ZIERLER: Okay. This is David Zierler, Oral Historian for the American Institute of Physics. It is April 30th, 2020. It is my great pleasure to be here virtually with Dr. Philip Anfinrud. Thank you so much for being with me today.

ANFINRUD: It's my pleasure.

ZIERLER: Okay, so let's start with your title and your institutional affiliation.

ANFINRUD: Okay. I'm a Senior Biomedical Research Scientist at the National Institutes of Health, but there are many institutes and centers at the NIH. The one I work in is the National Institute for Diabetes and Digestive and Kidney Diseases. A big mouthful, so NIDDK. In that institute there are many laboratories that focus on different things, and where I work is a really fantastic place. It's called the Laboratory of Chemical Physics. You've already interviewed a number of my colleagues. I like to call this the "Bell Labs of Biophysics." We have brilliant colleagues who are in the forefront of their respective research and focused on an understanding of protein structure and dynamics, and how we might understand how life actually works by probing these things at an intimate level of detail.

ZIERLER: That's great. I talk to people all the time who have spent formative years at Bell Labs, so I truly appreciate what you mean by saying this is the Bell Labs of Biophysics. Definitely excited to talk about that. So, let's start right at the beginning. Tell me about your birthplace, and your family background.

ANFINRUD: I was born in North Dakota, in a small town.

ZIERLER: Are there any others in North Dakota?

ANFINRUD: Well, maybe 700,000 people there, or something like that. It's a big state, but sparsely populated, and primarily agricultural. I consider my hometown to be Aneta. It was a town of about 300 people. My father was a Lutheran pastor, so what do you do in the summer for employment? Well, when I got old enough to be able to hop on a tractor, I was out working in the fields to earn some money and save up for my college education.

ZIERLER: Were your parents from North Dakota also?

ANFINRUD: My mother was, and my father was from Minnesota. He served a number of parishes around North Dakota, and just before I turned six, we moved to Aneta, and that's where my really formative years were. I stayed there through high school, and then went on to college. I always had an interest in science, and some of that actually was spurred by the church. In fact, I learned about the theory of relativity at church before I learned about it in school. They had these Moody Institute films that we'd have on family nights, and I was just wowed by all this stuff. What is this relativity thing? How you can go near the speed of light, and dimensions change, and all that. As a kid, I couldn't really wrap my mind around it, but it sounded really cool. So, I always had an interest in science. When I was a junior in high school, a science teacher mandated that we do a science fair project. So, what do I do? At the time, the ozone hole controversy was raging. So, I thought, I'm going to study atmospheric chemistry. How do you do that when you come from a really tiny town like this? Well, I started going to the University of North Dakota to meet some of the faculty there, and these guys were very generous with their time, and very helpful. At the time, I had not yet had a course in chemistry, so I was learning chemistry on the fly. They were very supportive, and I found myself just so inspired to work on this stuff that most of my waking hours when I wasn't in school was spent doing this. One thing

led to another, and I was invited to go to the International Science and Engineering Fair in Denver, Colorado, and guess who are my judges? Faculty from the University of Colorado at Boulder, and researchers at the National Oceanic and Atmospheric Administration. Oh, they loved this atmospheric chemistry stuff that I was doing. It was quite relevant for the time, and so they awarded me with the honor to represent the United States at what was called the Science Fair of the Americas. It was the first time they brought together kids from Central America, South America, and North America in one site to present their research, with the inaugural site being Sao Paulo, Brazil.

ZIERLER: How old were you for this?

ANFINRUD: I was 17, and a junior in high school. So, this really got me inspired in science. I flew on my first commercial airline trip going to Sao Paulo. I had never been out of the -- well, Canada doesn't exactly count. Of course, I've been to Canada many times growing up because we're right next to the border. So, my formative years were spent in a tiny town where everybody knows everybody. You can't get away with anything because by the time you got home, if you did something wrong, your parents would have heard about it. But it was a wonderful place, a wonderful town. Fantastic people, and I treasure the time that I had there.

ZIERLER: Did you think that you were going to pursue atmospheric chemistry in college? Was that the original plan?

ANFINRUD: Well, also raging at the time was this energy crisis. We had an oil embargo and rising gas prices, and I got very interested in energy-related things. So, when I decided to go to graduate school, I ended up working at Iowa State University for a professor who was doing solar photoelectrochemistry. As an undergraduate, I got involved with undergraduate research

early on. I had a professor that picked me out and said, "Would you like to come work in my group?" I said, "Well, I've got to earn money toward my college education." He said, "Oh, I'll pay you." "Really?" It wasn't a huge amount, but I earned some money, and I could work there in the summer, embedded in the university environment, and learned a lot of things that you wouldn't learn in a normal classroom by being in a research lab. I learned about electronics and did some electrochemistry. I did some glass blowing, and worked some in a machine shop. So, I gained a lot of skills that proved quite valuable later on.

ZIERLER: Now did you want to stay -- I assume, given your interests, if you wanted to go to a little better-known school -- did you want to stay close to home? Was that part of the matrix of considerations?

ANFINRUD: I assume you're asking about my choice for graduate school. Well, if I stood up next to Ad Bax, you'd understand how I've been looking up to him in more ways than one. I'm about 5 foot 4. So, here's a shy kid from this tiny town, and the prospect of going far away to a big city was threatening to me. Iowa State University is a college town next to cornfields. It was more familiar to me, and more comfortable. Of course, I didn't want to let that dictate where I would go for university education, and I talked to some of my professors about that. I said, "Should I be considering some out east universities like Harvard?" One of the guys who was from New York said, "Well, Harvard's not really what it's cracked up to be." This from someone who was teaching at Fargo, North Dakota. Nobody encouraged me to apply to some of the schools that were famous, even in North Dakota: Harvard, Yale, Princeton, whatever. So, I never bothered applying there. But I did apply to a number of other good schools, including Berkeley, which accepted me. The weekend that I spent there was kind of interesting. When choosing a

graduate school, I did not want the surrounding environment or school reputation to dictate my decision. I wanted to go where I thought I had the best prospect for doing something exciting, and thought that if I could get immersed in what I was doing, it wouldn't matter where I did it. So, I didn't have the mindset that I had to go to the 'best' school. I wanted to get into a project that I was most excited about. There were some interesting things at Berkeley that I could have gotten to work on. But getting back to that 'interesting weekend.' What do you do when you're footing your own bill to fly out and visit, and don't come from wealth? You have a Saturday night stay-over to get a cheaper airfare, and so I had a Saturday to spend in San Francisco. I had never been there before, and went to the BART having not a clue "How do you operate this, how do you get on this?" A stranger picked up on my cluelessness and was very helpful. She showed me how to get a ticket and how I could navigate my way on the BART successfully. So, I went to San Francisco, visited Chinatown and a few other places. I thought I wanted to end up at the Academy of Science in Golden Gate Park. It was getting toward nightfall, and I was navigating my way. There weren't many people around, and I got there too late in the day. They were about to close, but I could see through the windows these dinosaur bones. I said, "Could I just go in and see the lobby?" No, they wanted to charge me full admission, but I was a poor cheapskate, so I decided to head back to my hotel in Berkeley. By that time, it was getting pretty dark, and I had to walk a fair distance to get to a bus stop. Things weren't looking very familiar anymore, and when I walked around one building, I saw the chalk outline of a body on the sidewalk. And there I was all alone, this shy kid from North Dakota. I picked up the pace and found myself frequently looking over my shoulder, and when I got to the bus stop, I was quite relieved to get there. Well, I got on the bus back to the BART, got on the BART, and here across from me was some guy -- late 20s, maybe, three-piece suit, curled up in a fetal position lying on the seat, perfectly

motionless. All these other people were just standing around as if nothing else was going on. For me, it was, "What? What is this?" When we came to the next stop, the deceleration caused him to slide off the seat, and after falling to the floor, he scurried underneath the seat and resumed a fetal position. I thought, "Well, at least he's not dead." Everybody else seemed oblivious to this, and here's this kid from North Dakota. What is going on here? And then at the next stop, here come in a couple of police officers. They looked around and spotted this guy, and they picked him up off the floor and took him away. I thought, wow, big brother must be watching here. They must have cameras in here. Then I got to Berkeley, where they put me up at a hotel near the campus. It was a Saturday evening. That's a happening place, and people there looked a lot different than I did. Long hair -- this was 1981. I was accosted by a panhandler who wouldn't take no for an answer. I didn't smell anything on his breath, but this guy was very clumsy, so I imagine maybe he was high on something. He was following me, and he was much bigger than me, and I was afraid he was going to fall on top of me. I navigated my way around the crowd and went out of my way, turned around, and got into the hotel. I thought it was amusing that in my hotel room there were about five different locks on the door. We never bothered locking the house where I grew up, and there were about five different locks on this hotel room door. I set every one of them. I thought, okay, there are some interesting things going on here. Do I want to come here? I did not want to let that experience affect my decision, but when I visited this professor at Iowa State University who was doing solar photoelectrochemistry, I thought it was really exciting and maybe I could solve the world's energy problem, and elected to work in that area. It was a day's drive from home. So, as a shy kid from a tiny town, I found it within my comfort zone to go to Iowa State University in Ames, Iowa. Little did I know that my research path would migrate eastward, with my first stop being post-doctoral studies at University of

Pennsylvania. Being in a big city environment was a new experience for me. From there, I got a job offer at Harvard, and became an Assistant Professor of Chemistry.

ZIERLER: When you were thinking about graduate school, was physical chemistry the game plan the whole time?

ANFINRUD: Yes, it was. My undergraduate Organic chemistry professors didn't inspire me. What I especially loved about Physical Chemistry was the Physics aspect. I loved the mathematical nature of things and viewed Physical Chemists as physicists willing to get their hands dirty.

ZIERLER: Even more than an experimentalist? (is this how you framed your question?)

ANFINRUD: Physicists are more purists in my view. When I took quantum physics, you learn about the Bohr atom, and then quantum mechanics on a hydrogen atom, but chemists actually look at molecules. Now it gets messier, and you have to do approximations, so that's kind of what I mean by that. A physical chemist is willing to get a bit dirtier. Physics likes simplicity and mathematical elegance, and they're really good at that. But physical chemistry is kind of a blend of physics, but you have to be willing to get your hands a bit dirty.

ZIERLER: Did you take physics classes as a graduate student, or this is mostly as an undergrad?

ANFINRUD: I took physics classes both as an undergraduate and graduate student.

ZIERLER: What was the split in graduate school between lab work and course work at Iowa State?

ANFINRUD: Well, in PhD programs there isn't a whole lot of coursework required, and I got that taken care of in the first two years. For example, I didn't have the greatest inorganic background, so they made me take another inorganic chemistry class. I also took solid state physics and a course in complex math that went beyond all the calculus that I had taken as an undergraduate. I found the graduate course in quantum physics I took as an undergraduate was a nice compliment to the quantum chemistry I took as a graduate student. But the coursework occupied a relatively small fraction of my time, as I was much more heavily invested in the laboratory research.

ZIERLER: Who was your advisor in graduate school?

ANFINRUD: Walter Struve [00:15:56], who has since retired. He was a Harvard graduate student, did a post doc at Bell Labs, and then came to Iowa State University. He was deaf and learned how to read lips to communicate, and because he couldn't hear himself, his speech was not all that clear, so I had to work hard to understand him. But he was a very inventive, creative guy, and a good writer, and we got along very well. I really enjoyed my time there working with him. The funny thing is, while I was making progress on our solar photoelectrochemistry project, he went off on sabbatical to the University of Chicago and came back all excited about new research areas that did not include my solar photoelectrochemistry project. I was given a choice to switch areas or go elsewhere.

ZIERLER: So, you switched areas.

ANFINRUD: I switched areas. I found that I could get interested in a lot of different things, and found his new research direction kind of inspiring as well. He became interested in energy transport and trapping, which is relevant to photosynthesis. How do you harvest light energy? I

thought, okay, that's energy related, one way or another, and it's using lasers. These lasers are really kind of cool, so I ended up doing my graduate thesis work working with picosecond lasers, and then went on to femtosecond lasers. I've been basically a time-resolved person my whole research career.

ZIERLER: Do you remember the title of your dissertation?

ANFINRUD: Oh, man. What was my thesis title? It basically was a series of publications stitched together. I gave it a title, wrote an introduction and experimental section, and the papers we published on the work that I had done became the main body of my thesis.

ZIERLER: So, what was the basic research? What was your dissertation on? What did you study?

ANFINRUD: It was mostly focused on energy transport and trapping processes. I studied dye molecules that were in solution, and then also on surfaces. The surfaces in this case were Langmuir-Blodgett film surfaces. There was a Professor at Stanford University, Michael Fayer, that had published some new theory on how to understand excitation transport and trapping, because this is very relevant, again, to photosynthesis. He had used a different experimental technique, transient grating approaches, which was laser based. I was doing studies with time-correlated single photon counting, and I could get very high sensitivity, and provide a more rigorous test of his theories, so we embarked on that. We pursued studies in 3-dimensions in solutions and ran into complications experimentally when we cranked up the dye concentration to really challenge the theory for rapid rates of energy hopping. When a dye molecule absorbed a photon, it could fluoresce, it could internally convert and dispose of that energy as heat, but if another dye molecule was near enough, its excitation could hop to its neighbor without losing

energy. So, you have an energy hopping type of mechanism that's important for photosynthesis. How do you get the energy from an absorbed photon in the antenna chlorophyll to the reaction center? It's expensive to make a reaction center, but it's cheaper to make the antenna chlorophyll. So, you have all this chlorophyll out there that funnels the energy from absorbed photons to the reaction center. When you get to high concentrations of dyes, where you have rapid energy transfer, how well does the theory do? So, we developed improved experimental methods to test the limits of this, and found that in 3-dimensions, it's very challenging, because once the concentration was high enough to achieve rapid energy transfer, some of the dye molecules tended to dimerize and then acted like traps that would truncate the hopping mechanism. That's not what happens in leaves. I found that we could do a better job of dispersing the dye molecules in a Langmuir-Blodgett film, and then went to a 2-dimensional arrangement of dye molecules. That actually worked much, much better. So, there's a string of papers that we did on excitation transport and trapping of dye molecules in 2- or 3-dimensions. The title of my thesis is something like: "Dynamics of Energy-Hopping and Trapping in 2- and 3-Dimensional Systems."

ZIERLER: Were you involved in thinking about any possible practical applications of this research, or this was mostly just about figuring out how all these things worked?

ANFINRUD: It was a basic research project. If you can understand the theory of excitation transfer, then you can conceivably design artificial antenna to harvest light energy in a more robust way. We think about photosynthesis as being this great efficient biological process, but guess what, when you have your first frost, what do you see? The leaf color changes. Why is that? There are oxidation reactions going on, which means these proteins have to be replenished daily. So, if you understand these mechanisms, can you come up with other approaches that are

much more robust, and more efficient? But to get there, you first need to have a basic understanding of these mechanisms and how you transport this excitation to a reaction center where you can do some good.

ZIERLER: So, it's 1987, and you defend. What are the various options that you're considering? Did you ever think about going into industry, working at a chemical firm or something like that?

ANFINRUD: Yeah, in fact, I turned down a job offer from Dow Chemical in Midland, Michigan. That was a nice place, a company town that's kind of like a college town. I flew up there for an interview, and soon after they offered me a job, which was tempting. At the time, the job market wasn't the greatest, but I was one of the luckier ones to have more than one option. I was considering post-doctoral work as well. I was thinking I could settle in Midland, Michigan, and I bet I could have been happy there, but I really loved working in a lab, and found the academic environment to be really exciting. When I was younger I thought Bell Labs would be a great place to work. Bright people doing all kinds of amazing things. But in 1987, Bell Labs was becoming a shell of its former self. So, academia -- I wasn't really thinking that much about academia at the time. But I thought if I managed to get a job offer in industry fresh out of my Ph.D., I could only enhance my future job prospects by pursuing post-doctoral research, which would allow me to remain in the stimulating academic environment.

ZIERLER: But in pursuing the post-doc, that would open up more faculty opportunities for you. You were thinking along those lines?

ANFINRUD: Yeah, but I wasn't thinking that strongly about it. Of course, the academic environment intrigued me, but these guys were brilliant, coming from fancy places. I didn't know what cloth I was cut out of. Though I wasn't focused on the academia route, I recognized that as

a possibility, and certainly did enjoy the academic environment. So, in the back of my mind, I thought that would be wonderful, but it's probably too much to hope for.

ZIERLER: Why Penn? How did Penn come together for you?

ANFINRUD: One of the faculty members on my thesis committee at Iowa State University, Gerry Small, was the first graduate student of Robin Hochstrasser. Robin Hochstrasser was famous in Chemical Physics and had done quite well for himself at the University of Pennsylvania. Gerry recommended that I consider post-doctoral research with him. At the time, I didn't know anything about him and what he was doing. So, Gerry contacted Robin Hochstrasser and said, "I've got this kid who might be interested in a post-doc with you. Do you have any openings?" And he says, "Sure, have him send me something." And then he very quickly made me an offer.

ZIERLER: Were you looking in the post-doc to refine and continue with your dissertation research, or were you looking to take on whatever project the professor was working on?

ANFINRUD: I wasn’t seeking a continuation, but, of course, was interested in knowing what I might be doing should I go there. He told me about his interest in pursuing time-resolved infrared spectroscopy on the femtosecond time scale and offered me the opportunity to help open up that field.

ZIERLER: How much experience did you have with spectroscopy up until that point?

ANFINRUD: Well, what I was doing was spectroscopy related and was time-resolved, but on the picosecond time scale. I had been using lasers to excite dyes and was looking at time-resolved fluorescence from those dyes. My post-doc project would be a continuation of working with

lasers, but Robin had a much better-funded operation than what we had when I was at Iowa State University. He had lots of powerful lasers, and it looked quite exciting to get into this infrared area. When you think about it, electronic transitions are generally broad and somewhat featureless. You can put a photon in, can watch a photon get spit out, and can learn something about that from the dynamical point of view, but when you look at infrared, now you have vibrational groups that contribute to the absorption spectrum. The environment can affect the vibrational frequencies, so it's going to be far more selective than electronic spectroscopy. I thought this would be very exciting, especially when pursued on very fast timescales. People hadn't done that yet, femtosecond infrared spectroscopy, so my charge was to help open up that field. As an experimentalist, I was at home in the lab and in the machine shop designing things, building things, and trying them out in the lab. So, guess what? When I arrived, Robin went on sabbatical to Grenoble, France. So, when I started my graduate work, my thesis advisor disappeared for a year, and then when I started my post-doctoral work, my post-doc research advisor disappeared for a year. In both cases, the first year of my time there, I had to be self-motivated, and took that opportunity to learn a lot about what's going on in the lab, build some things, pick up some machine shop skills, and do something. Those were really exciting times. And we're still in exciting times. Life is interesting -- amazing.

ZIERLER: So, it was a good experience, then?

ANFINRUD: Oh, yeah. Very much so. We got along very well, and when I was applying for faculty jobs, I didn't shy away from where I applied to. The funny thing is, the five or six places I applied to and interviewed at led to only one job offer.

ZIERLER: Harvard.

ANFINRUD: Yeah.

ZIERLER: That's not a bad one to get if you only get one.

ANFINRUD: It was very threatening to me. I was kind of hoping for an alternative that I could compare with. When that didn't come, I thought, okay, I'm going to dive into this. So, one of my colleagues, Bill Klemperer, kind of joked that I'm in finishing school there, because he saw this hick from North Dakota, you know? I didn't know anything about sushi, or fancy restaurants, and so they tried to teach me some culture.

ZIERLER: How long before you stopped being intimidated when you were at Harvard, when you sort of felt comfortable in your skin?

ANFINRUD: That's a good question. Uniformly, the people I met there were really sharp. You find really smart people everywhere you go, but these were pretty uniformly sharp people. But after being there, I suppose, two years, my lab started to get some interesting results, and I could see that what I've been working toward was coming together. Then I felt like I was one of the guys, but of course, I was a junior faculty member, which is a different class citizen at Harvard.

ZIERLER: What kind of teaching did you do when you first got there? You taught undergraduate and graduate classes?

ANFINRUD: Yeah, both, but then I quickly focused on undergraduate classes. When I started, I was one of four junior faculty members, and by the time I left 8 years later, it was almost down to me. During that time, Harvard Chemistry did a poor job of recruiting at the Junior Faculty level, and Chemistry classes had to be covered by fewer faculty. I taught the accelerated freshman chemistry course, Chem 10, with Dudley Herschbach. I thoroughly enjoyed that.

Dudley is a very engaging guy, and he really worked to be engaging with the students. The course had a lab component, which required a fair amount of work. He said, "I'll do all the lectures if you run the lab." I said, "Well, I've got to get some experience lecturing as well, so how about if we do a different split. I'll do the lab but let me teach a third of the lectures." So, Dudley taught the first third of the course while I was busy getting the lab going and training the staff, and by the time the lab component was running itself, I would give the lectures for the middle third of the course, and then Dudley returned to lecture for the last third, which freed me to spend more time on research. That actually worked well for me. I taught Chem 10 for I think about six years out of the eight years that I was there. It was a lot of fun. Our students asked tough questions and kept me on my toes, which was good.

ZIERLER: Mostly pre-med, the undergraduates, or from all over?

ANFINRUD: Oh, they were from all over. Certainly, there were some pre-med in there as well, but they were from all over.

ZIERLER: What were some of your major research projects that you were involved in during your Harvard years?

ANFINRUD: I was setting out to extend this capability of femtosecond infrared spectroscopy by enhancing its sensitivity to broaden the range of systems that it could study. So, the research was highly technical. I had to be a laser jock, building up a lot of homebuilt equipment. You could buy lasers that could generate certain colors of light, but I had to diversify that and use nonlinear optics to generate a wide range of colors, and then keep pulses short. Those were exciting times. What was my typical week like when I was teaching? Well, I'd have to spend time preparing for Monday/Wednesday/Friday lectures, but when I'd come back from that lecture, I would

disappear in the lab and spend the rest of the day there to unwind. Monday afternoon, Wednesday afternoon, Friday afternoon, my time was in the lab.

ZIERLER: This was your lab, or you shared lab space?

ANFINRUD: It was my lab.

ZIERLER: Did you come in on the basis that you'd have your own lab? Was that part of the deal?

ANFINRUD: Oh, yeah. I was a tenure track faculty member hired as a junior professor, was provided with startup funds, and they renovated laboratory space according to my specifications. I was quite busy filling it with optical tables and laser equipment, bringing in graduate students, trying to get money from external sources, and getting this operation off the ground.

ZIERLER: What kind of grant support did you have for your lab? Did it come internally, or was it NSF?

ANFINRUD: The NSF and NIH were my primary sources of support. I also got some money from Mitsubishi. This was the early '90s when Japan's economy was flourishing, and they had more money than they knew what to do with. I suppose it was a matter of good will to spend some of it in America.

ZIERLER: Were they involved in the laser business, Mitsubishi?

ANFINRUD: It was kind of interesting how this materialized. The chairman at the time I was hired, George Whitesides, was well connected. Some high-up people from Mitsubishi paid a visit and asked "What can we do to help?" I don't know if they were aiming to buy influence, or

whatever you want to call it, but they threw some money at him, at other faculty members, and he encouraged them to consider throwing some money my way too, because I was just starting out. So, they sent me some money. I think it was about $40,000, or something like that. No strings attached. So, that was kind of nice.

ZIERLER: In terms of the instrumentation, how much were you putting the stuff together yourself? How much were you in contact with engineers, or with companies and simply describing what it was that you needed?

ANFINRUD: Well, typically what I would do is buy what I could off the shelf from laser companies, and then start modifying them to improve their performance. We'd acquire optics and nonlinear optical materials to generate the wavelengths we wanted. We built a lot of hardware and electronics components, and stitched everything together so in the end, we had a few commercial boxes on the optical tables, but the lion's share of the layout was custom stuff.

ZIERLER: Did you take graduate students from the beginning, or they started coming afterwards?

ANFINRUD: I was successful in getting a couple of graduate students to join me right at the beginning. Of course, what I was doing was technically demanding, and a typical chemist with an undergraduate degree didn't know much about lasers and optics, electronics, or computer programming. All those things were really critical to pursue our femtosecond time-resolved infrared experiments. My students had much to learn before they could become proficient in my laboratory. We had to interface electronics to control the timing of when the laser pulses arrived, move translation stages to control time delays on ultrafast time scales, change polarization and power levels, and do so with high precision and high repeatability. They also had to write

software to properly sequence our data acquisition, and then to analyze the data. So, the skill set required for our research is generally far outside what students acquire in their undergraduate studies. So, guess what? It would typically take about three years before I could get somebody to the level where they could run with an idea and accomplish something useful in my laser lab.

ZIERLER: Who were some of your real standout graduate students?

ANFINRUD: Only a few students completed their Ph. D. in my group. One of my first graduate students, Manho Lim -- is a faculty member at Pusan University in Korea. The second post-doc I had was really fantastic. Feng Gai, is currently a chaired professor at University of Pennsylvania. I had a guy who ended up deciding to go to medical school after he obtained PhD, and subsequently earned an M.D. degree at Harvard.

ZIERLER: How reliant were you on advances in computational power for your lab? Were you really taking -- I mean, this is a time of significant growth in what computers were able to do, and I'm wondering what kind of impact that had on your lab.

ANFINRUD: Not so much for me, because my use of computers was focused more on controlling instrumentation, synchronizing everything to make measurements as precisely as possible, which included normalizing intensity fluctuations in real time, because lasers weren't always the most stable beasts out there. We set up arrays of numerous photodiodes to monitor laser intensities at different stages of generation , and then wrote programs to monitor the performance and provide the input needed for feedback loops. Temperature stability in my lab wasn't the greatest, so as the temperature changed, thermal expansion caused the distance between optics to change, and then the laser performance changed. So, the computational horsepower required wasn't that high, and what was available at the time was fine. In fact, I

managed to do a lot of my data analysis in Microsoft Excel. If one wanted to do molecular dynamics simulations, computer horsepower was everything. So my colleague, Martin Karplus, who was an molecular dynamics person, benefited enormously from the rapid advance in computational power at the time.

–ZIERLER: You were promoted to Associate Professor at Harvard. Did you get the sense this was in recognition of any specific research accomplishment?

ANFINRUD: To clarify, Associate Professor is not a tenured position at Harvard. Harvard is an interesting place. To become a full professor with tenure, they generate a comparison list of around 10 accomplished, supposed peers, and you compete with them for your job. One of the candidates on my comparison list was already a tenured, chaired professor, and well on his way to becoming a Nobel laureate. I have no shame in losing out to him. Incidentally, he turned down Harvard's offer and went to Stanford instead.

ZIERLER: So, what exactly is the promotion to associate? How does that work? What does that signify?

ANFINRUD: Well, that's an external review as well, and at Harvard, it occurred after five years. I was promoted to Associate Professor without fanfare, but the accompanying pay raise was certainly welcome, as assistant professors were not paid very well, considering the cost of living in the Cambridge area. So, that happened at five years, and then at eight years, one can be considered for promotion to full professor with tenure.

ZIERLER: So, it's only full professor that is tenured at Harvard.

ANFINRUD: That's right.

ZIERLER: They do it their own way there, I guess.

ANFINRUD: That's right.

ZIERLER: What was your experience like at the synchrotron facility in France?

ANFINRUD: That was really fantastic. Over my career, I had to reinvent myself, which keeps life very interesting. I went to the ESRF to learn about x-rays and protein structure determination, which was quite a switch from the femtosecond infrared spectroscopy project I was working on, which incidentally, made the cover of Science.

ZIERLER: Oh, what was that?

ANFINRUD: It was a study of myoglobin using time-resolved infrared spectroscopy to probe the binding of, in this case, poisonous carbon monoxide. We all know about carbon monoxide poisoning. How does that work? Well, CO binds strongly to hemoglobin in your blood. It also binds to myoglobin, which is found in your muscle tissue. When CO displaces oxygen, you become oxygen starved and everything shuts down. Scientists thought they understood how these proteins manage to suppress the binding of carbon monoxide, but that classic example of protein structure-function was debunked by the time-resolved infrared spectroscopy techniques we developed, where we could look at the vibrational signature of carbon monoxide when bound to myoglobin, and shortly after it dissociates via a photolysis laser pulse. It has a characteristic vibrational frequency when bound, but a very different frequency when detached. By time resolving its characteristic vibrational frequency, before and after photodetachment, we could watch what happens to it in real time. We used a polarization trick to probe the relative orientation of the CO when bound, versus when it's not. The classic structure-function paradigm

for how this protein functions focused on a distal histidine, whose steric hindrance purportedly forced carbon monoxide to bind at a non-optimal angle, which helps suppress it's poisonous binding so oxygen can effectively compete with it. Well, what did we find? Basically, CO binds straight up, in spite of the presence of this histidine.

ZIERLER: Which told you what? What did that tell you?

ANFINRUD: It told us that the classic structure-function paradigm taught in biochemistry textbooks is not correct. What we found instead was when you break this bond, CO rotates and lays down horizontally. In order for it to bind, it's got to get upright to bind, but the structure of the surrounding protein actually holds it at bay off to the side of the binding site. That buys the protein enough time for CO to find a channel to escape, which took a fair amount of time. By studying the dynamics of this process, and observing step-by-step the sequence of events that happened after we break this bond, we developed a very different view of how this protein works to excrete CO and allow it to be replaced by oxygen, which is what you want to be binding in the first place. So, anyway, that story made the cover of Science, which was very exciting. We went on to study mutants of myoglobin to learn more about these pathways and which attributes of the protein's internal structure facilitate this excretion. John Olson, a collaborator from Rice University, supplied me with several different mutants of myoglobin, and when we studied those, and we saw very different dynamics. The frustrating thing was I couldn't make sense out of the differences in those dynamics. Here, you make a very well-defined change, and you see very different behavior, but it wasn't predicted. How do we understand that? Well, it would be wonderful if we could actually see the correlated motion of the CO and the surrounding protein, because this protein is not just a static molecule frozen in space that the CO rattles around in

between, like a billiard ball. Everything is in motion. The key is understanding how things work. To understand how things work, you really need to know about correlated motion. That means you need a technique that can see all the atoms, not just the CO. Then, in 1996, Keith Moffat published a paper in Science about Time Resolved X-ray Crystallography. I thought, wow! If we could do that on sufficiently fast time scales and observe the time-ordered sequence of structural events that occur as a protein executes its function, we could really understand mechanisms of biological molecules, which do amazing things.

ZIERLER: Had you had any experience with crystallography before?

ANFINRUD: No, none. Nothing with X-rays, nothing with crystallography. I started pursuing that area as I was getting close to my tenure decision at Harvard but hadn't yet gotten anything significant done in that field before they decided to send me on my way.

ZIERLER: So, you made the cover of Science Magazine before the tenure decision at Harvard?

ANFINRUD: Yeah.

ZIERLER: And they weren't impressed enough with that, I guess.

ANFINRUD: No.

ZIERLER: I think you have to go to Harvard to get tenure at Harvard. Right? Isn't that part of the deal?

ANFINRUD: Not really, but it surely doesn’t hurt. Look, I learned a lot while there and am grateful for the opportunity they provided. It was an exciting time, I accomplished some interesting things, which then pointed me into a new research direction. So, I started traveling to

France to learn about X-rays. I never really had a sabbatical, but I call the summer of '97 my mini-sabbatical, which came shortly before my tenure decision. I brought my family to Grenoble, France, a beautiful city nestled in the Alps, and then spent time with a bunch of creative physicists at the European Synchrotron Radiation Facility (ESRF). Those were heady times. The physicists at the ESRF were wonderful. They enthusiastically explained to me all these different things you could do with X-ray radiation and crystallography, and how synchrotrons generate these X-rays in the first place. It was really exciting.

ZIERLER: How international? Was it mostly French physicists, or from all over?

ANFINRUD: The ESRF is a European consortium that happens to be located in France, so people come from all over the continent. The fellow I worked with, Michael Wulff, was an enthusiastic and engaging Danish Physicist who built up the ID09 time-resolved x-ray beam line. He had a graduate student working with him, Friedrich Schotte, who was from Germany, and is now a staff scientist with me at the NIH. It was an exceptionally stimulating and exciting summer, and though I continued to work with lasers, it shifted my research focus to how we could combine the use of lasers and X-rays to probe atomic motion in proteins in a time-resolved fashion. This project proved very technically demanding and took about 6 years to achieve our first really significant results, which we published in Science in 2003. The NIH has proven to be a fantastic place in which to pursue longer-term types of research projects such as this. When I think back, it would have been quite challenging to accomplish what we did had I been tenured at Harvard. In an academic environment, you have students cycling in and out, and often required approximately three years' training before they could start doing something useful in my lab. Soon after, they're out the door. At the NIH, I have a couple of very talented staff

scientists who have been with me for quite some time. We talk the same language and can divide our efforts as we work toward our long-term goals. I'm very grateful for the opportunities afforded me by the NIH, which has provided an environment where I could focus on research without the distraction of teaching, which, by the way I loved to do when I was at Harvard.

ZIERLER: So, this was a sequential matter of timing, the tenure decision at Harvard, and then the opportunity at NIH? You weren't thinking about NIH before this?

ANFINRUD: No, the NIH wasn't on my radar screen, but when I learned I wouldn't be tenured at Harvard, I had to start looking for a new job. I ended up with offers from a couple of academic institutions as well as the NIH. I loved academia, but as I thought long and hard about this, I realized the things that excited me most were going to require some really focused effort. If I went to the NIH, I could immerse myself in research and see how far it goes. I was originally thinking I'd give myself five or ten years at the NIH and then consider a return to academia, but in the meantime came to the conclusion that the Laboratory of Chemical Physics in NIDDK at the NIH, which I like to describe as the Bell Labs of biophysics, is a fantastic place to work. Wonderfully talented and collegial colleagues. I can't think of a better place to be.

ZIERLER: So, how much were you interested, before you were even thinking about NIH, how much were you thinking about your research within the context of human health issues? Was that part of the equation at all?

ANFINRUD: Though my undergraduate coursework focused on topics more relevant to physical chemistry, such as Physics and Math, I did take a number of polymer courses, which was required by the terms of a scholarship I received from the Polymers and Coatings department at NDSU. I also took a biochemistry course but didn't like it. They had us memorizing the Krebs

cycle. What's the point of that? You can look it up. The only thing I remember from that cycle is acetyl coenzyme A, but I don't remember what it does. And they had these Pacman-like pictures of biological molecules. I'm a chemist. Biological molecules are essentially linear polymers consisting of atoms forming molecular bonds and folding into unique three-dimensional structures. The Biochemist's view of things at the time, which admittedly preceded the structural revolution that followed when x-ray structures became more commonplace, didn't really inspire me. But as a post-doc, when I started studying hemoglobin, I came to realize how remarkable these macromolecules are. They're molecules, and I can think about them from the perspective of a physical chemist. How they fold and function is a very interesting problem. How do we understand that? So, I got really excited about biomolecules during my post-doctoral work and has been the main focus of my work at Harvard and the NIH.

ZIERLER: Yeah. But, I mean, my question is in terms of be it motivated to be part of some research that might be useful for health science research, or you never really thought in those terms?

ANFINRUD: I'm not much into the bench-to-bedside mindset. When you look at advances in medicine, how much has happened by serendipity, accidents here and there? Most often it's not been by rational design. As a physical chemist, I'm convinced there exists a physics explanation for everything. You've just got to find it, and you can't quite get there doing statistical analysis of poorly-defined results obtained from questionnaires. If you can understand from a mechanistic point of view how biomolecules interact, and how their structures confer upon them the ability to do what they do -- the amazing things they do, we can better understand how and why things sometimes go awry and lead to disease. That's a rational, structure-based approach that requires

putting your thinking cap on. But how do you get there from here? You have to be able to study things at the most intimate level of detail. On a computer, you can study things at the most intimate level of detail, but guess what? What comes out of the computer is whatever you put in, which is defined by the forcefields used to describe molecular interactions. You need to have experimentalists, like myself, who are driven to try to measure things as precisely as possible on the timescales at which computers can actually look at motions. After obtaining experimental structural data with as high a level of detail as possible, we can compare our results with computer simulations and thereby assess and validate the potentials used. Over the years, I've had collaborations with computational chemists who have taken some of our data and then try to do simulations and see if they can reproduce what we see. It's interesting, and it goes back and forth. Sometimes we see something that we're not quite sure what to make of, and then challenge a computational chemist to come up with a plausible explanation. Sometimes they come up with an explanation that makes you say, "Oh, yeah. That makes sense." And sometimes you see something in their computational studies that we don't see experimentally, and when they look in more detail, change the potentials, and then better reproduce what we observe. It's a two-way street.

ZIERLER: So, you come here in 1998. The Laboratory of Ultrafast Biophysical Chemistry, did this exist before you, or did you create this lab?

ANFINRUD: I created that.

ZIERLER: Okay, so let's break down the meaning. Ultrafast. Is there a technical -- why not super-fast? Why not really fast? What is ultrafast?

ANFINRUD: So, when I started as a graduate student, picoseconds represented the fastest time scale you could look at with lasers.

ZIERLER: How fast is a picosecond?

ANFINRUD: 10 to the minus 12 seconds.

ZIERLER: And for comparison, how fast is the speed of light, just so we understand?

ANFINRUD: Well, that goes 3 times 10 to the 10 cm per second.

ZIERLER: Okay, so a picosecond is relatively slow compared to the speed of light.

ANFINRUD: Yeah. Light doesn't go that far in a picosecond, only 300 microns. I remember being fascinated by Doc Edgerton from MIT, whose stroboscopic photography allowed him to freeze motion in time. Here's this bullet slicing through a deck of cards. You know the outcome, but now we see the process frozen at a well-defined instant of time. That's what we can do with very short pulse lasers, but on the molecular scale. When I got my start, picoseconds were basically the best you could do. There was an annual conference called Picosecond Phenomena. Then, clever researchers at Bell Labs figured out how to generate femtosecond laser pulses. Okay, now it's Femtosecond Phenomenon -- what do we do? Well, let's just call it "ultrafast", because what happens if we get to attoseconds? We don't want to keep on changing the name of the annual conference. So, at that time, we came up with "ultrafast", with femtoseconds being the ultrafast of that era. Now, some experiments obtain results on the attosecond time scale, but those experiments are more relevant to atomic physics, and haven’t captured my imagination the way molecular motion on the femtosecond time scale has.

ZIERLER: I can't help but think of ludicrous speed from Spaceballs. That kind of sounds like what we're talking about here. So, do you take on post-docs right away with the lab?

ANFINRUD: Yeah, I've taken on post-docs here, and like I said, a couple of them have converted to staff scientists. But I run a fairly small group. I'm a hands-on person, so on any given day, I might be in the machine shop fabricating something, or I might be writing some Python code, or I might be aligning some optics on the laser system or designing some electronics or soldering connections on my electronics bench. For example, I worked out a design for a Field Programmable Gate Array (FPGA) based timing system with 24 programmable inputs/outputs and made four copies of them. One of them operates the BioCARS time-resolved beamline at the Advances Photon Source (APS). Another is in my laser lab at the NIH. Another was used for an experiment conducted at the LCLS. Friedrich Schotte, one of my staff scientists, has written all the code that controls the FPGA and allows us to coordinate the choppers, shutters, lasers, and motion systems operating on the x-ray beamlines, and allows us to control the laser to x-ray timing with 11 picoseconds precision over a dynamic range of time scales spanning picoseconds to seconds. The X-ray pulses generated at the APS are a bit longer than 100 picoseconds in duration, but the laser pulses are much shorter than that. We have to synchronize the relative time of their arrival. The FPGA timing system we developed receives a reference frequency from the machine and generates all the other frequencies necessary to operate choppers used to isolate single x-ray pulses. These choppers have to rotate with a very precise phase relative to the X-rays generated by the synchrotron. The FPGA also triggers oscilloscopes at the right time, trigger lasers at the right time, and triggers any motion required for an experiment. I've spent a considerable amount of my time developing and fabricating hardware and electronics, and coding software to analyze our data. My group size is small, but

consists of talented coworkers who work very well together. It's exciting. I feel like a kid in Legoland. Every day, I can do something new.

ZIERLER: Is there an obvious reason why you're in NIDDK? Is there something about what you do, and what NIDDK's mission is that it makes sense why that would be connected?

ANFINRUD: The lab I work in is called the Laboratory of Chemical Physics (LCP), which may seem unusual. Why would the NIH have a Laboratory of Chemical Physics? This designation was made long before I arrived. The PIs in LCP focus on basic research, primarily, with an emphasis on biomolecular structure, function, and dynamics, and include both experimental and theoretical/computational scientists. Some use analytical or computational approaches to try to understand biology. Some experimentalists pursue single-molecule studies of biological processes via fluorescence. There is a very strong contingent of scientists using NMR as a means to study both dynamics and structure in biomolecules. I'm a time-resolved person, and study how ensembles of molecules behave following a perturbation that triggers a structural change. When we use X-rays to probe structure, we can get information down to the atomic level. In my final year at Harvard, I started doing time-resolved crystallography, which I continued after coming to the NIH. But then I got interested in doing studies in solution. When you crystalize a protein, you put it in a straitjacket. Though this environment is rigid, molecular motion still occurs, but can't span the full range of motions that can occur when it's tumbling in solution.

ZIERLER: What's the value of seeing the full range of motions?

ANFINRUD: Proteins in our bodies are generally not found in a crystalline form. Though aggregates of certain proteins can form plaques that do us harm, such as Alzheimer's disease. To understand how proteins actually function, you need to understand how they behave in the

solution phase. NMR can probe the structure of biomolecules in the solution phase, but can't track structural changes with fast time resolution. Time-resolved X-ray scattering studies of biomolecules in solution lack atomic specificity, but one can still extract structural information from the scattering data over a large range of length scales with time resolution down to the duration of the X-ray pulse, which is about 100 ps at the APS. For example, we've pursued both time-resolved X-ray crystallography and time resolved X-ray scattering studies of a very interesting protein called photoactive yellow protein. A bit of background. How is it that I can see you? My eye contains a photoactive protein called rhodopsin, whose retinal chromophore switches from a strained 13-cis structure to an all-trans structure soon after absorbing a visible photon. [01:00:15]. That happens really fast, in just a few hundred femtoseconds. Then, the structure of the surrounding protein changes, which ultimately triggers a chemical cascade that generates a neural impulse and gives us sight. When dark-adapted, we can actually detect single photons. Back to PYP, which is found in a photosynthetic bacterium that swims around in salt marshes looking for green light. It has a flagellum that generates forward propulsion, but how does it decide where to swim? It requires a signaling mechanism that says if you're moving away from green light, you better turn around. In response to this signal, it reverses its flagellum rotation, which points it in a new direction. In a random-walk type of motion, they manage to congregate where green light is found. Switch the color of light from green to blue, and they scatter. They don't like blue. What's going on? Photoactive yellow protein absorbs blue light, which is close to ultraviolet. We can lather on sunscreen to protect ourselves from the harmful effects of ultraviolet light when we go outside, but these bugs have no such protection, so what do they do? If they detect blue light, the danger of uv damage is heightened, so they reverse their flagellum and hopefully resume swimming in a direction away from blue light and toward green

light. How does that work? Well, absorbing a blue photon triggers a trans to cis-isomerization event in photoactive yellow protein. Then what happens? Scientists have studied PYP with time-resolved spectroscopy and reported a rapid initial change to the absorption spectrum. Then you wait a while, and it changes again. Wait a while longer, and it changes again. What's happening here? Well... we did time-resolved crystallography on PYP to find out. Each stop along the way, we found different structural states that correspond to spectroscopic states, and now see where they come from. Then, we discovered an early structure that no self-respecting organic chemist would draw but exists inside this protein. This structure finds itself in a tug-of-war involving hydrogen-bonding interactions and cannot promptly complete the motion it wants to do. One of the hydrogen bonds breaks with a time constant of about 600 picoseconds, and the highly twisted intermediate structure is then able to adopt a lower energy planar structure. We needed sub-nanosecond time resolution to capture this short-lived intermediate and characterize this process. Then we watch it go through a series of structural changes and return to its initial state. Since this process is reversible, we can send it through this cycle over and over and acquire accurate structural data at each step along the way. But as I mentioned before, the protein in crystalline form is in a straitjacket. What happens in the solution? Is it the same, or is it different? We used small and wide array X-ray scattering to investigate what it does after photoexcitation. Internally, it does much of the same things, but guess what? Late in the PYP photocycle, we found the shape of the protein changed dramatically. As if it popped its lid. It turns out there's a 25-residue N-terminal domain that fashions a cap on this protein. That domain becomes disordered, which presumably allows the protein to interact with some receptor somewhere. When the lid pops off, it exposes a hydrophilic histidine in the midst of a hydrophobic patch. Presumably, that patch engages with a signaling partner to elicit the bacterium’s response to the detection of blue light.

That's where the biology comes in, of which I'm pretty ignorant. Nevertheless, when it finds a signaling partner, it tells this bug, "Hey, you're getting too close to ultraviolet light. You should do something about that. Reverse your flagellum." Then it goes in a new direction. It might go in the right direction, it might go in the wrong direction, but eventually it manages to swim away from the blue light. So, the small and wide-angle X-ray scattering was able to illuminate processes that could not be illuminated from the crystallography study alone, and they complement each other very well. We are currently set up to do time-resolved spectroscopy, time-resolved crystallography, time-resolved small and wide X-ray scattering. These methods provide different portals through which we can view what's happening over a wide range of time scales with different levels of structural detail.

ZIERLER: Does the solution impose its own limitations in the way that a crystal straight-jackets a protein? Are there different kinds of ways that your ability to see how a protein really acts is affected by the fact that it's in a solution?

ANFINRUD: When in solution, proteins rotationally tumble, so all measurements are orientationally averaged unless you employ a trick, which we've done on occasion. If we can trigger a process with laser light, we can usually take advantage of its polarization. For example, optical transitions typically have a direction vector relative to the molecular frame. Therefore, even when all this stuff is tumbling and its orientation is isotropically distributed, we can preferentially excite those molecules that are oriented along the laser polarization direction vector. Then, if we can probe them before they tumble any further, we can get some additional structural information. But this structural information is, admittedly, fairly coarse-grained. So, when a protein is in solution, it is free to do whatever it is capable of doing. Thanks to advances

in x-ray crystallography, we have near-atomic resolution of protein structures, which provide us with glassy sphere depictions of their structure. They're depicted as static, but they aren't. These proteins are dynamically fluctuating and can sample different structural conformations. There might be a conformation that basically doesn't do anything useful, and a conformation that does, and they might be switching back and forth between them. That's where single molecule spectroscopy is really wonderful, because you can find these things switching on and off as it switches between active and inactive conformations. You can learn more about its functional mechanism by understanding how its structure relates to function. So, all these different techniques provide us with a different vantage point for understanding how proteins function. We can go the X-ray route and do crystallography or small and wide-angle X-ray scattering, or the NMR route, which is ideally suited for solution studies. By the way, the opportunities for collaboration at the NIH are abundant, which has provided me with the chance to reinvent myself on occasion. So, my colleague just a couple of doors down, Ad Bax, came to me just a couple of years ago asking if I was interacting with biomedical engineers that helped me build the instrumentation I need to do the stuff I do. I said, "Actually, no. I design and build this myself." He was very disappointed, because he thought I could point him to someone who could help him pursue an idea he had to do time-resolved NMR. Well, I'm a time-resolved person, and said, "Tell me more. This sounds intriguing." He explained to me that many proteins unfold when put under very high pressure. That's interesting, because if you can pressurize it and make it unfold, then rapidly depressurize it, you can make it fold. Being able to follow the folding process with near-atomic resolution in real time could provide the breakthrough needed to help answer the decades-old question of how do proteins fold into the right shape almost all the time?

ZIERLER: What does that mean, the right shape? The original shape?

ANFINRUD: So, when a protein is being synthesized by the ribosome, you're adding one amino acid at a time. They emerge like beads on a string with 21 different flavors lined up along its length, and somehow it folds into a 3-dimensional structure that is functionally active. How does that happen? There are many possible ways. Imagine taking a strand of yarn and throwing it. What does it look like when it hits the floor? Different every single time. When proteins come off the ribosome, guess what? It folds into the same shape, presumably, every time. Actually, not every time. Sometimes it can mis-fold, and there are proteins called chaperones that can help facilitate folding -- giving them a second chance to get it right. So, there's all kinds of really amazing things going on out there. But the fact remains that many proteins will spontaneously fold correctly the first time. Somehow, its sequence codes for a folding pathway. What is that folding pathway? This protein folding problem was a really big deal in the '80s. People had been talking about it before that time, but there was a lot of experimental and theoretical effort on that from the '80s forward. Since NMR can look at near atomic resolution structures in solution, perhaps we can explore this problem in a new way. If we can pressurize a sample and make a protein unfold, it becomes disordered and flops around. Then, if we suddenly depressurize the solution, we can watch it fold, and could perhaps address the folding problem at a much more atomic level than ever before. That got me excited, so I built an instrument to do time-resolved NMR. Along the way I learned a few things about NMR, at least on the hardware side. But what these guys do with pulse sequences, and how they extract all this information is still beyond me. I ended up building several pressure-jump instruments that Ad Bax and his research group are using. One of the problems we're tackling is personal, as my father passed away last year after having suffered from memory loss. I'm not aware of a formal diagnosis of Alzheimer's, but you might as well call it that. The plaques that can form in the brain basically destroy your ability to

make new connections and remember things, which is really tragic. How does that happen? Well, this is a protein misfolding problem. Somehow, a protein misfolds into a structure that encourages other proteins to add on to that misfolded structure, and as these plaques grow, the body doesn't know what to do with them. As these plaques occupy more and more volume and neural connections are broken, you develop this terrible problem. I'm really hopeful that this time-resolved NMR via pressure-jump apparatus can help address this problem. In fact, they're working on this very problem.

ZIERLER: When you say "address" it, I'm curious about how you seed the connection between your research and some therapies down the line. What's the relationship there, between the research and the clinical output?

ANFINRUD: From a mechanistic point of view, what's really going on here? Cells in the body are busy creating new proteins and then digesting old ones that aren't working anymore. It's the ultimate in recycling. However, some proteins can get into a misfolded state that the body doesn't know how to chew up, so they accumulate into plaques that can cause terrible problems. How does it rain? You can have super saturated water vapor in the air, and it doesn't rain. But if you have a dust particle that can nucleate the deposition of water, then it can grow into a drop, and when it gets heavy enough it falls.

ZIERLER: I like how you're bringing your atmospheric chemistry right to the present.

ANFINRUD: There you go. So, you need a nucleus to start it. Many people die without ever suffering from any of this stuff. The nucleation step is a rare event, but once it occurs, and if the body doesn't know how to digest it, another protein could come and add to it, and another, and another, and then you have this growing plaque. So, nucleation is key. Is there a way where you

can, from a structural point of view, recognize what a typical nucleus looks like that can lead to the formation of these plaques? Could there be a drug that interferes with its growth, or better yet, its nucleation? But how do you avoid nucleation? You have to know something about structure. What is the key event that leads to the formation of something that can grow into a plaque? Since those are rare events, will we ever be successful at capturing them in the lab? But with this time-resolved NMR approach, you have a chance of doing repeatable measurements at near atomic resolution and try to explore what a nucleus might look like. If you had that understanding, could you imagine a drug therapy that could interfere with that? Then you could actually test that and say, if this is a structure that leads to the formation of plaques, if we could interfere with the nucleus that forms that structure with this drug, can we actually stop it from happening? And you can test that in the lab before you actually give it to a person. Many advances in medicine arise from serendipity. You try a bunch of different things, and something seems to work, but you never know why. I'd like to approach this from a different perspective and at the most fundamental level. Can you understand the mechanism of how things work in general from a structural perspective? And then you can say, well, here's the outcome that we know is bad. How do you get there from here? If you can identify the pathway of how you get there from here, then somebody smarter than me is going to come along and say, "Oh, all I have to do is do this, and now I can interfere with that." So, we're providing a framework to be able to think about these problems from a higher level, a structural level, that hopefully can then lead to great breakthroughs in medicine.

ZIERLER: The fact that you're at NIH, and there is this natural umbrella that has both the research and the clinical aspect, just by virtue of you being at NIH, would you find yourself ever

in a situation where you're dealing with the people that are doing the clinical studies, or is that essentially separate worlds?

ANFINRUD: These are separate worlds, and it hasn't happened to me yet. That doesn't mean it couldn't, but I remain focused on generating a fundamental understanding into mechanisms of how these things operate. Then, when I think we really understand it well, it opens up more opportunities to talk to people on the clinical side and learn about the problems they're facing, and see how we might be able to recognize causality from fundamental mechanisms of which they might not be aware. So, hopefully, down the road -- I'm not getting any younger, though.

ZIERLER: So, who have been some of your major collaborators, outside of biophysical chemistry? Here, at NIH, or beyond, who are some of the major people you've been collaborating with over the years?

ANFINRUD: When I got my start with X-ray crystallography, I began working with Michael Wulff at the ESRF in Grenoble, France. He had set up a time-resolved beam line, and I learned a lot from him. I spent about a decade going back and forth to the ESRF spanning 1997 to 2007. Then, there's a group at the University of Chicago that operates a time-resolved beamline at the APS. It was originally developed by Keith Moffitt but has since been taken over by Rama Ramanathan. [01:16:38]. My group an I developed much of the infrastructure needed to pursue picosecond time-resolved x-ray studies of proteins on that beamline, as well as time-resolved SAXS/WAXS. John Olson, a collaborator from Rice University supplied us with protein and protein crystals, but he has since retired. So, those are my principal outside collaborators. Internally, the one I have worked most closely with is Ad Bax with the NMR stuff, and with the COVID stuff. Prior to that, I worked very closely with Gerhard Hummer, a computational

chemist, who currently heads the Max Planck Institute of Biophysics in Frankfort, Germany. He has his own building and is a big-shot there. But most of my day-to-day activity boils down to what fun can I have in the lab today?

ZIERLER: Well, Phil, before we get to your current work, I want to ask you a few more retrospective questions that would allow you to assess your career in broad strokes. The first is -- this is particularly for -- our research crowd at the Niels Bohr Library, where they'll be accessing this transcript -- I wonder if you can explain how some basic fundamental concepts in physics inform your work, either on a day-to-day basis and how you set up research projects, or in how you understand the kinds of things you're trying to accomplish.

ANFINRUD: What I really like about physics is this concept of scaling laws. When I think about new problems, I like to think about them in terms of scaling laws. How does this change when you change that? Physicists are great at writing equations to try to explain observable phenomenon. So, Newton, in trying to understand the motion of the planets, had to invent some new math to tackle that problem, and came up with calculus. When I took calculus as an undergraduate, I was amazed at what you could do with it. I'm not fond of mathematics from the abstract perspective but am quite enamored with it from the applied perspective. What can you do with this? So, physics basically takes calculus-based mathematics and applies it to generate equations that can describe physical phenomenon. I can still differentiate and integrate equations to a certain extent, and routinely use calculus to try to optimize what I'm doing, because it provides a systematic approach to do so. When the Romans learned how to build long-lasting structures, it required a lot of trial and error. When Stradivari made violins, there was a lot of trial and error, and along the way he continued to refine his techniques. With calculus, you can

find optimal solutions, as long as you can describe it mathematically. But to describe it mathematically, you've got to think of it in terms of scaling laws. How does this behave as function of that? As a function of time? As a function of size? As a function of density? Whatever. So, physics is basically my everyday existence and provides a platform for how to think about fundamental problems. So, while I might not remember all the coefficients that go in front of those equations -- the fact that air resistance goes as the square of the velocity is a very useful thing to know. The scaling laws that come from physics is really applied mathematics, and I use that all the time, as it informs me regarding how to tackle a project. For example, when I'm doing an optical design, I'll write out the relevant equations and start calculating. If I do this, what could I expect to get there? What about this instead? And I try to optimize my design on paper -- on computer, actually. Probably using Excel or Python. The equations specify the things are that are under my control as an experimentalist, and calculus helps me optimize the choice of parameters. The laws of physics define the parameter space within which I can operate, and then I go to the web to find companies that can supply off-the-shelf components that fall within that parameter space. If I can't buy what I need, I'll often go to the machine shop and expand my parameter space by modifying something I can salvage or purchase. Once you write an equation to describe a phenomenon and specify your operating parameters, you can find optimal solutions for achieving your goals. It's very powerful. Though trained as a physical chemist, I have to admit that as a student I loved physics a bit more than chemistry, perhaps because it provides a more elegant, mathematical description of how things work.

ZIERLER: On the interpersonal level, you have a remarkable record of service in your field. Whether serving in advisory committees, or professional associations, and things like that, and I wonder if you can talk about what some of your basic motivations are in spending your time in

this way. What are the kinds of things that you hope to achieve by all of this involvement on these committees and associations?

ANFINRUD: Well, these have come in bursts, and right now I'm not on any of these panels. When you're getting into a new field, how do you make advances? You interact with experts and listen carefully to what they have to say. As an outsider, you can think outside the box and may be able to offer fresh insights. You exchange ideas. So, when I started working with X-rays, it opened up a whole new field for me. I didn't have any crystallography courses, and I didn't know anything about X-ray generation with synchrotrons. I was on a steep learning curve and found it very stimulating. As we were pursuing picosecond time-resolved crystallography, we pondered whether we could extend it to the femtosecond time scale. At the time, Stanford was proposing to build a linear collider light source as the successor to SLAC. Instead of colliding particles at high energy, use their linear accelerator to generate x-ray pulses that are very intense and very short. I served for a number of years on an advisory panel at Stanford as that process was getting underway, and they were negotiating with DOE to get funding to actually make this thing happen, and ultimately made it happen. Femtosecond crystallography is now a reality, and that capability inspired other places around the world to build instruments to be able to compete with the LCLS at Stanford. So, when I was asked to serve, I was happy to do so. But it also gave me an opportunity to interact with some of these smart people and learn a few things along the way, too. I'm not getting any younger, and still have a vision for what I would like to accomplish, and think I have the background needed to make it happen. So, I'm currently very focused on getting that stuff done, and am not currently serving on any external committees, nor am I advertising my availability as I'd rather not have that distraction at this point in time. Once all the needed technology is in place, and we can actually achieve my vision of what I think we can accomplish

with these techniques -- we're not quite there yet -- then maybe I'll feel compelled to serve, and can devote some of my time to do so. But right now, I'm really highly focused on the research. I'm as happy as I've ever been.

ZIERLER: This might be a harder question for you, because coming from Harvard where you were surrounded by smart and impressive people, and you had solid budgetary support, I still want to ask: what is it about NIH that allows you to do what you do that you might not be able to do elsewhere? What really about either opportunities of collaboration, or not worrying about funding sources, or the intellectual stimulation, what is it about NIH that really allows you to flourish with regard to your research?

ANFINRUD: In academia, a significant fraction of your time is spent writing research grants, progress reports for those research grants, and tons of letters of recommendation for students that come and go. NIH funding gets distributed among the various labs and the Director of Intramural Research has significant say in who gets what. Our Director basically says, "Okay, here's how much money I'm going to give you this year." I don't have a huge budget, but guess what? Based on past experience, I've been provided with what I needed when I needed it, and the Directors I've worked under have come through for me time and again. Thanks to this environment, it's minimized the time I have to spend thinking about fundraising, which is a big job in academia. This has freed me to think deeply about my research and focus on it. It has allowed me to work on longer term projects than can be readily pursued in academia. For example, what is a lifecycle of a graduate student? There's a period of training, where they finally get to the point where they can do something useful, and once they become useful, they write up their thesis, apply for jobs, and then they are out the door. You have this revolving door and have to think about projects that

could generate meaningful results for them within that kind of time frame. I embarked on my time-resolved crystallography adventure in 1997 and published our first major paper on this topic in Science in 2003, six years later. A lot of hard work, blood, sweat, and tears went into that. It's hard to identify in advance how to break down that process, which was highly exploratory. Trying to accomplish that feat with graduate students while teaching and writing research proposals would have been quite challenging, even with the caliber of students found at Harvard. At the NIH, I'm free to pursue much more long-term projects, and have the opportunity to employ and work with highly skilled post-docs and staff scientists. Post-docs arrive with much more experience than a typical graduate student. Nevertheless, there's still training, due to the breadth of skills required to succeed in my lab, but there's certainly less effort to train a post-doc to become proficient in my lab than a graduate student. So, I think this environment at the NIH is fantastic for me and the way I approach science. When I was young and thinking about my future and wondering what I could accomplish in science, Bell Labs really intrigued me, and if not Bell Labs, maybe a government lab. So, those thoughts had crossed my mind, but got pushed aside when I had the opportunity to go into academia. Of course, I loved academia, but I love this place, too.

ZIERLER: On the question of all of the projects that you've been involved in, if you think about them from the view of 35,000 feet, do you see an overarching research question, or a curiosity that connects all of them, or do you approach projects as islands, and you're working on whatever you're working on, and that's more self-contained?

ANFINRUD: I see them as highly intertwined in the sense that I would love to understand how these folded structures we call proteins achieve the myriad of tasks that they can achieve with the

efficiency that they do. How do I understand that from a mechanistic point of view? As a physical chemist, I like to think about mechanism. What is mechanism? It's a time ordered sequence of events. So, we say, "A picture is worth 1000 words." What's a movie worth? 1000 pictures? One analogy I've sometimes used is imagine a pygmy coming out of the rainforest and seeing this locomotive sitting still on the tracks. Never seen anything like that before. They walk up to it, touch it, and it feels cold. Why is that? Well, metal has a high heat capacity and decent thermal conductivity. When you touch it, it feels cold. Well, it's the same temperature as everything else, but it feels cold. And it's hard. You bang on it, and it hurts. It's hard. That's unlike what they normally experience. Now, if it was just sitting there, they'd not have a clue what it does. But what if he hangs around and sees somebody fill a big tank with water. Well, he knows what water is. Then, here's some lumber -- some wood. You throw that in the fire pit and light it on fire. That's generating a lot of heat. Then, that heat turns water into steam, and it's pushing on these pistons, and as the pistons move, the wheels start turning and the locomotive moves down the tracks. You see a sequence of events, you see causality. And then you see people hopping on the train, and through no effort of their own, get from point A to point B. They didn't have to walk there. Imagine if you were a curious pygmy and you observed that. You start connecting all this stuff as it happens. I would like to think that they could generate some semblance of understanding that this is a machine that's created to do some useful work. In biology, we have molecular size machines that are doing amazing things. What are the pistons, levers, wheels, and gears of biology? When I'm looking at these things from time-resolved crystallography, time-resolved spectroscopy, time-resolved small and wide X-ray scattering, time-resolved NMR, we have different ways of viewing these pistons, levers, wheels, and gears. If we can understand those things from a fundamental level, why couldn't we explain all that ails

us. If we could explain the origins of all that ails us, why couldn't we be clever and come up with interventions to minimize those things that ail us? So, from my bird's eye view looking down, these things are all well-connected. It's trying to understand from a mechanistic point of view how these molecular-based machines really work. If I could put together a movie of a time-ordered sequence of events, this happens first, then this next, we could see how it's all connected. That would reveal multiple places where the process could be disrupted or derailed. Many diseases are actually genetic based. There's one mutation in a protein that causes it to do something wrong, and that can have very ill-health consequences. Is there a way of rescuing correct behavior, or do you have to do gene therapy to actually get the right protein expressed in the cell? If you can understand from a mechanistic point of view how these things really work at that fundamental level, then why couldn't you, in a rational way, address all these things that ail us, and why we can't we fix them?

ZIERLER: So, when you use the phrasing, "I would love to understand how these proteins work," it suggests that you don't understand yet, but that it's possible at some point to understand it. Right? So, I guess my question is what do you see between now and then? What's it going to take for you to say, "Now we get it. Now we see how these things work."?

ANFINRUD: Well, take for example a paper we published in PNAS on photoactive yellow protein studied with time-resolved crystallography, which is probably the paper I'm most proud of from the crystallography point of view. Our study unveiled a time-ordered sequence of structural changes at a very high level of detail. But it doesn't capture the final stage of the signaling event, as I told you before, because it's in a straitjacket. We had a follow-up paper where we used time-resolved small and wide-angle X-ray scattering to fill in some of those

details. We now understand this system at a pretty high level of detail. People can then model this observed behavior on a computer. One of the problems when it comes to computational modeling is the time-scale for this protein to go into its signaling state and then back to its ground state. Hundreds of milliseconds. Now, the fastest computers get you up to a millisecond, but hundreds of milliseconds? This time scale issue remains a challenge. Now that we understand from an experimental perspective the time-ordered sequence of events that lead to the signaling state, what we need from the computational side are potential energy surfaces that capture what we see experimentally accurately enough, and fast enough computers that can start looking at single molecule behavior, which I can't look at. I can only look at ensemble behavior with my techniques. But if they can look at the single molecule and show that, statistically, the single molecule behavior averages out to be what I see, then you can argue that the potentials used are good enough, and the single molecule behavior observed on a computer is credible. If we can look at a handful of systems at the highest level of detail possible and use that to validate the potentials that are used in computational approaches, then I'm out of a job, because now computational approaches will basically say, "Oh. It's simple. Here are the potentials. Here's what's going to happen if you wait long enough." Then, answers to many of our questions will come from computers. But we're not there yet. I still have a few more productive years left in my career, I hope, and will continue to delve into the experimental side, and measure with as high a precision as possible the time-ordered sequence of events that give rise to the behavior that makes these things work -- the mechanism.

ZIERLER: Yeah. And when you say, "All that ails us," do you see this beyond cognitive degenerative diseases like Alzheimer's and things like that? Does this extend to other maladies that we deal with?

ANFINRUD: Well, here's a classic example: the chief of our laboratory, Bill Eaton, has long had an interest in sickle cell disease. What is that? There's a single site on the hemoglobin molecule that has a mutation that creates a sticky patch when in one of its two main quaternary conformations. So, when blood travels from the lungs to the tissues and oxygen comes off, there's a conformational change of the protein. When it goes into its deoxygenated conformation, this sticky patch becomes exposed, hemoglobin molecules stack on top of one another and weave together into long rods that distend the shape of the red blood cell so it's no longer a nice donut, but it gets distorted into a sickle shape, which gives this disease its name. A mouse manages to squeeze through an amazingly small hole in the wall. Likewise, a donut-shaped red blood cell is very deformable and can squeeze through a very tiny capillaries, but not when you have this rigid rod inside it. It gets stuck in the capillaries, blocks blood flow, and causes very painful episodes. So, here's a genetic disease, and he's working on trying to find a therapy for it. Now, a lot is known about it. Here's the sticky part, and here's the origin of this patch. The challenge is to figure out how to hold off or better yet prevent the nucleation event that triggers the formation of these rod-like structures inside the red blood cell. That's a tougher problem, because we still don't understand the nucleation event at a structural level of detail. This is one of numerous genetic diseases. Healthy cells remain so when their signaling machinery works properly, but sometimes the signals can get out of control. I've heard and read that with COVID-19, it's not necessarily the virus that kills some people, but it's the immune response to the presence of that virus. It can go into overdrive and cause extensive collateral damage. Well, there's a mechanism for that as well. If we had a molecular level understanding into how all this stuff works, wouldn't we have better targets for how to intervene? So, you can think of health in a very broad context, but I would hope that if you understood how these proteins behave, how signaling molecules

interact with each other at the most fundamental level, that we would be primed to come up with therapies to address all that ails us.

ZIERLER: So, that's a great segue to the last thing that I'd like to talk about with you, and that is your current work on the Coronavirus crisis. So, my first question there is, I'm very curious -- first of all, I'm talking to physicists who were involved in this in remarkable ways. Dick Garwin is doing government policy stuff, and Art McDonald is an astrophysicist, but he's working on ventilators now. So, I'm really fascinated at how we have this, hopefully, Manhattan level project where it's an all hands-on deck situation. So, I'm curious with you, did you think creatively about -- here's what I might have to offer, or was there more a directive on high that said, "Drop everything. This is what everybody has to work on now." So, I'm curious how you got involved in this.

ANFINRUD: That's a good question. It was like five and a half weeks ago, we were told that we're going to have to go into a new mode of operation, a minimal maintenance mode of operation, where we're supposed to stay at home and telecommute. At the time that was being formulated, I had experiments planned at the Advanced Photon Source and was busy preparing for them, all the while wondering if it's going to happen or not. Then, Ad Bax came to me and told me about speech droplets. I had never heard of speech droplets before. That was not on my radar screen. He said, "The coronavirus that causes COVID-19 seems to be very infectious." He was wondering if speech droplets might be a principal mode for transmission. When someone coughs or sneezes, we all know that stuff comes out of their mouth, and we kind of go, "Ew." We recognize that, but talking? And then he said, "It's been documented that simple speaking can generate droplets, and they could contain this virus, and that could be a means of spreading." I

was kind of skeptical, but he said there was some literature on this. He was thinking maybe vocal cords are at play. My wife is a singer, and when she hits a high A, her vocal cords are vibrating 880 times a second, and they are covered with mucus. So, when they're vibrating like that, perhaps they could be shearing off droplets that can be emitted from the mouth. If the viral particles are spread all through your body, maybe some could be shed from the vibrating vocal cords and get into the air where someone else could inhale them. I was intrigued and said, "Let me think about that." He asked me, "Can you think of a way of being able to visualize these? It's known that they occur. Perhaps a fluorescent dye or something?" I said, "Oh, no, not a fluorescent dye." He said, "How else can you see them, because they're small." I said, "I don't need a fluorescent dye to see them. I think I can see them by light scattering." In my laser lab, I have hepa filters above my laser table that blow down filtered air over the laser beams. When I shut off the lights and my eyes become dark adapted, I can see my laser beams. Rayleigh scattering. The laser photons hit nitrogen and oxygen molecules and can scatter into a new direction. It's a rare event, but when you have so many photons going through the air, you can see it. If I don't have my hepa filters running, then the laser beams can light up like a Christmas tree. You see all these fireworks and flashes. So, I keep my hepa filters running to keep the dust under control. I told Ad this story and explained, "I don't need fluorescent dye to see that. I think I'd be able to see pretty small particles." He was skeptical, but that's understandable as he's an NMR person. Then he kept coming to my office that week and badgering me. "What do you think? Can you make this happen?" So, I'm still working on my preparations for my APS beamtime, but by the end of the week it became clear that my beamtime was not going to happen. Illinois decided they were going to shut everything down. So, I said, "Okay, this weekend, I'll see what I can do." On that Friday, I started scrounging around for optics, and got a

spare green laser ready. I thought I could paint the inside of a box black and send a laser beam through slits cut on its sides. I salvaged some cylindrical optics that I thought could transform a small beam of laser light into a light sheet. So, with that plan in mind, I found a box in my garage on a Friday night, grabbed a can of black spray paint I had in my basement work shop, cut slits in the sides, and painted its interior. I woke up early in the morning and was in my lab before 6 a.m. and started setting up the optics for this experiment. By mid-morning, I had a laser sheet going through the box and enlisted the assistance of our machinist, who happened to be in that morning trying to finish off a project that he didn't finish during the week. We have dedicated people here at the NIH. I grabbed him, and I said, "I need your help. I want to talk through a hole on the back side of this box, and I want you to stand on the opposite side and tell me if you can see any flashes coming from the light sheet." When he confirmed that he saw a lot of flashes of light, I picked up my phone and called Ad and said, "Ad, I have a laser running and we're seeing speech droplets. What do you want to do?" He says, "I'm on my way in." So, I summoned one of my post-docs and we set up my iPhone to take a bunch of video footage. We wrote up a narration to go with some of that footage and uploaded a YouTube video. We just spent the entire weekend working on this thing because it seemed so important. As I mentioned, I didn't know anything about speech droplets, but when we saw lots of droplets come flying out of my mouth, we realized that we had to get the word out and get it out in a hurry. People needed to know, because if you're a carrier and don't know it, you're not symptomatic yet, guess what? You go about living like normal, and you're talking to people face to face." Now, what we're learning is, as we're talking, we're just spitting out a bunch of droplets of various sizes. Big ones can fall to the ground fairly quickly and probably don't do much harm. Intermediate size ones evaporate and form smaller particles, which actually hang around in the air for a good while. We have a follow-

up paper we're trying to get published in PNAS where we see these things lasting for perhaps 10 minutes. So, if you were 3 feet away from me and I'm talking, and 10 minutes later, some of those droplets are still hanging around, what's the chance of you inhaling some of those droplets? I mean, it's 100% chance you're going to be inhaling my saliva, and I'm going to be inhaling yours.

ZIERLER: So, these droplets are essentially light enough where they can just hang out in the air?

ANFINRUD: Yes, when small enough, they can hang around for quite a while. And this, again, is where scaling laws come into play. So, think about terminal velocity. I've long known that if you jump out of an airplane, and you tumble, you fall at about 120 miles an hour. That's basically dictated by our density, which is a bit above 1 gram per centimeter. When you get to smaller particles and get into the Stokes regime, the scaling laws change. In the Stokes regime, the terminal velocity scales as the square of the size. So, at the same density, if you have a ten times smaller particle, it falls 100 times more slowly. Consequently, a 100-micron sized particle, roughly the diameter of a human hair, is going to fall at approximately one meter per second. A ten-micron sized particle is 100 times slower. Say I'm in a room with a ventilation system. Air is always being stirred up. This thing is falling slowly, but it's getting stirred up, so it percolates up and down. A glider plane pilot looks for thermals that can carry them to high altitude. Though they're much heavier than air, they can stay aloft for a good amount of time, but eventually are forced to glide back to the ground. When speech particles are spewed out into the air, guess what? Air currents stir things up, and if the speech droplet fall slowly, they can ride the room air currents over large distances. The larger droplets fall more quickly to the ground and won't spread nearly as far. You can't say they're harmless, because they could contain virus, too. But if

you think about modes of transmission --this is me thinking about it from a physical chemistry point of view – transmission of virus via speech droplets in the air seems a more plausible route of transmission. What was the emphasis before we did this study? Wash your hands for 20 seconds. Use disinfectant on your hands. Don't touch your face. Scrub your doorknobs and your iPhones.

ZIERLER: Cough into your elbow.

ANFINRUD: Yes, cough into your elbow, that's a good thing, right? I didn't learn that as a kid, but I've learned that since. Try to control that spray. We never heard anyone say talk into your sleeve. Guess what? Speech also generates particles that can be infectious. In fact, they could potentially be even more so. So, that weekend, I built a really crude apparatus with an Amazon box painted inside, and then after a week of testing with that, I built another box that we used to collect data for our PNAS paper. Now, that's stripped down and I'm building my third-generation box, which is almost done. We aim to make much more detailed, more quantitative measurements. I bought new cameras and lenses and worked out an optical design for all this stuff. We hope to be able to characterize the size of particles emitted, their number, and their fate. The thought is this: if I just say, "Ahh," and get my vocal cords vibrating, there's going to be a characteristic size of particles coming out. How big are they? How many? How long do they stay in the air? When we vocalize, we really need to know some of those things. If we can understand how long these particles stay in the air, and that's basically determined by terminal velocity, and how much room air stirring you've got, what's the probability that they could contain a virus and then transmit disease to others nearby? We're talking about a direct route of infection. So, if you and I were having this interview in my office, how many droplets would I

have spewed out in this few hours of conversation that we've had? Millions of droplets. What's the chance that you'd breathe some of those? 100%. That's a direct route, because if that gets into your lungs, it's not coming out any time soon. If I was infected, what's the chance that you would become infected too? I'd say the probability would not be small. What are they talking about? Wash your hands. Well, when I speak, I spew out droplets, and they settle on my desk, they settle on my computer, and they settle on whatever I'm around. I touch these things, so now I get some on my hands. Some hours later, it's no longer infectious. There are variations in how long. Maybe it's eight hours, maybe it's three hours. Whatever. People argue about how long it might stay infectious. But if I speak and it falls on a surface, I have to touch that. Now, my skin is a pretty good barrier. These things just don't go through the skin. So, I have to get it on my skin, and then I've got to rub my eyes. If I get it into the fluid of my eyes, that's going to be a hospitable place. But it's still got to diffuse around and find a tear duct and actually be able to navigate in. Maybe that can infect someone, and maybe not. But this is a respiratory virus, so we should be worried more about how it might get into our lungs. Well, if it's on my hands and I sniff my hands, maybe I can get some particles in my lungs, but that's a more indirect route. Speaking is a really direct route. How can this be overlooked? So, like I say, five and a half weeks ago, I hadn't even heard of speech droplets. Now I'm thinking, how is it that so few people recognize this as a potentially major pathway for this?

ZIERLER: So, if we were to go back in time, and everybody was wearing masks from early March, we'd be in a lot better place than we are now. Is that fair to say?

ANFINRUD: I don't think we'd be looking at 60,000 deaths in the U.S. at this point in time. I think it would have been far less than that. So, getting back to your question about were we told

to drop everything and do something about Covid-19? There was no directive that came down from on high. I wasn't thinking about this. But Ad came to me and told me something I had no clue about and put it on my radar screen.

ZIERLER: And this was Ad's own vision? He had this spark himself, or where did he get this idea from?

ANFINRUD: Well, he's got a daughter who's in medical school, so he's more closely connected to the medical community. He was learning about this, and of course, she's sequestering at home, and then he told me about these speech droplets. What got me curious was his comment that perhaps vibrating vocal cords were generating them, and since my wife's a singer, I thought, okay, this is potentially interesting. Let me see what I can find out about this. Then I was very surprised to find out how many droplets you can actually generate by just simple speaking and vocalizing. As we tried to get the message out, it was Ad who really pushed this into the public forum. He contacted CDC, he contacted the White House, of course he also contacted NIH administration. I don't have time to think about that. I'm thinking about calculations, and how do I optimize this experiment? What am I measuring? How do I improve my measurement? Whatever. So, I've been focused on the instrumentation side of this and let him handle the policy side. By the way, we're not supposed to handle policy.

ZIERLER: I get the sense that Ad is a unique character, though, that he does his own thing.

ANFINRUD: Yeah. He's a member of the National Academy of Sciences. He's very highly regarded, and highly respected around here. He can get away with it. So, we submitted this YouTube video. It was his idea to do this. Between my post-doc, myself, and him, we got this thing together. I don't know if you saw that or not.

ZIERLER: I did. He shared that with me.

ANFINRUD: CNN actually did a little thing about what we were up to last week and aired that.

ZIERLER: And the Washington Post has covered this research as well.

ANFINRUD: Yeah, and the timing of the CDC recommendation to wear masks, where do you think that came from? A week after we were pressing these buttons -- Ad was pressing these buttons. I was vigorously working in the lab trying to get new results. He was helping push the buttons to get the word out.

ZIERLER: Now, on the other side, in terms of visualizing coronavirus, are you involved in that as well?

ANFINRUD: What do you mean by visualizing?

ZIERLER: I mean, understanding the structure of coronavirus.

ANFINRUD: No, I'm not involved with that. China has done a lot of that early research. They came up with a structure, and now the structure is known. That gives targets for people to work on. To me, the transmission question is really crucial. What's frustrating about this is you see so much defiance and non-compliance. If you say, "Let states do what they think is best for those states." Well, guess what? All states have borders with other states, and then we risk getting into a mode of playing whack-a-mole. Imagine, you knock it down here, and it pops up there. You knock it down there, and it pops up here. How do you control this? Assuming speaking is a primary mode of transmission -- by the way, I don't talk to anybody outside my family without putting my mask on. What do you think would happen if everybody did that? Now, this mask

doesn't protect me from dried out droplets that somebody else might have left behind, but guess what? The droplets that come out of my mouth are wet. They're easily trapped by an absorbent material. Cloth, paper towel -- Ad Bax wears the paper towel in front of his face. I've got my version of a paper towel mask that I've created, with rubber bands that hold it on my face. So, the droplets that come out are wet, and you can trap them. If you trap them in the mask, then you're protecting others. Here's the problem: once they get out into the air, they dry out, and when they dry out, they become smaller, and this R-squared terminal velocity scaling law comes back to haunt you. They float around for a long time and can remain viable for a long time. And guess what? Is six feet safe? How can you say six feet is safe, knowing what we now know?

ZIERLER: Right. Six feet just seems kind of arbitrary. It's just a number.

ANFINRUD: I don't know where that came from, but people still talk about that. I'm of the mindset that if I'm going to interact with somebody and talk to them, I'm going to be wearing a face mask. Any droplets that I generate is going to be stopped at the source. "Stop it at the source," that's what I say. If you stop it at the source, and I stop it at the source, then we're at very low risk of transmitting this thing. If we had compliance, why couldn't you be working in your office? I'm coming to work every day, because I have dispensation to do so. I have to do this here. But most of my colleagues are not here. Why can't they be? If we understand the mechanism of transmission, and then take appropriate precautions, we could squelch the spread of this stuff and get our economy going again. If we had a united front -- and it's not just the U.S., we need to do this internationally, and get everybody else on board -- but everybody's doing their own thing. We need leadership to make this happen.

ZIERLER: Yeah. So, Phil, I guess for my last question, it's on that issue. Looking forward, what are you optimistic about, and what are you pessimistic about in terms of how we come out of this?

ANFINRUD: The coronavirus?

ZIERLER: Yeah.

ANFINRUD: You know, it kind of fluctuates from day to day with the news. Once there's a vaccine for this, now you have another problem. Let's say, today I know how to make a vaccine. I know the vaccine works. How many billions of people do we have in the world? How do you vaccinate that many people?

ZIERLER: So, you see the scalability as much of a challenge as the creation of the vaccine itself?

ANFINRUD: That's going to be a big challenge, right. So, the first thing is finding something that works. You have to do trials to demonstrate that. Then, you have to actually scale that up, and get broad enough coverage. Now, there's this thing called herd immunity, and if you get enough people that are immune to this thing, then you can stop it in its tracks. You won't have this runaway problem. But the thing is, we don't have immunity out there. So, until we get this, we could find ourselves playing whack-a-mole for a long time. Even if we get this under control, it could reappear, and then, who's going to want to shut down the economy again once we restart it? There is going to be tremendous resistance to that. I'm working alongside Ad to try to get the science done as quickly as possible, and as accurately as possible, to inform policy makers so that when we make this transition, we do it right. We want to minimize the risk of having a

recurrence. Fauci's talking about, "Hey, it's not going away. We could see this come up again in the fall, or in the winter, and it could be even worse." Until you have this herd immunity, then you have this risk of the virus coming back in a big way. So, some days, I feel more optimistic than others. Get the word out. The thing is, when driving around, or walking around in my neighborhood, I saw a lot of people starting to wear masks around the time of that CDC recommendation, so I'd like to think that this has played a role in that, but I still hear health experts talking on the news who are not getting it. They talk about coughing and sneezing, washing your hands. They're not quite getting the message that if you're going to be conversing with somebody in a closed space, you should wear a mask. When my family and I are outside for a walk, we wear our masks, which is trying to set an example for others. Maybe it's not necessary, but it certainly doesn't hurt. But I also think it is helpful to standardize behavior -- just like I buckle up in the car every time I go somewhere, not because I'm expecting an accident, but because it's the safe thing to do. Look at this video. Look at these speech droplets come flying out. That's what's actually happening. I can understand it. Now I understand why you and I should both don a mask, but that message is still not out there in a big way. If we could get everyone to understand why we should adopt this habit… Some people are getting it. Sanjay Gupta, I think, gets it. He actually asked to interview me.

ZIERLER: Are you going to do it?

ANFINRUD: We are all set up for the interview, but then the office of the Vice President said, "No." So, the segment that aired last week was supposed to include an interview with me. Instead, they got an MIT person, who talked about coughing and sneezing.

ZIERLER: Well, I'm glad I didn't go through the White House to get this interview with you. Well, Phil, it's been an absolute delight speaking with you. I really appreciate your time. I really appreciate your explanation, particularly, of how physics informs your work. That's a beautiful explanation that applies to not just yourself, but to so many of your colleagues. It's just a tremendous value. So, I'm really happy we were able to connect. Good luck getting the word out, because we all definitely need that.

ANFINRUD: Okay, thank you very much. Again, I'm sorry that I have been so slow to respond to your emails.

ZIERLER: No worries.