SMB by David Zierler

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Remote Interview

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DAVID ZIERLER: This is David Zierler, oral historian for the American Institute of Physics. It is April 20th, 2020, and it is my great pleasure to be here virtually with Robert Tycko. Dr. Tycko, thank you so much for being with me today.

ROBERT TYCKO: Happy to be here with you.

ZIERLER: To get started, can you tell me your title and your institutional affiliation?

TYCKO: I'm a senior investigator in the Laboratory of Chemical Physics in the National Institute of Diabetes and Digestive and Kidney Diseases, which is one of the NIH institutes. I've had this position for about the past 25 or 26 years.

ZIERLER: Now let's take it right back to the beginning. Tell us a little bit about your birthplace and your family and your early childhood.

TYCKO: Well, I grew up in the New York area. I was born in New York City. I grew up primarily on Long Island, in Stony Brook. My father has a PhD in physics, Daniel Tycko. He became a computer scientist. Actually his PhD thesis involved using early computers for wave function calculations. So he became an expert on that, and then eventually became a computer science professor at Stony Brook University, the State University of New York at Stony Brook. So that's where I spent most of my childhood.

ZIERLER: So you grew up around physics, because of your father. He exposed you to the discipline, a little bit?

TYCKO: Not in a consistent, concerted, deliberate way. It was around me. It was something I was familiar with. Growing up, it was not something that I—I didn't know what I was going to do when I became an adult. [laugh]

ZIERLER: You wrote in your biographical article that you liked to tinker when you were a kid.

TYCKO: Right. So I enjoyed building things—model cars, little electronic slot cars. So I started soldering when I was ten or 12, so I'm very good at soldering. It's one of my strengths, one of my main strengths. And I did that partly with my father, but it was just something I gravitated towards. Maybe there's genetic factors, but it's not because it was pushed on me. And my brothers are not like that. I have two brothers; they don't have the same interests. Actually, my older brother is a scientist, but not interested in building things, doesn't have the same precise interests. My younger brother is a lawyer.

ZIERLER: Did you go to public school or private school?

TYCKO: I went to public schools. Public high school.

ZIERLER: And in high school, were you particularly good in the math and sciences?

TYCKO: I was always a good student, yeah. [laugh] I was a very good student. Yeah, math was something that I enjoyed. I happened to have a very good math teacher in high school, Mr. Skrzypeczki. I'm not sure I can spell his name for you. He was an interesting character, because [laugh] he was—this was the 1970s, mid-1970s, beginning of the disco era, so he would wear polyester pants and flowery shirts and stuff like that, and he would work as a bartender in the summer. But he was interested in mathematics, so he taught a class my last year in high school that—it was a course that he just designed himself, which was basically advanced topics in mathematics, and it was in that class that I got exposed to how to symbolic logic and formal methods for proving theorems, and just various aspects, just a hodge-podge of topics in mathematics. So I enjoyed that kind of stuff. So I enjoyed math, and I enjoyed building things, and that's really why I became a scientist, I would say, actually not because I was interested in scientific questions. I liked the day-to-day aspects of it. That's what attracted me to it, initially. But when I went to college, I didn't go to college thinking I was going to be a scientist. I wasn't sure.

ZIERLER: You majored in chemistry at Princeton. Is that right?

TYCKO: I did major in chemistry, but see, once I got to college, it pretty quickly became clear to me that that's what I was good at, compared to other things. I wasn't as good—I mean, I'm a reasonably good writer, but I'm not a great writer. And it's just what I gravitated towards.

ZIERLER: What about engineering, given your interest in building things? Did you ever consider that?

TYCKO: I considered it. I don't know. Maybe it would have been—I think as a young person, you make certain decisions that are [pause]—can you hear me OK?

ZIERLER: Yeah, we just cut out for a second. The last thing I heard was when you said, "When you're younger, you make certain decisions" in response to my question about engineering.

TYCKO: Yeah. Maybe it would have been a good idea to study engineering, but that's a decision that people usually make when they're applying to college, and at that point in my life, I wasn't ready to commit to that.

ZIERLER: Did you have a senior thesis at Princeton in chemistry?

TYCKO: There was a requirement that everybody at Princeton had to write a senior thesis, and my senior thesis was about photosynthesis. But actually I spent most of my time fooling around with microwave electronics for electron paramagnetic resonance. So that was my first exposure to magnetic resonance. It was a project to look at EPR signals from photosynthetic reaction centers. It was fun. I grew my own spinach and isolated the chloroplasts from the spinach, and I also fooled around with some electronics as part of the thesis, to try to adapt the EPR machine for time-resolved EPR measurements. And it involved pulsed lasers to excite the photosynthetic cycle. I don't remember most of this, actually. I don't remember most of the details. It was a long time ago. But that was my first exposure to magnetic resonance.

ZIERLER: Now was this because of a class that you took, or a professor that you became close with? How did you get involved with magnetic resonance? How did you know to be interested in it?

TYCKO: Again, I—it was not done in a very systematic way. I mean, prior to that, I had actually worked in the physics department. I had a paying job in the physics department building electronics for high-energy physics experiments, working for an electrical engineer who was employed by the physics department. So I spent a couple of summers and I spent a few hours a week or something during the school year assembling electronics, mostly. I learned a little bit of electronics there. Not that much. I got even better at soldering, though. But in chemistry, I was working in a surface chemistry lab initially, working with ultra-high vacuum systems, the kind of experiments to study simple chemical reactions on very carefully prepared clean metal surfaces. I did that for a while. But then when it came time to choose a senior thesis project, I think I just looked around at what the options were, what the different professors were doing. See, I had always been interested in biological things, at some level. I wasn't exactly sure. I always had the sense that biology is important, and that there's a lot of—it has a lot of implications and a lot of open questions and all this kind of thing. So I guess I wanted to try my hand at doing some biological—or biophysical chemistry, biologically related work. That's probably why I chose that.

ZIERLER: How many courses in biology and physics did you take as an undergraduate? A lot?

TYCKO: I took very few biology classes, and I still—my knowledge of biology is actually very scanty to this day, I would say. [laugh] Because my formal training is very weak. I took a cell biology class. This must have been back in my—maybe it was in my junior year? I forget. Sophomore or junior year, so it would have been 1977 or 1978. So that's my [laugh] knowledge of cell biology. I think a lot has happened in cell biology since then. [laugh] So I pick things up here and there, but my formal training is not very good. I never took an actual biochemistry class. I never took an introductory biology class. I never took a biology lab course. I took physics classes. I took freshman physics classes. I took sophomore physics. I took this advanced classical mechanics class at Princeton, which is the Goldstein Classical Mechanics textbook, which is really a very difficult book. I always did very well in those classes, but I was killing myself to do that, and I felt like I wasn't—I was just learning a bunch of mathematical tricks and basically complicated problems involving balls rolling down planes. I didn't feel like I was learning enough about real stuff, real phenomena. So that's really why I ended up going into chemistry for my undergraduate degree and then later for my PhD, because I felt like I wanted to learn more about real stuff.

ZIERLER: And was there a particular connection that drew you to Berkeley for graduate studies? Did you want to work with a particular professor there?

TYCKO: I applied to lots of good chemistry departments. In those days, each chemistry department—there was no internet, of course, so you'd write to the chemistry department, and they would send you a brochure listing the faculty members and their interests. And I looked through those. I knew I wanted to do something in physical chemistry, more on the physics side of chemistry. So I applied to schools that were reputed to have strong physical chemistry divisions. And then I looked up some of the papers from people I was interested in, and I ended up doing my PhD with Alex Pines at Berkeley. So I looked up some of his papers, and there was complicated mathematical stuff involving quantum mechanics and quantum statistical mechanics and things that I didn't know but it looked like that would be interesting to learn. And he was talking about applying those to liquid crystals, and liquid crystals sounded interesting. I ended up not really doing anything with liquid crystals, but—and then also there was some description of building magnetic resonance equipment that involved electronics, which I liked. And then

also having spent four years at Princeton, I was looking for a different environment, a different type of physical environment and university environment, and Berkeley was quite a different place. So that was attractive, also.

ZIERLER: What was Alex's own background? Did he have a physics background?

TYCKO: No, he also had a chemistry background.

ZIERLER: Coming from Princeton, culturally, did you enjoy the significantly different change in scenery at Berkeley?

TYCKO: Yeah. Princeton wasn't a good fit for me, personality-wise, and socially-wise. I'm not, I don't know—it was, to me, a very strange place, honestly. Very different than anything I had been exposed to prior to going there.

ZIERLER: You mean because it was a party school?

TYCKO: No, not party school. No, just the more upper class prep school kind of environment. Which was OK, but that's not who I am, so it just didn't—

ZIERLER: There were not too many public school kids from Long Island?

TYCKO: There were some. There were some. But they were not—that wasn't the dominant culture there. So Berkeley was a little bit more—

ZIERLER: Diverse?

TYCKO: Had more—yeah, I don't know—maybe a better match for me. Just a bigger place was good. I play music. That's my main hobby, both classical and jazz music. I was interested mainly in jazz music at that time, and I couldn't find that many people to play with at Princeton, because it was a relatively small place. And Berkeley was—

ZIERLER: What do you play?

TYCKO: I play saxophone, clarinet, drums, a little bit of keyboard. But at Berkeley, because it's a big place, there were lots of—there's thousands of students, tens of thousands of students, so some of those people are going to be good musicians. So I ended up having a lot of fun playing music with people I met at Berkeley. It was easier to find those people.

ZIERLER: What was the split between lab work and course work at Berkeley? How much were you in each?

TYCKO: Very little course work. When you arrived, you had ten weeks to choose a group to work with. By the time I got there, I had already narrowed it down in my mind to just two or three people I was interested in, probably. And they just really wanted you to get into the lab and start churning out research. So I forget exactly, but you only had to take, I don't know, maybe four classes or something total. Some small number of classes. The only specific class that was required was a thermodynamics class, a one-semester or one-quarter, I think, thermodynamics class. But I did take—there was a quantum mechanics class. I had taken a very good quantum mechanics class as an undergraduate, I should mention, with James Peebles, who won the Nobel Prize this year.

ZIERLER: Yes, yes.

TYCKO: He was a fantastic teacher and just a nice guy, and really one of the best teachers I had.

ZIERLER: What was so effective about his teaching?

TYCKO: He just explained things very clearly, and obviously knew his stuff, and I guess probably told little stories to go along with it? I don't remember exactly. But it was all taught from his own notes. I think later he wrote a book, which I now have a copy of, which was probably based on the notes that he had prepared from teaching this class. But after I saw that he got the Nobel Prize, I wrote to him by email, and I said, "Congratulations. I'm so happy to see that you got the Nobel Prize. Because I was in your—you don't know me, but I was in your [laugh] class, whatever it was, 30 years ago." Longer than that. Almost 40 years [laugh] ago. "And it was one of the best classes I ever took, and I still use the material that you taught me, to this day."

ZIERLER: Oh, wow.

TYCKO: Which is true. And amazingly, he wrote back to me the next day. He said, "Oh, it was so good to hear from you." Of course, maybe he probably wrote—he must have gotten 10,000 email messages, right? He just won the Nobel Prize. But at least he took the time to respond, which was very nice.

ZIERLER: What was it that he taught you that remains close with you to this day?

TYCKO: Just the basics of quantum mechanics, which we still use. That's one of the things that attracted me to magnetic resonance was the fact that we actually use—because in magnetic resonance, nuclear spin systems, coupled spin systems behave—there's a small number of energy levels, and the spin system evolves according to the Schrödinger equation, according to the laws of basically non-relativistic quantum mechanics, and we're actually watching that evolution. That's what we're seeing when we detect NMR signals. And they evolve in a coherent fashion over long periods of time, milliseconds or seconds, and then we design—then you can manipulate that evolution by applying external fields, by giving radio frequency pulses. And so there's a lot of richness to that, which attracted me, that you can actually use the quantum mechanics, and you manipulate the quantum mechanical evolution in order to affect the NMR signals in ways that allow you to get useful information out of whatever sample it is that you're studying. So that kind of thing, it's very unique—still pretty much unique to NMR, that you can do those kinds of experiments. So now that's become quantum information, the whole field of quantum information is based on those kinds of ideas. But it's the kind of ideas that have been around in NMR spectroscopy for a long time, and which quantum information didn't—the field of quantum information or quantum computation didn't exist back in 1980, when I started graduate school. But those ideas or very closely related ideas existed in NMR. So I enjoyed that. And that kind of thinking, I think I was first exposed to that kind of thinking from my undergraduate quantum mechanics class.

ZIERLER: Now the lab work that you did, it was only with Alex Pines, or you were doing lab work for other professors as well?

TYCKO: Just with him. My first experimental project was actually with a visitor. He was a sabbatical visitor, a guy from Germany named Dietmar Stehlik. So my first paper—I think my first paper for my graduate work was with Alex and with Dietmar Stehlik. But I didn't collaborate with other—we didn't work with other faculty members.

ZIERLER: And what was that collaboration on? What were you working on?

TYCKO: If I can remember, it was an optical nuclear polarization effect. So there's certain molecular crystals—it's kind of a specialized thing—molecular crystals where you shine light on them to create electronic excitations. The electron spins that you excite are spin polarized, and then through couplings between electron spins and nuclear spins, you can end up generating large nuclear spin polarizations, which means large NMR signals. In these molecular crystals, it's an effect that occurs at very specific external magnetic field strengths and particular crystal orientations. The experiments that I did were experiments in which I could very rapidly switch the magnetic field into the value where this optical polarization effect happens and then very rapidly switch it away, and I could synchronize the field switching with a pulsed laser excitation. And I showed that—we predicted and we showed that by doing this, you could actually enhance the effects a little bit. But that kind of thing. So that, and then we dropped those experiments. But this business about optical polarization or various ways of polarizing nuclear spins to get enhanced NMR signals is something that has come up in my own career and in the field in general, over and over and over again. Because NMR is a tool that has a very high information content but low signal-to-noise, so you need big samples. And that's always a problem. That always limits your ability to study things that you would like to study. So any technique that enhances the sensitivity and enhances the signal strengths is very valuable. And so we're always interested in ways of enhancing the nuclear spin polarizations, which is what determines the strength of the signals.

ZIERLER: And did this research directly play into your dissertation work?

TYCKO: No, actually. That wasn't in my PhD at all. What my PhD thesis was about was actually mostly mathematics. So I ended up doing mostly mathematics. You asked about collaborations with other faculty members. So actually about half of my PhD thesis was a collaboration with a mathematician who at that time was at the University of California at Santa Cruz, John Guckenheimer. And he was an expert on mathematical non-linear dynamics. And so we had some ideas about how to use ideas from mathematical non-linear dynamics as a way of constructing radio frequency pulse sequences that would be useful in NMR, in particular pulse sequences that could generate specific types of excitations of nuclear spin systems over broad ranges of experimental parameters. So the simplest one, and probably the most successful one being just a spin inversion. So you take a sample in NMR, you put it in a magnetic field; the nuclear spins tend to line up, say, parallel with the magnetic field direction. And then by giving a radio frequency pulse on resonance, you can flip them from being parallel to being anti-parallel. You can flip them from pointing up to pointing down. That's called a pi pulse, because it rotates them by an angle pi. You can do that if you tune your RF pulse to being exactly on resonance with the precession frequency of the nuclear spins in the magnetic field, in other words the NMR frequency. But if you go off-resonance, if your pulse—if the RF carrier frequency of your pulse doesn't exactly match the resonant frequency of the spins that you're exciting, then you don't get a perfect inversion, a perfect spin flip. But by constructing, rather than using a single pulse, constructing sequences of pulses with different RF phases and different pulse lengths, in principle you can rotate, you can construct pulse sequences that rotate spins by an angle pi, so flip them from pointing up to pointing down, over a large range of their resonant frequencies. And this turns out to be useful in certain circumstances in NMR spectroscopy, but it was—the interesting thing [laugh] about my thesis was really the mathematics. It was an approach for doing that.

ZIERLER: In retrospect, was a chemistry department the best home department for this kind of a thesis? How much chemistry did it have in it, at the end of the day?

TYCKO: So there was no chem…in the end, I learned no chemistry, I learned no biology, and I learned some mathematics. I learned a little bit of physics. That's what I got. And a little bit of electronics. That's what I got out of my PhD. So I got my PhD in four years. After four years, it was clear to me I wasn't really going to learn much else.

ZIERLER: [laugh]

TYCKO: [laugh] So I learned enough of that, and then it was time to move on to something else.

ZIERLER: Who else was on your thesis committee?

TYCKO: Well, the thesis committees honestly really weren't taken that seriously at Berkeley. There was no thesis defense. You had to write a thesis, and then you had to get, I don't know, three or four faculty members to sign off on it, including your own thesis advisor. So maybe just three. You just needed three signatures, something like that; two people within your department and then one person outside the department. They ended up signing off on it. I don't know if they read it.

ZIERLER: [laugh] So at that point, were you pretty certain that NMR was going to be your career specialty, at that point?

TYCKO: I don't think I was thinking that far ahead, I would say. I didn't know. So at that point, I ended up going as a postdoc to—so then for my postdoctoral work, I wanted to do something biologically related. So actually biological NMR was just blossoming at that point.

ZIERLER: When you started to develop an interest in biological NMR, were you aware of the work that was being done at NIH at that time?

TYCKO: There wasn't very much, actually. At that specific time, there wasn't a lot being done, really. So this was 1984. In 1984, I don't know if there was very much really biological NMR. There was some.

ZIERLER: And you don't mean just at NIH? You mean anywhere.

TYCKO: No, in general, the field was starting to take off. Because multidimensional NMR had been proposed some years earlier, and was gradually getting better and better, and a lot of developments in that. And that allowed people to look at biological molecules where there are many different atomic sites, many different hydrogen atoms, and many different carbon atoms and nitrogen atoms. And to actually resolve the signals from individual atomic sites, you need to use multidimensional NMR techniques to spread the signals out, and to also figure out which atoms are next to which other atoms by looking at correlations of NMR frequencies in different dimensions of a multidimensional experiment. You already talked to Ad Bax, and he's one of the masters of that field, and he made a lot of contributions in that area. So that work was just starting to take off around 1984.

ZIERLER: And you were interested in developing an interest in biological NMR. Were you also interested in health science research and advancing human health issues from an NMR perspective, or you were just interested in the biology of it?

TYCKO: I didn't know enough about it. I didn't really know. I didn't know any of the specifics. I just had this general sense that it would be interesting to work on something biological. [laugh]

ZIERLER: And so how did the postdoc at Penn come about?

TYCKO: I just thought about—well, I was doing—the lab I came from at Berkeley was a so-called solid state NMR lab, so it was a lab that specialized in NMR techniques that were applicable to solid materials. So solid materials just means something that's not a small molecule, that's not a small molecule that's tumbling rapidly in solution. So I was looking for biological solid state NMR groups, because I knew about solid state NMR and I thought it was interesting. So in biological systems, it was, what does a solid mean in biology? At that time, the main idea for what solid state NMR would do in biology was that it would allow us to determine molecular structures and properties of proteins that are embedded in biological membranes. So this was a big unsolved problem, is how do you study proteins that are stuck in or stuck to biological membranes, rather than just being in free solution. Solution NMR methods could be used to study proteins that are just tumbling in free solution, but solid state NMR measurements could be used to do membrane associated or integral membrane proteins. So I was looking at groups that were doing that kind of work. I looked at a variety of labs.

ZIERLER: And what was Stanley Opella doing at that point?

TYCKO: He had been trained in solid state NMR, and the reason I guess I went to his lab was that he had background in solid state NMR. He had an interesting lab with reasonably good equipment. And he seemed to be somebody who was the most—more serious about the biological questions themselves, so I thought I would learn the most from going to that lab. I spent two years there, and I learned a little bit of biology. In the end, I spent some time building equipment, and developing some pulse sequences that we could use to—I guess my main thing was ways of looking at nitrogen NMR signals. Nitrogen-14. Nitrogen-14 is the most abundant isotope of nitrogen, so all proteins and nucleic acids have Nitrogen-14 in them. Nitrogen-14 is normally difficult to look at because rather than being a spin-one-half nucleus that has only two energy levels, it's a spin-one nucleus, with three energy levels. And the separation of those energy levels is affected by what are called nuclear quadrupole couplings. And the nuclear quadrupole couplings are large on the NMR—on the scale of NMR interactions, interactions that affect NMR spectra, nuclear quadrupole couplings are large. And so this gives you very broad NMR lines, NMR spectra that span several megahertz in frequency. And for spin-one-half nuclei, they usually span just several kilohertz in frequency, so it's like three orders of magnitude broader than a spin-one-half spectrum. So how do you get those kinds of spectra? So most of my postdoctoral work was looking at so-called overtone signals. These are signals where you're looking at transitions from the lowest energy level of a three-level system to the highest energy level. So you're jumping over the intermediate level. And these transitions occur at roughly twice the frequency of the standard NMR signals from Nitrogen-14. Anyway, they're called overtone—we called them overtone spectra. So that was the main thing I did, was to develop methods for observing overtone signals and characterizing their properties.

ZIERLER: When you talk about building equipment for your postdoc, can you help me visualize—what does that mean in an NMR context, when you're building equipment? What exactly are you putting together, and with what materials?

TYCKO: So some of it is electronics, the various electronic circuits that generate radio frequency pulses that you apply to the sample, and then for detecting the radio frequencies, the signals that come back,

that are emitted by the sample. So the electronics is a box with a bunch of components in it that are connected to one another by cables in those days. And designing that—choosing those components and how to wire them up properly. So that kind of thing.

ZIERLER: Are you relying on your soldering skills for this?

TYCKO: There was some soldering involved there, yeah. And then the NMR probe itself is the piece of equipment that you insert into the NMR magnet that contains your sample and contains a resonant RF circuit that you can tune to the NMR frequency of the nuclei that you're observing in that particular magnetic field. So there's the construction of the probe. The probe is a piece of metal. Some of that is machining just the mechanical components, the structural components of that probe, and then adjusting the inductors and capacitors to get the right resonant frequency. That thing.

ZIERLER: And when you talk about samples, in a biological context, what are the samples? What would be a good example of a sample?

TYCKO: Well, so the samples—in those days, what I was doing in these overtone experiments, we actually were just looking at really simple chemical compounds, really, for the most part. So just a powder—just a powder of some compound that you pack into a little glass tube, and you'd insert it into an RF coil inside of your NMR probe. These days, in my lab, we do more sophisticated things, so we're looking at real—by now, we're looking at things that are more complicated and actually more directly relevant in biology and medicine. So the samples now are various kinds of protein assemblies. They can be protein filaments, or we've looked at components of viruses, protein shells that contain the genetic material of a virus. We've done work on the HIV virus. So the HIV capsid protein, we've published some papers about that over the past five or six years. So now, the samples are protein assemblies that are typically prepared in some suitable buffer, and then we record electron microscope images, use electron microscopy to get pictures of what these assemblies look like. These are assemblies that have typically nanometer, sub-micron dimensions. And then we pellet them in an ultra-centrifuge to concentrate the protein assemblies, and then we pack them into a little cylindrical capsule and we use a technique called magic angle spinning, which is a very pervasive technique in solid state NMR for narrowing the NMR lines and giving you tractable, interpretable spectra. So we pack them into these little capsules that are then spun very rapidly during the NMR measurement by a pneumatic turbine system. So it's gotten a little bit more complicated in the past 30 years. By now, we're looking at, I think—back in those days, with my postdoc, there was a lot of time spent just looking at very simple model systems, and just doing demonstrations of—proof-of-principle demonstrations of techniques or ideas. And by now, we're actually able to study real things that are—so by now—I guess jumping way ahead, I think the—when I went to the NIH, now about 25, 26 years ago, my goal was to try to do something in biology with NMR and biology that would actually be of interest to real biologists. So by now, we've achieved that, I think. [laugh] So we've achieved that goal.

ZIERLER: In those early days during your postdoc, you characterize the field as really just developing. Were you hooked into a community of researchers who were interested in this? Were there conferences? Were there journals? What were the opportunities to collaborate with other labs around the country and around the world on all of these new developments on biological NMR?

TYCKO: Certainly there were conferences. The big conference in the U.S. was called the Experimental NMR Conference, or the ENC, which still goes on to this day, once a year. A meeting of about a thousand

people. So I would go to that almost every year, probably, and at that conference, I would hear about developments in other labs and exchange information and get to meet people. Of course, there were journals—the Journal of Magnetic Resonance was the journal that published a lot of the basic methodology in those days, and that journal still exists. We still publish papers there. I'm not exactly sure how to answer the question. I mean, it was not a highly organized community in those days. It was just individual labs. They knew each other, knew about each other's work, followed each other's work, but there was no effort to coordinate. There wasn't a process or really an interest in coordinating efforts among different labs. It was more like the usual competitive spirit of science, where you hear about somebody else's work, and it suggests something to you, and maybe you want to try to do it better than they did or something like that.

ZIERLER: In the development of any new field, there's always going to be the questions of, "Where is this headed and what is it going to be applied towards?" So what were some of the possible answers in those early days about where the field was headed and what possible applications this research might be put toward?

TYCKO: In those days, the main emphasis was on structure, determining molecular structures. In those days, the competitive technology was x-ray crystallography. But back in the mid-1980s, x-ray crystallography was not so easy, either, so there weren't that many crystal—protein structures determined by crystallography. And when a new protein structure was determined by crystallography, by x-ray crystallography, that was big news. And so there was a possibility that NMR would turn out to be an easier and better way, faster way, more general way. You wouldn't have to crystallize things. Just crystallizing in those days was—finding conditions under which a protein forms crystals of sufficient quality and size that you could actually do x-ray diffraction was a challenge. And then there was the possibility also that structures of proteins in a crystalline state were distorted by the fact that they were in a crystal, and that in their actual more realistic, non-crystalline context, their structures might actually be different. So that was another motivation for doing the NMR. I mentioned that solid state NMR methods in principle could be used to determine molecular structures of proteins that are embedded in or associated with biological membranes. And in those days, it was impossible to crystallize anything that was associated with membranes. So those were the kind of opportunities that people thought about back in the mid-to-late 1980s. Most of that has changed in various ways. Things don't go the way that you think, at that time, because by now—I would say by now, current NMR techniques are much better than 1980s crystallography, but it's a moving target. So crystallography has gotten a lot better, NMR has gotten better, and then electron microscopy has gotten much better in the last few years. So things evolve, and it's hard to predict how they're going to evolve. But that's what people were thinking in those days. And then also you get dynamics. So you can probe molecular motions with magnetic resonance techniques, which you can't really get from electron microscopy or diffraction techniques, which mostly give you a static picture of a system, whatever system you're studying. So NMR, one of its strengths is you can study motions, time scales, amplitudes, symmetries of motion, of molecules. That remains one of its unique strengths, I think.

ZIERLER: When you finished up at Penn, 1986, was your original intention to go into academia, to get a faculty job, to run your own lab? Was that your idea?

TYCKO: I never really knew what I was going to do with my life.

ZIERLER: There's no grand plan, you're saying?

TYCKO: I never had a plan. When you make decisions, as I said before—I think now I'm 60 years old, but looking back, you make decisions when you're 20, based on what you know at that time. Maybe it was the right decision. Maybe it wasn't the right decision. But you just go. So I think in the end I just always just took what was the best option available to me at that time. [laugh] I worried about it. I worried about, "What am I going to do with my life?" I have my own children now who are in their twenties, and they worry about this "what am I going to do with my life" kind of thing.

ZIERLER: Were you married when you were a postdoc, or you were a bachelor back then?

TYCKO: No, no, no. Later.

ZIERLER: So it's 1986. So what are your options? What are your prospects at this point?

TYCKO: I had never really—I hadn't really planned to be a professor, but then by the time, after doing a postdoc and I was going to look for jobs, so what can you do? That's one of the things you can do. So I applied for academic jobs. And I had a good publication record at that point. I got a lot of interviews. I didn't really know how to interview. I had no experience with interviews. I had never really had to sell myself. As a student, you have to do well in your classes, and as a graduate student or a postdoc, you have to write papers and be productive, but you don't necessarily have to sell yourself to strangers in a one-on-one conversation. So I didn't know how to do that.

ZIERLER: And even with funding, you never had to do that?

TYCKO: Well, I didn't have to raise—actually, I guess I had an NSF fellowship when I was a graduate student. I had later a fellowship as a postdoc. But it was just based on things I wrote. It wasn't based on an interview. So I didn't know what to do at an interview, really. I wasn't good at that. I went into it thinking, "Well, I have this very good publication record. Obviously, I've done a lot, so what else do you need to know about me?" [laugh] Sounds like an arrogant attitude, but it actually makes sense, and it's still true. But that's not how things really work in the real world. So now I tell my postdocs, when they're in my lab now, the main advice I give them is when you're applying for jobs—"Everything you've done up to this point just gets you an interview."

ZIERLER: [laugh] Right.

TYCKO: [laugh] And all the hard work as an undergraduate, graduate student, postdoc—that gets you invited for an interview. But what determines whether or not you get a job offer is the impression you make on that day.

ZIERLER: Right.

TYCKO: Which, it took me a while—so when I started applying for jobs, I didn't know that. No one had ever told me that.

ZIERLER: [laugh]

TYCKO: And it's a simple thing, but no one had ever told me that. So it took me a while to figure that out. Eventually, I figured it out.

ZIERLER: Given the inherently multidisciplinary nature of your work at your postdoc and before that, I'm curious—the jobs that you were applying to, all the interviews that you got, what were the

most natural fits in terms of departments for your research focus? Were you applying for faculty jobs in biology departments, physics departments, chemistry departments?

TYCKO: They were in chemistry departments, because my—you know, departments are—maybe somewhat less so now, but in the 1980s, the boundaries between different departments were very rigid. So a physics department would not hire someone with a PhD in chemistry. That never happened. Biology department might, but I wasn't really—I didn't—I'm still not a good biologist. So I didn't think of applying to biology departments. So I was applying to chemistry departments.

ZIERLER: But that says more about your PhD and less about the field of biological NMR, right? Or is that also the same?

TYCKO: Biological NMR was still—well, in those days, it was still—let's see. So were people getting jobs in—? Maybe people were starting to get jobs in biology departments.

ZIERLER: OK, so the most natural fit for NMR in those days would have been chemistry departments.

TYCKO: Yeah. So I did get—I got a number of interviews, so they were receptive to the idea. I just didn't make a good impression at most of the interviews. I guess one of the things that you're interested in is about how does all of this relate to physics and the field of physics. So that has changed, really. So in the 1980s, I think the physics departments were still—had much less flexible ideas about what was an appropriate activity within a physics department. So there was real high-energy or elementary particle physics, astrophysics, and I think in some departments even solid state physics or condensed matter physics was considered too applied, right?

ZIERLER: I've heard this said about Princeton. The Princeton department of physics had a very hierarchical view of what was real physics and what was not.

TYCKO: Yeah. So later, much later, when I was at Bell Labs—and my postdoc Sean Barrett, who's a physics professor at Yale University now—he did some interesting stuff, completely non-biological—we did some stuff that was interesting in condensed matter physics, low-temperature physics. When he was interviewing—he had a good publication record by that point, and he was a good candidate, but when he was on his interviews, he was being asked, "What's physics about what you're doing?" He had published—everything he had published was in the Physical Review, Physical Review Letters. Clearly there was nothing multidisciplinary about it. [laugh] But still, certain departments—certain people, anyway—certain people that he ran into would still ask him, "Well, what's physics about this? What's the fundamental question that you're trying to answer here?" But that group of people—it's what they grew up with. There was this very exciting time in the history of physics when there was a lot of very fundamental ideas being developed. And that was great. [laugh] I wish that would happen more often! [laugh]

ZIERLER: So how did the opportunity at Bell Labs come about for you?

TYCKO: So I was applying for these academic jobs, and like I said, this had not been my career goal my whole life, at all, but it was just that was what I could do. When I went on these interviews, number one, I didn't—until I figured out how the system worked, I didn't make a very good impression, but also I didn't enjoy—I didn't really like what I saw that much. Most of the people I was talking to, they didn't

seem like they were having that much fun, really. They were mostly talking about how difficult it is to get money to support their research, blah blah blah blah blah, which they still—professors always talk about that. So it was not a [laugh]—so then I had—I got lucky. Because I knew a guy named Dean Douglass who worked at Bell Laboratories. He had been a department head there. He had recently stepped down from that position, but he was at Bell Labs. He was a magnetic resonance guy interested in various kinds of materials—polymers and piezoelectric materials, things like that. And I had met him I guess at a—now, how did this work? It was a complicated story. I think when I was a graduate student, I had [pause] asked Alex Pines, my thesis advisor—I was going home to visit my parents over vacation, whenever it was, on some holiday vacation, and this was getting towards the end of my time as a PhD student. I was starting to think about what did I want to do in terms of a job. And I had heard about Bell Labs, so I asked Alex Pines, "Is there somebody that you know at Bell Labs whom I could contact to go visit there? I'm interested in seeing what that place is." And so he said, "Oh yeah, why don't you contact Dean Douglass?" So I had—Dean Douglass was this very nice, older guy, who I think maybe I had already also met him at a Gordon Conference. We used to have Gordon Conferences devoted to magnetic resonance, and he would go to those Gordon Conferences. Maybe I had met him there; I'm not sure. But anyway, so I went to—he very graciously arranged a visit, a day for me to come to Bell Labs and just see the place. So I did that. I don't know—I don't remember very much about what I saw or why he did that. I don't know why he set that up for me. I don't know. Anyway, when I was a postdoc, he contacted me and said that there might be an opening in the Physical Chemistry Research department at Bell Labs, and would I be interested in that opening? And he called me, I think; just a phone call. And I think I said to him, "Well, no, I'm applying for academic jobs, and I'm kind of interested in biological stuff, and I don't think so." But then after—like a month or two later, I called him back and said, "Well, you know, maybe I've changed my mind." [laugh] And he said, "OK, I'll see what I can do." So then he actually set up an interview for me there.

ZIERLER: You made a good impression, obviously.

TYCKO: Yeah. And by that point, I had figured out how to do an interview. And then John Tully was a theoretical physical chemist, very smart guy, also a very nice guy, who was the—had become the head of the Physical Chemistry Research Department there. And he, for some reason, was interested in magnetic resonance because he had done some magnetic resonance research as an undergraduate, and he said he really loved it. That's what he told me. And so he ended up hiring me. And that was great.

ZIERLER: I've talked to a lot of people who worked at Bell Labs in the '60s and the '70s, and I've heard so many amazing stories about, you know, it's a monopoly, and money is no object, and it's a purely academic environment where the opportunities for collaboration are just unlimited and you can do whatever you want. And obviously that story comes to an end later on, in terms of the breakup and the lack of funding and things like that. But I'm curious, in your timeline, where are you in that larger narrative? Did you feel like when you got there in 1986 that it was still the heyday of what Bell Labs had been?

TYCKO: Yeah, that's a good question. So I was offered a job at Bell Labs, and I heard various things from different people, like people telling me, "Oh, that's a dying place. Why would you want to go there?"

ZIERLER: Oh so you did hear that, right from the beginning?

TYCKO: Because some of the people—there were people who left. It was around the time of the breakup of the Bell system. So maybe certain aspects did die, of their work. Various people had left either to go to universities, or there was something called Bellcore that they went to, because they thought that might be better. Turned out that wasn't better. So there was this idea that it was in decline. But it was not. It really wasn't true. When I first got there, it was still a very good place. And then you said about money being no object; it wasn't that there was a huge amount of money. That's not what made it successful. What made it successful was the way it was managed, really, which made a big difference. The structure was very unusual. So they had people who were hired as principal investigator-type people. They were called Members of Technical Staff. Everybody was a Member of Technical Staff. A lab was one Member of Technical Staff, one MTS; you could have one assistant, technician-type person; and you could have at most one postdoc, after you had been there for a while. So when you first got there, you just had a room, and then some money to set up a lab. Not a huge amount of money. Not really huge compared to what people get in academia, not by an order of magnitude or anything. I mean, they had some money, but that wasn't the key thing. So they would just give you a room, and then they wanted you to succeed. It wasn't a sink-or-swim situation. A new person would come in; other people would immediately be very interested in, "OK, what does this person do? What does this person know? How can this person contribute? How can this person fit in with things that we're doing?" And because the groups were so small, it was very advantageous to interact with the people around you. You couldn't just wall yourself off into your own lab. And there wasn't an obvious hostility or competition between different labs, which was surprising, because all the money did come from one place. So in a sense, different labs or different departments were competing with one another for those resources. But they managed to keep that competition, to really minimize it, and to really make it so I didn't even notice. Maybe it was going on at higher levels, but me, working in the lab, I never detected really anything like that, like internal competition. Really much more of a cooperative spirit, and this idea that—and then they would tell you—we had annual performance review. Everybody—there was a process where the heads of the departments would get together, and they would rank people, and this would basically decide what your salary would be in the next year, and would decide whether—"OK, now you've been there for a few years. Are you ready to have a technician work with you? Are you ready to have a postdoc?" So they would decide those kinds of things. But they told us that one of the main factors was, "Is what you're doing interesting to the people around you?"

ZIERLER: I didn't mean necessarily money is no object. I meant really, more accurately put, is that it's a corporation, there's an economic bottom line, and yet a lot of scientists never felt any pressure to demonstrate that their research was something that could be profitable for the company. I guess that's more what I was getting at.

TYCKO: Yeah, and that was still true for the—I was there for eight years. For the first six years or something, that was true, still, of the time I was there. But AT&T is a very large company, so in a way, it was a drop in the bucket for them to support basic research. And by having that basic research operation, in terms of prestige, it was great for them. And it also probably made it much easier for them to hire people into AT&T or into Bell Labs who were not doing basic research. Bell Labs always had a big development area as well. The basic research area was a small fraction of their total effort. The development people were working on developing processes or materials that were supposed to be of more immediate technological importance. But just by being—just having a job at Bell Labs was considered a great thing, and part of that was because it had this very strong basic research component

to it. So even if you weren't part of that basic research component, even if you weren't doing basic research yourself, just being part of Bell Labs, you felt good about—you felt like that that would be a good place to work. So I think it helped them recruit people into other areas of the company. And then now and then, maybe something would be discovered that actually would be useful, but it wasn't a huge investment on the scale of the company as a whole.

ZIERLER: And in terms of discovery, can you relate that story about this insight that came to you in your Brazilian hotel room?

TYCKO: Oh. Well, that was the first project I worked on at Bell Labs, was this zero-field-NMR-in-high-field project. I think that's what you're referring to. That was a technique where you could—by appropriate manipulations of radio frequency pulse sequences and also rotations of the sample about particular axes, you could average out the orientation dependence of magnetic dipole-dipole couplings. So if you have, in principle, a system of coupled spins that are coupled by magnetic dipole-dipole interactions, those depend on orientation. And so the NMR spectrum depends on the orientation. And so if you're looking at a sample that's not a single crystal, you have a superposition of spectra from lots of parts of your sample that are all at different orientations. So the spectrum is a blob, is a featureless blob. And so the idea was, can you remove that orientation dependence of the couplings so that even if your sample is not a single crystal, so if your sample has molecules or crystallites that are at random orientations, could you arrange it so that they all have the same spectrum? One way you can do that is just by taking your sample out of the magnet. The orientation dependence exists when your sample is in a strong magnetic field, which is what a normal NMR experiment involves. Because then the magnetic field direction defines the preferred quantization axis, a preferred direction in space. If you take your sample out of a magnetic field into a region of zero field, then all the orientations become equivalent, but then you can't actually observe the NMR spectrum. So there were techniques that had been developed involving field cycling, where you take a sample and you move it between zero field and high field by mechanically shuttling it or pneumatically shuttling it around, moving it around. And by doing that, you could get spectra—zero-field-like spectra. So I was wondering if you have to actually take it out of the strong magnetic field. Is there something more clever that you can do? So I was thinking, "Why can't you—?" In solid state NMR, there's a long history of manipulating nuclear spin Hamiltonians by applying radio frequency pulses and by rotating samples in specific ways, you can change the nature of the interactions between the spins, average them, average the interactions to produce some effective Hamiltonian that has some desired properties. So I was thinking, "Isn't there some way that you can do that? Can you just use pulse sequences and sample rotations to manipulate the Hamiltonian to make it look like it's in zero field instead of in high field?" And it seemed to me, "Why can't you do that?" So yeah, I figured out a way of doing that. So then I spent—that was one of the first things I worked on at Bell Labs, was to try to develop that idea and demonstrate that it actually works.

ZIERLER: Did you see this work as a natural continuation of what you were doing at Penn, or was this a new direction for you?

TYCKO: That was just one idea that I had. That wasn't the most significant thing I did at Bell Labs. That was an idea that I had just before I went there, and so one of the first things I did there was to try to explore that idea. It turned out it was not easy to implement, so I spent the better part of two or three years working on it, which was probably too long. [laugh] But while I was doing that, I did some other things along the way.

ZIERLER: What was your most significant research at Bell?

TYCKO: In terms of the impact and in terms of what I learned from working on it, the next thing that happened—I had been working on this zero-field thing. I had done some other things. I had done some experiments with scanning tunneling microscopy, because there was a bunch of groups working on scanning tunneling microscopy. And one of my friends was doing that, so we together did some STM experiments on conducting molecular crystals, electrically conducting molecular crystals which I had read about in the past. So we were able to actually image molecules on the surface of a conducting crystal, which hadn't been done before, so that was one of the things I did towards the beginning with my friend. Tycho Sleator is his name. Then, let's see, so what happened? Soon after I got to Bell Labs, the high-temperature superconductors, ceramic superconductors, were discovered, so there was a lot of work on that. I did a little bit of NMR on that. I didn't know that you could get NMR spectra of superconductors, but then it turned out that—I learned that actually there was a long history of doing that. So I did a little bit there, so I learned a little bit about superconductivity. And then the first major thing that happened was the buckyball. So there was the discovery of molecular forms of carbon, the simplest being the C60 molecule, which was shaped like a soccer ball. So we heard about that. Turns out some of my colleagues at Bell Labs had been—the idea that molecules like this might exist had been around. But the new thing was that somebody, a couple of people in Germany and Arizona, figured out a simple way of making macroscopic quantities of these molecules, so you could actually make a sample of C60 powder, and it was supposed to have this soccer ball shape. And so I thought, well, if it's a solid and the molecules look like soccer balls, they're probably spinning around inside of the solid. Because there are solids called plastic crystals where the molecules within the—it actually forms a crystal and lattice, but within that lattice, the individual molecules are rotating almost isotropically, like little so-called molecular ball bearings. So I thought, "Well, this molecule is very spherical. It should be rotating quickly, and that would be an interesting test of, is it really what we think it is?" So then I hooked up with one of my colleagues, Robert Haddon, who—he was actually a physical organic chemist by training, so he had done molecular orbital calculations for a putative C60 molecule, and predicted what its NMR chemical shifts would be, and things like that. Its magnetic susceptibility. And so he was interested in it, so I don't know, somehow we were talking about this and I said, "Well, why don't we make some? Why don't we make some of this stuff?" So that was I think the first thing I did at Bell Labs that actually attracted the attention of the Bell Labs management was that I put together in my lab a simple crude device for actually making these C60 samples.

ZIERLER: And why did that attract their attention, do you think?

TYCKO: Because I was actually making something. I wasn't just doing some NMR pulse sequences and fancy mathematics. I was actually [laugh] making some real stuff. Actually, my department switched its name from Physical Chemistry Research to Materials Chemistry Research, so we were I guess maybe supposed to be developing materials. So here it was the first time that I was actually doing some real materials-based stuff. So I actually made some of the C60, and then we handed it out to other people at Bell Labs. Eventually they—so it turned out that yes, I got the NMR spectra, and from the NMR spectra, you could tell that the molecules are in fact rotating like little ball bearings. So that was interesting. We could characterize that rotation in various ways. There's a phase transition. The nature of the rotation changes at a particular temperature—around 250 Kelvin. So there's some interesting things that we discovered there. My colleagues at Bell Labs discovered that you could actually make a material that has interesting electronic properties by doping this C60 with alkali metal atoms. So you can diffuse—you

take the C60 powder, you expose it to a vapor of alkali metal—sodium, potassium, rubidium, cesium—and then the metal ions actually diffuse into the C60 lattice and they donate electrons to the C60 molecules, and so then you get conduction bands and things like that. You get interesting behavior. Depending on which metal atom you put in, you get different kinds of phases. And then if you cool it down, it becomes superconducting. So actually these so-called alkali fulleride materials became superconducting at around 30 Kelvin, which was actually rather high. [laugh] Would have been the highest temperature superconductor known to man if it had happened five years earlier or something, but it was still pretty high. So then I started doing—because I had made the C60 in the first place, and by that point, I knew a little bit about superconductivity from my exposure to high TC materials. And so then we did some NMR measurements on these alkali fullerides to characterize their properties in the conducting state and the superconducting state. So that was interesting. And I just learned a lot about—I mean, some; I'm still not a real expert—but I learned something about those fields, which I previously had known nothing about. And it was an interesting experience for me, because first of all, the NMR measurements were very simple. I was used to doing these very complicated NMR experiments. But to characterize materials like that, you just measure something actually rather simple as a function of temperature. And from measuring something simple as a function of temperature, you actually learn a lot about the materials. I had never just done that. So it was an interesting experience for me personally.

ZIERLER: Like what? What are some examples of what you were really learning, as a result of this?

TYCKO: Well, for example, you learn the density of electronic states at the Fermi energy in a conducting material by measuring the NMR spin-lattice relaxation times, which is a very straightforward measurement. Measure that as a function of temperature. In a conducting material, that has a certain temperature dependence. It should in fact be inversely proportional to temperature until you get down to the superconducting transition. As you cool down to the point where the material becomes superconducting, the spin-lattice relaxation suddenly changes, and it starts to become—relaxation rate becomes slower, following an exponential dependence from which you can get an estimate of the energy gap in the superconducting state, the energy gap between the ground state in which you have these Cooper pairs—the electrons are forming Cooper pairs—and excitations where they become unpaired. And then for other kinds of alkali fullerides, you can tell what kind of materials they are. So some of them are conductors. Some of them are just paramagnetic materials. From measuring the temperature dependence of the NMR relaxation time and the temperature dependence of the NMR spectrum itself, you can figure out what kind of a material it is, what kind of magnetic and electronic properties it has. And it was also a time when there was intense interest in those materials. There was a period of a couple of years where there were a lot of meetings devoted to this, where there would be hundreds of people in the audience, and things happened very rapidly.

ZIERLER: Why so much interest in these materials at that time?

TYCKO: Oh, because it was a new type of a material, a molecular superconductor. It was just something new, so there was a lot of potential for—what is it going to be good for? And what kind of theories does it follow? Why is it a superconductor? What is the nature of the couplings? Is it electron-phonon coupling, or is it some other kind of coupling that leads to superconductivity at low temperatures? How does it relate to the mechanism of superconductivity and the ceramic high-temperature superconductors that had been discovered a few years earlier? Just part of the way solid state physics

works or condensed matter physics works is a new material is discovered, and then everybody jumps on it. So everybody has their own type of measurement that they specialize in, so they all want to—"I want to do my measurement on that material, and see what I learn." And the theorists all have their own pet theories about what kinds of materials might exist. And "OK, does this one fit into my theory, or can I construct a new theory that explains its properties?" So that can happen very quickly. That happens within a space of one or two years. So there's a flurry of interest. And the materials people—"Can we make it better?" You already got up to, whatever, 32 degrees. Can we get to 50 degrees by changing something?" So there's a lot of people just cooking things. You know, taking different mixtures of stuff and applying pressure to it and seeing what happens, a lot of that kind of thing, just to see, "What is this stuff and how does it behave?" So you go to one of these meetings, and there would be hundreds of people there, and you give a talk there—and these weren't magnetic resonance experts; these were experts in various aspects of condensed matter physics—and they would be very interested in your result and how that relates to other things that they know. So that was a new experience for me. I learned a lot from that, and it was fun.

ZIERLER: You talked about the first six years at Bell; it still had that heyday feeling. But then things started to change in your seventh and eighth years there?

TYCKO: Right. And this happened in all companies. The whole industrial support for basic research was gradually declining. But in particular in the communications field, that was changing obviously very rapidly, just with the development of cell phones and the internet and all this kind of stuff. It just changed in ways that nobody at AT&T had predicted, I don't think. So, I don't know, that affected their thinking. But I think also these large companies, in terms of their support for basic research, they don't really quite know how much to invest of whatever their total income is. How much should we—their total sales or something, how much should we invest in basic research? It's hard to quantify that. It's hard to really—you're really just hoping that basic research will produce something for you in some way, directly or indirectly. So they don't really know how to assess that, so they just look at one another. They look at what they think are their corporate peers, other large companies—DuPont, IBM. So they tend to follow one another. One company decides to shed their basic research, and the other companies are more likely to do the same thing. I think. That's my take on the situation. So throughout that time this was happening at a lot of large companies.

ZIERLER: And you really felt this, in terms of your own work, what you were able to do, what you weren't able to do?

TYCKO: Yeah. Just the rhetoric started to change within Bell Labs, that it wasn't enough just to publish papers in Phys Rev Letters. There started to be—there was this phenomenon that I called PRL bashing, where people would give talks and say, "Well, we made this discovery, but we didn't want to just publish a bunch of papers in Phys Rev Letters, so we want to see if we can make some device out of it that will be—" So there was more and more kind of—

ZIERLER: Pressure to monetize things.

TYCKO: Yeah, or encouragement to become part of some team that was working on some technological development project. They didn't quite know what it should be, what those teams should be. The Bell Labs people really weren't so good at choosing the problems to work on, I don't think. Because really they were [laugh] scientists themselves—most of them were basic research scientists.

ZIERLER: So to what extent did this cultural or economic transition encourage you to start thinking about life after Bell?

TYCKO: Yeah, partly it made me think that it wasn't going to continue the way it had been forever. But at the same time, in the back of my mind, while all this was going on—but basically by being at Bell Labs, I learned really a lot about being a good scientist, because I was just surrounded by people who were good scientists. And I really learned the importance of trying to do work that has an impact outside of your own specialized area. So in academia people tend to—at least in the 1980s, through the 1980s, the emphasis was on just doing something that was interesting to your own little group of people who speak your same language, and if you could do that, that was the key to success. Which never—I always thought that was a little weird. But at Bell Labs, I really got to participate in some projects where they turned out to be of interest to large communities of people who knew nothing about NMR, didn't really know how the measurements worked, but were just interested in the answer and how it related to their own work. Which is obviously the way science is supposed to be, but it's not always like that. So that was very valuable training to me. While all of this was going on, in the back of my mind, I still had this idea that eventually I was going to go back to biological systems, so I wanted to do that at some point. And then also in my own personal life, I got married to my wife, who at that time was a psychology professor in Connecticut at Wesleyan University. So then we were looking for—and I was in New Jersey, and we were driving back and forth, and we needed to make a move so we could be together more easily. So then we started applying for jobs. And then I saw—again, I was looking at academic jobs, and then I came across an advertisement for a position at the NIH in this Laboratory of Chemical Physics, which I knew nothing about. And I didn't really know how the NIH intramural research program worked at all. But I knew a couple of people there. I knew Ad Bax from just the NMR field and from conferences. I didn't know him really well, but I knew him. So I called him up and said, "I saw this ad. Is this something I should apply for?" And he said—there was an ad for a position in his department, in the Laboratory of Chemical Physics, which is where I am now. So I just asked him, "Is this something I should apply for?" And he said, "Oh, I didn't know you were looking for jobs. Yeah, you should apply for it." And I said, "Well, you know, I don't really know anything about proteins or anything." He says, "That doesn't matter. I don't know [laugh]—" He says, "I don't know anything about proteins either." [laugh]

ZIERLER: [laugh]

TYCKO: So I applied there, still not really knowing what the place was like. And then my wife saw an advertisement for a job at the University of Maryland, not far away, in College Park. So both of us were invited for interviews, and the interviews went well, and so both of us were offered jobs, and we ended up coming here. So that's really how it happened.

ZIERLER: I want to ask—I've asked this many times already with some of your colleagues—I still don't have a clear answer, and maybe you can help me, or maybe there isn't a clear answer. Why is NMR concentrated in NIDDK? Is there a reason for that, or do you see it more as a historical accident?

TYCKO: It's a historical accident. Yeah, it was not a deliberate choice. Well, I think NIDDK—it stands for diabetes and digestive and kidney diseases—so these are diseases that related to endocrinology. They depend on hormones or other signaling molecules interacting, sticking, binding to other—to receptor proteins and things like that. So they depend on intermolecular interactions that are themselves very dependent on molecular structure and on the details of interactions between molecules. So I think for that reason, my institute, NIDDK, has developed an interest in understanding molecular structure that

goes back to the 1950s. In the late 1950s, I think, a bunch of people were hired who had backgrounds in physical sciences, mostly physical chemistry. There were some people who had been postdocs or graduate students with Linus Pauling who were hired to work in the NIH intramural program and in particular my institute. So there was this long-standing interest in molecular properties, I think, maybe more so than other institutes. And probably just the individuals who happened to be in charge at that time were sophisticated enough that they understood the importance of that kind of work, and invested in it. As far as specifically NMR—so that's more general about let's say molecular properties, molecular structure, molecular biophysics—NMR in particular, NMR evolved into a technique that could provide insight into those things.

ZIERLER: Now, when you were thinking at the end of your time at Bell that you wanted to get back into biological NMR, had you kept up with the field? Were you aware of the advances that were going on, or were you—?

TYCKO: Not completely. Just peripherally. Because for a period of eight years there, I was more or less focused on condensed matter physics. So by the end, we were really just doing semiconductors and quantum wells and low-temperature things and stuff like that. So I was learning more about that. I was aware of things that Ad Bax was doing and other people. Not all the details of it.

ZIERLER: So when you got to NIH, what were your first projects? What were you working on?

TYCKO: I didn't know. Actually when I was hired there—so people asked me, "Well, what are you going to work on?" And I said, "I don't really know." I said, "It's probably going to take me about five years to figure that out." Because that's actually—at Bell Labs, it took me about five years, [laugh] almost five years, to find things that were really interesting to the people there. So I said, based on that experience, that it was probably going to take me five years to figure out something. That turned out to be almost true, [laugh], really. So we dabbled in a bunch of things at the beginning. I mean, I spent the first year or two really just reading and looking for things to work on.

ZIERLER: And was there always an element of how do you use NMR to advance human health? Are you thinking specifically in terms of NIH's overall mission? Or that really is not necessarily part of your thinking?

TYCKO: Certainly wasn't when I started out. Now, maybe more now than in those days. But I was more interested in—well, at Bell Labs, when I was doing all this solid state physics stuff, I was still interested in NMR pulse sequences, and I had some ideas about those things. And it was also clear to me that those technique-related ideas that I had were more likely to have an impact in biological systems than in solid state physics systems, because they were techniques that were really for molecular structure, and molecular structure is not so important in solid state physics, but it's very important in biology. So that was part of it, also. So when I went to the NIH, I wanted to see whether these techniques that I had worked on and that other people in the field had worked on—could we actually use those techniques to learn something that is really interesting to biologists? I wasn't thinking about human health, but just in terms of basic understanding of biological molecules.

ZIERLER: So then five years come around. What is it that you've developed at that point?

TYCKO: Eventually, we hit on this amyloid fibril business. And the way that happened—we had tried some other things with some simple peptides that interact with membranes, and antibodies, peptide-

antibody complexes. I mean, some of that was interesting, and it was good work, but it didn't have a big impact. And then around 1998, a fellow named Oleg Antzutkin who was a Russian guy who was getting his PhD in Sweden in an NMR lab there, wrote to me about doing a postdoc position in my lab. He wanted to apply for fellowships from some Swedish funding agency, postdoctoral fellowships to support his postdoctoral work. And he was trying to think of, what's a good proposal, what's a good research proposal to include with his fellowship application in Sweden. So there were some people at the NIH who had done experiments on the amyloid-□ peptide, which is the peptide that forms senile plaques in the brains of Alzheimer's disease patients, which we continue to study to this day. But back in 1998, the way that got started was people at the NIH in my institute actually had done experiments studying how this peptide forms pores or channels in biological membranes, and how that might relate to Alzheimer's disease as a potential disease mechanism, which at that time was not taken very seriously, actually, but in subsequent years, that idea has resurfaced. But anyway, they were interested in channel or pore formation by the amyloid-□ peptide. And other people at the NIH had actually developed a detailed molecular structural model for what these pores or channels might look like, based on no experiments at all. And so my suggestion to Oleg Antzutkin for his postdoctoral fellowship application was, "Well, here's these papers that have demonstrated channel formation by the amyloid-□ peptide, and some papers about a possible structural model. Why don't you propose that we'll do the NMR measurements to test that structural model?" Which was something that we could do. And so he wrote that fellowship application. He eventually got the fellowship support and eventually came to my lab. But in the interim, 1998, I came across some other papers by a group collaboration involving people at the University of Chicago and at Argonne National Labs, who had studied the amyloid-□ peptide, and not the pores, not the ion channels or pores, but the actual amyloid fibrils, which are these filamentous assemblies formed by the amyloid-□ peptide. A peptide is a small protein, a short protein chain, or polypeptide chain. And they had done solid state NMR measurements on these fibrils, proposing that within these amyloid-□ fibrils, the molecules align themselves in a parallel fashion relative to one another to form what are called parallel □-sheets. And this was very controversial. Actually, I initially got one of these papers to read—to review, rather—and so I looked, I did some reading, and this was a controversial proposal, that these amyloid fibrils might be parallel □-sheet structures.

ZIERLER: Why was it controversial?

TYCKO: Because everybody else thought they were anti-parallel □-sheet structures, and the evidence for that was very scanty. And there were various models that had been proposed, I learned. When I started reading up about this, there were various proposals for what the structures might be that all involved anti-parallel □-sheets, but the evidence for that really was almost non-existent. So I think I gave the paper a good review, but then I decided, "Well, maybe—" They had done a certain type of measurement to support this idea, and then I was thinking, "We should check and see if they got it right, by doing a different kind of measurement. Is there a different way to do it that might be more informative or more robust?" So we started doing measurements. And so then when Oleg Antzutkin came to my lab, that's what we started doing. We started doing measurements on these amyloid-□ fibrils. And initially we found that these papers from David Lynn and Steve Meredith and Bob Botto in Illinois at the University of Chicago and at Argonne National Labs—they were actually right. So they got it right. But then we started to go beyond what they had done. And eventually tried to get more information about the structures of these amyloid fibrils and eventually we were able to develop complete molecular structural models for these amyloid-□ fibrils, which hadn't been done before. And

there's a huge interest in these things now, which already existed to some extent at that time, but it has continued to grow, because the interest in just—these amyloid-□ fibrils are involved in Alzheimer's disease, possibly cause the disease or contribute to it in some way. And exactly what causes the disease, what actually kills neurons in your brain in any of these neurodegenerative diseases, is not completely known, for sure. There's various proposals. But anyway, these amyloid fibrils formed by the amyloid-□ peptide in the case of Alzheimer's disease, or formed by other proteins in other neurodegenerative diseases, are very widely studied now, and of great interest. To the point where when I go to visit universities, physics departments, chemistry departments, biology departments, medical school departments, there's always people working on this. Everywhere. Thousands and thousands of groups. It's really a huge field now, I guess partly because as the population ages around the world and in the United States, age-associated neurodegeneration becomes a bigger problem, affects many families obviously. And there's a hope that we can do something about it. Right now, there's not much we can do about it. So it's an unsolved problem.

ZIERLER: Does this avenue of research start to get you more involved with MDs at NIH? Are you working more now in a clinical or adjacent to a clinical environment in terms of thinking about patients?

TYCKO: No. I mean, I do interact with some MD people and have collaborated with some people who have MDs, but they're not real clinicians, I would say, for the most part. So the work that we do is still very basic research lab type stuff, where we're—I don't know, it's hard to—

ZIERLER: I just wonder if you can map out how it all fits together in terms of your basic research, and how that translates ultimately to therapies, to drugs, to—what exactly is the line between the things that you're researching and the impacts that can be felt among the people that are suffering from these illnesses?

TYCKO: Well, it's still very long-range and indirect, I would say. [pause] It's not a connection that I even try to make, really. It's just [laugh]—I mean, the best way to answer that is just by telling you a little bit more of the details of what we're doing. Maybe it will become more clear, because I don't really have a general answer to that, or abstract answer to that question. So in the case of our amyloid fibril work, we used solid state NMR measurements and then some electron microscopy to develop molecular structural models for the amyloid-□ fibrils that are involved in Alzheimer's disease. The fibrils that we've studied initially were just prepared in vitro, just synthetically, not involving any human tissue or any biological tissue, so just chemically synthesizing the peptide, and then assembling the fibrils in a test tube, and then studying those fibrils by NMR. One of the things that we discovered, though, is that there's multiple structures. And this turns out to be true of not just the fibrils that are associated with Alzheimer's disease but in most neurodegenerative diseases in which various proteins self-assemble to form structures that are generally some type of a fibrillar structure, some filamentous assembly. So in general, for a given protein that forms fibrils, there are multiple distinct fibril structures that can form depending on the precise details of the fibril growth conditions. So these fibrils are called polymorphic. And we showed that the polymorphism is actually at the level of the individual—the structure of individual molecules, the conformation that an individual molecule adopts within these fibrils varies from one fibril to the next, or from one sample to the next, depending on how you prepare the fibrils. So we discovered this polymorphism. And that raises a question of whether it has biological significance or not. In the case of Alzheimer's disease in particular, it's controversial whether the amyloid fibril formation is actually causative in the disease. So Alzheimer's patients, the actual definitive diagnosis of

Alzheimer's disease is obtained by a pathologist from an autopsy. They examine the brain tissue, and then they find that there are plaques, which are deposits, clumps of these amyloid-β fibrils, primarily.

ZIERLER: You mean we only know if a person has Alzheimer's after they've passed on?

TYCKO: You only know for sure, yeah.

ZIERLER: Huh.

TYCKO: Yeah. But it's also known that the development of amyloid plaques—or senile plaques; there's various words for this—amyloid deposits in brain tissue, this is something that happens to many elderly people who are not cognitively impaired. So there's not a black and white, not an on-or-off association between amyloid formation in brain tissue and the development of neurodegenerative disease. That leads some people to say that the plaques are just insignificant. It's something else that's important. But then in our basic research in vitro experiments, we discovered that not all plaques are the same. There are multiple different molecular structures that could form. So it could be that some of those—in vivo within brain tissue, some of those fibril structures may be inherently more neurotoxic than others. And then it's not just the total quantity of amyloid that develops in the brain; it's the actual details, the molecular structural details of that amyloid may be important. We suggested that a long time ago, and then we've been following up on that since. So in terms of the relationship to human health research, I think what we've done is basic research experiments that raise questions that may be relevant to human—that have opened up an avenue for research that may have implications for human health. This idea that there may be an association between molecular level structural polymorphism in amyloid fibrils and the development of a disease, or the severity of a disease, or the rate of progression of the disease, this idea that there might be an association there is something that really comes out of our research. But now it's an idea that other people are investigating. We continue to investigate it. But it's an idea that has gained some traction in the sense that at least it has attracted other research efforts. We don't know the answer yet.

ZIERLER: Right. And so because the connection at this point is tentative or provisional, what do you think needs to happen in terms of making the connection more clear or more obvious? What does that look like?

TYCKO: We have to do more measurements. And so what we're doing is by actually doing NMR measurements on amyloid from brain tissue—so in the past, I don't know, less than—I don't know, what is it now?—seven years or something?—we've been doing experiments where we take brain tissue from autopsies, and we get that tissue from MDs, people have access to—or we can order it from brain banks—so we have some interactions with the medical profession that way, so we get the brain tissue. And then we would like to directly do measurements on the amyloid that's in that brain tissue. We can't actually use NMR—we can't do that with NMR, because we need larger quantities, and also for our NMR measurements, we need to have isotopically labeled material, Carbon-13 and Nitrogen-15 labeled material, because we observe NMR signals from Carbon-13 and from Nitrogen-15 in the measurements that we're doing. The isotopic labeling is essential. So what we do is take the brain tissue from autopsies, we then extract the amyloid from that brain tissue and then use that brain tissue amyloid as a seed for growing fibrils with isotopically labeled peptides or proteins. So the fibrils that grow from the seeds—the seeds again coming from human brain tissue—the fibrils that grow from those seeds are then isotopically labeled, because we use labeled peptides or proteins in the growth process. And we

also amplify the quantities that way so we can get to milligram-scale quantities, which we can't really get from the brain tissue itself. And we had shown from in vitro experiments that when you—I mentioned that in vitro, you can prepare different fibril structures depending on what the precise details of the growth conditions are. And then we've shown in in-vitro experiments that if you prepare fibrils with a particular structure and then you use those as seeds for growing a subsequent generation of fibrils, the fibrils that you grow from those seeds have the same molecular structure as the seeds had themselves. So you can propagate the molecular structure when you use seeded growth. So that's something that we established in our in-vitro experiments. And we're using that idea to now prepare brain-derived fibril samples that we can do NMR measurements on to identify the structures that are actually present in brain tissue. So we're doing that. Your question was, how do we test this idea that the polymorphism actually makes a difference in the development of the disease? The way to do that is to actually see whether it does. You just get tissue samples from many patients and compare results from patients who have Alzheimer's disease with patients who don't have Alzheimer's disease but have amyloid in their brain. There are different subtypes of Alzheimer's disease and you can compare patients with different clinical histories, and by doing these fibril-seeded growth experiments figure out, is there some difference in the molecular structure of the fibrils that you derive from their brain tissue? So we're working on that, those kinds of experiments. Is that making sense to you? [laugh]

ZIERLER: Yeah.

TYCKO: So we're trying to use NMR to actually identify the structures that form in brain tissue, but we have to do it in an indirect way. Other people are trying to develop more direct ways of doing it, which would be better, and more high-throughput ways. Is there some other way of actually identifying the precise molecular structures that develop in the brain tissue of a particular patient without having to do this seeded growth and amplification? For us, we do these experiments, but they take at least three or four days per sample, so it's not high-throughput. So is there some way of more rapidly screening to build up some statistics?

ZIERLER: So to broaden out the question a little bit, looking to the future, when there's going to be a breakthrough in Alzheimer's disease research and related research, what do you see as that breakthrough, and where do you see your research fitting into achieving that breakthrough?

TYCKO: Well, I think it would be—your question presupposes that—

ZIERLER: —there will be. [laugh]

TYCKO: —that there will be a breakthrough. And that it will somehow relate to our research. And I don't [laugh] know—I don't know if either of those things are true.

ZIERLER: But it's what motivates you, right? I mean, that's why—

TYCKO: I would like to know whether the—what I just described. So is it true that the molecular structure makes a difference in the disease? If it does make a difference in the disease, then that has potentially some implications. One is that maybe you can develop drugs that—if the fibrils can form—well, if the protein or peptide in this this case—in the case of Alzheimer's disease, it's the amyloid-□ peptide; in other neurodegenerative diseases, it's other proteins. In Parkinson's disease or ALS or other things, there's other proteins that are involved. So if that protein can form multiple different structures, self-assemble into multiple aggregated states, fibril or aggregated states—some of those are more toxic

than others—then what you'd like to do is guide that process away from the more toxic structures and towards the more benign structures. You could imagine doing that with a drug. So can you find an injectable or ingestible drug that guides the fibril formation or protein aggregation process away from the more neurotoxic species and towards more benign species? So that could be an implication. That could be a treatment, a prevention of the disease. Then there's diagnostic imaging. Particularly positron emission tomography imaging, PET imaging or radioactive compounds that are injected into patients that go to the brain, and they bind to the amyloid plaques, and so you can now assess the development of amyloid deposits in the brain of an individual before death, so you can tell whether they're developing amyloid plaques. Those tests exist now, but they're not really very useful because they don't have predictive value, because some people get amyloid deposits in their brain that show up in the PET imaging, but they don't actually progress to developing Alzheimer's disease. Other people do. And maybe that's because of these structural differences that I've been talking about. Maybe the people who progress to Alzheimer's disease, it's because they have particular structures that are absent in other patients. So then if that's true, what you want to develop is PET imaging compounds that bind specifically to the more toxic structures, that can differentiate between different molecular structures that are actually developing in brain tissue. So far, we don't really know. The PET imaging compounds that are used, we don't really know what they interact with. There's evidence that they don't interact equally with all possible structures, but which structures do they actually bind to? Which structures don't they bind to? Nobody knows the answer to that. So that I think could be a productive avenue of research that would have some effect on the treatment of the disease, or at least on the decisions that families make about the prognosis, if you want to make some plans for the future. So having that information, knowing with more certainty whether a particular individual is going to progress to full-fledged Alzheimer's disease or not would be a useful thing to know. And so that depends on having imaging compounds that actually have the necessary specificity, and that relates to the work that we're doing. So there's potential impact.

ZIERLER: You mentioned you've done work on HIV research as well.

TYCKO: Right.

ZIERLER: When was that? When were you involved in that?

TYCKO: That's ongoing, all during this. We have many projects—we typically have four or five projects going in the lab at once. So that's another thing that we've been working on.

ZIERLER: What can be the contributions of NMR on viral research?

TYCKO: Well, we've worked on two things that are potentially of interest. One of the early things that we did, the first few years that I was at the NIH, was to study a peptide-antibody complex with a—studying the complex between an antibody that was known to neutralize the HIV virus, to render it non-infectious by sticking to particular proteins on the surface of the virus. We were studying a complex of the neutralizing antibody with the piece of the protein that it actually sticks to, on the surface, and trying to elucidate the molecular structure of that peptide in its bound conformation. So that kind of research, peptide-antibody—so we were just showing that solid state NMR could be used to study the structures of complexes like that, the bound conformations of peptides bound to antibodies. I guess that could have some impact on vaccine development, design of antigens that would elicit particular antibody responses that would be neutralizing against the HIV virus. That's one avenue of research that

could have an impact. I don't think our research had that impact, but it was interesting. It turned out—it was the first demonstration that you could do that kind of a measurement with NMR. Our more recent HIV-related work has been on the immature state of the HIV virus. So in the case of HIV, the virus—a cell gets infected with the virus. The infected cell then generates more copies of the virus that bud off from the surface of the cell. In the case of HIV, when new viruses bud off of an infected cell, they are released initially in an immature state. Immature state means that within the virus, the viral genetic information which is RNA—which is encoded in RNA chains—the viral RNA in an immature virus is not yet encapsulated within a protein shell that's called the viral capsid. So in the immature state of the virus, the capsid has not formed yet. The capsid is a protein shell. That protein shell is formed by a particular protein called the capsid protein. So we've studied the capsid protein, and we've learned some things about the structures of these shells that the capsid protein forms by doing solid state NMR measurements on capsid protein assemblies. The most recent experiments that we've done have been on the immature state. In the immature state, the capsid protein itself, which forms the shell inside of a mature virus that contains the viral RNA, that capsid protein itself is still part of another protein shell which is called the immature protein lattice. The conversion of the immature protein lattice to the mature capsid shell involves an enzymatic cleavage of the immature protein at a particular point, and that enzymatic cleavage can be inhibited by certain drugs that are called viral maturation inhibitor drugs. So in our most recent work, we've looked at this immature protein lattice, a protein shell that lines the interior of the HIV in its immature state—we've looked at that lattice and what the effect of drug binding is to that lattice, to try to get some information about what the mechanism of action of those drugs are. How do these maturation inhibitor drugs actually prevent the enzymatic cleavage that is essential for forming the capsid shell within the mature state of the virus? It's a lot of details here. [laugh]

ZIERLER: It's OK! It's great!

TYCKO: You have to see a picture. If I could show you some pictures of the virus, you would understand more clearly. It's harder to describe in words, or it's more cumbersome to describe it in words. It's easier to see it in a cartoon. But anyway [laugh] we've done NMR measurements on this immature protein lattice with and without the viral maturation inhibitor drug, to look for differences, to see what this drug is actually doing. And what we found is surprisingly the impact of that drug on the structure of the protein in its immature state is actually quite minimal. There's very little detectable structural change, but there's changes in the motions, so the binding of the drug, the interaction of the drug with the immature state of the protein inhibits the flexibility of that protein, limits the amplitude of motion of that protein. And so it's the amplitude of motion that's—so apparently in order for the maturation process of the drug—the maturation process of the virus depends on having adequate flexibility, adequate mobility of the protein in its immature state, to give access, so that the enzyme that catalyzes the cleavage that leads to maturation has access to the site it needs to gain access to. Again, a cumbersome explanation. So we've learned that the main effect of these maturation inhibitor compounds is to limit the dynamics, the molecular motions, within the immature state of the virus.

ZIERLER: I can't help but ask, given that your research is relevant for HIV research, I wonder if that some point, NMR is going to be useful for coronavirus or COVID-19.

TYCKO: I'm the president of the International Society of Magnetic Resonance, so just a few weeks ago, as president of the International Society of Magnetic Resonance, I decided to organize an online

international conference on exactly that question—what can magnetic resonance contribute to the COVID-19 situation? So there will be—maybe you want to tune in on this. I can send you the link.

ZIERLER: Yeah!

TYCKO: There will be an online meeting two days from now, on Wednesday, about magnetic resonance research related to COVID-19. And surprisingly, six or seven people have actually volunteered to give short presentations about their research. Which is a little bit surprising, because everything is in the initial stages now. This is one of the interesting things about the COVID-19 pandemic, that it challenges the normal paradigm by which research is conducted, where some problem comes up and then lots of groups start working on it. And at least at the beginning, people are leery about sharing results, because they're not sure yet what they want to do, and they don't want to commit themselves, and they don't want to say something that's wrong.

ZIERLER: But this is upending those rules?

TYCKO: This is upending those rules, just because it's so important, right? So I wasn't sure what the response was going to be, but actually—and I've had some people say, "Well, we're starting to work on things, but we're not really ready to talk about it yet."

ZIERLER: It's interesting, though—that's an important insight in terms of how things work at NIH. I would have assumed, given the nature of the crisis, that this wouldn't have come from you saying, "What can we offer?" I would have thought that it would have come from on high. You know, "All hands on deck. Think about how you might be able to—"

TYCKO: No, no, no.

ZIERLER: No?

TYCKO: I mean, that's not how scientists work. Scientists don't like having someone telling them what to do, but—

ZIERLER: Right, of course. But in terms of this concept of the nature of the crisis upending those traditions or those rules, I'm just a little surprised that this wouldn't have altered that way of doing things. So that's interesting.

TYCKO: Yeah, yeah. I mean, at the NIH and elsewhere, I think at other institutions, they've shut down most normal research.

ZIERLER: Right, right.

TYCKO: So that also encourages people—but they're allowing coronavirus related research to proceed, because that's our mission, right? So if you want to continue to—if you don't want to just spend all day at home every day, if you want to actually get back into the lab—or in my case, I have a group of postdocs and a couple of staff scientists, and some of them have things to work on; other ones don't really have anything that they can do from home. So I'm thinking, "Well, is there something—?" They're not happy sitting at home, they want to do something. Is there something that they can do? And there are current restrictions—if it's something related to coronavirus, then they can probably do it. So there's that practical thing. But that's a small factor. I think most scientists, both for your reputation, but also just for your self-satisfaction or just your own feeling of self-worth, you want to know that you've

actually done something. And here's an opportunity. Here's an opportunity. If you do something, maybe it will actually make a difference.

ZIERLER: I appreciate that your answer, by definition, would be highly provisional, but I wonder if you could extrapolate from your work on HIV, if you could take a guess at how NMR might be useful for COVID-19 research.

TYCKO: Well, the shortest-term impact is probably screening drugs. So with NMR, you can—with pretty simple solution NMR methods, you can take a protein—if it's a protein that you can easily make, and the protein itself is not too big—so there's these viral proteases that are important in the life cycle of the coronavirus and in other viruses, and in HIV. Particular enzymes that are important for the life cycle of the virus. If you can make those enzymes, then you can make samples where you just take that enzyme and you add a drug to it. And you look at the spectrum, the NMR spectrum of the enzyme, and if the drug actually interacts with that enzyme, it will change the spectrum somehow, change the NMR signal somehow. So you can quickly identify drugs that actually interact with the target enzyme that you'd like to—you'd like to disable this enzyme. You'd like to inhibit this enzyme, prevent its function, because it's essential for the life cycle of the virus, and if you shut it off, the virus can't propagate. You've cured the disease.

ZIERLER: That's the prize.

TYCKO: That's what AIDS patients take. They take protease inhibitors, cocktails of protease inhibitors, mainly. This maturation inhibitor thing I was talking about is a more advanced concept. It's not what they actually use. What they use are these protease inhibitor cocktails. So can we find drugs that will inhibit the analogous proteins in the coronavirus? And the answer is probably yes. But can we do it quickly? The quickest thing is to take drugs that already exist. So there's libraries of drugs that are already—that were developed for some other purpose. They've been tested for safety, so it's already known that people can take them and it doesn't have big side effects, or the side effects are already characterized. So can you just screen these libraries of existing drug compounds against this new protein of interest and identify the ones that actually interact? And then those become your candidate drugs. That kind of thing can be done with NMR, particularly if you have an NMR system with robotics that allow you to change samples quickly. And there are systems like that. We don't have them in my lab, but there are labs that have systems for rapidly screening. This kind of a measurement can be done in ten or 15 minutes, really. So you can go through—so what does that mean?—a hundred per day or something. So in a month, you can do lots of compounds. Those kinds of efforts are in progress.

ZIERLER: That brings us right to the present and even looking into the future, so I think for my last set of questions, I want to ask more broad-based questions that survey your career and your research in a broader lens. The first thing I want to come back to—I was intrigued—you were talking about Professor Peebles and how he taught you quantum mechanics and how this has influenced your understanding of NMR. I wonder if you can flesh out just a little bit, just to understand, what is it about quantum mechanics that allows you to understand how NMR works? Or what's the relationship between the two?

TYCKO: NMR, of the type that I do anyway, is highly quantum mechanical [laugh], so if you want to calculate NMR signals, the way you calculate them is by essentially solving the Schrödinger equation. The signals are a direct result of quantum mechanics. If you know the Schrödinger equation, that allows

you to calculate what the signals will be for some set of nuclear spins that are coupled to one another with certain kinds of couplings. So there's a very direct relationship there.

ZIERLER: And when you say you're making these calculations, does this mean that you're making these calculations on a day-to-day basis in the lab, or are these general principles that you're relying on to understand the signals?

TYCKO: Not every day, but there are times when you do these calculations. If you're trying to develop a new technique that you're hoping will give you signals that have certain information in them that you're looking for, then you would do calculations of this type to test whether your technique, which is maybe some sequence of radio frequency pulses with particular pulse lengths and phases and things like that—particular timing sequence—you want to test whether it actually works, so you could do a simulation on some simulated spin system and calculate what the signals would be, and then you can compare that with real data. Those kinds of calculations—I've written my own programs that do that kind of thing for special cases, and other groups have written more general software packages that allow you to do those kinds of calculations. And they're all quantum-mechanics-based.

ZIERLER: I wonder if you could talk a little bit about some of the inherent advantages of working at NIH in terms of research, either from a budgetary perspective, from a collaboration perspective, from a technology perspective. What are some of the things? Particularly because you have experience in an academic setting and in an industry setting at Bell, you have a pretty wide perspective of various institutional settings to do this research. So can you explain what are the kinds of things that you can do at NIH because of what NIH offers, that you might not be able to do anywhere else?

TYCKO: Yeah, yeah. I'll do that. And I think what the best environment is, is very individual-dependent. I think the NIH environment or the Bell Labs environment, they're similar in some respects. The research groups at the NIH are bigger than they were at Bell Labs, so that's different. Certain types of research, you need a big group, because there's just lots of things that have to be done. Other research, you don't really need—you just need a few good people. Both environments, the main difference compared to academia is that we don't have to get approval in advance for an idea or a project, so the evaluation of our success is done retrospectively. Maybe you've already heard that. You might have heard that from other people—those words—

ZIERLER: Sure.

TYCKO: We use those words—"retrospective evaluation"—because it's true, and it's very different. So we get a certain budget, which at least supports our basic activities and pays the salaries of a certain number of people. That was true both at Bell Labs and at NIH. And then when we have special needs, we need a new piece of equipment, we can request that. We get a certain level of support. And then if we want to start a new project, we don't have to get approval of some review committee to start that project. In the end, as long as it works out and something comes out of it and we're able to publish papers and stuff, that's a success. So that gives us a lot of freedom to pursue new ideas that may be out of the box or not trendy or just not ideas that other people are working on. I have some projects in my lab that are really technology development projects where I just have a feeling that this would be a good thing to work on. We're working on magnetic resonance imaging methods to try to see images within individual cells, eventually. Very high-resolution magnetic resonance imaging, which has to be done, it turns out, at very low temperatures, with special kinds of home-built equipment and things like this.

When I describe that to people, they say, “Well, why do you want to do that? You can already use a microscope. Just an optical microscope, you can see what’s inside of a cell, so what are you going to learn from that? “And the answer is, “I don’t know yet.” [laugh] But I have this idea that probably we'll find something. Once we get it working, probably we're going to find something. And I trust my own judgment about that kind of thing.

ZIERLER: And it’s OK at NIH not to know. You can do that.

TYCKO: Yeah, I can do that. And you can’t do that in academia, because you wouldn't get the funding for it. And plus, you don’t have the time. So the other thing is, both at Bell Labs and at NIH, I have a lot of time to do things myself because I'm not teaching. I mean, the teaching is—it would be nice to teach, actually, and that doesn't necessarily take that much time. But the grant writing—you know, just talk to academics, this is how they spend their time. Committee meetings and stuff—we have minimal time spent on that. And this means that if I have some project that I'm not sure it’s a good idea or I want to do it right away or everybody else in my lab is already busy with something else, I can just go in the lab and do it myself. So I spend a lot of time working with my own hands. The NIH is a good place for people like me, I think, who really like to be in the lab themselves, who still actually enjoy the day-to-day lab work. Some of it gets tedious after a while, but I still enjoy a lot of it. So I run my own experiments. At the same time, I'm also very closely involved with the research that my postdocs are doing. I have time to work with them very closely. So that’s a different environment, and I think my academic colleagues don’t have that same situation. Also, I would not be good—it’s also what I'm good at. I wouldn't be so good in—running a large group in academia, other people are better at that than I am. I mean, I'm just astonished. I see pictures of people with groups of 20, 30, 40, 50 people, and I'm thinking, “How can you do that? [laugh] I can’t imagine!” I can’t imagine—I mean, I have a group of four postdocs. I don’t want more. That’s enough! I'm busy enough trying to figure out what those four people should be doing and making sure that they're making progress and stuff like that.

ZIERLER: I wonder if you can survey—long career in NMR, and you can either talk personally or as a representative of the field—because of NMR and all the research, what is understood today that wasn’t understood when you started, either in biology or physics or chemistry, that really like was a mystery then and is not so much of a mystery now?

TYCKO: So there are the specific examples, including some of my own work that I've done. But you're looking for a general—you're looking for some kind of very broad contribution.

ZIERLER: You know, like the metaphor of “Everybody in science is a brick, and everyone is building towards a cathedral” or something like that. Like the greater—what is your role or what is NMR’s role in like the larger understanding of how physical reality works?

TYCKO: I think that’s maybe too broad a question, because it’s—the reason I've been doing NMR all these years and that we still do it is you can apply it to almost anything and learn new things about it. So I think it’s essential in lots of fields. In synthetic chemistry, it’s probably the most essential. A chemist synthesizes a new molecule, and they want to know what they've made. The NMR spectrum is the best way to confirm that you've actually made what you think you have. So there, that’s maybe the clearest example. In molecular biology, for structures of biological molecular structures, NMR is not the only technique, but it’s one tool, and there are certain cases where NMR has turned out to be the way to do it. Like the amyloid fibril work that my lab has done, at least when—now, you can do it with electron

microscopy, because electron microscopy has gotten better in the last couple years. So we're doing that also. But until two years ago, solid state NMR was the only way to do it, really—to get molecular structures of amyloid fibrils. So everything that we've learned about, really our current understanding of amyloid fibril structures comes mostly from solid state NMR, I would say. In other fields—a big thing in magnetic resonance now is battery materials. If you want to see what's happening chemically inside a battery as it's operating, as a battery is discharging it and you're recharging it, what's actually happening inside there, NMR I think is the best way to do that. So there are groups that are doing in situ measurements, NMR measurements, on functional batteries, or at least samples that very closely mimic what happens inside of a real battery, so you can actually see all the chemical and structural transformations that are going on and figure out why, after you charge and recharge the battery a hundred times, it starts to fail. What has made it fail? So you can actually—that kind of thing. There's just lots of examples like that, where NMR has made contributions. But at the same time, other techniques have also made essential contributions. All the different scattering and diffraction methods that exist are absolutely essential, too. You couldn't get anywhere in physics or in chemistry without diffraction and scattering techniques, and optical spectroscopy, measuring ultraviolet and visible absorption spectra, and various fancy laser techniques. All these things are essential, and in terms of building the structure brick by brick, all of these techniques—I think they all work together. I don't think you can really separate—it's hard to separate it out and say, "Oh, this particular tower was constructed from NMR, and this tower was constructed from diffraction" or something like that. They really work together.

ZIERLER: I think for my final question, I want to ask you a forward-looking question, and that is both—you can answer again personally or as a representative of your field—and that is, what are you most excited about for the future? What continues to motivate you to discover, to work in your field, to contribute broadly? What are the things that excite you about the future?

TYCKO: I won't speak for my field, but just at a very personal level. I'm someone who is never satisfied with what they're doing, so I'm always—I work on something, and I'm really happy when we get something to work, and then soon thereafter, I start to feel like, "OK, well, now what are we going to do?" And I'm never sure. So it's a constant struggle, just in my own head, trying to answer that question that you just asked. "OK, what am I excited about now? What should we do next? What's our goal now?" I never really know the answer. Which is one of my problems. [laugh] So I'm not the right—I don't have a good answer for that question.

ZIERLER: But it sounds like you're just excited about the next thing that you're working on, without have the larger plan.

TYCKO: I try to be. [laugh] When things go well, I'm excited about it. But you know, a lot of ups and downs.

ZIERLER: Yeah. Well, Dr. Tycko, it has been a great pleasure talking with you today. I really appreciate your time and insights.

TYCKO: It was my pleasure. I hope that is not too much babbling, and I hope you can make some coherent transcript out of that.

ZIERLER: Definitely.

TYCKO: So you're going to try to—I guess we're going to reduce this? You're going to distill this down to—?

ZIERLER: Well, it will be your choice. I'll cut the recording here.

[End]