Eaton, William 2020 B

Dr. William Eaton Oral History

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Dr. William Eaton
Interviewed by David Zierler

Date: June 12 & 16, 2020

ZIERLER: Okay. This is David Zierler, oral historian for the American Institute of Physics. It is June 12th, 2020. It is my great pleasure to be here with Doctor William Eaton. Bill, thank you so much for being with me today.

EATON: It's a pleasure to be here.

ZIERLER: Okay. So to start, please tell me your title and institutional affiliation.

EATON: I have two titles. One is called NIH Distinguished Investigator. The other is Chief of the Laboratory of Chemical Physics in the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.

ZIERLER: Okay.

EATON:, which is in Bethesda, Maryland.

ZIERLER: Let's take it right back to the beginning. Tell me about your parents. Where they came from and what were their professions?

EATON: My mother was the daughter of a Latvian tailor who was born in Riga. He married his 16 year old Lithuanian bride when they were both 16 to escape the pogroms in Latvia. Around 1880, they went to England. Some of the family went to South Africa. This was very typical for Eastern European Jews. My grandfather got fed up with the fact that his oldest daughter was being held in the fourth grade for three years because she was smarter than everybody else in the class and had skipped two grades. He couldn't stand the discrimination against Jews any longer in England, so he went to Philadelphia in 1908. So, my mother came to the US when she was 10 years old. She was the first in her family to go to college and graduated first in her class at Temple University in Philadelphia. She then went on to get a Master's degree in Latin at University of Pennsylvania, one of the very first women, possibly the first, in the history of the University of Pennsylvania to get an advanced degree in the classics.

ZIERLER: Oh wow.

EATON: She then taught Latin in high school. She would take a train from Philadelphia to Mays Landing, New Jersey, to teach Latin in the high school there. My father didn't go to college originally. He was very skilled at electronics and started a small electrical business, but it went under during the Great Depression.

ZIERLER: Where was he born, your father?

EATON: He was born in Philadelphia. His family came to Philadelphia in the early 18th century. Originally, we thought his family may have come with William Penn, but nobody's been able to prove that his family was in Philadelphia before 1713. William Penn came to Philadelphia in 1682.

ZIERLER: So your father's the non-Jewish side of the family?

EATON: My father was a Methodist. He loved to sing "I'm a Methodist 'Till I Die" just to have fun with my Jewish mother.

ZIERLER: (laughs)

EATON: I still remember the tune. (sings) I'm a Methodist 'Til I Die. Something like that.

ZIERLER: Where did they meet, your parents?

EATON: A very close friend of my mother when she was an undergraduate at Temple University was a woman named Leona Dickhart. Her maiden name was Leona Eaton, and she introduced my mother to her brother, George Washington Eaton Jr. Washington was a very common middle name to people who were born in the late 19th century. My father was born in 1899. My brother George is now George Washington Eaton III. Although now that he's traced the family back, he claims he may be George Washington Eaton V. My father did take a lot of engineering courses at the University of Pennsylvania, but he never did receive a degree. He was one of the very first ham radio operators in the United States.

ZIERLER: Oh wow.

EATON: One of the things that I regret as a child is that my father was extremely skilled at mechanical and electrical things. He was famous in South Philadelphia when he and a friend took a Model T Ford completely apart, laid it out on a blanket on the sidewalk, and then reconstructed the car. As a result, he knew every part of a car and he would always take care of all the family automobiles. I remember that he was very proud of his 1928 Packard that he bought during the World War II, which weighed about 4,000 pounds., One night he came home and told my mother that he had a head-on collision with a large truck, so she was scared of what happened to the Packard. He told her: "no, no, no, just the cast iron bumper got bent, but you should have seen the front of the truck".

ZIERLER: Right, right. So Bill, when do you come on the scene? When are you born?

EATON: I was born on June the 4th, 1938.

ZIERLER: Okay. Do you remember the war at all.

EATON: I remember as a child being told to get under the dining room table during blackout periods, where there was always this fear that the country would be bombed during the war. We had black shades for all the windows in the house, which we would be pulled down during these air raid drills. All five Eaton children would have to climb underneath the dining room table. The other thing I distinctly remember was in April of 1945, when Roosevelt died. I was almost seven and I'll never forget walking out of the house to see that everyone in the neighborhood was out on the street with most of the people were crying. They were actually weeping when Roosevelt died.

ZIERLER: Right. Right. And you were born in South Philadelphia?

EATON: I was born in West Philadelphia.

ZIERLER: Okay.

EATON: Our house was on 44th Street, between Locust and Spruce streets, about a mile west of the University of Pennsylvania.

ZIERLER: Now your father's scientific interests and abilities, did he involve you in those? Did he share his interests with you?

EATON: Well, he wanted to, but I was more interested in playing baseball and basketball than sitting with him in his room learning how to build an electrical circuit. He was very good at mathematics, and he always helped me with math when I was in high school.

ZIERLER: Did you go to public schools in Philadelphia?

EATON: Yes. I went to West Philadelphia High School.

ZIERLER: And were you a standout student in science?

EATON: Well, I was actually an incredibly standout student. I graduated with a 99.6 out of 100 possible grade point average. That was my average, 99.6, which is a little bit crazy because I tried to get a perfect score in every single exam. However, my official graduation average was 97.6, because I was caught smoking in the fire tower, and as punishment, my grade point average was lowered by two points so that a close friend of mine whose average was 97.7 won the Phi Beta Kappa award.

ZIERLER: Well you made amends by having a career in NIH.

EATON: Yes. But that was actually a very traumatic experience when I think back about it, because I lost a full scholarship to Penn, which automatically was granted to the number one student at West Philadelphia High School. Penn always had a full tuition scholarship for number one. However, one of my teachers, a Miss Deglin, appealed to the university and they also gave me a full tuition scholarship.

ZIERLER: Now, when you were thinking about school, was physics specifically on your mind, that you wanted to major in physics?

EATON: No, actually, I always liked physics, but my sister went to the University of Pennsylvania, where she majored in chemistry. I liked chemistry a little bit more than physics. I did win the physics and mathematics prizes when I graduated from high school, so I was good at physics. I thought about majoring in physics when I was an undergraduate, but I always had to have part time jobs to support myself, because my family had very little money, and physics students seemed to be working on homework all day long. I had very extensive part time jobs when I was an undergraduate. I was always working at least 20 hours a week in some kind of job.

ZIERLER: So what was your major as an undergraduate?

EATON: So I majored in chemistry and I ended up doing mostly physical chemistry. I did, of course, study physics and in my senior year I took an atomic physics course with a professor named Thomas Wood, who was interested in biophysics. He wanted me to go to graduate school in physics, even though I'd already been accepted in medical school and I was off to Berlin for a year. When I graduated, he gave me about a half a dozen textbooks, including the standard textbooks of electricity and magnetism, the standard textbook of classical mechanics, a quantum mechanics textbook, and a statistical mechanics textbook. He wanted me to spend the year in Germany studying these textbooks and come back to take the PhD entrance exam in the physics department, which I did not do for reasons which I'll explain later.

ZIERLER: So he wasn't successful in attempting to make you a physics graduate student?

EATON: No. I worked in his lab for two summers doing research with him.

ZIERLER: What was his research? What was he working on?

EATON: He was an old-fashioned biophysicist. Biophysics in the 1950s was radiation physics because of the atomic bomb. Wood did what I thought to be rather crude experiments by irradiating yeast with x-rays and different dosage regimes, followed by looking at survival. This was very typical biophysics after the war. It was Stone Age biophysics. It was the 1950s.

ZIERLER: Did you think about moving to a different program or a different school for graduate school? Or you knew you wanted to stay at Penn?

EATON: No, being brought up in Philadelphia and being so academically oriented as I was because of my mother, being admitted to the University of Pennsylvania School of Medicine was considered a major academic prize in Philadelphia. It was considered the highest academic achievement, much more than getting into graduate school in physics at Princeton, or physics at Penn. That was my focus, even though I really wasn't ever interested in practicing medicine.

ZIERLER: So how much of your des--

EATON: --a little bit of an obsessive-compulsive student.

ZIERLER: How much of your decision to apply to medical school was because of your own interests in medicine, and how much was it to make your Jewish mother happy?

EATON: It certainly was to make my Jewish mother happy, but also as I said, it was a prize. It's still true today to a certain extent; it was a ticket. A medical degree from the University of Pennsylvania meant that one was going to lead an affluent existence.

ZIERLER: So what happened? How'd you change course?

EATON: When I got to medical school I became more and more confident that I did not want to practice medicine and became more and more interested in doing scientific research. The summer after my first year of medical school I worked with a biochemist named Robert E. Davies, who treated me badly. He was very nasty to me. My research was on muscle contraction. I devised a rather clever experiment for which I won a prize from the medical school, which showed that adenosine triphosphate, ATP, actually broke down in proportion to the amount of work that was done by a contracting muscle. No one had ever demonstrated that before, even though everybody thought it must be. Nobody had ever done an experiment to demonstrate that ATP is the energy source. He went on to publish many papers on it. I was told 40 years later by a physiology professor, Bill Harrington, at Johns Hopkins, that my experiments started him on a path that got him elected to the Royal Society. (laughs) He was British. It really was a very clever experiment, although I don't remember all of the details of how I actually decided to inhibit an enzyme called phosphocreatine kinase, which showed indirectly from the changes in phosphate and creatine I measured that it must have been ATP that was breaking down. A graduate student then showed it directly in a later experiment. So that was my first year

ZIERLER: Still as a medical student, Bill? Or when did you--

EATON: I was a medical student.

ZIERLER: Okay, okay.

EATON: I think what really motivated me to become a research scientist was the second summer. I started medical school in September 1960, so my first summer was the summer of 1961 with Robert E. Davies. During that summer, I went to the Federation Meeting in Atlantic City and attended a symposium where I heard Khorana,

Nirenberg and Brenner talk about cracking the genetic code. The first two lectures were really terrific, but then this guy Sydney Brenner with a South African accent stood up and mesmerized the audience. He pointed out how he and Francis, that is Francis Crick, his buddy, had predicted everything that they had said and that the previous speakers were in their labs doing the technical work just to prove that he and Francis were correct. Brenner and Crick knew that it was a non-overlapping degenerate triplet code and he implied that the other guys were just showing how right they were. So, I wrote a letter to Brenner in the fall asking if I could come to his lab the following summer. I got a letter of recommendation sent to Brenner from a microbiology professor who knew him. A thin aerogram came back that said, "Dear Bill, come if you like, Sydney." In my letter to Sydney, I had told him that the medical school would pay all of my expenses. I took Sydney's response to the dean, who said, "I don't think we can give you a summer fellowship and pay your airfare, as well as all your living expenses for 3 months, if this is all he's going to say." But the microbiology professor told the dean that this was an enormous coup to be able to get to the Brenner lab, because he didn't take students.

ZIERLER: And the lab was in South Africa?

EATON: No, the lab was in Cambridge.

ZIERLER: Oh, okay.

EATON: This is the famous Medical Research Council Laboratory in Cambridge. They had a bad relation with the university because they were treated so badly and wouldn't take any Cambridge graduate students. This laboratory had Francis Crick, John Kendrew, Max Perutz, Sydney Brenner, Fred Sanger, and Hugh Huxley. These six group leaders won six Nobel prizes. Six!. It's a historic lab and a singularity in the history of science. The seventh group leader was Aaron Klug, who joined the MRC lab in September 1962 and also won a Nobel prize. They were all hired by the head of the lab, Max Perutz. His first seven hires won seven Nobel prizes. Sanger won two, one for sequencing proteins and one for sequencing DNA. Hugh Huxley didn't win any.

I should have mentioned before this that my research interests really were kindled as an undergraduate for two reasons. One is, I already mentioned, that I had to have jobs to make money to support myself. As an undergraduate, I was very good at mathematics, and the mathematics department recommended me to a research group led by John O'Mara Bockris, a famous electrochemist, who was involved in the cold fusion scandal. There were no computers in those days. There was one in the basement of the physics department called the UNIVAC, which was one of the first large computers in the country. But the physics department wouldn't let anybody in the chemistry department use it, so the chemists had to do their calculations by hand. The Bockris group needed someone who was reliable at doing calculations. Bockris paid me well, $4 an hour as an undergraduate, which today is equivalent to about $40 an hour.

ZIERLER: Yeah.

EATON: (laughs) It was a great hourly wage for an undergraduate. All I had was a Friden mechanical calculator, tables of integrals and functions and a slide rule. I worked about 20 hours a week in that research group, and I became very friendly with a lot of its members. I really liked the atmosphere of a research group. One summer, I got a research grant from an organization called the Wagner Free Institute of Science (laughs) in Philadelphia. The idea of the experiment came from a botany professor who was also a geologist. His idea was to repeat the famous Miller–Urey experiment of sparking methane, ammonia, hydrogen and water that produced amino acids. His idea was that levorotatory amino acids came from the fact that these amino acids were synthesized on the surface of levorotatory quartz. So, he had a friend send him a large crystal of l-rotatory quartz, and my sister, the chemist, was working at the Frankford Arsenal in Philadelphia that had a ball mill, which ground the quartz crystal into a powder. So, I redid the Miller-Urey experiment with a Tesla coil and a powder of levorotatory quartz. I sparked the Miller-Urey mixture for a week and out came a yellow solution which I took to the chemistry department's Rudolph polarimeter for measuring optical rotation. Nobody in the chemistry department knew how to operate the polarimeter and there was no instruction manual. There was no way I could figure out how to calibrate this instrument. So, I actually never got a result. To this day, when I speak to origin of life people, they say, "You know that's a really good experiment and somebody should repeat it." So that was my first research project.

We're back to my second year of medical school. Every summer starting from my sophomore year in college all the way into my second year of medical school, I was interested in research. Now, about Cambridge and Sydney Brenner. It was a fantastic experience because Sydney Brenner and Francis Crick were widely considered as two of the smartest scientists in the world. Crick was a physicist and Brenner was a biologist, but I don't recall the field of his PhD. He was certainly known as a biologist because he won his Nobel prize for work in neuroscience. Every day there was coffee in the morning, lunch in the afternoon, and tea at four in the canteen on the top floor of the lab, where Brenner, Crick, and their postdoctoral fellows would sit together. None of the post-docs ever said a word because Brenner and Crick were so intellectually intimidating. In fact, I think I said one sentence to this group the entire summer, and I remember being thrilled by Francis Crick saying, "Hey, that's pretty smart." (both laugh)

ZIERLER: Do you remember what the question was?

EATON: No I don't remember what it was. I really didn't understand what these guys were talking about, even though I had a very strong biology background, from two years of medical school. They were defining the major questions of modern biology. By the way, one of the things that I noticed when I was in Cambridge is that I knew so much more basic science of medicine than the Cambridge medical students whom I met. So Penn Medical School was really a fantastic medical school with a strong emphasis on basic science. The basic science faculty tried hard to lure medical students to become researchers. They succeeded with me, and one other student, out of our class of 125, who eventually went into full time research. My project was to purify something called peptide bond synthesis factor B. This was supposed to be an enzyme that catalyzed the formation of the peptide bonds when proteins were synthesized.

ZIERLER: Now you're talking about your research at Cambridge?

EATON: Yes, this was my research with Sydney Brenner.

ZIERLER: Right.

EATON: I was married on June the 16th, 1962, a couple of days before we flew off to Cambridge. For my wife, this was supposed to be a honeymoon in Cambridge, and she'll never forget the fact that I worked from morning until very late, often midnight, five days a week and also Saturdays and Sundays. I got nowhere. I was supervised by one of Sydney's postdoctoral fellows named Robert Munro. I used an in vitro protein synthesizing system and used it over and over and over again, but I got nowhere. I couldn't get any increased activity. Namely, there was no more protein being synthesized no matter how much I purified this alleged peptide bond synthesis factor B using every purification method known to the MRC, where they had Fred Sanger who was of the very best protein chemists in the world. Nothing worked. In retrospect, had Sydney Brenner listened to me, he might have won his Nobel prize many years before Thomas Cech won his in 1989 because peptide bond synthesis factor B wasn't a protein; it must have been RNA.

ZIERLER: Now when you say, "had he listened to you," were you in a position to really tell him what was going on? Would he have listened to you?

EATON: No, because he was too intimidating. As I said, I would tell Robert Munro, who would tell Brenner. All he had to tell Brenner was that I wasn't getting any increased activity in this in vitro synthesizing system. Although Sydney invited me to his home for cocktails and parties, he never talked to me about exactly what I was doing. I was scared to tell him what I was doing. I was doing what I was told to do, but just wasn't getting anywhere. I guess he thought, I was a nice medical student from Philadelphia but not very good at research. He liked me, because he knew that I suggested him to be the keynote speaker at my medical school graduation when he was “Mr. Super Famous.” He came and I was his host. Also, I met him on several occasions over the years at scientific meetings, and he always set aside time to talk to me. I could have won him his Nobel prize. Of course, I didn't know what was going on, but he could have figured it out.

ZIERLER: Bill, I'm curious the process where you decided to stick it out in medical school. You mentioned that Penn was supportive of the idea of medical students going into research. So how did all of that play out? How did you not simply switch into a pure PhD, scientific research program?

EATON: Well, I thought that having started medical school, and having completed two years, that it would be, I thought, stupid not to finish and have this degree, which as I said earlier was a ticket, because you could do anything with a medical degree. You could do research with a medical degree. You could sit back and review insurance claims (laughs) and still have a good income. The world was open to you to do so many things. It was clear after the summer in Cambridge that I wanted to do research as a career, but I went through with the painful process of all the clinical training. I had a big setback in my senior year. I was supposed to have 24 weeks, almost half of the year for electives to start my PhD thesis, so I was one of the first, not ***the*** first, but maybe the second or third so-called MD-PhD student at the university. Biochemistry was the only one subject that I was good at in medical school because it was the only subject that interested me a lot. I didn't like anatomy. I didn’t like pathology. I didn't like pharmacology. I didn't like physiology. But I did like biochemistry. On rounds in my third year, there was a hematologist named William Williams, who wrote the hematology textbook that many medical schools used. He thought that he knew a lot of biochemistry. But I thought I knew more than he did. I would ask him difficult questions and he got fed up being embarrassed by me by not being able to answer my questions in front of the other medical students. So, he went to the dean, who was a PhD - the only PhD Dean in the history of the medical school, Sam Gurin, a nucleic acid biochemist, and told Gurin that the medical school should not be graduating people like me without adequate clinical training. So instead of working in a physical chemistry laboratory for a PhD, I was sent off to the Presbyterian Hospital in West Philadelphia to do 12 weeks of surgery, holding retractors in the operating room, sewing up knife wounds in the emergency room, and taking histories and physicals for another 12 weeks in the Department of Medicine. So, I graduated from medical school with nothing done towards my PhD, even though I was supposed to be an MD-PhD student.

ZIERLER: Looking back, Bill, was that clinical experience valuable in retrospect?

EATON: Yes. Yes, it was very valuable.

ZIERLER: How so?

EATON: For many reasons. It actually was part of the motivation for me going into research on sickle cell disease. I think that was the big payoff of going to medical school. Also, the medical school had just started a new fellowship program. I think I was the first or one of the very first fellows in this program. It was called the Pennsylvania Plan to Develop Scientists in Medical Research. This was another inducement to get medical students to become scientific researchers. I went to the dean, who told me to go right directly for the PhD. He told me not to take an internship, because if I took an internship I would be subject to the doctor draft. And if I didn’t take an internship, I wouldn't be drafted because I was not a licensed physician. So, I took his advice and I immediately entered graduate school. I remember going to the chemistry department, thinking I would do my graduate degree in chemistry, and spoke with a professor who was an author of a quantum mechanics textbook. Hank Hameka was his name. He may have been chair of the chemistry department at that time. I said that I was just about to graduate from medical school and I wanted to know what I would have to do to go to get my PhD in chemistry. He didn't even want to discuss it with me. It was this prejudice that faculty had against pre-meds at Penn. He knew that I was a pre-med with a major in chemistry but didn't know anything about my academic record in chemistry. I was by far the best student in physical chemistry as an undergraduate. He just sort of laughed at me and said, "Oh no, this is way beyond what you could possibly do," because I was coming from a medical school. So, I entered a program called molecular biology. The program was designed for people who had gone to medical school, because they accepted all basic science credits from medical school. I only had to take one required graduate course. I audited several in the chemistry department. I audited quantum mechanics, I audited statistical mechanics, I audited thermodynamics, but I didn't have to take any for credit. This enabled me to spend most of my time in my first year as a graduate student doing research instead of taking courses and studying for exams. It was to a great advantage to get a PhD in molecular biology, even though I ended up working in chemical physics for my PhD.

ZIERLER: How much, in terms of infrastructure, how much involvement was there with the medical school after 1964?

EATON: In terms of infrastructure... I'm not quite sure what you mean.

ZIERLER: Were you working there at all? Were you interacting with your colleagues in the medical school?

EATON: No. Not at all. In fact, I was a maverick in medical school, because most medical students who did research or went into an MD-PhD program, where they did their degrees in pharmacology or biochemistry or neurology or whatever. Whereas I was working in a chemical physics group in the solid-state physics research building. Actually, I started out doing thermodynamics with a physical chemist, Philip George. I did that for about a year, doing calorimetry and potentiometry. During that period, I became friendly with an assistant professor named Alan Adler, who was friendly with an associate professor named Robin Hochstrasser, a spectroscopist. The two of them were friendly with a statistical mechanic named Joe Higgins. These three young faculty would gather every night at the Deck bar next to the university campus to have a beer. I became part of the group. This was another wonderful part of my education. They would argue every night. Alan Adler arguing that the only useful theoretical subject is thermodynamics, because it's the absolute truth. Robin Hochstrasser would claim that quantum mechanics was most important because Schrödinger's equation explained everything in principle. Joe Higgins would explain that statistical mechanics was most important, especially if you wanted to understand any molecular system, because the world is governed by Boltzmann. They would argue back and forth, so I learned a lot about quantum mechanics, statistical mechanics, and thermodynamics in the bar. Then one evening, Robin Hochstrasser actually took the time to ask me what I was doing. I told him that I was working on a protein called cytochrome c, and that because of my being able to make beautifully purified cytochrome c, the leading cytochrome c biochemist, Emanuel Margoliash from Northwestern University, who became a friend of mine, gave me a very large single crystal of cytochrome c, a big, beautiful, black crystal. When I told Robin that, his eyes lit up and he said, "We have to look at its optical spectrum." So, at midnight, and a little bit drunk, we went to his laboratory. He basically took a Leitz polarizing microscope, turned it on its side, took out the ocular, put some lenses in front of it, used the microscope source as a light source, focused the light into a spectrometer, and took an image of this crystal in the near-infrared spectral region in plane-polarized light. It was black in the visible. It was a rather crude experiment, but I had told him that there was an optical absorption band at 695 nanometers, where the crystal would be much more transparent, that was sensitive to the structure of the protein. He came out of the darkroom after developing the plate, and he said, "Your 695 band is z-polarized. We've made a discovery!"

ZIERLER: Wow.

EATON: I said, "What are you talking about? What's z-polarized mean?" He said, "That means the transition moment direction is perpendicular to the plane of the porphyrin ring. This is incredible!" He was very excited. I said, "Robin, what's a transition moment? I don't know what that is." He said, "Come on, it's the integral over the electric dipole of the wave functions. What's the matter with you?" I said, "I don't know what you're talking about, Robin." I didn't know anything about transition moments. Two weeks later, Robin mesmerized the audience at an international biophysics meeting at Britton Chance's Johnson Foundation talking about the z-polarization of this 695 nanometer absorption band with the same charisma as a Sydney Brenner. He just wowed the audience with his obvious brilliance. Robin made molecular spectroscopy sound to me like the absolutely most exciting field of science.

ZIERLER: Did he have as high opinion of himself as Brenner did?

EATON: Robin? Yes, he did. He did. He said that I should come to his laboratory. I got the word "Stone Age" from him. He told me that doing calorimetry and potentiometry was stone age science. I should come to his laboratory, where I could do a great PhD thesis in molecular spectroscopy by building a proper microspectrometer and measuring polarized absorption spectra of single crystals, which I did. That was my PhD thesis. I was Robin's first student working on a biological problem.

ZIERLER: Did you feel that you needed to learn more quantum mechanics in order to complete the dissertation?

EATON: Oh yeah, I had to. I actually had a little molecular orbital derivation in my thesis and became very involved with quantum mechanics, especially crystal field theory in my first years at NIH. I found myself studying group theory. The only thing I regret as a graduate student is that I spent all of my time first studying thermodynamics with Philip George and then quantum mechanics and group theory with Robin. What I should have been studying the whole time was statistical mechanics, because useful theory in biology is statistical mechanics. You've got to get the thermodynamics right, even though it is just bookkeeping. It's not really the science. The science is all in statistical mechanics. Biological physics is all about statistical mechanics. So I had to learn it as an adult, but got lot of help from my colleague Attila Szabo, who is brilliant at statistical mechanics.

ZIERLER: Who I might add, Attila is the only person in my whole project who has refused to talk to me. So the legend of Attila only grows.

EATON: (laughs) I see. Attila doesn't like to do things that normal people do.

ZIERLER: (laughs) Right. I've been told not to take it personally.

EATON: He refuses to take graduate students, even though he's a fabulous teacher. He refuses to give talks, even though he gives fabulous seminars. He will not go to a meeting to give a scientific talk. He always has to make up some reason why he's using government money to go to a meeting when he's not invited to give a talk. So, he gets people to invite him to chair a session, and then often finds someone to replace him as chair when he gets there. (both laugh) Yeah, he is an unusual guy. I'll see him today at two o'clock, we're going to play tennis today.

ZIERLER: Bill, when you were finishing up your dissertation, did you know that military service was on the horizon? Was that a surprise to you, or you knew this was coming?

EATON: No, that was a shock. It was the big shock.

ZIERLER: The shock. The shock of military service.

EATON: Yes, it was in the fall, I guess it was around September of 1967. I had been in Robin

Hochstrasser's lab for about two years and did collect a large amount of data. I got my draft notice. So I went to the draft board and spoke to this middle aged, mean spirited bureaucrat and told her that I'm not a physician, “I'm a scientist, so why am I in the doctor draft”? She opened up this big, thick book and read the draft law. She said, "Do you have a Doctor of Medicine, Dr. Eaton?" I said, "Yes, I do." She said, "You're drafted." It turned out that one of my classmates ignored his draft notice, because he also didn't take an internship based on the advice of our dean, who had obviously misled us. Otherwise I would have done something like an internship in pathology for a year. My classmate was arrested by federal marshals and drafted into the army. Because he ignored his draft notice, he was punished by spending two years in a boot camp in Georgia teaching corpsmen how to do blood smears. That's what he did for two years.

ZIERLER: Wow.

EATON: So even though this bureaucrat was mean-spirited, I asked, "Is there some way I can do something else to do research?" She said, "Well, there is an organization called the United States Public Health Service, and they do research. Why don't you see if you can join the Public Health Service?" I said, "Where are they?" She said, "Well, they actually have an office on Front Street in Philadelphia." So, I went to Front Street where there was this little office and these two guys dressed in what looked like Naval uniforms, but were a bit shabbily-dressed. They were quite friendly. They told me about the Public Health Service, and said, "There's a place called the National Institutes of Health. It's very difficult to get into; everybody wants to go there, but if you can get in you can do research there. First you have to pass an exam to get into the Public Health Service." So, I came back the next day to take the exam. It was a multiple choice exam and I did horribly. They said, "You barely, barely passed." I had flushed all information about infectious diseases out of my brain. Their job was to prevent people from coming into the country with infectious diseases, even smallpox in those days. That's what the Public Health Service did; they inspected people. Philadelphia was a major seaport then. They would inspect all the sailors coming off ships to make sure that they didn't have any infectious diseases that they could transmit. So, the question was, how to get a job at the National Institutes of Health?

ZIERLER: Had you ever heard of the NIH before?

EATON: Yes, I had been there once, actually, two years previously, to do some experiments on calorimetry with Philip George. We actually drove to Bethesda and went to the laboratory of a guy named Robert Berger, who was an instrument developer, to use his calorimeter. It was a really horrible-looking lab that we went to, and the atmosphere of the place seemed depressing. His lab was in this huge building, Building 10, the clinical center, which is a very dismal-looking building. Fortunately, Philip knew one of the well-known NIH scientists at that time, Gary Felsenfeld, who was a student of Linus Pauling. Felsenfeld told Philip that he was no longer doing physical chemistry or spectroscopy, but there was a spectroscopist, Elliot Charney, who might be interested. Philip contacted Elliot, and I went to Bethesda for an interview. Elliot immediately accepted me as a postdoctoral fellow. That was one of the great breaks I got in life. I didn't have to compete to become a Research Associate, where you had to take a medical exam, which I might have failed. (laughs) 1968 was the age of Vietnam. The NIH developed as a great research institution because of the MD's that went there during the Vietnam War. The smartest medical researchers in the country, rather than go to Vietnam, wanted to go to the NIH and had to compete to get in there. The Research Associates program was incredibly competitive. A lot of the most famous scientists you hear from the NIH came through the Research Associates program.

I left Philadelphia on January 15th, 1968, and took a rare right turn onto the New Jersey turnpike instead of a left to go to New York, and drove to Washington. I've been here ever since. It really was a great break. Interestingly, I never had to make any difficult decisions about my career. Whereas most people have to make decisions about whether to do this or do that, I basically ended up landing on my feet by going to a place, which was perfect for me.

ZIERLER: So this was actually pure serendipity?

EATON: Yes.

ZIERLER: I mean, looking back, probably-- What were you thinking about your next move anyway? I mean, imagine an alternative scenario where this draft notice never came up. What were you thinking was your next move?

EATON: No one in Robin's lab, when they heard I was going to the NIH, ever heard of the place. They just knew that it was a federal research institution and federal research institutions at that time had very bad reputations. The researchers in these places did unimportant research. (laughs) So Robin's group felt sorry for me. I and they always thought that, because Robin was well-connected with the top spectroscopy labs in the world, that I would go off to do a postdoctoral fellowship in a major research university, and then have a career in academia. Didn't work out that way.

ZIERLER: No. (laughs) So at what point--

EATON: So it's interesting, he said that--

ZIERLER: At what point at NIH did you say to yourself, "You know what? This is pretty good. This could have been the best-case scenario even without the draft."?

EATON: Yeah, I guess that was the case. I did two years in the Public Health Service, and now it was time to move on, and the question is what to do? A year earlier, after just one year there, I was offered a permanent position by Elliot Charney. He was impressed with what I was doing with circular dichroism, micro-spectrophotometry, molecular spectroscopy, and crystal field theory. I sort of laughed it off. The lab, except for Elliot and two other people, was a second-rate research lab, or even third-rate. I didn't see myself having a career there. It was in late '69, early '70 that I was looking for a position at a university. I was having no luck at all because there was, I don't know if you remember, a big recession at that time. Universities weren't hiring at all. I remember that there was only one university looking for somebody in biophysics at the time, the University of Minnesota, and I did send an application there. It was a stupid application, I guess, because I never got any response from them. I was crying on the shoulder of a close friend of Elliot, a very smart geneticist named Marty Gellert, who discovered important enzymes involved in protein transcription. He said to me, "I thought you really liked the life of research from what you've told me about being at the MRC with Crick and Brenner. Well, let me tell you something. The NIH, maybe not your lab, but the NIH as a whole is the best place in America to do research. So if you want a career in research, why don't you just stay?" That had a huge impact on me, because I was in my early 30s, and he was in his 40s, and already ka very successful scientist. I said, "Well, if it's good enough for Marty Gellert, then it's good enough for me." So I decided to stay, and I only thought of leaving once after that.

ZIERLER: Did it occur to you even from the beginning, all of the benefits of just not having to deal with grant writing all the time? Was that an immediate attraction?

EATON: No, I didn't think too much about that. I knew that people at universities had to spend a lot of time writing grants. I think it was because I was not that interested in teaching, and I knew that people had to spend a lot of time teaching. Although, of course, at the major research universities, they hardly did any teaching. I didn't know that at the time. I thought that at a university as a professor, you had to teach. So I only seriously considered leaving once. And that was when I was offered the position to become head of biophysics at Harvard. Which is an interesting story.

ZIERLER: When did that opportunity come about?

EATON: I gave a biopolymers Gordon conference lecture in 1974 on my research on sickle cell disease, and it was a very good lecture. As a result, I was invited to give a seminar at Harvard that fall and a week earlier, at Princeton. I like to tell people the difference between Princeton and Harvard by the introduction that was given prior to my seminar. The introduction at Princeton was given by John Hopfield, who was later president of the American Physical Society. He's still probably one of the most famous biological physicists today. John introduced me to the audience at Princeton. This was the physics department at Princeton. He said that, "Bill Eaton did his undergraduate degree at the University of Pennsylvania. He did his medical degree at the University of Pennsylvania and he even stayed there long enough to do a PhD." The whole audience laughed. "And then he went to the NIH, where he is now a Commander in the United States Public Health Service." Stony, reverent silence. The next week, I was introduced at Harvard by Walter Gilbert.

EATON: Gilbert was a famous theoretical physicist. He was at the 1974 Biopolymers Gordon Conference, where we went out on a little sailboat together. He explained to me why he went into biology. Gilbert told me in this boat that he left physics because he couldn't compete with Gell-Mann. He said Gell-Mann was a singularity.

ZIERLER: Right.

EATON: There was no way he was going to succeed in a field where Gell-Mann worked, so he decided to go into biology. But he realized that the most important problem in biology was a chemistry problem, which was to figure out how to sequence DNA. He looked at that as the Holy Grail. Crick and Watson had solved the structure of DNA, but to be able to determine the nucleotide sequence of DNA, to him, was the most important problem.

He introduced me by saying, "Bill Eaton did his undergraduate degree at the University of Pennsylvania. He did his medical degree at the University of Pennsylvania, and he stayed at the at the University of Pennsylvania to do his PhD." No response. "And now, he's at the NIH, where he's a Commander in the United States Public Health Service." Laughter.

ZIERLER: Right.

EATON: I told that story at a seminar at Johns Hopkins. I didn't get a smile out of either story, neither the Princeton story nor the Harvard story.

ZIERLER: They didn't get it.

EATON: That's my description of Johns Hopkins. They didn't smile at either one. In any event, I was invited to be a visiting professor at Harvard in the spring of 1976 to share teaching a course in physical chemistry. It was a senior undergraduate, first year graduate course in physical chemistry with Stephen Harrison. He taught statistical mechanics and structural biology, and I taught kinetics and quantum mechanics. We didn't do any thermodynamics since it was part of the statistical mechanics. I remember my first lecture was a total disaster., That evening I had dinner at one of the college houses, where one of the undergraduates sat down next to me and explained that Harvard students want to have their lectures spoon-fed to them. He said what you have to do is go slowly and carefully and write everything down on the blackboard. They'll like your lectures much better. For my next lecture I decided to spend a lot of time and I worked like hell on it. It was a lecture describing the difference between classical theory and quantum theory. And it actually was a pretty smart lecture. I wrote it all out on a blackboard the night before. I kept a scoreboard. I called it the Quantum-Classical Scoreboard on what classical mechanics could explain and what quantum mechanics could explain. Each would get check marks. Quantum mechanics won, and I actually got a round of applause, which is what they did at Harvard. I don't know if they still do it today. At that time when you gave a good lecture, the Harvard students actually applauded. German students knock on their desks. I think I ended up giving 16 lectures and remember getting applause on more than half my lectures. I recall the head of the biochemistry department coming to me and saying that, "I hear you're giving really great lectures. You must be working hard." He said, "These students are not worth it; you shouldn't be working so hard on these lectures." Then at the end of the semester, Martin Karplus asked me whether I was interested in joining the faculty at Harvard. This happened right after I gave a really good lecture, or what I thought was a really smart lecture. The thing I liked about Harvard was it was fun to lecture to smart students. I changed my mind a little bit about teaching, because I remember a student asking me what I was talking about in quantum mechanics. I was telling them about time-dependent perturbation theory of absorption and induced emission. An undergraduate raised his hand. Undergraduates rarely asked questions because they don't want to sound stupid in front of their colleagues in case the professors made some nasty remark to them. I remember a student raising his hand, and saying, "Is that similar, absorption and induced emission? He said, "Are they really similar?" And I said, "Yeah, that's a very smart question. I guess you must have recognized that all you do is exchange the states in the energy difference in denominator, and you change one theory to the other." It was this kind of thing that I really enjoyed.

One of the things I did in a special lecture at the end of the semester to the physical chemists, where I again talked about my research on sickle cell disease was telling them about exponents. I told them that the concentration-dependence of the characteristic time, the delay time, depended inversely on the 30th power and that it depended on the 28th power of the solubility, but they're really the same. So I remember going to the blackboard, and writing, "Let 28 = 30." The audience laughed, because they thought this was kind of clever. That's what I really appreciated, that you could make a mathematical statement like "Let 28 = 30," and people thought that was amusing. I thought it was amusing at the time. There was a lot of laughter in the audience when I did this

I didn't hear anything for about four months later. Arthur Solomon, who was the head of the biophysics graduate group, was retiring. It wasn't a department, it was a graduate group that granted PhD's. He told me that there were faculty from applied physics, biology, chemistry, all the different science departments, and they called themselves the graduate group in biophysics. He said, "The graduate group had unanimously selected you to become the new chair of biophysics, and it goes with an appointment in a department. The physical chemists in the chemistry department are offering you a full professorship." I said, "Wow, but I have to think about it. It's a big change to move my family from the NIH at this point."

ZIERLER: And how long had you been at the NIH?

EATON: This was 1976, I'd been there for eight years. The next morning, before I even had chance to discuss it with my wife, Solomon calls me, "I'm sorry, I have to take the offer back. Apparently, the organic chemists were not consulted, and they didn't like the idea that the physical chemists were making an appointment of a professorship in the chemistry department without their knowledge. So, they want you to come back for an interview." I went back in February of 1977, to be interviewed primarily by the organic chemists. I had lunch with Karplus and Bill Klemperer and in the morning I talked to a guy who became my good friend. He was George Kistiakowsky, who told me "knock 'em dead Bill." Do you remember the name Kistiakowsky?

ZIERLER: No.

EATON: George Kistiakowsky was Eisenhower's science advisor.

ZIERLER: Oh, okay. Okay.

EATON: He was the guy who taught the physicists at Los Alamos how to ignite the atomic bomb. He was an explosives expert. And the physicists had this bomb, but had to somehow ignite it. Kistiakowsky went to Los Alamos to teach them how to set off this atomic bomb. He became very famous for that, and he loved to tell me how he was as smart or smarter than the physicists there. "Kisti", as he was known, was also a pretty confident guy. He and I became good buddies because as a retired professor he sat alone in his office on the second floor of Gibbs and I was one of the very few people who ever came to talk to him, which I did almost every day, at least for a little while. He had fabulous stories to tell when he was science advisor under Eisenhower.

At four o'clock, I went to give this seminar. It was not in Mallinckrodt, which was the lecture hall in the basement of the chemistry building that I was quite familiar with. It was in a brand new building called the Biolabs. It had only been completed about six months earlier, and the chemists had never held a seminar there before. The seminar was at four o'clock. I started the seminar with a brief introduction, asked for the first slide. The bulb burned out.

ZIERLER: Not a good sign.

EATON: Not a good sign. So even though there were some famous experimental physical chemists sitting there, they didn't know how to change a bulb in a projector. It took them about ten minutes. I just waited and didn't say anything because I expected to have my slides back up to continue the lecture in just a few minutes. They finally got the bulb out, but they didn't know where to get a replacement bulb. So, they sent a graduate student running back to the chemistry department to get a replacement bulb. The student never came back. Now it's about 20 after 4, and I said, "Okay, I've transparencies with me. I'll write on transparencies. Does somebody have an overhead projector?" But they were in the Biolabs. They sent off another graduate student to the chemistry department to find a projector. That graduate student never came back. Now it's 4:30. No slide projector, no transparencies. It was almost all data that I wanted to show them - new data that the physical chemists hadn't seen, because I didn't want to give exactly the same seminar. So I said, "Okay, I'll do it on the blackboard. Where's the blackboard?" I'd become a skilled lecturer in Mallinckrodt giving lectures on the blackboard. Somebody mentioned, "Well, there's a whiteboard behind the screen." So, I went over, turned the switch to raise the screen. The screen wouldn't go up. So, no whiteboard. I said, "You know, I am finding it difficult to give a lecture" An aside for a moment. I heard Perre de Gennes do it. In fact, one of the most brilliant lectures I ever heard was listening to de Gennes describe how without a single slide he thinks DNA gets into cells. Unbelievably brilliant lecturer. After the lecture, I said to a French theoretical physicist friend of mine, "This guy gave the most eloquent scientific lecture I ever heard in the English language." His response was, "You should hear his lectures in French."

ZIERLER: (laughs) That's great.

EATON: Anyway, it's now 20 of five, and students are roaming in. Unbeknownst to the chemists, at five o'clock there was a major undergraduate biology course. Many students typically come in early, chat with their friends, so there was noise. The room became noisy. I couldn't go on. I said, "I give up" and walked out. I simply walked out of my Harvard job interview seminar. My last meeting of the day was with the major organic chemist, in terms of the politics of the department. His name was Frank Westheimer, famous for the influential Westheimer report in chemistry. I sat in his office for an hour. He talked non-stop for one hour about the experiments he was doing and how wonderful they were. Here was I sitting there as somebody interviewing for a full professorship in chemistry, looking down at my feet the entire time, glancing up only every once in a while, not asking a single question, and totally discombobulated from this horrible experience that I just had of never giving my interview lecture. There was no offer from Harvard. I never heard from them again. Not a word from anyone to this day.

ZIERLER: That sounds like a-- Right. You know, whether you believe in a higher force or not, it certainly sounds like this was not meant to be.

EATON: It's interesting that you mention that, because my wife has often told me it would have destroyed our marriage. The way I describe some of the faculty that I knew there was that they ate each other's bones for breakfast. Students from one group were not allowed to talk to students from another group, for fear that they may give away some secrets. The faculty effectively competed with each other.

ZIERLER: It sounds like you couldn't come up with a more perfect opposite of the environment and culture at NIH.

EATON: Exactly. One of my first experiences at the NIH was walking into the laboratory of a man named Harry Saroff and asking him if I can borrow some potassium ferricyanide. He looked at me and growled, "Don't you ever come into my laboratory again and ask if you can borrow some chemical. Next time you walk in here, you just say, 'Harry, where's the potassium ferricyanide?'" That was the culture of the place then, and that still is the culture. It's a place where people help each other and rejoice in the success of their colleagues. When I first came to the NIH, everybody was so friendly that I was a bit paranoid, because I had come from this hostile-aggressive Northeastern university. I describe the NIH as the optimum of the intellectual aggressiveness of the North and the civility of the South.

ZIERLER: Nice. Well Bill, on that note, and looking at the clock, why don't we hit pause for now and we'll discuss a round two. How does that sound?

EATON: Yeah, I think so. I really do have to attend this meeting.

ZIERLER: Okay so I'll hit end here.

ZIERLER: Okay. This is David Zierler, oral historian for the American Institute of Physics. It is June 16th, 2020. I'm delighted to be back for round two with Doctor Bill Eaton. Bill, thank you so much for joining me again.

EATON: I pulled up a couple of documents. I don't know whether you can you let me share the screen?

ZIERLER: Absolutely.

EATON: Let me tell you the story first. Remember I mentioned that I had this physics professor at Penn with whom I worked, who did radiation biophysics with yeast. He wanted me to go to graduate school in physics instead of going to medical school. When I arrived at the NIH on January 15th, 1968, I brought my box of books into the lab with me on my first day and on the front door of the laboratory that I was going to work in, it said "Frederick S. Brackett." I wondered if that's the Brackett I remembered from my atomic physics course. So looked at my atomic physics textbook, which was this course I took with Wood as a senior and I looked it up. So, I knocked on the door of the inner office and opened it. There was this elderly gentleman, he was only a few years older than I am now, sitting at a desk. I introduced myself saying that I was the new postdoctoral fellow with Elliot Charney, and I'm pleased to meet you. "Are you in fact the Brackett of the Brackett series?" He acknowledged that he was. We had several conversations about it afterwards.

ZIERLER: Now that was an innocent question, Bill? You weren't really sure if he was the same Brackett, or you knew?

EATON: No, no. He said he was the Brackett of the Brackett series. I just asked him whether he was the same, because he had the same initials. My atomic physics book just had F.S. Brackett, and he was Frederick S. Brackett. I asked him to tell me the story about his discovery.

ZIERLER: As much as-- I got mine too. I'm just iced. We're on the same page.

EATON: His series was the first series after the Bohr atom. That's why it's one of the most notable series of all the series, you know, Lyman, Balmer, Paschen, Brackett, Pfund. Brackett's was not empirical. Bohr predicted that you would see emission from a hydrogen atom if you looked in the near-infrared for the n=5 to 4 transition. Brackett built a near-infrared spectrometer, which was no mean feat, because it was necessary to build an achromatic lens system, so as the wavelength, was varied everything would stay in focus. Second was, and this part I'm not sure of, that he had to build a new kind of detector. I think he built some variation on a lead sulfide detector. But I'm really not sure of that. I have his paper and I should dig in there to see what he said about it. In any event, when he finished his PhD, he was told by his supervisor that he should not put the quantum interpretation in his thesis, because the head of the department at Hopkins physics at the time, R.W. Wood, who was a great experimentalist in optics, didn't in believe Bohr's theory.

ZIERLER: And how outlandish was this at that point, not to believe in quantum theory?

EATON: Maybe. it wasn't that outlandish -- there wasn't quantum mechanics yet, because it was 1924. It was before Schrödinger and Heisenberg. I'll show you the original paper. Hopefully I have it here on my desktop showing somewhere. Oh ratty rats rats rats. I have to close.

ZIERLER: Take your time.

EATON: It's a really interesting story. When I told Dudley Herscbach this story, the guy at Harvard who won the Nobel prize, he said I should publish it. Brackett went off to Berkeley to teach physics. I remember him telling me that he had some pretty smart students. He remembered this kid, E.U. Condon. (laughs) G.N. Lewis, the famous chemist, would send his students to Brackett's course to learn about quantum theory. Brackett also got these super smart chemistry students. He only stayed at Berkeley for about three years, and then came back to Maryland. I haven't been able to document it, but the legend in the lab was that during the first World War Brackett took a captured German set of binoculars and used it to teach Bausch and Lomb how to build similar binoculars. During the First World War the Germans had much better binoculars and could see the whites of the eyes of the Americans, while the Americans couldn't even see the Germans. This is why he taught Bausch and Lomb how to build binoculars that were used in the first World War. In the Second World War, he was working on bomb sites, and at one point was almost arrested because developing bomb sites was a secret of the second World War. Somehow Brackett got involved with a government contractor and was building a really super bomb site. After the war, he came to the NIH and he's probably the responsible for physics at the NIH. He didn't do physics at the NIH but became a photochemist and also did not do much photophysics.

The much more interesting part of the story is that he immediately knew when he was about to finish his thesis that he could also measure the next series, to n= 5. His PhD supervisor told him, "No, Fred, leave that for another graduate student." The next year, he picked up a paper by Pfund on the n = 5 series. Pfund was his supervisor. What Pfund apparently did was go into the laboratory and basically use Brackett's instrument to discover the Pfund series. It really should have been the Brackett-Pfund series because it was Brackett's instrument and Brackett's idea. I have a reprint on my desktop, if I could ever pull it up. I'll send you these papers, because I think it's interesting. There's a little bit of research to be done. This is the Pfund paper. Can you see it now?

ZIERLER: Yes.

EATON: So, this is September 1924. Brackett's first paper was published in Nature in February 1922. It looks to me like Pfund's paper could have been a cover-up, because Pfund even starts out the paper by saying... "It's a preliminary note on the results obtained from a study of the infrared emission of the above gases, nitrogen and hydrogen excited to luminosity in a vacuum tube and studied by means of a rock salt spectrometer and a vacuum thermopile." The

rock salt spectrometer vacuum thermopile was Brackett's. Pfund doesn't even acknowledge Brackett in his paper. All he says in the paper is, "For the study of hydrogen, the same apparatus was used. Both spectrometer slits, however, were widened. In consequence of the smaller dispersion and greater thermopile sensitivity and general sensitivity several times as great as that employed by Brackett was obtained." Then he goes on to say, "A qualitative survey of the spectrum revealed the prominent Paschen and Brackett lines. After much labor, the tube was finally brought to the black stage, and the region between 5 and 10 microns was explored for new lines." So what he's saying is that he could see the Brackett lines, but he had to bring the tube to the black stage described by R.W. Wood before he could see the Pfund series. That could be the cover-up line. One would have to study the papers to see if this is what he made up so he could claim the series was his, and that Brackett's instrument could have never seen the transition to n = 5. I'll send you these papers.

ZIERLER: Great.

EATON: But you may have to get an expert on (laughs) thermopiles or something to figure out what the truth is. I think it's really worth investigating whether Pfund stole the series from Brackett.

ZIERLER: Okay. I'm well-positioned for that kind of investigation. That's great.

EATON: Okay, so that's the end of that story. And I can stop sharing now. All right, I'm back.

ZIERLER: Okay.

EATON: So that was the beginning of my first day at NIH.

ZIERLER: What a way to start. (laughs) So let's pick up the narrative from where we left off last time, which is you had that perfect storm at Harvard where the universe told you clearly this wasn't meant to be, and you head back to NIH, and then that's where you decide to stay.

EATON: I think what happened was that I was highly motivated because I was surrounded by a rather mediocre group of scientists. There were few good scientists there. Ted Becker was a good scientist, Elliot Charney was a good scientist, and Ira Levin was a good scientist.

ZIERLER: Ad Bax wasn't there yet, was he?

EATON: No he wasn't there yet, no. I decided, screw Harvard. I can build a better biophysics group at the NIH than they have at Harvard and I set my mind to that. I actually did it!

ZIERLER: Now, did you think that Harvard was the gold standard in terms of what the biophysics group was at the time? And that's what your measuring stick was?

EATON: Maybe. The University of Michigan had the first biophysics department, and I never really made any comparisons. It was just my personal experience, that I will show those guys that they made a mistake. I'm going to be the head of a department, and this is what I can do. My first hire was in 1981. I was not chief of the lab yet. I got a phone call from Martin Karplus, who told me about his student, Attila Szabo, who just didn't get tenure at Indiana. He said that Attila was the smartest graduate student he ever had and that I should I hire him. We didn't have any space at all in the building, but I convinced Gary Felsenfeld, who kept chickens in a cage near the loading dock, that his area could be renovated to make an office for Attila. Gary agreed and moved his chickens elsewhere. Attila came and gave an interview seminar. It was an hour and a half, a bit overdone. He seemed like a pretty neurotic guy, which he remained to be but in a lovable way. I arranged to have him offered a job, which he accepted. That was my first great hire. Attila has a fantastic personality, which made him a great help in recruiting other people. I became the lab chief for first time in 1983. We had a rotating lab chief system, and I was the acting lab chief that year. Ted Becker, who was the chief of the laboratory from 1972 to that time had become Director of the Office of Research Services at the NIH and retired from his position as lab chief and cut back almost all of his research. When he left he wanted to be replaced by another NMR spectroscopist. He wanted me to hire Regitze ("Guida") Shoup, who was a postdoc with him, and actually a friend of mine. Guida was a very nice Dutch lady who went to California with her husband. They wanted to come back to the East Coast. The way the NIH worked in those days, there were no searches; if people did well and their supervisor liked them, they would be offered a permanent civil service position. That's the way federal laboratories operated. But I rejected Ted's idea, not because I didn't think Guida was good, but because I thought we could get somebody better. So, I decided to start an international search, which is the way every science position, non-tenured and tenured science, is handled these days. I believe I did the first one in the history of the NIH. We had lots of applicants. One of them was a guy named Geoffrey Bodenhausen, who was also a friend of Ted Becker. A very smooth, rather sophisticated NMR guy, also Dutch. He was considered one of the top guys in NMR at the time. He was thinking of moving to the US and applied for the job. We interviewed him. Ted had a nice cocktail party for him at his home and all the tenured scientists in the lab talked to the him. He was impressive. Then we had this young guy, Ad Bax, come for an interview. At that time Ad was 26. I was enamored with him because of a couple of things. One, I never saw such fantastic recommendation letters, especially from the Oxford, where letters are always very understated. One guy, Ray Freeman, said that Ad Bax would become a star in science if he didn't kill himself. Ad would race bicycles up mountains and then down mountains at very high speed.

ZIERLER: (laughs) Right.

EATON: He did crazy things. He still does it today. He doesn't race down mountains today, but his cyclist daughter Christina might. In any event, he interviewed. I'm dyslexic for magnetic resonance and hardly understood a word he said, that is in terms of real understanding. But I did understand one thing. I knew, this kid knows what he's talking about.

ZIERLER: And did you know, Bill, at that time that NMR was going to become such a big deal for NIH?

EATON: No, because I was fed up with the type of NMR that was going on at the NIH. People did only one-dimensional NMR, which is all they could do in those days. They would do experiments such as titrate histidines and determine PKs of individual histidines in a protein, which you could do, even though proteins are big with many histidines because the histidine resonances are well-separated and their chemical shifts change when the histidine binds a proton. So, you could actually get a very nice individual titration curve for all the histidines in a protein. The people who used the spectrometer didn't seem to know very much of the physics of NMR. This is why I was impressed with this guy Bax. He obviously had a deep understanding of the physics. The guy was inventing novel pulse sequences. I found out later he could do pulse sequences in his head. It's may be similar to multiplying Mueller matrixes to come up with algorithms. (laughs) And he would do it all in his head. Ad Bax will dispute this story about our hiring him and Attila is on the fence about it. We had a lab meeting to vote on whom we should offer the job to. Everyone, except me and Attila, voted for Bodenhausen. I forget the details, but Bodenhausen didn't come for one reason or another. So we then offered the job to Ad Bax. Ad was already well-known at that point, because as a PhD student he wrote a book on 2D NMR, which was the first book that was useful for NMR spectroscopists on how to do two-dimensional nuclear magnetic resonance experiments. Ad had several good offers. At that time he was a postdoc at the University of Colorado. I had to figure out how to get him to the NIH. Ted Becker was extremely helpful. He knew the dean at Georgetown University, who got a graduate fellowship for his girlfriend, Ingrid Pufahl, whom he married a couple years later. It was a full tuition fellowship with maybe a bit of a stipend also, I don't remember, to get a PhD in sociolinguistics at Georgetown University. That sealed the deal, I thought, but Ad claims at the very end, he just flipped a coin (both laugh) between the NIH and one other place. So we'll never get the story straight. I know that I was much more impressed with Ad than I was with Bodenhausen, although Bodenhausen was an obviously a competent researcher. Bax was of a different caliber. Now I had the combination of Attila and Ad Bax to help in the recruitment.

ZIERLER: That's a powerhouse team already.

EATON: Yeah, the three of us; we had the nucleus of a good group. (laughs) I guess we could just continue the recruitment story and then come back to the research. So, the next step was in 1986, the congress legislated 8 million dollars for AIDS research. The 8 million was evenly divided between intramural and extramural evenly, which is very unusual because the NIH budget is usually a 9:1 split. 90% goes to universities; 10% funds research on the NIH campus.

ZIERLER: Has that ratio been consistent over the years, or has it changed?

EATON: It varies from institute to institute. In some it is as low as 9%, and in some institutes it goes up to 12%.

ZIERLER:. But that basic disparity, that major disparity is more or less constant?

EATON: Yes

ZIERLER: Okay, interesting.

EATON: This is why at the NIH when times are very bad, things are only a little bit bad, and when times are great, things are a little better. We're buffered by this constant ratio. Resaecrh support goes up and down as it does in the extramural world, but with a smaller amplitude at NIH. The frequency is the same, but the amplitude is much smaller. In 1986, the Director of the NIH was James Wyngaarden and the Scientific Director of the NIH was J. Edward Rall. Wyngaarden asked Rall to find an intramural scientist to run this program who wouldn't have a conflict of interest because he wouldn't be working on AIDS himself. Rall asked me to do it, and interestingly, I think it was in part because I had already been suffering for two years from severe sleep apnea and my research had consequently considerably slowed down. This is a part of my story I don't think I ever told anywhere.

ZIERLER: Sleep apnea is no joke.

EATON: It's not only no joke, it had a huge effect on my scientific career because I was slowing down enormously.

ZIERLER: Did you know? Did you get an early diagnosis? How did you know you had it?

EATON: Oh no, it was one of these things where I kept denying, denying, and my wife told me there's something wrong, there's something wrong but I didn't do anything about it.

ZIERLER: So another MD-PhD who's a terrible patient, is what you're telling me.

EATON: Exactly. I didn't do anything about it until the early 90s. In any event, I took over this program- I'll come back to the sleep apnea in a second - but I knew there was this new development in NMR by Kurt Wüthrich in Switzerland, and I knew from Ad that there was a couple, Marius Clore and Angela Gronenborn, who were Max Planck Directors in Munich, that we might think of hiring using this AIDS money to build infrastructure. The original purpose of my intramural AIDS program was to do structural biology, that is, determine the three-dimensional structure of the HIV, proteins. Ad convinced me that we could use this money to buy spectrometers to determine the structure of the proteins of HIV. He said it could be done by NMR, because it had been done by Kurt Wüthrich. I went to an International Biophysics meeting in Sweden in the fall of '86, where Clore was there. He gave a really impressive talk. I briefly spoke with him afterwards, and then I went back to the NIH, and told Ad, "Yes, this guy's really impressive." So, Ad contacted him and said, "We're going to be putting out an advertisement looking for somebody, and you should apply." So Marius and Angela applied. Thanks to Ad, mainly, and some help from Attila, they quit their jobs as Max Planck Directors. They said they only needed a small group and that they only work with a few people, but in fact they had a huge group in Munich. We could only offer them two postdoc positions. They came anyhow because Marius couldn't stand living in Munich any longer. (laughs) He's Jewish and he married a German, but he didn't like Germany and wanted to leave Munich. So that's how he ended up coming to the NIH. Now we had Szabo, Bax, Clore, and Gronenborn, and the Laboratory of Chemical Physics was clearly the world center for NMR.

ZIERLER: Right.

EATON: We then moved from Building 2 at the NIH, which was a small building, to a larger Building 4 that was completely renovated. We moved there in 1994 so we had space to hire more people and did another search. Ad knew of a scientist at Bell Labs, which was closing at the time. All the top people in Bell Labs were leaving and going to universities. Ad knew about Robert Tycko, who was one of the very top people in solid state NMR, so we thought he would also be looking to leave Bell Labs. Ad asked him to apply for the job we advertised. He applied and we hired him in 1994. Even though we already had three NMR spectroscopists, unlike a university, we didn't have to hire people to teach different kinds of courses. My philosophy, which I adopted from Max Perutz in Cambridge was to hire the best scientists and let them do what they want.

ZIERLER: And it's not like there was any concern that between Bax and Clore and Gronenborn Tycko there was going to be any redundancy in their work?

EATON: No, because solid state NMR is very different than solution NMR.

ZIERLER: Right.

EATON: Later in the 90s Attila was collaborating with a guy in Los Alamos named Gerhard Hummer. Attila had never met Gerhard, but had lots of telephone conversations with him when they were writing a paper together. We thought it was time that we got somebody who was really good in computational biophysics who also did theory, so we asked Gerhard to apply. He did and we hired him in 1999. At that time, we had this strange scientific director Allen Spiegel. Hummer should have been hired with tenure, but Spiegel would not do it. Allen Spiegel had problems as scientific director. He would never listen to anybody. He wouldn't hire Hummer with tenure, but did so after one year, instead of the usual three to five years. Hummer came entirely because of Attila. Another attraction for Gerhard to come was Robert Zwanzig. In 1989 Zwanzig spent a sabbatical at the NIH, also because of Attila, and decided to quit the University of Maryland and move to the NIH. Having one of the top theorists of the 20th century in the laboratory was also an attraction for Hummer. Zwanzig loved to talk to people and Gerhard loved to talk to him. So we had Hummer, Anfinrud, Zwanzig, Szabo, Tycko, Bax, Clore, and Gronenborn.

I should have told the Phil Anfinrud story before Gerhard. I would visit Harvard frequently in the 1980s and 1990sto give seminars and lectures in courses. I stayed in touch with some of the faculty there, especially Steve Harrison, Don Wiley, and Eugene Shakhnovich, because he was an assistant professor and worked on protein folding. At that time, there was an assistant professor at Harvard named Philip Anfinrud. Phil did his postdoctoral fellowship with Robin Hochstrasser, so I knew Phil extremely well from my frequent visits to Philadelphia and his work with Robin, where he did the first femtosecond infrared spectroscopy. I advised him very strongly to no avail not to go to Harvard, because they hadn't given tenure to any physical chemist at Harvard in the past 25 or 30 years, since Roy Gordon. I told, "You're not going to get tenure there, and then you're going to end up at a third-rate university. Why not go to an A- or B+ university rather than go to Harvard, the A+ university and then end up at a C university?" He didn't take my advice. He went to Harvard. Phil is not intellectual type.

ZIERLER: But he's super smart and a really hard worker.

EATON: Yes, super smart, and also a great, great experimentalist. I knew back then that he was a great experimentalist. I asked him to apply and he won the competition and we hired Phil Anfinrud with tenure in 1998.

ZIERLER: You're building an empire here, is what you're doing.

EATON: The next hire was not until in 2012. There's a very charming and very bright scientist in Cambridge named Jane Clarke. Jane had a graduate student named Robert Best from South Africa. She recommended that I hire Robert as a postdoc. Robert had already done lots of beautiful work with her, so I offered him a position, but he also wanted to work with Gerhard Hummer. The deal was that he would come and work halftime for Gerhard and halftime for me. What happened was that he came to the NIH in 2004 and out of the three years he was here, he worked two and a half years with Gerhard and six months with me. (laughs) He did fabulous stuff with Gerhard. Gerhard described Robert by saying: "I would give Robert just a very brief description of an idea, and he'd come back with a completed paper with perfect figures and ready for submission. Robert could turn a few notes into a symphony." My experience with Robert was that I wanted him to do single molecule spectroscopy and to correct errors in some experiments I had done earlier, where I didn't realize that polyproline was not a perfectly rigid rod but a fraction of the molecules could have bends. We made a mistake in our first paper on polyproline, which was Lubert Stryer's "spectroscopic ruler." The first Förster resonance energy transfer experiments were done by Lubert Stryer, a famous biochemist. He used polyproline as a spectroscopic ruler, because it was thought to be a rigid rod and he could attach a donor and acceptor at either end and know the distance between them. So we did the same experiments on single molecules with laser dyes, but we didn't account for the fact that polyproline could bend. I asked Ad if he would do the NMR of our polyproline for our single molecule experiments, so we would know exactly where it is bent and what was the length distribution to correct our FRET efficiency data. Ad agreed, but only if I could get somebody to help. The way Ad describes it was: he briefly showed Robert Best how to use an NMR spectrometer, which Robert had never done before. Robert did know something about NMR theoretically. Ad said he never saw anybody learn how to use an NMR spectrometer as fast as Robert Best. Robert then went off and did all the experiments. Robert also did all the single molecule experiments and the analysis of the results. I remember telling Robert, "maybe we can use molecular dynamic (MD) simulations to predict measured transfer efficiencies for polyproline if we allow the dyes to move around on the ends, to take into account the fact that they have long linkers and that the FRET efficiency would be time-dependent, and we'd have to worry about the correlation time of the motion and the inter-dye distance distribution. So, we went into Attila's office and asked, "How do we calculate the FRET efficiency from an MD simulation?" Attila went to the board and wrote down a Feynman path integral. I didn't know in detail what a Feynman path integral was at the time, but I knew from Attila that it was a powerful method for attacking a lot of different problems. Robert had never seen one before. Robert just looked and looked at this integral, left the room and a half an hour later came back with the results. He had opened up the simulations and done the calculation. Attila was astounded to see he did everything perfectly correct. (laughs)

Robert went back to Cambridge on a Royal Society University Fellowship as an independent investigator. There are these famous fellowships that you can get at Cambridge, similar to being a Harvard Junior Fellow, where you're not faculty, but you have the privileges of faculty. You have your own space and research group and can be a PhD supervisor of graduate students. He did extremely well in Cambridge. As an inducement to keep Gerhard from going back to Europe, we hired Robert in a tenure-track position. I thought that having Robert as a colleague would keep Gerhard.

ZIERLER: What was it that was so strongly connecting Gerhard and Robert?

EATON: Gerhard thought that Robert was a fantastic scientist. Gerhard was in the midst of wavering as to whether or not he should accept a very attractive offer to be a Max Planck Director in Frankfurt. Gerhard's parents were in Europe. They were both old and one of them was ill and as an only child he felt guilty about being so far away. I always thought his wife was the one who wanted to go, but since then I learned that she loved Bethesda, and she'd return at a drop of a hat. In any event, Gerhard's not out of the picture. He thinks he is, but he's not in my mind because you were asking me about who's the next lab chief. It's I hope it will be Gerhard Hummer. His two daughters would have to decide to live in the US. They were brought up in the US and were teenagers in the US. That could do the trick.

ZIERLER: Because there was the chance that they would go back, you're saying?

EATON: If his children want to live in the US, Gerhard Hummer will take over the Laboratory of Chemical Physics. Robert was hired in 2012. There was no issue. He was so much better than any other candidate. Unfortunately, Gerhard left anyhow. Robert easily got tenure. In fact, when I went to the central administration's tenure and promotion committee and they saw his record of publications and his letters, the only question I got when I had to give the presentation on why I he should get tenure was: "What did you do to get him. How do you get people this good?" That was the only question I got.

ZIERLER: So what happened to Gerhard? Why did he leave?

EATON: They made him a fantastic offer. They gave him something like 10 positions and very good research funding. To keep him at NIH, I got a million and a half dollars from the central administration to buy nodes just for him at the NIH central computing facility. Nobody was allowed to do this before. This is on the Beowulf cluster. These one and a half million dollars were given to Gerhard Hummer for his MD simulations. I got Gerhard appointed Deputy Lab Chief, which was a signal that he would replace me and overall did somersaults to keep him. But it didn't work. In any event, Robert has turned out to be a great find. He's going to be nominated for both the Royal Society and the National Academy within a few years. As soon as he becomes a citizen, which he will in a couple of years, he'll be nominated for the National Academy. He'll be nominated through the temporary nominating group that is looking for young candidates. There's a well-known Russian theorist named Dmitrii Makarov at the University of Texas Austin. Makarov's recommendation letter about Robert said if he had any question about how to do a computation, especially in the area of molecular dynamics, the first person in the world he'd consult is Robert Best.

ZIERLER: Right. Because that's, as I understand it, the Academy, is there's an emphasis on bringing younger people in also.

EATON: Yes, there's a big emphasis on younger people. He's in his middle 40s now. He just won the most prestigious prize in biophysics - the Raymond and Beverly Sackler International Prize in Biophysics. He shared it with somebody, so they each get $25,000. There's no other biophysics prize for young scientists even close to that. It's a wonderful accolade for him.

Those were all the tenured members. We have one non-tenured member who was a postdoc with me, Hoi Sung Chung, who did his graduate work with a guy now famous for non-linear spectroscopy at the University of Chicago, named Andrei Tokmakoff. He was at MIT at the time, and his recommendation letter said that Hoi Sung got him his tenure at MIT.

ZIERLER: (laughs) Pretty good.

EATON: Hoi Sung also made me well-known in the single molecule field, sitting in my office just listening (laughs), telling him what's the next good experiment, and then having him tell me the results and interpreting them. He will almost certainly get tenure. He's done some really brilliant experiments. He's one of these extremely soft-spoken guys, so his only problem in getting elected to the National Academy will be his reserved personality. Robert Best has a very reserved personality, but not nearly as reserved as Hoi Sung.

ZIERLER: Wow.

EATON: So I don't think Robert will have any problem. He certainly will make it before he's 50. Back to Phil now. Phil's problem is that he doesn't publish because he can always do a better experiment. It's why he runs into problems with his collaborators. Based on the quality of what Phil has already done, he should be in the National Academy now. What I reminded Ad yesterday in an email to tell Phil is, "Let's not let the not being perfect stand in the way of the good."

ZIERLER: Exactly. Right.

EATON: Phil's done something, which allowed Ad to do what he regards as one of his best experiments ever. It couldn't have been done without Phil, not in a 1000 Sundays.

ZIERLER: What's the experiment?

EATON: This is the pressure jump experiment. Where unfolding is induced by raising the pressure. Then the pressure is rapidly dropped to fold the protein. Have you spoken with Ad?

ZIERLER: I've spoken with everybody. Everybody.

EATON: Didn't he brag about these experiments? The pressure jump? Did he tell you about that?

ZIERLER: I want to hear from you, though.

EATON:. In NMR, in the field of protein folding, experiments on observing proteins as they fold were limited to many seconds to minutes. So, NMR has played a minor role in the protein folding field. It could be a powerful method to study protein folding, except for the poor time resolution. Ad's brought it down to millisecond time resolution with his pressure cycling experiment. He can investigate structure in much, much greater detail than the methods currently being used. It was Phil who enabled him to increase the pressure to several kilobar to fold and unfold a protein thousands of times without the oil blowing up the machine and ruining the probe and all the accidents that happen when you work at high pressures. Phil's responsible for getting the experiment to work. But now he drives Ad bit crazy, because the experiment is working beautifully and Phil wants to make it even better! So that's Phil's problem. In fact, he was about to be scooped from some of his best work by a Korean collaborator who had been ripping him off. Phil made an agreement with the guy that they'll just go their separate ways and the guy thought he had one-upped Phil, because he knew that Phil's so incredibly slow to publish and he could take his time. I stepped in after I heard the story and told Phil on a Friday that if you have a manuscript on my desk on Monday, I'll make sure it gets in the PNAS within the month, which I did. The Korean guy then had the chutzpah to write to the editor of PNAS and the Director of the NIH demanding that Phil hold up his paper until he could get a paper written up and submitted. They both ignored him. (both laugh) In any case, I love Phil. He's just such a great innovator. He's always thinking about things that people have never done before. Phil's reaction is: "I can do it!"

ZIERLER: Bill, I want to ask. Besides the obvious pride in having all of these people be recognized by the Academy for their work, do you see anything substantive about being elected to the Academy? Is it good for your lab to have all of this recognition, or is it just a nice thing?

EATON: At NIH, it's the coin of the realm. In fact, for the 10 to 15 years before I was elected, my NIH colleagues thought I was a member. I didn't get elected until I was 68 years old, which nowadays is not that old. Very few are getting elected these days until they're after 60. But people were getting elected in their middle 50's when I got elected. NIH scientists just assumed that I had to be a member of the National Academy, because I had a reputation of being a productive scientist at the NIH for many years. They would ask me to communicate a paper for them to PNAS. When I did get elected, I got a $30,000 salary increase. That's how serious the NIH takes it. It could be that the NIH takes it more seriously than it should, because for every person that's elected, there's three or four people equally as accomplished who don't get elected.

People in the lab have also won a lot of prizes. I just mentioned the Sackler prize, but you know that Ad won the Welch Award. What I tell people is that it's more important than the Nobel prize in Chemistry. Why? Because the committee that decides on the Welch Award is a committee of the most accomplished American chemists. Whereas the committee that decides on the Swedish prize is a committee of Swedish chemists. The Swedes don't think that's funny, but I think it's funny. (both laugh) And it's as much money. The Welch award is $500,000, and that's more than one third of a Swedish Nobel prize in chemistry, which is frequently given to three people. Also, you don't have to wear a white tie and tails and bow to the king and queen, although it was a black-tie dinner in Houston, Texas. The Italians have the best prize. I helped get a very important one for one my friends at the NIH, Ira Pastan. It's called the Feltrinelli Prize. The only people outside of Italy that I have ever met who know of the Feltrinelli Prize are people who have won it.

ZIERLER: Right. (laughs)

EATON: It's a 250,000 Euro prize and it varies from the arts to medicine, to biology, to mathematics, to physics. It rotates each year. I forget exactly the categories. The award ceremony consists of the president of the Academia announcing the award at the annual meeting and asking the audience not to applause while he announces the top ten awards with one-sentence citations, one of which is the Feltrinelli Prize for 250,000 Euros. All the recipient does is stand up, listen to one sentence about what they did and sit down. That's it. No white tie, no tails, no king and queen. There's not even a dinner, not even a luncheon. You just go to the luncheon after the morning annual meeting of the entire Accademia and have a buffet lunch. Even if you're the Feltrinelli Prize winner, you have to wait in line for the pasta at lunch, just like all the Accademia members. I always look at it as the Italians sort of laughing at the Swedes about their Nobel prize with a five-day affair and a white tie dinner with the king and queen. Feltrinelli winners just stand up for 30 seconds and sit down, and that's it.

ZIERLER: Bill, can you talk a little bit more about how NIH got involved in AIDS research and specifically your role in that? How that got started?

EATON: This was legislation in 1986. As I said, I think that part of the reason that Rall asked me to run the program -. later I was called the scientific director of the program - was because my research had slowed down to an extent that he thought I'd have time and that I wasn't doing very much. But I was suffering from sleep apnea. In the early 90s, I realized I had to do something about it, I went to an ENT guy who said I was suffering from severe sleep apnea and that he could do surgery on my throat to fix it. I went to Ira Pastan for advice. Ira is also a very smart physician and my close friend. He said I was being stupid and that I should immediately go to Hopkins where they have a sleep apnea center. I did. I had a sleep test and I met a guy named Philip ("Flip") Smith, who's the professor of pulmonary medicine. He said that I should use a continuous positive airway pressure device, a CPAP. I went back to the sleep center on October 24th, 1996. I fell asleep at about 1 am. They kept changing the pressure until the apnea was relieved at 8 cm of water. I woke up at 4 a.m. in the morning feeling more rested than I had in many years. I was an absolute tiger after that. If you look at my citation record, you will see that it was dead flat and then took off like a rocket in 1996. This was all because of the relief of my sleep apnea. I'm totally indebted to Ira. He saved my life and my career by advising me to do this. I drove all my friends crazy because I was hypo-manic. I had an enormous amount of energy. When I played tennis with a semi-professional player, I would wear him out, because he was so out of breath. I had all this collateral circulation in my heart from having poor perfusion for so many years. The hypo-mania lasted for over a year. I'd come into Attila's office every day with what I thought were five new great ideas. (both laugh) He couldn't take it any longer. This is when I started working on protein folding and was talking a lot to Peter Wolynes. Peter spent a sabbatical in my lab for a year. So, my research took off in 1996.

ZIERLER: So let's get back to 1986. Was your sense immediately that starting AIDS research in 1986 was already too late in the game? Should this have been done earlier?

EATON: No, no, There was HTLV-III and there was LAV, so there was this issue still in the mid-1980s. Which virus caused AIDS?

Of course it was the French virus, LAV. The story that I believe most is that the French gave Bob Gallo the virus and that the virus was rediscovered in Gallo's lab. Gallo claimed that he had discovered the virus independently based on the sequence, because the nucleic acid base sequence of his virus was so different from LAV. At that time, Gallo was not aware of the fact that the polymerase of this virus is so error-prone, that you can take the virus from a patient and after a short incubation period it can have a different sequence. Malcolm Martin's a top virologist at the NIH. He told me that when he told Gallo about it Gallo didn't want to listen. This error prone property of the virus was studied by a kid named Arnold Rabson. Al Rabson was the scientific director of the Cancer Institute for many years, and his son was a very smart postdoc with Malcolm Martin. Arnold was comparing the sequences of the different strains of the virus that were in the Los Alamos data base when he discovered that the virus mutated at an extremely rapid rate. So. the field was not ready for structural biology until 1986. Then, it was dead certain that this was the virus that caused AIDS, so we knew the proteins. What we had to do was make these proteins, now that we have the DNA or RNA sequence and use that sequence to synthesize the proteins in bacteria or eukaryotes. I was asked by Wyngaarden to come to a meeting of the NIH advisory council to tell them about this new program. This is in late 1986.

ZIERLER: So it's because of the protein structure issue that this is located in chemical physics? That's the natural home for this research to take place?

EATON: No, not yet. I'll explain that in a second. I went to this meeting to talk about what we were going to do with the money from this program and that one of the things we could do would be to buy spectrometers, which were extremely expensive, to determine the 3D structures of the HIV proteins by NMR. Some of them are quite small and were easily amenable to structure determination by NMR in 1986. At that meeting was a famous crystallographer named Michael Rossmann. Rossmann was an x-ray crystallographer famous for solving virus structures. Before the meeting, Ad gave me a tutorial on the nuclear Overhauser effect and the nuclear Overhauser effect is used to detect hydrogen atoms separated by about four angstroms or less. With a sufficient number of such inter-proton distances, it is possible to do a geometric reconstruction to build a three-dimensional structure of a protein. I had some slides and explained it as best I could at the time, although I am still dyslexic for NMR (laughs). I thought I did a really good job. Michael Rossmann stood up and told the Director of the NIH that it's a waste of money to buy these spectrometers. He said that it is not possible to determine the structure of a protein by NMR. He might not have been aware of, or he didn't believe the work, which had only been published six months earlier by Kurt Wüthrich. I was enormously embarrassed. Rosssman was basically saying to the NIH advisory council that what this guy Eaton was going to do with this 4 million dollars was a waste of money and that what he said was nonsense.

ZIERLER: Do you think he had a natural bias towards crystallography?

EATON: Oh sure, as did all crystallographers at the time for many, years. It wasn't until the mid-90s that the crystallographers started to accept the NMR structures as real structures. Wyngaarden told Rossmann that, "I'm sure Doctor Eaton knows what he's talking about. Let's move on to the next subject." He basically defended me. Wyngaarden was also my occasional tennis partner at the time, by the way.

ZIERLER: That helps. (laughs)

EATON: We played about once a month so he wasn't a regular partner.

ZIERLER: Now, was Anthony Fauci part of this council?

EATON: No. He was the Director of the infectious disease institute (NIAID)—The Council consisted of people from outside the NIH.

ZIERLER: Oh, I see. I see.

EATON: These were not institute directors. These were advisors to the Director of NIH.

ZIERLER: Okay.

EATON: So they were all a bunch of famous guys.

ZIERLER: Was Fauci involved in this at this point yet, or he came later on?

EATON: Fauci was very much involved right from the beginning. He was a great spokesman for the NIH and was very supportive of our program. We got it up and running in just a few months. We had a committee meeting in January of 1987, and NIH scientists had money in their pockets by March of 1987, so it was the fastest funding that the NIH has ever had. One of the reasons it was done so quickly is that Ed Rall and I decided that the best way to make decisions was to give people a month to prepare a proposal and give the review committee two weeks to rank them. The committee was a group of the smartest scientists at the NIH. They're not all necessarily members of the National Academy, but they're really very, very smart scientists. I would run all the meetings. Money was transferred from the Office of the Director to their laboratory budget. I know that when people have nominated me for prizes, sometimes they add on the fact that I was scientific director for 30 years and that the NIH should be proud of the way the institution immediately stood up during the AIDS crisis to do such important research. The first drug for AIDS was discovered by Sam Broder, AZT at the NIH. The first coreceptors for HIV were discovered at the NIH by Ed Berger. Most of the structures of the HIV proteins were done at the NIH, either by NMR in my lab or by x-ray crystallography. So, the NIH has had a sterling record and I think they're going to have a very similar record for the coronavirus. Ad Bax's experiments, for example, have been important in the world accepting the fact that masks can be effective in slowing the pandemic.

ZIERLER: He involved me in that in every step of the way.

EATON: I've also been involved. Ad got me interested in it and I got a theoretical physicist in Germany interested, a close friend, Roland Netz, at the Free University Berlin, where I was a student. Roland also got me an honorary degree in physics from the Free University Berlin, which I'm very proud of. The rector of the university pointed out when I got this honorary degree that he heard I hardly ever went to class (laughs), which was true.

Roland and I have a paper that might get the grand slam. You want to know what the grand slam is?

ZIERLER: I would love to.

EATON: My most spectacular paper on kinetics of sickle hemoglobin fiber formation was the one showing an 80th power concentration dependence. This is obviously an unheard of concentration dependence. We showed that the characteristic time depended on the 40th power, but that the homogeneous nucleation rate depended on the 80th power, exactly twice the dependence of the characteristic time, which our theory with Frank Ferrone predicted to differ by a factor of two. I sent the paper to Nature; it was rejected without review. I sent it to Science; it was rejected without review. I sent it to PNAS; it was rejected without review. I then sent it to Cell, which is a biology journal. I knew that would be rejected; I did it just so I could get the grand slam, and it was rejected without review. (both laugh)

ZIERLER: Well done.

EATON: So I just wrote a paper where Roland derived all of the equations. I wrote the paper, so that's my contribution. The paper explains the physics behind the propagation of the coronavirus by transmission from speaking droplets. It's called the “Physics of Coronavirus Transmission by Speaking Droplets.” The thesis of the paper is that while this has been a subject of theoretical study for 100 years, all previous papers either do numerical simulations of complex mathematical equations, or just do empirical calculations. Our paper presents two simple algebraic equations that can be understood by anybody who has had seventh grade algebra. The equations tell you exactly how long it takes a droplet of a given size to sediment and exactly how long it takes a droplet of a given size when it's emitted from your mouth to dry down at a given humidity to a smaller size from evaporation. You then consider these two times to decide the fate of a droplet. It's a beautiful paper and it's gotten a different kind of slam. It wouldn't even be accepted by a preprint server. Now preprint servers (laughs) don't review papers, they just make sure that you're not lying or cheating or stealing? So we submitted it to bioRxiv, and they rejected it. They wouldn't accept it. They said to send it to physics preprint server, arXiv. But arXiv already had the long derivation of all these equations by Roland. So amazingly, it was accepted by medarXiv, a medical preprint server. I kid my theoretical physicist coauthor by saying, "Look at that, doctors really are smarter than physicists, they recognize the importance of our work, and they accept it for their archive." But it has been turned down by Science and by Science Advances. I was really pissed and sent a nasty email to the editor of Science Advances. It was irresponsible to take a month to make a decision without a review it. Now we've sent it to PNAS as a “Brief Report.”

ZIERLER: Bill, I want to return to coronavirus in a second. I do have another question about the NIH's response to the AIDS crisis in the 1980s. So as you well know, Anthony Fauci had a very contentious relationship with people like Larry Kramer, and other outspoken activists who were very upset that maybe the NIH as the public face of the government's response, or however you want to understand that, but what was your response at the time, or looking back, in terms of the validity of those criticisms? Which were quite angry and harsh and basically accused the NIH of, you know, not taking this seriously earlier on? What was your response then, and what is your response now, to those kinds of criticisms?

EATON: Well, I just read about them but didn't pay that much attention to them. The only one was from the head of what’s the name ACT UP?

ZIERLER: That's right.

EATON: Was that the organization?

ZIERLER: That's right.

EATON: The only thing I recall, and I wish I could document this, was told to me by one of the people in the upper administration at the NIH, whether it was Wyngaarden or whether it was Ed Rall. I forget now. But I was told that when the ACT UP people met with the Director of the NIH, the only thing they liked of what the NIH was doing at the time was our program. It was a program that expanded from just structural biology to molecular and cell biology by the mid-90s. This is around the time that the ACT UP people apparently made some comment that ours was the only program they liked. I didn't pay much attention to their criticisms of anything else when I heard that comment. I really didn't follow it. I think that Fauci was the hero, because he convinced Koop, who was the surgeon general, to convince Reagan that AIDS was a physical disease and not a social disease. Tony was, as you know, always a great spokesman for NIH. However, I think he might have spoken sooner and more emphatically about wearing masks to prevent transmission of the Corona virus. in Vietnam, masks are mandatory. If you don’t wear a mask in public, you suffer a hefty fine. Do you know how many deaths have been reported in Vietnam from the coronavirus? Zero.

ZIERLER: Yeah.

EATON: Maybe there are more, but there are zero reported, which means there are very few. Also, Taiwan has had very few. They've reported seven.

ZIERLER: Basically, if everybody was serious about wearing masks, we'd be in good shape?

EATON: My contention is, and I think Ad would probably agree with this, that if everybody in this country wore a mask every time they walked out the door, it would quickly end the pandemic in the US. The virus wouldn't have any place to reproduce. What about the people who got sick and you were in the home with them? Well, those people would all get infected and some of them would die, but nobody else. It would be the end of the pandemic here. I don't think this is an exaggeration. But of course, we have an idiotic president who's going to show up without a mask and very few of the expected 20,000 people in the auditorium at his upcoming rally aren't going to be wearing masks, and a lot of people are going to die.

ZIERLER: I wonder if you see any parallels in terms of the difficulty of conveying scientific information to the public, looking back at the beginning of the AIDS crisis, and comparing that with public messaging for coronavirus? In other words, people are frustrated. They want quicker action, and they need to be made to understand that these things take time.

EATON: I've been remiss in that. Some scientists get very interested in education, educating younger people, educating the public, giving lectures to laymen about scientific subjects or volunteering to lecture in high schools. It's been one of my failings. Given all of my experience being at the NIH, I do know a lot that I could transmit to the public, but I never have. The problem is that a huge fraction of the country doesn't believe in science, as evidenced by creationists versus people who believe in Darwin. I don't know what the statistics are, but I wouldn't be surprised if more than 50% of the country are creationists. Would you? Do you have any idea what it is?

ZIERLER: I don't know the number. But even if people have, a lot of people have very poorly-developed understandings of science, right? There still is a legitimate need to convey that these processes to understand the virus, they do take longer. That people should not expect that just because there's a new issue, the new virus, that we can wham-bam come up with a vaccine no problem.

EATON: Well, one thing that Tony has not emphasized frequently enough, although he keeps warning people that the earliest we can have something is early next year, is that we don't have a vaccine for HIV 34 years later. As far as wearing masks, though, that's frustrating. You don't need a science education to know that if you sneeze on somebody who has a cold, you might get their cold. So all you have to explain to people is that when you speak, it's a little bit like sneezing, not quite as severe, but it can be just as bad. This hasn't been documented yet. Ad's very interested in this. He's been talking a lot to German scientists who are of the opinion that a single virus can cause an infection.

ZIERLER: That the whole idea of viral load is... One virus can do it, you're saying. It doesn't have to be a whole big dose.

EATON: Yeah, It's something that virologists have believed in for 100 years.

ZIERLER: Right, right.

EATON: Ad thinks they really have to change their view. With AIDS it was complicated because people didn't know early on exactly how it was transmitted, so it could be that if you touched a gay person, or you toughed a hemophiliac, that you might get infected. It wasn't realized for many years that it was only transmitted by very intimate contact of one form or another. And then there were people who wouldn't provide needles, forcing drug addicts to use the same needles.

ZIERLER: Right. Right.

EATON: That caused them to be infected with HIV.

ZIERLER: And Bill, the other issue with the mask, you know, not wearing masks is that it's not just scientific ignorance. It's that people take like a libertarian view of this, and they say, "Make me wear a mask. It's my right, it's my freedom not to wear a mask." It's a sign of American freedom. That's a big part of this as well.

EATON: Yeah, I know.

ZIERLER: Might be hard to understand, but that's still, it's a part of the equation.

EATON: I know, those are the people who are not wearing the masks. So, the question is, how do you convince them that wearing a mask is being a patriot? There is something called patriotism, when you just don't worry about yourself, right?

ZIERLER: Right.

EATON: You worry about your neighbor and stop talking about freedom of the individual and liberty, part of being a good citizen is being a patriot. Maybe those kinds of words are the only thing that'll affect these people.

ZIERLER: Do you think scientific ignorance has gotten worse over the last 30-40 years?

EATON: Certainly hasn't improved. Whether it's gotten worse, I don't know. I think in general, understanding of physics has probably gotten worse. Simply because of the academic disciplines, along with mathematics, it's harder to grasp unless you think and spend a lot of time at it as a student. Also, there's a tendency in the society not to work as hard, compared to when I was a student or as hard as when I was a young scientist. When I was at the NIH as a young scientist, I would work every day and every night. I worked from ten o'clock in the morning until midnight, but came home for dinner with my wife and children for an hour. I would take Saturdays and Sundays off. So, I only ended up working 65 hours a week instead of more than 80. That way I could come in to the lab on Monday morning refreshed, so it was a good thing to do. Now on weekends at the NIH, the parking lots are empty. The building is almost empty. Phil is there, Ad is there, and just a few other people in our building, when it used to be full on weekends. Postdocs wanted as much time in the lab in order to get their experiments done. Now it's a quality of life issue. I saw it with one of the smartest postdocs I ever had. A guy named Stephen Hagen. Stephen Hagen worked on low temperature physics at Princeton and had to find a job in this area because his wife was doing a residency at Hopkins. Bob Austin at Princeton recommended that he come to my lab. He got an enormous amount of excellent research done, but he didn't show up until nine o'clock, and he left every day at five o'clock. He never came in on weekends. He was extremely effective. When I would question him about this, he would just say, "What, are you complaining about the work I'm doing?" He was an exceptional person, because he was so damned smart that he could do it in a 40 hour a week, while other people required working 80 hours a week and still couldn't get done what he could. When it became time to look for a job in a physics department, Zwanzig said he's the only postdoc he has ever met that he would recommend for a faculty position at any physics department in the country. You name it. Harvard, Stanford, whatever. He had such high regard for Hagen. Let me tell you one cute short story about him. We wrote a paper together on using a room-temperature glass suggested by a guy named Austen Angell, a famous glass physicist. A glass at room temperature slows kinetics or stops them completely based on Kramers's theory, because the pre-exponential factor has a diffusion coefficient in it, and the diffusion coefficient depends on the friction, and the friction depends on the solvent viscosity. So if you make a glass, the solvent viscosity goes up to 10 to the 15th centipoise or so and stops everything. Austen told me about this. He said insects in the desert make tons of a sugar called trehalose to make a glass so they can “close up shop” when it doesn't rain. They can then come back to life, which could be several years later when it rains. This experiment worked beautifully. We sent the paper to PRL on “protein reaction kinetics in a room-temperature glass”, a sexy title. Steve was the only postdoc I ever had, apart from Robert Best, who could write a complete draft of a paper, where I would just edit a few words. For every other paper that I co-authored. I ended up writing or rewriting almost every sentence. Hagen could do this because he was so intelligent. To write a clear, concise scientific sentence you have to be smart, because you have to be careful that you're not making a wrong statement or oversimplifying. You can always write a run-on sentence to take care of all the caveats, but then it's not understandable. Hagen could write beautifully clear, concise sentences. So I told him, “okay Steve, you write the first draft and remember one thing, though. You're writing for physicists and Steve, physicists may be smart, but they don't know anything." I did not realize until later that he took such serious offense to that statement. I found out when we were sitting at my PC and I'm editing the paper with him watching, just changing a "the" or an "a." He's not saying anything. Then I take out this whole phrase, and I replace it. And he literally yells at me "Wrong!" I said, "What do you mean Steve?" "That is damned stupid and it's wrong. Don't you dare put that in my paper." It was a bit of a subtle point, but Steve was right and I was wrong. So I put it back. And he said, "You know something, Bill? Chemists may know a lot, but they're not very smart." (both laugh)

ZIERLER: That's great.

ZIERLER: Bill, could you talk a little bit about your developing interests in sickle cell? How did that get started?

EATON: As a graduate student with Hochstrasser, what I did was make polarized optical absorption measurements on single crystals with a microspectrophotometer that I built. When I got to the NIH, I built a very similar one and was making measurements on nucleic acid base crystals in the ultraviolet. Nobody had ever measured accurate single crystal spectra of nucleic acid bases. I was able to purchase some lenses from Zeiss called Ultrafluars. These are lenses that are chromatically corrected all the way to 230 nanometers. That means that you can focus on an object with visible light and the object would stay in focus all the way to 230 nanometers. I heard about some experiments by a Japanese scientist in our institute, named Makio Murayama who was looking at the birefringence of sickled erythrocytes. These were red cells from patients who were suffering from sickle cell disease, which have these curved, elongated shapes. He only made birefringence measurements. If you get the sign of the birefringence wrong it's very easy to get the orientation of the chromophore and therefore the structure wrong. What I mean by "structure" is the orientation of the hemoglobin molecule in the fibers that are inside these sickle cells. The four heme planes in the hemoglobin molecule, are roughly parallel. They're tilted a bit, but still roughly parallel. The question is, if you take the unique axis as the perpendicular to that plane for all four hemes, how does that relate to the fiber axis? Murayama concluded that it was perpendicular to the fiber axis, and I knew that I could see whether he got things right by measuring the optical absorption in plane polarized light, which is unambiguous. Which orientation absorbs the light more strongly? With the electric vector of the plane polarized light parallel to the long axis of the sickled cell, assumed to be the fiber axis, or perpendicular to the axis? It turned out the sickle cells absorbed more strongly perpendicular to the fiber axis, because the hemes absorb more strongly with the light polarized parallel to the heme planes, which means the perpendicular to the plane was parallel to the axis. While I was making these measurements, a new postdoc came to work with Elliot Charney, James Hofrichter. He became interested in these measurements that I was making and wanted to work with me on them. Elliot was a very generous guy, and told Jim that, sure, take some time from my project and work with Bill on this. So we determined that that the long axis of the hemoglobin molecule that's perpendicular to the heme planes, which is called the x-axis of the molecule, is within 22 degrees of the axis of whatever fiber is inside these sickle cells.

We then got a visit from a computer scientist named Shoshana Wodak, who was a postdoc with Cyrus Levinthal at Columbia, who told us about a paper from John Finch, the electron microscopist at the MRC in Cambridge working with Max Perutz, that they had proposed a structure for the sickle hemoglobin fiber. Their structure was a stack of rings of 6 hemoglobin molecules, where each ring is rotated slightly relative to the adjacent ring, so the overall structure was a tube made up of six slightly helically twisted strands, if you can picture that. The hemoglobin molecule has a true two-fold symmetry axis. Finch and Perutz had this symmetry axis pointing perpendicular to the long axis of their fiber. So, Jim and I went over to the computer division, where there was a guy named Richard Feldman. Richard was a very clever programmer and developed the first molecular graphics program of a protein molecule by continuously rotating the image, which produces a three-dimensional image. So, we were able to look at the hemoglobin molecule for the first time and to imagine how it was sitting in the Finch-Perutz structure. We realized that if the two-fold axis was perpendicular to the fiber axis, the mutation that caused the disease was pointing into the solvent. So how could this mutation from glutamate to valine ever possibly cause the protein to aggregate if it's nowhere near an intermolecular contact? So, I wrote a letter to Max Perutz saying that he had made a mistake, telling him that the two-fold axis cannot be perpendicular to the fiber axis, but that an intermolecular contact involving the mutation site could be made with their structure that is consistent with our optical measurements by tilting the molecule. The response was another one of these thin aerograms from Cambridge. This one not saying, " Bill, come if you like," but saying, "Dear Bill, please come to my Royal Society meeting in London next month to tell us about your experiments. All travel expenses and hotel expenses will be paid by me."

This is of course very unusual. How many people today would invite somebody to their meeting that they've organized to say that one of their main results is wrong? Max did. I went to the meeting. Stuart Edelstein, who was doing electron microscopy was also there. We weren't on the program because we were both invited at the last minute. The guy who was chairing the session said, "Okay, I'll give you two guys 15 minutes to divide between you." I sat up the whole night before worrying about what I was going to say and what happens if they only give me time to show a single slide. I had no idea that I was going to get any time at all from the day before discussion with the session chair. I was surprised when he gave us 15 minutes. It turned out that Edelstein took 13 of the 15 minutes, so I really only did get two minutes. I presented my work in these two minutes with a single slide and it actually had a big impression on people. In fact, it was one of the reasons that Frank Bunn, the famous hematologist at Harvard and I became very good friends. I was a young guy, incredibly enthusiastic, talking about his results. Frank thought it was good work. So did John Hopfield, who was the leading biophysicist in the world at that time. Still is. Hopfield had planned to have dinner with the other super smart guy at the meeting, Robert Shulman from Bell Labs, his buddy. Shulman, whom I met in Cambridge in 1962, asked me if I would join the two of them for dinner. Of all these people there, all the top people in the field, they wanted to have dinner with me. You may understand this; it may have happened to you. When people who are really important in your field think highly of what you're doing and want to have dinner with you to talk about it, it's a big thrill when you're a young person. I remember being absolutely thrilled having dinner with these two super smart guys in London in February of 1973. When I came back the obvious question on my mind was how do these fibers form? I knew how to purify hemoglobin. So, I purified this mutant hemoglobin and used my microscope to observe the fibers form by monitoring the birefringence. Jim Hofrichter was watching what I was doing and made some suggestions on how to improve the measurements.

He also made a beautiful thermostated housing for the microscope slide and improved the data acquisition method. He and I became collaborators in sickle cell research ever since. Elliot Charney, again, being the generous guy that he was, saw that Jim was really excited about what we were discovering and told Jim, "Okay, I think what Bill's doing is so much more important. Why don't you just go work with him?" What we discovered was that there was this long lag phase, a delay before the fibers form. You also see that with Alzheimer's peptide and amyloid aggregation. What is different is that we found this characteristic time to depend inversely on the 30th power of the concentration. It also had a gigantic activation energy of 90 kilocalories per mole. That's a very large activation energy and the 30th power concentration dependence is the largest concentration dependence for any molecular process ever observed in physics or chemistry, and still is today.

ZIERLER: Why? Why is it so unique in that regard?

EATON: It's because the nucleus itself is very large. That's one contribution. And it's because of the activity coefficients, which are a measure of the non-ideality that result from the molecular crowding in the red cell at the very high hemoglobin concentrations. The concentration dependence is defined as the logarithmic derivative of the characteristic time with respect to the concentration, so it's d-log-t, d-log-c. If the nucleus is large, all nucleation theories predict a large concentration dependence. The first nucleation theory relevant to proteins was done by the famous Japanese physicist Osawa, who published a book on protein polymerization. In his theory, the concentration dependence depends on the size of the nucleus divided by two. That's giving you a hint of where the 80th power comes in.

ZIERLER: (laughs) Right.

EATON: The activity coefficient, which comes into the kinetic theory that we developed with Frank Ferrone, is also highly concentration-dependent. So you have these two concentration dependencies, which results in an overall gigantic dependence on the measured concentration. I then had what I called, can' t think of the word.

ZIERLER: Eureka?

EATON: Well it was a eureka, and there's another word - epiphany. What I immediately realized, which made it worth going to medical school, was that the reason people survive the disease is that this delay allowed most red cells to get through the narrow vessels of the tissues before the fibers form and block the circulation. That was the fundamental idea. The delay before fibers form allows the cells to escape the smallest vessels in the tissues, where they can get stuck and occlude the circulation, and escape to the large vessels, where the decreased flexibility of the cells from fiber formation do no harm. The cells get back to the lungs, where oxygen melts the fibers very rapidly and then make another round trip. That realization initially had a big impact on the field. However, the impact was seriously diminished for many years by an NIH colleague, a guy named Alan Schechter. He is an MD biochemist and apparently was very envious of what we had done. He became interested in sickle cell disease because of our work and came up with an alternative hypothesis, which never made any sense. The hematologists finally stopped listening even though he continues to publish it.

ZIERLER: Where did you leave the state of play in 1990, and how has it progressed since? Absent your ongoing interest?

EATON: In 1990, I finished a very large article, which is really a small book. It's 214 pages in Advances in Protein Chemistry. I wrote the entire article and did all the calculations myself, but argued with Jim who did not want to be a co-author because I did everything. But the work wouldn't have been done without him. He was so essential to our original research that I insisted he be a coauthor. There were just two or three papers over the next 15 years on sickle cell disease. In the early 80s, I got interested in time-resolved spectroscopy which started with the picosecond experiments on hemoglobin with Robin Hochstrasser in the late 70s.

ZIERLER: No.

EATON: Robin had built a picosecond spectrometer, which was the first spectrometer to measure optical absorption at multiple wavelengths simultaneously with picosecond time resolution. It had about 10 picosecond time resolution using Neodymium glass lasers that took weeks to align instead of seconds or minutes with today's laser. Robin's idea was to determine how long it took the hemes of hemoglobin when it was excited with a picosecond laser pulse to return from the excited electronic state to the ground state. Hemes do not fluoresce or phosphoresce, so they would just undergo a radiation-less transition from an electronically-excited state to the ground state, which Robin wanted to observe with his picosecond spectrometer. So, I brought some purified hemoglobin with me that was in the oxidized form, which doesn't undergo any photochemistry to make the measurement. Robin's student Benjamin Greene and post-doc Bruce Weisman worked with sample for several days, all day long and at night, but couldn't get a signal on the multi-channel analyzer. I brought another sample with me. It was the carbon monoxide complex of hemoglobin, which has a unit quantum yield, so that every photon that is absorbed dissociates the carbon monoxide, which results in a huge change in the optical absorption spectrum that is very easy to detect. So, I gave them this sample. I remember them finding that the signal on their optical multichannel analyzer was off-scale and I kept saying, "Turn the sensitivity down." They replied. "It's still off-scale." I kept saying, "Turn the sensitivity down." They kept on turning the sensitivity down and down to its lowest possible sensitivity to see this gigantic signal because the absorption spectrum changed so much. They were thrilled to death. That experiment got me interested in time-resolved spectroscopy. I didn't have the skills to build a picosecond system, but I thought my lab could build a nanosecond system. I went back to the NIH and it ended up being built by Jim Hofrichter, with a lot of help on the data analysis from a new postdoc, Eric Henry, who got his PhD with John Hopfield in physics at Princeton. So, the 1980s was spent writing the article for Advances in Protein Chemistry and working on time-resolved spectroscopy on hemoglobin that persisted into the early 90s when I stopped all of that and switched to protein folding.

The switch was motivated by a conversation over a glass of vodka in Moscow with Peter Wolynes. The papers we published on time-resolved spectroscopy did have an impact, especially the work of Steve Hagen on time-resolved spectroscopy of myoglobin in the trehalose glass. Those were photo-dissociation experiments. Also, Anjum Ansari, who was a student of Frauenfelder did the experiments published in Science, which first suggested that he was using up his PhD students measuring the well-known glycerol water glass transition temperature using myoglobin kinetics as a viscosity probe. Ansari and I published a paper on the effect of viscosity on the protein conformational relaxation. There we discovered non-exponential relaxation, which became a hot theoretical topic, and we discovered non-Kramers viscosity dependence, which demonstrated that there was friction coming from the residues of the protein dissipating energy by interacting with each other. We now call it internal friction, and that's become a subject in protein folding, which remains a major area of investigation in the protein folding field today. Other than that, the work didn't have a huge impact, although it helped solve the hemoglobin allostery problem, which is my collaboration that went on simultaneously in the 90s in Parma, and how I became an Italianophile. That's a separate area. There's sickle cell disease and hemoglobin allostery with the Italians, and there's protein folding and time-resolved spectroscopy. However, when I summarize my research over the years, I spend rather little time on the time-resolved spectroscopy.

ZIERLER: Why is that?

EATON: Well, I think other than the work that I did with time-resolved spectroscopy in Parma, it hasn't had the impact that the other areas have had. The biggest impact as far as citations are concerned has been protein folding first, sickle cell disease second and allostery third. The prize I'm most proud of is the Delbruck Prize in Biological Physics, which was for protein folding with no mention of sickle cell disease. But most people think the most important research I've ever done is the work on sickle cell disease.

ZIERLER: And Bill, when you talk about importance or impact, do you delineate between how well your research has moved the science forward and how well it's actually helped people in a clinical sense?

EATON: The two are intertwined. Some people who do basic research, as you well know, whether it's physics, chemistry, or biology, justify it to themselves and the NIH for purposes of getting a grant by saying, "this could be important for understanding some human disease." There's no doubt that I originally got involved in sickle cell research because it had a direct connection to human disease, but then it very quickly became pure physical chemistry. It was thermodynamics and kinetics and some spectroscopy. In the case of protein folding, I only use it as a throwaway sentence by saying there are diseases which are called misfolding disease, but if you want to understand misfolding, you have to understand protein folding. It's just boilerplate stuff for justifying the work on protein folding, although I never really have to justify it, working at the NIH. I don't have to apply for a grant. But the sickle cell disease has always been motivated in large part by the human interest. In fact, now I collaborate with hematologists, I recruit patients. I worry about patients. I make measurements on patient samples participating in drug trials and I occasionally actually discuss drug treatment of patients with NIH hematologists. I could not have done any of that without medical school and my interest in the human side of the problem.

ZIERLER: And where is sickle cell today as a matter of prognosis as it relates to your research? How much better is it than 20, 30 years ago?

EATON: It's a lot better. The first drug that really helped people came out in the mid-90s, hydroxyurea. My research explains how it works. The mechanism of the inhibition of sickling by hydroxyurea is that it ends up diluting the sickle hemoglobin by inducing fetal hemoglobin synthesis, but it is complicated because of non-ideality, which is unfamiliar to hematologists. Hematologists are working extremely hard to figure out how to induce fetal hemoglobin to find a better drug than hydroxyurea. I have to figure out a way of explaining it as we did in the speaking droplets paper with Roland Netz, so that the hematologists can easily understand it. Hydroyurea treatment was a big turning point in drug treatment of sickle cell disease, and hydroxyurea is still the only successful drug that works by inhibiting sickle hemoglobin fiber formation. There are a couple of other drugs. One of them also works based on my original idea. It works by preventing cells from sticking to the endothelium, the inside cells of the capillaries and the small vessels. So when the cells pass through, they transiently stick, which slows the blood flow and increases the probability that occlusion of the small vessels is going to occur, because the transit time is longer. So, the basic idea is that it's always the delay time relative to the transit time. If the transit time is long, it's bad and if the delay time is short, it's bad. Conversely, if the transit time is short, it's good, while if the delay time is long it's good. Now there are two drugs, one acting on the delay time and the other on the transit time. There's a third one, which I criticized in the hematological literature that changes the oxygen affinity of sickle hemoglobin. It's a controversial issue that is not going to be settled for quite a while.

The main advances in this country and also in Europe, especially in France where there's a lot of research on sickle cell disease, is what's called stem cell transplantation. That's when you take the stem cells out of a patient's bone marrow, virtually destroy their bone marrow with chemicals and X-rays, and give the patient stem cells from a sibling that's immunologically compatible. It's a very serious procedure. As John Tisdale, the most successful guy in doing it, who's at the NIH and a colleague of mine, says that you take somebody who is very sick and then make them even sicker before they're cured. John has more than a 90% cure rate. It only works for about 15% of Americans, because that's the percentage of patients with a sibling match. He is working on stem cell transplantation methods where you can inject stem cells that are just a partial match. The success rate so far is about 50%. Then of course, there is the holy grail, which people around the world are working on, which is to remove the stem cells and use CRISPR-Cas technology to edit the gene, that is, replace the codon for valine with the codon for glutamate, then put these cells back in the patient. Now an immunological match is not required because the patient's own stem cells are being used.

Drug therapy is what I do. The basic idea is that 98% of the people with sickle cell disease in the world are not going to have access to curative therapies such as gene editing or stem cell transplantation, because they requires very advanced medical facilities. It will be many decades, before these curative treatments are available. What's needed now is an inexpensive pill. That's what I spend all of my research time on, except for the tiny foray into coronavirus with Roland Netz in Berlin, because of Doctor Bax.

John Tisdale spoke with Bill Gates two years ago when Gates came to the NIH to learn about what could be done for sickle cell disease. The Gates Foundation had never done anything on sickle cell disease. At this meeting John Tisdale told the people at the Gates Foundation about my research. The Gates Foundation funded a project with the Scripps Institute where Gates gave them something like 25 million dollars to synthesize every compound that has ever been tested in a human. In the past couple of years, we've worked out a very high through put assay, where we can screen thousands of compounds a week. Scripps has given us that library free of charge. We have gone through it in one pass, at one concentration, where we screened 12,657 compounds to find what which ones increase the delay time for sickling. Now we're looking at the ones that have some promise as a function of concentration. So far is we have 101 candidates for new drugs. That's a lot, which means we're going to end up with several. I'd bet my house on it (laughs)

ZIERLER: When?

ZIERLER: When? When are these drugs going to come available? What do you think?

EATON: I don't know. It's a multi-month project. The hardest part right now is finding out the concentrations of these compounds that are found in humans. For most, it's just unavailable. I'm going to have to write to the pharmaceutical companies and lawyers are going to get involved. So, each of the 101 compounds is going to be a multi-week project of emails getting the information we need for each compound on what's called the pharmacokinetics. How fast does the concentration in the plasma arise? For a given dosage, what is the maximum concentration, what is the decay time from the maximum, and what are the side effects? Most of these compounds have never become FDA-approved drugs, probably only a few percent, but they've all been tested in humans. So there's information on them, but getting that information is a real struggle. We have the capability of making the measurements to proceed further, but we desperately need more information. Swee Lay Thein, the Chief of the Sickle Cell Branch at NIH, is my closest clinical collaborator, who is waiting for us to propose compounds for clinical trials. It's a very high-profile project. It's great for the NIH because it's a wonderful achievement to report to the Congress that a drug for sickle cell disease has been developed at the NIH. So, I'm very happy. It's a great way to end my research career. The experiments and the interpretation of the experiments use sophisticated physics that has to do with nucleation theory, including our 80th power concentration dependence.

ZIERLER: Well Bill, on that note, I think in terms of what a nice way it is to end a research career, I want to ask you two basic questions. One is sort of retrospective and one is looking forward. Coming back to the MD-PhD question, do your unique experiences suggest that that's a good way to go for people who want to enter into scientific research as it relates to human health issues? Is the MD-PhD really an advantage, and it's something that you would recommend for people?

EATON: I recommend the following: If you're interested in scientific research in the medical field, then the MD-PhD gives you a great advantage. The MD does not teach you how to do research, even though a lot of fantastic research has been done by people at the NIH who came as MDs and then learned how to do research here. The MD gives you an awareness of a vast number of biological problems to be solved. Intelligent people can learn how to do research without a PhD. The PhD gives you a leg up on doing research because it allows you to take on problems that you would be afraid to take on with only a medical degree and without a well-rounded graduate education. The best graduate education, or undergraduate education, is in physics. Physics provides the tools to do anything. For a graduate degree in physics, it is probably best to work in an area of biological physics, where you use the physics and not just be a physicist working on some biological problem in the same way as a biologist. But what happens with a lot of MD-PhD students, and this is what I warn them, is that if you think you can do clinical medicine and do basic research and have a successful career, you're kidding yourself. I know only a very few people with medical degrees and PhDs who can compete in the world of clinical medicine with the MD's as a clinical investigator and simultaneously compete with the PhD's in the science world. There's a few, super smart guys. I could name a few names, but I'd rather not that go on record, because I'll end up insulting people that I left out. I also know of some guys who just have MDs that are so good that they actually compete in both clinical research and the basic sciences, but they're rare. I will mention one guy, because he's a close friend of mine who does compete in both the basic science and the clinical research areas - Frank Bunn at Harvard. He wrote this perspective with me in the journal Blood a couple of years ago on the different mechanisms of inhibiting fiber formation to treat sickle cell disease. I will send you a reprint. I'll also send you the R.W. Wood paper for your own physics research project to see if Pfund did steal the series from Brackett. It's something worth publishing in a physics journal if you can figure it out.

ZIERLER: (laughs) There you go. It's a deal.

EATON: It would be an intellectual challenge, It is worth publishing in *Physics Today* or someplace like that.

ZIERLER: Absolutely. You send it to me, and we'll take it from there.

EATON: A journal would love an article from a physics historian showing that Pfund stole the Brackett series from Brackett, with input from a colleague of Brackett**.**

ZIERLER: There you go.

EATON: The truth, and nothing but the truth.

ZIERLER: Let's do it. Well Bill, on that note I want to ask you my last question, the forward-looking question. You've been with the Laboratory of Chemical Physics for so long that your powers of extrapolation, I think, are quite strong. And so the question is, where is the Laboratory of Chemical Physics headed next? What are the big issues that the laboratory should be focusing on for the next 5, 10, 20 years from now?

EATON: Well, two things. One is I think any new hires should use the Perutz criterion. Hire the best scientist who applies for the job. Ad Bax didn't know what an amino acid was when he applied for the job. He did not know the structure of a single amino acid. The second thing is that we should focus on hiring people who are or will be one of the world's experts in a methodology. The value of our laboratory at the NIH is related to the fact that people in biology are now using all kinds of methods. They solve x-ray structures. They use NMR. They go to an NMR core facility and hand a sample to somebody and they're given back a series of structures using some program. So there has to be a center with experts in each of the important physical methodolgies that are being used at such a large research institution. The reason why our laboratory exists is because we are the experts in each of the methodologies that we use, so that people can come to our laboratory if they really want to understand something in depth about the results they're getting, Otherwise, we would just become another very good laboratory at NIH, and eventually fade out like many laboratories have, because they're working on problems which are no longer of great interest or that they're no longer biomedically relevant. This is what could maintain the Laboratory of Chemical Physics for many years. Maybe we should change the name. It should be something like the Laboratory of Molecular and Cellular Physics because chemical physics does not reflect what we do. It's actually a subfield of physicists in Europe, but not in this country. European physicists who work on molecules are called chemical physicists.

ZIERLER: Maybe that could be your parting gift to NIH. A more accurate name for the lab. Well, Bill, it's been so fun talking to you. This is such a tremendous addition to the historical record. And it's a great capstone to this project, where I've talked to every major physicist at the NIH, and I'm so delighted that you were the last one for this whole project, because you added so much context to all the things that I've learned already. So I really appreciate your time.

EATON: I should just make one last comment. Of all the prizes and awards and societies and things that I've won, the one that I'm most proud of is the Delbruck Prize, which is the highest prize that the APS gives in Biological Physics. I'm one of the very few- I don't know how exactly many - without a PhD in physics who have won the prize.

ZIERLER: Yes. Right, right. Right.

EATON: Had I won the Delbruck Prize and not gotten elected to the National Academy, I would retire a happy guy.

ZIERLER: (laughs) That's the real club that you wanted to be a member of.

EATON: Yeah, that's right.

ZIERLER: Okay, Bill, thanks again so much.