Maret Traber Oral History Interview, June 23, 2014

Title
“The Long Journey to Understanding Vitamin E”

Date
June 23, 2014

Location
Linus Pauling Science Center, Oregon State University.

Summary
In the interview, Traber discusses her upbringing in Stockton, California, her family background, her earliest interests in science, and her undergraduate experience during a tumultuous period at UC Berkeley. She notes meeting and marrying her husband while still an undergraduate, and describes her Ph.D. studies at Berkeley, a time period during which she also gave birth to a daughter.

The family's move to New Jersey, Traber's experiences as a research scientist at the NYU Medical School, and her mixed feelings about that time period are a major component of the interview. In discussing her seventeen years at NYU, she reflects on her group's initial work on LDL receptors, the beginnings of their interest in Vitamin E, the growth of her technical skills in the laboratory, and the politics, personality issues and gender barriers that dotted her tenure in New York.

Memories of returning to the West Coast and working in Lester Packer's laboratory at UC Berkeley comprise the next component of the session. Traber reflects on the role that Packer played in helping her to re-establish herself once returned to California, and discusses the lipoic acid research that she carried out while in his laboratory. She next describes her move to UC Davis as well as an important visit that she took to the German Institute of Nutrition before outlining her recruitment by the Linus Pauling Institute and her move to Oregon.

The remainder of the interview focuses on Traber's scientific development while a principal investigator at LPI. In this, she outlines her group's accomplishments in researching Vitamin E, provides a glimpse into the development of the Institute over the years, and shares her impressions of day-to-day life at the Linus Pauling Science Center.

Interviewee
Maret Traber

Interviewer
Chris Petersen

Website
http://scarc.library.oregonstate.edu/oh150/traber/

Transcript

Chris Petersen: Okay, Dr. Traber, if you wouldn't mind introducing yourself with your name, and today's date, and our location?

Maret Traber: My name is Maret Traber. This is the Linus Pauling Institute, and we are in my office in the Linus Pauling Science Center.

CP: And today is June 23rd.

MT: Today is June 23rd, 2014.

CP: All right, so we're going to talk about your life and your career. And the first thing I would ask is where were you born?

MT: I was born in Stockton, California.

CP: Were you raised there?

MT: Yes. In fact, I didn't even get out of state until after I was married.

CP: Oh, wow!

MT: [Laughs] Considering I travel the world now, yeah, that's a pretty big, "Oh, wow!"

CP: And what was Stockton like growing up?

MT: Well, Stockton was a very divided city. There were the white people on one half of the city, and the black people and colored people on the other side. It was a farming community, so there was a lot of—my father was a milkman; my mother worked for the City of Stockton as a bookkeeper. And so I lived a really quite kind of idyllic life, in the sense that we stayed close to home, didn't have a lot of money, had a big back yard, and we should play in the back yard, and avoid places like Skid Row. I don't know that anybody even talks about skid row anymore.

This was really before the times when we had kind of revolution of all kinds of things going on, and the Vietnam War was just going to be beginning when I was in high school. My parents had not gone to college, and so UC Berkeley was kind of the local university that wasn't in town, so they thought it was perfectly okay for me to go to UC Berkeley. I don't think I really knew about the Free Speech Movement. I wanted to go to Berkeley to learn about chemistry, because when you pour two different colored liquids together they form a different color, so was that cool, or what? And then we get into what happened at Berkeley. But I think, you know, the *Father Knows Best*, *Donna Reed* 1950s show? That was my existence. *American Bandstand* was—I can remember you had to come home from school in time to see American Bandstand.

CP: You're the first child of a milkman I've ever interviewed.

MT: [Laughs]

CP: I'm interested in knowing what that was like. What was the life of a milkman like?

MT: So, the implication of a milkman is really important for a kid, because my father left early, early, early in the morning. And so he would come home three o'clock in the afternoon to sleep, so that he would be awake in the evening. And so that meant tip-toeing around and being very quiet, because you didn't want to make Daddy mad. So that was one implication. Another: you probably have really great bones, because we had lots and lots of milk. We had, as I said, a big back yard and not a lot of money, so we had a giant garden. We even had a pig.

You're chuckling, but it's a kind of thing where we had fruit trees. We had walnuts; we had almonds. We had cherries, we had apricots, we had peaches. I know all of these things because I had to pick them, and learn how to can peaches. We had

peaches like—I can peel a peach so fast! And so that was part of the—I suppose there's a certain amount of good nutrition that came from, okay, you have milk as an important thing in your diet.

CP: Any siblings?

MT: Yes. I had three younger sisters, and so by the time I was ten, the baby was born. And that baby was a lot my responsibility to take care of, because my mother then went back to work. [0:05:01] I was probably one of the few kids I knew whose mother worked outside the home. I can even remember, one time my sister Annette was going to be getting out of school, and I took the baby, put her in the stroller, and off I walked the six or eight blocks to school, to go meet my sister. And when we got back home, my mother was like, crazy, with, "How could you just leave? How could you just take the baby and go?" Well, we had a nice walk.

CP: [Laughs]

MT: But I was terribly, terribly smart as a kid, and I think my parents actually fed into that. They would ask my opinions of stuff. I was probably the most egotistical child ever, because of that.

CP: So school was something that came naturally to you, then?

MT: Oh, yeah. I can remember in the 5th grade—I liked sweets too, and because we didn't have a lot of money, we didn't have candy; that was really special. And so my parents promised me if I got straight As, I would get a box of chocolates. So this was an enormous, important thing, and I got all A's except a C+ in Book Reports, because I liked reading; I didn't like writing about other peoples' stuff. And so, I can to this day remember my parents being angry about the C+. And these were the old fashioned report cards where it's not just two or three subjects, but it's a whole long list. It's a two-page thing. [Laughs] They cared about the C+, not the A's.

CP: What were your earliest interests in science? How did you get into an interest in science as a girl?

MT: Well, I was one of four children, and we were all girls. So I mowed the lawn. I took care of the other kids. I learned how to cook. So I was very much encouraged to be a helpful person around the house. At the same time, my mother was from Estonia. She was a big advocate of education, to the point where she could speak Estonian, English, and German, and being from Estonia, the Germans had taken over Estonia. It was free in between World Wars I and II. And she was working for a German bank. When it looked like the Russians were going to invade Estonia, the bank was going to leave. And so she could go with the bank to be a bookkeeper in Germany, and so she chose to leave.

She was one of thirteen children, and she was the only one who got out. She went to Germany and was in Dresden when the Americans bombed Dresden. The only reason I'm here is because somebody had said, "If the city's on fire, walk into the wind." And she walked out of Dresden burning with, as she put it, one very small suitcase. So, the end of that story is that she then could work for the American government because she could speak English and German. And because she was a displaced person, she was given the opportunity to come to the United States, because Estonia was now communist.

So it was her feeling education, what you have in your head, is something nobody can ever take from you. And this was—my father, on the other hand, had just a high school education. He thought it was very important, again, this whole philosophy about learning, and both of them were very serious. Now, if you've heard about the Estonian revolution more recently, it was a singing revolution. My entire family on my mother's side are musicians, very talented, sophisticated conductors. They run choirs. I think it's because they're very smart people. They're very successful people; they are driven, and at the time the communists were there [0:09:59], you couldn't be successful in something that might be considered dangerous to the government. So singing—everybody likes singing.

Well, I like singing. I loved singing. I thought it was wonderful! It got to the point where we were in 5th grade, or maybe it was junior high—I guess it was junior high—there was one elective. I wanted to take choir; my father said science. He won, and that was the end of my singing career. I had a wonderful science teacher! He also flew a very small plane, and he crashed his plane and died. And I think that was a kind of, "Gee, I should work harder in science," moment. I always enjoyed it. I enjoyed science more than I enjoyed math, and that will get to us in the Berkeley story later.

CP: Well, yeah, I'm ready for us to move on to Berkeley. You mentioned that you decided to attend it because it was fairly local and was acceptable to your parents. It was not in town, though.

MT: It was cheap.

CP: Mm-hm.

MT: I was a California State Scholar, which meant that I did exceptionally well in grades in school, and I'd done exceptionally well on the SAT tests for the time. And so, the University of California Berkeley was free. It was not a private school. I also wanted to go to Stanford, but Stanford was, number one, expensive, and number two, I didn't get in there. But Berkeley, it was a shoo-in, just because of what I had done in high school. And so my parents thought that was fine. I think it was $200 a quarter in fees. The first year I was going to live in the dorm.

I was going to be a Chemistry major; it all was going to be just—and I actually got there, and learned calculus is really, really hard. And it was hard, because I think at the time, my background in math was not that strong. The faculty at Berkeley—at least for math it was a Chinese guy who had learned English in Germany. I'm sure he was an excellent mathematician, but learning calculus when you're challenged with understanding the words, and then you get to QED. And it was like, okay, I get it, I get it, I get it. What do you mean, QED? I don't get it. How did you get from there to there? And I found that—I think if I started over I could do calculus, but at the moment I'm, like, I didn't know what was going on.

And it turned out, too, this was a very dramatically different place, going from my very sheltered *Donna Reed*, *Father Knows Best* existence to the Vietnam War, demonstrations every quarter, hippies, drugs, college in general. I mean, this was a revolution that was going on. And it was a very exciting place, Berkeley. [Laughs] When I think back, if I knew as a mother what college was like, I certainly wouldn't let my kid go there. But I think it was very challenging.

Berkeley at the time was very much, "We let you in. You are smart. Deal. Figure out what you need to figure out. And if you can't, you don't belong here; thanks for coming." And I got really sick the first year I was there, and discovered chemistry was not this really cool thing of pouring things together. It was actually very complicated math. It was complicated molecular structures. And trying to figure out, how did you get from this really cool equation thing that I could follow, and now we're talking about pie orbitals? And, no, no, no! This is just not interesting. This is not fun. It's not intuitive; I don't like it.

So there was that realization. [0:15:01] When you're sitting in the hospital with severe diarrhea from salmonella poisoning, that is not fun. And what you're going to do with your life is not fun. And so I thought, okay, chemistry is not me. Maybe biochemistry. And I read the catalog carefully, and I discovered biochemistry is enzyme kinetics. We're back to math; we're back to big machines. I don't see how I can do this. Lots of time on our hands; we're reading the catalog. It's a big, thick catalog—a lot of different things you can do at Berkeley. And I think by starting in Chemistry, I had a huge number of: these are absolutely required to do almost any science. So I was not in a position of going, "Oh my God! I have to start all over to be a history major." History was not my thing, either.

So when I discovered nutrition, it was a godsend! It was like, okay, these people are talking chemistry and biochemistry. You need all of the math. You need the strong science background, but it's for an important problem. How do you make people healthy? What are the kinds of nutrients the body needs to work? It was like, okay, this is exciting. I can do this. And I just threw myself into nutrition, went from teetering on the edge of a C to, "Okay, I've got it." A student, right? No. It turned out it still took a little bit of time to figure out: all right, this is what it means to go to college. This is what it means to figure out how to study, how to learn everything. But we got there eventually. And I liked nutrition so well that—lucky for me they liked me also, and I was invited to be in their PhD program. Finished the PhD in four years, and then it gets even more complicated.

CP: Well, I guess I'm interested in knowing—you'd been at Berkeley for quite a long time, just the sense of transition from Stockton to Berkeley, socially, culturally, academically.

MT: [Laughs]

CP: We sort of touched on this a little bit, but if you could give it—?

MT: Okay, so there was a 500-person peace march in San Francisco. I marched there. That was going on. And at the same time I found this very lovely man, who later became my husband. I was actually married at the end of my junior year. Probably that was a conflict, with my parents being very upset about me not focusing on my studies, and so to solve all of their problems. But that's not really true. I really liked the guy, and so [laughs] what can I say? We'll be married 43 years next Thursday, so that's worked out very well.

But I think there was all of the turmoil, the hippies, free love, all of the changing in music. I went to the Woodstock Museum and I was kind of horrified. It's like, that's my childhood they're displaying. We have, you know, the Kennedy assassination. We have Martin Luther King, Robert Kennedy. We have the Vietnam War. We have the Beatles; we have the Jefferson Airplane. I mean, these are like everyday occurrences kinds of things that were going on. Cambodia was invaded in my junior year, and that year the campus closed down. There were no classes spring quarter. And you could choose to independently go to class. It was kind of a weird kind of thing, but I was doing physical chemistry at the time, and really enjoying it very much. So I continued, and finished physical chemistry. So there was that sort of thing.

I can remember having a very difficult time, because at summers you would go home, and summers going home from this kind of wild environment that I was living in to the very restrictive environment [0:20:00], ended up with kind of a schizophrenic personality, where [laughs] you don't want to get the two mixed up because you couldn't maintain. But eventually I got over that, but yeah. I can remember my husband-to-be's parents being very horrified because we were both juniors at Berkeley at the same time we were getting married, and they were kind of worried that I was looking for a meal ticket, and their brilliant son, who they had such great aspirations for, was getting sucked into something that was going to be bad for him.

And that really came to pass when we'd been married a year. He finished at Berkeley and went to work for the Bank of America in San Francisco, in their—computers were going on, too, so he was one of the first people working in an IT department for the Bank of America at the time. And I was going to graduate school, and it was kind of like, "Well, how come you're paying her to go to graduate school?" Because I'm smarter than he is.

CP: [Laughs]

MT: No, we didn't tell them that. That would have been—because he was searching for himself, and wanted to see what the real world was like first.

CP: What did your parents think of Berkeley as it was unfolding while you were there?

MT: My mother said something pretty interesting once. She said that people were sort of horrified that she would allow her daughter to go to Berkeley. And she said, "Well, in order to get roses you have to put some manure on the plant sometimes."

CP: [Laughs]

MT: I thought, "Well, okay." [Laughs] There you have it. I think she was sufficiently impressed with Berkeley's reputation as an important university. And I think there was this sort of: well, if this is what's going on in the university and this is what university's about, okay. I mean, I remember the Blue Meanies. I don't know how I would have dealt with this, because the National Guard came to Berkeley. We had People's Park, which was a block away from my dorm. And the whole of People's Park, there was National Guard bivouacked there. They were coming over to use the dorm restrooms. It was kind of like, really? When I think about it now, it's all kind of—but it was sort of, "Well, okay. I have to get over to my physical chemistry class. And just, these are things I have to do." I remember sitting on the grass in front of Dwinelle Hall, and there were demonstrators in Sproul Plaza, which was like a half a block away. And then there was tear gas, and the demonstrators ran past, and the National Guard ran past, and we continued with our class.

CP: [Laughs]

MT: [Laughs] It was like, this all kind of crazy—this is what school's about. And I suspect, honestly, the reason my parents were sort of glad with us getting married thing, is that, well, there would be some man to protect her.

CP: Mm-hm.

MT: That was the philosophy in those days. You needed a man to protect you.

CP: Yeah. Well, tell me about the transition to graduate studies.

MT: Oh, that was a piece of cake. I had already taken all of the Nutrition classes they owned. I then took the Biochemistry classes and the Physiology classes. I mean, by the time I got into graduate school, I was like a totally serious student, and I was there to learn, like a big sponge, everything there was to know. I think the harder part was the—I had a very perfect existence, and I had a nice home life. I was coddled. I had a nice position as a graduate student. I had a full ride, so no tuition, no money worries. I had an interesting project.

It didn't turn out quite so rosy, because my PhD mentor, Rose Marie Oswald, her husband died during this, and probably the last two years she was not there at all. So that was probably hurtful for a PhD. [0:25:03] But on the other hand I was such an independent soul already that I had a really strong group of lab people I was working with. I was looking at a project that was really well described of what I was supposed to do. I was using radioactivity, radioactive cholesterol, to look at cholesterol absorption and transport in guinea pigs. There's a great rationale for it, but the techniques that I learned I'm using today to do projects in people. The mathematical modeling that I learned, that I'm putting into place. So, all of that worked.

What didn't work—well, at the same time, there were multiple things going on at once. I can talk forever, by the way. [Laughs] The chair of the department, her graduate student was pregnant. What a good idea! And the chair was working on getting her graduate student to be a faculty member in the department. So the end of the career does not happen when you have a baby. And the kind of scuttlebutt among the graduate students is, well actually this makes a lot of sense, because if you collect all of your data, in the year when you're writing it up you can have your baby, and take care of your baby at home, and then you can take off and it will all be great. Okay, we have a plan.

We put the plan in action. Yes, we're pregnant. Everything's a go. And I even talked to the radiation safety people; they said, "Eh, don't worry about radioactivity. The amount you are using is not important." I said, "Okay, good." And the project is all a go. And it's about August when I'm to the place where I'm going—the baby's due in October, at the end of October. So I've collected all of my data, starting to look at the numbers, and sitting and looking at the computer. And things are wiggling in front of my eyes, and I'm going, "This does not seem right."

So I had preeclampsia. They threw me into the hospital and said, "Sit still." I was a pretty lousy patient. They wanted to measure protein in the urine. Well, I do protein assays all the time. I know it takes twenty minutes. So it was like, what do you mean, I have to sit here for another day that they didn't get the assay done yet?

CP: [Laughs]

MT: "I don't believe this." But they kept me around sitting still for a while, and the idea was, okay, I can see the light. We'll just sit quietly and be a more meditative, not running around like a crazy woman person. That was not working out real well, but then labor started, only two weeks late, and my husband had gone off to class. He'd gone back to get a master's degree. And so he comes back home and says, "Okay, I can drive you to Oakland." So we're going to Kaiser Hospital, and everything's going to be great, right?

So it takes all day long to deliver this baby, and everything's going to be great, and we're not going to have preeclampsia anymore. Everything's going to be wonderful. So three days later, take the baby home, watch TV all day long. Baby's great; baby's sleeping! About 9 o'clock at night, about the time she's born, 9 o'clock at night, she wakes up. She's hungry. I'm useless as to feeding her. She's screaming; she's mad. She's mad all night long. This is not good. And then Biff is really quite good staying up with her, because I was totally wiped out. All day long he keeps her awake so that she has to sleep at night, so we switch that over.

And then Monday off he goes to class. And Monday, of course, now that I'm a free woman I can run around, I can do stuff. It took me about three hours before little things are floating in front of my eyes again. And off we go to Kaiser, and they say, "Huh-uh. You have to slow down." [0:29:58] And they put me on Phenobarbital, and so I had to take the entire fall quarter off. What a drag! But after that, we got going again and finished up. And the degree says December of '76, but I was actually finished in July. And then we moved to New Jersey, which is a different story.

CP: Well, how did that happen?

MT: [Laughs] The New Jersey story happened because, remember, Biff was in Computer Science, and he'd just got a master's degree in operations research, and he got three different job offers. One was—or maybe it was two—but one was Bell Northern, which would have been in Palo Alto, and the other job was Bell Labs, the amazing and wonderful Bell Labs. And so Bell Labs offered him 5 dollars an hour more than Bell Northern. And Bell Northern said, "Nope, we can't match that."

And we looked at each other, and Biff said, "You know, this is the opportunity of working at a place not like Bank of America, where they were just using canned programs, and really, these people were cutting-edge. It will be developing stuff; it will be incredible." Keep in mind this was the time when Apple Computers are invented in peoples' garages—that kind of excitement. So, yeah, let's go to Bell Labs. And I said, "Well, I've never been out of the state. Sure, why not? We can go to New Jersey." And my father thought we were joking. You can't possibly be serious about moving to New Jersey! We already house a house in Berkeley.

So we sold the house, moved. New Jersey was a horrible place. It was hard to find a job in New Jersey for me. I started off at Rutgers, a part-time position, and basically they thought a woman with a young baby could be working if she really needed the money, but certainly research was not something you should be doing. And so I was helping their graduate students, and suddenly the graduate program—these graduate student projects were making sense and coming out well. And then the next year they had all kinds of faculty positions opening, and I wasn't offered any of those. I was offered: I could have the same job I had, which was teaching a seminar on aging, for twelve months, for the pay that I got the previous year for nine months. And I thought, "No, this is not a good thing."

And so I started looking for something else, and that's when I discovered an ad in *Science* for a research—I think it was a research scientist at NYU Medical Center, to study LDL receptors. And so receptors were a whole new field. Brown and Goldstein had not yet gotten the Nobel Prize for discovering the LDL receptor, so this was a very exciting new field. And so it meant commuting to New York City, which meant an hour on the train. It took fifteen minutes on one end to get to the train, and it took a half hour on the other end to get from the train to NYU Medical Center. So an hour and 45 minutes each way, which was closer than Albert Einstein, which was the other possibility.

So NYU it was, and the baby was now two years old. So I found a nurse who would stay home with the baby. This was not a money-making venture! She was—I say it's a nurse, but she was actually like a two-year degree person, but she liked kids and wanted to stay close to home, and that solved her problem; solved my problem. My husband was working at Bell Labs, having a great old time. The next year, I think we figured out we should figure out a more [0:35:00]—a better situation, where our daughter could actually meet other kids and have fun, and become socialized. And therefore it was: find a daycare center. There weren't any in all of Monmouth County, which meant the only one we could find was like a half hour's drive. So we did that. So Katrina went to daycare.

I went on the train; my crazy husband got to drive around. He had work that was three minutes from home, but he got to go on this long adventure. So that worked until Katrina started kindergarten, at which point we had to find some other solution, and the solution then was one of our neighbors was undergoing a messy divorce, and her daughter was the same age as our daughter, and she was happy to have money to take care of both of them. So she would see that they got to school; take care of them until Katrina's crazy parents got home from all of the things they were doing. So that worked out, and it just—you keep doing it, and seven years later you go, "Really?"

CP: So you rode the train all those years, huh?

MT: Five days a week, seventeen years.

CP: Oh, wow!

MT: Yeah. The nice part about riding the train is we didn't have cell phones. There was nothing you could do on the train. You could sleep; that seemed wasteful. So I would read papers. The only *New England Journal of Medicine* article I have, I wrote in one train ride going home, because the physician I was working with—it was a collaboration between the group at NYU and a physician in Denver, who had very unusual patients. And he didn't appreciate how fantastic

measuring vitamin E in peripheral nerves was, and so I thought burying this data in a crummy paper someplace was not what I wanted. So he was perfectly happy that we send it off and see. We tried *The Lancet* first. They didn't want it, but *New England Journal of Medicine* liked it, and so there you have it.

CP: Well, as you mentioned, you were at NYU for quite a while, and this was an important period for you. Do you want to talk a little bit about the work?

MT: [Sighs] So, I went to NYU to learn about receptors, LDL receptors. And I got there thinking that these people knew what they were doing. Didn't actually turn out to be the case. Turned out that the physician I was working with, Herbert Kayden, had been collaborating with Brown and Goldstein in Dallas, and had sent people from his lab to learn how to measure LDL receptors. Unfortunately, when I got there, the people who had actually done it had already gone, so the people were missing. The pieces of paper that said, "This is what you do" were there, and there was a technician. And the technician's favorite saying was, "It really doesn't matter." This is a very bad saying, because in science it usually does matter. It matters very much, and attention to detail? Yeah, that's sort of the key—if you're going to get a PhD, you have to be really careful about detail.

So here's the story. The idea was really good. The people my boss was studying—he was a physician. He was very interested in inherited disorders of metabolic diseases, which meant he had a collection of people that he had gathered over the years who had very strange disorders. And he was interested in a disorder called a-beta-lipoproteinemia, which means that when you took these peoples' plasma, normally you end up—we now know LDL and HDL in peoples' plasma. [0:40:01] At the time, nobody even knew what lipoproteins were.

So there was a band that had alpha mobility, and a band that had beta mobility, when you looked at these fractions that floated. And the beta mobility was completely missing from these people. You look at their red cells, and instead of looking like a donut, the red cells had all kinds of poking-out shapes to them. They were called spicules—very descriptive; nobody understood anything. So, what is wrong with these people, and why is it important?

Well, it turned out that—and I'm not exactly sure how he figured this out, but the neurological abnormalities seen in patients with a-beta, those neurological abnormalities turned out to be vitamin E deficiency symptoms. So you could figure that the beta lipoproteins were involved in absorption of fat, because one of the characteristics of these people is they didn't eat fat, because it gave them diarrhea. And so they wanted to avoid fat at all costs, which means fat-soluble vitamins—we're in trouble there—and once you absorb those fats you have to move them around. And so we were getting to the place where we were understanding that lipoproteins were the transport mechanisms for lipids.

So, sort of fast-forwarding a little bit, it turned out that all of this stuff we started with being excited about, LDL receptors—it took me a long time to figure out, number one, everything they were doing in their lab was wrong. I had never done tissue culture; I was working with animals, and so I didn't know what tissue culture was. They showed me what they said were cultured white cells, and I look at it, and it's a stringy mess. And looking at what's in the literature, that is not what white cells look like. And the Hematology people were down the hall, and I went to talk to them, and they said, "Those are not white cells. Those are dead cells." Dead cells. Well, the technician who said it really doesn't matter decided it was not important to put serum into the culture because it's too much work, and it really doesn't matter because her cells died anyway. So we got rid of that.

And so, I learned how to culture white cells. But the culturing of white cells, while we're screwing around and not getting this off, the project off the ground, the group in Dallas has already figured it out—how to do lymphocytes, and how to do LDL receptors in lymphocytes, and there's like, well, there's nothing we can do. Well, it turned out we were using a white cell concentrate. This was from plasmapheresis, from the Red Cross Blood Bank. So they were collecting platelets for transfusion into cancer patients. They, in order to get the platelets, had to essentially put the red cells back in the person, and collect all of the white cells out of the person. Then they had a special technique for separating the platelets, and they were throwing away the white cells.

So we got the white cells. The Hematology people I made friends with said, "That is a really crummy source of lymphocytes, because it's all contaminated with monocytes." Well, give me lemons; I make lemonade. So I learned, taught myself, how to isolate monocytes from this white cell concentrate, grow them in culture, get them to differentiate. They

grow ten times bigger. They're really beautiful. It's just, wow, exciting! So, we are now running out of money and it's time to renew the grant proposal, and what happens?

Well, here is this great idea. [0:45:01] Brown and Goldstein already showed that lymphocytes have LDL receptors. Maret Traber shows that monocytes also has LDL receptor, except Brown and Goldstein didn't call them monocytes converting to macrophages; he calls them, or they call them, scavenger cells. Scavenger cells don't have LDL receptors. They engulf LDL that's become oxidized, that's become somehow ruined, and they engulf it because the patients they were studying, patients with familial hypercholesterolemia—these are five year old kids that have cholesterol levels over 5-, 600. So, normal is less than 200. And they don't have LDL receptors.

So their solution to this problem was: the scavenger cells are taking up this LDL and making atherosclerotic lesions. So Maret Traber comes out with a paper that says, "Hah! You're wrong. Scavenger cells do have LDL receptors." Well, if I was doing this today myself, I would have contacted my colleagues who gave me the methods, and said, "This is what we've been doing. These are the results we're finding. We're thinking about publishing them. These are the circumstances. What do you think?" No, that is not what we did. What we did was we published in the *PNAS* this amazing paper, saying monocyte macrophages have LDL receptors, la la, those guys in Texas don't know what they're talking about.

Well, when you try and write a grant proposal and you say, "See how smart we are?" What you end up with is: gee, the leaders in the field say you don't know what you're talking about. Number two, you have a very small lab: Maret Traber, the boss who's never there doing anything, and the technician. You need an army to isolate LDL, isolate the components to grow the cells, grow the cells. You need a whole army to ionate lipoproteins. You need a bunch of people to be able to do these experiments and interpret them. You cannot do these experiments in such a tiny lab as you have. I already did it. So Herb Kayden told me, "Well, now that you lost the grant for us."

CP: [Laughs]

MT: So it was now my responsibility to figure out how am I going to get funding for my salary? Because keep in mind, I started as a brand new PhD, and now I've been there a while, and every time everybody says, "Oh, great job," and gives you a raise, well, now you have to get even more money to pay your own salary. So at that point, I pointed out—you remember the a-beta patients. Well, the a-beta patients were getting vitamin E, and the a-beta patients were serving as subjects for clinical trials, and we got this state-of-the-art high pressure liquichromotography system with a fluorescence detector. I think we got the first one in NYU—certainly NYU, maybe New York City. It was a brand new piece of equipment, and we had it to measure vitamin E.

And I said, "Okay, vitamin E—fat soluble. Nobody knows how it's absorbed. Nobody knows how it's transported. It's in lipoproteins. What if we propose to study the transport of vitamin E in lipoproteins, as a grant?" Yes! We got that baby funded! Three years, because we didn't have any preliminary data, but okay, good enough. So I start doing really fun experiments, like, we knew how to isolate LDL; we knew how to measure vitamin E in LDL. We could do tissue culture; we could look at uptake of LDL. [0:49:59] We could look at transfer mechanisms from triglyceride-rich lipoproteins into cells. It was just a heyday because all of those lipids people had figured out all of the methodology.

I was in New York City, where all of them were. I knew them all. I toodled around town, got methods on how to do stuff, how to—everybody wanted to help because I was not competition. Who cares about vitamin E? It's not important. You know, lipids are important. We're doing the important stuff, but yeah, we'll help you. So it was a nice position to be in; worked out very well. We then, at a meeting that I didn't go to but Herb Kayden went to, he met some people from Canada—Keith Ingold, Graham Burton. And they had just made deuterium-labeled vitamin E. And this was exciting because Keith Ingold was a very famous chemist. Unfortunately for me, Keith Ingold's father was an even more important and famous chemist, and was knighted. So Keith Ingold never felt he lived up to his dad.

So he was old-fashioned kind of guy, and he really liked the idea of working with this fancy New York physician. But maybe you're getting the idea already that the fancy New York physician very happily took ideas and talked them around, and didn't do a lot of idea-generating himself. So, when Ingold and Kayden got together, they agreed it would be a good idea to give deuterium-labeled vitamin E to people, and our whole thesis of looking at transport in lipoproteins—we could do this. Remember the guinea pig studies? We're taking the kinetics of guinea pig studies and moving them in to vitamin E. Good, good, good. Wonderful collaboration! They gave us some material.

It was before the days of the IRB caring much about anything, and physicians certainly could do anything. And so, yeah, we can give deuterium-labeled vitamin E to people. We did that, usually the people in the lab. I don't know how many times I've been stuck. But we got some nice papers showing absorption, transport. At this point there was a paper that came out that said: "Gamma tocopheral. If you feed alpha tocopheral to people, gamma tocopheral goes down in their plasma." And Herb and I looked at each other and said, "Really? I don't think so." And the reason we said, "I don't think so," is I had been looking at absorption and techniques for absorption, and we'd measured in chylomicrons, and there was no competition there.

And so Herb Kayden said, "Okay, I'll go ahead and take a really big dose of vitamin E and we'll see what happens. And, [gasps] oh my God! Exactly what this paper said was true, that if you took alpha tocopheral, plasma gamma tocopheral went down. And now we have this really difficult problem, because in chylomicrons there was no competition. We also had the group in Denver who were looking at patients who had neurologic abnormalities but nothing else wrong with them, so their lipoproteins were fine.

And so the guys in Canada gave us the—so, vitamin E is complicated. Largely every nutrient you can chemically synthesize easily. Vitamin E is difficult because you have right-handed and left-handed forms. And the left-handed form appeared to be disappearing from the plasma. And everybody knew this for 30 years already; they just didn't know why, and the numbers in rats never added up to any sort of sensible conclusion. So the reason for doing deuterium-labeled vitamin E is those guys in Canada, chemists, understood right and left chemistry, and they thought, "Aha! The membrane is all right-handed. It must be right-handed fits into the membrane better, and left-handed slides out faster." [0:55:00] Good hypothesis.

So, we got our deuterium-labeled vitamin E. We had the patients in Denver. And somewhere along the lines here we had gotten all kinds of samples from the patients in Denver and I'd already measured—remember that *New England Journal of Medicine* paper—that the adipose tissue had lots of vitamin E in the patient who was given supplements. That means if you're given supplements and you can absorb the vitamin E, but I'm looking in your plasma, that means vitamin E is disappearing quickly, somehow. We tried doing oxidation experiments. Nothing really panned out.

And so I was thinking, you get absorbed, you get a chylomicron that takes this through the body, the vitamin E gets distributed everywhere, adipose tissue that we're measuring gets enriched. Then the vitamin E gets to the liver, and the liver is supposed to put out that triglyceride a second time into the circulation, so that it can go around again. If there is a mechanism to put vitamin E into those newly secreted lipoproteins, then the patients could be lacking that protein. And in fact, there was a protein, a vitamin E-binding protein, that had been described in rat liver. So my next big guess was the patients in Denver must have a defect in that protein. So our plan was: get right and left labeled vitamin E, feed it to the people in Denver, also feed it to some normal, healthy people, and compare the kinetics and the transport.

Yay! [Claps hands] I love it when it works. The normal people absorbed both forms of vitamin E. The left-handed goes down fast; the right-handed stays up in the plasma, and in the people who we had already found were vitamin E deficient, they absorb both and both disappear fast. So the hypothesis was: they have a protein in the liver, and it's defective. Hooray! Now, remember, we were talking about alpha and gamma. Well, could it be that the protein is only recognizing alpha and not gamma? And so I did an unlabeled study, and then I got the guys in Canada to make me deuterated gamma. Yes, that worked too.

I guess this is actually a two-part story in the Denver patients. We used just the right-handed stuff first, and they were in agreement with the transport in lipoproteins. When we put the left-handed stuff in, this suddenly blew a hole in their hypothesis, because if the reason the left-handed stuff did not stay in the plasma is not because the protein was putting it back in, but that the two disappeared together, it was not matching what they thought. And they so hated the hypothesis! Keith Ingold told me to my face.

He used to go to New Jersey to meet with the people at Exxon, where he was helping them understand oxidation of rubber and oils, and chemistry. And so I went to meet with him at a hotel nearby the airport where we had dinner, and then he was catching a plane back to Canada, and I was going home. And he basically got really, really angry, and told me to my face that I was not a scientist, that this was absolutely not a viable explanation of what was going on, that it was clearly not anything to do with the protein. So that was pretty much the end of that collaboration, and no more deuterated tocopherals from those guys.

I collaborated a little longer with Graham Burton, but it was a not-easy situation. And I think by this time, my husband, who is working for Bell Labs—AT&T is falling apart—not falling apart by accident, falling apart intentionally [1:00:00], and Bell labs is a free-standing unit. And then the computer part of AT&T Bell Labs spun off, and Unix Systems Labs spun off, and then Unix Systems Labs sold Unix to Santa Cruz Operation. My husband, in his entire career, had one job; he just got bought and sold.

CP: [Laughs]

MT: And basically, or I guess in between there was—and this is the important part—Novell owned Unix for a while, and the people at Novell wanted to know—did you want to move to California? Because they wanted to put the Unix in the Silicon Valley, so to speak. And I said, "Yes, let's go." And basically, this is committing scientific suicide. Being in a place like NYU, I had been promoted to research professor, or research associate professor. This was not a tenure track. I was in the Department of Medicine. It was quite clear I would never be considered a real faculty at NYU. You had to be an MD. You had to be able to teach other MD's, or wannabe MD's how to be MD's.

And clearly too bad for me, no grants in my name and no possibility of getting grants in my name, because any grant I wrote—there was a little thing I did on the side, learning how to grow intestinal cells in culture, and make them actually have little microvilli and sealed borders, and study lipoprotein secretion from these cells. Again, I was told I was too small an operation, not physically possible to do, la la la. KCO2 cells are still used as a model of these defined apical and basal lateral layers of cells. [Sighs] So I said, "The writing's on the wall." Herb Kayden dies; I'm unemployed. It's a long way to go, an hour and 45 minutes. My husband's job had moved, so he was driving not three minutes, but an hour from home.

And so we said, we always wanted to live back in California. It was never a plan to move to the East Coast permanently. Let's go. So our daughter graduates from high school. We sell our house; we move to a house that was actually closer to his work, but that only lasted like three months before we said, "Nah, this is not a good idea." And so we moved to California. Daughter's going, "I'm going to college and my home has disappeared!" So, "We'll give you our address when we get to where we're going in California."

CP: [Laughs]

MT: And basically moving to the Bay Area. Basically there are a hundred thousand graduates every year in the Bay Area. There are no jobs in the Bay Area for somebody who has not been a faculty member, has no grants, been a research scientist for seventeen years. I managed to get a part-time teaching job at the local junior college. And the only person who was willing to help me was Lester Packer, and Lester Packer said, "You can come and be a volunteer in my lab. If you can get funding for your salary, you can be paid." And that was the best offer I got.

There were other people who—they would talk to me, but that's about it. There was no—and these were the days when there was actually a fair amount of funding around. So I was just plain-old too expensive, and there was always this question of, "Those grants you claim you wrote? Did you really?" And I basically left Herb Kayden with a five-year grant that I'd spent one year of, so I left his lab in good shape except for the fact I was leaving. He had a technician. So, it took me about two months in Lester's lab before I had my salary. Lester Packer was very good to me. [1:05:00] He did something which on reflection is probably the best thing ever. He said, "You know all kinds of stuff about vitamin E, but I would like you to learn about lipoic acid, and I would like you to write an NIH grant proposal on the molecular mechanisms of how lipoic acid works." And I said, "Really?"

CP: [Laughs]

MT: Okay. So this is where it's very nice that the internet was starting up. You didn't have to go to the library to read everything. You have PubMed, and now I did what I called a PubMed experiment. I read all of the papers that were laying around the Packer lab on lipoic acid, and I began to understand what is lipoic acid about. And so I would go, "Aha! This key word, this key word, this key word," put them in to PubMed. Has somebody done this experiment? So I could now read the papers on the next iteration. And you keep going. I understand where the science is, until you got to the place where you go, "Okay. I am now at the cutting edge of what is known on this topic." And you know, the Packer lab had being working for some time on lipoic acid, so there was a fair amount known in the lab. I didn't know it, so I had to learn that. I also didn't know anything about free radicals.

So, this was a wonderful opportunity! So I went from nutrition, lipoprotein metabolism, to a brand new area where we're learning about antioxidants, free radicals. And now the hypothesis for why does atherosclerosis happen is because atherosclerosis—those scavenger cells that I was expert in growing are taking up modified LDL. And the thinking is the modification is oxidation. And the whole, while I'm busy studying vitamin E, the atherosclerosis people have figured out that what happens when you have high levels of LDL, it goes under the cell lining in the artery wall. It gets trapped there. Macrophages try and get it. They spit out bleach, which oxidizes the LDL lipids, and we have a whole oxidative theory of atherosclerosis.

Now, you end up then with macrophages scooping up all of these LDL particles, digesting them. Cholesterol accumulates; bad things happen. We recruit some more; more damage happens. Pretty soon you have a big atherosclerotic horrible lesion. And, "Hah! We figured it out. All we have to do is eat vitamin E to protect us from atherosclerosis." And the very first study that was done in 1996, the CHAOS [Cambridge Heart Antioxidant Study] trial, proved—they gave vitamin E to people and those people had fewer second heart attacks! Since that time is a whole another story and that's a long and hairy thing, but I only stayed on the periphery of atherosclerosis, because that was not what I was interested in at the time.

I was trying to learn about lipoic acid. And long story short, I actually put together a pretty good grant on lipoic acid, and it got funded. So Packer Lab got funded. Meanwhile Maret's going, "This is not getting any better. Packer Lab is funded; Maret Traber still isn't funded and has no money in her own name." And UC Berkeley, if you were not hired to be a faculty member, you were not a faculty member, and you cannot even write a grant, let alone get your own money. So being in the Packer Lab—good for intellectual stimulation, very bad for your future.

So, I made friends with people at Davis. Davis was much more open-minded. They said, "We like indirect costs. If you want to write a grant proposal, and you get it funded, we're happy. Just send the money our way." [1:10:00] I said, "Well, what choice have I?" So at that point was the tobacco settlement. And so I came up with some proposal on: we now knew there was a protein in the liver of mice, the tocopheral transfer protein. We'd done some mice studies. Now we're going to take those mice and see if we can expose them to cigarette smoke. Would they get atherosclerosis faster than—? All kinds of crazy stuff!

But good enough, Maret gets her first grant. Meanwhile, I'm looking for a real job. And the real job is the Linus Pauling Institute! Hooray! So the very first grant I get in my own name is from the California Tobacco Research—gee, I've forgotten their whole title, but it was TRDRP—maybe it's the Tobacco Research Program. It was from the tax money that went to the state to do research on tobacco. And there I was, now going to Oregon. My money's in California. However, the people in Oregon are very open-minded. They said, "Sure, you can get money. You can be a member of the faculty at UC Davis. You can get your California money, and you can live here in Oregon. It's perfect." And I said, "Really? Everybody's okay with this?" Everybody was okay with it, and that's what happened.

CP: Wow. So when you started at LPI you were actually at UC Davis?

MT: Yeah.

CP: How did the connection with LPI come about in the first place?

MT: Okay, so the connection with LPI came about because I was recognizing that Lester Packer was not a young man, either. And when I'd first asked how many people are in his lab—remember, I came from a lab that had usually three and sometimes four people, and I was the one that was really driving everything in that lab. And so, to find out—I was talking to a group of maybe ten or fifteen people at this meeting that I went to in Charleston, South Carolina. This was a dinner party for the LPI—excuse me, for Lester Packer's lab. And I was like, "Wow! So many people! How many people are in the lab?" And they all kind of look at each other and chuckled. Nobody knew.

The reason nobody knew is because usually there were at least 30 people in the Packer lab. He had people who would come for sabbatical. He had people who would come for a couple of weeks. He had people who were there for years. It was, like, chaos. And he had three or four different areas. There was the skin group. There was the lipoic acid group. There was a couple of other things that were going on with different—you know, "What is the antioxidant of the week?" studies going on. And so it was all kind of crazy stuff going on. And part of the having a bunch of people visiting the lab

is senior scientists who had some time to kill, or wanted to do something different, kind of sabbatical, but they never were actually lab people that I saw.

But one of them was Leopold Flohé. He came to the lab, and he basically was retired from his job in Germany and he was looking to start doing something else. And Lester invited him to come and write a grant proposal. It was kind of the typical thing that Lester does with people—

CP: [Laughs]

MT: —that he doesn't know what to do with. And so Flohé was incredibly smart, incredibly good. He had been in a company that had a gazillion people. He was a selenium expert. And so selenium and vitamin E have been working together for years and years and years, so it was obvious that I should help Flohé. And I can type, and he can't. He can think; I can think. He can think better than I can think, but I can change his English to a more American English, so it was okay. And he had no control over what went on the paper, because I was typing. So this all worked really well, and so we got to be really good friends. [1:15:00]

And he told me about what his wife was doing, and his wife was at the German Institute of Nutrition in Potsdam, and Potsdam is in East Germany. Only, this is the—all kinds of exciting things going on in politics—this was the time of German unification. So West Germany had taken over East, and they were now trying to turn this Institute of Nutrition into real science. So they had sent this molecular biologist to be in charge of the nutrition program. And the nutrition program was not stellar by any means, but what they had been doing was looking at vitamin E metabolism.

So I had been looking at its transport. Oxidation was entirely too much chemistry; I didn't want any part of that. But metabolism, this was like something totally new. So vitamin E is a couple of rings and a tail coming off. And at the end of the tail we're putting oxygen, and turning it into a carboxyl, and then beta-oxidizing the tail away, and now we turn vitamin E into a water soluble compound that's excreted in urine. So this was like, really? That's crazy! So I got an invitation to got to Potsdam, so I could go for a couple of months and learn about this vitamin E metabolite.

Very interesting experience. The people in East Germany were on ultra-slow. You come in at eight o'clock in the morning. You have a coffee, then you wash the dishes. Then at ten o'clock, you have a coffee break, then you wash the dishes. At twelve o'clock you go home for lunch for an hour, and you come back. You don't have a coffee in the afternoon because that's just too much, because you have to be ready to leave at four o'clock so you can go home. And the Institute of Nutrition was in this old, crummy building, and they had done some remodeling of it. The woman who was doing tissue culture was doing tissue culture because she had been employed as a technician for over twenty years. She had worked in that one room and they were going to make that a tissue culture room, so she was going to learn tissue culture so she could stay in her room.

The method for the vitamin E metabolite involved taking a urine sample, lyophilizing it, digesting it, taking some period of time to transform it, and then do mass spec. And any experiment would take months, because the philosophy here was: reagents were expensive; they were hard to come by. You had to sit around a table and do a lot of thinking, and carefully design so that you could carefully order exactly the chemicals you needed, and you had to be very judicious in the use of these things.

So to have some crazy woman from the United States come in, who abandoned her husband, and start first thing in the morning, skip coffee break, eat her lunch at her desk—and they knew I did that because my office desk was in the coffee break room where they were having their coffee break. And then I would stay late and get two eight-hours in a day done, because I didn't have anything else to go home to! I didn't understand most of the TV channels on the German TV. I didn't have a car. So I might as well stay there, get my experiments done, so I could learn about—I was actually trying to clone the tocopheral transfer protein, which I was unsuccessful at—but in my spare time, I was learning about this vitamin E metabolite.

And so I got some deuterium-labeled vitamin E, the right and the left stuff, and we gave it to people in Germany and collected their urine, and looked at the metabolite in the urine, and lo and behold, it's actually more aggressively metabolized, the left-handed synthetic form. So that was exciting! So I had all of these things that I wanted to do, and there I was, and you wanted to know how did I get to Berkeley—or how did I get from Berkeley to the LPI?

Well, when I got back to Berkeley, it was like [sighs]. There was an announcement, an ad. [1:20:00] And I knew that Lester was writing a letter for Chandan Sen, and I thought, well, if I'm supposed to be this independent soul, I should be able to find people around the world who know me who can write me letters of letters of recommendation, and I could look a little more independent. I wasn't going to work on lipoic acid; I wanted to work on vitamin E. And so here were some new things, and here were some things I was interested in. And so I sent in my application. I think I told Lester I was going to do this, but basically didn't have a lot of optimism.

I did get an interview. I came up. I was so excited about the prospect of becoming a professor! It was like, "Wow, I can have my own lab. That would be so wonderful!" And there was the kind of thought that maybe, well, they might be hiring two people, but they'd already picked out one. So, I was very disappointed to hear that they picked Tory Hagen over me. He knew about lipoic acid too. He'd been working in Bruce Ames' lab. He knew Balz for a long time. I was like, "Oh, this is terrible." So I was so depressed and unhappy that we went to Fry's—Fry's is that giant electronics department store—and we bought a big TV. My husband was standing in front of a 48-inch TV, and there was a 60-inch TV, so I said, "What's wrong with this one?" So we went with a giant TV. So I got a giant TV.

And about, I don't know, a month, maybe three weeks later, Balz calls me up and says, "We've decided to invite you for a second interview, and you have to give another seminar. And we're considering that rather than doing another search, that we would have another position." And I said, "Okay, great. I'm there." So I came up again and I gave a research talk on a entirely different topic than the first one, because I figured, if I can do everything, I might as well tell them I can do everything. And lucky for me, yay, they offered me the job, which was good.

And then, even better, I got the money to do research on those knock-out mice that I had down in Davis. And so it was actually the research office that basically said, "Okay, we can see that this would work out okay. So, fine. You can be a faculty here and you can be a faculty there." And I think California didn't have any rules so long as the money was going to UC Davis. And Carroll Cross, a faculty member down at UC Davis, worked with me. He was the one that managed the money. He had the mouse colony. The post-doc was down there.

The mice were never terribly successful. I've run out of ideas of even how to approach the mice. The problem with the mice—vitamin E is required to prevent fetal resorption, which means that if you're trying to get mice to breed and have babies, so you can have mice, you have to feed them enough vitamin E so that they can breed and have babies. If you do that, you have babies that have lots of vitamin E. So now you don't have really good subjects for your studies. Other people have gone to the feed the mice with vitamin E-deficient diets, all kinds of little tricks. We were to the place where we were getting one homozygote mouse for every homozygote mouse we were starting with. And it was like, very expensive and not very productive, and it wasn't obvious that there was anything we could do there that was terribly useful.

CP: Well, tell me about the transition to Corvallis, sort of initial impressions of OSU, Corvallis, LPI, and settling in.

MT: I died and went to heaven! This was the first time I get to do whatever I want. That was exciting! I had my own lab. I had my own office, which was too hot to even sit in in the summer in Weniger, facing the west. [1:25:00] So I moved into the lab across the way. I mean, I was thrilled! My husband walked around, looking at the ceiling and saying, "Why are all of those pans in the ceiling?" Well, they couldn't figure out how to fix the leaks in the ceilings, so what they did was they put pans in the ceilings that collected drips.

Turned out—fast forward. I finally got my own mass spec, and there was a student upstairs in the greenhouse who forgot to shut off the water. We had a flood upstairs, dripped over my mass spec. So, Facilities came in and put in a pan in the ceiling over my mass spec, and a drain, so when it dripped on my machines it was—. So I think, remember we were talking about Berkeley and machines, and how I didn't want to do math? I would tell you my lab now—machines, very expensive, fancy machines. We are trying to measure very small quantities of metabolites we're interested in. Requires very fancy math.

I have a NIH-funded project that's going to take place at the NIH any day now. It's to study vitamin E pharmacokinetics in women, obese women, obese women with diabetes. We're going to feel one dose of labeled vitamin E and inject another dose of labeled vitamin E. And that study is what I did in guinea pigs with radioactive cholesterol when I was a graduate

student. So, what goes around comes around. But basically math, fancy machines—that's my life. At least I can see how to get from the machines to people, so that makes sense.

The thing about coming here is I was then—so, you heard deuterated tocopheral lots of times already, but basically I felt there were a lot of studies we could do that hadn't been done, looking at oxidative stress. Because when I had done them before, we were looking at transport. We now understood transport very well, and well, if you have oxidative stress, do you need more vitamin E? A relatively straight-forward question—not too easy to answer.

We did that by looking in exercisers, cigarette smokers—you can't really do it in diabetics normally, because if somebody's got high sugar, ethically you ought to take care of the high sugar because you know that's bad for them. But if a person is generating the oxidative stress themselves, like with an ultramarathon runner? Ultramarathon was a 50 kilometer race run up and down the hills in Peavy Arboretum. So that was my first PhD student's project. We had people who ran the race, and then sat in front of their computers for all day long, and how did the turnover of vitamin E change? And what about oxidative stress? So, answered that question. We did it then in smokers, and began to understand: what is the importance of metabolism?

So I think I'm one of those people that facilitates other peoples' being able to do research, because I had such difficulties, and nobody would help me, that I guess I'm pretty sympathetic. So Angela, who did the exercise study—her husband wanted to live in Bend because he could get a job there. And I said, "Well, it's up to you. If you want to drive through the mountains, sure, go ahead. Move to Bend, and we'll communicate by email, and we'll get things done." And we did. So that was the first of the commuting students.

Then I had a student, Tyler Barker. He was working with me, but his wife hated the rain in Corvallis. She thought it was awful. And he was really unhappy. And so I said, "Well, yeah, if you want to go back to Salt Lake," which was his plan. [1:30:01] He had a group of physicians and a physical therapy place where they wanted to employ him. I said, "If you can figure out a project there, and get all of the IRB approvals there, and get the physicians to work with you there, and we collect the samples, I will let you do this remotely." And we worked it with his committee, and so once he passed his orals, off he went. And I'm thinking he may have actually done his presentation, his project, to his committee. He physically came here, but the whole thing was going to happen there.

And everybody said, "Well, if you can make it happen, good for you." Angela, the first student? She was studying the runners. Well, she decided she needed an exercise science degree. So I went over to Tony Wilcox in the Exercise Science Department and said, "Tony, I have a student who wants to be a graduate student in your department, and I want her as my student, so could I please be faculty in your department?"

CP: [Laughs]

MT: And he said, "Oh, okay. Sure." So we just make things happen. I'm trying to think.

The zebrafish! That's my other student, Galen Miller. I told you the mice didn't work out well, and I was worried that the mice didn't work out well because E is needed for implantation. So if you go to a fish model, the fish lay eggs, the eggs get spawned; they turn into little embryos and turn into swimming fish. And with zebrafish, this happens in five days. So hooray, hooray! And if you've ever talked to Robert Tanguay, he could talk the birds out of the sky. This man is so convincing! He's wonderful. He's fantastic! High Throughput Screening. Evaluation of toxicity.

I'm thinking, "All right. If I make the zebrafish E deficient, it'll be like they're toxic. We can figure out what's wrong with them. It'll be perfect—great model." I talk to Robert. He says, "Sure, come on by." So I bring over my student; hooray, hooray, it's all going to work. [Sighs] The actualities of science are never as easy as the, "Yay, these are the successes!" It took some time. We figured out how to feed zebrafish. Zebra fish were, at the time—if you go to the aquarium store, you buy fish food, and you drop fish food, they eat fish food. What's in fish food? Fish meal, fish oil, stuff, things, wheat, who knows what? Other stuff. Nobody knows what's in fish food.

I said, "Okay. I'm a nutritionist. We need proteins, we need calories, we need carbohydrates, we need fat, we need some vitamins and minerals. Okay, let's try something." And so we figured out a diet. It took a little coming and going, but we got the diet. Then I said, "Okay, we can feed the fish. Now we can get E-deficient eggs, because we can put the E in or not

in." Good, we got E-deficient embryos. The little bitsy, baby five-day-old fish are swimming around. They have mouths so tiny they eat paramecium that are swimming around. They don't eat giant flakes. So we've got this problem. We can make big fish E-deficient. We can get eggs E-deficient. We can keep the eggs for five days, but between five days and 40 days, we have a problem. So we still haven't figured out that problem.

So, the other thing with zebrafish—we discovered that those embryos, they have fertilized eggs, they turn into little fishies, but by 48 hours they are not looking good, and by five days, 70 percent are either dead or so sick-looking, they're not going to make it. So we discovered the embryo needs vitamin E. We've just published a paper on: what are the genes that are important? [1:35:00] I'm not so sure I buy what the genes are important, but that's a different story. I think what's important about vitamin E is it's protecting polyunsaturated fatty acids, which is why I need really fancy, very expensive pieces of equipment, to look for oxidized fatty acids, depletion of which - fatty acids in which lipids...that's another story.

But it turns out there's a special thing you can do with zebrafish. When you have the egg, you can inject a morphelino. Morphelino is a special sugar that binds to where the RNA is being translated. So you take the gene and translate it into messenger RNA. The morphelino binds there, screws up the machinery, and you can specifically target a given protein. So we could knock down the tocopheral transfer protein, and that was really the major part of Galen Miller's project. So if you inject the TTP morphelino, you knock down TTP, and where it's being expressed is in the brain. And the brain expression—if you knock that down, those animals are dead by fifteen hours. And what it looks like is the vitamin E is in the yolk, has to get from the yolk to the brain somehow. We don't know how.

Once it's in the brain, it has to be trafficked properly by the tocopheral transfer protein. At the same time, the brain is starting to form. It's making the polyunsaturated fatty acids you've heard about: fish oil, DHA, EPA. Arachidonic acid is another one. Those are polyunsaturated, ultra-polyunsaturated. They have five and six double bonds. They are highly oxidizable, and the brain is chock full of them. And just when you're starting to up-regulate the synthesis of those fatty acids, getting the brain ventricles to inflate, that's when the brain doesn't form and [sighs]. So that's how I got to the LPI, and that's what I'm doing, and that's how much fun I'm having!

CP: Well, in listening to you and hearing your story, it strikes me that your career has flourished at the same time the institute itself has flourished. It came here as a struggling organization, really on life support, looking for a home, and now it's a thriving organization that's a source of a great deal of good publicity for the university. I wonder if you could—you've been here almost the whole time it's been at OSU. Could you comment on sort of the advancement of LPI, Balz's leadership, and very consequentially, this new building that we're in?

MT: Alright. So I came here in 1998, in May, which already tells you something about the lack of understanding of how the quarter system works when you're doing research, because you don't care about the ebb and flow of students. You want to get going; you want to set up your lab and make things happen. We started off in Weniger. It was me, Tory, Rod Dashwood, Balz, Barbara MacVicar. We had to get people. We had to make that place work. I was especially in a bad position, because Balz said, "Yes you can have a faculty position, but you're coming in as an associate professor and without tenure." And so it was clear in order to succeed, I needed to get money, and I needed to get money fast. So I worked very hard early on at getting money, getting equipment, getting an NIH grant. I think that was really the push. I think what's been fantastic about Balz is he's very much a, "Go do whatever fun you want to have. So long as you don't need anything, don't bother me."

CP: [Laughs]

MT: And that's been fantastic. The idea of having an oxidative-nitrosative stress core lab largely came because of this idea of measuring oxidized molecules. While I said athlerosclerosis was not near and dear to my heart [1:40:02], it was very much on Balz's agenda. And we both were very interested in oxidized lipids. So that's how we got the triple-quad mass spectrometer. That was the beginning of being able to really be acknowledged as leaders in oxidized lipids, which I think we are probably one of five labs in the world that do that very well. Most people say, "Gee, that's too hard." We're now working on metabolomics, measure everything.

So I think what you see is if you give people the right environment, you can expect all kinds of exciting things to happen. And I think it's been fabulous, because whatever I want to do? "Sure, go ahead. Do it." And I think it's been a fantastic nurturing environment. And I think Balz's vision of recognizing that people on the outside don't understand that, "Why

is vitamin E important?" is an important question. They think, well, why would you care? I care about my health. What about Alzheimer's disease? What about heart disease? What about cancer? Could you please work on those instead?

And what they are missing, but Balz did not miss, is that you need vitamin E to protect you from all of those diseases, and we're at the step before you even get to those diseases. But to understand that, and to get the public to say, "Oh, okay. Vitamin E really is important for my brain." They may not appreciate the zebrafish brain story, but they certainly appreciate when they see on the news vitamin E supplements are beneficial for Alzheimer's.

So at the same time we have this LPI growing and flourishing, what we also have out in the science world is: antioxidants, your name is mud, and worse, going on. And there's been a huge backlash. I think part of it is the medical community. They understand a drug; they don't understand good nutrition. No doctor wants to sit around for an hour discussing your diet and explaining to you that, "No, you really shouldn't eat hamburgers and French fries. You should eat a nice, green leafy salad and some salmon. That is what you should eat." They don't have the training; they don't have the background. They don't have the knowledge of what is good nutrition.

And I think part of the reason LPI gets the publicity they get is that people can actually relate to what we're talking about. They don't have a good source. I mean, I think the crowning achievement, of anything of the LPI, is the Micronutrient Information Center. When it first started off, it was like, "Really? This is stuff I already know. Why would anybody care about this?" Now, literally, the USDA links to us to find out about nutrition.

So that's the kind of leadership that Balz has had. That lovely building, Weniger—when I first got there it was heaven because it was my very first lab. I was looking at pictures of the place the other day, and I was like tears in my eyes. I left my first lab. I think I was more broken up about leaving my first lab than leaving my first house. But the labs here are fantastic! They are beautiful. They are modern. They are easy to work in. I don't know if I should say, but I will anyway because I always say the wrong thing. They are too big!

CP: [Laughs]

MT: They are so big, I have my labs in the middle of the big, long—so, to explain how big they are, the labs are one big lab the length of the entire building, and that's a city block. [1:45:02] My lab is in the middle of those. My lab is also the Oxidative Stress Core Lab, which is down at that end. And over here in the middle I also have a small area off to the side, where on one side of the hallway I have some more fancy equipment, and on the other side a tissue culture room that we use as a dark room because vitamin K, which is my new passion, has to be done in the dark. And we have huge, big windows the whole length of the building.

So to do vitamin K, my technician has to go like into this little closet to work, to isolate the samples. But if I need to find somebody? I mean, it's like you put GPS on them all and just say, "Where are you, so I can follow you around?" You start walking one way, so I have my step counter on so I can find out: how much did I walk around the LPI today? But that's kind of a, gee, what a horrible problem to have. We've been very happy with the facility. We had our big flood; that was a disaster. The good news was none of the labs got impacted at all. My office got ruined and I had to move out for six months, but really not such an awful thing. As long as I have my computer I'm a happy camper.

One of the neat things is when you go to meetings and you're wearing the badge that says Linus Pauling Institute, it's amazing how people come up to you and say, "I knew Linus Pauling," or, "I admired Linus Pauling." I'm always disappointed I didn't ever get to meet him. But I think he'd be pretty excited about the work we're doing to figure out the right molecule in the right place.

CP: I'm sure, yeah. It must have been a special thrill for you to become an Endowed Chair in 2011, considering you had such a hard time finding a scientific home. It must have been very gratifying.

MT: It's like a miracle! [Laughs] The endowed chair is thrilling, because it sort of sets you apart. I still have the goal of becoming a Distinguished Professor, so there's always—you know, it's never enough. You want the next big thing. And really, the becoming Distinguished Professor made me a little bit looking back, and how do you integrate the whole thing?

And it's kind of—it's kind of scary when you look at, okay, now I have published over 180 peer-reviewed papers. What did all of those papers say, and how did they fit together? What kind of story? I have really tried to focus on vitamin E,

despite my little junket into lipoic acid. I guess I have kind of the infamous ability to—I've done studies in pigs, in sheep, in cows, zebrafish we talked about, rats and mice, people. I've done tissue culture studies; I've done guinea pigs. Most of them, except for the guinea pigs, really have all been related to vitamin E. I don't like tissue culture studies of vitamin E because of the specific transport mechanisms.

So once we figured out the transport mechanisms, tissue culture is not useful anymore because now I'm studying interactions. I moved—the first one was easy. That's E and C, and I did that because it's well known in chemistry that these two talk to each other. It was really hypothesized that E should be recycled by C. And so to do the studies in people to show that's true, that was kind of a no-brainer. The harder one, that's been difficult to work on, is vitamin K. So I was on the panel that came up with the latest recommended dietary allowances [1:50:00], and it was called the DRI Committee, Dietary Reference Intakes.

And that committee, for the first time ever, they took a new approach to figuring out dietary recommendations. They said, "We are going to read the entire literature. We are going to pick out articles that have bearing on what we want to know. We are not going to be limited to studies in humans, but we want to focus on humans, so human studies would clearly be the best." And the antioxidant panel I was on, we had the charge of vitamins E, C, selenium and the carotenoids, and anything else. And we threw anything else out the door, because we said that was too much. I became the chair of the small group working on vitamin E, and part of our charge was also to come up with: well, how much is too much? And nobody had ever done how much is too much for vitamin E. For selenium, this was kind of well-known from industrial sites. You could actually have toxic levels of selenium. But for vitamin E it was kind of like, well, it's the non-toxic vitamin. A and D are the lipid-soluble toxic ones. And long story short, the estimates were 36 grams a day for a 70-kilo person, based on rat studies. And since there was a lot of concern on the part of the toxicologists: really? 36 grams? That seems like a lot. [Phone rings] Oops, my phone's ringing. We'll ignore it. Do you want to stop?

CP: We're almost done.

MT: So the toxicologists basically said, "Uncertainty. We have uncertainty." And the uncertainty factor they came up with was 36. So they get a nice number of one gram, and it's based on absolutely nothing. The idea is, if you eat too much vitamin E, you get bleeding. And that was seen in rats, and they could give the rats more vitamin K, solve the problem. So the kind of impression I'd had from being in the vitamin E medical world was: E and K interactions? We don't actually think they happen.

I then heard John Sutty. John Sutty gave a talk for his retirement. He is, like, the giant in vitamin K. And John Sutty was explaining the different forms of vitamin K, and I'm looking at it and went, "Wow! The tail of vitamin K is the same as the tail of vitamin E. Hm." And he pointed out to activate K in the body, you take off the tail, you put on an unsaturated tail, and now you have the tissue form. And I said, "I know how that happens!" He said, "I've been working on this my whole career. There is no enzyme that unsaturates the tail." I said, "Well, of course not. It's vitamin E metabolism. You put oxygen on the end, you beta-hydroxilate this thing, you get it down to a carboxyl group. You can now hang on another tail—easy, easy peasy." I've got it! I figured it out! I wrote a grant proposal. It was convincing.

We did the first experiment! I was entirely 100 percent wrong. Not only that, but vitamin K concentrations in the plasma —10 thousand times lower than vitamin E. My student, my technician—they're looking at me going, "Maret, this is not easy. This is a noise-peak-noise." I went, "Yeah, well, you've got double the baseline! What more do you want? Just calculate that. It'll be fine. We'll think about it. It'll work."

CP: [Laughs]

MT: We used labeled vitamin K. We gave them huge amounts of vitamin E. Everything we tried—and the most exciting part of this project? So the study design is you feed rats labeled material. [1:55:00] You inject them with vitamin E. You should be able to see: where did the label go? And from all of my experience with labeled vitamin E in rats and animals, I knew it takes a long time. So where? The brain. The brain with vitamin K changes very quickly from this saturated to unsaturated form. Three weeks we fed them deuterated vitamin K; one week we injected them. The end of the week, sacrifice the animal, look at the brain. Ninety percent is the unsaturated form of vitamin K. No change in vitamin E. Look at the liver. It's all the original form we fed. The vitamin E is 100 times higher than normal, the metabolite 1000 times

higher than normal. I'm looking at it going, "[Sighs] What is going on? How can the brain change so fast? What's going on in the liver?"

We have some new hypotheses, but we have rats down in the basement we're feeding right now, in the hopes of trying one more time to come up with: okay, we got it this time. But I think one of the things that are hardest to do in nutrition are these interactions. And where you have clear chemistry, that makes sense. The E-K interaction seems almost accidental. Something else is going on. And so to kind of tease out how to do this, how to figure it out, and with having the challenge of K, there are 17 different K-dependent proteins. They regulate calcium. They are important everywhere in the body. K has this very fancy system for oxidation and reduction, so K gets oxidized to the epoxide, and then gets reduced again. And this cycle, 500 times that happens for a given molecule. It's just mind-boggling, how complicated K is.

And the antioxidant property of vitamin E is like peripheral to the whole issue of what's going on with K. Yet, I got into this because we're looking for adverse effects for vitamin E. In the human literature, there's the meta-analyses that said vitamin E kills you. I said, "How could this possibly be, if vitamin E—I can't even kill rats with vitamin E. How can it kill people?" But I've been thinking very carefully. What you see with excess vitamin E in people—hemorrhagic stroke, left ventricular dysfunction, which means the left side of your heart that pumps blood into the circulation, that side of the heart gets bigger and proliferates because it has to work harder. It has to work harder because of high blood pressure. The other things that go wrong? Bleeding, oh, and there's effect in bones. There are people who claim that high levels of E did bad things and causes bones to weaken. What does that have to do with E and antioxidants?

I think it's K. You heard it here first! I think what happens is there are those 17 K-dependent proteins regulating calcium. Vitamin E is decreasing the vitamin K levels down, so there is no—there is not enough vitamin K for those proteins. Hemorrhagic stroke? That's easy. That happens in babies. They're given vitamin K at birth because of brain hemorrhages. Left ventricular dysfunction? What happens is there is a protein called matrix gla-protein. It's chelating calcium in the artery wall. If you don't have enough vitamin K, it doesn't chelate. The calcium precipiates on the wall. [2:00:01] You have a stiff artery. Blood pressure goes up; left ventricular dysfunction happens. Bleeding? Everybody knows vitamin K is important for bleeding. Turns out if you have bad enough vitamin K, you will bleed.

So it's probably happening in the liver, and it's probably secondary to all of those things we've just talked about, brain and heart. And then bone is the most exciting, because we really haven't heard a lot about bone and vitamin E. There's only one study that was in rats, and our study in rats didn't support the study that was published, so I think the amount of K in the rat diet for the published study wasn't enough. So I have the hypothesis. I've written the grant proposal once. They didn't like it, but they didn't like it too badly, so I have the chance to turn it back in. So that's what I'm thinking about these days. But that's the adverse effects of vitamin E, and I forgot what the question was.

CP: [Laughs] So did I.

MT: [Laughs] I can talk all day long.

CP: Well, I really appreciate this, this has been a lot of fun, and I appreciate you sharing your story and participating in our project. Thank you very much.

MT: Thank you.

[2:01:19]