210 mouse leukemia. These were all identical twin inbred strains of mice so you could transplant the leukemia from mouse to mouse. He found that when you treated, for example, with methotrexate, initially the tumor would respond very nicely, but with continuing treatment, the leukemia eventually became resistant; that is, the tumor that originally responded to methotrexate now grew in the presence of methotrexate. By complex studies which involve what's known as a fluctuation test, he was able to demonstrate that the resistance was due to the selection from the original population, of a population of cells that were resistant to the selecting agent. A better way of thinking of this is simply to tell you that what happened when he treated 6 MP resistant leukemia with methotrexate, 6 MP resistant methotrexate, the second agent was effective. So that when you got resistance to agent A, it still responded to agent B. And all of that suggested that a way to prevent the development of resistance would be to give A and B concurrently. We found that that was true. Give A you get resistance, give B you get resistance, give A plus B, yes you will eventually get resistance, but it takes much, much longer. So those were very important studies.

At the same time in England, they were doing studies with tuberculosis that were very important from the experimental design point of view, but also important to us from the scientific point of view. They had discovered that streptomycin antibiotic was effective in the treatment of tuberculosis, but not for long. The tuberculosis would come under control, but after about one to two months, it would take off again in spite of continuing

streptomycin because of resistance development. Another drug that came along, 4 amino salicylic acid, was effective in the treatment of tuberculosis when used alone. But again, after about a month, resistance developed so that was a problem. When they put the two together, streptomycin plus the salicylic acid, resistance took much longer, and in some instances never developed even after six, nine, twelve months of treatment. Our studies indicated there was heterogeneity, if you will, in the cancer cell population such that one drug couldn't destroy all the cells. For that, you needed combination of agents. That was a very fundamental observation and a fundamental insight. We put it together in terms of how do you apply this to the clinical cancer situation. And one way to do it would be to just take methotrexate, 6 MP, and put them together and see what they did. We did that, but we did it in a context of an experimental design that provided the answer. A third of the patients got methotrexate, a third of the patients got 6 MP, a third of the patients got the combination. And we found that the CR [complete response] rate for, say, drug A was 20 percent, drug B was 30 percent, the combination was something like 45 percent. A big increase that fit with the mouse leukemia model and with the tuberculosis experience. We had learned, and I mentioned earlier, that the patients who got a complete response were the ones that benefitted in terms of survival. So the goal was to increase the complete response rate. If in the individual patient the CR was good, in terms of survival, then quite obviously one goal would be to get a high complete response rate. And we were able, by the discovery of new agents, such as vincristine, prednisone, along with 6 MP and methotrexate, to show that we could in fact get the CR rate to over 90 percent. The combination of vincristine and prednisone, for example, produced complete remissions in 90 percent of patients. Thus over a seven or eight year period, the CR rate went from 20 to 90 percent. It really was miraculous if you looked at the individual patients. They would come in with fever, with weakness, with pallor,

with infection, with bleeding, with bone pain, sick unto death, and the median time from diagnosis to death prior to 1955 was four or five weeks. A bad disease. However, with combination, within three days, the bone pain would be gone, leukemic infiltration would start retreating, that is the spleen would get smaller, et cetera. By a week, the patient would be substantially better. The bone marrow first before treatment was 100 percent replaced by leukemia cells. By three weeks the bone marrow was often free of leukemia cells. None. Zero that you could see under the microscope and the normal cells had returned. By definition, a complete response. We do it now so regularly that it's sort of the expectation, and everybody says, oh isn't that wonderful. But back then, it was really like a miracle. If you hadn't seen that before, it was very impressive. And it helped us morale wise, because we had the sense that we were doing something that was important. But it turned out that there was a problem that is the patients did get into complete remission but all of them relapsed. We had hoped that some of them would be cured, but they all relapsed in those early days. The problem was why did they relapse. They were doing very well, they got into complete remission, but they relapsed. There were a lot of theories. One is maybe they were cured and whatever triggered the leukemia in the first place triggered it again. So you had a new leukemia emerging. That was a possibility. Another was that the tumor cells were just differentiated. They were still tumor cells, they just looked better. But the possibility that turned out to be true was that we had reduced the tumor burden from something that you could see and feel and determine under the microscope to one that was microscopic, that is below the level of clinical detection. The needle in the haystack if you will. But what happened was that over time, that needle, as leukemia cells will do, grew, and eventually months later, maybe a year or two later, produced relapse, that is grew up to the point where it was clinically detectable, so what to do. Well, actually Ed Gehan and J Freireich were

primarily responsible for this study. It was one wherein we put patients into complete remission with combination chemotherapy and then randomly in a double-blind study—this is all again derivative of the experimental design stuff I talked about earlier—put half of the patients on a compound that was known to be active in producing remission and that was 6 MP. The other half of the patients went on a placebo. A placebo is no treatment. The median time to relapse in the no-treatment patients was one-and-a-half to two months. The median time to relapse on 6 MP was eight to ten months. A huge difference. All eventually relapsed, but we could show that one way of detecting an active agent was in its ability to prolong the duration of complete remission.

So that told us all we had to do was use maybe the same strategy against minimal disease. One way of thinking about it is initially the patients have big-league disease. You've got to get them into complete remission. In complete remission they've got micro disease and what you've got to do is eradicate that if you're going to get a cure. We conducted a series of trials of agents given in CR, looking at variables such as dose, schedule of agent, combinations of agents, and reinduction. We found that we progressively prolonged the duration of remission from two or three months out to the median time of sixteen months, a big improvement. You'd think some of the patients would be cured. A few of them were, but the majority relapsed. Now they were relapsing not in their marrow, which is where you expect them to relapse, rather in the central nervous system. They developed meningeal leukemia. The reason for this, to make a long, investigative story short, was that leukemia was present in the central nervous system in microscopic form initially when you start treatment. When you treat, you get rid of all systemic leukemia because it's drug-sensitive. But our drugs don't pass the blood-brain barrier, that

is, they don't get into the central nervous system. These few cells in the central nervous system grow in the presence of systemic treatment, eventually to the point where they cause blockage of spinal fluid, and that causes headache and eye changes and can cause death if it's uncontrolled. So what we were seeing was the result of what we called a pharmacologic sanctuary. The science of all of this was very interesting. Why should leukemia drugs be excluded from the central nervous system? Why do you think that would be so? Because in evolution, toxins in nature would be very damaging to the central nervous system so what evolved over time was a protective mechanism for the central nervous system was to have drug efflux systems that excluded toxins. And of course these were toxins. Now these specific toxins were not used in evolution. Methotrexate didn't exist prior to ten years before and the same is true for 6 MP. But there are certain drugs in nature, poisons in plants for example, that also don't pass the blood-brain barrier. And that was probably crucial to grazing animals and so forth, that they were not killed by those kind of toxins, or the central nervous system wasn't affected. Anyhow, it's a very interesting phenomenon.

What you have to do is eradicate these cells from the central nervous system in the beginning. Patients with overt meningeal leukemia will on spinal tap, have increased pressure and leukemia cells in the spinal fluid. If you inject methotrexate back into the spinal fluid, the meningeal leukemia gets better. But it doesn't go away. The reason is that the meninges go all the way up over the upper reaches of the central nervous system. When you inject materials into the low back spinal fluid, it has to go against the flow and you don't get adequate concentrations in the brain area. You get an effect, but the effect is incomplete and transient.

What had to be added to that was irradiation to the brain area so when you gave drug into the intrathecal space, you got the lower part of the spinal fluid containing meninges, if you will. If you did brain irradiation, you got the upper part. Together you got the whole thing. We added the intrathecal methotrexate. Don Pinkel at St. Jude's added the brain irradiation. Those two things together, plus treatment of patients in remission that I described earlier, plus combinations of agents to get a high proportion of patients into complete remission. Now with the addition of spinal fluid methotrexate and brain irradiation, 40 percent of the patients were being cured. A great triumph.

GC: Yes. Did you expect this kind of result, this kind of success?

EF: You mean when we started out?

GC: Yes.

EF: Well, we thought we could make progress. It was Dr. Zubrod who said at a meeting where we were being attacked to some extent on the platelet issue, we'll get to that later. You see, the argument always was why do this to the patients? They're going to die in any event. The drugs are toxic. They have to have procedures like bone marrows and so forth.

Zubrod said something to the effect—this had to do with platelet transfusions but it's generally applicable—he said, "We're not going to cure leukemia tomorrow, and we're not going to cure it in one step. It's going to take a number of steps. One of the things

we have to do is control meningeal leukemia. That's an increment. The cure of leukemia will be a multiple step process."

So, yes, there were a few of us who thought that we would cure the disease. Exactly how we would get there, of course we didn't know. But there were many more people who thought we would not, that's for sure. The trouble with the history I've just given you is, though, it hits the triumphs. It doesn't tell you about all the frustrations, all the wrong turns, et cetera.

GC: Any in particular? Did you take any side roads that just went nowhere? Any investigations that really didn't pan out at all?

EF: Yes. We should get to supportive care. We did one study that was really far out and didn't work and was criticized. But I think in retrospect it was a study that was worth doing. This was probably 1956, '57 that we did this study. It's a disease called pernicious anemia which is a disease which mimics and looks like leukemia. If you look at the marrow, it's chock-full of these juicy, big, rapidly dividing cells. They spill out to other sites just as leukemia will. And patients died of their disease. A hundred percent fatal, pernicious anemia.

GC: Untreated.

EF: Untreated. Until 1923 when liver [dosage] was discovered and in 1928 when B_{12} was discovered. If you give them B_{12}, that's what they lack, those cells mature, behave. Instead of killing the patient, the patient's fine. So what was pernicious anemia which

looked for all the world like leukemia? It was a vitamin deficiency. So we thought, well maybe leukemia is a deficiency of a vitamin essential for the growth of normal behavior of white cells.

So we decided, okay, where would that be? B_{12} is primarily in the liver, so this leukemia thing could be in the liver. So we went to Lloyd Law again, and we had inbred strains of animals, of mice, different inbred strains, some of which were high leukemia producers, others low. We actually ground up—this is a colloid mill—the high-leukemia strain mice, that is, they were sacrificed and were fed to the low-leukemia strain to see if that would—but that went up. Or if the low leukemia strain eaten by the high would protect the high from leukemia.

GC: Now did you grind up the whole mice or certain organs or—

EF: Generally the whole mouse. And nothing happened. But that system is so different from the clinical situation. It's hard to produce pernicious anemia, for example, in experimental animals so we were worried that our model was misleading us. This is from the experimental farming station outside Beltsville, Maryland.

We prepared from immature pigs a brew. [Laughter] It looked like a strawberry milkshake. We fed it by tube to patients—I mean, the patients knew what they were getting. We told them what they were getting and what the goal or the purpose of the experiment was. I guess we treated some twelve or fifteen patients, but none responded. So that was a false lead. It turned out that leukemia is much more complicated than pernicious anemia.

But there were a number of experiments that we did, a number of new agents that we tested that didn't work, a number of combinations that we tested that didn't work, a number of supportive care approaches that didn't work. But that's the nature, particularly the nature of clinical research. You have your peaks and your valleys. You've got to have a high frustration threshold, and you've got to be able to see the distant shore. If in 1955 we looked at just what was happening in 1955, we would have been pretty depressed. But if you have your eyes on something in the future that might be better, you can sort of get through the rough parts on a day-to-day basis. We supported each other. Dr. Freireich and I were very optimistic. Dr. Zubrod was optimistic. Dr. Jim Holland, with whom we worked very closely, was an optimist. Some people said we had rose-colored glasses or we were too optimistic. That might be true, but the people that were pessimistic that rotated through, like some of the fellows, just didn't stay in the field because it was difficult. The patients who were as sick as some of our patients were tough. So they just didn't stay in the field. So that's one of the frustrations. That's a good example of a study that didn't work. Very important is the fact that we supported each other.

GC: Platelet transfusions? Do you want to talk about that now?

EF: Right the whole business of supported care.

GC: Okay.

EF **:**The major cause of sickness and death in patients with leukemia was the fact that the normal marrow was crowded out with leukemia cells. It's being crowded out meant that normal white cells were not produced, and normal white cells protect one against infections. Our patients got infections. But even more important early on is that the platelet-producing cells, these are megakaryocytes in the bone marrow, were crowded out so the platelet count in the purple blood, instead of being, say, a hundred and fifty to three hundred thousand which is normal, was low, often five thousand or less. And platelets are important to maintaining the integrity of small blood vessels.

So if the platelets are very low, patients bleed, and that was a horrendously difficult complication to deal with because you've watched the platelet count going down. Before we could do anything about it, it would go down, down. It would hit the level where bleeding would start, nosebleed. Couldn't stop it. Or you could stop it initially, then it started again, you put in a pack. If you've ever had an anterior pack or particularly a posterior pack—I'm sure you haven't—but that was morbid. And then often when you take the pack out, which you'd have to do after a couple of days or it would get infected, the bleeding would start again.

Or the bleeding would start from the mouth or coughing up blood or a rash, a red rash on the skin typical of bleeding, would occur. Or a massive bleeding into the skin or bleeding into the urine or the bowel or even the brain. And once it started, it would progressively get worse. And the parents would know it, and the patient if he was old enough would appreciate that this kind of thing is happening. And of course it would be dreadful for the nurses and for the doctors and so we were trying to fend that off. Also it made treatment with chemotherapy very difficult because most of our chemotherapy

agents affect the marrow in a way that it decreases the platelets. So it would actually make things worse before they got better.

So what to do. Well, there were platelet substitutes—there were things that, in the test tube, did things like platelets did, that is, caused the platelets to adhere to the vessel wall and so forth. But these didn't work particularly well because they didn't get to the right place. There was reasonable evidence that if you could transfuse platelets, you could control the bleeding, and theoretically that ought to be so. They don't have platelets, they bleed. Replace the platelets, that would stop bleeding.

It made a lot of sense, only it didn't work, and it was counter-dogma. Again, the senior people in the field said that it didn't work, the textbook said that it didn't work, platelets had been tried and didn't work, and so forth. So we had in mounting the experiments to show that platelets work, one of the things we had to do was to get platelets from the blood bank.

The blood bank at the clinical center was very devoted to the heart transplant, the heart surgery program, for which they needed a lot of blood. So they weren't too anxious to supply us with platelets unless there was some reason to think that they worked. And nobody thought that they worked. That is, the power structure didn't think that they worked.

I had reviewed some of the patients before who had received platelet transfusions, and it wasn't true that they absolutely didn't work. If you looked carefully at the patients in the wake of the transfusion, let's say they got transfusion on a given day, usually the bleeding

did lessen over a period of a couple of days. It was controversial—it's hard to quantitate bleeding in any event. It wasn't dramatic. It didn't stop.

So we wanted to do a platelet transfusion study but they wouldn't let us, and there was a fair amount of high decibel arguing about that. There was a lot of controversy. And that was where Zubrod stood up and said something about, "We may not cure leukemia today or tomorrow or ever, but if we're going to cure it, it's by incremental steps, by facing each obstacle as we go along. One obstacle is bleeding. One possible way of controlling that is with platelet transfusions and we have got to do that. I, as clinical director for the National Cancer Institute, am obligated to see that that's done."

That was after we had made our presentations and the negative view had been expressed by the senior hematologist. So that was the kind of support we got from Zubrod which was very important.

Well, what was agreed to finally was that we would trot out the most powerful tool for determining the benefit of a given pharmacotherapy. And that was a randomized comparative study which we had pioneered for patients with cancer. I mentioned that earlier. Freireich was chairman of the study and put together the protocol where patients, when they had low platelet counts then started to bleed, would be randomly allocated to a bottle of fresh blood from which the platelets had been removed or a bottle of fresh blood which contained platelets.

We treated something like twenty patients on each arm, and eighteen of the twenty who got the platelets responded. Two of twenty who didn't get the platelets responded. So it

was a highly positive comparative study. That was an extremely important study, not because of what it meant to us, because we were pretty certain it was going to come out positive. What it proved was to the rest of the world that platelets do work.

And the argument that they didn't work forever disappeared, and that allowed us to do further studies that made platelet transfusions better. One of the big ones was that a single unit of platelets is very marginal in terms of raising the platelet count. What you have to do is get six units or eight units and give them as a pack which is what we do today and what we gradually worked up to. So if you get a large enough number of platelets which you are going to acquire readily by modern techniques, you can effectively control and prevent all thrombocytopenic hemorrhage. And that was a major contribution. That the incidence of death from hemorrhage, which was 80 percent of patients died of hemorrhagic deaths, often in the central nervous system, prior to platelet transfusions, that dropped to less than 10 percent after platelet transfusions. It made chemotherapy better and it lead to the development of a three-bag system for acquiring platelets from donors, and that was important finally to the continuous flow centrifuge which allowed for the collection of large numbers of platelets from a single donor. The derivatives of that machine are right downstairs in our blood bank and we acquire platelets. Bone marrow transplantation would not be possible without platelets. Intensive chemotherapy would not be possible without platelets.

But the story didn't stop there. Directly analogous to the platelet situation, was a white cell situation. When patients didn't die of bleeding, which was true after platelets were given, a major cause of death was infection due to a lack of granulocytes. These are the white cells that fight infections. We had a patient on thirteen who had a white count of

something like four hundred thousand, which is way up from the normal five-to-ten thousand.

The reason it was so high is that he had chronic granulocytic leukemia, which is a very indolent form of cancer, of leukemia, wherein the white count is usually very high and almost all of the white cells in the peripheral blood appear normal; that is, they are mature and they're capable of phagocytosis that is of engulfing bacteria. So we acquired his blood, concentrated it, gave it to a pediatric patient, a two-year-old who was dying of pseudomonas septicemia. That's an organism that causes infection and septicemia and is 90 percent fatal in kids with leukemia.

This kid had a temperature of about a hundred and four. It promptly came down to normal when we gave him the white cells. His fever came down and stayed down, and the infection was controlled. So we developed a program of white cell transfusions and showed definitely that they worked. But obviously that was not for export because the donor cells were in fact leukemic. But it did lead to efforts to get normal white cells from normal subjects.

In contrast to platelets, you couldn't do that with regular donation because white cells have a very short half-time in the blood. Their presence in the blood is very low, and therefore, you can't acquire enough by any reasonable technique. That led to a relationship with IBM wherein the machine was developed, the continuous flow centrifuge was developed, initially to get larger amounts of white cells. In that sense, it was not very effective. It took further developments for that. But it was very effective

for platelets. But the whole scene developed in the setting of platelet transfusions and supportive care.

GC: I had wanted to ask you about that centrifuge. Was it tested in your labs at the NCI?

EF: Yes.

GC: Did IBM scientists come in and work with you?

EF: Yes. Well, both ways in a sense. That's a very important story. I had a patient who was ten years old who had chronic granulocytic leukemia whose father was a scientist at IBM. What the father wanted to do is to help us do cancer research in any way he could. He didn't have a lot of money, so giving money was not his bag. He wasn't a doctor so he couldn't do the biology kind of thing. But he sort of went around, he talked to various people. The idea of having some kind of a centrifuge that would be continuous flow that would allow for the collection of platelets, white cells, subsequently all different kinds of cells, was one that attracted him.

Freireich was his counterpart on that on the medical side for the most part, though other people were involved as well. So he and J started this relationship where they actually fabricated the machine piecemeal. We actually saw it develop in the room. All of us helped with it, but J and this IBM scientist were there for the most part. The IBM scientist would often go back to IBM to fabricate a seal or something like that and then bring it down. So there was work going on at IBM. But the central work, the assembly and the adaptation was done at NCI.

The real genius of the machine is fairly simple. It's a complex machine and it has all kinds of computerized gadgets on it today so it looks like a Rube Goldberg thing. But the real genius was the continuous flow to the machine, to the centrifuge, from the body and then back to the body out an artery into a vein, and that required that there be a seal on which the centrifuge spun that allowed for the collection of buffy coat while it was spinning. That was really very clever. That was the genius of the machine, if you will. That's what made it work.

There were technical aspects of that that are very complex. But when you spin the blood, the red cells are heavy, they go down. The plasma is light and stays up. The white cells and the platelets which you want to collect are at the interface between the two. There's actually a white band, and what you do is put the tube that goes out the seal, down to that white band and collect selectively the cells from that band. That gives you platelets and white cells, they go out to your collection bag. Everything else goes back to the patient. So it's really a very clever, extremely important machine. So that made a big difference.

GC: What kind of scientist was the IBM scientist? Was he an engineer?

EF: He was an engineer. Yes.

GC: Do you remember his name?

EF: Yes. George Judson. Now, he was succeeded by a fellow by the name of Kellogg, who probably had more to do with the development of the machine than Judson. Judson did the start of it, and the seal was pretty much developed by Judson. There was a "falling out" between Judson and Freireich that complicated things for a while. I'm not sure what happened. Scientists don't always necessarily work together smoothly.

GC: What happened to Judson's son?

EF: His son died.

GC: Did you become very close to your patients in general?

EF: Yes. It's said that doctors can be detached from patients, but that's just not true. Or at least it wasn't true for me. If you really care for patients, and particularly patients that you've gone through so much with, the patients and the family, you become a part of them and they become a part of you.

GC: Did you ever have trouble convincing a patient or a patient's family to try out one of those new protocols?

EF: The fact of the patients being there usually meant that they had taken the steps further. They didn't come to the National Cancer Institute to get routine treatment. They came there for something special because it was known as a research center.

I don't remember very often talking to patients or parents and have them refuse a reasonable proposal for research. But that's not surprising because most of the research we did was therapeutic research. It was done with the intent of making them better. And if you've got a disease like leukemia, which in the 1950s and '60s was pretty bad news, anything that offered you a chance of getting better was something that you were likely to take. But they would talk to other doctors who might have a very dim view of the potential for therapeutic research in leukemia and so forth. One of the things that characterized many of the patients was uncertainty. We had that problem, too. We didn't know necessarily what was going to work. We had differences of opinion as to how important different things were, and to some extent, that was important to the patients. I think the main thing that made it possible for most of the patients is identification with one or more of the physicians, and vice versa. I'm trying to write a book on that subject, the whole issue of the interface between medicine and patients in the treatment/research cancer arena. Because I think it's the ultimate, ultimate vulnerability for a patient in a sense, and it's a very important thing to handle properly from a physician's point of view. Anyhow that's an important subject.

We had many patients that, well just yesterday one of the first patients cured of Hodgkin's disease in the MOPP program comes back every year. We call it—he lives in Fort Wayne, Indiana, and I treated him first actually in Texas and we call it Les Willig Day. He doesn't have to come back, but he comes back just for the social event. His picture was taken; he's going to be in our local magazine. He was interviewed and so forth. He went back this morning. But he and I have been very close over the years.

The treatment for him at the time was very controversial because he had a lot of prior treatment, and we didn't know at the time that the MOPP program was curative. But we did have every reason to believe that the more prior treatment the patients had, the lesser was their chance of responding and the greater was their chance of having toxicity. But he was one of these proactive patients who just wouldn't give up and I didn't say no. Several people that he had gone to, he'd gone to NCI and Memorial, and they didn't want to treat him, but finally I elected to treat him, with a modification of the MOPP program. By gosh he went into complete remission and stayed there, and he's been there ever since.

GC: It's another miracle.

EF: Yes, that whole experience was that. When J and I won the General Motors award for cancer research in the mid-'80s I think, we were in New York at the press conference. I had talked and J was talking, and I was standing and there was this lady standing by me, she was about thirty-five, forty years old. She said, "Dr. Frei, do you know who I am?" And I said, "No." I didn't recognize her at all. And she told me her name, and I didn't know that name. She said, "But my maiden name is 'blank.'" And of course I knew her immediately. She was seven years old when we had treated her at NCI. This was something like twenty years later. She was the mother of two children. We hugged and I told her that this was what it was all about. It's a life and death situation here thrown together.

Of course, that was something that NCI was set up for. Managed care is a problem because managed care doesn't allow for that kind of relationship. It's not that it deliberately doesn't do it, but you've got to see patients at certain intervals and so forth.

That's great for the bottom line, but it's not conducive to research and certainly not conducive to the kind of relationship you have to have with patients for their goodwill.

If you're doing a study in women, let's say of the adjuvant chemotherapy of breast cancer, and you want to know whether AB is better than A, so it's a randomized study. To present that to a patient is something that they always have lots of questions about. And if you've got patients lined up pounding on the door to get in, or if you shorten the time interval, it's really not optimal patient care to do that. So it's been a challenge, but it's been fun all the way.

GC: Let's talk about the Hodgkin's program. You said some of that came out of the leukemia program.

EF: Leukemia. Right. I mentioned that we used combination of two drugs to get to a 90 percent complete response rate, and then we used combinations in complete remission to prolong the duration of remission. One of the things that we did in between there at NCI was to use four drugs all at once. In a conversation between J and myself, we came to this idea—J thinks it was his idea, I think it was my idea, but the truth of the matter is that we both came to it, I think, at the same time from both derivation and from insight—but it had to do with the appreciation that the best and most potentially curative treatment for a disease ought to be combinations of agents given at full doses if possible, given intensively, given early in the disease, and ideally given intermittently, that is, courses of treatment I'd say in monthly intervals for maybe four to six courses. That led to the VAMP program in acute lymphocytic leukemia which produced a high complete remission rate and did produce a couple of long-term disease-free survivors, but that was

before we had meningeal leukemia under control. So it didn't turn out to be as good as meningeal leukemia treatment, as the other program that I told you about.

So given that experience, we had a Hodgkin's disease program that Paul Carbone and I were primarily responsible for that was doing pretty well. We had discovered that the vinca alkaloids were active, we had discovered that methotrexate was active, we knew that the alkylating agents were active. So that, like leukemia, there were multiple agents active in Hodgkin's disease so you had the opportunity to put them together.

But we didn't have to go through the whole chain of events like in leukemia that led us from one drug to two drugs to four drugs, et cetera. We went from one drug to four drugs in Hodgkin's disease, and what we put together was not the VAMP program which we had for leukemia, but the MOPP program which emphasized agents which are active in Hodgkin's disease naturally.

And what we observed in the first patient—Hodgkin's disease often involves the mediastinum, that's the center of the chest—this was a woman who was probably about thirty-five, forty years of age who couldn't breathe because of a tumor which was impinging on her trachea, her air passages. And we knew that if we treated with a single agent, we knew from a long experience, that the tumor would decrease in size, but slowly, over time and it rarely went away completely. We also knew that x-ray treatment would probably be the standard treatment for this kind of thing, but she had tumor not only in the media sternum, she had tumor in multiple other places.

So we wanted to treat her with systemic treatment. So we put together the protocol of MOPP, four drugs in combination. This is another thing that was really miraculous in the setting in which it occurred because the tumor, instead of going down slowly like this, went "chunk!" and her breathing improved within about a day or two. And a repeat chest film, I think about maybe five or seven days later, having been big initially, was now way, way down, almost normal. I think by three weeks, it was gone.

EF: Anyhow, the patient had a dramatic response. We had a couple more patients like that in succession that had very, very good responses. It's not only how far down the tumor goes, which is obviously important, hopefully it goes down and out, but the rapidity with which it goes down is a very positive sign in terms of how well the patient is likely to do or that patient's disease is likely to do. Long before there was reasonable evidence that we were curing patients with Hodgkin's disease, there was clear evidence that we were in a new treatment mode because instead of partial responses developing slowly, we had complete responses developing very rapidly in the majority of patients.

The evolution of that was that with the VAMP program, that combination for leukemia, the combination of MOPP for Hodgkin's made sense. Vince DeVita had started as a fellow and took over the program from the clinical point of view as a fellow. That was his identification with it early on, and he did an excellent job. The same was true, somewhat less so for non-Hodgkin's leukemia, not in Hodgkin's lymphoma rather, and we actually developed a four-drug program for patients with solid tumors including breast cancer. That was a prelude to combination chemotherapy for breast cancer.

GC: When Dr. DeVita came in to the NCI he had been trained to think that you did not give drugs in combination, and that was something that you overcame with him. That yes, you would try drugs in combination. Is that true?

EF: Well, combination chemotherapy at the time it was relatively early in its development, particularly the four drugs. I think it was true of all of the fellows coming in that they were told as physicians at the—the NCAB said that you don't use four drugs at once. You use one drug if you need it, but ideally you don't treat them at all because they're going to die of their disease. So I think they all brought that prejudice to it. I dont remember Dr. DeVita being any better or worse than the others in terms of overcoming it.

GC: So it was a pretty standard belief coming in?

EF: Right. You see, the argument that the senior hematologists made at the NCAB is that the drugs are toxic, that there's a lot of belief that they were not effective enough to be able to cure under any circumstances. If you believe that, then using two or three or particularly four at once is pretty horrendous. You're pretty prejudiced against that if you've come to it with those premises, which most of them did. We came to it from a different premise, but it was sort of a local one, it was one that was developed at NIH. We saw Lloyd Law's data, we had our preliminary data in acute lymphocytic leukemia and so forth, so we were able to do it and believe that it would work. That's why I think it would have been difficult to do in an outside hospital because the tradition there was, you do what the textbooks say, and the textbooks did not say combination chemotherapy for Hodgkin's. Not then, but they did subsequently.

GC: Did you ever doubt your work or doubt that this could work?

EF: Sure. If patients did well, you were up. If patients didn't do particularly well, you were down. It's nice to say that you felt secure all the way through and you knew it was going to work from the beginning. But nobody was sure about it. A lot of smart people were sure it wouldn't work. A lot of people who were interested in me advised me to go to graduate school, to get a Ph.D. in biochemistry someplace and do basic research, and then come into cancer treatment because they thought this would be better for one's career, because they didn't think what we were doing was likely to go very far. Descartes, some of the great philosophers of science, have said that doubt is the driving force of science. If you were secure in your knowledge, you wouldn't acquire knowledge. It's doubt that is the driving force. Certainly in western civilization that's true. For a long time, everybody believed that medicine was what Galen, the Romans, and the Greeks taught us, but it was. It took real pioneers to break that. Descartes was one of them.

And that's what we were. We were pioneers because we weren't supposed to be able to treat cancer with chemotherapy agents. I think very importantly a small group of us did support each other, you know, very strongly. I mean talking to Freireich particularly but Zubrod and Holland and so forth, either on a one-on-one basis or in a group was very helpful.

GC: You must have felt immense pressure from the outside at times that this was not the way to go.

EF: Yes. Sometimes, when I'd go back to a reunion at my medical school in St. Louis where I had interned, had my residency and so forth, when I went back there and talked to the doctors back there, some of my friends, et cetera, they were pretty negative about it in the main. Over time that can get to you. My dad used to say that what you should do for a career is pick a tough problem and stay with it, and that turned out to be very prophetic. Because there are a lot of easy problems. It's true today in a sense that it's easy to get the young doctors to work on leukemia, lymphoma, things that they can cure. They can see a patient and three weeks later the patient's going to be much better and so forth. It's tough to get them to work on, say, metastatic lung cancer. And it's kind of the same problem we faced. It was hard to get doctors in 1955 to work on leukemia or any form of cancer because it was such a challenge. But there are enough like myself around that it's happening.

Dr. Farber who was the founder of our institution used to say that this was a pediatric institution for its first twenty-five years. He wanted to develop the adult program, and he coined the phrase, "For cancer treatment, the child is father to the man." And actually this was true. A lot of what we learned about the principles of cancer treatment that now are so effective across the board were learned back in the 1950s initially in children. So yes, there was a lot of doubt. One of the things that I thought was important, just seeing people come into the field and some staying and some not, is support from the family. If there was trouble in the family and a problem with family support, it was difficult for somebody to stay in a field like that, which is so challenging and you have to have a very high frustration threshold. It's not very peaceful at work if you've got patients who are bleeding or patients with those kinds of problems, so you've got to have peace at home.

GC: What was a typical day for you? How long would you be in the lab or on rounds or in the hospital?

EF: Well, a typical week . I used to get to work at seven thirty, quarter of eight in the morning, leave at six or six thirty, and work a half-day, two-thirds day on Saturday. After a while, you get to the point where you don't have to do too much of that, but in the early years you were on call much of the time. If a patient started bleeding at two in the morning, we came in. Fortunately I lived just a hop and a skip from the clinical center so that was doable.

GC: So why did you leave the NCI?

EF: Well, mainly for personal reasons. In 1965, we had five children. The oldest in '65 was 17. We were facing the college crunch. My wife's sister in Boston had eight children. Her husband had advanced emphysema to the point where he couldn't work, he was in and out of the hospital, and was on oxygen most of the time. So it was having a very adverse effect on my wife. My wife and her sister were very close. Indeed our families were close. We vacationed together. My government salary was as good as they could have given for what I was doing. But government salaries are very limited, particularly for physicians as compared to what you could do on the outside. I was offered a very good job at M.D. Anderson, a major cancer center, at a much better salary. My wife's sister and children moved to Houston with us. So I had major responsibilities that I could not have handled in the government. By the way, Freireich . . . there was a group of about six people, key people in the department of medicine who went with me to

Houston. So, in a sense, I didn't leave because the ambiance was really the team, and the team moved together.

GC: Who else came with you besides Freireich?

EF: Ed Gehan, a biostatistician; Ti Li Loo, a pharmacologist; Evan Hersh, a medical oncologist; Jerry Bodey, a medical oncologist. I think that's it.

GC: Did you keep up with what was going on at the NCI after you left?

EF: Yes. Sure. The cancer research world is a small world. They were close to us, and a lot of the support that we had was grants from NIH. As a matter of fact, we used to go back and forth frequently during those early years because we were involved in a number of collaborative studies.

GC: So when the National Cancer Act came through in 1971, which radically changed the way things ran at the National Cancer Institute, what did you think?

EF: The National Cancer Act resulted in increased support for cancer research. While there was some concern about programmed research, in general, the Cancer Act had a very positive effect. The funding problem has gotten worse in recent years. The number of really good ideas that could be funded are always greater than the amount of funds that are available. It's not that there's a shortage of ideas and it's certainly not that there's a shortage of patients or challenges in the scientific arena. The shortage is in money. The fact that they're seriously talking about doubling the NCI budget over the next five

years is wonderful. At the present time, when you apply for a grant, you've got a 14 percent chance of its being funded. The careers of medical researchers are often dependent upon a grant funding. If every three to five years you have to compete at the level of 14 percent, you've got to be mighty secure. If they double the budget, it'll go up to maybe 25, 30 percent and that's a much better figure. Because people will stop coming in to cancer research and other types of medical research if they've got to compete at the level of 14 percent.

GC: You said you had some concerns, or that there were concerns about programming research. Can you talk a little bit more about that?

EF: There were two programs that they focused o, n the virus program and the CCNSC which is a treatment program. In the virus program they saw, by electron microscopy, what looked like virus particles in the peripheral blood of patients with leukemia. Not always, but often enough to be provocative. This was by electron microscopy. So that a great deal of focus went on in the clinical area, and they have a whole series of studies as to what to do with the blood (process it, maybe give it to guinea pigs or what have you to see if they develop leukemia), to look for certain types of particles under the electron microscope, to analyze that sample of blood by various biological techniques, biochemical techniques, to look for virus footprints, et cetera. It was all targeted on, eventually demonstrating that a virus caused leukemia and then treating the virus and treating the leukemia. Money was allocated to the different slots. A lot of people were very critical because they thought it was programming research. We didn't really know enough to stereotype things that strongly, and it would be better to support people that

develop their own independent ideas and would work on the problem and hopefully surface something highly original.

If you analyze the virus program, all of the things they programmed for didn't happen. So the critiques were correct. But they were incorrect in saying that it wouldn't work because a lot of the people that did discover major things, Bob Gallo for example on the IL-2 and HIV and reverse training use, Sol Spiegelman, many things were discovered at a biochemical or a basic science level that had to do with a cancer virus that came out of the cancer virus program that were not derivative of the original planning of the program at all. That just came because good people were supported and good people will do good things.

GC: Was there any kind of advocacy group, any kind of pressure like that, like there is now?

EF: Well, there were not patient advocacy groups. There were Congressional. Let's see, what had happened, Bob Taft was a very great Republican senator, much loved in the Senate. And he developed lung cancer. This was in the mid-'50s, or maybe the early '50s, and that had a lot to do with money coming to the National Cancer Institute because all of the other senators, his friends, et cetera, admirers said, "We want to do something for good old Bob." Well what's the best thing to do for good old Bob? Well one thing was to create a fund, a big fund at NCI in his name or in his honor, all because of the disease he had. And all of that was done. And that's happened intermittently over the years and that's one of the reasons why the cancer budget goes up. The other reason is the so-called "cancer conspiracy" which is a very interesting thing.

GC: That's an interesting term.

EF: Yes, it's always used in quotes because by "conspiracy" it's not pejorative, it's positive. But one of the reasons that the cancer program has been so well funded and been so effective is a very limited number of highly effective advocates, not specific patient advocates. One of them was Mary Lasker. I don't know if you've heard that name.

GC: Oh yes.

EF: Her husband was very wealthy and she used the money to specifically augment political support for the cancer program, and the money comes through politics. A lot of people like to say, "Keep politics out of science." But the truth of the matter is that NIH got its budget from Congress, and Congress allocated its budget in accordance with political influence and other people. Sidney Farber from here was a member of the "conspiracy." He was a Harvard professor and he was very well spoken. He would go down to Congress and talk about this new treatment or what have you, and that would release money. Another person was Lister Hill who was in the Senate who was a very effective advocate for NIH and Fogarty in the House. So there were a group of seven or eight people who, over the years, had a great deal to do with the expansion of NIH. It's more complex now because back in those days the Senators I don't think even knew where NIH was.

EF: Except a very few of them. Now they all do. Now it's much more political than it was back then.

GC : Did you ever meet Mary Lasker?

EF: Yes.

GC: While you were at NCI?

EF: I met her there and I met her subsequently. I had to testify before Congress so I was sort of a junior member of that "conspiracy." A part of the reason I'm here [at Dana-Farber] is that Sidney Farber, when he would go down to testify before Congress in the late '50s, would after he'd been downtown he'd come out to NIH and make rounds with you.

I shouldn't say he did this every time, he probably did it a total of four or five times. But at the end of rounds on at least two or three occasions, he said, "Tom, some time I want you to be with me at the Farber or in Boston." Which he called it the "Jimmy Fund." I thought he was just flattering me. Because he never followed through with anything until some seventeen years later, when he recruited me for the position here. He was a member of the "conspiracy," too.

GC: When did you testify before Congress?

EF: Well I was on the committee that put together the Cancer Act. I testified before then, probably about four or five times. A couple of times it was at the request of Senator Kennedy whom I got to know well because I took care of his son, Teddy.

GC: One thing you skipped over, I'd like to get back to for just a minute. How did the clinical center change in the years you were there? You mentioned when you first came in, it had just started out, a lot of the beds were empty.

EF: It was brand spanking new. How did it change over time? Well, those beds got filled up.

GC: Quickly? Slowly?

EF: Deliberately, I'd say, sort of in between. The laboratories got filled up. We were there during the halcyon years. Halcyon in the sense that the resources were almost more than we could use, so it was never a matter of limitation of resources, be it personnel, be it equipment, be it travel, whatever it was. I guess you could say we were in the halcyon years in terms of the opportunities because we were in the right place at the right time in terms of the development of a cure for acute lymphocytic leukemia and so forth. Also the NIH campus was very pastoral at the time. I mean now it's become parking lots and new buildings.

GC: Did I miss anything? We can pretty much wrap up here unless you'd like to talk a little bit more about the changes.

EF: There are a lot of things we could talk about, but I think the essence is there. A very positive experience.

GC: Working at NCI.

EF: Yes. Very positive. We really had an opportunity that was unique. I think if we had all gone to one of the other cancer centers we would not have found that. It was a constellation of people. It was the "conspiracy" that was very important. It was some of the high directors at NCI that were critical, such as Zubrod particularly but some of the cancer directors as well.

GC: You mean Endicott?

EF: I don't know what names you have.

GC: If you'd just throw out a few that come to mind immediately I can tell you if I have them.

EF: Zubrod.

GC: Yes.

EF: Freireich.

GC: Yes.

EF: Carbone. Karon is dead. Lloyd Law, Mike Potter, and probably somebody like Tony Meade, he was with Abe Goldin, DeVita, Dave Rall, R-a-l-l. Those are the key people who were there at that time.

GC: Okay.