Combination Chemotherapy and the Cure of Acute Lymphoblastic Leukemia in Children

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THOMAS COLE, PHD
Welcome to the third of our History of Medicine lectures and core sessions for this year. As you know, the theme of the year is living history, and we have in the Texas Medical Center examples of the most amazing stories and progress in the history of medicine in the twentieth—in the twenty-first century. Today, we are delighted to have Dr. Emil Freireich who's been at MD Anderson for forty years?

EMIL J. FREIREICH, MD
Fifty.

THOMAS COLE, PHD
Fifty years, sorry about that. Dr. Freireich is someone you may have seen in Ken Burn's documentary, The Emperor of All Maladies. It's also—he plays a key role in the book by that title. I won't take up too
much time introducing him. He has agreed to let me interrupt him. So I will feel free to do so when necessary. But there are just a couple things I wanted to say about him to set the stage.

When Dr. Freireich went to medical school, he graduated in 1949, there were no courses on cancer. He was a hematologist, and he was told by one of his bosses, “Go cure childhood leukemia.” And when he began, children were bleeding out. They were dying of all kinds of hemorrhages, blood all over the place. And one of the first things he did was to figure out how to get the blood coagulated so that they could be stabilized. Another thing he did that’s completely revolutionary was he invented, with an engineer, he invented the blood separator, separation of plasma, white cells, and red cells, which you will find in every single hospital in the world and absolutely necessary for many procedures including heart—including transplants.

And the last thing just quickly to mention—I asked him yesterday what were the three major contributions—the last thing, which is equally if not more important than the others, is Dr. Freireich invented ways of curing childhood leukemia. He had the idea that cancer could be cured. And he began experimenting with multiple chemotherapeutic agents. And today we are in a situation where 92 percent of all children with leukemia survive. So you can tell we are in the presence of a truly great physician, scientist, and human being. So I thought I might start at the human level with your 1946 Pontiac Fastback and when you got a call that you and your wife and children had to move to Washington DC or Bethesda and how that happened.

EMIL J. FREIREICH, MD
How did it happen?

THOMAS COLE, PHD
What happened? What call did you get? From whom? And what did you do?

EMIL J. FREIREICH, MD
Well, during the war there was a doctor draft. And I got deferred because I was working on radioisotopes with a famous doctor, Joe Ross, at Mass. Memorial Hospital in Boston for my hematology fellowship. And the Supreme Court ruled at that moment in history that it was unconstitutional to draft people based on their profession. So the doctor draft ended and the army reacted by drafting every physician who had not served a two-year term in the military. And I got a letter one day when I was working in the lab in the middle of the night, married to my wife with 1 one-year-old child and a pregnant wife. And in those days, the fellows did all the research as you know. And we were doing—we were—Joe Ross was one of the first to get radioisotopes to study the lifespan of red cells with Iron-59, treat thyroid with I-131, get FE-
55, Chromium 51 for labeling platelets and so on. So we were radioactive anything. And I got this letter one day, and it said you're now a Second Lieutenant in the Army Reserves. So I didn't know what that meant. I called the guy. He said, "We'll call you when we need you."

So I kept doing my work, and one day I got a call from the president of our institution, Dr. Chester Scott Keefer. And probably most of you don't know Dr. Keefer. He was very famous physician/scientist. He was the president at Mass. Memorial. And when Eisenhower was elected president, he consolidated three cabinet levels, health, education, and welfare. The first secretary was Oveta Culp Hobby who was the publisher of the Houston Post. And she immediately appointed an Under Secretary of Health, an Under Secretary of Education, an Under Secretary of Welfare. And Dr. Keefer agreed to be Under Secretary of Health. But he maintained his role as the president of the Boston University School of Medicine, which by the way had research institute analogous to the Rockefeller Institute, that is we had physicians whose responsibilities were primarily their clinical research and little service work. separate from the runnings of the Boston Memorial Hospital.

So I got a call one day. Dr. Keefer said to come to his office. I came to the office. He said, "Your boss, Dr. Ross, says you're doing a good job on research."

I said, "Thank you, sir."

He said, "Have you ever heard of the National Institute of Health?"

"No sir."

"Well," he said, "Dr. Ross tells me you've been drafted. It turns out that if you enlist in the public health service before the army gets you, you can serve your mandatory military time in the public health service. And you can do research at the newly opened clinical center of the National Institute of Health." He said—so he picked up his hotline, "Fred, there's a guy coming to see you tomorrow. Freireich, F-R-E-I-C-H."

So I jumped in my little car, drove to Washington, met Fred. Fred said, "Get on the bus. Go on to Bethesda. Interview with all the clinical directors." I met Gordon Zubrod, who had come out of the malaria program. He was the scientific director of the Cancer Institute. And he said, "Freireich, what do you do?"

I said, "I'm a hematologist." As you said, "You're out to cure leukemia?"
I said, "Yes sir." So we began our career immediately. From the time I met Zubrod, went home, twenty-four hours later, I got orders from the public health service to report to active duty in the clinical center. And I was in the midst of all my research. I hadn't finished any of the publications. So we packed everything we had. We took our one-year-old child, and my pregnant wife, and we went to Bethesda, and we met Dr. Zubrod. He said, "Your office is on the tenth floor."

I went up to the tenth floor, and I'm walking down the hall. Emil Fry the third. Golly, isn't that like the government. They can't even spell my name right. [laughter] So I walked in there. There was this tall, skinny guy with no hair. So I said, "Sir, you're in my office."

He said, "No, you're next door. I'm Fry. You're Freireich." And we became life-long friends and associates, his family and my family. He and I were like brothers. And we collaborated on all of our research. Tragically, about twenty-five years ago, he developed terrible Parkinson's Disease, which took him out of medicine entirely. And we watched him—if you've ever seen a Parkinson's patient—we watched him get separated from the world in the most painful way. And he's passed. But we went to work.

Dr. James Holland, who has been ninety years a scientist, had preceded me to the clinical center. And he started treating children with these drugs, methotrexate, 6-MP, prednisone. And he was getting some progress, but he got a job offer to go to Roswell Park. He left. And the reason Zubrond hired me is he needed someone to take care of these kids who were dying in the hospital. So I walked in the first day and the chief—Dr. Fry—said, "Those are your patients. Well, the first thing I did was read the literature. And everything that was published by the world's experts said that what we're doing with these drugs is prolonging the agony of dying in these children. Hopeless.

Remember, in 1965—correction, 1955—the ethos in the academic medical center, medical community, was that there would never be a chemical that would cure a cancer because the cancer, as far as one could tell biochemically and biologically, was a part of your own genome. They were not aware of whole genome sequencing and mutations and all that stuff. So everybody thought it was foolish to think of curing cancer. But we decided we would try.

So the first thing we did was take a lesson from the infectious disease community and start using drugs in combination rather than in sequence. And for tuberculosis, it turned out that if you used streptomycin alone they'd all become resistant. And if you followed with PA—Para—PAS, they would get responses, and they would relapse. So all the TB patients with systemic disease died. Well, when they discovered that you've used the two of them together you would avoid the development of resistance, a fraction of the
patients were cured with that combination. And so Dr. Zubrod and the infectious disease guy said that's the way to start. So we started looking at a combinations of the three drugs we had and different permutations. And we made some progress. When our first publication came out the cooperative group was Dr. Holland in Buffalo and us. Our second protocol, we had ten academic institutions. Everybody realized that doing objective, quantitative, clinical research, you could build on your knowledge and make progress.

**THOMAS COLE, PHD**

These were the first randomized clinical trials in cancer?

**EMIL J. FREIREICH, MD**

In cancer. It was the first cooperative group in the United States called—it was called the Acute Leukemia Cooperative Group. When Birchenall was at Memorial made a second cooperative group. He called it Leukemia 8 to discriminate it from us, but no one could discriminate, so we called it B. So acute Leukemia Cooperative Group B, was the first cooperative group.

**THOMAS COLE, PHD**

You told me yesterday these kids were dying, right? They were bleeding out.

**EMIL J. FREIREICH, MD**

One hundred percent mortality by a year.

**THOMAS COLE, PHD**

You couldn't treat them because they were dying.

**EMIL J. FREIREICH, MD**

They all bled to death. And if you can imagine a four-year-old child in his mother's arms bleeding to death, that's what we had to face. So Dr. Zubrod came on rounds one day, and he said, "Freireich, you've got to do something about the bleeding because none of the chemotherapy could be administered because the children died of hemorrhage before we could get to them." Hemorrhage and hemorrhage and infection combined counted for 95 percent of the deaths before leukemia could get them.

So I went to work on that problem, and as you had mentioned, it had been conclusively shown in experimental animals, dogs, cats, rats, monkeys, that the cause of the hemorrhage was not the low platelets, which was true. It was some circulating anticoagulant. The way it was proven is they pheresis the animals till they had no platelets in circulation. And they still didn't bleed. But if you gave them a little bit of heparin, they bleed to death. So the ethos was that platelet transfusions were futile as long as
you had this anticoagulant. So the anecdote—I told this in a book—is I had a patient—I don't know if I told you this, but I remember it like it was today. His father was a minister in Washington DC. And I had the idea that if we could exchange transfuse the child who was bleeding we would replace the platelets and the blood.

**THOMAS COLE, PHD** What does exchange transfuse mean?

**EMIL J. FREIREICH, MD**

Exchange means that you're going to replace the patient's blood with normal blood. That's done for erythroblastosis fetalis in children. And the way it's done is I get a normal donor and I take 50 CCs of blood out of the donor. Then I get—with the anticoagulate—then I get the patient, 50 CCs out of the patient, squirt it into the trash can, put the 50 CCs in. And it turns out that the arithmetic of that is that if you trans—if you replace two times the recipients blood volume, you'll have 50 percent of all the values normal. All the values will be 50 percent like the donors, normal. So we did that to this young child. His name was Scotty Dinsmore. I'm sure his father wouldn't mind me—I've actually published his name in a book when I told this anecdote. And after we did the exchange transfusion, Scotty stopped bleeding entirely. He was a normal child. Jumped out—

**THOMAS COLE, PHD** Where did you get the blood from?

**EMIL J. FREIREICH, MD**

The father brought ten volunteers from his church. They lined up, and each one donated 250 CCs, which is less than a blood donation. Then the next donor came. So I sat there for about six hours doing this procedure. We didn't have any house staff or technicians. But Scotty stopped bleeding immediately. So we had proven that if you replaced the plasma and the platelets, you control the hemorrhage, but we were smart. We kept counting the platelets. And as the platelet count—platelets have half-life of about four days—as the platelet count went down, when it got to a level of about 5,000, the bleeding recurred. Aha. So I went to the medical records of the children who died, and I compared the notes of the doctors and the nurses for when the patients were bleeding and what their platelet count was, and we showed that there was a direct relationship between the platelet count and the occurrence of hemorrhage. So that's not a coincidence. And Scotty's platelet count followed the pattern. He started bleeding when the platelet count got below 5,000. So with that knowledge, I knew what I had to do. I had to transfuse platelets. Problem. Shall I go into this?
THOMAS COLE, PHD
Yes.

EMIL J. FREIREICH, MD
Well, the way we collected blood in 1955, steel needles, rubber tubing, glass bottles, everybody knows what happens to platelets in that circumstance.

THOMAS COLE, PHD
Everybody does not know what happens to platelets. [laughter]

EMIL J. FREIREICH, MD
Platelets adhere to wettable surfaces. So there were no platelets in the blood. So if you transfuse fresh blood, collected that way, no platelets. So we had to go to Fenwal who invented plastic bags for shipping plasma overseas during the war. We got plastic tubing, plastic bags, coated our needles with silicone so they were non wettable, collected the blood. We had 100 percent of the platelets in the bag. Problem number two, how long do the platelets stay in the bag? So we counted platelets for the next five days, and it turns out that by forty-eight hours the platelets are all dead. We need fresh blood. Yeah, that's a long story. We had to fight to get fresh blood because banks, blood banks, only issue the oldest blood, not the youngest blood. If you distribute the young blood for transfusion, the blood bank runs out of blood, right? So we had a big social battle and with Zubrod's support, we succeeded, and we demonstrated quantitatively that platelet transfusion could control hemorrhage. We got volunteers to donate platelets so that we could define limits of donation. We demonstrated that a normal adult could donate two 500 CC units of platelets twice a week and his platelet count would not go down. Those are standard that are still used today, fifty-five years later. And so we could get one adult volunteer, a parent usually, to maintain a child free of hemorrhage by giving platelets twice a week, half-life four days. And hemorrhage as a cause of death vanished. in a week.

THOMAS COLE, PHD
It seems to me you're very meek and mild in pursuing this. [laughter]

EMIL J. FREIREICH, MD
We were meek and mild. We had to fight the entire establishment. It turned out that the director of our laboratory of medicine program, George Breker, was one of the pioneers in identifying the causes of hemorrhage after the atom bomb events in Japan. And he was—he could never be convinced that his animal data was wrong. So what Dr. Zubrod thought of doing was we did a randomized trial, fresh blood versus banked blood. In children with the same indication, we measured all bleeding parameters. We
quantitated the amount of blood out of the nose, mouth, urine, stool, bleeding time so we didn't have subjective, but objective data. We did the randomized trial. It was done blind. We had a statistician. We had the blood bank people. We had Dr. Zubrod. After we did something like fifteen patients, we broke the code, and it was obvious that the fresh blood worked and that none of the patients that got banked blood worked. And the consequence of that positive result was a citation classic in the New England Journal and Dr. Breker refused to have his name on the paper.

**THOMAS COLE, PHD**

Why was that?

**EMIL J. FREIREICH, MD**

Well, because he wasn't convinced. It turned out, once we knew the truth, that the reason Breker was convinced is that when you eliminate all the platelets in an experimental animal they bleed into the soft tissue and the red blood cells are picked up in the thoracic duct lymph and poured back into the blood. So there is no visible hemorrhage when an animal is depleted of platelets. But in humans, we are—all our vessels are on the surface. We don't have animal skin. So it was clear that when we learned to cannulate the thoracic duct, we were able to show that in the dog, in all the species, the rats, rabbits, the same physiology occurred, when the platelet counts, there's a direct relationship the platelet counts and the amount of blood in the lymph.

**THOMAS COLE, PHD**

So once you got the bleeding stopped tell the story of the blood separator.

**EMIL J. FREIREICH, MD**

Well, once the blood bleeding was stopped, the leading cause of death was now infection. And we had antibiotics, but a limited spectrum of antibiotics, and the children all died of infection when their counts were low. So we, Dr.—one of my good friends and I were in the backyard—and we said, "You know what we need to do? We need to transfuse white cells." So we did the same kind of a study that we did with the platelets that we looked at the charts, we compared the level of neutrophils to the occurrence of hemorrhage, and again, a citation classic, there was a direct relationship between the number of neutrophils—we all know that now—

**THOMAS COLE, PHD**

Tell the rest of us who don't know neutrophils what they are.
EMIL J. FREIREICH, MD
Polymorphonuclear leukocytes.

THOMAS COLE, PHD
Tell us what leukocytes are. White cells. You all got that? Okay.

EMIL J. FREIREICH, MD
They're leukocytes. And so when we showed that the level was directly related to the occurrence of infection. We wanted to repeat the platelet scenario. So we had to collect white cells. Problem. I spent a year trying to figure out how to collect white cells. And the reason that they're hard to collect is that in a centrifuge the plasma is in the supernate. If you centrifuge at a low centrifugal force, the platelets remain in the plasma. So we can collect 80 percent of the platelets by separating plasma from the rest of the blood. But the leukocytes are trapped in the trapped red cell layer. So the buffy coat is devoid of white cells. So you've got to get some way to get the white cells out of the red cells. And I scoured the literature, and I discovered a good friend of mine who had used hydroxyethylated starch for treating shock to expand plasma volume. And it turns out that any macro molecule will make red cells rouleaux. Everybody knows what rouleaux is.

THOMAS COLE, PHD
Well, I don't think so.

EMIL J. FREIREICH, MD
Rouleaux is what you do when you're gambling when you stack up your coins. Red cells will stack up in layers.

THOMAS COLE, PHD
I didn't know you played poker? [laughter]

EMIL J. FREIREICH, MD
I've seen it. [laughter] So we added fibrinogen, and it worked beautifully. But fibrinogen carries viruses and so on, and it's not a suitable thing. We discovered hydroxyethylated starch. It worked as well as fibrinogen, We got all the clearances, in those days. You couldn't do it today, but since it had been given to man as a volume expander, we added hydroxyethylated starch to the incoming blood and separated the white cells into the buffy coat. And the next problem was how to collect supernate, precipitate, and buffy coat.
THOMAS COLE, PHD
Explain those three terms for those of us who don't quite get it. Supernate?

EMIL J. FREIREICH, MD
Supernate, just the top. Precipitate on the bottom. Buffy coat's in the middle. So is started working with pumps from the Heart Institute and tubing and plastic bottles and I was building a centrifuge. And one day, a young engineer from IBM appeared in my office. He said, "My name is George Dodson." His son had developed leukemia, And he came to the clinical center. And his doctor was Jerry Block, one of my colleagues. And he said to Jerry Block, "Is there anything I can do as an engineer to help my son?" Jerry block said, "There's a crazy guy on the twelfth floor who's trying to build a centrifuge. Go see him." So he appeared in my office, so I explained what I wanted to do. I wrote down the ten things I wanted the instrument to do, you know, not damage the red cells, collect the platelets, so on and so on. And he took those ten things and he went away. And I thought that's be the last I'd see of George. But what he did is he got sabbatical leave from IBM to spend his full time on this project. And in about three months, he came back with a contraption. Twelve pieces, you know, this, this, this. He said, "I think we got it." And he set it up in my lab. And we ran blood from the blood bank, which was not transfusable. And by golly, the thing had promise. We had to solve a number of problems of course. So in order to do that, we needed money. We applied for a contract at the Cancer Institute, and it was approved. So the instrument was developed with funds from the Cancer Institute, not IBM. So the consequence is that even though I invented the machine, there's no copyright. It's in the public domain. So I didn't make any money, but that was okay.

THOMAS COLE, PHD
This is very unlike contemporary commercial interests in experiments in biotech.

EMIL J. FREIREICH, MD
Yes. It's different now. So we went to work, and the main problem we had to overcome was the connection between the rotating drum, which is the centrifuge, and the stable part, which collects stuff. And we discovered that Oakridge had used what's called face shields to connect rotating separated parts. And a face shield is a collection device, which is flatter than one wavelength of light so no cell could cross the border. And we use these face shields—it's a long story. But anyhow, we subsequently found that we didn't have to be so technical. You could use the jump rope principle. You know, if you jump rope, one guy holds it and the other guy twirls. And that actually works in the blood cell separator now. There's three jump ropes that collect supernate, precipitate, and buffy coat. And we had to work out how to visualize the buffy coat. We did it with a strobe light manually, but now it's all automated. We have an
instrument, which any technician can operate. You plug in vein to vein, hydroxyethylated starch, the plasma in one thing, red cells another thing, the buffy coat in the third thing. And you can do whatever you want. And the important thing is that one of my associates, Ken McCready, discovered that hematopoietic stem cells are circulating in the blood—another citation classic—and we then looked for where the stem cells were in the blood cell separator, and they were in the buffy coat. So we could do allergen—we did the first allotransplants and autotransplants using peripheral blood instead of bone. The way bone marrow was collected is you had to do multiple punctures along the hip. You had to go in the hospital. You had to get a blood transfusion because you lost a ton of blood. But now blood donation, you get stem cells, and you do an allogeneic (per EF) transplant.

THOMAS COLE, PHD
So let me just interrupt again here. So after you got the blood separator, what was the clinical importance of this, and how did it help you move on to the next stage of what you were doing?

EMIL J. FREIREICH, MD
Well, the blood cell separator can do everything, stem cells for allotransplant, red cell exchange for treating sickle cell anemia. It's used to deplete patients with hyperleukocytosis who are susceptible to having cerebral hemorrhage. You can deplete platelet in excess for patients who have thrombocythemia and so on.

THOMAS COLE, PHD
What did it do for your children?

EMIL J. FREIREICH, MD
It did exactly like the platelets. We discovered that there was a dose response. We knew how many platelets, limits of donation worked out in volunteer donors. We got as many—we found that one donor could donate white cells every other day because the granulocytes have a half life of six hours in the circulation. There's an enormous granulocyte reserve in the bone marrow. So we give them a mobilizing agent to get them out of the bone marrow so we get their counts up to 10,000 to 12,000. We take out all their white cells. We give them to the children. And hemorrhage and infection was controlled not as effectively as the platelets and hemorrhage because there were organisms that are not as susceptible like fungal infection and some of the gram negative organisms, but to a large extent, infection was controlled.

THOMAS COLE, PHD
Okay, so let me stop again. So if I understand you, first you stopped hemorrhaging. Then you stopped the infection that they started dying from. And then—?
EMIL J. FREIREICH, MD
Now, we could start the chemotherapy experiments because the children could resist the major side effects of the chemotherapy. So then we went from two drug combinations to three drug combinations to four drug combinations. And the fourth drug was the amazing drug Vincristine, which is still used today. Vincristine, amethopterin, mercaptopurine, prednisone were the four drugs. And we put them together because they had different dose-limiting toxicities. Methotrexate and 6MP are IM suppressive Two-thirds of a dose of these two, full dose of prednisone, full dose of Vincristine, the results were miraculous. Of the first twenty or so children, ninety percent went into remission in two weeks. So a child came in bleeding to death, with infection, ready to die. We give them VAMP. In ten days, they were normal.

THOMAS COLE, PHD
Many people objected to treating dying children.

EMIL J. FREIREICH, MD
Oh yeah.

THOMAS COLE, PHD
They thought you were just prolonging their agony. What did you say to that?

EMIL J. FREIREICH, MD
Well, I said what my wife says. Every day's a different time. You may prolong the agony, but the parents are very grateful. And the kids are happy. We had a colleague, Myron Caron, who was a pediatrician. And he used to sit and interview the children to see what they thought about it. And they didn't think they were being tortured. They were happy, playing. A four-year-old's major concern when he's dying of leukemia is don't tell my mother I'm sick. They're major concern is how their parents react. But they were sure happy to be cured. And by the time we had followed them for about three years, well, we learned several things about how to do this. We got them into remission. They all relapse. Then we had to intensify the treatment while they were in remission; then we had to do intermittent reinduction. And finally, we published in 1964 a paper that claimed that we had cured childhood leukemia, which proved to be true. And of the thirty children that we treated on those early studies, something like fifteen of them are still alive. They appeared on the cover of Cancer Research when they had an anniversary issue. And I still hear from them.

THOMAS COLE, PHD
Amazing.
EMIL J. FREIREICH, MD
So that's the reason I came to MD Anderson. Dr. Clark said, "You've got to come here and cure childhood leukemia." I said, "Great." And then I met Sutow and Sullivan. And they said, "This is too toxic!" Pat Sullivan, she was a pediatrician, staff, and the cooperative group, Don Fernbach, and the group at the Children's Hospital. Too toxic. They wouldn't do it. So I became an adult doctor. I tried to apply the same principles to adult leukemia. And of course we've succeeded. Now, adult leukemia's much more complicated than childhood leukemia. These are partially differentiated cells. They have very complex mutations, so their genetic background is much less homogeneous. But in the fifty years I've been here, we've seen a disease which is 100 percent lethal become—let's see—about thirty percent of the patients are literally cured. The other 70 percent have very substantial palliation amounting to almost to cure. We have palliating therapy for all kinds of leukemia. The ones who have complex cytogenetics with advanced disease are still a problem for us. But in the chronic leukemias, CML, Gordon Guterman, Evan Hersh, discovered interferon. Interferon suppressed the Philadelphia chromosome, which is a marker of CML, that Dave—what's his name in Portland—the idea of small molecule inhibiting the binding site of BCR–ABL, which is kinase. And if you inhibit the binding site, it's paralyzed, and the patients go into complete remission.

THOMAS COLE, PHD
Okay.

EMIL J. FREIREICH, MD
Magically.

THOMAS COLE, PHD
I think you may have lost two-thirds of us there, but let's go back to coming to Houston. How did Dr. Clark get you all the way to Houston? Houston was not very much of a significant city. It had no serious medical center. He must have done something.

EMIL J. FREIREICH, MD
No and MD Anderson was a dig place. I don't remember the number of beds. It was about eighty-five.

THOMAS COLE, PHD
What year?

EMIL J. FREIREICH, MD
Sixty-five. I've been there fifty years. And the Texas Medical Center was—thank goodness for Mike
DeBakey. They brought Baylor—you know, the Texas Medical Center purchased Baylor Medical Center School, brought it here so we had an academic center. A lot of our beginnings were collaborations with Baylor, the Children's Hospital. But we came—I give a little talk about Dr. Clark; he was a remarkable person because he recognized that Houston had all the ingredients to be a boom town. It was located upstream of Galveston where the major medical school was. No hurricanes. It was located on the ship channel, which had been built. And he saw the petrol chemical industry booming and becoming a major industry. And he realized Houston would become a major port, major center of commerce. He predicted it would become a large city in Texas and one of the biggest cities in the country. So when I arrived, they put me up in a motel. It was pretty decent.

**THOMAS COLE, PHD**
Well, let's go back to the story of how he got you here. He drove all the way to your house in Maryland.

**EMIL J. FREIREICH, MD**
He came to Bethesda on an airplane. He was rich. He actually found my home and came to my house, and ate dinner with my wife and my children—they were ages five to eleven—and convinced my wife [laughter] that we had to go to Boston; we had to go to Bethesda. He was a remarkable person.

**THOMAS COLE, PHD**
You had to go to Houston.

**EMIL J. FREIREICH, MD**
Houston, had to go to Texas. My wife, when she heard the news, she ran out and bought nylons; she thought we'd see Indians in 1965. It was a dink town in 1965.

**THOMAS COLE, PHD**
What were nylons going to do to protect her?

**EMIL J. FREIREICH, MD**
She could look good in her stockings. She thought they didn't have them yet in Texas.

**THOMAS COLE, PHD**
Well, okay.

**EMIL J. FREIREICH, MD**
You know, in 1965, Texas was a very small state just about to boom. But everything Dr. Clark predicted came true. He predicted MD Anderson would have no limits. Cancer was the number one problem. He
had all the ingredients. He only needed a medical school. And if we came and brought NIH, investigative medicine, that MD Anderson would boom. And it did.

THOMAS COLE, PHD
And you were a key part in the booming of MD Anderson. Tell us a little bit more about what he gave you and how you helped grow MD Anderson.

THOMAS COLE, PHD
Well, Clark was politically very important. And we had come from the Cancer Institute. And in the sixties, when everybody realized the importance of full-time clinical research, all the academic medical centers wanted NIHs. At that time, there was only Boston University had a clinical center, Rockefeller, very few academic medical centers had full-time clinical research centers. But— excuse me—I think I'm talking too much.

THOMAS COLE, PHD
No, not yet. We'll take questions in a few minutes. Most of us could listen a lot longer.

EMIL J. FREIREICH, MD
So—we utilized Clark's political influence and our experience at the clinical center to start applying for grants. The grant program started in the early sixties. So we had served on study sections, so we knew how it worked. So we applied to grants. We got a clinical center grant which allowed us to fund several projects. And we got a training grant, the first training grant in Texas. And the training grant allowed us to recruit young physician scientists and cover their salaries and their expenses so they had no service requirements. They simply could do their research. They could do academic things, take courses at the university and so on and so forth. And the consequence of that was that we had a Freireich Day on the twenty-third of October.

THOMAS COLE, PHD
Honoring you? Honoring you?

EMIL J. FREIREICH, MD
Yeah; and we had ten of our alumni from the seventies came back. These people were giants. They were people who cured lymphoma and leukemia and cancers of all organs, testes, breast cancer, colon cancer. They gave talks. We recruited men who were motivated like the clinical center. And they came, and they had enough salaried people like Michael Keating who cured chronic lymphocytic leukemia, Ken McCready who found the stem cells, Cabanillas who cured large cell lymphoma, Dr. Hortobagyi who made a tremendous advance in breast cancer, so on and so forth. So these young men were highly
motivated. They came because we had a training grant. We gave them a time and the freedom and the resources. And the consequence of that was our practices grew. And the patient income grew. And the hospital grew.

**THOMAS COLE, PHD**

Let me say one thing that should be obvious, but you must have been one hell of a mentor to attract so many people who went on to be so good.

**EMIL J. FREIREICH, MD**

I am so honored in my old age. Just last month I received the lifetime mentorship award at MD Anderson. There's only been one. There will be others. Mentoring is my skill. And I've spent the last ten years of my career, full-time, 70 percent of my time, in education. I teach in the graduate school. I've been a full member of the graduate school from day one; I've been a full professor from day one. And I love to teach. And my students are all smarter than I am. They all do more than I do. They accomplish more than I do. I get credit for them, but they're—we've got a tremendous group of people, Evan Hirsch, Jerry Bowdy.

**THOMAS COLE, PHD**

I want to get into a topic that I know you have very strong feelings about. And we may need to—I may need to cut you off before we go too far so we'll have time for questions. But we talked about this yesterday. If you tried to do these—

**EMIL J. FREIREICH, MD**

Impossible.

**THOMAS COLE, PHD**

Yes. These experiments today, why would they not be possible?

**EMIL J. FREIREICH, MD**

Well because the federal government. [laughter] You know what the definition of a liberal is? Liberals know best what's good for you than you do. They're always making rules. The federal government regulates all aspects of medicine, in particular, investigative medicine. The FDA—if you go to Washington, you look for the FDA, they have a bigger building and more employees than MD Anderson. I mean, they've got thousands of people whose job it is to interfere with research. That's their job. You hire a guy to the FDA. He's smart. He's capable. He's well educated. And you say here's your job. Freireich wants to give patients four drugs. What do you think? So he looks at it. He says great idea. But
if I approve this and somebody in Keokuk, West Virginia, dies that's my ass in a sling. I'm not going to approve it. If I approve it and it cures everybody, I don't get any credit.

**THOMAS COLE, PHD**
But what about local IRBs? What about the experimentation that still goes on?

**EMIL J. FREIREICH, MD**
The IRBs are a derivative of the FDA.

**THOMAS COLE, PHD**
But you do plenty of research at MD Anderson?

**EMIL J. FREIREICH, MD**
We do a lot of research, but it takes— I did a white cell protocol about three years ago. It took, on average for our IRB to approve a protocol on average, fourteen months. By that time, the problem's solved. But once you get through the IRB, if you're doing anything to patients, you've got the FDA to contend with. Even when IRBs approve it and you have preliminary results, the FDA—shall I tell you the anecdote that I told you?

**THOMAS COLE, PHD**
I don't think I could stop you. [laughter]

**EMIL J. FREIREICH, MD**
Well, does anyone know who George Hitchings was? George Hitchings was a biochemical pharmacologist who worked for—it will come to me in a moment—pharmaceutical industry, Burroughs-Wellcome. And he won a Nobel prize for devising antimetabolites which interferes with purine and pyrimidine metabolism. So the whole genetic, the whole basis of genetics was worked out by having specific antimetabolites that interfere with each step in the biosynthesis of the macro molecules, DNA, RNA proteins and so on. So Hitchings got a Nobel prize.

His collaborator, Roseworth Ellison—Gertrude Elion—Hitchings and Elion devised the drugs that cure viral infection that are used everywhere in the world. They synthesized 6-MP and many azathioprine. A giant in research. And he was a good friend of mine. We all respected him. He was our mentor so to speak. And I was sitting at a lunch table one day, and I happened to be sitting next to him. And I said, "How are things going at Burroughs-Wellcome."

He said, "Well, I'll tell you an anecdote. I think we will have no new drugs in the future ever."
I said, "Why do you say that?"

He said, "Well, we discovered "in our labs that if you combine an aniline with sulfonamides in a fixed ratio that it's the most powerful antibacterial agent we know of. But the ratio has to be right. If you have too much aniline or too much sulf—it doesn't work. So we went to the FDA and said we want to market this drug in a fixed ratio in a single pill. The FDA laughed. No way." So they went back to the lab and they did thousands of experiments. And he said this actually happened.

They loaded all the data into a truck, into a van, and they went to the FDA. And they said, "Where do you want this data?" The guy said, "Put it over there." They took these trolleys, and they piled up a half a room full of the documents. And the guy, the FDA official, said, "It's a shame you went to all this trouble. We're not going to approve it." And they didn't.

So the way it got approved was by sheer brute force. Burroughs-Wellcome had enough resources and enough money to do it. The drug is Bactrim, which we all take every day today. Within a month of its approval, it was the bestselling antibiotic in the world. And Burroughs-Wellcome became rich on it. And it's true. We face this obstacle. It's so insane. We have a protocol for patients who we know for sure have less than six weeks to live. And the patients are begging us to do something. And they have ten brilliant ideas of which we pick the best one. It takes a year for the FDA to approve it if they do. And if you take what we did in one year, it would have taken us ten years—I would have been in Houston before we cured childhood leukemia, but in those days we had an external advisory committee to be sure weren't experimenting on people. It was a new thing. And Max Winfield was on it, and he came around and said, "This is terrible. You shouldn't be doing this."

We did bone marrows to quantitate the effect on them. He said, "You shouldn't do bone marrows. To painful. Just count the blood." So our advisors were very negative. But our leadership was very positive, Dr. Zubrod, all the Cancer Institute leadership. They wanted to make progress. They had to make progress to justify their budgets. They had to go to congress every year and say, "Here's what we're doing." So we were able to move, but today we have—-we have drugs that can prolong—a patient with chronic granulocytic leukemia had an expected life span of about three years. and 100 percent mortality by ten years. Today, at ten years 90 percent are not only alive, they're free of disease. And all they do is take a pill every day. A pill. Not a shot. Nothing.

THOMAS COLE, PHD
Can I interrupt you there?
EMIL J. FREIREICH, MD
Well, the amazing thing is that that took so long to do. You had no idea what we had to go through to get Gleevec approved a randomized, double-blind study where patients who had the disease had to be randomized to getting nothing. That's human experimentation at the worst. If I were a patient, I would never agree to that. We knew Gleevec worked. It worked in tissue culture. It worked in animals. It worked in transplant. Gosh. Crazy.

THOMAS COLE, PHD
So there are many ethical issues and strong opinions about clinical research today and the limits of IRBs and the limits of the FDA process. I wish we had time to talk about your childhood. It was very rough and tumble childhood in Chicago. I think it might have given him some of the toughness that he needed as he made his way through the ranks.

EMIL J. FREIREICH, MD
You know, Malcolm Gladwell wrote this book. I forgot what the title was, but his thesis was that disadvantages are advantages because if you're crippled or blind or whatever your problems is you get resources that you would not normally use. And growing up in a bad environment going to a dink high school that was like Kotter on TV, there was no teaching, there were no professors, that was a big disadvantage. But in order to overcome it, I wanted to be a doctor. It took—when I tell all young students, all you have to do is know what you want to do and be persistent.

THOMAS COLE, PHD
In Yiddish, we call this chutzpah. So how about some questions before we have to break?

FEMALE SPEAKER
Did you ever go back to pediatrics?

EMIL J. FREIREICH, MD
Could you repeat it?

MALE SPEAKER
Did you ever go back to pediatrics?

EMIL J. FREIREICH, MD
Go back to what?
MALE SPEAKER
Pediatrics.

EMIL J. FREIREICH, MD
No. The pediatricians in the group voted that you had to have boards in pediatrics. I applied to the pediatric board. I said, "I'm the only one who's cured childhood leukemia." They said, "Well, if you do a year of residency, we'll approve you." [laughter] So I worked on that also. But the pediatricians have done very well. Once the door was opened, I mean, all the principles were there. We knew early intensification, intermittent reinduction. You had to treat them for a year. Now we treat them for two years, intermittent reinduction, and the answer's in. And cure rate's 92 percent.

FEMALE SPEAKER
[unintelligible]—schedule, you were just starting some new combination therapy.

THOMAS COLE, PHD
How did you determine sequence and schedule when you were just starting to do the experimentation?

EMIL J. FREIREICH, MD
That's a very good question. When you're doing chemotherapy, the first thing you want to know is something about the pharmacology. When I came to Texas, the first person we recruited was Ti Li Loo, the head of pharmacology department. You want to know where the drug is absorbed, where it's excreted, and so on. If you know it's metabolism, then the second thing you know is the maximum tolerated dose. You know, we did a study, which is a citation class another citation class. I have a hundred citation classes. But this one, what we did was we took animal data from Skipper and Schabel at Southern Research and clinical data, and we made a model for predicting where you should start treatment. And of course the principle is that if you use the animal's surface area and the human surface area, you can find the common ground. And we came up with the slogan of two-thirds of the maximum tolerated dose in the most sensitive species.

It's used all over the world. It has been for the last twenty-five years because it's safe. We showed that if you get 10 percent of the MTD in the most sensitive species, you could increase the dose 100 percent and never reach an LD10. So the way you start, get the MTD, show the MTD, give it to patients. If there's no toxicity, you double the dose. There's are things—there are escalation schemes that two-thirds of the 7nth of the fifteenth. It's all a bunch of bologna. You're wasting your time. And you're wasting the patient's time. To get an effective dose you have to be aggressive in phase one. And we systematically do that. We
start with a dose, 100 percent increments. When you get any side effects, then you go in small increments. You work out the pharmacology. Is that responsive?

**THOMAS COLE, PHD** Well as you can see, this is a person who transformed medicine in the twentieth century, and it's an honor to have you with us. Please give a round of applause to Dr. Freireich. [applause]