Ad Bax
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by David Zierler
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DAVID ZIERLER: This is David Zierler, oral historian for the American Institute of Physics. It is March 16th, 2020. It is my great pleasure to be here at NIH with Dr. Ad Bax. Dr. Bax, would you please state for us your title and your affiliation here at NIH?

DR. AD BAX: I'm a section chief here in the Laboratory of Chemical Physics. The section officially is called Biophysical NMR Spectroscopy.

ZIERLER: All right. So we are going to start, as we said, as a life history, right at the beginning. And this is a unique opportunity. I've never had an up close and personal opportunity to learn about childhood in the Netherlands. So tell us about your birthplace, tell us about your family, tell us about where you grew up.

BAX: I was born in a family of six children on a farm in the southwestern part of the Netherlands.

ZIERLER: What year?

BAX: 1956. Close to the Belgian border. A rather impoverished part of the country, south of the river. Mostly Catholic, but my parents were Protestant. Very religious. But on a farm, you sort of grow up rather independently, and with six children, we could basically do whatever we wanted.

ZIERLER: What kind of farm was it?

BAX: It started out as a horse farm. That's the way my father inherited the farm. Which was a problem, because horses got out of vogue in the early '60s, late '50s, when the tractor made its inways. So he inherited a fortune in worthless horses.

ZIERLER: [laugh]

BAX: [laugh] And over his time, he had to switch to agriculture—potato farming, sugar beets, corn, what have you. Flower bulbs.

ZIERLER: Were your parents born in that area?

BAX: Both from the southwestern part, yeah. He was born on the farm. It was at least five generations that the farm was in the family, as far as being able to track it back.

ZIERLER: What was his education? How far did he go?

BAX: He just had basic local education.

ZIERLER: High school?

BAX: Yeah, whatever was the equivalent of a high school degree. He was actually quite intelligent, I think. He was a locally competitive chess player. He taught himself Latin. Was proud of that. He never wanted to be a farmer, but he inherited the farm, so he had no choice.

ZIERLER: And your mom, what was her background?

BAX: She was born also in a farmer's family, on one of the little islands. And so the whole family was into farming. She was not really keen on science, but supportive—my father was interested in science, in exact things like chess, theory, chemistry, math, but never had a

chance. My mom really never was interested in that. She had enough to deal with, with six children, and keeping us all alive, and fed.

ZIERLER: And what were your parents' experiences during the war? Not affected too much?

BAX: I mean, they were barely born, right? They were born in the late '20s. So relatively isolated on the island. Particularly my mom, was minimally impacted. My dad was much more affected, because he was in the part of the Netherlands that got liberated in 1944, and there was some pretty heavy fighting. Plus, on the farm, during the war, they played sort of a role in smuggling people out of the country. So hard to tell in retrospect how much of that was just stories passed on, but there were hiding places on the farm that as kids we played in, and we knew that they were constructed for this purpose, like a false roof in the closet, false hidden closet with an invisible doorunder the staircase where you could sort of hide as a kid\.

ZIERLER: Who were they hiding?

BAX: People that were moving down to France, to Spain, that came from the northern part. So presumably Jewish population that was trying to escape. I don't know how risky, how dangerous it was, but apparently my grandpa played a role in some of this, and got decorated for this after the war, some time in the '50s , with the Dutch queen, Wilhelmina, visiting the farm.

ZIERLER: And what language was spoken at home? Dutch?

BAX: Just Dutch, yes.

ZIERLER: No Belgian? No French?

BAX: No, no French. But the Dutch accent is very strong in the southern part. The Flemish accent, I should say.

ZIERLER: So I'm hearing a Flemish accent right now?

BAX: Somewhat, yes, and I've never really lost that. The soft "g", for example. I went to high school north of the river, and I grew up south of the river. So when I tried to speak High Dutch, in high school, people would look at me like, "Where is this guy coming from?" They wouldn't understand it, even, because my dialect was so different. That has dissipated over the last 40 years, I'd say, with more bridges across the river, and a lot more traveling and mixing of the population.

ZIERLER: And High Dutch means like what they speak in Amsterdam? Is that the idea?

BAX: Well, not really, that's an Amsterdam dialect. [laugh]

ZIERLER: [laugh]

BAX: Like the newscast on TV, I'd say, would be High Dutch.

ZIERLER: So where were you in the six children? What order were you in?

BAX: I was number three.

ZIERLER: Right in the middle.

BAX: Right. A good place to hide.

ZIERLER: Brothers and sisters?

BAX: Yes, I had an elder brother, and an elder sister. They both passed away of cancer about 20 years ago. Lung cancer. My older sister originally became a dietician. That's what my dad wanted her to do. But then later, she got a law degree and ran her own law practice for about a dozen years in Amsterdam. My brother, very bright guy, but had a severe case of ADHD, I think, and never really got a chance to study.

ZIERLER: Undiagnosed, too, probably?

BAX: Undiagnosed. It was before it was being recognized as a disorder. Very good athlete, but he didn't want to follow the religious rules that were rather stringent in the family, and he sort of took off on his own at the age of 14.

ZIERLER: And your younger siblings?

BAX: Younger siblings were kept on the straight and narrow church path.

ZIERLER: And which church was this?

BAX: This was and still is a Dutch Protestant Reformed Article 31. It sort of like splits up in many different denominations, and this is one of the splinter groups that take themselves very seriously, have their own schools. And I was the last one to not go to such a school, after my parents saw that I wasn't going to stick with the church.

ZIERLER: Because you weren't conforming so well?

BAX: No, no, and I sort of went to university at an early age, at 16.

ZIERLER: Now, did you develop an interest in science as a child? Did you naturally gravitate towards biology and chemistry?

BAX: Not to biology. I did gravitate to chemistry and physics. I loved physics, especially in high school. Chemistry was sort of a natural thing on the farm. Making bombs with my brother behind the barn.

ZIERLER: [laugh]

BAX: I was one of the natural experimentalists [laugh]. I'm lucky I still have ten fingers, ten toes.

ZIERLER: [laugh]

BAX: And both eyes are still intact.

ZIERLER: You had nitroglycerin? What were you working with?

BAX: Fertilizer, gasoline.

ZIERLER: Oh, fertilizer. OK. [laugh]

BAX: Hydrogen gas. Like that kind of stuff.

ZIERLER: And there was no internet back then to follow a recipe, either. You just have to figure it out.

BAX: Exactly, this was just totally empirical.

ZIERLER: [laugh]

BAX: And the idea was bigger is better. But we had a couple of close escapes.

ZIERLER: So in high school, you already knew that you had a talent for the sciences.

BAX: Yes, I was considered a little brainiac. In elementary school, I skipped a grade because apparently I was bored out of my mind, and my parents took the initiative to have me skip a class. But as a consequence, I was a year younger than all the other kids. And growing up on a farm makes you socially less developed, I think, because you grow up more in isolation, just with my brother and my other siblings. So going to high school, it's sort of like I was two years younger than my classmates, effectively. So that first couple of years was kinda rough, I think, in retrospect. But I loved science. After I figured out how to communicate, I did very well at it.

ZIERLER: And then what were circumstances leading you to Delft? Am I saying it correctly?

BAX: Correct, right.

ZIERLER: So was that the one place you applied to? You knew you wanted to go there? Or you applied many places?

BAX: No, Delft was known as the top physics place, and I loved physics. My physics teacher in high school stimulated it. And it was sort of a natural choice.

ZIERLER: So is it kind of like an MIT? Sort of an elite school focused on technology?

BAX: Well, the educational system in the Netherlands is a little bit different from here, so you don't really have elite schools like in this country. But it was a very reputable university with a long history that was sort of presumed to be the best in the applied physical sciences.

ZIERLER: Were you getting a classical degree as well there? Were you learning classics, literature?

BAX: No, no.

ZIERLER: So it was all sciences?

BAX: It's all science, yes.

ZIERLER: You regret that?

BAX: After high school, I dropped all my non-science classes and never had much of a taste for that.

ZIERLER: Do you regret not having that exposure, or you were happy to be that focused really on science?

BAX: I don't regret it. Some people especially in the physics community I think, they're keen on music or on some other alternate interest. For me, the alternate interest has always been sports. I didn't have time to deal with arts or music. Mostly focused on sports as an alternate.

ZIERLER: Do you have a close mentor that you're working with as an undergraduate at Delft? When you go in, are you just taking classes from professor to professor, or are you working from the beginning with a mentor in a lab?

BAX: The first four years, three and a half years, you're basically anonymous. Then you select a group. [break] When I found nuclear magnetic resonance, really a main motivation there was that I had just taken a course in quantum mechanics, and you could actually apply the things that you learned in quantum mechanics, second order perturbation theory, directly to a physical phenomenon. So the fact that you could actually do something with that elegant theory.

ZIERLER: This was satisfying to you.

BAX: This was very satisfying, yes.

ZIERLER: At this early stage, were you already motivated by the idea that your research could advance human health, or were you more sort of theoretically based and not so applied at this point?

BAX: Totally theoretically based, and zero even inkling that this might have applications in biology or biochemistry. Interesting—the group that I was working in, half of it was focused on developing MRI, and the other half was more on spectroscopy, tunneling methyl groups, understanding relaxation, and things like that. And even while I realized that imaging was potentially feasible, I thought it was going to be technologically so hard that we weren't going to be able to do it. And in retrospect, of course, this was a serious lack of vision. The reason why I think I was half correct is that the technological hurdles were enormous at the time—self-shielded gradients, all the kind of things that one would need to do this. And I realized that, yes, if you had the heart for it, you could do it, but it would be very hard to develop it. What I didn't realize was that there was so much money behind imaging technology. And with enough money, if a problem is not a fundamental problem and there is enough interest in developing it, people will develop it.

ZIERLER: How do you define a fundamental problem?

BAX: Imaging, for example. If the signal to noise—you can calculate it, and we had calculated that. There was certainly no fundamental barrier there in doing imaging in a reasonable amount of time, because the amount of NMR signal that you can get in a magnet, at the time we were thinking about a quarter tesla, maybe a half tesla, would be enough to get a good image in a matter of minutes. But the technological problem was to suppress eddy currents, related tothe gradient recovery times, to obtain sufficient field homogeneity, to achieve

radiofrequency penetration, things like this—those were technological problems that at the time I felt were not going to be solved for a long time to come. And I was wrong, because obviously the medical world had so much interest that they coughed up the money, billions of dollars, to develop that technology in like less than ten years.

ZIERLER: Now, were you aware at this time that there was such a field called biophysics, or was this a new concept to you?

BAX: There was barely anything that is now known as biophysics. It was chemistry, it was biochemistry, and that's sort of where it stopped. Biophysics was mostly patch clamp kind of experiments, very far removed from NMR spectroscopy.

ZIERLER: So you didn't see your developing interests as gravitating towards biology at this point. It was still in a purely physics department framework.

BAX: Absolutely. Zero knowledge or interest in anything biological until my postdoctoral work.

ZIERLER: Now, you finished your undergraduate in three years—'78 to '81?

BAX: No, '72 through '78. Took five years.

ZIERLER: Oh, it was a five-year program.

BAX: Well, it's a four-year program that has an extra year. Well, hang on. Let me correct this. I started in '72, and I finished in '78, my undergrad, including an extra year for what here might be considered a masters thesis.

ZIERLER: OK, it was '78. Right.

BAX: So it's a six-year—it was a five-year program. It took me six years, in part because I switched groups, and in part because I was the president of the Delft university rowing club, Proteus.

ZIERLER: That took up a lot of time?

BAX: That took a fair bit of time. And trying to compete actively took a lot of time. We were practicing twice a day. I was racing bikes at the same time to make a living. So I mean, six years was nothing out of the ordinary. It was good. It was about average, I'd say. And then I worked on my PhD from '78 to late '81.

ZIERLER: Now, you were at Oxford during this time as well.

BAX: Correct.

ZIERLER: Did you shuttle back and forth, or you were exclusively at Oxford from '78 to '81?

BAX: I shuttled back and forth, but spent I'd say 80% of my last two and a half years at Oxford University.

ZIERLER: What was the connection to Oxford? How did you get involved there?

BAX: It started out with my undergrad work, where we developed a novel instrument that was far ahead of its time, really by at least a dozen years. An NMR spectrometer, designed by my advisor, direct advisor, who was a staff scientist there.

ZIERLER: What was this person's name?

BAX: Toon Mehlkopf. Later became professor. Brilliant guy. Engineering expert. Very foresighted. And he saw basically in the ‘60s that NMR equipment was far deficient from what would be needed to enable the kind of versatile experiments that people were proposing but unable to do.

ZIERLER: So in the ‘60s, the theory outpaced the technology.

BAX: Absolutely. Yes, very much so.

ZIERLER: And so what was needed? What technological breakthroughs were needed so that the technology could keep pace with the theory?

BAX: In NMR spectroscopy, there’s something that’s now known as pulse sequences, applying more than two pulses. It started out, of course, in the physics community, and there the effect of spin echoes was discovered in the ‘50s by physicists. In the ‘60s, people in the chemistry community started putting those experiments to use for studying chemical compounds, measuring J-couplings and things like that. My PhD mentor at Oxford University, Ray Freeman, was one of the guys spearheading that work. But the commercial equipment was basically very difficult to use for that purpose. It didn't have any flexibility to program those kind of experiments. My advisor, Toon Mehlkopf, realized that one really has to design an instrument with those experiments not as an afterthought, but design it so that you can do any experiment you want. And as an undergrad, I was involved in helping him develop the software for it.

ZIERLER: Now did you see, in your department and at your university, were you operating in a provincial world? In other words, was your physics world mostly Dutch? Or were you

connected internationally, and you were aware and keeping pace with developments that were happening with physicists across the world?

BAX: I should say as a student, just living on your little island. You're blissfully unaware.

ZIERLER: What about your advisor? Was he collaborating internationally?

BAX: Yes, let me get to that. It sort of started out with building this instrument. Once it had been built, we did some experiments that caught the eye of the leaders in the field—Richard Ernst, who later got the Nobel Prize; Ray Freeman—who were sort of like friendly nemeses of one another—

ZIERLER: [laugh]

BAX: —both absolutely brilliant guys. And Ray Freeman invited my advisor, Mehlkopf to spend a year in his group, hoping to take over and pick up some of the technology. And Mehlkopf already was established with a family and said, “Hey, I really can’t do this, but I've got this student who might be interested.” So that’s how I got invited to spend three months at Oxford University.

ZIERLER: Now, how was your English at this point? Did you take English in high school?

BAX: Yeah. We take a lot of English, both high school but start already in elementary school. So that’s not that difficult. Of course, a very strong Dutch accent, which I never lost. [laugh]

ZIERLER: [laugh] So tell me about your experience at Oxford when you got there. Was this your first experience traveling abroad, so to speak?

BAX: Pretty much. I mean, I had spent a lot of time vacationing, of course, all over Europe, but the first time I spent an extended period away from home, outside of the Netherlands.

ZIERLER: Besides the language, culturally was Oxford a very different experience for you?

BAX: Oh, this was a very pleasant experience.

ZIERLER: Oh yeah?

BAX: Absolutely. Yes. It's the best time of my life, looking back.

ZIERLER: Really!

BAX: Yes, definitely. I mean, in the Netherlands, the system is what you might call more German-like. You have—

ZIERLER: Rigid.

BAX: —somebody who tells you what to do, and there was the big professor, Jaap Smidt. He was the big boss, and we didn't get along that well. And you're being controlled, basically, to do this, that, and whatever. Oxford was the exact opposite. I could do whatever I felt like. I could come in and leave whenever I felt like. There were very bright students in the group at the same time, overlapping with me, many of them now professors. So we had enormously lengthy discussions. Our coffee, tea times, ran over. Invariably, we got kicked out of the coffee room basically ten times a week, every day, [laugh] morning and afternoon.

ZIERLER: Now your fellow graduate students was fairly international, people from all over the world, or mostly British students?

BAX: Mostly British, but then there was an American, Tom Mareci, now professor in Florida. AJ Shaka, professor at Irvine. Malcolm Levitt, who now is back—he is British, and is now back in Southampton. Gareth Morris who just came back from Vancouver. He is British. There was Ole Sørensen [?], a Danish guy that spent time in the group. So, it was somewhat international.

ZIERLER: And when you came in, was your lab work assigned to you, or you came in with your proposed project ideas?

BAX: When I went to Oxford, I just came in, and I could do whatever I felt like, and talk to the guys, and we would do whatever we felt like. And Ray Freeman would ask what we were working on, and keep on asking questions and make us understand what we were working on.

ZIERLER: And so what exactly was the institutional relationship? Because your dissertation, your PhD degree is with Delft, but it sounds like the majority of your work was actually at Oxford. So what was the arrangement between the institutions?

BAX: Well, I was a volunteer at Oxford University and still paid for by Delft University. And that caused some friction, because I only—

ZIERLER: Yeah, what does Delft get out of this?

BAX: Right. I had three or four papers while I was in my first half or first year at Delft University, and I got like a dozen with my advisor, Ray Freeman, and Oxford University. So there was some friction with Professor Smidt, who was perhaps jealous or somewhat uneasy about the fact that I got all this nice and visible work at Oxford without him getting any credit for it, with some of the money still coming from Delft University. It was, for a while, somewhat uncertain, whether I was going to get a PhD for my work, because—

ZIERLER: Oh, really?

BAX: —he would have to approve it.

ZIERLER: And you're not in regular contact with him at this time?

BAX: Well, I was being called back, sort of like once a month, to fix something on the spectrometer, or to expand software. And of course that couldn't be done over the internet because there was no internet. You had to be physically present, and usually I was able to do that in a day or two.

ZIERLER: Now in terms of you tinkering with the equipment, are you self-taught with this, or did you take engineering classes where you had a solid educational basis for dealing with the instrumentation?

BAX: I never got a lot of formal education, although at the University of Delft, I did get a course in electronics engineering, so we knew what integrated circuits, transistors, flip flops, and all the kind of stuff that you had at the time, what they were. And that came in very useful particularly during my postdoc time. So, yes, there was some formal training. On top of that, Mehlkopf , my direct advisor, he was a real engineering wizard, and he would explain things to

me. And the big advance at the time was something called EPROMs—programmable read-only memory chips. This was like an eye-opener that made a lot of things possible that had been totally impossible until then.

ZIERLER: So you were experiencing advances in computational power that were having a real impact on your work, even when you were a student?

BAX: Absolutely. I basically got in at the ground floor, now looking back. When developing that spectrometer that I mentioned, it was Mehlkopf's project really. I mean, he had the choice between a PDP-8 or an HP21M20, and decided to settle on the HP21M20 because it had more memory. It had like eight kilobytes of memory.

ZIERLER: [laugh]

BAX: It got upgraded to 16 and then later 32 kilobytes [.

ZIERLER: And is this punch card technology or this is beyond that?

BAX: No, we had punch tape, already. Punch tape, which was a big advance. But the main thing was that I had direct control over the disk drive with micro assembly language, and that allowed me to really work with 300 kilobytes of data coming in, which was way more than anybody in any lab could deal with. And so like I was involved in how to store data, this massive amount of NMR data—kilobytes [laugh]—

ZIERLER: Right. Relatively speaking. [laugh]

BAX: Hundreds of kilobytes. Exactly.

ZIERLER: But this is cutting-edge stuff at the time.

BAX: Absolutely. Right. And Mehlkopf had the foresight that this should be possible, and I was the one that implemented it.

ZIERLER: Right. And was your sense that Oxford, the budgetary environment at Oxford, they spent lavishly on these programs? You had good resources to work with?

BAX: No, the exact opposite, actually.

ZIERLER: Oh, really?

BAX: The exact opposite. They were living on a shoestring. Ray Freeman, despite being internationally highly recognized, he was still having a CFT-80 NMR spectrometer, a very primitive iron magnet beast, whereas in Delft, we already had this 300 megahertz NMR magnet, which was the highest field anywhere at the time. The computer technology, like having your own latest version computer rather than what you get from an instrument manufacturer, and of course it's night and day. So when coming up with new experiments while I was working on my PhD at Oxford, sometimes I had to go back to Delft to actually do the experiment, because the hardware we had back at Delft was way more flexible than what I could do at Oxford University.

ZIERLER: Now, were you going to Delft just because that's where you were comfortable, or were you aware that there was even more advanced technology elsewhere in the world? You know, like at a Stanford or an MIT or something like that.

BAX: There probably was not.

ZIERLER: So Delft is really—was like a leader in this?

BAX: At that point, in NMR spectroscopy, technologically in terms of what an NMR spectrometer could do, absolutely.

ZIERLER: So the Dutch were really leaders in the NMR field at this point.

BAX: The Dutch were leaders in NMR spectroscopy, but they were using commercial equipment. There was Rob Kaptein.

ZIERLER: Where is he?

BAX: He was at Groningen University, moved to Utrecht University, very famous guy. Very, very intelligent. Very accomplished. There was Cor McLean, who started at Nijmegen, went to Amsterdam. Very bright guy. So those were the leaders in the '60s and '70s, and Kaptein up until basically ten years ago. He only—he's now probably in his late '70s. But those guys were the leaders in applying and innovating. Cees Hilbers at Nijmegen University, another very bright guy, leader in nucleic acid work. So, NMR was one of the strengths of Dutch science. The Netherlands had a very strong position in NMR spectroscopy, and that enabled Mehlkopf to develop this kind of hardware because he realized there was a need for this. There was zero interest in the chemical community in his project, however. When he applied for money for me to do my PhD, they laughed him away and said, "There is no need for that kind of playing. We have all the hardware and the equipment we need."

ZIERLER: So what did Mehlkopf see that they did not? How was he ahead of the curve in terms of identifying this need?

BAX: He had the vision that the technology would keep on developing. Pulse sequences and more advanced experiments. He was aware of the work that Richard Ernst was doing with

multi pulse NMR. And he was interested in engineering and designing things. He later got to work for Philips working on the MRI development there as an advisor. And I was just a lucky guy entering that group at the right time with the right kind of background and interest. And after developing the hardware and the capabilities, being in Oxford, getting my eyes opened to the opportunities in spectroscopy, realizing our equipment back in Delft can do this, and yes, there was so much excitement.

ZIERLER: And how did you define your dissertation topic? How did that process play out?

BAX: That played out naturally, because I had co-developed, played a role in development of this instrument back at Delft University. Applying it to new experiments was of course an easy thing to do, because we had the hardware and the software. And I was basically the guy that [laugh] developed that software, so I could do anything I wanted. And other people in the world might have had the same idea. Richard Ernst had some of the same ideas but couldn't do it. So in the land of the blind, one eye is king, and—

ZIERLER: [laugh]

BAX: —having a little bit of background in physics and some understanding of the chemical interest made it very easy for me to enter this field at the ground floor and do a lot of interesting work.

ZIERLER: Now, did you have coursework at Oxford, or it was strictly lab work?

BAX: At Oxford, it was strictly lab work.

ZIERLER: OK, so were you taking courses at all between ’78 and ’81?

BAX: No, not between—well, in ’78, I still took some specialized courses back in the Netherlands.

ZIERLER: So the vast majority of your work as a graduate student was in the lab.

BAX: Absolutely. That’s the way it’s structured in the Netherlands. Or was structured; I don’t know whether it still is this way. And after you're done, you wrote sort of like the equivalent of a master’s thesis.

ZIERLER: So anything you picked up about chemistry at this point was on the fly, essentially.

BAX: Absolutely, right. And it was very little, I must say, until I really left for England. Even at Oxford, I didn't really learn a lot of chemistry.

ZIERLER: Right. And biology is like zero.

BAX: Oh, zero point zero.

ZIERLER: Fascinating. OK, so you defend when? In 1981?

BAX: Late 1981.

ZIERLER: And who was on your committee?

BAX: Ray Freeman. Rob Kaptein, Cees Hilbers—the two leaders in the Netherlands. Jean Jeener, the smartest, brightest physicist I probably have ever met. Very laid-back kind of guy. Still quite active.

ZIERLER: Really!

BAX: Genius guy.

ZIERLER: Where was he?

BAX: He was at University of Brussels, Université Libre. He developed or at least was the first to propose two-dimensional NMR spectroscopy, but so laid-back that he never really wanted to publish it, really. It was like—to him, it was so obvious.

ZIERLER: [laugh]

BAX: So he talked about it at the Basko Polje summer school and—

ZIERLER: When did you first meet him?

BAX: I met him first for my PhD defense.

ZIERLER: Oh!

BAX: Interesting story—I had to pick him up from the train station. And I had just come back from Oxford, and everything that I had needed to be transported back from Oxford to the Netherlands.

ZIERLER: All of your equipment?

BAX: Well, my belongings, my bikes, whatever. So, I had taken all the seats out of my car, so it was just the driver's seat. No passenger seat, no [laugh] rear bench.

ZIERLER: [laugh]

BAX: And I forgot to put the passenger seat back in the car when I picked him up from the train station.

ZIERLER: Here's this world-famous scientist. [laugh]

BAX: World-famous guy. [laugh]

ZIERLER: You don't have a seat for him.

BAX: Right. Shows up. And he had to sit on the spare tire. [laugh]

ZIERLER: [laugh]

BAX: Fortunately, this guy, like I said, he's very laid-back. Very easygoing. And I think he sort of was actually very happy to [laugh] get the experience of sitting on the spare tire.

ZIERLER: When a graduate student picks you up, this is what you have to expect. [laugh]

BAX: Right, right. So he didn't take any offense to that.

ZIERLER: So the defense was at Delft?

BAX: Correct.

ZIERLER: In what language?

BAX: In English. Yes, it was in English. Because of course Ray Freeman—

ZIERLER: Common language.

BAX: —was one of the overseers, and he didn't speak a word of Dutch. Now, he does. His daughter married a Dutchman. But at the time, he wouldn't have understood a single word of that.

ZIERLER: Now, I'll test your memory. You remember the title of your dissertation?

BAX: Yes. "Two-Dimensional Nuclear Magnetic Resonance."

ZIERLER: OK, and what did you feel at the time was your main contribution to the field? How did you advance the field based on your research, as you understood then?

BAX: It was quite obvious that we had developed some experiments that were extremely useful to the chemical community. One of the experiments was called INADEQUATE, which for organic chemists was a new way of determining molecular structures of unknown compounds. We were able to connect carbon nuclei to one another and basically outline the framework which we thought was very important. There was a lot of interest by the chemical community in that kind of work. We had developed better ways of understanding what is known as the COSY experiment that again became very widely used—it became obvious to the chemical community how exciting and important that was going to be, and so those experiments, we were the first ones or among the first ones to do those, and to show how to do them properly. At the time, my PhD thesis was published as a book.

ZIERLER: Really!

BAX: Yes. In part because of this friction between me and my advisor, Jaap Smidt. A guy I knew, whose name I have forgotten, but who had an undergraduate degree in chemistry, he sort of urged me to actually consider publishing my PhD thesis as a book because he realized

that NMR spectroscopy was going to be important to chemistry. So to write it a little bit more general. And this was encouraged by my direct supervisor, Toon Mehlkopf , who liked the idea.

ZIERLER: So you revised it for a broader audience.

BAX: Well, not even revised—when I was writing it, I tried to make it—

ZIERLER: Oh, with in mind that it would be published as a book.

BAX: Right.. And as it turned out to be—I mean, everybody was waiting for Richard Ernst to write *the* textbook, but Richard is a detail-oriented man and never satisfied with anything until it's absolutely perfect, and as a result, Ernst's book only appeared in 1988. So, for about six years, my PhD thesis, published and available as a book, was the only thing that really dealt with two-dimensional NMR spectroscopy.

ZIERLER: And you wrote it as a textbook or as a monograph?

BAX: As a monograph, but sort of in a way that it could be used for teaching purposes. So it was used for graduate courses worldwide.

ZIERLER: Now, your contributions, you saw them—as a ratio, how much were your contributions applied and how much were your contributions theoretical?

BAX: I'd say 50/50. I mean, theoretical is a bit of a relative term, right? What a chemist considers theoretical, a physicist would consider totally applied. [laugh]

ZIERLER: [laugh]

BAX: But I met Nicolaas Bloembergen and he said, well, for him, the interesting stuff about NMR was basically done after he developed the theory of relaxation in the mid-'50s. So, he got out of it and went into optics. For me, theory was understanding second order perturbation theory and applying it to transition probability in NMR spectroscopy. I considered that theory. But of course for a physicist, that's no theory.

ZIERLER: Right, right. So it's the chemists who are mostly excited, because they can take your theory and apply it practically. Is that the idea?

BAX: It's not just the theory; it's the experiments. So we designed—and most of my work for the past 40 years has been designing pulse sequences—sequences of radio frequency pulses that can probe specific interactions in molecules, and do it better, more sensitively, and more uniquely, than other methods can do.

ZIERLER: So this has been a constant in your career, from your graduate days all the way to the present.

BAX: Yes, completely. And of course when you get older, you get more interested in what you can do with it, rather than in the game itself. Starting out in the '80s—

ZIERLER: You were less concerned about applications then than you are now?

BAX: Right. It was more how interesting it was that you can do this, not why do you want to do it. Now, of course, we are driven by why would you want to do it, and can we do it better. So, it's a bit of a different perspective.

ZIERLER: So at that time, in the early ‘80s, what specifically was the chemistry community excited about, that they could take your experiments and theory and apply them? What would be the practical output of these advances?

BAX: Originally, just studying molecular structure. Chemistry, stereochemistry, natural products, confirming or elucidating molecular structure. And it was a big deal, those days. It was before crystallography really was mainstream. NMR as an analytical tool is incredibly versatile.

ZIERLER: OK, so you defend. What’s your next move? You're on your way to Colorado immediately, or there’s an interlude here?

BAX: No, I went to Colorado immediately.

ZIERLER: And personally at this point, you're single, you're married?

BAX: [laugh] Also an interesting story. I did have a new girlfriend that I met at Oxford University. Part of the reason my time at Oxford was as happy as it was. [laugh] Interestingly, we met on a demonstration against the United States.

ZIERLER: Ah!

BAX: They were going to place cruise missiles near Oxford University. And of course my now wife, then girlfriend, is German.

ZIERLER: So she’s all ready to be active in this kind of a thing.

BAX: Well—

ZIERLER: West German or East German?

BAX: West German. Neither of us were really the natural activists, but it's an interesting thing to go on a demonstration, and it's a good purpose.

ZIERLER: Well, listen, placing nuclear weapons near campus, that can make an activist out of anyone, right?

BAX: Exactly.

ZIERLER: [laugh]

BAX: So I thought this was a perfectly valid purpose to go demonstrate for, or against. So we had a happy time. She went back. I moved to the U.S., but we kept in touch, and she joined me about a year later, year and a half later.

ZIERLER: What was her field? What was she studying?

BAX: Linguistics. Sociolinguistics.

ZIERLER: Oh! OK. So really different part of campus.

BAX: Well, campus—no, not really, because it's all intermingled. It's colleges, right? Oxford is very differently structured. But we met through one of my lab mates, Malcom Levitt, who had a house mate who was living in a shared house with a dozen grad and undergrad students. Interesting environment. You had to bring fivepence pieces to keep the lights going. [laugh]

ZIERLER: [laugh]

BAX: So he had organized for us to go on this demonstration with the whole house, and after a party, and only the two of us showed up the next morning. [laugh] The rest, I think, were still hung over.

ZIERLER: [laugh]

BAX: But yeah, so that's how that happened. And when I got the chance to do postdoctoral work in the U.S., I took that with both hands.

ZIERLER: Now, at this point, you're doing pathbreaking research. You probably had a lot of opportunities available to you. Why Colorado State? What was the draw there?

BAX: Again, interesting. Even while you would think that I had a lot of opportunities, I applied for two jobs in the Netherlands—at Shell Labs, and at Nicolet Instruments, and at both places, I was turned down.

ZIERLER: This is industry? This is not academia?

BAX: Industry, right, but they had fundamental research labs at the time. So it would have been a research position, but in industry. It's very different from what it is these days. It's more comparable perhaps to what Bell Labs was for a long time in the U.S. Shell Labs had a basic science lab.

ZIERLER: So you never seriously pursued an academic professorship?

BAX: I wouldn't say that. That came later, when I realized that—Ray Freeman was the one that stimulated me to consider an academic position, sort of after—applying for jobs at Shell and Nicolet came before Ray Freeman really suggested I should look for an academic job and do

postdoctoral work. To me, the choice for going to Colorado State was motivated by two things. One, they had the national NMR facility, so it was technologically in better shape than probably any place in the United States, besides MIT.

ZIERLER: Really!

BAX: Yes. So Gary Maciel was heading the national NMR center, solid state NMR facility there.

ZIERLER: At CSU?

BAX: At CSU. Brilliant guy, trained by John Waugh, National Academy member, at MIT. And they had some really pretty advanced equipment setup. So that was one consideration. The second consideration was that I had been busting my butt for three years working long hours as a grad student. Like every grad student does, but by my standards, I was thinking I was really ready for a break. And I wanted to try out my chances in cycling.

ZIERLER: Oh!

BAX: Seeing how well I could do in Colorado. Colorado was the mecca of United States cycling. But the level in the Netherlands was way higher than it was in Colorado, so when I got there, it was relatively easy picking. And so even while in the Netherlands I never was more than a mediocre cyclist, in the U.S. I immediately was able to butt heads with some of their best cyclists.

ZIERLER: What are you riding at this point? Steel frames?

BAX: No. Oh, those days, yeah. All steel frames. I got onto a team there, a locally sponsored team. They gave me a bike. And I spent a fair bit of time racing to the extent that Gary Maciel, my advisor, was wondering where I was on the weekends.

ZIERLER: And you have access to mountains now like you never had before.

BAX: Exactly. I didn't know that I was good at climbing, and it turned out that was my strength.

ZIERLER: Really!

BAX: Yes. So, I was as surprised as anybody that the longer, the bigger hills, turned out to be my fortes. So, I had a great time there.

ZIERLER: So what was your arrangement for the postdoc? Were you teaching at all, or you were exclusively in the lab?

BAX: No teaching, just lab work. And Gary Maciel—he passed away a half dozen years ago—a super guy—he let me work on whatever I wanted to work on. So even while his money that he was using to pay me came out of fossil fuel research, I think I've only got one or two papers that dealt with fossil fuels, and a dozen papers that he didn't even want to be part of. He didn't even want to be a coauthor on those papers that I did in his lab.

ZIERLER: Because it wouldn't be good for his funding?

BAX: No, basically he said, “I didn't contribute anything to your paper.”

ZIERLER: Oh, I see.

BAX: I did solution NMR. I did solid state NMR. The solid state NMR papers that I worked on in his group, he was a coauthor because he knew a lot more about it. The solution NMR, I had basically taken over from—I brought into the lab, coming from Oxford, and he said, "That's your baby. You do what you want. And take all the time. Whatever you do is great. Publish it." He was very generous. Never tried to slow me down on anything we did. And I was lucky that there were a couple of guys in the group—Nick Szeverenyi, a postdoc who had fantastic engineering skills; Bruce Hawkins, a great electronics engineering background—that we could develop the kind of experiments that we ended up developing, both in solids and in solution NMR.

ZIERLER: And this was your first time to America, was as a postdoc?

BAX: Yes, totally. [laugh] I showed up with two suitcases and knowing nobody. Of course the communication had all gone by mail—snail mail, that is, or air mail—that would take a week and a half. So I had absolutely no idea what to expect, just that Ray Freeman told me Maciel was a great guy, and that's how I ended up there.

ZIERLER: And Colorado Springs, even then, it was probably a pretty conservative town, right?

BAX: This was Fort Collins, not Colorado Springs.

ZIERLER: Oh, this is Fort Collins, OK.

BAX: Yeah. And that was actually pretty easygoing. Cowboy town, very provincial. And when I was considering getting a faculty job after a year and a half, Gary Maciel was pushing me already—postdoc periods were less lengthy then than they are now, so after a year

and a half and maybe another dozen papers, Gary suggested, “Hey, you should go look for a faculty job.” And one of the places was Fort Collins, and my wife thought that, “No, this is not going to work for me.” [laugh]

ZIERLER: [laugh]

BAX: “There’s nothing—this is too much of a cowboy town.” Since then, I think Fort Collins has nicely developed and become a much better place to live. But at that point, I had the choice of going to the University of Houston. They were very generous.

ZIERLER: And this is 1982, 1983?

BAX: 1983. Mid-1983. MIT was an option. Tallahassee had a big magnet lab and they were making a nice offer. And the NIH. The NIH was for me almost an afterthought. I knew NIH was a funding agency, but that’s about as much as I knew about it. I had been out here to give a talk at a meeting when I realized there was a big campus. And I did know the name Ted Becker, because he had published some of the first pulsed solution NMR experiments. Farrar and Becker was a classic textbook for modern NMR in those days. And it was actually his position that I ended up taking. Becker had moved into administration, had become the director of research services here at NIH, so there was this opening. We didn't have an official tenure track kind of hiring system here at the NIH those days, but it was obvious that it was a position where you could do independent research. And I saw it as a stepping stone to go back to the Netherlands and pick up a faculty position there.

ZIERLER: Because your first job here, the title was visiting scientist?

BAX: Well, that's because if you don't have a green card or a U.S. citizen; the visiting scientist title was the equivalent of a tenure track position here.

ZIERLER: I see. So at this point, I'll return to the same question. At what point do you start to realize that your research is headed towards advancements in human health and science research?

BAX: That actually only came—well, it came in part when I was a postdoc at Colorado, where we developed the first indirect detection experiments that allow you to detect Nitrogen-15 at greatly enhanced signal to noise. And that was a collaboration working on transfer RNA, an experiment that even by these days still is somewhat challenging. Working on a couple of hundred micromole solution of N15-labeled tRNA. It was mind-boggling that with the kind of equipment that we had, we were able to get the spectra we were able to get. So that got me excited, and it was the first inkling that perhaps this kind of pulse gimmickry, as I considered it at the time, might actually become useful to biology—

ZIERLER: Clinically.

BAX: —biochemistry—not clinically, but biochemistry, and sort of like my first encounter with anything that wasn't organic or inorganic chemistry.

ZIERLER: I see.

BAX: And here at the NIH—this was the early '80s. It's when Kurt Wüthrich was pushing this protein NMR work for studying protein structure. And that involved doing pedestrian, by my standards, experiments—COSY and NOESY—that you would plot out on humongous pieces of paper, put on a drafting table on top of one another, and try to trace like a

jigsaw puzzle how resonances would join together and tell you something about the structure. It was basically solving big jigsaw puzzles—mind-bogglingly, numbingly tedious. But of course some people like to puzzle, and some are very good at it.

ZIERLER: And computers were not helpful for this?

BAX: Not really. Not in the early to mid-'80s. And my lab chief at the time, Bill Eaton, he tried to encourage me to get interested in protein NMR. And the idea of staring into a light box and trying to do this kind of stuff—

ZIERLER: Not for you.

BAX: Not for me. That clearly wasn't my forte.

ZIERLER: Now, when you were making these decisions—Houston, Tallahassee, and so on—what ultimately sealed the deal for you to come to NIH? What was exciting about being here?

BAX: To be perfectly honest, I flipped a coin.

ZIERLER: [laugh]

BAX: [laugh] I was talking to my girlfriend, Ingrid, at the time, and—

ZIERLER: Did she end up joining you at Fort Collins, or she waited until you were done there?

BAX: She waited until I was done there.

ZIERLER: Did she end up finishing her degree at Oxford?

BAX: She wanted to start working on a PhD, and she was offered a fellowship at Tallahassee where they had a decent linguistics program. And there was an option for her here at Georgetown University. And so we were talking about the different options—"What do *you* like better? What do *you* like better?" And to me—I mean, Tallahassee actually sounded pretty good, because their hardware, their spectrometers, were somewhat better than what they had here at the NIH.

ZIERLER: Oh, really!

BAX: Yes. So it would have been easier to get a quick running start in Tallahassee than it was here. But—

ZIERLER: Did you ever think, though, that even if the equipment here wasn't as good, being a funding agency, you can just ask for better equipment?

BAX: I was very naïve, and had absolutely no clue—

ZIERLER: How the system worked.

BAX: —how the system worked. And to be perfectly honest, the money didn't grow on trees here for a long time, and that only sort of became more generous in the late '80s. Early on, a lot of the work was done on a shoestring. I was very lucky by having a very bright engineer—I'll come back to that in a minute—that I inherited from Ted Becker. The guy's name is Rolf Tschudin. Brilliant guy, worked for Varian Incorporated before Ted hired him to come to the NIH. In any case, I was hesitating between Tallahassee and coming to D.C. And this sounded to me less exciting, more stuffy, government, than academia at Tallahassee. It was a pretty vibrant place there.

ZIERLER: What about the spirit of collaboration? In other words, was there anything exciting to you that you can interface with scientists and researchers across a wide range of disciplines? Or are you so laser focused on NMR that it didn't really matter who your colleagues were.

BAX: I was laser focused on NMR spectroscopy at the time, and so making a choice between Tallahassee and here, I was talking to my wife and we couldn't figure it out. And I said, "I'm going to flip a coin." And the coin landed heads up, and that was D.C. I called up Tallahassee and said, "Sorry, I'm not coming."

ZIERLER: Honestly?

BAX: Honestly. Within 15 minutes—

ZIERLER: If it landed on tails, you were going to go to Tallahassee.

BAX: Absolutely.

ZIERLER: Amazing.

BAX: I mean, I'm that kind of guy, you know?

ZIERLER: Amazing.

BAX: It's a tossup, and what are you going to do?

ZIERLER: Now, were you married at this point, or are you still just dating/

BAX: No, no, no, just having a girlfriend. Not even engaged. We were just—

ZIERLER: When did you get married?

BAX: 1986. So three and a half years later. But in any case—

ZIERLER: Where did you move? Did you move to Bethesda?

BAX: We moved to Bethesda right away. But let me finish the story, because it's sort of interesting. Fifteen minutes after I called Tallahassee to tell them, "Sorry, I'm not coming," my wife calls me—or my then-girlfriend calls me and says, "OK, let's go to Tallahassee—

ZIERLER: [laugh]

BAX: —because there I've got my graduate fellowship and—

ZIERLER: Oh no.

BAX: —we can start and—" Right. I said, "Sorry, too late." [laugh]

ZIERLER: [laugh] She was aware of the coin toss, though? You did this with her?

BAX: Well, sort of. I said, "I'm going to toss a coin." And there wasn't—

ZIERLER: And was in it with you? Whatever happens happens?

BAX: Well, it wasn't quite clear. Our phone calls then were not like these days. Phone conversations were expensive. They were dollars a minute. And a dollar then was not what a dollar is now. So we had 60 second conversations looking at the clock, because one minute, and then there would be another $2. So this was all done very rushed. In any case, it was what it was, and—

ZIERLER: [laugh] That's so funny.

BAX: —and I ended up coming here. And she ended up getting a fellowship to study at Georgetown University and got her PhD in sociolinguistics.

ZIERLER: So that worked out for her.

BAX: Worked out great. And I ended up getting again super lucky that even while the hardware wasn't all that great that I inherited, the engineer that was here, Rolf Tschudin, was a genius. He helped us build and expand the hardware capabilities. And I was very fortunate that Ted Becker had set up a very collaborative environment here. A colleague, Dennis Torchia, from the Dental Institute, had his solid-state NMR equipment in the same room that my solution NMR equipment was located, so we had a lot of intellectual interaction at the time. And he was expressing—bacterially expressing his protein to do solid state NMR experiments, getting selectively labeled N15 amino acids in his protein. And this was just at the time that I was applying the natural abundance NMR spectroscopy to more interesting larger organic molecules, antibiotics and things like that, and realizing that, hey, if you get a factor of 300 out of N15 enrichment, if this is a legitimate strategy, sure, we can do all kinds of experiments on proteins, and I can make Bill Eaton happy by working on proteins and at the same time do advanced experiments. So, without staring in that light box, right?

ZIERLER: So you made it work for you, it sounds like.

BAX: I made it work for me. And being again serendipitously in the same lab as Dennis Torchia who was developing that technology, when the rest of the NMR colleagues were thinking of isotopic labeling as sort of cheating. You had to work on natural proteins.

ZIERLER: Why would they think of it as cheating? What was the idea?

BAX: Natural proteins were the main thing, and bacterially expressed proteins were sort of considered, well, that's a little bit cheating. That's a special protein because you can express it in E.coli. That's not the natural protein. Whereas Dennis Torchia convinced me that, "No, my collaborators tell me that ten years from now, everybody is going to be doing this." So I was willing to learn that and take it to heart.

ZIERLER: So is this the time at which you stopped thinking of NIH as a stepping stone back to the Netherlands, and you started to think, "I could really build a life and a career here"? What was that process like?

BAX: No, this was still a stepping stone. We were definitely both—my wife and myself were living here with the idea of, "We're going to go back to the Netherlands." She never would have stayed here for more than a week if the idea would have been that she would be, quote unquote, "stuck here for the rest of her life." And of course—

ZIERLER: And the Netherlands was acceptable to her? Not going back to Germany? That was good enough?

BAX: The Netherlands or Germany or anywhere in Europe would be great. And of course when that opportunity came because my career took off here and I was still interested in it, and I was offered a very nice, very generous position back in Nijmegen, the Netherlands in 1992 or 1993, we already had decided to accept it. We had two young children at the time, and went basically to look for a house and negotiate as generous a deal as I could get. And already with the idea that yes, we're going to go back. But of course you don't sign anything.

ZIERLER: Were you on a tenure clock here from 1983?

BAX: I already got tenure effectively in 1986 or ’87. The tenure process then, at the time, was like a couple of years. Three years was sort of it, before you were converted into a permanent or semi-permanent—well, permanent, I’d say. So that was with your understanding—so there was no formal tenure process, but when it got me a Green Card, which was in 1986, that was basically the commitment that I could stay as long as I wanted.

ZIERLER: Right. And NIH sponsored your Green Card.

BAX: Correct.

ZIERLER: Did you pursue citizenship?

BAX: Well, yes, but I postponed it for quite a while, because I was living with the idea that I was going to go back to Europe anyway.

ZIERLER: So this job offer in 1991, you already have tenure here at NIH, and you're still seriously considering this.

BAX: Yes, I had other offers both in the U.S. and going back in Europe. But the Nijmegen facility, where Cees Hilbers was looking to go with retirement, that was a stronghold in the country there, had a lot of equipment, and an intellectual infrastructure. It’s physical chemistry, not biochemistry or biology. So this really was quite attractive. It’s the southern part of the Netherlands, a little bit easier going.

ZIERLER: This is home. This is home for you.

BAX: This is home, exactly. So I was looking forward to that. And the fact that they were going to be able to pay me more money than any other Dutch professor was an attractive idea. And we flew back with the whole family for a week, looking for a house.

ZIERLER: How old were your kids at this point?

BAX: Two and [laugh] zero. So very young. And that played a role in—

ZIERLER: What's the language in the house? What's your two-year-old understanding?

BAX: German. German only at the time.

ZIERLER: So you speak with your wife in German.

BAX: No, no. My son at the time, he would speak with my wife in German, obviously.

ZIERLER: And what do you speak to her in? English?

BAX: I spoke with my wife in English. But he knew that—or he thought all men speak English, all women speak German.

ZIERLER: [laugh]

BAX: So when he first met—he was like three and a half or four—he met my wife's stepfather, and he comes to me and says, "What's wrong? Isn't he a man?"

ZIERLER: [laugh]

BAX: I ask, "Why?" "He doesn't understand English."

ZIERLER: [laugh]

BAX: [laugh] So to him, the world was "All women speak German, all men speak English."

ZIERLER: So you have a real family decision to make here, whether to stay here in Bethesda or to move back to southern Netherlands.

BAX: Exactly.

ZIERLER: And what was your wife thinking? What's her career at this point? Is she working professionally, or she's home?

BAX: She was at home then with the two young kids. She had been a postdoc for a while doing sociolinguistics and technical applied linguistics. But basically she had her hands full with the two little kids.

ZIERLER: Of course.

BAX: We go back there, and it was a bit of an eye opener, because we had always been thinking, "Everything is better in Europe." Right? The only thing that's better in the U.S., from my perspective, was research. Here, it's not bad if you want to work on the weekend. You can work day and night. You can rapidly advance. You don't have to wait for an old guy to die before you move up. So I was sort of like a bit of an aggressive career maker, being able to rapidly jump and do stuff, and not go through all the bureaucracy. And being in charge of my own program, being a senior professor at Nijmegen University, was quite appealing.

ZIERLER: What was the package? They were going to give you your own lab and postdocs?

BAX: Hardware, my own lab, graduate students. Pretty generous funding.

ZIERLER: Teaching requirements?

BAX: Yes, of course.

ZIERLER: Was that attractive to you or that was—

BAX: Not particularly.

ZIERLER: —something that you felt might slow you down?

BAX: It would slow me down. But at that point I thought that everything that needed to be developed was already pretty much developed. I mean, we were doing interesting things, but not like there is that much more to be done. So teaching is part of it, right? You're a professor. And that wasn't that big of a concern. You get some helps you get staff scientists, and there's a lot of technological and technical infrastructure. You get technicians. You get three technicians to work and help you. So that's all paid for by the university. So all hard money effectively. And here in the U.S., positions, well, you've got to hustle for money. It's still the way it is now. So endowed positions, effectively, very well endowed. But after spending a week in the rain, cold, and then my wife figuring out that perhaps it's not all that kid-friendly here—kids are not allowed to play with toys in the toy store.

ZIERLER: [laugh]

BAX: People don't take it very well if your kids are not very well behaved if you take them to a restaurant, and let them run around and do stuff. It was sort of like on the way—the flight back—we hadn't found a house that we liked.

ZIERLER: So socially conservative. She felt that southern Netherlands was strict?

BAX: Well, no different—not socially conservative, but it wasn't the kind of place we remembered as being "Everything is better back home." You don't appreciate what you've got until you sort of realize what you don't have. And so we got things here that we never knew that we didn't have when we were in Europe. So like the opportunities, but also the kid-friendliness, the easy way of dealing with one another, the lack of formality. So on the flight back, I was like, "I thought you wanted to go back." She said, "No, I thought *you* wanted to go back." [laugh]

ZIERLER: [laugh] I see you have a problem communicating with your wife at these monumental points of decision.

BAX: Well, it was understood that both of us wanted to go back. And her mother was living there, is still living there.

ZIERLER: So you wanted to go back as an ideal, but then when you actually got there and you saw the reality, it didn't seem so ideal, is what it sounds like.

BAX: It was less ideal than it was in my memory —

ZIERLER: Now was NIH aware of the offer that they were giving you, and did they look to match it to keep you happy here? What were the politics there?

BAX: Yes, at that point actually, I skipped over that, but in the late '80s, with the HIV crisis developing, it was clear to NIH that structural biology might have a big role to play. And Bill Eaton, still our lab chief now, had the vision that NMR spectroscopy could actually get funded through that mechanism. And NIH then became very generous in funding our program and we hired two senior investigators, both now National Academy members, Marius Clore and Angela Gronenborn, to come and help with getting protein NMR spectroscopy established here.

ZIERLER: Where is Angela now?

BAX: Angela is at Pittsburgh. So we had two of the world's top experts jumping in, helping us out with actually applying this to proteins and further developing the protein technology. I was still sort of like more of a physicist than a biophysicist or a protein chemist or whatever you might call me now. So that all of a sudden gave us incredible amounts of funding. So when I had the opportunity in 1992 to go back to the Netherlands, of course they heard about it, and that sort of doubled my salary, I think, here [laugh]. There's nothing like something like that to give you a little quantum jump.

ZIERLER: Especially with two small kids and trying to make a life in Washington.

BAX: Yeah, right. On the other hand, money never was a main concern. We always were able to make it work. Both my wife and myself, we were brought up very thriftily, and I've done for my entire life to this very day shopping at secondhand stores [laugh], repairing old stuff, repairing my old car, changing the oil myself. Not doing that anymore, but 15 years ago, I would change the oil on the car myself.

ZIERLER: So Bill Eaton was instrumental on amping up the budget here.

BAX: Absolutely. Had a clear hand in that. And NIH has been extremely generous over the years. So I developed some loyalty to the institution.

ZIERLER: Bill—would you say—was he politically savvy? Is that what allowed the budgetary funds to become more generous?

BAX: Politically savvy is an understatement, I think.

ZIERLER: Oh, really?

BAX: He's a very smart, perceptive guy.

ZIERLER: So who was he connected with to make these things happen? If you can give us a sense of where—because the idea is that NIH is already the government. So it's the source of money, so if NIH is the source of money, where is NIH getting its money from? How does that work?

BAX: Well it's more complicated than that, right? NIH intramural program is only a very small component of the National Institutes of Health. So we are more visible to the people downtown perhaps because we've got the big hospital here, but basic research—

ZIERLER: Downtown, you mean Congress?

BAX: Congress, exactly. Capitol Hill. The basic research here lives basically at the grace of the clinical program, let's face it. But the fact that we are allowed to do research that doesn't have to be justified ahead of time gives us more freedom. So we can jump on something that we think is novel without having to justify in advance of why is it important. And development of this three-dimensional NMR spectroscopy and this isotopic labeling strategy that I had a big role in never would have gotten funded by an NIH grant for that matter because the peer review system would have said, "Sorry, we don't need that. We've got our light box, and that works perfectly well." And it's expensive. Those isotopes are expensive. Here at NIH, I could get money for it. So I was very fortunate to be here. And Eaton was extremely supportive in his role, and he had these connections with Building 1. That's where basically the administration is located. And so research funds never really were a major concern. Again, I

mean, we lived thriftily. That's how I've been brought up, and that through my research career has played a role as well. But at the same time, they've been very generous purchasing equipment for us, having state-of-the-art equipment, and we've been able to stay competitive with the rest of the world. But it's not just the equipment; it takes more than that. It takes the, I'd say, ingenuity, the ability to do things that are a little bit outside of the box. You've got to make the judgment ahead of time what's going to be important. Is it worth putting my money on this or on that? I've made a number of lucky bets over the years. And being at the NIH has allowed me to do it. I mean, you can be ever so bright in academia, but if you're short of money, and you've got to get your grant renewal, you've got to make sure that you get this project that you promised completed. And here, I can jump to a different project because I think it's important.

ZIERLER: Now, to return to this proportion of applied versus theoretical, how have these ratios over the course of your career changed? Do you go back and forth in terms of pursuing things that have theoretical value versus applied value, or do you think of these things as dual tracked?

BAX: It's dual tracked, so it's always developed for a purpose. I don't just develop it just because it might be interesting. But at the same time, if I think it's interesting, it's got to be interesting for a reason. And if something is interesting, it usually has applications outside of just pure spin physics, and that makes it interesting.

ZIERLER: Now, at what point are you developing research that does have clinical value?

BAX: Clinical value, I'd say I'm still not there yet. [laugh]

ZIERLER: You're still not there yet. [laugh]

BAX: The technology that I helped develop has been used by people in pharmaceutical industry and in many laboratories worldwide to develop drugs that are now in the clinic. So it's the tools that we've developed that have been used by people to develop drugs that hopefully make it through phase two into phase three and perhaps into the clinic. And there's only a small handful of those.

ZIERLER: So you're more removed from that.

BAX: I'm more removed from that.

ZIERLER: So in your work, you never come up with a situation where a clinician, where an MD, will come to you with some issue where they need you to work on it to help them on a specific patient? Your world is simply too removed from the clinical world.

BAX: Yes. That being said, I would talk to—my clinician would be a mouse guy, or a drosophila person who deals with animals or works with worms. So there's a Parkinson's model in C. elegans to study Parkinson's disease rather than trying drugs in patients. It's not directly clinical, but we have a drug that is, for example, developed with NMR spectroscopy—squalamine—tested in C. elegans, that is in clinical trials right now.

ZIERLER: OK, so let me ask the question in a different way. Why should NMR research be located within the NIH? What's the big connection between NMR and advancing human health as you understand it?

BAX: It could be located outside of NIH, but it wouldn't have developed as rapidly as it has. Because you see, outside of NIH, you need to justify applied projects, and for that, you justify in the '80s the use of a light box that now nobody uses anymore. So we were able to

develop the technology to do the kind of stuff that is now done worldwide, and we try to keep on doing that. So it's hard to justify that ahead of time, because people say, "Why am I gonna need it?" And I can tell you why it's going to be needed—because you're going to be able to do stuff faster, better, and more precisely. We do get reviewed here, once every four years, and their main question is not, "What are you going to do the next four years?" Yeah, they ask us that, too, but the main criterion is, "What did you do the past four years? Did you do anything useful? Did you develop anything that might actually become usable to the community?"

ZIERLER: So the review is more retrospective than forward-looking.

BAX: Completely retrospective, at least in our Institute. The Cancer Institute is a little bit different in that sense. They want to see more applications apparently directly to cancer. We in the Diabetes Institute are allowed to work on rather basic science. I'm having my first project on amylin right now, hopefully studying fibril formation related to type 2 diabetes. But the ability to develop the infrastructure at NIH to do high risk research—high risk means it has a high chance of failing.

ZIERLER: So you had a leeway here that you might not have had at like an MIT or a Chicago or something like that, where there was more room to fail here, and that would have been OK.

BAX: It's OK. You can fail for four years here.

ZIERLER: And in an academic setting, you're operating on a much tighter timeframe.

BAX: Yes, you would have lost your grant funding. So you can't afford it.

ZIERLER: So what does failure look like? I mean, in science, failure is also success, because you know when you hit a wall that you have to pursue another avenue. So what does failure mean in NMR?

BAX: Failure in NMR means if you no longer get invited to come to conferences.

ZIERLER: [laugh]

BAX: [laugh]

ZIERLER: You know what I meant. In a lab setting, what does failure mean?

BAX: Your research funding gets scaled down. The number of positions. The number of square feet.

ZIERLER: But I'm saying what's the feedback where you know that something that you're pursuing in a research environment—when it, as you say, it fails, what's the feedback where it tells you that it fails?

BAX: It fails—remember in research, most things fail. We have so many great ideas but I'd say 90% fail. So it's the 10% that doesn't fail that's why I'm well known.

ZIERLER: Because of the 10%.

BAX: Most people, 99% fails or 100% fails.

ZIERLER: Yes, but let's define success and failure. What does success mean, and what does failure mean, in any of these things? Ninety percent fails means what? That the experiment didn't end up the way you thought it would?

BAX: Correct. You didn't get the results that you were hoping to get.

ZIERLER: But even if you get different results, is there not research value in those results? Or is it always how well it adheres to a preordained assumption of how the research is going to play out?

BAX: It's difficult to really separate. I mean, there's a grayscale here. Experiments fail for a number of reasons. Either the signals are too weak—you can't observe them. Your sample wasn't good enough. That's a project doomed to failure. We would like to work on the biggest, most challenging proteins we could get our hands on, but if you don't get enough signal out of it, that project will fail.

ZIERLER: What does a challenging protein look like? What does it mean for a protein to be as challenging as possible?

BAX: As close to natural, perhaps, in an integral membrane environment. G protein, coupled receptors were a very hot target for a long time. A third of all drugs target GPCRs, as they are known. We knew that conceptually it should be possible, but the challenge was developing technology to prepare the samples as good as you can. I don't have that kind of training, background. We've never managed to do it. Other labs, a former postdoc, for example, who is now a director at Biozentrum in Basel, Stephan Grzesiek, he's getting dynamite results. And so are others, but using the kind of technology that Stephan helped develop when he was a postdoc here at the NIH, right? So for me, it would have been—I would have given my left hand to be able to work on GPCRs, but we never could get it to work. I never was able to get the kind of sample preparation that would have been needed. In retrospect, it was perhaps sort of fortunate that we didn't get those samples, because I was forced to work on other experiments.

ZIERLER: But that's what I mean, about there being benefits in failure itself, because it pushes you in different directions.

BAX: Correct.

ZIERLER: So in four decades of research—maybe this is a better way to ask the question—what's your most spectacular failure? What's the avenue of inquiry that you pursued with the greatest amount of vigor and resources that just went nowhere?

BAX: I put a fair bit of effort in studying membrane proteins, but it was my lack of training in biochemistry, protein chemistry, that sort of doomed that effort to failure. I was quick to realize that, early enough, I think, that we sort of pulled our hands back from that, before it was too late.

ZIERLER: But surely you knew you didn't have the background in biochemistry. Wouldn't you have had a postdoc or a collaborator that would? Or you thought, "I can teach myself this stuff and we'll work it from there"?

BAX: No, I did have collaborators here at the NIH, but I mean, you need somebody who's more focused at the interface between structural biology and protein chemistry to pull that off with an interest and a genuine training in membrane protein biochemistry. And we didn't really have that here.

ZIERLER: And what were you looking to accomplish with this project?

BAX: Study G-protein coupled receptors, ligand binding, things like that.

ZIERLER: That would have pharmaceutical applications?

BAX: Pharmaceutical, clinical, you name it. That's what Nobel Prizes have been given for, to Brian Kobilka and Lefkowitz, for example, and they did it by crystallography. So I had the dream back in the early '90s that we should be able to do that with NMR spectroscopy, and this was very premature. And even now, it remains very, very difficult.

ZIERLER: So what would you identify as the major shortcoming of that project? Technology?

BAX: Technology. But mostly not radio frequency technology or NMR hardware technology; really a shortcoming in the protein chemistry and the molecular biology needed to make the stable mutants to develop this.

ZIERLER: Have you returned to past projects that failed because of where you were in your career or where the technology was, that you could pick up later on and say, "Let's give this another shot"? Or that's not how it works?

BAX: No, for me that has never happened, really, although I wouldn't mind perhaps at one point or another if the opportunity happened to come about to go back to membrane proteins. I mean, we've got so many exciting projects going on right now that I don't want to diverge and run after too many balls at the same time.

ZIERLER: So I asked you the more difficult question first. Now the easier question is, what do you see in four decades of research as your greatest success, your greatest contribution to the field? The project that led to the most satisfying result for you, either intellectually or technologically or in industry.

BAX: That's an interesting question, really. Looking back, I think a number of technological milestones that we developed that are now so commonplace throughout the entire world. Like triple resonance NMR spectroscopy has been used in literally thousands of laboratories across the world.

ZIERLER: For very different applications or mostly the same application?

BAX: Mostly the same application, but notched up a couple of levels in terms of degree of difficulty than I was able to deal with myself. It's amazing to see what some of my colleagues can do with this kind of technology. And I'm proud of it, in a sense, to see what those guys can do, which I never would be able to do myself, because it requires a combination of skills that I myself don't have. I have the technical skills, but you need to know enough about biology and about how to deal with and negotiate in a field to advance it. And I'm still pretty isolated here. I can tinker on my own, develop technology. Right now, we've developed new hardware in collaboration with a colleague here, crystallographer, Phil Anfinrud, brilliant guy, absolutely fantastic physical chemist. We have technology in our lab that nobody else in the entire world has, to rapidly change pressure in an NMR sample cell. We can use that for studying the initial events in Alzheimer's disease, how the first peptides get together and start aggregating to form oligomers, which nucleates the disease process. The same for Parkinson's, and the same for type two diabetes. So we've got technology that I can look at now and get excited about, and that's why I still go in on the weekends and at night to change samples, do it myself, be the first one to actually observe this. And it's very satisfying to see that yes, we've done a lot of interesting things that everybody is using, and we haven't stopped doing it, so it stays exciting.

ZIERLER: You mentioned earlier in our talk that over the course of your career, you have gotten more interested in the biological value of your research. So where are you today in terms of your interests in advancing, from NMR to advancing biological knowledge and advancing clinical knowledge?

BAX: Well, again, I wouldn't dare to call it clinical knowledge, but I'd sort of call it basic knowledge that perhaps is at the basis of clinical diseases, like the amyloid diseases, like a lot of us are very focused on. I'd say I've got my feet in both worlds. And I realize my shortcomings. I also realize what my strengths are.

ZIERLER: What are your shortcomings?

BAX: My shortcomings are that I know nothing about biology really. I mean, perhaps compared to you, I might know something—

ZIERLER: [laugh]

BAX: —but compared to—

ZIERLER: Some of your colleagues.

BAX: —my colleagues, I know nothing. And in a sense—

ZIERLER: And that limits you because no amount of collaboration can serve as a substitute for your own knowledge base of a given area? Is that the idea? Why can't you just say, "What I don't know I can just slot in a collaborator, and he or she will serve as a substitute for what I don't know"?

BAX: Oh, that's exactly what I'm doing, and that's what has made our program as successful as it has been. So the ability to collaborate, especially here at a place like the NIH, where there's plenty of people that know the biology and that are interested in the kind of work that we're doing. Let's face it; if nobody were interested in what I can do with nuclear spins, I might have lost interest myself.

ZIERLER: Because the theory only gets you so far.

BAX: Right, exactly. But it's because the whole world is clamoring to find out what we can do and what we—because they've known that, hey, you've done interesting stuff in the past. They know I'm excited about what I'm doing right now. So it helps to keep driving that excitement, knowing that you might actually do something that eventually proves to be important.

ZIERLER: So what are they clamoring for? They're so excited. What is it that they're clamoring for in your research?

BAX: Clamoring to find out, for example, right now, how oligomers form in amyloid diseases. That's a very hot topic for the last ten, 15 years. We believe we're at the cusp of really uncovering this, at least for Abeta. That's the Alzheimer's related peptide that is relatively NMR friendly and that allows us to do tricks that are more difficult to do with, say, alpha-synuclein that's at the basis of Parkinson's disease. Even there we've been sort of lucky to get in more or less at the ground floor, through collaborators, and collaboration with Michael Zasloff at Georgetown University, having a drug in phase 2A clinical trials.

ZIERLER: So you are closer in the clinical world than you've been letting on previously.

BAX: Well, it's exciting. Only—so like I had really very little to do with it, but it's sort of satisfying to see that samples that were in an NMR spectrometer sort of were motivating moving this forward and trying it in C. elegans, and with those results, moving it forward to trying it in patients. So I guess it's because I've been in this NIH environment for 30-some years now—

ZIERLER: Sooner or later, it was going to happen.

BAX: Right. You know what's important in life. You get older, you know you're gonna die [laugh] at one point. It would be nice if you could do something that has broader impact than just how a spin rotates around a magnetic field. I mean, it's like—you broaden your horizon a little bit.

ZIERLER: So for the last portion of our discussion, I'd like to ask some broader questions, bigger questions that have a more philosophical basis to them, I suppose. At this point in your career, do you still think of yourself as a physicist who's working in other applications, or have you moved beyond—not that there's anything to—you can't really ever move beyond physics, but in terms of your own work, are you not working as a physicist day in and day out?

BAX: I believe my thinking is still based in physics, because at the root, I'm still thinking technically. But I'm embarrassed to admit I've basically forgotten most of what I learned in college about physics. The hard core classes that I took, it's gone. So calling me a physicist is clearly inappropriate today in the sense that any real physicist, I have little common ground with. Calling me a biochemist, absolutely not. A biophysicist? Perhaps. But my knowledge is still rather narrow. Even after working in this area for over 30 years—

ZIERLER: You still have an identity crisis of what you really are. [laugh]

BAX: Absolutely. Completely.

ZIERLER: Are there fundamental concepts in physics that you keep coming back to, day in and day out, that inform your work? Even if you've forgotten 90% of all of things you learned as an undergraduate and in the lab at Oxford, are there certain fundamental laws of physics or theories or principles that constantly inform your work, the way you put together research, the way you define success or failure?

BAX: Again, a very complex question, but one aspect of NMR that sort of remains closer to physics and to theory—and [laugh] forgive me for the word—relaxation—has a very different meaning to the rest of the world than it does to NMR spectroscopists.

ZIERLER: What does it mean to you?

BAX: To me, it means how nuclear spins relax back to their equilibrium. It's all based in physics, the kind of work that Nicolaas Bloembergen worked on back in the '50s. And that's where—

ZIERLER: What did he discover?

BAX: He described the theory of why fluctuations in the magnetic field, and how they impact the recovery of magnetization to its equilibrium state based on second order perturbation theory. Even to this very day, the most interesting physical aspects of NMR spectroscopy remain in that area of physics. And that's the only place where I'd say theory and calculation still have an exact role, and where—

ZIERLER: It's still with you.

BAX: It's still with me, and with some of my more exact oriented colleagues. I'm worried that it's a bit of a dying art, that there are very few of the younger generation that have picked up and fully understand how this comes about, the theory behind it. And if this training were to disappear, that would really become a big setback for NMR spectroscopy and its future.

ZIERLER: How do you see yourself as a mentor in terms of keeping this—it's not really a tradition, but it's an intellectual heritage—if you see value in keeping it alive, what might your own role be in doing just that? With postdocs, with graduate students, with junior colleagues?

BAX: Right. You correctly say it's an intellectual heritage, really, because that's what it is.

ZIERLER: And where does Bloembergen come from? Where does his heritage trace to?

BAX: He was trained in physics back in the Netherlands before coming to the U.S. and getting a Nobel Prize in optics. But effectively, this basic theory—for him, the novelty was sort of gone after they understood the basic concept of relaxation. For us, understanding relaxation in proteins is different. It has to do with complex transitions that take place in proteins that we can try to understand. That proteins are not static objects. Relaying this information to postdocs is important. Now, a problem with that is that the postdocs are typically lacking the training in physics that they need to get a quantitative understanding of this phenomenon. So I sort of feel a little bit uneasy for the last five to ten years that the postdocs that come to this lab haven't had the education as an undergrad or grad student in the more hard core physical chemistry, quantum mechanics, setting up a Hamiltonian, solving a wave function, to understand what nuclear

relaxation is. And it really is a danger. And it's because it's such basic science, funding in academia is much less available now than it was back in the '80s. Especially the Netherlands thrived in NMR spectroscopy because there was funding for basic science, and it lasted until the mid-'80s. And the Netherlands, besides exporting cheese, they've exported more NMR spectroscopists than any other country. [laugh]

ZIERLER: [laugh]

BAX: Because we were having this emphasis on basic knowledge. So a lot of—

ZIERLER: So NMR spectroscopy, it's really a national treasure for the Netherlands in a sense.

BAX: It was, it was. And it still is, to some extent. But there too, the focus has become on applied research. And it will be a challenge to keep this alive for generations, I think. The textbooks, of course, are eternal, so smart young guys can always go back and read it back from Bloembergen's papers or from Lewis Kay's papers or from any of the other bright NMR spectroscopists.

ZIERLER: So getting back to your question as a mentor, how do you see your own role in preserving this intellectual heritage? Are you emphasizing certain ways of doing things in the lab, certain courses that need to be mastered? Or are you not involved on that level?

BAX: I'm basically—let me be honest—I'm too selfish.

ZIERLER: [laugh]

BAX: I'm more interested in doing novel things than I am to preserving it for eternity. And I still sense too much excitement of new opportunities that are available rather than trying to preserve what we've done. We've published it. People can read up on it. What I try to do is when we do a new experiment, we try to document it as completely and as fully as possible, such that 100 years from now, 1,000 years from now, people can go back and read it and say, "Oh, can you see? Can you believe what they did in 2003?"

ZIERLER: Now, the things that you're excited about now—I'm always curious, are there things that were fundamentally mysterious to you when you were starting out that now are clear? Or are there things that were always mysterious and even with all of the advances that you can foresee into the future, will remain mysterious?

BAX: Those are broad, deep questions. Things that were mysterious—it's sort of like—one of the things that we really never quite understood is how proteins move. The whole picture of a protein came from crystallography, and trying to see what role does movement play in how proteins function, that has been a bit of a driving force behind a lot of what we've done. That question still is an open question. I've been arguing with many of my NMR colleagues that had ideas of proteins being like spaghetti, or proteins are like bricks. And it's a little bit of both. Their switching modules, how do they work. And in some cases, they've been solved. In other cases, they have not yet been solved. So there remain so many questions to be answered, because everything—I mean, we're looking at the smallest possible object. It fits in a bigger object, fits in a human cell, it fits in an organism, and eventually it fits in a human. See? So those questions—there are always bigger questions.

ZIERLER: There's always bigger questions.

BAX: There's always bigger questions to answer.

ZIERLER: And there's no end to that. There's no natural end point of total knowledge. I mean, the Socratic idea that the more you know, the more you know you don't know, does that basically make sense to you?

BAX: That totally applies to pretty much everything I do.

ZIERLER: So what do you know you don't know now that you didn't even know you didn't know 30, 40 years ago?

BAX: What do I know now?

ZIERLER: What do you know that you don't know now? Because of what you know.

BAX: What I don't know is at the slightly higher level of why proteins don't play the role in human cells that I naively had thought they did, in terms of signaling. This was so oversimplified, the picture that we had, and that becomes increasingly apparent. That cellular life is far more complex than I was aware of. And that doesn't mean that we can't keep on working on it, but you can only solve one little bit at a time. And there are so many of my colleagues that have more expertise in it, that I'm sort of trying to pull out of that area, and trying to work on something where I feel that I can more rapidly contribute to knowledge.

ZIERLER: Do you feel at the later stages of your career that the urgency to contribute practically, so to speak, has increased for you? This desire to have a concrete usable end product that you can show as a result of your research?

BAX: Yes, although to qualify that, my research doesn't really have a clear end product. For me, there are two end products. One, to see the technology that I develop to become widely used. And that might be reflected in, say, an impact factor, to sort of put it profanely. [laugh] But it would give me even greater satisfaction if any molecule that I had ever worked on and that I could sort of point to and say, "This molecule made it into the clinic, and now patients are being helped by taking this as a medication to extend their life, to improve the quality of their life, or otherwise have a benefit." Even if nobody ever published it, this would give me immense satisfaction.

ZIERLER: And is this still a theoretical proposition for you, or have you ever already established this narrative in your career so far where you can trace your work to a patient's better health outcomes?

BAX: Well, I can trace that, but that's like embracing a lot of things that I only take very, very indirect credit for, right?

ZIERLER: That's fine.

BAX: So a lot of—

ZIERLER: Not everyone has to have a Jonas Salk moment in their career.

BAX: No, right. [laugh] But almost any drug that makes it to market these days, NMR spectroscopy has played a role in.

ZIERLER: And you've played a role in NMR spec…right.

BAX: Exactly. None of those were developed without using the experiments that I developed. So in a sense, I mean, I could say, "Hey, I deserve credit for all of that." But that's of course overhyping it, because somebody else would have developed that experiment a couple of years after we did.

ZIERLER: So maybe it's more like your contribution is a brick in the wall.

BAX: It's just a small brick in a big wall. But at the same time, something like the development of squalamine as a drug, if this were ever to make it through phase three clinical trials, I would be ecstatic about it, even while I have zero to do with it, really, except for collaborating with the guy that was pushing for that, Michael Zasloff. So yes, getting older makes you more mature. At the same time, I'm still young at mind. I still stay excited about the technology, but I would be giving anything I had to sort of have the satisfaction to see a direct link between this is what I worked on and now, this patient is benefiting from that.

ZIERLER: So I guess for last question, looking to the future, what are the things about your research that you're most excited about? What are the areas of knowledge that you feel are within your grasp to understand and really to contribute to your field, broadly conceived?

BAX: Right now, the project I'm most excited about is this oligomer formation in amyloid diseases. That definitely is within grasp. It's a project—

ZIERLER: What is amyloid disease? What is that?

BAX: Amyloid disease is related to many of the neurological disorders such as Alzheimer's, Parkinson's, type 2 diabetes, Huntington's disease. A very wide spectrum of those. ALS. So we've got projects related to many of those diseases ongoing. If any of those prove to be

successful in terms of helping contributing to a development of a cure or even an understanding of the molecular basis of the disease at a better level—

ZIERLER: So how does your work contribute to that understanding in terms of what you're doing now?

BAX: Well, if we can understand how the initial first event of Alzheimer's aggregation, oligomerization occurs, we might be able to interfere with it.

ZIERLER: In its early stages.

BAX: In its very early stages. It could potentially, conceivably, but this is very, very far-fetched, start thinking about developing an inhibitor for this event to occur.

ZIERLER: Pre-emptively.

BAX: Pre-emptively.

ZIERLER: Like a multivitamin that you take so that you don't get Alzheimer's.

BAX: Perhaps.

ZIERLER: Forgive me, but that's the idea.

BAX: For example. And of course many people have tried this empirically with let's say green tea extract or whatever. And I don't want to poo-poo that, but in principle, we have a possibility to study in an NMR sample cell whether this has potential or not. With ALS, we can look at superoxide dismutase, look at mutants that are disease related, and see why is the disease

related mutant behaving different from the wild type protein. What different instability? Can I change it with pressure? Can I see how the protein reacts?

ZIERLER: And you're looking at these cells still as a physicist would you say, or not really so much as physicist?

BAX: Well, more as a physicist, really. Because anybody here from the clinic would sort of think, "What are those guys doing? They have zero understanding of what's really needed for this patient."

ZIERLER: [laugh] So by default, you're seeing this as a physicist.

BAX: Absolutely.

ZIERLER: Very good. Well, Dr. Bax, it has been an absolute pleasure talking with you today. I really appreciate your time.

BAX: Thank you. You're very welcome.

[End]