Interviewee: Richard Leapman By: David Zierler

Place: Remote Phone Call Date: April 13, 2020

ZIERLER: This is David Zierler, oral historian for the American Institute of Physics. It's April 13th, 2020. It is my great pleasure to be here over Zoom conference with Dr. Richard Leapman. Dr. Leapman, thank you so much for being with me today.

LEAPMAN: It's a pleasure to be included in this. Thank you.

ZIERLER: So, for starters, would you please tell me your title and your affiliation at NIH?

LEAPMAN: Yes. At the moment, I sort of wear two hats. I'm a senior investigator in the National Institute for Biomedical Imaging and Bioengineering, with a small lab on cellular imaging and macromolecular biophysics. And my other role for the last 13 years or so, is as the scientific director of the intramural program. My institute, the National Institute for Biomedical Imaging and Bioengineering, is one of the smaller institutes at the NIH. But it's a great privilege to have served in the role as the scientific director for some years now. One of the things I really find satisfying is the recruitment of other young scientists to come into our institute and I've enjoyed that aspect of it as well. So I try to juggle some science and science administration.

ZIERLER: Excellent. Alright, so that's very current. Now we're gonna rewind right back to the beginning. Tell me a little bit about your birthplace and your early childhood.

LEAPMAN: Oh, okay. Well, I was born in England in the town of Bath, which is quite an historic place. Originally it was a Roman town with baths supplied by hot springs, and then it became popular in the Georgian era, in the 1700s, for its mineral waters, which the Georgians believed cured gout caused by their excessive alcohol consumption. My father, who was one of five siblings, was born in 1900 in the final year of Queen Victoria's reign. He had to leave high school when he was 15 to help look after the family's clothing business. He was 50 years old when I was born, and we moved around quite a bit in my early years, living in Bath and Cardiff. Although my father had no formal education after the age of 15, he was something of an intellectual. He loved history, and unfortunately, that was not my best subject, you know? (laughs) He read a lot, and amongst the things he read were articles on science, which appealed to him as well. I remember he bought an optical microscope for me and my twin brother. So the two of us had this microscope, which my father had found in a secondhand store where we lived — it was constructed from brass with several objective lenses and a mirror to reflect the room light. And I recall being fascinated looking at all kinds of specimens including plant cells and insects. I also remember when I was around 11 years old, he told me about something called an electron microscope from an article that he'd been reading. He and I had absolutely no idea what it was. (both laugh) But somewhere, in the back of my mind, I must have sort of put that little snippet of information, because it turned out that 10 years later, I started doing some research in electron microscopy.

ZIERLER: Now what about your brother? Did he pursue a career in science also?

LEAPMAN: He did in fact pursue science initially and he obtained a B.Sc. degree in biology, but then he decided it didn't offer enough of an opportunity to make a living. (both laugh) I think a lot of us find that. So he decided to do something else, accountancy.

ZIERLER: Was your father from Bath also?

LEAPMAN: No, he was from London. We lived in Bath for only a few years when I was born. Then we moved to South Wales. And we lived there for a number of years until I was the age of 11, when we moved to a town about 30 miles from London, mainly because my father's job had changed. Two years later, I had the opportunity to attend Sevenoaks school in the county of Kent, where I had some good teachers in physics and math. In fact, because I had been doing quite well at Latin, the school tried to groom me to do classics, Latin, Greek and Ancient History. Fortunately, I managed to escape that, (both laugh), and I insisted on doing physics and math instead. The school was very disappointed that I didn't choose the classics.

ZIERLER: Uh-huh. And your high school was a public school or a private school?

LEAPMAN: It was actually both. It was a public school for the people who lived in the area, but part of it was also a private boarding school. Sevenoaks school has now become well-known in the UK, although it wasn't quite as well-known when I was there.

So, returning to my family, my mother used to tell me that she enjoyed doing mathematics when she was in high school. She was a talented pianist and after graduating from school, she proceeded to

obtain a degree from a music academy. But she was quite adventurous and, when the second World War broke out, and she was in her mid 20s, she drove ambulances around during the Blitz in London.

ZIERLER: Oh wow.

LEAPMAN: And then she joined the ATS, the Auxiliary Territorial Service, which was the women's branch of the army. She became a captain in the same regiment as Winston Churchill's daughter, Mary, whom she knew. Because my mother was familiar with trigonometry, I suppose she was able to understand something about how radar could be used to track the location of aircraft. I don't know how she learned that, but she was in charge of an anti-aircraft gun site in the south of England. She had to get the ranges and coordinates of enemy planes as they came in.

ZIERLER: Wow.

LEAPMAN: And then they tried to shoot down enemy aircraft coming in to bomb England.

ZIERLER: Wow.

LEAPMAN: My parents encouraged me to do whatever interested me. I had applied to Cambridge University and was accepted into the oldest college, Peterhouse, which was founded in 1284. I remember that I had done absolutely no biology at all when I had finished high school, not a single course. As was typical in those days, I took a gap year between high school and college. And I was sent a reading list, which included the Molecular Biology of the Gene by Watson. I remember being

really fascinated by that book which I couldn't put down and read cover to cover. But when I went to Cambridge, I did only physics, mathematics and a lesser amount of chemistry.

ZIERLER: Now, in high school, just to orient us, I mean, for you to be accepted at Cambridge, what is that like? I mean, to the extent that it would be like the equivalent of Harvard here. To be accepted into Harvard, you have to be like valedictorian plus. Is the same true to be able to get into Cambridge, or is that not a fair comparison?

LEAPMAN: I don't think it was quite that difficult, although it's true that they don't take many students. But I remember that you had to go for an interview, so I went up there by train while I was still a high school student and stayed overnight in the college, Peterhouse. I was interviewed by a physicist called Aaron Klug, and 13 years later in 1982 Klug received the Nobel prize in chemistry for work in biology to solve the structures of viruses.

ZIERLER: Right, right.

LEAPMAN: But at the time I didn't know anything about Klug or even that he would be interviewing me, along with a history professor.

ZIERLER: Now, in the British system, you declare right away, right? You go in with the intention of studying-- So right from the beginning, you were gonna pursue a bachelor's in physics?

LEAPMAN: That's right, yes.

ZIERLER: And how was your physics education in high school?

LEAPMAN: I mean, it was definitely strong then, more physics than what you would have in the US system, at least at that time. This was because the last two years of high school, all I studied was physics, math, and chemistry.

ZIERLER: Right, right. Because you had already chosen that track as a 15 year old, essentially.

LEAPMAN: In high school, exactly. I think it forces you to specialize a bit too early, so there's a lot to be said for the American system. I believe that's the way it still works in the UK. So anyway, I found myself in Cambridge studying physics. But at the back of my mind, I was always sort of interested in the possibility of studying biology. I think that Watson's book had stuck with me a little bit. In those days, for physicists the idea of doing anything with biology was absurd, really, for most people. They considered biology not to be a "pure" quantitative subject. It was a much more of a sort of descriptive thing.

ZIERLER: Although, in the States, at places like Hopkins, there was an established biophysics department.

LEAPMAN: Oh yes. Of course, and it was definitely in the mind of my physics professor Aaron Klug in Peterhouse, but it wasn't in the mind of most physicists.

ZIERLER: Right, right.

LEAPMAN: Now, it's changed. Now a great many physicists are very much aware of biology.

ZIERLER: Oh yeah.

LEAPMAN: But in those days, physicists, at least the ones I knew, were completely unaware of it.

ZIERLER: Right, right.

LEAPMAN: I mean, there was obviously a lot of biophysics going on, but it wasn't in the mainstream of physics.

ZIERLER: Now, your education as an undergraduate, how much were you exposed to physics on the experimental side, and how much were you exposed to physics on the theoretical side?

LEAPMAN: Physics undergraduates were exposed to both experimental and theoretical topics. You had some choice of the courses that you would do. So maybe I didn't choose the most theoretical

ones in my third year, and focused more on topics that related to experimental physics. I avoided the most difficult courses in my third year. The curriculum was fairly advanced. For example, in I think the first semester as a freshman, we studied special relativity in some depth. You know, that went past pretty quickly.

ZIERLER: Were you able to pursue your interests in biology as an undergraduate at all?

LEAPMAN: I didn't at all. There was no opportunity really to do that, at least for me.

ZIERLER: Because the program was fairly rigid? You just had to (**LEAPMAN**: Right.) stick within the bounds?

LEAPMAN: Yes, exactly.

ZIERLER: And how much, was there a mentor component to it? Did you become close with professors as an undergraduate and get involved in their lab work? Was that available to you?

LEAPMAN: Not really, not so much regarding the lab work. But there was very good teaching within my college. In fact, Klug, who had a position in the Medical Research Council at Cambridge was also the Director of Studies for all of undergraduates in the natural sciences in Peterhouse, and it was he who supervised me in physics. The supervision at Cambridge was a tutorial, in which just two students would be tutored for an hour a week with the professor.

ZIERLER: Did you have any idea who he was? What a luminary he was?

LEAPMAN: I didn't really have much idea at all, although it was well known among the students that he was doing some amazing research but we didn't know exactly what that was. This was before the internet and you couldn't easily look things up. (laughs) But I remember that he had several briefcases in his office and would search them to pull out notes that he wanted to use. He'd pour the two of us a glass of Peterhouse sherry before we started because that was the time of the day: just before dinner.

ZIERLER: Of course.

LEAPMAN: You know, you can drink in England at age 18. So the glass of sherry would relax us a little bit, and then he would bring out some of the textbooks. And sometimes he had annotated the textbook to show where the author was actually wrong (both laugh) and to explain what the author should have written. That was quite interesting.

ZIERLER: Did you get a sense what he was working on at that point? His own work?

LEAPMAN: No, I had no idea. Absolutely no idea.

ZIERLER: Yeah. Yeah. Was there a senior thesis?

LEAPMAN: Not a thesis but we did spend a few weeks over the summer working in the lab between the second and third years, and I recall analyzing particle physics bubble chamber tracks and writing up a project on that.

ZIERLER: Okay. So you graduate with a BA in physics, and then sort of staying on for the masters is a natural progression for you?

LEAPMAN: There wasn't a master's degree that involved course work, and you just went straight to the PhD.

ZIERLER: And the masters was earned incidentally?

LEAPMAN: At Cambridge, the master's is an automatic degree that's given to everybody who has received a bachelors, after waiting another three years. Everyone who goes there receives a MA degree in addition to their BA degree.

ZIERLER: I see. I see. So at this point, you're well on your way to being a Cambridge man, right? You want to stay there?

LEAPMAN: Well, I took the path of the least resistance, which was just to continue on there. In fact, I only spent a total of six years there, because the undergraduate degree was three years, and the PhD was three years. That was typical, that was not unusual. That was the standard in those days.

ZIERLER: So "the path of least resistance." I mean, different schools have their own idiosyncrasies. Some people like students to not to stick around. But at Cambridge, you were encouraged to do so if you had the aptitude?

LEAPMAN: Some students moved to a different university for their PhD work, but if they had the opportunity, they often stayed. That seemed to be the case.

ZIERLER: Yeah. So in three years, that's a, I mean, from an American point of view, that's a pretty quick thing. So how--

LEAPMAN: Yes, the time does pass quickly.

ZIERLER: Is there, what's the divide between coursework and lab work as a graduate student?

LEAPMAN: As an undergraduate, you had a lab once a week and a mountain of course work and problem solving. But as a graduate student, there was no compulsory course work although you could attend lectures if they helped with your research. For an experimental physicist like myself

working in the Cavendish Laboratory, you spent most of your time in the laboratory doing experiments and analyzing data, and reading the literature.

ZIERLER: And were your, what were your career aspirations at this point? Were you thinking about an academic job, entering industry? What were you thinking?

LEAPMAN: In my third year as an undergraduate, I applied for some jobs in industry, before I knew I was going to stay on. Those jobs didn't really appeal to me very much, but I did go for some interviews, and I think I was offered some jobs that I wasn't really interested in. I didn't know what an academic career would involve. There was very little career guidance (both laugh) in those days. I had no idea of what it would be like to be doing research.

ZIERLER: When you, what was the process of you identifying your dissertation topic? How did that come about?

LEAPMAN: Well, that's interesting. I was asked to choose between three research topics before I started my PhD degree. The topics were somewhat related but they also went in different directions. I remember Klug invited me to his office to discuss the possible projects, and I hadn't seen him for quite a while, because he hadn't tutored me in my final year as an undergraduate. But I went down to the Medical Research Council. And it was Klug who suggested the project that involved measuring inelastic scattering of electrons in the electron microscope, as a way to perform elemental microanalysis. He thought it would offer a really interesting opportunity if I could incorporate some physics on scattering cross sections. That is how I decided on that topic and I joined a research group

in the Old Cavendish Laboratory under the direction of Dr. V. Ellis Cosslett, who was a well-known developer of electron microscopes.

ZIERLER: Right.

LEAPMAN: I didn't know exactly what the research was going to involve, but only the general area.

ZIERLER: So as you're peering down into this microscope, I have to ask, where is your education in biology? Zero?

LEAPMAN: At this point, none. My training was all in physics.

ZIERLER: So anything that you learned in the realm of biology you were teaching yourself, essentially?

LEAPMAN: Right, but I didn't really know that much biology. It was just a memory after high school of what I had read of Watson's book and occasionally reading some other articles. But it was sort of stuck in my mind that there was something really interesting there.

ZIERLER: Uh-huh, uh-huh.

LEAPMAN: Actually, I did do some crystallography, but it was crystallography mainly in the context of inorganic materials although occasionally there was a reference to the use of crystallography for determining the structures of proteins as well. So I was aware that some of these techniques could be used not only for inorganic materials but also for biological materials. After all, Cambridge was the home of William and Lawrence Bragg, as well as Perutz and Kendrew, who received the Nobel prize for determining the structure of hemoglobin.

ZIERLER: So at this point, you're not thinking at all about health science research? You're not thinking about advancing human health? Not at all.

LEAPMAN: Not at all. No.

ZIERLER: Not at all.

LEAPMAN: No.

ZIERLER: I'll test your memory. What was, do you remember the title of your dissertation?

LEAPMAN: Yes. It was called, "Electron Energy-Loss Spectrometry of Inner Shell Excitations"

ZIERLER: Okay. And what did you see as your contribution with this work?

LEAPMAN: Well, okay. In those days, there were very, very few people working in this area of electron energy-loss spectroscopy. Most of the theory of image formation in the electron microscope was based on elastic scattering, and it is even today. All the advances in cryo-electron microscopy are based on elastic scattering. But in fact, at least for the lighter atoms in the periodic table, there's more inelastic scattering than there is elastic scattering. And inelastic scattering is usually treated as a nuisance; it's the reason why you can't look at thick samples in the electron microscope because you get multiple inelastic scattering of the electrons, which messes up the image formation. But there was a very, very small number of people around who said, "Well, we could use the inelastic to do elemental microanalysis or nanoanalysis of the samples." This is because a small fraction of the incoming electrons are scattered inelastically by knocking inner shell electrons out of the atoms in the sample, and that gives you a characteristic signal at the ionization energies of those inner shell electrons, and providing signatures of what elements are present. Most people thought it was pretty unlikely to ever work. The signal was so weak and the instrumentation was really not fully developed, so you had trouble even detecting the signals. I persisted with experiments which worked well enough to demonstrate the feasibility of performing microanalysis and also to make some measurements of cross sections and angular distributions of the scattered electrons, as well as to analyze so-called fine structure in the energy loss spectrum. I was fortunate in being one of the first to work on this: perhaps there were half a dozen labs in total around the world. And I was able to pull a dissertation out of the work after three years. The findings were not entirely new but they were new in the context of electron microscopy. For example, a technique had been developed called EXAFS (extended x-ray absorption fine structure) spectroscopy, which provided information about the local atomic environment around specific atoms in a specimen. And I was able to obtain similar data in

electron energy loss spectra, which opened up the possibility of being able to look at local environments of atoms on a nano scale in the electron microscope.

ZIERLER: And so this would have benefits both for material and biological sciences?

LEAPMAN: Probably not so much for biology. Because of the radiation damage. But I wasn't even thinking in terms of that. It was more in terms of looking at amorphous materials. Things which couldn't be identified so easily by diffraction patterns, by crystallography.

ZIERLER: So you were essentially operating on a frontier. You were looking at things that had never been seen before?

LEAPMAN: Perhaps somewhat. Looking back at those days, there weren't that many people who were familiar with the fine structure in the energy loss spectrum. I certainly wasn't the only person in the world who understood the potential for using the fine structure to obtain useful information, but there weren't that many people who did.

ZIERLER: So what were the theoretical ramifications of this? In other words, the things that you were seeing had only been theorized before. And now you were seeing them. Were you involved at all in terms of the impacts of what you were seeing on the theory? In terms of proving or disproving it?

LEAPMAN: Well, immediately following my Ph.D., I went to Oxford for one year, into Dr. Mike Whelan's group in the Department of Metallurgy and Materials Science, which was in many ways really a physics department, because many of the faculty there were trained as physicists. So I continued my dissertation work to show that we could use electron energy-loss spectrometry (or spectroscopy) to perform microanalysis. I looked at some metal alloys containing precipitates like carbides and nitrides, which determine the mechanical properties of various types of steel. And we were certainly able to detect metal carbide precipitates and even to do some rudimentary analysis to quantify the carbon-to-nitrogen ratio in carbonitrides. Then one day in Oxford, I saw an advertisement pinned to the Department notice board, and it was from Professor John Silcox at Cornell University. I wrote to Professor Silcox and he offered me a postdoctoral position in his group in the School of Applied and Engineering Physics. So that's how I came to the US, originally just for a two-year visit. But of course, things don't work out as planned.

ZIERLER: I'm curious, you have a unique perspective, coming to Oxford from Cambridge. Did you detect any differences in the Cambridge approach to physics versus the Oxford approach to physics?

LEAPMAN: There are some differences, I know, but in those days, I was just a lowly postdoc, you know? (both laugh) I don't think I understood the subtle differences between the two different places.

ZIERLER: And when you went to Oxford, is that because you were able to do things there that were not available to you at Cambridge, or you wanted to just sort of mix it up a little bit?

LEAPMAN: I think it was partly because I liked the idea of trying to put my work to some practical use. So in those days, I was thinking, "Okay, we could use the physics of the spectroscopy to actually apply the technique to metals". In fact, many of the faculty in the Department of Metallurgy and Materials Science in Oxford at that time had come from Cambridge, led by Sir Peter Hirsch.

ZIERLER: Oh right, the great migration, I've heard it called.

LEAPMAN: There was a migration, yes.

ZIERLER: So when you saw this note to come to Cornell, this is really the first time that it dawned on you to think about the United States?

LEAPMAN: Pretty much, yes. Actually, in the summer after my first year as an undergraduate, I had visited the United States. There was a special program for college students in those days in which you could do that, so I knew something about what it was like here. This was not many years after the first man on the moon and all that. So there was an excitement in those days. America seemed definitely the place to be in terms of high technology and physics.

ZIERLER: You mean even, I mean, coming from Cambridge and Oxford, presumably you were exposed to the best that the UK has to offer, and even that can't compete with what's available in the United States?

LEAPMAN: Well, there was obviously great work going on in lots of different places. But I think it just seemed an exciting place to be, especially for somebody who was quite young at the time. And also there just seemed more opportunities in the US in terms of jobs and those things.

ZIERLER: And what were your impressions of Ithaca when you arrived?

LEAPMAN: Well, it was a beautifully scenic place, but I remember that we had two extremely cold winters.

ZIERLER: Welcome to upstate New York. (laughs)

LEAPMAN: Yes. They just happened to be very bad winters, and I remember I had my car parked on the street in downtown Ithaca, where I had the upper floor of a typical wooden house. So the rule was that the car had to be parked on alternate sides of the street on even and odd days of the month. I had my little VW Beetle (or Bug) on the street, and there was a lot of wet snow one night, but then the temperature dropped by about 40 degrees overnight, and so it was about 5 degrees Fahrenheit the next morning, and there was this massive wall of ice surrounding the car, that you needed a pickaxe even to make a dent in it. And then what happened was that I got a parking ticket every two days.

ZIERLER: Of course. (laughs) Welcome to America.

LEAPMAN: So Washington seemed like a good place to be after that.

ZIERLER: Right. So what was the research culture like as a post doc at Cornell? I mean, what were some of the big projects that were going on? Were you involved in things beyond your particular area of study? Were you mostly working on your own? Were there collaborations?

LEAPMAN: I was mainly working in the lab in the School of Applied and Engineering Physics. Professor John Silcox who was in charge of the group there was very good at creating a relaxed yet stimulating environment. There were other postdocs there with whom I interacted, as well as a lot of excellent graduate students. I really enjoyed my stay at Cornell even though I only spend two years there, but it was a very productive time and I was really fortunate in getting some nice work done. There were many other people involved as well. it was just a very collaborative atmosphere.

ZIERLER: And what was your funding source at Cornell?

LEAPMAN: I believe that it was mainly through an NSF grant.

ZIERLER: And you know, in the School of Applied and Engineering Physics, again, biology is nowhere to be found in your day to day?

LEAPMAN: Well, it turned out that I wasn't involved in the biology being done at that time, although there was in fact quite a bit of biology being done at that time in the School of Applied and Engineering Physics.

ZIERLER: Really?

LEAPMAN: There was Professor Watt Webb, for example, who was very well known.

ZIERLER: Yeah, sure.

LEAPMAN: He was working on optical fluorescence microscopy and spectroscopy. And so there were some really excellent biological science, biophysics researchers there. I was aware of the work but was not doing it myself. And, at that time, I was more interested in solid state and atomic physics research.

ZIERLER: And then what was the opportunity that opened up NIH to you?

LEAPMAN: Well, yes, that's another curious thing. So I went to some interviews at various universities, and got married at the very end of my time at Cornell. I met my wife in New York City where she'd been living, and she definitely did not want to move to some remote part of the country. I was going to these interviews in Ames Iowa and Urbana-Champaign, Illinois and they didn't seem like good places for me to end up in. But in the spring of my second year at Cornell, I received a phone call from a scientist at NIH. I went down to visit NIH, I think in the early summer. What I learned was that somebody had agreed to come to the NIH from Bell Labs, to work in the field of biology, and NIH had purchased an electron microscope together with the first commercial electron energy loss spectrometer prior to his arrival, so that he could start work immediately. But then he changed his mind, and he decided not to come. (both laugh)

ZIERLER: Oh no.

LEAPMAN: So they offered me a position!

ZIERLER: They didn't return the microscope. They kept it.

LEAPMAN: They kept it — apparently, they were unable to return it. So my two colleagues and I inherited this microscope. The position was more than a postdoc position. I was hired as a "Special Expert". NIH does not have that position anymore. But I was an “expert”, I guess, in electron energy-loss spectroscopy.

ZIERLER: Now, did you look at this as, I'm very fascinated at NIH, as how people see it as an analog to an academic track. So entering NIH in 1980 as an expert, is that like the equivalent of an assistant professorship? Or is it more like a glorified post doc?

LEAPMAN: I think it was more like a glorified postdoc at that time. But things really changed about a decade later when Doctor Harold Varmus took over as the NIH Director in the early 1990s. Varmus wanted to create a more academic track, and to appoint Principal Investigators and Tenure-Track Faculty.

ZIERLER: So they had an electron microscope and it wasn't Iowa, so you said, "Sign me up"?

LEAPMAN: Right, right. (laughs) That was pretty much it. So anyway, when I arrived I had a colleague, Chuck Fiori, who was quite a bit more senior than me, who had come from the National Bureau of Standards, now called the National Institute for Standards and Technology (NIST) and another colleague, Carol Swyt, from another NIH Institute. And we got together with a group in NIH's Division of Computer Research and Technology, now called the Center for Information Technology. That group was excellent at building hardware for computer control of scientific instruments, as well as designing software for acquiring data, and for making non-standard software packages. Such a capability was quite unusual in those days. The group worked together to automate our electron microscope, which was set up to form a focused probe on a sample, and to scan the beam across it, instead of using a broad beam as is the case with the conventional transmission electron microscope. We were able to use an electron energy-loss spectrometer, as well as an x-ray spectrometer mounted on the microscope to perform elemental microanalysis of biological specimens. The modified instrument was I believe the first elemental mapping system that was ever built to image the composition of biological specimens at the nanoscale in an electron microscope.

ZIERLER: And what possibilities did this suggest to you? Beyond the immediate research? Like where could this have gone?

LEAPMAN: Well, we were trying to solve some biological problems by looking at cells and measuring elemental distributions inside subcellular organelles. We had some limited success in determining at the distributions of elements in secretory granules, and I was sort of learning some biology as I was going along, so it was not as efficient as it could have been. Anyway, there was enough interest in the system that we put together to get some attention paid to it. And that was quite helpful for my career, I think, in those early days.

ZIERLER: How so?

LEAPMAN: Well, the instrument that we had been working with wasn't really the state-of-the-art. But at that time in the early 1990s, the state-of-the-art instrument had been adopted by a number of other researchers, mainly in materials science labs and physics labs. That type of instrument was referred to as a "dedicated" scanning transmission electron microscope (STEM), which operated with a very high brightness source, a so-called field emission source, which allowed you to form an extremely small, sub-nanometer probe, on a sample. It was hard to get funding in those days, but after a couple of attempts, we managed to form a collaboration with NIST to purchase one of these instruments. In fact, it originated from the United Kingdom. And that instrument really was the thing that I think helped my career even more, because it had a very impressive performance and capability to form a probe of sub-nanometer size. It enabled chemical analysis at the nanoscale, and it was in principle possible to detect a single atom of an element by focusing the probe down to about a nanometer diameter, where there aren't that many atoms within the probe volume. And then you could detect just one or two atoms of a specific element. And so this was quite a lot of progress.

ZIERLER: Now, what were the technological innovations that allowed for this instrument to be created in the first place? I mean, what were the breakthroughs that made this possible at this point?

LEAPMAN: So the technology for making the STEM came from University of Chicago, originally. Then there was a commercial company (Vacuum Generators) that started making dedicated STEM instruments in the 1970s in England. And so that technology had been around for a bit. But there was also a company on the west coast, Gatan, which had developed an electron energy loss spectrometer with a high energy resolution as well as a high efficiency, because it could detect the spectrum in

parallel using what was initially a photodiode detector, and this was later replaced by an even more efficient high-performance CCD detector. I also knew the most senior research and development physicist at Gatan very well, since he also obtained his Ph.D. degree from Cambridge a year before me, and this connection was very helpful.

ZIERLER: This had commercial value, theoretically?

LEAPMAN: Well, we didn't develop the spectrometer ourselves in the lab: that was designed and manufactured by Gatan. However, I had been co-mentoring a graduate student, John Hunt, from the Materials Science Department at Lehigh University in Pennsylvania. John was superb at writing code, and for his dissertation work, which he applied to materials, he built a prototype STEM-EELS "spectrum-imaging" system in my lab. "Spectrum-imaging" enabled entire 1000-channel spectra to be obtained at each pixel in an image, which was acquired in the STEM by scanning the electron probe point-by-point across a sample. This resulted in extremely rich data-sets from which one could determine all kinds of compositional images (elemental, chemical, and even electronic structure) by using sophisticated spectral processing methods, which previously could only be done at a few locations in the sample. After obtaining his Ph.D. degree, John took a position at Gatan and eventually became the head of Research and Development with the company. The company commercialized John's spectrum-imaging software by expanding it, and integrating it into special hardware, and today numerous laboratories around the world use it. Spectrum-imaging made a tremendous difference. We could now apply the scanning transmission of electron microscope (STEM) together with the electron energy-loss spectrometer (EELS), as well as another imaging mode that collected the elastic scattering with an annular detector positioned in front of the spectrometer to provide a powerful combination of techniques that we could try to apply to biological samples.

ZIERLER: Now what kind of interest was this garnering throughout NIH more broadly? I mean, were people in other institutes getting wind of what you were doing and were they interested in how it might be useful for their own research?

LEAPMAN: Yes, that's an important question. For example, we collaborated with Bernard Moss's lab, in the National Institute for Allergy and Infectious Diseases, to determine the organization of subunits in the envelope protein of HIV, which plays a key role in attachment of the virus to the target cell and the fusion of their membranes. And we were able to obtain this information by analyzing elastic scattering images recorded in our STEM. Also, I think you've already met, or will be meeting, with Rob Tycko (another physicist), in the National Institute for Diabetes Digestive and Kidney Diseases, who has been a pioneer in developing solid-state NMR spectroscopy to solve structures of proteins, whose structures cannot be solved by x-ray crystallography or other approaches. Rob had been doing extensive work on determining molecular models of amyloid fibrils that are associated Alzheimer's disease. In this case, we were able to acquire STEM images that gave us the mass-per-length of the amyloid fibrils, which helped Rob and his group refine their models of amyloid fibrils grown in vitro under different conditions. Perhaps I'll be able to say a bit more about this project later?

ZIERLER: Orient me chronologically. What year would this be now?

LEAPMAN: So that was later, that would have been around 2000 and continued for around 8 years.

ZIERLER: Oh, oh. Okay. This is much later, right, okay.

LEAPMAN: Yes, it started about 10 years after the instrument had been delivered. But we didn't really get everything working for the first few years and we had to wait for a high quality digital acquisition system, not just for the spectrum-imaging but also for collecting the elastic scattering signal used for the work on amyloid fibrils. It took something like seven years before we routinely started collecting data high-quality data. We were also using the instrument to measure low concentrations of calcium in frozen samples of brain that were cryosectioned, put it in the microscope at low temperature, and then imaged. We were able to detect very small accumulations of calcium in synaptic structures. This work was done in collaboration with Brian Andrews in the National Institute of Neurological Diseases and Stroke. We also worked with Tom Reese's Lab in the same institute to analyze cytoskeletal components of neurons — neurofilaments and microtubules, and other structures including post-synaptic densities, which play an essential role in learning and memory.

ZIERLER: Now your first eight years, your appointment until you moved to NCRR in 1988. Where are you at this point? What institute are you attached to for those first eight years?

LEAPMAN: Good question. I think we were part of an organization called the Division of Research Services.

ZIERLER: Kind of a catch-all, it sounds like.

LEAPMAN: Yes, it was pretty much a catch-all name. In those days researchers in the fields of bioengineering and biophysics had to be in one of the categorical institutes named for a disease or organ system, or like us, who weren't really associated with a specific disease or organ system, they were relegated to some part of NIH with, as you say, a catch-all name that encompassed everything that didn't involve particular biomedical problems, even though the work involved sophisticated principles of physical science and engineering.

ZIERLER: Right, right. And then your move in 1988, when you move over to NCRR, is that more formally like the beginning of an assistant professor kind of track?

LEAPMAN: I think so. I believe at that time, or shortly afterwards, I was given a title of a Principal Investigator. But I didn't actually know that I was, for many years. (laughs) It was only much later that they said, "Oh yes, by the way, you know you're a PI" Apparently, someone had filed a record in the Office of the Director, but I was never told about it!

ZIERLER: (laughs) Congratulations. (both laugh)

LEAPMAN: It took about another 10 years to learn that! But it didn't really matter.

ZIERLER: At what point, I mean, is this the point at which you decide you're essentially gonna be an NIH lifer? Like this is where you're gonna make your career?

LEAPMAN: Yes, I think that's about right. But then there was another opportunity that came along quite a bit later, in 2006, which definitely sealed it.

ZIERLER: But earlier in your career, when you move over to NCRR, this must be where you're asking these existential questions about, is this the best place for me to pursue my research? Where is the best opportunities for collaboration and funding? So clearly, that's a crossroads for you, where you are thinking about staying at NIH versus pursuing possibly other academic jobs. So I guess my question is, what, besides inertia, what were the things that really attracted you to stay at NIH? What were the things that allowed... What were the things that were attractive that NIH offered for your career in particular?

LEAPMAN: Right. Well, I think my biggest reason for deciding to stay at NIH was the opportunity to have some really beautiful new instrumentation — the scanning transmission electron microscope and electron spectrometer, which I've already mentioned. That instrument produced spectacular data for the best part of 20 years, and I think that it would have been very difficult to get that with a grant at a university.

ZIERLER: Just because it's so expensive?

LEAPMAN: Yes, it was expensive, but it was due more to it being somewhat unproven technology in the field of biology. Although there were a few biomedical labs around the world with STEMs, it wasn't the standard approach that everyone would say you should use to solve biological problems. I should add that we were greatly assisted by Dr. Dale Newbury at the National Institute of Standards and Technology, who was able to contribute critical funds to set up the instrument on the NIH campus as a joint NIH/NIST facility. In the past few years, conventional TEMs have been adapted to

perform high-quality STEM work, so dedicated STEMs are no longer essential for biological STEM experiments, but our instrument was extremely valuable for the 20-year period from 1990-2010.

ZIERLER: But the budgetary environment at NIH is such that you have that appetite for those risks? You have that leeway at NIH to do these things?

LEAPMAN: I think so. At NIH you could take a few more risks in the research. And then the other thing was the great number of collaborators that you could work with at the NIH.

ZIERLER: Right, right.

LEAPMAN: And there have always been quite a few physicists scattered around the various institutes at the NIH, although not in any one location.

ZIERLER: They're everywhere.

LEAPMAN: If you took them all, and you put them together in one building, it probably would actually be a very impressive set of people.

ZIERLER: Yeah, that's right. That's right.

LEAPMAN: So I think that NIBIB's new Director, Dr. Bruce Tromberg, as well as NIBIB's founding Director, Dr. Roderic Pettigrew would think of NIBIB as a place where you can develop

the quantitative physical sciences, and interdisciplinary sciences with the goal of solving some really important problems in biomedicine.

ZIERLER: Now, the question of collaboration. Would collaborators include MDs? Were you dealing with clinicians who were presenting problems from patients? Because one of the exciting things about NIH is that all of the patients there are exciting, that's why they're at NIH.

LEAPMAN: Right, right.

ZIERLER: So I'm curious how your line of research bumped up into the clinical arm of NIH.

LEAPMAN: We did have some clinical collaborators even in the early days, although we've had more clinical colleagues in recent years. Initially, those projects weren't necessarily the most interesting in terms of the physical science, but we did try to address some of them. One of the early applications, which I remember, involved the analysis of lavaged macrophages from the lungs of patients, who had been exposed to harmful environmental substances like asbestos and metallic particles that got engulfed by the macrophages. We were able to identify the particles, which provided some useful information for the clinician. Very recently, we have started to look at blood platelets from COVID-19 patients (from an out-of-state medical center), who have been experiencing blood clotting, to determine the types of ultrastructural changes that have been occurring. However, most of our applications have involved basic science experiments, but with a strong link to better understanding of diseases.

ZIERLER: Now, in 1990, you become the chief of electron beam imaging and microspectroscopy. Were you the inaugural chief for the electron beam imaging?

LEAPMAN: I think I was the inaugural chief of that. I probably made up that name myself.

ZIERLER: (laughs) How did that come about?

LEAPMAN: You know, it wasn't a very big organization and my group only had a staff of three or four people.

ZIERLER: You could give yourself these exultant titles. (both laugh) So how did that come about, having that program, the electron beam imaging program?

LEAPMAN: Well, that describes the work that we were doing at the time. Also, we preferred not to call the technique "electron microscopy" or "electron spectroscopy" because we were trying to develop new methods and thought that "electron beam imaging" sounded more appropriate.

ZIERLER: So this wasn't a departure for you? This was a continuation of your work.

LEAPMAN: I think it was more a continuation, but we tried to reinvent ourselves from time to time — to try to stay current with the important problems in the field. And today, I've moved away somewhat from the spectroscopy. We're still working with electron spectroscopy, but we think that similar instruments and similar physics, which you need to understand the electron scattering, can be

applied to solve problems in structural biology. So for example, if we move forward to the more recent work that we've been doing, it turns out that the scanning transmission electron microscope has some interesting advantages for imaging 3D structure of cells. Conventional transmission electron microscopy runs into a problem when imaging thicker samples because the transmitted electrons have a range of different energies due to multiple energy losses in the sample, and the electrons having different energies are not focused into the same plane due to the chromatic aberration of the objective lens. This results in a highly blurred image, especially when doing tomographic 3D reconstructions from a series of tilted views of the sample . But we showed that all this goes away in the scanning transmission electron microscope (STEM), where you're forming a very small focused probe that's scanned over the sample because there are no imaging lenses after the sample. We've been able to apply this approach to a wide variety of specimens (malaria parasites, blood platelets, neuronal structures). We published that work in 2009. Electron scattering theory is really important for understanding how any of these electron optical techniques works. However, most labs working in the field of biology don't really incorporate electron scattering theory into how they try to improve the quality of images or understand the limitations of forming the images. And so we're able to put some effort into that. And using Monte Carlo simulations and that type of thing.

ZIERLER: The question of "reinventing yourself", right? In terms of staying relevant. I'm curious, what kind of collaboration are you pursuing beyond NIH? Do you have colleagues in the academic world, in the industry world, or are you really working, you know, as an island unto yourselves at NIH? What's the collaboration there?

LEAPMAN: Absolutely, we collaborate with a number of labs outside of NIH. For example, we've been collaborating extensively with a lab at the University of Arkansas for the Medical Sciences with Professor Brian Storrie to improve our understanding of the structure of human blood platelets

(which I mentioned in the context of an earlier question). Blood platelets are fascinating cells, which appear quite simple, but in fact there's a lot of complexity in how those cells function. They contain several different organelles and hundreds of different compounds that get released, and that are involved in blood clotting or prevention of blood clotting as well. The project wouldn't have been possible on the NIH campus because, as far as I know, there isn't currently anybody studying this, or the way in which structural changes in blood platelets correlate with the function of these cells. And our collaboration has been very fruitful. We've also collaborated recently with a Department of Energy (DoE) lab at the Advanced Photon Source (APS) in Argonne National Lab, and researchers in the Neurological Disease and Stroke institute to combine electron microscopy with x-ray imaging using APS's synchrotron beam lines. The aim of that project is to localize an NMR contrast agent in mouse neurons. So that's another way that we're trying to collaborate.

ZIERLER: In 1998, you become chief of the supramolecular structure and function group. At what point, we've missed-- we've missed tenure. When do you get tenure at NIH?

LEAPMAN: Yes, I somehow got tenure. I don't quite know how it all worked, but we did have reviews of our lab, but that was before I moved to NIBIB. And so the way it works now, you know, for pretty much everybody, is that you compete for a principal investigator position. You probably come in as a tenure-track investigator and work for a number of years, and go through two separate reviews by the Board of Scientific Counselors of your institute (one after 3 years and the other after 6 years), in which they'll read your progress report and hear your presentation. They will write a report which is sent to the Scientific Director, which hopefully recommends tenure after 6 or 7 years. The

Scientific Director then presents the proposed request for tenure to NIH's Central Tenure Committee, which is the committee that actually confers tenure.

ZIERLER: But that's a much more formalized process than what you went through, it sounds like.

LEAPMAN: It was. Because I probably went through that process without knowing it. (both laugh) But also because I arrived at NIH before the formalized process was in effect.

ZIERLER: So when you took over the supramolecular structure and function group, was this new research? Or this was still a continuation of what you had been doing up until this point?

LEAPMAN: I think that during the course of my career, I've been fortunate, I guess, in being able to think of my research as something of a continuum.

ZIERLER: Yeah.

LEAPMAN: And if I were to compare what I did for my PhD work with what I'm doing now, they might seem completely unrelated. They all deal with electrons, but that's about it. I started as a graduate student quantifying the electron energy loss spectrum of precipitates in metal alloys, and now we're using machine learning to understand the 3D changes in blood platelet ultrastructure caused by the COVID-19 pandemic. The techniques are quite different but they've evolved continuously during my career. Although I'm sure this doesn't apply to everyone, I do think that you learn methods or approaches in one area that you can bring to another. And even if you're not

gradually changing the methods that you use in a continuum throughout your career, I think it's often helpful to try to bring certain ways of thinking, or certain approaches to translate from one time of your career to another.

ZIERLER: And what does supramolecular structure, what does that mean?

LEAPMAN: So, basically, it's a meso scale between the near atomic resolution structure that you would have in protein (on one hand) and the cellular structure that you see when you look at an electron microscope image of a cell (on the other hand). But in between there are structures – parts of organelles – which are assemblies of proteins or other molecules that are sometimes visible in cellular images. So the term "supramolecular" bridges in between those scales. We're not looking ourselves at atomic resolution structures, but we're sometimes able to obtain better information than purely morphological images of a cell. For example, you can sometimes see the location of receptors in neuronal membranes, structures with molecular weights in the multiple millions of atomic mass units.

ZIERLER: And this work is still, it's not... You're still in discovery mode, you're still essentially finding out what it is that you're able to see. You're not in diagnostics, you're not in pathology, you're not involved in any of that.

LEAPMAN: Right.

ZIERLER: You're just pushing the boundaries of what can be seen.

LEAPMAN: I think that's right, yes.

ZIERLER: And what, I mean, what are you learning? As you go through this? What are the big things that you're learning as you're seeing things that have never been seen before?

LEAPMAN: Well, in addition to the great recent progress in determining the high-resolution 3D structure of proteins based on cryo-electron microscopy (including recent Nobel Prizes), there has also been great progress in determining 3D structure of cells. One obvious thing is that for many decades biologists have looked at electron microscope images and observed slices through cells — basically two-dimensional views of cells. But when you look in 3D at cells and tissues, everything looks completely different. And this is what is now achievable. You can use a series of relatively new techniques, which we've also been adopting, to look at large numbers of cells and even tissues at pretty high spatial resolution of a few nanometers. It's now possible to see all the organelles in a cell and to visualize the connections between those structures, which are nearly impossible to see in two-dimensional slices through those cells. As one can imagine, the amount of data that you're collecting can be enormous if you consider, for example, a 100 micrometer cube of material. That contains a lot of cubic nanometers (10^{15}) and a lot of voxels (10^{12}) assuming a 10-nm voxel size. The problem is not so much with the acquisition but with the analysis. If you've got all these data, you have to sort through a massive amount of information. How do you even visualize it? So that's another thing that we're trying to get into. Along with a lot of other researchers, we're trying to apply machine learning to automatically segment subcellular structure. This is an impossible task with a human doing the segmentation, because it would take forever to do that. It's a challenging problem but there are signs of breakthroughs in this area too, and we're hoping to play a role in that, in the context of segmenting the densely packed 3D ultrastructure of cells.

ZIERLER: Now, as the instrumentation gets better and the technology gets better, so goes with it your capacity to just look deeper and deeper and deeper, and so I wonder if I could pull out the budding philosopher in you as a high school student, and ask you what do you make of the seemingly unending complexity of the things that you see? I mean, does that... what is your reaction to that, beyond, you know, your instincts as a scientist? In terms of how truly complex nature can be at that level.

LEAPMAN: Yes, it's something that I've thought about a bit, I guess. But although the structures you see can seem endless with endless complexity, it seems to me that there must be some underlying principles that are not so complex. Because, for example, all our cells comprise a set of proteins that are coded for by a relatively small number of genes. And those small numbers of genes in the cells somehow code for our brain, and the development of our brain, and everything about its complex structure. So I think there must be some underlying principles at play. Whether or not we are able to find out what those are, I'm not sure, but somewhere underneath the complexity, the seemingly endless complexity, are some principles, which probably have to be understandable in some way.

ZIERLER: So would that suggest that, in fact, as Socrates would say, you know, the more you know the more you know you don't know? Which is an unending loop, of course.

LEAPMAN: Right, I suppose so.

ZIERLER: Are you suggesting, then, that at a certain point, there is an end stage of discovery? And that discovery would be those unifying principles?

LEAPMAN: You know, that's a very interesting philosophical question. I'm not sure whether we'll ever understand everything.

ZIERLER: Right.

LEAPMAN: You know, I think that that's a tall order. But I think that all of science really is based on recognizing patterns. In order to even talk about something, we need to make a mental model of it. Imagine if one knew the structure of the whole body at incredibly high spatial resolution, and you had the coordinates of every single atom. That would be the ultimate image that you could have. But it wouldn't tell you much, because it wouldn't tell you how anything worked.

ZIERLER: Right.

LEAPMAN: And so, in order to understand anything, you have to have some model, otherwise it's unintelligible. So I think that's what we try to work out, and if the model is able to predict something, that you didn't know, and it turns out to be borne out by experiment, then you know, in some way, there's some truth to that model. Because it gives you an experimentally-observed right answer.

ZIERLER: And by "truth" do you mean it has both theoretical and experimental truth?

LEAPMAN: Right. I think so. And to some extent, I think it relates to what we mean by having an understanding of something. It's the difference between understanding and just information. The information by itself doesn't really tell me much. It's how you understand that information.

ZIERLER: So back to the more prosaic realm, in 1999 you're named director, the Division of Bioengineering and Physical Science. I'm curious at what point on this trajectory, this, you know, rapidly rising trajectory at NIH, are you ever concerned that your bureaucratic responsibilities would overwhelm your research interests as you move into higher and higher roles?

LEAPMAN: I don't think I'm going to reach a higher role because I'm happy where I am. But there's always that little bit of tension, you know, the way NIH does things. I think even at the institute director level, the idea is to have people in charge who stay in touch with the science. That's why the majority of Institute Directors run labs even though they are responsible for the much larger funding levels of their extramural programs. And as Scientific Director of my institute's intramural program, I have a small fraction of the administrative responsibilities of an Institute Director.

ZIERLER: Right.

LEAPMAN: I'm responsible just for the intramural program of a fairly small institute. And we have a lot of good people to help as well. But it's a privilege to be involved in some way in helping these other outstanding scientists to realize their goals.

ZIERLER: Yeah, yeah.

LEAPMAN: But there's always a tension between trying to do some science and trying to help with the administration.

ZIERLER: Now, you mentioned, in your initial comments, your interest in mentoring and fostering careers of your (**LEAPMAN**: Right.) young colleagues. At what point in your own career did you feel you were really best-positioned to take on that role? Would that have been in the late 1990s in the directorship position? Or even before that?

LEAPMAN: I think I've always enjoyed just talking to other people about what we do, and I believe that most scientists should be interested in communicating to others around them what they're doing, because it adds to the whole environment. So I think in that sense, all scientists should be in some ways taking on some of that responsibility regardless of their level.

ZIERLER: Yeah.

LEAPMAN: Unless you're a student at the very beginning of your career. So if you're a postdoc, you can mentor the postbacs, and if you're a staff scientist or PI, you can mentor postdocs. So although science is a very absorbing pursuit, you know, it also it needs people with people skills. (laughs)

ZIERLER: Right.

LEAPMAN: This is very important too.

ZIERLER: Sure.

LEAPMAN: And at all levels, not just when you become a director of something, but even at the very beginning, you need to have the people skills to get on with your advisor, to get on with the other students, and to try to help other people around you. So I think that's something which should be encouraged at all levels of scientists.

ZIERLER: Now, when you're named scientific director in 2006, is this an incremental step or is this like a quantum leap? In terms of hierarchy.

LEAPMAN: There are some more responsibilities. I must admit, when I first took the job, it was a bit daunting. You know, what have I let myself in for?

ZIERLER: Yeah.

LEAPMAN: But actually, it's not something that is impossible to do. You do have to go to quite a lot of boring meetings. (both laugh) That's one thing, but I'm sure it happens in every job.

ZIERLER: Sure.

LEAPMAN: You know, there's always some stuff that you do that's not the most exciting. But it can be important, even though it may not be very exciting.

ZIERLER: So what are some of your unique responsibilities as scientific director? You said there's an intramural component to it?

LEAPMAN: It's all intramural. The scientific director is the director of the intramural program of the institute, basically.

ZIERLER: Which means what, exactly?

LEAPMAN: Well, if you look at the investment in research, 90% of the NIH funding goes to the extramural program.

ZIERLER: External grants.

LEAPMAN: Yes, to academic institutions around the country, and the Institute Director has to deal with all that, and has to make sure that the funding decisions and the funding areas are the best. The Institute Director also has a role in the intramural program as well, but the day-to-day running of the intramural program is the job of the Scientific Director. Which is a bit confusing, because it may appear that the Scientific Director is in charge of all the science, but it's only the intramural program that they're in charge of.

ZIERLER: So by definition, there's, I mean, just scientifically, there's so much overlap in what any given institute can do or should do. How much involved are you with sort of carving out that

disciplinary territory for the NIBIB? As in saying, "This is in our portfolio, we're gonna do this, not you guys." Is that a big part of the job?

LEAPMAN: I wouldn't say that's a big part of the job. There must inevitably be some overlap, and we, the Scientific Directors, meet twice a month to discuss all the issues that come up, both scientific and administrative. In terms of the science, I think that there an awareness of what's going on in other institutes. And so nobody wants to reinvent what's already been done somewhere else. For example, we have some excellent PIs who are working in optical imaging, developing new optical techniques. And there are some other labs doing that too, but the particular optical techniques that we're developing in NIBIB are different from ones being developed in the other institutes. Importantly, there are many trans-NIH Scientific Interest Groups where scientists with common interests participate and present seminars, so that the scientists themselves tend to be very aware of what their colleagues are doing, even if the Scientific Director doesn't know. So there's sort of a complementarity there and by and large, you don't have two people in two different institutes doing the same thing. It must have happened occasionally in all the history of the NIH, but it's very rare that people would be doing exactly the same thing.

ZIERLER: And from your vantage point, to the extent that the NIH has a singular or a unifying mission, what is the NIBIB's role in furthering that mission?

LEAPMAN: Yes, that's something that we have discussed quite a bit in the context of our institute's strategic plan, which is required every five years or so. Although this exercise has been put on hold due to COVID, broadly NIBIB develops and disseminates transformational technologies that span the range from bench to bedside. This involves applying the approaches of physical sciences,

engineering and mathematics to solve problems in basic research, as well as in clinical research, including sensing, diagnostic imaging, disease prevention, and therapeutics, with computation and data science playing an increasing role.

ZIERLER: And to shrink down that same question, what is your role as chief of the Cellular Imaging and Macromolecular Biophysical lab? What is the role of that within the overall role of the NIBIB?

LEAPMAN: Well, we are trying to understand processes in cells based on 3D imaging, which gives information about cellular structure, as well as spectroscopy which provides information about the subcellular composition of organelles. We believe that a combination of structure and composition, will give us a better understanding of disease processes in addition to how normal cells function. There are also some ways in which we can use our microscopic scale to interpret some features of medical images. If one is using nanoparticles in diagnostics, we can use the spectroscopy to characterize those nanoparticles. For example, there was a project with Dr. Jeff Duyn in the Neurological Disease and Stroke Institute, where we showed that some specific contrast features in magnetic resonance images (MRI) of human brain were due to iron-containing proteins that are distributed in different brain regions at different concentrations. So there is some feedback here into diagnostic applications, which is a big part of the NIBIB's portfolio.

ZIERLER: If you could talk a little bit about open loops and closed loops, over the course of your career. Projects that you had to leave open that you never returned to, or projects that you left open and that you were able to return to? Do you ever feel like, is your general work style that you won't

let go of a project until you feel it's reached completion? Or are there projects that you just simply, for lack of time or resources, never were able to return to?

LEAPMAN: Yes, there have been a couple of projects that we couldn't complete, although a lot of time was spent on them. It's happened a couple of times. One involved a collaboration with the National Cancer Institute on trying to identify uptake of a cancer drug (cisplatin) into tumor cells, which required some special sample preparation methods. It was a difficult experiment because the drug concentration was very low. We almost made it, but couldn't quite get the data we needed due to the departure of the postdoc who had been doing the work. Sometimes it's just very hard to get experiments finished.

ZIERLER: Yeah.

LEAPMAN: But we've been lucky that for most projects, we've been able to get things finished in some way.

ZIERLER: And that leads me, I mean you have a unique vantage point as both a scientific director in a bureaucratic capacity, and as a chief of a lab. And the question is, how do you define success or failure in real time? In other words, how do you know that a given project deserves, you know, ongoing commitment in terms of time and resource, or how do you know that it's time to jump ship because you're not getting anywhere? When you're working at your level, and you're seeing things that are never been seen before, never even been theorized before, how do you know on a day-to-day basis when to keep going and when to stop?

LEAPMAN: Yes, that's a good question. We sometimes approach this by doing a pilot study. Let's just try something and see if it's possible to do this or that? And we may find that it's just impossible to detect what we're trying to look for. In that case, we usually try to find a fundamental reason for why it's difficult to detect. It might have seemed a good idea, but actually, when you put the numbers in, it can become clear why we couldn't detect a particular signal. So you can rationalize why the experiment is not working in terms of some physical principle, which explains why detection was not feasible. And you say, "Well, okay, we'll try something different." But when something starts to work, we try to complete that experiment since we know we can get data. Maybe the answer won't be what we were hoping for, but at least there will be an answer, one way or the other.

ZIERLER: And completion is the answer? It's not just gathering the data? It has to be what the data means?

LEAPMAN: Right, I think both. You have to collect the data, and then you have to see what the result is. Perhaps you have a hypothesis that if you manipulate the cells in this way, there will be some effect that we can measure, a different behavior from the control. And if it doesn't happen, if there isn't a difference, well, that's a result. It may not be the most exciting result, because there was some hypothesis that you put in, and the result didn't support the hypothesis. I guess that's going on with the COVID-19 pandemic now. People are developing these drugs, and some of them will work and some won't. It's still a result, and it should be published, but it's not going be the most exciting thing, if something doesn't work.

ZIERLER: For your own career, I wonder if you could think about, what was the single most exciting insight or discovery that you made? That was sort of the most satisfying to you sort of personally or as a contribution to your field?

LEAPMAN: Yeah, that's a good question. It's funny, because some of the things which I could mention seemed to me at the time to be quite exciting, but probably the rest of the world doesn't think they're very exciting at all. (both laugh)

ZIERLER: Well, I'm asking you, in your own personal capacity, what was most personally satisfying?

LEAPMAN: One thing that seemed fascinating to me was when we were making spectroscopic measurements while we were looking at frozen samples in the electron microscope. Cryo-electron microscopy researchers had been acquiring images from frozen samples for a long time, and they saw bubbles that were produced in the samples due to the radiation damage. But nobody really knew what those bubbles were, although there were some theories. But then, we were looking at the electron energy-loss spectrum while we were exposing the frozen sample to the beam, and we could see the bubbles form in the ice. And then I looked at the energy-loss spectrum, and I had no idea of what I was observing. I was seeing some strange spectral peaks appearing and disappearing as the bubbles formed. I thought there must be some charging up of the sample, or that there was something screwy going on with the electron energy-loss spectrometer. But then I had this eureka moment. Suddenly, I realized the cause of the strange peaks. I was looking at the Rydberg energy (13 electron volts) corresponding to the ionization energy of gaseous molecular hydrogen. Nobody had ever looked at hydrogen gas using electron energy-loss spectroscopy, at least not in the electron

microscope, and yet, suddenly it was the realization that I was understanding for the first time the process of radiation damage in cryo samples because I was seeing the hydrogen release. I quickly calculated the pressure inside the tiny 100-nanometer bubbles from the size of the peak in the energy loss spectrum and found it to be several thousand atmospheres, enough to distort the ice in the liquid nitrogen cooled specimen.

ZIERLER: So how did you know it was a eureka moment?

LEAPMAN: Well, because I had no idea what it was, and then I suddenly, I looked up the spectrum of hydrogen gas, and there it was.

ZIERLER: Yeah, yeah. And was that over the course of your career, I mean so much--

LEAPMAN: No, no. That was just a very minor eureka moment.

ZIERLER: No but I mean, I mean in terms of, you know, the vast majority of progress in science happens incrementally, right? It's not dramatic. (**LEAPMAN**: Right, yeah.) It's not like those kinds of moments. So have you, I mean, how often do those moments come around where you feel like in a burst of insight, you've really pushed the ball forward? You've really moved the needle on a particular thing?

LEAPMAN: Another time was when I was looking at some samples in our scanning transmission electron microscope, and after putting in values for the scattering cross sections, I realized that I was

seeing single atoms of calcium. Because the magnitude of the signal fit exactly with the expected signal from a single atom.

ZIERLER: Right.

LEAPMAN: So I thought, wow, there's a single atom of calcium.

ZIERLER: Right.

LEAPMAN: Although the biological applications of such analyses is limited by radiation damage, it showed me the unprecedented sensitivity of the technique.

ZIERLER: Now, if I could turn those questions, in terms of usefulness, if I could turn those questions inside out, I've been asking you their impact on you personally. To the extent that the H index is a reliable barometer of such things, how do you understand your contributions to the field in terms of, what work have you done that's been most cited, that's been most useful to your colleagues?

LEAPMAN: I've already briefly mentioned my collaboration with Rob Tycko to determine the structures of amyloid beta fibrils, which are associated with Alzheimer's disease. Two or three papers with Rob have been very highly cited, with one receiving over 2,000 citations. In that study, we used our scanning transmission electron microscope to measure the mass-per-unit-length of amyloid beta fibrils, grown under different conditions from which we could deduce the arrangement of beta sheets. Rob was then able to obtain atomic-scale models of the fibrillar structure by combining our STEM data with his solid-state nuclear magnetic resonance data. Moreover, in one of

our papers, it was found that fibrils with certain arrangements of beta sheets were more toxic to cultured neurons than other arrangements.

Another paper that's well-cited is work that I did as a postdoc at Cornell University, which was published in Physical Review. I believe that work has been cited more than 700 times. I certainly didn't realize at the time that it would be, but it continually gets cited every year, and it's built up that many citations.

ZIERLER: What was the paper? What were you writing on?

LEAPMAN: I was studying the core level excitations of the first-period transition elements using electron energy loss spectroscopy in a transmission electron microscope. We showed that there was a difference in the so-called "white line ratio" of the L3 to the L2 edges, as a function of the atomic number and oxidation state through the period of transition elements, a variation that was not understood at the time, and which has subsequently been much better understood from theory. At that time, we put together some relatively crude theory, which was able to partially explain the data, and the white-line ratio is used even today by researchers in the field of material science.

ZIERLER: Now, your educational trajectory up to NIH from the perspective of NIH was very unorthodox, right? This is not a traditional biophysics kind of entree that other, most other physicists have had. So I wonder, you know, if you can reflect on the extent to which your unorthodox background was beneficial to the development of your career, and in what ways was it a detriment to the development of your career at NIH? Coming from, essentially, as an outsider to the field.

LEAPMAN: Right. I think that I've always felt a little insecure in my knowledge of biology, because it's hard to be knowledgeable about all aspects of a multidisciplinary field (physics, chemistry, biophysics, structural biology, cell biology, molecular biology, physiology, et cetera…). But, as a physicist working in the field of biomedicine at NIH, it's very important to avoid staying within one's comfort zone of physics, and to embrace learning about the other sub-disciplines of this multidisciplinary field, even if one doesn't become an expert in those areas. In my case, I do feel that I've gradually improved my understanding, at least, of cell biology. One of the advantages of coming to the NIH with a training in physics is that perhaps one tends to think in a more quantitative way than people who are trained more conventionally. So, biologists probably don't ask quite the same questions that I might ask. I want to know how many copies of something there are — how many molecules of neurotransmitter are in each synaptic vesicle in a synapse? And if the molecules of neurotransmitter bind a particular element, how many atoms of that element would be present? The biologists tend to think in terms of neurotransmitter concentrations or ion concentrations (in units of millimoles per liter) but they might not have thought about the numbers of copies. That's just one example, but I think that looking at cells and tissues in a more quantitative way, and trying to understand things from a slightly different angle can be useful.

ZIERLER: To what extent do you think that the traditional distinctions between physics and chemistry and biology are really artificial and it's a really just a human construct for the way that we organize our own education? Is it all really one large scientific field, and this is inevitably how we have to break it up in order to function in society? Or are there objective distinctions between the fields that suggest that they really do have these differences?

LEAPMAN: Well, in my way of thinking, it's all one science. In physical reality, there's no separation between these fields. On the other hand, for convenience, since it's impossible to learn

everything, it's certainly helpful to divide scientific endeavor into sub-fields. But in reality these boundaries don't exist.

ZIERLER: Right.

LEAPMAN: Biological systems ultimately operate on an atomic scale. It's just that when the number of atoms gets large, then properties can emerge on a coarser scale (for example, cellular ultrastructure, tissue structure, and organ structure), so that you might not always need to be working at the atomic scale in order to push forward the science. On the other hand, biochemistry, which operates at the atomic scale, affects all biological scales.

ZIERLER: Thinking back to the beginning of your career, you know, at NIH in 1980, I wonder if you can reflect on what were some of the things that were fundamentally mysterious, either to you personally or to your field, that are no longer mysterious as a result of the work that you and your colleagues have done. And what remains as mysterious today as it was 40-some years ago to you personally or to your field?

LEAPMAN: Philosophically, I think it's interesting that ultimately everything works according to quantum mechanics. Yet, there's sort of a lack of understanding of quantum mechanics, even today.

ZIERLER: You mean among biologists and chemists? Not among physicists?

LEAPMAN: Amongst physicists.

ZIERLER: Amongst physicists, wow, okay. (laughs)

LEAPMAN: So, you know, when you look in an electron microscope at a thin crystal, you see a diffraction pattern. But you know that there's only one electron in the microscope at any one time. So the electron is apparently interfering with itself, and it's not considered to be interfering with other electrons. So how do you--

ZIERLER: Wait, I have to stop you there. What does it mean that an electron is interfering with itself? What does that even mean?

LEAPMAN: Well, exactly. So that's the question. That's what physicists don't know. (both laugh)

ZIERLER: Okay, good, I'm in good company then. (laughs)

LEAPMAN: Well, some of them do — the quantum theorists have some ideas about what that means. In fact, it has forced some contemporary physicists, most notably David Deutsch, to think of quantum mechanics from a "many-worlds" standpoint. In their view, the phenomenon of diffraction of a single electron by a crystal lattice in an electron microscope, can be explained by the electrons in one branch of the multiverse, interfering with "shadow electrons" in other branches of the multiverse. Now, the electron no longer has to interfere with itself, but this requires acceptance of the multiverse! The traditional standpoint of quantum mechanics and the many-worlds standpoint explain the same physical observations, yet their view of physical reality is entirely different. So even looking at seemingly mundane diffraction patterns in an electron microscope at the NIH can sometimes confront you with interesting philosophical questions! This illustrates that some observations that

seem obvious, might in fact be more complicated to fully understand. So I think as a physicist and a "doctor of philosophy", you get used to those things.

But on a more practical and less abstruse level, let me answer the question in the context of the particular things that I've worked on. When I began my career, there was a lack of knowledge about the form of the electron energy-loss spectrum — about the shapes and intensities of the peaks that are characteristic of different elements and compounds. Knowledge has improved a lot, and now there are calculations that give you reasonably accurate spectral shapes, which weren't available certainly when I started. Our knowledge at that time was more empirical and there was much less understanding. So that's been a definite advance, as also has been our understanding of the fundamental limits of these techniques, and of what you can and cannot do with them. Ultimately, in the electron microscope, electron irradiation damages a sample and makes it difficult to detect small structures and to determine their composition, but those limits are better understood too.

ZIERLER: And what, I mean, the question is, the other side of the question is, what is as mysterious to you today as it was 40 years ago? That has just like, you feel like despite all of the progress, the technical progress, the intellectual progress, the funding progress, right? You're still nowhere as you were 40 years ago. Like, really like fundamental things that are just, it seems to elude all of those efforts or those areas of progress, it's still like you're still where you were in 1980.

LEAPMAN: In my field, you're saying?

ZIERLER: Correct. No I mean, but I would love for you to wax philosophical.

LEAPMAN: We can now use electron microscopy and electron spectroscopy within the limits of radiation damage to understand the 3D structure of a cell and to determine its composition within the bounds of the technique. But can we really improve our understanding of how cells work? Also, if you look with electron microscopy at things that are very small, it's very difficult to look also in the time domain, and the best you can do is to look at snapshots in time. Optical imaging can look at the time domain as well, but it doesn't necessarily give you the structural context of everything in the cell. And one might ask the question, is there a way to have the spatial resolution of the electron microscope, while also watching the three-dimensional structure evolve in time. Of course, that's an impossibility right now.

ZIERLER: Is that a-- That's a technological impossibility, or a theoretical?

LEAPMAN: No, it's technologically impossible, because electron microscopy requires that you take a snapshot of the living cell, either by chemically fixing it or by freezing it by using cryo-preparation techniques.

ZIERLER: But theoretically, it's not-- Theoretically, it's not impossible. There could be a technology at some point in the future that could give real time information from this instrumentation?

LEAPMAN: It might be interesting to imagine using machine learning to blend together the high spatial resolution of electron microscopy images with the time domain of the optical microscope. If that were possible, one could perhaps obtain a four-dimensional movie of a cell, with the electron

microscopy resolution superimposed on it. I don't know and it might not be possible, but it's an intriguing idea that maybe one could do that.

ZIERLER: So on the question of how science advances, how progress is made, if you could very roughly sort of quantify how much of it is advances in technology, how much of it is advances in human ingenuity, in terms of insight and intellect, how much of it is simply a matter of funding and resources? And then finally, how much of it is just the sort of daily grind of being in the lab and doing a little bit more each and every day? I mean, how do you roughly see each of those areas and their role in the broader question of how science progresses?

LEAPMAN: These are very good questions. (laughs) Certainly there's a lot of work that has to get done in the lab, and that's maybe not always super-exciting. It has to be done in order to get data, to interpret something. Yes, the funding's always important, but I think that there's definitely an important place for ingenuity, and I wish I had more of it! When I look at where other people have made advances in other somewhat related fields, I find it amazing to see what people come up with to solve a problem: things that I could think about for 100 years and I'd never come up with. So I think that ingenuity is the key. One technique, which I found particularly intriguing, is not connected to anything that I'm doing, and at first seemed completely bizarre to most people who were introduced to the concept. I actually reviewed the paper by Edward Boyden from MIT, which described the initial report on this new technique called "expansion microscopy". The authors had solved the problem of the resolution limit of optical microscopes being constrained by the wavelength of light by literally expanding the sample, and it actually worked! You'd think it would never, never work, but the group who developed the technique, labeled cells and tissue with fluorescent-labeled antibodies, applied fixative, and put the cells into a gel, which inflated the entire sample so that a standard fluorescence microscope effectively became a super-resolution microscope.

ZIERLER: Yeah. Yeah.

LEAPMAN: And so, and that's why there's always the room for ingenuity. And of course, you know, I can't tell you what those things are, because if I'd thought of it, I would have done it.

ZIERLER: You'd have it, right. Right. (both laugh) Now, of course, there's the ever-elusive, in physics, there's the unified theory in physics, right? But from your perspective, you know, coming from a physics background, now in being you know, primarily in biology, do you think that there's a unified theory of biology that's out there to be discovered? Something that puts it all together in biological systems?

LEAPMAN: I have no idea. I should really defer to the people who think about these things. If I gave you an answer it would be purely as a layman. Not that I'm qualified to give an answer, but I think there probably are some principles that have yet to be found. The thing that fascinates me is that you can potentially work out all the structure in a mouse brain, and we know that we can get very similar behaviors from differently wired brains. We also know that different humans can more or less think in the same way, yet on a microscopic scale they must have very differently wired brains. So I think there must be some fundamental principles about the organization of neuronal circuits and how multiple circuits work together. And the exact layout of the circuit might not matter so much. Perhaps some, as yet unknown, basic principles are more important. So that's why it's not clear to me that you need to know the whole structure of a brain to atomic resolution in order to understand how the brain works.

ZIERLER: Yeah. I think--

ZIERLER: I think for my last question, a forward-looking question. You know, we've been very introspective and retrospective in terms of your career, your thought processes. I want to ask you, what are you most excited about personally, and what are you most excited about for your field broadly conceived? And that can be either the institute or your lab. Within your own lifetime, what you think that you can achieve, and where you see the field headed, and what's exciting to you about the future?

LEAPMAN: Yes, another great question. In terms of my own research and my NIBIB colleagues' research, I like to envision a far-reaching goal of obtaining improved models of how cells function using a combination of structural and functional methods based on electron and optical microscopies, in terms of the three-dimensional structure of all the organelles, and ideally as a function of time too. In terms of our institute as a whole, I'm excited by what's possible in imaging in general. And so I find the work of my colleagues who are developing optical imaging on fast time-scales, and at high spatial resolution, are doing very exciting work. For example, we have a Principal Investigator, Hari Shroff, whose name you may have seen.

ZIERLER: I spoke to him.

LEAPMAN: That's great.

ZIERLER: I did an interview with him.

LEAPMAN: You did already? That's fantastic.

ZIERLER: Yeah.

LEAPMAN: Great. So Hari is able to do amazing work on the structures of cells. And as you know he has been able to look at the development of a model animal, C. elegans, from a single cell to an embryo, to the adult worm, which represents the first time that the development of an animal has ever been imaged continuously from a single cell to an adult. I think that's very exciting. You know, people are trying to understand how the human brain works, but as Hari likes to point out, nobody really understands how the brain of a C.elegans worm works!

ZIERLER: (laughs) Right, right.

LEAPMAN: So I think (laughs), I think we've got a ways to go. But I think all this work is very exciting.

ZIERLER: Yeah. It's exciting in the sense that you know how far there is to go, but there's also a roadmap in a sense of how to get there. Yeah.

LEAPMAN: Right, yes.

ZIERLER: Well, Dr. Leapman, this has been an absolute delight speaking with you today.

LEAPMAN: I don't know what you're going to make of this because I'm not sure whether what I said was coherent or not.

ZIERLER: I think it's been absolutely coherent, and I asked you questions based on the fact that I specifically wanted answers from you for them. So I really appreciate your time, and you know, this is an interview that's gonna be of immense value to people who are interested in, you know, how the NIH works, how your field of research works, and also the inevitable questions about the philosophical implications of the things that you do, and ultimately, where human knowledge takes us and how we get there. And you've brilliantly touched on all of those areas, so I'm tremendously grateful to you.

LEAPMAN: Well thank you so much for the opportunity. I hope we can stay in touch, and it's been very nice meeting you.

ZIERLER: Absolutely.