Han Wen
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by David Zierler
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DAVID ZIERLER: This is David Zierler, oral historian for the American Institute of Physics. It is March 2nd, 2020, and is my great pleasure to be here with Dr. Han Wen. And would you please spell your name and give your job title and affiliation here at NIH for our interview?

HAN WEN: Great. Yes. It's my pleasure to have this opportunity to talk with you, David. So my name is Han—H-A-N. That's my first name. [laugh] W-E-N is my last name. And my job here at NIH is a senior investigator. I run the Imaging Physics Laboratory in the Biophysics and Biochemistry Branch of the National Heart, Lung and Blood Institute, which is one of the institutes of NIH.

DAVID ZIERLER: OK, great. All right, so for this interview, we're going to start right at the beginning. Tell us where you were born.

WEN: I was born in Beijing, China, in 1968.

ZIERLER: OK. And your family? Talk a little bit about your family, where your parents came from, what their jobs were.

WEN: My parents were both researchers in Beijing, not in the physics field, but in the field of economy and transportation.

ZIERLER: Both of them were?

WEN: Both of them, right.

ZIERLER: Did they encourage you towards science? How did you develop initially your interest in science?

WEN: My parents did encourage me. And my father was in the field of truck design and vehicle design, so I had influence from him, and I got interested in engineering and tinkering with things at a pretty early stage.

ZIERLER: And you went to Peking University?

WEN: Yes.

ZIERLER: And so now we are 1989, and where are you placed in the United States?

WEN: I had some choices, and I picked the University of Maryland, here.

ZIERLER: And you never left the neighborhood? [laugh]

WEN: I never left the neighborhood. It felt like it was the right pick. So I came here.

ZIERLER: And what about the University of Maryland attracted you?

WEN: I was interested in sort of the broad range of physics that was going on here. So there was a pretty strong particle physics program right here, and there were people working at Fermilab back then doing experiments. And there were theoreticians also. There was Dr. Greenberg. I remember I was taking his particle physics classes. There was also an astrophysics program here that was pretty big, and I was really intrigued by that as well.

ZIERLER: So you weren't looking yet to specialize right away. You wanted broad exposure.

WEN: Right, right.

[location change]

ZIERLER: So what's an example of that as a graduate student at the University of Maryland, in terms of the lab work that you were exposed to, in terms of the kinds of classes that you were learning? How did you get that initial sense that it's being done differently here than it was being done in China?

WEN: Right. I don't remember a lot now, but I remember an experiment in microwave transmission and microwave absorption by a material, and I remember that this experiment was done at University of Maryland as part of our physics teaching, basically. I remember that we went in, and we collected data, and we basically scanned the spectrum of different wavelength going through. It might have been the Mössbauer effect, something related to the Mössbauer effect. But there was a theory, and then when we collected data, it came out that the spectrum had had a certain phase shift to it, and it looked different from what an ideal spectrum would look like. And I remember applying some of the math things that I learned in undergrad to the spectrum, and then tried to explain why was there a phase shift, what could possibly cause that. And I wasn't sure whether my theory made any sense or not, but I had to think of something that's actually practical on an experimental level to explain certain things of that sort. And then after submitting this to the teacher who looked at it, and I remember getting

the comments back to say, “What you said makes sense. It can very likely be happening. And therefore you did fine with this experiment.” So this, it feels different than the Chinese setting.

ZIERLER: Who were some of the mentors at the University of Maryland that you became close with, that you learned from, who guided you? Who were some of those people?

WEN: Michael Fisher was my PhD advisor at Maryland. So actually, my PhD was done—I switched groups a couple times at Maryland. So they gave us the opportunity to try out—

ZIERLER: Within the physics department, you switched groups?

WEN: Within the physics department, right. Then I went to Michael Fisher to learn about phase transitions and quantum statistical physics, essentially, and I was his TA for a bit, teaching a graduate level course I didn't take myself—actually I hadn’t taken.

ZIERLER: [laugh]

WEN: But he gave me the class notes, and kind of a draft of a book. I guess he should publish that book. So Michael taught me a lot about thinking about things intuitively, number one, as I was saying. And the other thing was organization. He was really an extremely good organizer of his thoughts and his material, and paperwork, et cetera. And I thought I organized things more or less, but then I learned what real organization was. And so he hammered into me to organize things and be precise about what I was thinking about or was writing down. So then part of the PhD—I did my PhD in a joint biophysics program with NIH.

ZIERLER: Oh, really?

WEN: Yeah. Between University of Maryland and NIH. So it was in two just totally different fields. One was statistical quantum mechanics where I did some things with Michael—and we actually had a *Physics Review Letters* paper published with Michael. And my other half was at NIH. And here my mentor who was Bob Balaban, Dr. Bob Balaban, who is now the scientific director of our institute, basically. And here I signed on to this program and they—I was I guess the only candidate for that year. So they took me around the different labs, and I had a choice.

ZIERLER: So there was a partnership between University of Maryland and NIH?

WEN: Yeah, right.

ZIERLER: And you applied for this partnership?

WEN: Yeah, I applied to it.

ZIERLER: So what was your status here? Were you a graduate fellow?

WEN: Graduate student.

ZIERLER: Graduate student.

WEN: Yeah. But they had some stipend support for this position. So they took us around to different labs, and eventually I was really intrigued by MRI. So Bob Balaban back then was doing high-field MRI, which I may have mentioned. I can talk more about that, but basically back then, high-field—the field strength has gotten to several teslas, like four teslas. And it was really just the very beginning of the exploration of what things were going to be like at such high fields, especially over the whole human body at that scale. So I got intrigued in MRI. I never

heard about MRI until then. And I thought this idea of converting a time domain signal into a spatial domain information is something I've never come across, actually.

ZIERLER: What does that mean—time domain signal into a spatial domain signal?

WEN: Right. So it turns out in MRI, the spectrum of the time signal, which would be a frequency spectrum, maps to space—where something is. So basically imagine you've got some sort of a profile in space. That basically gets turned into a spectrum in frequency and time. And this is what MRI does—this phenomenon. So it just converts between space and time. So I found this—I'd never come across this way of imaging. I mean, imaging would always be space to space. You would have lenses that convert some space profile to some other space profile. It might look different—it's transformed in some way—but here's something that converts a spatial distribution of some kind of spatial information to a time domain information.

ZIERLER: Now, was there something about Professor Fisher's research that guided you towards NIH, or this was your own independent interest in learning more about health science research?

WEN: It was my own interest. I remember there was a flyer somewhere that had that information, so I just looked at it and thought, "This is interesting." Yeah, so I signed on. I think it was at the end of 1991. And I started here in 1992. So I was doing some work over at Michael's lab and some work here at NIH.

ZIERLER: So what was your dissertation topic?

WEN: It was magnetic resonance imaging, so my thesis was written about MRI. I did have one chapter, I remember, on statistical quantum mechanics in that thesis [laugh] which is on a phase transition index estimate that I did with Michael that wasn't related to MRI. But Michael himself took interest in the MRI as well, so we actually had a lot of chats about MRI.

ZIERLER: So the technology of MRI in 1991, 1992, looking back now, how developed was the technology in terms of its usefulness as a diagnostic tool for patients? Was it very primitive at that point? Was it pretty well developed? Where did you enter into this field, would you say?

WEN: It was well developed at 1.5 tesla. So the MRI field at that point was moving up the tesla scale. So basically—

ZIERLER: Can you explain what that scale is?

WEN: [laugh] Right. So tesla is a measure of how strong a magnetic field is. And so the whole MRI is based on putting a person into a very uniform but pretty strong magnetic field, such that all of the protons are magnetized in a way. So we know that protons mostly in water—the two hydrogen protons, they're not paired, so they have their nuclear magnetic moment that's exposed to the magnetic field. So they are going to be slightly polarized by the field. They tend to line up with the field. And that's the whole basis for MRI, because one can then manipulate that spin or that magnetic moment as a little magnet. Make it precise essentially. And the precision is then going to generate a radio frequency signal that somebody—we can detect with radio frequency circuits. And that information then tells us quite a bit about—first of all, it's water. The proton—the hydrogen is mostly in water, so it tells about water content in tissue, number one. And number two, what the water is experiencing. What is it doing? Water is

pretty dynamic in the body, right? It flows around, interacts with protein, with all the macromolecules. So the way the little magnetic moments, they relax or they go back into somewhat equilibrium, has a lot to do with the environment itself. So everything depends on magnetizing the body [laugh] in a way. Turn the body into a little magnet, basically. So that basically means how strong the magnetic field can be. So technologically, back then, started out I think at 0.1-some tesla, and then 0.5 tesla.

ZIERLER: In terms of how strong the field was?

WEN: Yeah, right. And so by the time I started working in this field, it got to 1.5 tesla superconducting magnets.

ZIERLER: And this is a matter of how advanced the machines are?

WEN: Yeah, that's right. So it's basically a matter of the technologies to build superconducting magnets at this scale, at this size, that the whole person can go in. So it's a donut, basically. So hospitals back then all—at least in the United States, the more advanced hospitals—all had 1.5 tesla scanners already. And so basically from basics physics principle, you know that the stronger the magnetic field, the more magnetized the body is going to be, and that means a stronger magnetic moment, which means more signal can be received from the body. So the field was very optimistic that we should just keep going up higher and higher fields.

ZIERLER: Up the tesla chain?

WEN: Up the tesla chain. So at that point, GE—I think GE and Siemens both—started looking at 4 tesla whole-body magnets. So this was pretty hard to make from the wiring to make the superconducting wires and keeping it at the liquid helium temperature to remain

superconducting. So they made three such whole-body four-tesla magnets. NIH had one of the three.

ZIERLER: Very expensive, I assume.

WEN: Very expensive device. So it was a very expensive device, very experimental prototypical device. It had to have liquid nitrogen on the outside, then liquid helium on the inside, and in very inside is the superconducting coil that's actually sitting in a liquid helium bath, in fact. So the liquid helium has to be changed quite often—once a week or something like that. And the liquid nitrogen had to be changed on the outside almost every day, I remember, in the beginning.

ZIERLER: Now, I know that one of the reasons doctors like MRIs is because it's not damaging to the body like the radiation from a CT scan, for example, right?

WEN: Right, right.

ZIERLER: But as the tesla field gets higher and higher, is there some concern that the magnetic field can get so high that it could actually damage the body? Or that would never be a concern? That's just not how it works?

WEN: There's definitely concern.

ZIERLER: There is.

WEN: There is concern.

ZIERLER: What is that concern? What would happen at higher and higher fields?

WEN: Right. So for example, there are physiological effects we already experience even at 1.5 tesla fields, and at four tesla get stronger. One effect is similar to vertigo. It's that there's a—

ZIERLER: You get dizzy and disoriented.

WEN: Yeah. There's a magnetohydrodynamic effect associated with blood flow. So blood is a conducting liquid, so as it flows through a magnetic field, it can be polarized. The charges experience Lorentz forces.

ZIERLER: Is that because there are metals in the blood? Is that what the issue is?

WEN: There are ions in the blood. There's sodium. There's chloride. These are charged particles. So as they travel in a magnetic field, they're going to be bent by the magnetic field, so they're going to go one way or the other. So that kind of polarizes the blood flow essentially. And that has certain effects in the body.

ZIERLER: Aneurysms, ruptures, that kind of thing?

WEN: Not that strong, but it could potentially have neurological effects. So the vertigo feeling is essentially related to this. It's particularly strong—as we've been working in the magnets, when we crawled into the four-tesla MRI scanner facing down, and at that point—

ZIERLER: You're your own lab rat, essentially. [laugh]

WEN: Yeah, exactly. [laugh] We were going in, installing receivers, antennas, and things like that, and we could feel—the polarization in the ear canals gave us a signal of a certain orientation which conflicted with the little bones in the ear that gave us another sensation.

ZIERLER: Of balance.

WEN: That's right. So there was a conflict of the different signals from different ways we sense our orientation that caused a pretty strong vertigo effect. So definitely—and there were other concerns about, like I said, did that have some effect on the blood flow as well.

ZIERLER: So it sounds like 1991, 1992, there's an understanding that the higher the magnetic field, the better the imaging from a diagnostic perspective.

WEN: Right.

ZIERLER: But then the question is, how high can you go before you're creating new problems?

WEN: Right.

ZIERLER: Is that basically the major issue at MRI technology that you're entering into in 1991, 2992? Is that the major research question that you're looking into?

WEN: So the safety issue was not what I was interested in. So the safety issue really couldn't be addressed very well with short-term experimentation. So if we would do an experiment on let's say a mouse or something in the short term, we can do a back of the envelope physics calculation and we can basically dismiss all these factors. They're so small. I mean, there were some vertigo feelings, but what's the long-term consequence of that? We couldn't really answer in short term experiments. So those questions, they needed long-term statistical results from patients and from MRI technologists who work there day in and day out, to answer. And so when I entered, the high field MR influence on people long-term, the data had just started to be

collected. So we let that accumulate. That's fine. The question comes back to your first notion. As we go to higher fields, we expect the images to look better and better. But was that true or not? Was that really going to happen or not? And just to talk about Dr. Balaban a little bit—so I think what's great about Bob Balaban was that he was a physiologist by training. He wasn't a physicist by training. He didn't get all the math training that we got. But what he always made me do was to explain my equations with thoughts, with words. When I wrote down these integrals, whatever —"What are you thinking in the back of your mind?"

ZIERLER: And so what were you trying to discover? How to improve the diagnostic value of MRIs? What was the exact research question you were looking to answer?

WEN: So the very first question was a question that you mentioned. Was higher fields going to be just proportionately getting better and better? Especially for chest imaging. So we're in the Heart, Lung and Blood Institute, right? So we are interested in imaging the heart. And now imaging the heart meaning imaging the whole torso.

ZIERLER: And how do we define better imaging? Is it resolution? Is it the 3D imaging? What does it mean to have better imaging through MRI?

WEN: Right. So generally speaking—MRI is always 3D. It's able to either do a full 3…or do any sort of random cross-section through the body. So it has that capability. Better would mean higher signal to noise level, or higher contrast to noise level. So what that means is images, given the same amount of time we collect image, it would be less grainy and more clear. That's number one. Number two is that better contrast is important, too. That means that better

differentiation of different types of tissue, or pathology versus normal tissue. So contrast to noise is even more important in a way than signal to noise. And then the third thing is also uniformity. So it should look equally good across the body, the anatomy that we're looking at, as a diagnostic tool, essentially. And the last point also is safety. So it needs to be safe to be used in patients. And safety means no burning. No injury to the patients.

ZIERLER: And the burning is a concern as the tesla field gets higher and higher?

WEN: That's right.

ZIERLER: What kind of a burning? Like a heat burn? Like on the skin?

WEN: Internal burn. Which is pretty difficult to treat or even difficult to sense, sometimes. We may not have the nerves in the inside of the body to sense that until really later. The sensation could be different. Right. So let's—I just talked a little bit about that. So essentially the issue with high field, going to higher field, is that to excite the protons or to excite the hydrogens, one needs to put more power into the body. And it scales up roughly as the square of the tesla field. So one needs to then—if we double the field strength, we need to quadruple the power we put into [laugh] the body, to generate the same amount of magnetization, polarization, in other words.

ZIERLER: Can you just explain the basic math behind that? How does that work?

WEN: Sure. The way the spins are excited is by something called a transverse magnetic field, so it's a magnetic field that goes perpendicular to the main magnetic field. And when we apply [??] magnetic field, the little magnetic moments, they're going to then tend to—they precess around this transverse field. They're going to spin. So the dynamic change of these

magnetic moments of spinning action is what we can detect with other little antenna sitting on the outside. Now, whatever the field strength it is, we need to generate the same amount of transverse magnetic field to create the rotation or the precession, the spinning. And it turns out as we go to higher magnetic field strengths, something called a Larmor frequency goes up. Larmor frequency is the frequency at which the magnetic moments, they precess, right? So it goes up proportionally, actually, with the field strengths. And so associated with the increase in the Larmor frequency, we basically will have to generate—which basically creates a higher inductive electric field that's proportional to the Larmor frequency itself, and therefore proportional to the field strength. This higher inductive electric field is what creates heat, because it basically is like putting electrode in the body and apply voltage, or apply RF voltage. And you know electric field is associated with voltage, and power is associated with voltage squared, right?

ZIERLER: Right.

WEN: So there's a square relationship. And this really makes the power go up basically as a squared function of the field, roughly speaking. So as we went from 1.5 tesla to four tesla, it goes up to eight and nine times, the power that one needs to put in. So that definitely causes a big concern of heating in the body. So that's number one. Number two—

ZIERLER: And did you know this because of animal experiments, or this is just a theoretical proposition?

WEN: There were already heating accidents in patients at 1.5 tesla.

ZIERLER: Oh, there were? There were?

WEN: Yeah. So there were already issues back then. And this is when antennas were not properly placed on people, or people accidentally had metallic eyeglasses on them or metallic objects on them that the tech forgot to remove, or forgot to—or they didn't mention that they had jewelry on them and things like that. So there were already concerns. There were already incidents of this. So when I came in, the number one issue was, OK, regardless of the heating—safety aside; let's say the body can tolerate any amounts of heat—is the image quality just going to go up proportionally with scale, right? At least to the four tesla. And one interesting thing I found was that—I knew about electromagnetism quite a bit, about wave propagation [??] just from physics classes, right? One thing I thought was that the wave length in water at four tesla, which is—the Larmor frequency is 170 megahertz. The wavelength was actually not that long anymore. It's starting to approach the size of the body, actually, itself, or even swallowing [?] the body. So we should then start seeing how we have some problems with wave propagation effects in the body, of standing wave patterns. So that would really affect the uniformity of the image. It will create hot and cold spots in the body. The hot spots are great and we'd get a lot of signal. The cold spots are essentially going to be somewhat blinded, in a way. So I said I'd—I sent you a paper—I said I'll do some experiments, and I saw, yeah, the body—you know, we can get something that's like a body and basically will act like a resonator in there and create certain standing wave patterns that's really strong. Another issue of course is something called penetration depth. It's basically how well the body can absorb the energy we put in. And the better it absorbs the energy we put in, the less we can penetrate deep into the body. And then that would mean that a lot of heating on the surface, and not a lot of signal deep inside coming out that we can detect. So this is called a penetration depth issue. These two things got me a little worried. So I started to investigate the wave effect and the penetration effect. I published a

couple papers on this eventually and concluded that our understanding in the end was that four tesla was not good for whole-body imaging.

ZIERLER: Too high. Too much.

WEN: Too high already. It's too high already.

ZIERLER: So it seems to me that there's the hardware—there's the machine itself.

WEN: Right.

ZIERLER: There's the theory—the physics and the theory, like how the math and the equations work.

WEN: Right, right.

ZIERLER: And then there's the analysis of the imaging itself.

WEN: Right, right.

ZIERLER: So can you explain where are you on this collaboration, and then who are the people that you're working with to draw these conclusions? Are they engineers on the hardware side? Are they radiologists on the imaging side? Who's your team that's helping you make these analyses?

WEN: Good point. I myself work on the inherent theoretical side. I wanted to know that in the ideal situation—let's say engineers gave us ideal hardware. Is there a chance that we can make this four tesla work for the body, for instance, so we bring out the advantages? From the basic physics principle standpoint, that was my goal.

ZIERLER: So the engineers can deliver the technology for you.

WEN: Right. So I worked with Scott Chesnick who was an engineer back then, and there was a bunch of engineering staff people that were hired to the NMR center right here. They taught me how to make something called coils, which are basically antennas. They are either transmitting antennas or receiving antennas. And there were people who read our x-ray images—radiologists. Dr. Peter Troyke was one of them back then. And so we had engineering people, and they taught us what makes the hardware good, even better. So I'm a physicist, so my approach was basically to say, all right, in the ideal case, considering everything was as good as it could physically be, how good can these images be?

ZIERLER: And were you relying on the radiologists to tell you, "This is what a good image is, as far as us determining what we're looking for"?

WEN: We could already determine. So the issue here was—for instance, I talked about hot and cold spots, right?

ZIERLER: Yeah.

WEN: So it came down to uniformity in the chest. We could right away tell that some spots were very hard. You would get very clear-looking images. Other places were dark and blinded by—and it wasn't due to hardware problems. It was basically due to the inherent way the waves—the electromagnetic waves behave in such a large body. And it was due to the fact that the wavelength was approaching the size of the body, so wave effects started to take over. So we can't really think of it as a static magnetic field, a quasi-static magnetic field, passing through the body anymore. It was really a wave propagating the body at that point.

ZIERLER: So this was a theoretical discovery that you were part of.

WEN: Right, exactly. So because of the theoretical nature of it, it basically helped, in a way, to steer the engineering effort to—not against this wall, but to where it really can bring out the benefits.

ZIERLER: The best imaging.

WEN: That's right. So the torso—after our discoveries, the torso imaging, meaning trunk imaging, went—stayed at 1.5 tesla. So today, it's 1.5 tesla for body imaging. And three tesla, which is in between 1.5 and 4T, is also used in bigger hospitals primarily for brain—for head imaging. It's smaller.

ZIERLER: A smaller space.

WEN: A smaller space. It works better. And sometimes research projects would use three tesla for body imaging as well, but it's more limited to research projects. So yeah, so our contribution—my own—as somebody from a physics background, I felt my contribution to this was to think about things in a theoretical ideal situation scenario. This way, we don't have to put a lot of effort into engineering, then ultimately fighting a physics inherent problem. That would not have been a good way to spend our resources and energy.

ZIERLER: Now, we got off the chronology for a little bit. All of these things that we're talking about now, is this still while you're a graduate student? Or what's the transition from—you defend your dissertation and you become full-time employee at NIH? And also we should talk about who's sponsoring your visa to work in the United States and things like that. I'm curious about that, also.

WEN: Right. So this work went from 1992 into 1996, also. So I graduated in 1994 with my PhD and it went a couple of years beyond that.

ZIERLER: But by 1994, you were probably spending more and more time at NIH and less and less time in College Park.

WEN: Right. So once I got into the MRI field, got deeper into it, I was really more dedicated to MRI than my statistical quantum mechanics. So in the end, after my PhD graduation—both my mentors, Michael Fisher and Bob Balaban, were there in my thesis defense.

ZIERLER: Bob Balaban would have been the outside reader, probably.

WEN: The outside reader, exactly. And after that, I basically switched to MRI completely, fully, and then I was here as a postdoc fellow at NIH. So one thing I should mention is that in 1994, there was a political thing over—I think it was President George Bush was president?

ZIERLER: '94?

WEN: '94, yeah.

ZIERLER: Would have been Clinton.

WEN: Was it Clinton or—?

ZIERLER: Yeah.

WEN: Oh yeah, it might have been earlier.

ZIERLER: I'm the historian. That's my field.

WEN: [laugh]

ZIERLER: I know who was president in a given year. [laugh]

WEN:

ZIERLER: Of course. Your research is not limited to NIH. It's adopted worldwide.

WEN: yeah, so the work about high-field MRI and how it's going to behave, how the actual magnetic field is going to behave in the body at high fields, went beyond my PhD graduation and went into '95, '96. But pretty much by '96, we knew what was going to happen in the body at four tesla, essentially. So that question was answered. So on the image quality side, there was going to be uniformity issues. No doubt there would be very bright, nice-looking spots, but they were just spots, and there were also other spots that would just be dark, in like different corners in the body. Number two, associated with hot and cold spots in the image, there would be hot and cold spots in the heat deposition, and that was an even bigger concern. So instead of at a lower field where we can estimate the overall amount of heat that's going to be needed to excite a body—and we knew that the heat was going to be distributed fairly uniformly. At high fields, we will need eight, nine times the heat, and the heat would be not uniformly distributed [laugh] but focused in certain hot spots. And that was really a concern. I mean, that would really cause problems in patients. So the sort of hot and cold spots in imaging and also in power deposition were inherent. And that would really be a problem when doing whole-body imaging at high fields.

ZIERLER: Now you're reaching these conclusions because this technology is now being used on patients, and you're getting the feedback? Or these are still all theoretical discoveries that you're making at this point?

WEN: So in the mid-‘90s, they were not used on patients. They were used on normal volunteers. And I was one of them. I'm a skinny person, so I was an ideal person to do a high-field. And then we actually, in one of the papers, we did three different sizes of people. You know, somebody from me, and then medium size, to more like a cardiovascular patient who would be obese and all that. So we just found out that the problem gets worse, of course, with bigger people.

ZIERLER: Worse meaning that the imaging is worse.

WEN: Yeah, the imaging is worse, and the power, and the heating issue. So we don’t have to heat somebody to the level of causing injury to know that. We know we can apply a lower level and map out the distribution [??] the magnetic field. We already knew that things were going to go that way. So, yeah, essentially it’s from theoretical point of view with experimental confirmation in human beings, in normal volunteers. I should say that now NIH policy does not allow us to volunteer for our own research.

ZIERLER: You can’t self-experiment. [laugh]

WEN: No, right, [laugh] exactly. Back then, it was all right. So that question was answered. I was happy that that was answered. And up until today, we established that, and it’s today still being understood that way.

ZIERLER: And so personally, by 1996, did you feel like this was now your adopted country, that you were moving towards looking at your permanent residence to be the United States? Or are you still thinking at some point, "Maybe I'll go back to China"?

WEN: I think I felt I adopted this place, especially the MRI field, as a place to live and work. That's for sure. I think even until today, advanced medical equipment research is pretty difficult in countries that don't have a lot of resources.

ZIERLER: And was NIH good about managing your immigration status and your work status? Did they help you with that?

WEN: I didn't need their help. So that was one of the things that President George Senior did to students back then, was to say that—

ZIERLER: "You're welcome to continue working and living here."

WEN: Yeah, because there was basically a blank coverage for us. He said, "If you want to stay here, you are—"

ZIERLER: Indefinitely.

WEN: That's right, indefinitely. So they gave us green cards, essentially, back in the early '90s. Not early '90s; somewhere around the mid-'90s basically is when that happened.

ZIERLER: So this research is settled. You've made this discovery. This is your adopted country. What next? What are you doing now? It's 1997. What's your new field of research?

WEN: So one thing that came through this that was interesting was all these wave effects in the body, they had a lot to do with the connectivity of the tissue and dielectric constant of the tissue. So I started thinking, "This could be a good thing, though." Because one, how about we just map out the connectivity and dielectric constant of the body? Wouldn't that have interesting information in there? So one thing I started to do was to say could we use these hot and cold spot pattern [??] field and do some calculation, reverse calculation, and figure out a distribution of the conductive properties of the body? The electric conduction properties of the body. So I did that. I theoretically figured that out, essentially. Part of that was actually figured out in my PhD thesis in the Maryland years. So there was something called reciprocity, which I learned in quantum field theory [laugh] [??] was useful, but it applies to this. So used reciprocity principle, et cetera. So it turned out, yeah, one can do that. It does require high magnetic fields. So we need to observe the actual wave effect. Essentially it comes down to sort of a wave propagation time delay from surface to somewhere in the body. How long was the time delay? And that would give us information about the dielectric constant of the material that the wave has to go through.

ZIERLER: So how much do you need to know about anatomy and physiology? I understand as a physicist, you understand the theory and the math, but are you relying on your—you didn't go to medical school, right?

WEN: No.

ZIERLER: Are you relying on physicians to help you understand the anatomy and the physiology? Are you learning this yourself? Or is it really not important to understand the

anatomy and the physiology in terms of answering the kinds of questions you're after? How does that work?

WEN: It's really important. So I took classes when I was at Maryland in physiology, and also I took—

ZIERLER: Knowing you were headed towards NIH?

WEN: That's right.

ZIERLER: You needed this background.

WEN: I took two physiology courses. I took an organic chemistry course. I paid for those courses myself, actually, to take them. And that helped me tremendously. And then of course, I had that foundation of some knowledge. And when I'm in NIH environment, I then got a lot of help from radiologists. So there is now a very, very known radiologist—his name is Steve Wolff, actually. He came through NIH. He was trained at Hopkins and came through the Howard Hughes Medical Scholars program over here. I was working with him as a grad student when he was in residency at Hopkins, and then a little bit on, he was a fellow—he was doing a fellowship over here, and I was a postdoc, and I still worked with him. And I learned a tremendous amount of things about the human body from Steve, actually.

ZIERLER: Did you ever think about going for the MD, or that was not really necessary?

WEN: I thought about it a little bit. And Bob Balaban, my PhD advisor, told me, "No, that is not your path. [laugh] Because you would be spending too much of your precious time."

ZIERLER: With patients?

WEN: Well in an MD—in the learning. How many—five, seven years of learning, while all of this will just go by you. All of the exciting discoveries will go by you. So don't leave the field now. Keep going. So I was happy.

ZIERLER: That's a question I have about NIH in terms of the kinds of things that you can do here. In terms of you working with colleagues with different areas of expertise and the opportunities of collaboration, let's say that you were working for GE or Siemens, or let's just say that you were working for a hospital that was not NIH. What are the things that you can accomplish here because of what NIH is, and the kinds of collaboration that it encourages? How has that helped you advance your career and the theories that you've been working to understand?

WEN: I have not worked in academia, so I only know a little bit about those other environments through friends and colleagues, conferences. I think NIH is an environment that's very open. There's basically no limit on who—which department of medicine you can collaborate with, you can work with. And also there's less constraints from the funding side. So my university colleagues have plenty of collaborations. If they're in engineering and physics, they collaborate with MDs. But a lot of those things are underpinned by funding.

ZIERLER: Of course.

WEN: So they'd be writing a grant together with someone, and if the grant goes through, they will then go ahead and do the collaboration. If there's no money, then they probably lose that opportunity. And of course in the sort of grant-centric way, the collaboration could be a little bit limited and a little bit rigid, in a way. So one has to pre-arrange a certain group of people or one or two people together and lay out a plan and just go with it, whereas here, it's so open that you can do things just on the spur of the moment. If something comes up, you can collaborate with a cardiologist or radiologist or somebody from the Cancer Institute., just by an email and phone call—"OK, let's work on this." So it's more open here, in a way. And the other thing of course is that I felt at least in those days, those years, that one can look at more fundamental questions that may not immediately have some economic or even directly applicable to patients. But it's the sort of question, I think, that needs to be answered. For instance, we looked at the fundamental issue of doing body images at high fields, at 4T, right? So either outcome can be positive or negative. Either way, we want to know the answer. But maybe in a grant environment, one would likely more work on the positive side of things.

ZIERLER: Because they want to encourage—? Yeah.

WEN: Right. So if I were a grant-driven person, I would say, "I'll be working on a particular technology that would make high-field work better" as opposed to try to figure out whether high-field is ultimately going to be good or not. So that type of question probably you can do it here at NIH, but probably would be a little bit harder to get direct funding for.

ZIERLER: So it sounds like because you don't have that burden of funding, that in a way, that this is more a purely academic environment because you're asking open questions just to find out what the answer is.

WEN: Right, right.

ZIERLER: That's very interesting.

WEN: I would say at that time I was a postdoc and I was sort of a staff research scientist, so I didn't have the burden to go for funding. NIH still has a funding structure, so we still have—now that I know—I then became to run my own laboratory and we still [laugh]—we have to face—

ZIERLER: There still are budgets.

WEN: Yeah, there's still budgets, and we actually every four years go through something called a board of scientific review step, which is like a study section, basically. Outside experts review our work, our plans for next four years, and then our resources are based on that review. But what's good about it is even the BSC reviewers, when they come in, they get briefed by NIH directors, et cetera, who tell them that our mandate here at NIH is to do, let's say, this type of research. More higher risk, maybe things that other people really don't feel like they don't want to spend the time answering. But they are fundamentally important.

ZIERLER: Higher risk because it might not yield a financial benefit?

WEN: That's right. But the question needs to be answered in a way, right? Yeah. So it needs to be done. Epidemiology is a good [laugh] example. The Framingham Study. It won't generate direct economic benefit to a company, but one needs to have that kind of knowledge, and it's a large population of people. So the sort of questions that we answer also — the question that I talked about—whether high-field is going to be good for torso measuring—it needs to be addressed so then the engineering efforts can be directed in the right way. And people will then make money, either making three tesla working better, or better 1.5-tesla

machines. But they won't spend all the investment into four-tesla whole body imaging as a commercial platform, because they know they're going to run into these inherent issues.

ZIERLER: Right. Let's bring the process a little forward in terms of the feedback data that you get that tells you how well your theory is being applied in the real world. I understand there's the theoretical basis of understanding where you want that field to be, and then that helps you determine what the body can withstand and how good the imaging can be. So once you've established those ideal scenarios in a lab environment, that's all wonderful, but now, it's 2020. We're talking about 1998. Can you look at the data and say—cardiologists and pulmonologists, are they telling you that as a result of the advances that you and your colleagues have made, that there are improved health outcomes as an effect of these discoveries that you've made? Because the ultimate goal, obviously, is improving diagnostic and improving human health.

WEN: That's right.

ZIERLER: So the question at the end of that process is, what kind of feedback are you getting that shows that either yes or no, that that's ultimately what all of this research is being put toward? It's a very complex question, I understand.

WEN: [laugh] Our situation is a little bit different, and the answer isn't too hard. Let me talk about two things. One is that negative answer we got. High field was not good for full-body—

ZIERLER: Because of the burns and—

WEN: Because of burns, yeah. So this [laugh] I say 20 years—or not 20 years—what, 10 years or 15 years onward—we look at those papers. They've been cited. They started to get cited more and more and more.

ZIERLER: *Your* papers are getting cited.

WEN: Yeah. So the early papers, they—it's interesting, my things done at NIH always took a little time before they then became noticed by—

ZIERLER: They caught on.

WEN: Because—yeah—the questions were—we asked those questions quite early, and people then eventually arriving at those same questions, and they started to look back and say, "Oh, somebody already did something."

ZIERLER: So by quite early, you mean from the diagnostic—they weren't ready to have those questions answered, is what you mean?

WEN: They were not thinking about this. Because we had one of the three early 4T machines, and most people didn't even know they existed, four-tesla whole body. And then as physicists we were trained to think in a theoretical picture to, OK, ignore the engineering difficulties, what happens in 20 years from now when you have everything. So we tend to think that way. But eventually engineering does get on. Engineering would get to the point where it would say, "Hey, our cores are so good now. How about four-tesla whole body? How about seven-tesla whole body imaging? Let's see what people have done." So in fact after we did our work, four-tesla and then seven-tesla and even 11.7-tesla whole body machines became feasible

to build. But what I felt good about was that today, you look going into the hospitals, going into essentially where patients are being looked at, it's 1.5T and 3T. Nobody—

ZIERLER: And these are standards that you helped establish.

WEN: Yeah. Nobody wasted their time building huge amounts of 4T machines to go to the hospital.

ZIERLER: So 1.5T for torso, and 3T for the head.

WEN: Brain.

ZIERLER: And that's just standard. And you're saying nobody needs to waste their time with trying to figure out more or less. Those are the ideals that you helped establish.

WEN: Yeah. And actually we thought back then that in the head, one should benefit from going even beyond 3T. because it's a smaller space. Like you say, it's a smaller one and less complex. It's more or less filled. And I think the brain imaging will go beyond 3T. I hope they do. I believe it works well at 4T and maybe even 7T, seven tesla. Although that's when the physiological effect really gets pretty strong, so patient tolerance of the vertigo, et cetera, those things. But the body, until today, 15 years on, now people understand for body imaging, you stay at 1.5T, maybe push a little bit to 3T, but don't go beyond. [laugh] So our understanding became accepted and established that understanding. So that's number one. Number two, I was talking about mapping the electrical properties of the body. I published that in 2003. I wrote an *SPIE* paper, and then I left that aside. I had to do some other MRI stuff of the heart, basically more detailed technology development for the heart. And it was six, seven years on outwards that I found out that it got applied to mapping the electrical properties of the brain,

in fact, and more advanced mathematical, numerical tools were developed for it. But the basic theory was what I wrote down. And I still remember there was a factor of two I had introduced in the math equation, which was an approximation.

ZIERLER: How did you get to two?

WEN: To two? Right. Basically it has to do with the delay of the wave going in, and then the delay of the wave coming out. So theoretically, we knew back then—I knew back then that the two-way delays are not necessarily the same. It could delay a little bit more going in, and a little less coming out, or vice versa. Because basically the polarization of the wave going in and coming out were not the same. It was right-handed versus left-handed. But I said I had no way to figure out what's the proportion of one delay versus the other, because it's going to depend on anatomy, particular anatomy. So I'm just going to say it's the same. And so that gives me a factor of two. So I wrote that into my equation—a factor of two. To this day, nobody questioned that [laugh] factor of two. And I always thought that eventually somebody should look at that experimentally and maybe use some iterative way to then start with factor of two but then figure out eventually based on the particular anatomy what that factor really is. But I guess factor of two has been good enough for the rest of the years. Yeah. So in 2011 is when the brain stuff came out, and it became a subfield of MRI now. They gave it a name. It's called electrical tomography, which I never heard of until later.

ZIERLER: What does tomography mean?

WEN: Tomography means to map out spatial information in 3D. Three-dimensional. Yeah, it's able to basically map out electrical either connectivity or dielectric constant in an organ in 3D. That was the goal. And as I say, that came out of the negative effect

of wave propagation in the body. But on the plus side, it generated this whole subfield, which is to map out the electrical dielectric properties in the body using MRI data.

ZIERLER: And what about Hall effect imaging? Where does that come in?

WEN: Right. So that also was—it was about 1995 when we had to—I was doing cardiac imaging of the heart. It was also a problem back then. So basically with the electrodes looking at EKG signal in MR scanner, we were getting a lot of extra noise. That was from flow. The blood flow, like I said, is causing polarization of the tissue itself, and that then is picked up by the electrodes. So I thought, "Well, this might be a way to maybe map out flow in the body." But the problem is electrodes on the body don't localize. It doesn't know where inside a body that signal comes from. So there's no spatial information. So I then said, "Well, how about we induce some sort of vibration in the body with ultrasound, which we can control where it is?" Because ultrasound is a beam. So that led to this idea of Hall effect imaging.

ZIERLER: And who's Hall? What's the effect that Hall is named after?

WEN: [laugh] In physics, Hall effect is basically when you have a flow, a motion in one direction, and then you have a polarization in the perpendicular direction in the presence of a magnetic field, which is in a third direction. That's the Hall effect. So this whole scenario essentially to me is a form of Hall effect that we're looking at. Now, instead of a steady flow, we're introducing rapidly oscillating ultrasound motion. So I called it Hall effect back then. So we showed in principle it could be done, although the main issue back then was an engineering issue that had to do with the cross-talk between the ultrasound side and the electrical signal side. But then some years later, it developed into a field called magnetoacoustic imaging. Nowadays,

it's pursued as magnetoacoustic imaging. I left that field. I did the sort of fundamental physics part of it and left it to do more applied things—cardiac imaging, cardiac MRI work.

ZIERLER: And is that your current work now? What are you working on currently?

WEN: X-ray. X-ray. [laugh]

ZIERLER: X-rays.

WEN: X-ray imaging. So I currently work on, yeah, x-ray imaging. I work on two things in x-ray imaging. One is to address a fundamental issue in x-ray imaging. CT is one form of x-ray imaging. Radiography is another x-ray imaging. The fundamental issue compared to MRI is a lack of soft tissue contrast. So for instance, blood and muscle look quite similar in x-ray images, unless one injects a contrast agent to highlight the blood, for instance.

ZIERLER: But an MRI, that's not a problem.

WEN: Right. So MRI has greater soft tissue contrast, much greater. So coming from MRI background, it struck me when I looked at x-ray CT images how high the resolution is but how poor the soft tissue contrast is.

ZIERLER: So let me ask, before we get to x-ray, did you move on because you feel like the big discoveries in MR that needed to be made, that's done now?

WEN: Yeah, I had that feeling.

ZIERLER: That like there is no more on the horizon? You feel like these are settled theoretical questions, and that's one of the reasons why you moved over to x-ray? Because the technology and the theory behind MRIs now, you feel like you've—I don't know if hit the

ceiling is the right term, but the things that you wanted to discover and learn, you feel like that's accomplished? That's settled now? Is that fair?

WEN: I think it's the things that *I* would like to learn, I've learned about it. I'm sure there's a lot of engineering development to be done in the clinical MRI field.

ZIERLER: Would you be involved in the increased tesla rating for brain imaging, you were saying? Is that something that you would be involved in, but not necessarily?

WEN: Not necessarily. I felt that I was interested in certain questions, and they were answered, basically.

ZIERLER: OK. So that's how you feel like you've achieved that, and now you move over to—?

WEN: Right.

ZIERLER: Did somebody encourage you to move over to x-ray? Was this your own sort of interest?

WEN: No, it was my own interest, to an extent. It was my own interest. But again, in NIH environment, you are exposed to a lot of things. So one gets to see sideways different things coming at you, and then that caused me to be interested in this. I would say that having physics training helps a lot, because x-ray to us is just another form of electromagnetic wave, basically, so we are not intimidated by [laugh] x-rays as some people might be. It's ionizing radiation, but—

ZIERLER: And they both have their place. MRI will be useful for certain things, and CAT scans will be useful for other things.

WEN: Absolutely, yeah. So CAT scans, for instance, are really good at structural information, because the resolution is so high. X-ray wavelength is on the order of less than an angstrom—the type of x-ray we use in the body. So the inherent diffraction limit of x-ray resolution is incredibly high. We never got there, in fact, in clinical imaging. But it can achieve higher resolution in MR, for sure. So structural details are great. I was just a little bit struck by how poor the soft tissue contrast is in x-ray images.

ZIERLER: So that's what you're working to improve now?

WEN: Yeah.

ZIERLER: How can you get x-rays to see the contrast more effectively?

WEN: That's right. So x-ray is attenuation-based. X-ray imaging right now, it's mostly—clinical, attenuation-based.

ZIERLER: Which means what? What does that mean?

WEN: It just means the x-ray gets absorbed. It's ionized radiation. It gets absorbed by the body. And what we see in a CT is essentially difference in the amount of absorption by one type of tissue compared to another type of tissue. Soft tissue all more or less have the same density, and x-ray absorption is mostly a function of density and the type of x-ray energy we use to penetrate the body. And that's the basic reason why we don't see a lot of soft tissue contrast. Everything is mostly made of water. So fat, for instance, has the biggest

difference relative to the other in soft tissue because it's not made of water; it's mostly made of lipids. But even then, the contrast isn't that great. The difference in density between fat and other tissue is maybe 10, 15%, something like that. So I was trying to see if there's some other mechanism that one can—some other measurement we can look at with x-ray that would then have a bigger difference between different types of soft tissue. One would be scattering. So x-ray is also scattered by soft tissue, a little bit like light is scattered going through a fog, for instance. Soft tissues have a lot of heterogeneous structures, so there's a lot of interfaces where x-ray can be slightly diffracted, and there's scattering that one can look at. Another is refractive index. So x-ray is refracted also in the body. So the refractive index, one type of tissue might be a little different from another type of tissue also. So I did some theoretical work on that and some physics experiments on that as well, even to the scale of small organs, for instance, and worked with—again, in terms of ideal situation, not in a laboratory, we went to work with—Argonne National Laboratory has an advanced photon source there, which is a synchrotron beam, like an x-ray laser essentially. So that's about as ideal as one can get in terms of x-ray source. And did some benchmarking, proof of principle experiments on some physics ideas of how one can measure these properties. So did a fair amount of that work. And a big part of that depends on something called micro and nano fabrication. So the x-ray optics, the optical elements—to split the beam, for instance, or do some focusing, et cetera.—has to be made at that scale, micro and nano scale, because of the very short wavelength of the x-rays. So we had a fair amount of effort dedicated to fabrication, micro and nano fabrication, at least to make large enough parts that we can do proof of principle experiments to verify some of the physics ideas. So then the wall we hit is to scale it up to human size. Because micro fabrication is dealing with silicon wafers and some small parts, and while that is being slowly pushed larger and larger, I'm not an expert in

fabrication, and we rely on collaborators, essentially, for those things. The other thing I got interested in was resolution. So this actually was motivated by clinical colleagues. They come to me and they say, "Well, your x-ray images look very high resolution. Could you do some sort of microscopy in the body non-invasively, so we could then—?"

ZIERLER: What is microscopy?

WEN: Microscopy basically is to get images down to the micrometer scale, so almost like—or ideally it would be to replace biopsy procedures. So for instance, if somebody has a tumor or a certain pathology in the body that cannot be diagnosed in a definite way by—

ZIERLER: With just imaging?

WEN: —just imaging, what they would do is go in and take out a piece of tissue, and then they would section it—very thin sections—and mount them on microscopy slides, and literally put that under a scanning microscope.

ZIERLER: And see if it's malignant.

WEN: Yeah, exactly, what cell types are in there. So the clinicians come to me to say, "All right, your x-ray inherently has very high resolution. Could you then just do some form of microscopy from the outside into the body?" So instead of taking a chunk of the kidney out, which is so dangerous, you know—all the complications—we could do basically in vivo microscopy. And at least for some of the cases, if you can then reduce the need for biopsy, that's a great benefit.

ZIERLER: Is that happening already? Are people not doing biopsies as a result of having access to this technology? Or that's still off in the future?

WEN: So we just got—so he came—well, the one that had the particular question was Dr. Joel Moss. He's a pulmonologist, actually. He has these patients with certain lesions in the lungs and also in the kidneys that he really wanted to not biopsy, because it's just so painful and bleeds a lot. And I then said, "OK, I'll look into this." [laugh] And we then tried to figure out what's the best way in a physical sense to do this. Eventually we identified a way to go forward, at least with current available technologies. So part of this also, as a physicist, about this, is that I learned also beyond being a physicist that you have to be a bit of an engineer.

ZIERLER: Because the engineering needs to catch up with you.

WEN: That's exactly right, especially when clinical applications come to us, because they don't wait for ten years. They want it right now. So we have to put on a different hat and look at what is available now, and what potentially can be available in two, three years, and with this set of things available in two years, as a physicist, what kind of a thing you are going to do. What sort of a method you're going to create to best utilize these things. So we eventually decided on a way to do this, and the detector, which is a key part of this, was pending development even back then. So the detector eventually got delivered to us. This is really pushing the envelope in engineering now. It's a company in Sweden that does this stuff. Developed to us—

ZIERLER: The detector. What does it look like?

WEN: So it's an x-ray detector. It's a fancy camera is what it is. So what this x-ray detector needs to do for us, it needs to be able to count the photons. It needs to be sensitive enough to count the individual photons, number one. Number two, you need—

ZIERLER: Which tells you what? How the cell is acting?

WEN: No—

ZIERLER: Ultimately, don't you want to know if the cell is malignant or benign?

WEN: Right. So the basic idea is to go down to high enough resolution—well, ultimately, if you can go down to the cellular or subcellular resolution, you will then be able to see the shape of the cells and the way the cells are arranged.

ZIERLER: You mean what they're doing with microscopy right now?

WEN: Yes, exactly right. So that will be good. So now for us to do this non-invasively, we need to have a detector that has very high resolution. So the sort of detector that will eventually go to that resolution needs to be able to count photons. Because when we go to such small elements—

ZIERLER: Which is obviously much smaller than the cell. You're getting to the photon level.

WEN: Photon. So one has to be able to capture all these photons. So that's a sensitivity issue. We cannot—the current detectors, for instance, they will essentially integrate the energy, and they will essentially create their own electronic noise, and so there's a noise floor above it, and then whatever is above the noise floor is what's detected. But if one can count the

photons, then there's no noise. There's either we receive the photon or we're sitting waiting for photons to come. So it's an issue of sensitivity of the detector. A detector has to be very high resolution, of course. And then a detector has to be very fast. So this is because the human body has a lot of biological—

ZIERLER: Dynamic.

WEN: —you know, physiological motion going on. Yeah. One has to do things quickly and not just wait. I mean, a fraction of a second is all we have.

ZIERLER: To capture the protons?

WEN: Yeah, to cap…no, this is x-rays. We're talking about x-rays. So to capture let's say a simple projection image of some part of the anatomy at very, very high resolution, we've got to capture that image before peristaltic motions comes in, before the person breathes and things just blur out essentially. So there's a speed issue here. So all of these combine to put a lot of engineering challenge on the engineers. But I knew that they were about to get to that point, back then. So they delivered us this new detector the end of last year. We just did our first six patients this year, in fact. Or this week, we might do more patients.

ZIERLER: Who agreed to pursue their treatment without the invasive biopsy? Just being able to look at the imaging?

WEN: No. What we tell the patients is that this is still research, so we're not basing clinical decisions on research. As we know, IRB is the Institutional Review Board that reviews research. So at this point, the patients are just helping us. They'll say, "OK, you guys are going to develop something that ultimately is going to have benefit." And in the consent form—

consent form is what they sign—we tell them explicitly that there's no benefit yet to you. You are participating just to help research so it can benefit future patients. But we need human data, patient data, to then know the capability of these things. Number two, we need human data to be able to even interpret what we see. So once we get to resolution—we see things that have never been seen by radiologists before. So how does what we see, the new stuff, correlate with pathology, correlate with their clinical condition? That connection needs to be established.

ZIERLER: And once those correlations are established, ultimately the pathology is no longer necessary.

WEN: That's right. So then you can say—

ZIERLER: So you're going to put pathologists out of business is what you're going to do.

WEN: No. [laugh] I mean, hopefully. But I know that for many years to come, what this sort of thing is going to do is going to put—it's going to lighten their workload, is what they're going to do, so certain cases are clear-cut by imaging.

ZIERLER: It's going to be easy on the imaging—

WEN: Yes.

ZIERLER: —so don't mess them up with all the things where it's really difficult when we still need them for.

WEN: That's right.

ZIERLER: I see. I see.

WEN: So that pathologists don't have to look at so many slides.

ZIERLER: So what kind of tumor would that—? Like what kind of tumor would be very good for this kind of x-ray imaging that you're talking about, and what kind of tumor is something that the pathologists are always going to need to deal with?

WEN: We have to look at those.

ZIERLER: What kinds of tumors? Do you have any idea of like the difference?

WEN: No idea. We just need to look.

ZIERLER: Brand new. Right, right.

WEN: Yeah, we just need to interpret. And I think beyond pathology, this is more for patients. So where they want us to look at foremost is not so much what—I would like to answer your question—what's good—they want to look at patients that are at most risk of having problems with biopsy.

ZIERLER: Creating new problems just by going in and getting the—

WEN: In a biopsy, yeah. Because they have patients who really they weigh whether we should biopsy or not.

ZIERLER: Right. They're immunosuppressed, kind of thing.

WEN: Exactly. If they do any kidneys, they're going to bleed heavily. The lungs, they bleed heavily. You have vascularized organs that—

ZIERLER: I mean, that's the irony. They're sick already.

WEN: Yeah. [laugh] And you need to biopsy them to decide on the treatment. So they want us to look at—so the patients coming in are those types of patients. So this is now of course a team effort, so we then have to work with engineers on one side, radiologists, and pathologists on the other side, just to interpret what we're looking at.

ZIERLER: Right. Now, I wonder, is there a parallel track—in other words, with the MRI, there's the concern that as you go up the tesla field, that it might have negative consequences from a human health perspective, right?

WEN: Right.

ZIERLER: Is there a—? I mean, there has always been a concern with how much radiation a body can take from x-rays in general.

WEN: Yes.

ZIERLER: But is there specifically a concern with developing these new technologies that if they might create new and dangerous forms of radiation exposure, or is that not a concern for this field?

WEN: It's always a concern. It's always a concern, yeah. So I learned—I started to do x-ray stuff around 2016, 2017. Is that right? No, no, 2006 and 2007, so over ten years. It's still new. I'm a new—I still consider myself a newcomer. And I learned that in the x-ray field, every step of the way, safety is a paramount concern.

ZIERLER: Because radiation is inescapable. There's no way to avoid radiation.

WEN: That's right. So every new technology has to be carefully looked at. So when we do microscopy which basically means a lot of the radiation is focused to a smaller spot, the concern here, for instance, from a fundamental point of view—is there a difference between applying radiation to a large part of the body versus taking the same amount of radiation and putting all of that into a smaller part of the body? What's the cancer risk of the first versus the second? And so there's a whole field—it's called radiation biology, and a subfield of health physics—health physics is a field, by the way—where they evaluate these questions. So we must learn from those physicists also, and understand what they're saying, and apply to our situation and decide on how we should perform our protocol in these patients. Then ultimately, when it comes to clinical studies, we go through a radiation safety committee review. Number one is radiation safety committee review. Before even the science gets reviewed or the benefit to medicine gets reviewed, number one review is radiation safety.

ZIERLER: To the patient.

WEN: The radiation to the patient. It's reviewed by a radiation safety committee at NIH.

ZIERLER: How is that determined? Because epidemiological—I understand you don't want to create a new tumor when you're x-raying this tumor.

WEN: Exactly. Right, right, right.

ZIERLER: But from an epidemiological perspective, how do you know that it's your x-ray that's causing this tumor, and it's not just like that person got that tumor because they got that tumor? How do you make those causation relationships?

WEN: I think it's also a pretty tough question for health physicists. And so, like you say, it's all based on statistics. And interestingly, most of the statistics are still based on people who have massive amounts of exposure. So for instance, the atomic bomb victims had huge amounts of exposure, and then you measure elevated levels of different types of problems they have. And also people who have undergone radiation therapy, so that's very high amounts of radiation compared to the diagnostic imaging type of radiation, and what are the levels of various problems down the line. And these patients also need to be tracked many years, over time. So health physicists face a pretty daunting challenge, in that sense that they have to have large amounts of data for this. Sometimes the level of elevation is pretty small. So for instance, when we look at the radiation we give patients, it's compared to the natural radiation in the United States that everybody gets from—

ZIERLER: Yeah, just from living.

WEN: From living, exactly.

ZIERLER: Right. Airplanes, microwaves.

WEN: That's right. Radon gas in the basement, et cetera. So we give an incremental radiation on top of that. Now, what's the effect of this increment to cancer rates, et cetera?

ZIERLER: Very hard to determine.

WEN: This needs to be teased out statistically. But of course to have the statistical power, one needs to look at a large population of patients. So ultimately when we submit a research protocol to the radiation safety committee, they take a fairly conservative view.

ZIERLER: And that's external, the safety committee, or that's in NIH?

WEN: Internal. NIH level has a radiation safety committee, but their guidelines are based on established regulations and laws by the government, I suppose. So radiation safety in x-ray field is number one that needs to be looked at. And then the things we know, they need to be discussed with patients, so patients understand upfront what the risk they are taking when they participate in this research. This has to be explained to them completely, 100%, so when they sign on the consent form, they know as much as we can understand what they're getting into. Now, MRI, on the other hand, is a little bit controversial, because from the basic physics point of view, I can't imagine radio wave or even microwave being able to alter the molecular structure enough to cause physiological effect.

ZIERLER: So the burn is what, with too high of a field? That's not a physiological effect?

WEN: Yeah, there's a physiological effect, but does that have a long-term health effect on the patient or not?

ZIERLER: That has never been established?

WEN: That's not established, for instance, in—yeah, so far. MR hasn't been around for—

ZIERLER: No one has gotten cancer from MRI.

WEN: From the MRI, yeah.

ZIERLER: That's for sure?

WEN: Right, right. No patients or workers.

ZIERLER: Technicians.

WEN: Technicians, et cetera. But then again, it's a controversial field, because high tension power lines, for instance, also have very low frequency fields, and there might be some studies—there could—I think there were some controversial studies showing there's a correlation between where you live and elevated risk of leukemia, for instance. Now, is that causal, or is that correlative? It's hard to say. And the statistics of MRI hasn't been that long. MRI started in the 1970s, I would say, but it really got into hospitals maybe in the '80s. It hasn't been a very long time. And especially high-field MRI machines haven't been around for that long, either. Now anything beyond three tesla would be in research environments, which means much less number of people have gone through them, and so statistics are low. So human body is complicated, right? [laugh] Things happen in unexpected ways.

ZIERLER: So what do you hope to achieve for the rest of your career? Ten, fifteen years, however much longer—how do you establish your goals? Because it's interesting—you say you've been involved with x-rays for over ten years but you still feel like a newcomer to the field.

WEN: Right, right.

ZIERLER: So that has to influence how much you're willing to invest in learning about a topic if even after ten years you still feel like a newcomer. So that gets me back to my question. However much more time you have working in this field before—you're a young man; you're not going to retire for many years.

WEN: [laugh] No, I'm not a young man. [laugh]

ZIERLER: So that's my question. What do you hope to achieve for the remainder of your career? What are the big questions that are out there that you want to not just learn about passively but to actively be a part of making those discoveries? What are those things that motivates you to get out of bed every morning kind of thing?

WEN: Right. And now I think there are things with big benefits, and then there is even more basic questions as a physicist you'd like to look at. So for instance, the in vivo—let's call it live microscopy, in vivo microscopy.

ZIERLER: Which means what?

WEN: Which is the topic we talked about, which is to be able to perform some sort of microscopy from outside the patient's body, and look into it, and be able to then reduce biopsy. Performing some sort of microscopy from the outside of the body, deep into the body, most likely with x-ray technology. Right now, anyway. That is a big topic that I really want to push forward. I see benefits to patients.

ZIERLER: The goal being to reduce biopsies. That's the big goal.

WEN: That's the big goal.

ZIERLER: And also, as you said, if I understand correctly, reduce biopsies overall, and then reduce the workload on pathologists so that they can concentrate on the tumors that will never be able to be understood strictly through imaging.

WEN: That's right.

ZIERLER: But you don't know what they are.

WEN: No, we don't know. Even if it's a 10% reduction, that translates to a huge effect on the entire healthcare system, from the cost side, all the way to patient care.

ZIERLER: Everybody agrees, reducing biopsies is—

WEN: Absolutely. And this is something that came to us from clinicians.

ZIERLER: Coming to you saying, "Can we do something for this patient without having to biopsy?"

WEN: That's right. This is a question that we did not invent. It was posed to us. So we should serve the healthcare community by doing our—

ZIERLER: And the answer is x-rays. It's not MRI. That's what you're saying.

WEN: Right.

ZIERLER: The future of the field is—in terms of what the clinicians are asking for, the technology of x-rays is going to be responsive to this request, not MRIs, in terms of the live microscopy.

WEN: That's my understanding of it. I am a limited one physicist person [laugh] thinking with one mind, one brain, so I'm sure there are other people with different views. I have some experience with MRI, some experience with x-ray, and between the two, I thought and I pursued x-ray for this goal, and we made some progress.

ZIERLER: That's the future that you see for this topic.

WEN: I felt that. Right. So then beyond that, as a physicist you always think about on the fundamental side of things. And I felt that we should look more at—so in the imaging field—I am interested in the medical imaging field—in the medical imaging field, I think more fundamental thinking from the perspective of information theory needs to be applied here. So ultimately what we're doing is we're trying to get spatial and probably dynamic information out of the body. And right now we're essentially doing imaging, which is basically to map spatial information out, directly. But the ultimate question is not spatial distribution of something. The ultimate question is disease, is the diagnosis or the staging of the cancer, et cetera. Those are not spatial maps. They are one or two sentences in somebody's clinical report. So I think eventually the computation power and the whole field might eventually get to the point that we don't even need to reconstruct an image out of somebody's MR signal anymore or x-ray signal anymore.

ZIERLER: What would replace that?

WEN: It would be some algorithm or network that goes from input raw data—because all the information is there in the raw data we get. Some algorithm might just be able to do a very good job from taking the input to the final diagnosis.

ZIERLER: You would need a computer powerful enough to do that, also.

WEN: Right.

ZIERLER: Is that also something that's—?

WEN: This would involve computation—computer scientists and others where you can come in maybe from the information theory side. We know information from the

perspective of entropy —and what's the limit of what we collect in MR machines and x-ray machines? What sort of information have we actually got here? And ultimately what's the limitation of that information in terms of telling us something about the body itself? So now that's very far away type of questions that one might ask. But right now, we're focusing on reconstructing the image, getting the best resolution out of it. A lot of intermediate steps is where we're focusing on. But maybe ultimately one can skip some of these steps.

ZIERLER: Last question. It's a big question. So I love how physicists are always working towards the unified theory.

WEN: [laugh]

ZIERLER: Where everything is going to converge on this one universal understanding. And of course the amazing thing about physics is that you could be talking about photons at the subatomic level, or you could be looking at the nature of black holes and the expansion of the universe, and it's still physics, right?

WEN: Right, right.

ZIERLER: So here's my question for you. The work that you do—how do you understand it fitting into—particularly because of your intellectual path from Peking University to the University of Maryland to getting involved—it's all physics, the whole way through, whether it's the pure math in the Chinese model to the quantitative stuff you were doing at Maryland to what you're doing now. How is the sum total of your work contributing toward the larger universal understanding of how physics governs our reality? How would you insert your

own research and knowledge into that much broader question that ultimately all physicists are working towards? I told you it was a big question.

WEN: [laugh] It's a religious question. [laugh] I think up to this point, my contribution is really applying physics principles to questions in the human body. I really did not discover any new physics principle of anything. The one thing that probably comes closer to a more generalized discovery was this phase moiré effect that we discovered in the course of this x-ray imaging study which basically is something that probably can come up in various types of contexts. And moiré effect itself is pretty general. There's nothing fundamentally new about moiré effect. It's a beat effect, and it happens in spatial domain or time domain. Which time domain is how we tune guitars, right, with the beat effect between the two different strings. And in spatial domain you get what's called a moiré pattern. And what we basically found was that you get this moiré pattern with things that are transparent, but they introduce sort of different wave front, phase patterns, and phase patterns superimposed can introduce moiré effect. So that might be useful in different fields. But as a physicist, I learn to be humble. We always get taught by people like Isaac Newton's textbooks and that we apply what they have discovered to, at least in my field, to the human body and to imaging problems. Nothing I've done really have changed any of the fundamental understanding of nature or anything along those lines.

ZIERLER: So your contribution not is in new discoveries in physics, but in applying those universal laws of physics to human health and imaging.

WEN: That's right. That's what I felt is basically what I've been doing so far. And there's engineering discoveries, but looking back, it's just applying physics principles to different types of engineering problems, basically.

ZIERLER: OK. Thank you very much. This has been an absolute delight for this interview, and I really appreciate your time.

WEN: It was a pleasure. Thank you for coming by.

ZIERLER: All right, we'll end it here.

[End]