NIDCR Oral History Project

Interview with Dr. Pamela Robey

Conducted on December 11, 2023

KD:

This is an interview with Dr. Pamela Robey for the NIDCR Oral History Project. Today is December 11, 2023, and I'm Kenneth Durr. Dr. Robey, thanks for talking today.

PR:

My pleasure.

KD:

I always like to go back a little bit and put some foundation under things—I was interested to see that you started out in a liberal arts school.

PR:

Yes.

KD:

I wondered how that launched you into your scientific career.

PR:

Well, to be honest, it was not my first choice. In fact, I was bound and determined that I was going to go to Penn State. My father's family was centered in Williamsport, Pennsylvania, and I grew up going to Penn State on occasion for football games and was really determined that I

would go. But then we moved to New Jersey, and that means I was out of state. And I had pretty good grades and I submitted my transcript, but lo and behold, I got rejected.

And we were set to visit relatives and we stopped at Penn State and inquired exactly what was the story. It turns out that my guidance counselor had sent the wrong transcript. It was a student that had a very, very similar last name and nobody noticed it was the wrong transcript. So at that time it was too late, and my father said, "Well, there's this little, tiny school down the road called Susquehanna. Let's stop there." Because at this point I really wanted to be accepted somewhere. I was a good student. And they accepted me on the spot. And Penn State said, "Well, we can't accept you now, but if you apply as a transfer student, we'll consider you."

But I enrolled at Susquehanna, and it was a very challenging environment. It was in the middle of cow fields, and I had grown up in New Jersey. It was very rural, but it was very academically challenging, and so I actually decided to stay. I figured after a year I had kind of settled in and decided that I wouldn't transfer to Penn State, I would stay there.

And it was a very small liberal arts college. There were a total of 2,000 students on campus, which was smaller than my high school. And it took a little bit of getting used to the daily pastime of gossip, which was the big way that people would entertain themselves, but as I said, academically it was terrific. There were four biology professors and they were not really in the game of getting big grants. They got very small NSF grants and local grants for studying the microenvironment of certain areas and things like that. And they taught from the literature; they did not teach from textbooks. So when I graduated from college, I was still not a big fan of Susquehanna, but I did realize when I started going to graduate school that I actually knew more than my professors in certain areas.

So at the end of the day, it was a good experience. I am now a fan of small liberal arts. At the time I was not, I was a big-city girl stuck in a cow pasture.

KD:

Understandably.

PR:

But it worked out well. And what happened was, I was actually all set to go to University of Connecticut for a graduate program in marine biology. At the time I was really a fish out of water. I loved the water. I loved anything to do with marine. But one of my classmates from Susquehanna—and keep in mind that there were six of us that made it through. We started off with something like 25 that were pre-med, but they kind of fell by the wayside pretty quickly. And he said, "A friend of mine has this technician's job at the National Institutes of Health, and they're allowing him to do his PhD research there and he's got an affiliation with Johns Hopkins."

So I visited him on July 4th weekend and stayed for a week and walked around NIH and talked to various different students (there were very few students on campus at that time) finding out how they actually managed it. And basically what they said is if you find a graduate school that will let you do your research off campus, there are a number of people here on campus that would take a graduate student.

So I managed to find Catholic University, which allowed me to do my research here. And then I found a person in the Dental Institute, where I am now (but I actually made a circuit) who was looking for a part-time technician and so she offered me a job and I took it. I told the people at

UConn I wasn't coming. I'd just decided that biomedical research was much more interesting and more compelling, and I've been here ever since.

KD:

Who was the person who had the opening for you?

PR:

Very interesting story. Her name was Rosalind Orkin. She was trained at Harvard by the very famous developmental biologist Elizabeth Hay, and Roz is also married to Stuart Orkin, who is a very well-to-do and well-respected hematologist, also from Harvard and back at Harvard now.

KD:

So that took you into the Laboratory of Developmental Biology and Anomalies? Is that right?

PR:

Right. So the story continues because Roz was a fellow at the time and both she and Stuart came to the end of their fellowships and moved back to Boston. They both had positions in Boston and my advisor became George Martin, who is a connective tissue biologist. And I did my PhD thesis research under his direction.

KD:

And your work was in connective tissue then.

PR:

Yep.

KD:

Tell me about the lab when you came and NIDR, what you thought about the place, what your impression was.

PR:

Well, it was a bit overwhelming to a young person just graduated from college and not really quite sure about what direction I could go in in science. I knew I wanted to stay in science, but I just wasn't sure what I was going to do. Just walking into a lab was so exhilarating, seeing all of this equipment and talking to people about their experiences and things like that. It was definitely very male-oriented and male-dominated. There were only two women that were PhDs in the lab that I was working in at the time; it was Roz and then another lady by the name of Judith Greenberg, who went on to be in the leadership of the General Medicine Institute for many, many years. I think she retired recently, but she was in the lab for a while but then became an administrator in the Institute of General Medicine. I'm not sure that's the correct acronym, we have a lot of them around here.

KD:

That's for sure. How was George Martin?

PR:

Well, George was a very energetic, dynamic person. He did not wear kid gloves, let's put it that way. He was very critical of the work that was being done, and there were many, many people that were kind of put off by that. But I quickly realized that he just was really trying to make sure that people were questioning their own data and that he wanted to make sure that they understood what kind of controls you need to run and what you should be looking for. You

should always doubt your data. And he always said to me, "You've got to prove it at least two different ways. One experiment, one approach is not enough."

And I quickly realized that in spite of his gruff exterior he was a softie, and he really would give his shirt off his back to the people that were in his lab. But there were many people that didn't quite appreciate his kind of approach. But he always comes by to see me whenever he's in town. He works sometimes here in Bethesda; sometimes he's out in California. He hasn't truly retired. He's got a lot of affiliations with different companies and is always calling with some new stuff that he's been working on and finding out what I'm working on and things like that. So he was a great mentor. He really taught me a lot in terms of how to approach a scientific problem, how to get along in the lab.

I went into a lab after I got my PhD that was not quite so appealing. But he always said, "If you bring cookies and put them around the coffee pot, you can't go wrong." And I still do that. I'm always bringing in snacks and things like that. And he just always had very sage advice in terms of how to get along.

KD:

"If you bring cookies," that's the key. You said that he was interested in connective tissue. That was the work that he was doing. Did you pick up that kind of work because you were essentially assisting him?

PR:

Well, yes. Would I have picked connective tissue and basement membrane if I was coming in off the street? Probably not. But it was a very interesting time in collagen research. It was thought that there was only one type of collagen, that's Type I, which is the most predominant. It's found

everywhere in the body. But he and others in the field, a guy by the name of Ted Miller, were starting to be more analytical about their collagen preparations, and what they found is that, no, there is a lot of collagen—different types of collagen.

So the first was Type II collagen, that was found in cartilage. Then Type III, which was found where Type I collagen was, along with Type V. So there was I, III, and V. And what I worked on was Type IV collagen, which is a type that's found in basement membranes, which are very small layers of connective tissue that surround various different types of cell types and organs.

And so the Type IV collagen that we were working on actually came from a tumor. It's now called the Engelbreth-Holm connective tissue tumor, and it was initially very hard to get people to believe that it was a real type of collagen because it came from a tumor. And George was quoted at a meeting one time when somebody kind of raised this question and said, "It's not an alien. It didn't fall from the sky and land in this tumor. It's found in other tissues as well."

So I was actually one of the first to show that, unlike other types of collagen, it had two different types of chains. Collagen is a triple helical molecule that has three different alpha chains. And initially it was thought that Type IV collagen, basement membrane collagen, only had one alpha chain, but I found that there were two different alpha chains. And it turns out that it's a very important protein in terms of barrier function. It delimits certain tissue and says, "Okay, from this point on, I'm a kidney and you're a connective tissue like a dermis or something like that." So it's a delimiting kind of collagen and there are a number of diseases that are caused by mutations in it, and it turned out to be a pretty big deal.

And then others went on and I think we're up to 23 different types of collagen at this point. And this all arose from studying one major Type I and then looking for various different

characteristics. And they are kind of a variation on a theme, and they have different functions in different tissues.

KD:

This is laminin we're talking about, right?

PR:

Type IV collagen. Laminin came along as a major contaminating protein. So the tumor that we had, the Engelbreth-Holm tumor, had Type IV collagen in it, which we knew from some electron microscopic studies that we did, Roz Orkin did, with some collaborators. So we knew that there was a strange type of collagen in there. But when I started doing extracts, I kept finding this really hard-to-deal-with protein contaminant that was not collagen, and it had very strange properties.

So in the old days, we would grow tumor in about 50 mice and harvest the tumor. And we would do certain kinds of extracts and then we would pass the collagen through these very long, skinny columns. New technology is much different. So we would try and separate the proteins by molecular weight. So we would have these columns that were sometimes two or three feet long, and pass the protein extract through the columns.

And there was always something that came through in the very first fractions, and this protein would actually gel in the tubes. So you would take the tubes to pour them out, and there was this jelly stuff in there. And I figured out that it was not a collagen; it was a glycoprotein. And so as part of my thesis I also studied what came to be known as laminin. And that was done in collaboration with one of George's best friends and colleagues, Rupert Timpl, at the Max Planck.

And so we determined it was a non-collagenous protein, that it was found in basement membranes pretty exclusively, and we started to characterize it. And so it's a major component. It was hard to deal with because it's very sticky, would contaminate pretty much anything. I spent more time cursing it than actually studying it because it kept contaminating my Type IV collagen preps and all that.

And then, Hynda Kleinman, who I shared a lab with—I graduated and moved on to another lab, but she continued the work on laminin and determined that it was a cell attachment protein and that it was involved in many different processes. So the work on laminin flourished after that.

And then we thought it only had two different types of chains; it turns out that there are many different types of laminin chains that come together in different combinations. But generally they form this cross-like structure, kind of like a cross. And different chains have slightly different properties, and there are a number of people that came through the lab. Karl Tryggvason is of note because he went on to work at the Karolinska on laminin and did some different properties. But now he has a company called BioLamina, and they sell different peptides from laminin that has different cell-specific properties. So laminin was a big deal.

KD:

Yes, this must have been. And you were still very early in your career, still in graduate school. Tell me about the effect that that had, how that changed your direction maybe.

PR:

At the time, the importance of laminin was just beginning, so it's not like I knew then what we know now. So I was not first author on that paper, and that's something that George feels really, really bad about. And for a while, if he was giving a talk at a conference, he would say, "It was

actually Pam Robey working in the lab that first isolated and characterized laminin." He gave me this t-shirt that said, "the god of laminin" and that kind of stuff. I have it hanging on my bulletin board.

But I finally said to him, a number of years later, I said, "You know, George, if laminin was the only good thing that I do in my scientific career, I might as well hang up my lab coat now. I have other things that I'm working on. It's okay; you don't have to say it."

Laminin was a great thing, and I'm glad it's brought some importance to the work.

KD:

I noticed that the lab you were in had a lot of visiting fellows. There weren't many staff scientists, maybe one. Was that normal for NIDR at this point?

PR:

Yes, for all of NIH. Really and truly, the staff scientist position didn't come into play until maybe 20 years later. And the reason why it was established is because principal investigators noted that when you had such a rapidly turning over laboratory that sometimes consistency is a problem and that you need somebody, one person that really would have the corporate memory, so to speak, on how things are done and what was going on.

We had a couple of full-time technicians, but they weren't PhDs. They were very knowledgeable and very helpful, but they were much more specialized in terms of what their expertise was; whereas now the staff scientist has a much broader kind of expertise and can make sure that there's some continuity.

So that was an important step, I think, because to have people that are only there for two years, I mean, the staff fellowship starts off at two years, you can extend it to four and five years and sometimes a little bit longer, but science doesn't—although we think it moves rapidly, it doesn't move that rapidly and you kind of need somebody to maintain the corporate knowledge, the techniques. We do it this way. And you can change it, but it's a concerted change, not one that you do because you don't know how it was done before, that kind of thing.

KD:

Interesting. Well, speaking of continuity, you broke the continuity by you got your PhD and went to NIAMD, right?

PR:

Yes. Liz Neufeld's lab. And she was a biochemist that was interested in lysosomal enzymes and lysosomal storage diseases. And so George's philosophy was that you should not work in the same area of your PhD thesis work for your postdoc. That philosophy has changed in modern times, but I was gung-ho for it; I thought it would be good. So I moved to Liz Neufeld's lab and I worked on lysosomal storage diseases, in particular mucolipidosis I and II, two different forms of a disease that had a mutation in the same enzyme.

And so, the problem with these diseases is that they were not properly trafficked due to their mutations, and so they would not end up in lysosomes and carry out their important functions in glycolysis, those long-chain carbohydrates. And so Liz had a theory that she called secretion recapture, that the enzyme would be secreted from the cell and then be recaptured from the external environment by binding to the mannose 6-phosphate receptor. And it turned out that that was not totally true. It never really leaves the cell, except for in the in vitro cell culture situation.

In vivo, which kind of goes to the surface and gets trafficked back in. But still it was a major advance, and she was a terrific biochemist.

PR:

I was there for two full years. I did everything. I had my daughter, and while I was on maternity leave, I decided I wouldn't go back, that I was going to look for a different experience.

KD:

So you found something at the Eye Institute.

PR:

Right. That was also a very interesting experience, also a very male-dominated institution. They all were, but I kind of got used to it. And I was hired by David Newsom to look at connective tissue proteins in eye diseases, in particular macular degeneration and other eye problems. And so I worked on Bruch's membrane, which is a highly modified basement membrane, and tried to isolate and characterize the proteins in Bruch's membrane.

He decided to leave and he went to the Wilmer Eye Institute at Hopkins, and so I said, "George, what should I do?" "I know this guy who works on bone. He's looking for somebody. You might want to talk to John Termine."

So I did. I talked to John, and he told me what he wanted to do. He said, "What I really want you to do is to try and develop a bone cell culture system." Because at the time, the only cell culture systems that were available were derived from osteosarcoma and it doesn't take a rocket scientist to know that cells derived from tumors are not always normal. And so he wanted a way, in particular, to look at human bone cell cultures.

And I have to admit, he didn't win me over on the first round. I thought, Oh my God, bone is so boring. It's really boring.

KD:

Why?

PR:

Well, because unless you know bone, you think it's just a hard, dead tissue, but it's not. And I think that the appreciation of bone really has come up a lot because of osteoporosis, but at the time, osteoporosis was not such a big deal. And so he had invited a person from University of Toronto, Jane Auban, to come down and give a seminar. And he said, "This person is coming down. She's working on trying to establish rat bone cell cultures. You might get some insight from her." And the lecture was absolutely terrific, absolutely terrific. She won a big award in the bone society couple of years back. And I wrote to her that she was probably the main reason why I accepted the job in John Termine's lab, that I found her work so compelling. And I thought, Oh, it's possible. Oh, there's something living in there.

And so I started working on bone, and my friends in the Eye Institute would drop by sometimes and say, "Well, how's it going?" Bone is hard. It's really hard. And I didn't mean because it's hard, it's trying to get live cells out of there and trying to extract intact proteins. It was really a very difficult tissue to work on. And for that reason, I think bone research kind of lagged behind research in other areas in soft tissues because you could easily get cells and protein and RNA and DNA out of soft tissues. For bone, it's really challenging.

KD:

Were there other folks working on bone in your lab?

PR:

What John did when he established this lab was, he hired three of us. The first person that he hired was Larry Fisher, and Larry Fisher's job was to try and extract intact proteins from bone, which is what John himself was working on before he became first a Section Chief and then a Branch Chief. And then he hired me to work on the cells and then he hired Marian Young to work on the nucleic acids. So he had the three bases covered. And also in the branch he had an expert on mineral who looked at the size and the shape of the mineral crystals and how the mineral is deposited, so he covered the waterfront, and that was just a huge, huge advance in the bone field.

And so borrowing a technique from the proteoglycan people and modifying it, basically what John and Larry developed is that you take a piece of bone and you mince it up into really, really small pieces. And then you treat it with a de-naturing agent called guanidine hydrochloride, and that removes all of the softly adherent proteins in tissues. Then you treat it with a chemical called EDTA, which leaches the mineral out of the tissue, so the tissue would go from being very hard to being very soft. And then you extracted again with the guanidine hydrochloride, and that, because the mineral was gone, would release the soluble proteins of bone.

Now, there are a lot of insoluble proteins, but most of the insoluble proteins were highly cross-linked collagen, so this technique really revolutionized the study of bone matrix proteins. And so at my point, at that point after John and Larry had done that, the task was to look at the biosynthesis of the proteins using the cell cultures that I had developed and validated as truly being bone-forming cells. And so from that point, then Marian took my cells and isolated the

nucleic acids and got the messenger RNA for the bone matrix protein. So it was a sequence of studies that really kind of revolutionized the bone matrix field.

KD:

Your contribution was coming up with the method of growing the bone cells in vitro?

PR:

Yes, because you couldn't just take the cells and isolate them and then use them for extraction of mRNA because there wasn't enough. You had to expand them in culture. But we know that when you mistreat cells in culture they start doing things they don't do in vivo. So my job was to make sure that they were bona fide bone-forming cells, and that was basically what I did.

KD:

What was the trick to doing that?

PR:

I followed on the work that John and Larry had done by taking the bone and putting it … mincing it to the consistency of sand. And then they used guanidine hydrochloride to remove the soft tissues. Well, that wouldn't maintain viability, so what I did is I took a pretty mild enzyme, and I treated the fragments with the enzyme to remove any soft tissue that had cells in it so then I had a naked bone fragment. And then I put the bone fragment into a low-calcium medium.

Now the mineral in bone is a form of calcium phosphate, and what I think—and we still haven't proven it to this day—I think that the low-calcium medium induced the cells that were trapped inside, which were actually osteocytes, to undergo what is called osteolytic resorption. So they started decalcifying the matrix that was around them because they needed calcium, so they

liberated the calcium from the matrix. And I think because of the enzyme treatment the matrix was partially degraded. So I put these fragments in the dish and I'd say, "Okay, let's see what happens."

And so two weeks to by. Nothing goes on. John says to me, "Aw, Robey," he was a first-generation Italian, and he would say, "Aw, Robey, throw 'em out. It's not going to work. It's not going to work." "No, let's just wait." And then it would be like there was an atomic explosion, and you would see some of these fragments just burst apart into these little, tiny crystals, and underneath would be a cell.

So I switched the medium from low calcium to normal calcium and they began to grow. And those cells are what we call human trabecular bone cells. And that became the method that people used, and of course, they added variations and things like that, but that was the method that I developed for growing bona fide bone-forming cells. Then we verified that by the fact that they would make mineralized matrix with all of the bone matrix proteins in it.

Later, I developed an in vivo transplantation assay where we attached the cells to an inorganic scaffold and transplanted it into an animal and they would form new bone of donor origin. So we proved that they were bone-forming cells.

KD:

Just to get to this method of growing bone cells in vitro, you talked about at least three discrete steps, maybe more. And you used words like "may" and "should have" and "I thought it might." How long did it take you to work through all the different permutations to come up with these particular steps?

PR:

It took about two to three years, which is short in comparison to some other techniques. I came to the lab in 1982, and I think I published my first paper in 1985 (it might have been ‘86), which was really amazing when I look back on it. But I was very focused. And also, because I didn’t know much about bone, I wasn’t distracted by other things and other people and stuff like that. I just followed my hunches and learned some of the lessons that Larry and John had taught me about getting rid of soft tissue, because soft tissue would have contaminating cell types in it.

So my thought was, okay, we’ll just treat it with an enzyme, and the cells inside the bone will be protected from that. And then I got the idea for the low-calcium medium from somebody that was working in skin. His name is Stuart Yuspa. He actually only recently retired from NIH. And he said that in terms of trying to grow progenitor cells, that he found that low-calcium medium was allowing epidermal cells to proliferate and not differentiate, so I thought, hmm, just give that a shot and see what happens. And it kind of made sense to me that perhaps the low-calcium medium would help the cells liberate themselves from that extra-mineralized matrix that they were buried in. So yes, I was flying in the dark, but that turned out to be okay.

KD:

You’ve worked for a few lab chiefs at this point. Compare and contrast John Termine and the way he did things, as opposed to some of the other labs you’d worked in.

PR:

John was really inspiring because he worked in a very different area. He was kind of a mineral physical chemist, so he moved into a biological system. And he was so knowledgeable about the mineral, and very knowledgeable about matrix biochemistry. He didn’t know much about cells, but he knew enough to know to say, “I don’t know.” But he learned. He learned about cells, the

DNA, RNA, all those techniques. The techniques that we each used were very different, so he got up to speed on them very quickly.

He also had an open-door policy. There was never a time when you couldn't go in and talk with him. That's something I've definitely adopted. He would argue with you and he would let you argue with him, which I thought was great.

And he also, knowing that we were in the child-bearing years, he was very supportive. I had two kids under the age of three. And he always said, "Family comes first. You got to go, you got to go. I know that you will get the work done. I'm not worried about that at all. I know what you're doing, I know that you'll progress." And he was ahead of his time for that. And Marian has the same recollection of how kind and understanding he was during those young child-bearing years and things like that.

He had weekly meetings. If it was Friday at 10 o'clock, you knew you had a meeting. That seminar series went on until right at the beginning of the pandemic. I became Branch Chief after he left, and I continued that tradition. We have smaller group meetings instead, and we have a data session that's for the whole Institute that's on every—the day has changed so many times, I guess it's Wednesday at 1 o'clock, I'm not quite sure—where everybody's fellows present. We kind of rotate, so we don't have separate branches to have their own meetings. This is a way of unifying the Institute.

KD:

So the branches were taken apart sometime in the last few years, I guess.

PR:

Six years ago.

KD:

That leads us into what I wanted to talk about next. I've spoken to a lot of people in the intramural program, and they tend to talk about NIH. They tend not to talk about their institutes. And I want to get a sense of how important it was to be working at NIDR, what was then NIDR, rather than another institute. How different could the support have been? And how much did your lab get direction from the Institute as a whole?

PR:

I've been very Institute-centric. I've waved NIDCR's flag for many, many, many years trying to get NIDCR a little bit more in the view of others. There are many that think that all we do is work on cavities and fillings, and we're much broader than that. So NIDCR, a third of its portfolio is on musculoskeletal work. We had Hal Slavkin, who brought craniofacial into the name, because when you say "craniofacial" and you start talking about craniofacial diseases, that affects your appearance, it affects how you chew, and that's something that people can relate to.

But he did a lot by bringing attention to the fact that when your face is not right, it's a serious problem. So the Institute kind of redirected into craniofacial anomalies and the impact of those diseases on people's lives and how can we go about treating cleft palate, cleft lip, that kind of thing. And I think that did a lot to bring us up.

And then after Harold there was Larry Tabak, and he tried very hard to bring up the quality of the research that was done in the extramural program, because that would be the only way that they could bring up the total budget of the Institute. I think he had some successes. Then we had

Martha Somerman, who continued with the craniofacial theme, and also in terms of teeth. There are anomalies in teeth and chewing really impacts the quality of life.

I had one congressman say to me one time "You know, what's the big deal about teeth? You can live without teeth." I said, "Ask a person who wears dentures what their experience is without having teeth. It's not a pleasant experience and it's a major problem."

KD:

Was this testimony?

PR:

No, I have never been asked to testify, but I have been at a number of dinners where I've sat next to people and things like that and was never shy about saying things. Although I'm basically a shy person. That was George's biggest challenge, to get me to speak up. But when it comes to the Institute, I'm always trying to raise the awareness and recognition of the Institute. And I think that in terms of working on rare diseases, that has been one of the things that I think has made a big impact and has brought NIDCR a little bit to the forefront.

But we still always face the challenge of being combined with NIAMS. There was a big push, a number of years ago when Harold Varmus became the Director of NIH, to consolidate, and he was looking to combine. And at the time, Steve Katz was the Director of NIAMS, and he was keen to combine with NIDCR.

And I'll never forget. We had one of our former Scientific Directors—are you aware of the hierarchy?—when he first came, his name was Henning Birkedal-Hansen. So we went to a meeting where this idea of combining with NIAMS was floated, and we were walking back from

Building 31, and he turned to me and he said, "Do you think I should have given up my day job?" Because he had just come from Alabama to be the … He had a very Danish sense of humor, "Do you really think I should have given up my job?" It'll be okay.

KD:

Let's take a couple of steps back from there and talk about another Scientific Director, Marie Nylen. Did you get to know her?

PR:

I can't say I knew her really well, but I did know her. And she was a very principled, very tough person, but always was willing to talk and listen. Bruce Baum and I wrote an article about her. I wrote the article from the science point of view, the impact of her science, and he talked about her as a person.

And John Termine was just … he adored her; he really did. She really had the whole package. Rigor, but willing to be more of a human about things, and stuff like that. She is still alive, but apparently doesn't remember a lot of her time here. But we've been in contact with her off and on over the years. So she was great and she taught me some very, very important lessons, and I really appreciated that she did.

We had this system here for publication clearances, and before you send a paper out to a journal you have to get it read by— Now if it's peer-reviewed, we don't have to do the same process, but in the old days we had to have it read by two other PIs in order to make sure that it was rigorous and didn't say something that was against Institute policy.

And there was one paper that I read that I had major, major, major problems with. But the PI that wrote it was certainly many rungs above me on the totem pole and he just basically blew me off and it went on to her for final approval. And so she gets it and she calls me into her office and she says, "Do you agree with this paper?" I said, "No?" She said, "Well, what did you do about it?" I said, "I told the last author that I didn't …" And she said, "Never, ever, ever put your name on something that you don't agree with. Don't ever do that." And so I learned my lesson, I really did.

Not that I haven't signed off on things that I don't agree with, but if I do, I make sure that everybody knows what my opinion is. So they can't come back and say, "You never said anything." Well yes, I did.

KD:

You talk about learning lessons from Marie Nylen. As far as program is concerned, as far as structuring the work or prioritizing, how much influence do Scientific Directors have at NIDCR?

PR:

They control the purse strings, so they do have a lot of influence. And they use that influence. There have been very few times when anybody has said to me, "I don't think you should work on this," because my work has been very programmatic. I know that there have been a lot of times where people have been told they should not work on certain things. When I first became Branch Chief, there was a very nice Japanese scientist who was working on ovary and granulosis cells in the ovary. The Scientific Director at that time said to me, "You've got to shut that down," which was a very hard, painful experience. Fortunately, the person that was doing this work is a gentleman and basically doesn't hold it against me.

KD:

So this is the 90s. When did John Termine move into industry? Was that around 2000?

PR:

Yes.

KD:

I assume you're learning how to lead through this period, because you clearly don't just get shoved into the Branch Chief role and the Lab Chief role. What were some of the steps along the way to emerging into a leadership position?

PR:

Well, he would give me tasks to do. I can't remember off the top of my head. I can't remember exactly, but little things that I would do. Also, George Martin would have me do things for him. I'm an excellent secretary. I worked in New York City as a secretary in an advertising agency before I went to graduate school and I'm very organized. I can't say I'm as organized now as I was then because things happen; my time is not my own. But George would give me things to do that were highly confidential, and I think that it was not just because I was a good secretary; he just wanted me to know what was going on. And same with John. That would be his way of conveying the biopolitics of the situation and things like that. And organizing things. And I did a lot of observation. There were other Branch Chiefs that I knew here that I really admired, Bruce Baum and Ron Dubner. I watched them a lot in particular because I really wanted to do clinical research. That was one of the main things that I wanted to get started in the branch after Termine left. And I didn't get to do what I really wanted to do, I'm still not able to do.

But after I did the bone cell culture thing with the chips of bone, I went on and started looking at the precursors of osteogenic cells. And it turns out that those precursor cells in the adult come from bone marrow. And that is based on the work of Alexander Friedenstein, who I was able to get out of Russia to do a sabbatical in my lab to show me how to work with bone marrow stromal cells which contain the precursors for adult bone regeneration.

KD:

This is a big subject. This is a lot of the next big phase of your career. Was the concept of tissue engineering in the back of your mind at the beginning of all this?

PR:

Yes. Absolutely. Because I knew my bone cells could make new bone, but my bone cells were old. They would make bone and then they would give up the ghost. I wanted the precursor and also the stem cell. Remember, stem cells were starting to come into the picture. So I can't say that I said, "I want to go after the stem cell." I always said I wanted to go after the precursor. Stem cells came a little tiny bit later.

So yes, definitely. When I became Branch Chief—Alexander came before Termine had left and we remained in contact even after he went back. He was Russian dyed in the cloth. He just didn't like America much. And it was hard for him, because his friends—his wife had died, unfortunately, and he just was a little bit like a lost soul here. So he went back. He came back and forth a few times, but not as much as I would have liked. And then he caught pneumonia and died. He was a very small, petite man. He's exactly what happens to people when they have extreme famine and lack of food. Very little growth and development. But really brilliant.

KD:

What was it that he brought? What did you need him for and why did you want him to come?

PR:

He and Maureen Owen were the first to isolate skeletal stem cells from bone marrow. And bone marrow is a very, very complicated tissue and so his techniques were very simple, but you had to know what you were looking for. And so I brought him and then I brought his protégé, Sergei Kuznetsov, who became a staff scientist in my lab and only recently retired. So Sergei had the institutional knowledge from Alexander. What Alexander knew, Sergei knew. So even though I couldn't have Alexander here full time, I could have Sergei. It was knowing what you were looking for, figuring out a way to get these stromal cells, some of which turned out to be skeletal stem cells, out of bone marrow, free of blood cells.

The blood cells are really hard to get rid of. Even though now we have more advanced techniques like FACS and cell sorting, even with that you don't get pure populations because there is just so much blood. The cells that we work on are 1 in a million. That's pretty big odds. But we figured out ways, with Alexander's help, how to work with them.

He showed us what was called the colony forming efficiency assay, which is where you take the suspension of blood and you plate at a certain cell density, and very rapidly the stromal cells will attach to the bottom of the dish, but the blood cells will not. So that is an immediate way of purifying, as opposed to FACS, which kills half the cells, something hematologists will never admit to you except for under extreme duress. FACS is really rough. Cells are not happy.

KD:

What was that, FACS?

PR:

Yes, Fluorescence-Activated Cell Sorting.

KD:

How long did it take you to develop an efficient process for isolating these bone marrow stromal cells?

PR:

With the colony forming efficiency assay, it was only a matter of a year, a year to two years. Now, the problem is that is a very heterogeneous population and the heterogeneity drives the hematologists crazy. Doesn't drive me crazy too much once you understand the nature of it. And the nature of it is that you're isolating cells at different stages of maturation. It's not that they are that different from one another, they're just—It's like a family, the people are at different ages. And because they're at different ages, they behave in slightly different ways.

But they probably need each other. We can isolate the stem cell and it will recreate a bone tissue, but it takes time. But if you mix different populations at different stages of maturation, you can get that bone formed quicker because they are all doing slightly different things. The same is true in hematology. You don't isolate a pure hematopoietic stem cell and transplant it. You mix it with other blood cells so that the organism can survive while the hematopoietic stem cell is reestablishing that hierarchy. So you're not necessarily helping yourself by transplanting only stem cells. If you have some support cells that help them make their niche and get established, that's a good thing.

And I think that the epidermal stem cell people would agree that, Yes, you get complete tissue regeneration with one cell. But if you give them some support cells, they will work faster because they're not working all by themselves.

KD:

Sounds like you're consulting with, reading the literature for, all kinds of people doing stem cell research. Did you become part of this broader scientific community at that point?

PR:

They accept me a little bit because I don't use the term mesenchymal stem cell. This mesenchymal stem cell thing has turned out to be a huge hoax that's been hoisted on the field that these mesenchymal stem cells can do anything and fix anything. And people who are serious say, "Oh come on, Pam, people don't believe that anymore." I said, "Then why do nine out of ten manuscripts that I get to review regurgitate this garbage and try and get adipose tissue to make bone?"

There's a lot of crazy things out there. There are people that have invested a lot of money and their careers in trying to make this true. And it is true that you can take an adipose cell and you can molecularly engineer it to behave almost like a bona fide skeletal stem cell, but it's not the same thing. That's not the biology of the situation. That's cell engineering. And that's fine—if it works.

But this is the big thing: If the cell is functional. The problem that we had is that the cell surface markers are not specific. They are expressed by virtually any fibroblastic cell, but a fibroblast from bone doesn't do the same thing as a fibroblast from adipose tissue or from dental pulp or from muscle; they do different things.

They have a similar coat because that's the coat that they need to interact with the extracellular environment, which has a lot of collagen, and a lot of glycoproteins that are common amongst tissues. Collagen is a common extracellular matrix protein. And these cell surface markers give the cell the opportunity to interact with the collagen and with the glycoproteins and the enzymes that a tissue needs. Connective tissues have things in common; they also have very big differences. And to focus on the things that are common to make a common cell doesn't make biological sense.

So the stem cell field kind of accepts me, "but you work on that mesenchymal stem cell." No, no, no. I work on bone marrow stromal cells, a subset of which … I try and apply basic tenets of cell biology and stem cell biology. I don't believe in this common stem cell thing. And I had a collaborator, Paolo Bianco, he and I kind of joined forces in this area. And he was brilliant. He was probably the most intelligent and creative person that I've ever met. Unfortunately, he died a number of years ago. But he and I took on the task of trying to bring sense to the connective tissue field. I think we're partially there but we're not totally there. But because of the history the real stem cell biologists kind of view us with a little bit of uncertainty.

KD:

Interesting. I guess there's a draw to this notion of having a super stem cell that can do anything.

PR:

Yes. As Elizabeth Hay would say, it's the fertilized egg. That was her answer to toti potency; it's a fertilized egg. She was quoted as saying that.

KD:

There's more to talk about there, but let's go back to the early 1990s, when you had a visit from Allen Spiegel, and he brought you some samples. Tell me what was behind that and where you took it.

PR:

Allen Spiegel at the time was the Scientific Director of NIDDK, and he and Lee Weinstein and Andy Shenker, they found the mutation that causes McCune-Albright syndrome, which is a very intriguing disease. It affects skin. You get these café-au-lait hyperpigmentation areas. The patients have endocrinopathies, meaning there's over-production or over-influence of a hormone. It isn't necessarily over-production of the hormone, it's what the hormone does to the target tissue. And it has fibrous dysplasia of bone.

And this is a very potentially debilitating disease where the normal bone and marrow gets replaced with a very mechanically unsound bone and the marrow is completely obliterated with this fibrotic tissue. And I think that there was a realization pretty early in the game that it was a somatic mosaic disease, meaning that the mutation occurs after fertilization. Because you have normal tissues mixed in with abnormal tissues, and the only way you can get that, usually, is somatic mosaicism.

And the hypothesis was that if you had a germ-line mutation, it would be embryonic lethal. And so doing a variety of different things and playing the detective game, Allen recognized that all of the hyperfunctioning endocrinopathies were due to ligands that bind to receptors that bind to G proteins. That was the common link. So he reasoned that because they were all working through the G protein signaling system that perhaps the mutation was in a G protein.

So there are three different kinds of G proteins. There's G-alpha, G-beta, and G-gamma. They form a complex, and the complex activates adenyl cyclase. Or it can inhibit adenyl cyclase, depending on the mixture. There are many different kinds of G proteins. So he and his fellow, Andy Shanker, that's his name, started looking at the G proteins. They looked at the receptors in the G proteins and they found that GS alpha was mutated in McCune-Albright syndrome.

And so he came over and he said, "I understand why mutations in GS alpha would cause hyperpigmentation, because the hormone that controls formation of melanin goes through a G protein. I understand why the patients have hyperparathyroidism and hyperthyroidism and Cushing syndrome," which is over-production of cortisol. They all go through GS alpha, so that's how they focused on it.

And he said, "But I have no idea why it causes the bone disease." And so when I took the blocks and I sectioned the blocks and I looked in a microscope and saw that the marrow was gone and filled with this fibrotic tissue, I said, "My God, it looks like the stromal cells are on steroids." And the steroid thing is actually the opposite. If you have too many steroids, you get really bad bone but that was just my way of thinking about it.

And so that was when we started working on fibrous dysplasia of bone. And we isolated the fibrotic marrow, and we could determine that there was a proliferating cell in there that was really hyperactive, and then when we did the colony forming efficiency assay and we isolated different colonies, we found that there were a certain number of colonies that were mutated and there were others that were normal. So this was proof that this was a somatic mosaic disease.

And then we started studying what does it mean to have a mutated GS alpha? Well, it means that you have over-production of cyclic AMP. Well, cyclic AMP is a major signaling molecule that

controls downstream signaling pathways that control protein production and we found that the matrix protein expression was highly abnormal, and that is one of the reasons why the bone is abnormal, because the combination of the matrix proteins is abnormal.

But the big thing that we found was that the cells were producing FGF23, and that was a major breakthrough in the field. So there were other diseases that had similar characteristics as fibrous dysplasia of bone, and there was this group that was working on hyperparathyroidism, and they discovered that there was over-production of FGF23. And because we knew that hyperparathyroidism is a component of the McCune-Albright syndrome, we thought, okay, let's take a look at FGF23. And we found, lo and behold, that the patients have huge levels of FGF23.

And so what FGF23 does is that it blocks the action of some of the enzymes in the kidney that capture phosphate and put it back into the blood system. So all of the phosphate was going into the urine. So that was a major break because that now is one of the targets for treatment, and my colleague Alison Boyce, who's in the office right next door, is working on trying to treat the patients with a treatment that will block the action of FGF23.

KD:

One of your colleagues, Michael Collins, was involved in this work?

PR:

Yes. So I'm not an MD, and I got the idea that it would be very neat to study these patients. Number one, I having a hard time getting fresh bone samples from these patients. They undergo surgery all the time because their limbs get deformed and they go in and do osteotomies and they try and straighten the limbs out. But surgeons don't like to be bothered, and they're very fond of dropping a piece of tissue into a jar with formalin, which is great for histology; doesn't do much

for us in terms of studying the cells. And just getting them to accept containers that have nutrient medium and store them, it was hard to get them to do that.

Plus, we knew that there was a lot of variability in the patients and we suspected that the variability was not just due to the fact that they are somatic mosaics, that there was something else going on with them. Some of them had hyperparathyroidism, some of them didn't. Some of them had growth hormone excess, some of them didn't. So each patient was a unique situation. Trying to study them just by histology was not going to get us very far.

So we decided to set up a natural history study to bring them in on a Sunday night and to study them from head to toe and let them go on Friday afternoons. And this is where Mike came in, because I was not an MD. He was an inter-institute endocrine training program person. And that program is for two to three years, and they are free to go to any lab that they want to do basic research. And also, they had minimal clinical duties, but they had some, and he opted to come to my lab to work on bone and I tempted him to work on fibrous dysplasia of bone and he decided to stay, which was very good.

So we put together the natural history study, where we had the ability to take biopsies from the affected site. We also had in collaboration with us an orthopedic surgeon. His name was Shlomo Weintraub. He was from Israel and came over frequently to give us advice and things like that. And he said, "You're not going to pay the patients to come. You've got the fact that it's a rare disease and nobody knows what to do with it in your favor, but you want the patients to get something out of it."

And so we came up with two other clinical protocols. One was to try and treat the bone disease with alendronate, which is a drug that's used for treating osteoporosis. It's known as Fosamax.

And the thought was that we knew that the lesioned bone was weak. Well, if we treat them with this phosphonate, can we get that bone to mineralize and become stronger? Didn't work. We found that out pretty quickly.

And then we had a third protocol where we were going to take marrow from a normal bone and clear out the abnormal bone and inject the lesion with the normal bone marrow. That might have worked, except we had real problems, and that was that we didn't have an injectable carrier. And the only injectable carrier that was available was a collagen gel, but it had lidocaine in it, and the lidocaine kills the cells.

And we needed the carrier to hold the injected marrow in place, because when you clear out the lesion, you open up all kinds of blood vessels. And orthopedic surgeons will tell you that one of the fastest ways to infuse patients is to go into the bone marrow, rake the needle around a little bit to open up the vasculature, and inject. So we were losing the cells that we were injecting into the space. We needed something to hold the marrow in place.

I'm not a biomaterials person, I don't claim to be. I test biomaterials, I can tell you what's good and what's not. We still don't have a way of doing that, although there is somebody UConn, Ivo Kalajzic, who claims that he has a way of keeping the cells in place. But there are others that claim even if you do, that if you have any of the mutated cell left in that wiped-out lesion that it will grow back.

Now, I think that's true up to a point. I think that at some point the mutated cells burn themselves out, and we have evidence about that. We've published it. So that might not help a younger person, but it might help an older person that already has a lesion that's gone cold, and we can tell that pretty easily.

KD:

Was this the transplantation center at this point that's doing this?

PR:

It was something I was hoping to do. The transplantation center was based on what I wanted to do in bone and also what the field wanted to do. So we put the transplantation center together when it was thought that bone marrow stromal cells could cure everything. This was and at that time I thought there might be a chance. I didn't want to guess about other things. I thought, maybe we can do this for bone. But this was also around the time where we realized we needed a scaffold.

So because this was at a time when there was a lot of ethical issues related to using embryonic stem cells and IPS cells had not yet been invented, it was thought that maybe adult stem cells could perform some of the duties that an embryonic stem cell would do. So they gave me money to come up with a way of generating clinical-grade bone marrow stromal cells. And we did that and we were very effective in doing that.

We have a drug master file. We got through FDA. We ended up with three different INDs that were FDA approved. One was for the treatment of acute graft versus host disease with infusion of bone marrow stromal cells. The other was for injection of bone marrow stromal cells into dead regions of the heart after myocardial infarct. And the third was for treating inflammatory bowel disease.

This was at the beginning of this really big hype era. Bone marrow stromal cells can cure everything. Why did I think it would maybe work? Well, I knew it would work for bone if we could figure out how to hold the cells in place. But the other thing that bone marrow stromal

cells do is that they latch on to blood vessels that are not stable due to the fact that they lack a cell type called pericytes.

So my reasons were, okay, in myocardial infarct, you have a lot of injured blood vessels. And the investigator that was working on this showed that bone marrow stromal cells that were labeled with a fluorescent protein could indeed bind to those blood vessels. And I thought having intact blood vessels couldn't be a bad thing. Did I think that they would form cardiomyocytes? No. But the jury was out; that was my own guess.

The other thing is that cardiomyocytes and muscle cells, the immature cardiomyocytes, and the immature myocytes, they are born and raised to fuse with proteins. That is how you get myofibrils. And if you have a cell surface component that is similar to a myoblast, they will fuse. And they do. Are those myofibers totally functional? No, I don't think so, but nobody has ever tested it. This is one of those things that has fallen by the wayside. Yes, it will fuse, but you can actually put osteosarcoma tumor cells and they will fuse with myoblasts because they've got the right cell surface components. Would you want that? No, probably not.

So this was an era where there was a lot of speculation but not a lot of proof of functionality, and that was the point. So the center did what it set out to do. We made clinical-grade cells and people applied to use them. And we had three clinical trials. The first two actually published data. It looks like in the treatment of graft versus host disease that there were a population of patients that were positively affected and a population where there was no effect.

So what causes that? Well, we know that once the cells are released into the circulation they very rapidly get trapped in the lungs and disappear and die. But in their process of dying, there is a

process where they release cytokines and they release things. Could that have a beneficial effect? Maybe, and I think that that is what the story is. Has that been identified? No.

And Mesoblast recently tried to market their treatment for pediatric graft versus bone disease. I can't remember the name they gave their product, but the FDA did not approve it because the potential beneficial effects were very minimal, and their characterization of the product was less than optimal.

KD:

You've described a lot of points that can be put on a very large research agenda. And you're Lab Chief at this point?

PR:

No, a Section Chief.

KD:

Talk about your experience in leadership at NIDCR. How much did you bring people up? How much did you build out your lab? What were some of your keys to mentoring people?

PR:

When John Termine left, we had acting chiefs for close to two years before they finally appointed me. I was terrified. I will tell you, I was absolutely terrified because I felt that in terms of the bone matrix protein that even though we had not identified all of the bone matrix proteins that there were going to be hundreds more that are present in trace amounts. Because hydroxyapatite, which is the mineral in bone, is also known as the universal binder. It binds everything. So bone is bathed in blood, so you're going to find a lot of extraneous proteins and

also some intrinsic proteins, but they're not the structural proteins of bone. And we could go chasing factors forever. I was not interested in that part.

In terms of the gene regulation of bone matrix proteins, I was not particularly interested in that either, and neither was Marian Young, so I decided that I was going to go after the stem cell in the bone marrow and that this would be something that would resonate with other members of the group because they were, in essence, working with the progeny of the stem cell. And the other aspect was the rare bone diseases and tissue engineering.

Now I knew tissue engineering was going to be a longshot because, number one, we don't have orthopedics here at NIH. And number two, that is one of those things where it's really going to take some heavy lifting to do bone tissue engineering, and we just don't have the right people here. We don't have biomaterials here at NIH. We don't have orthopedic surgery.

But rare bone diseases we could do something with, and that's where fibrous dysplasia of bone came into play. We could do something that would be beneficial for the patients by studying them from A to Z. Mike found that all of them, even those who you wouldn't say have overt endocrinopathies, all of them needed adjustments in their various different hormonal levels. And there are drugs for that that are effective, so we could make them feel better.

We also enrolled them in a physical therapy program that was here at NIH. It's not as active now as it was then, but just trying to teach them how to get around on a daily basis for those that are wheelchair bound. We wanted to make them feel better and stuff like that. And just the fact that somebody was studying their diseases really helped a lot.

So we went off on that tangent, and Marian basically took the rare disease thing with the creation of transgenic animals that were deficient in certain bone matrix proteins and following up on

that. And she did a little bit of bone work and cartilage work. And Larry got off on evo devo, the evolution of a family of proteins called the SIBLINGs. In bone matrix we have proteins that probably arose from an ancient gene that was duplicated and then modified. So we have bone sialoprotein. We have osteopontin, we have dentin matrix protein, dentin sialo phosphoprotein, MEPE. So they're a family, they're in tandem.

And so he got into the secretion of these proteins, which is actually very interesting, and how the cell deals with getting them out and the chaperones that get them out of the cell and things like that. And it turns out to have significance in other areas too. There are other proteins that have similar characteristics, like chromogranin is one of them. Secretory cells have to deal with special things and so that was interesting and when Larry left, it went with him. And that's one of the characteristics of NIH. It's not a given that when a PI retires that that area will be continued. It's an opportunity for an institute to change directions.

KD:

Did you change direction significantly when you were leading?

PR:

No. I went from working on bona fide card-carrying bone-forming cells, and then I worked on the skeletal stem cell, which makes the bona fide bone, but they also do other things. They support blood formation and also make marrow fat. I haven't gotten into the marrow fat side much, but there is a whole society now called The Bone Marrow Adiposity Society because nobody really knows what the function of bone marrow fat is. It was originally thought that it's just a space filler, but it's more than that. And it also has a part in controlling blood formation.

So I've been more interested in the blood formation side of things. I studied a disease called dyskeratosis congenita, which has a mutation in TERT, which is one of the enzymes that controls telomere formation. And these patients get bone marrow failure, and it was always thought that it was because of the fact that these cells, the hematopoietic cell couldn't self-renew and therefore their marrow failed.

But a long time ago we got some cells from the hematologist here at the NIH, Neil Young, he's like our guru in hematology. And we did our transplants and we went back to him and said, "Neil, we have some cells from some of your patients where they didn't make bone and they didn't support hematopoiesis, so is there any chance that our patients also have a bone defect?" And he's all, "No, Pam." He poo-pooed us.

Eight years later, sure enough, we found that in some patients with certain mutations that they had early onset osteoporosis and that when we put them through the paces, they had the propensity to make fibrotic tissue, did not support hematopoiesis. So the proof in the pudding came when one of the hematologists came to us and said, "Well you know we do have a group of patients where we treated them with bone marrow transplantation which cured some of the patients, but we had some patients that were not cured." And that said to me that their stroma was not functional, and so it kind of came together. So we've done a little bit of work in what the stromal cells do in terms of controlling hematopoiesis.

And then the other thing that I've gotten into is their ability to form cartilage. Bone marrow stromal cells also make cartilage. The problem is it's a temporary cartilage and it usually undergoes hypertrophy and then it forms bone, which is not terrific if you're trying to resurface a joint. So then we kind of stumbled across a scaffold that actually supports stable cartilage formation, and that's what we're working on now. And we're trying to figure out by attaching the

cell to the scaffold what downstream signaling is instigated so that the cartilage is stable and doesn't undergo hypertrophy.

KD:

What's the scaffold you talk about? Is it an actual implement?

PR:

It's a fibrin microbead that's coated with hyaluronic acid. So the hyaluronic acid is the ligand for one of the receptors on the cells called CD44. And it's covalently attached to the fibrin microbead. And the fibrin microbead is degradable, but it's slowly degradable. Part of the problem with scaffolds is sometimes they last forever, sometimes they don't last long enough. You want to get it tuned just right. And that turns out to be a species-specific thing, which is a pain in the neck, but that's the way it is.

So we're kind of following up on this. I had not intended to go into the cartilage field, but sometimes when you are hit in the face with something, you think this could be significant. The fibro microbead has been patented, and we also have worked on a way of getting IPS cells to form stable cartilage, and we're working on a patent for that as well. We also have developed a way to make IPS cells make good bone, too. Because even though bone marrow stromal cells are terrific, sometimes you can't get enough of them to do a really huge bone regeneration kind of thing, so it's nice to have Plan B.

KD:

Am I right that at some point you were Acting Scientific Director?

PR:

Yes, I was. At one point, Larry Tabak decided to move Henning Birkedal-Hansen out of the intramural program into the extramural program. So once you do that, then you have to advertise, and that takes a long time, so somebody has to be in charge. I did not want the job, so I volunteered. People said, "Why did you do that?" And I said, "I know how fast things can go downhill when somebody is in charge that doesn't know what they're doing." And so I have been here for a long time. I've been here since 1974. I know the ropes and so I volunteered because I didn't want the job—And traditionally, people that were going to apply for the job were not asked to be acting because that was considered to be a conflict of interest, so I was the perfect easy date.

KD:

Did you learn anything from that experience?

PR:

Oh yes.

KD:

You're looking at a much broader swath. And you may have been familiar with what people were doing, but did you have to study up and learn a lot more?

PR:

I knew a lot, but there were certain areas that were not as familiar to me as others, one of them being salivary gland. That was a challenge for me. But basically, my main problem with salivary gland is that it's a field that is heavily engaged in using acronyms and abbreviations which I didn't understand and had to keep constantly looking up. It was almost like a foreign language.

But I finally caught on. The neurology wasn't as bad, the pain part was not as bad as the salivary gland.

But the big thing that happened when I was the Scientific Director was actually two months after I was appointed. On Super Bowl Sunday 2004, it was 16 degrees outside and I was sitting here in my office and I heard bump, bump and then the fire alarms went off. Well, this building is a really old building, and fire alarms go off all the time, so I was like, oh geez, not another one. So I didn't even take my gloves with me. I went out and the fire department came, and he came in and he went into the building. I expected him to come right out. He comes running out. He says, "Get at the top of the hill." We have a hill that's behind us. We went to the top of the hill and we looked and there is this smoke billowing out of the top of the building.

So what happened was that the physical plant had turned off the steam for some repairs but not thinking about the fact that it was 16 degrees out and the pipes on the roof of the building ruptured. And water goes to the lowest point in any building, which happened to be our transformer vault, which blew up.

KD:

This is Building 30?

PR:

Yes. And it also took out Building 29 and 49, so it was a very serious thing. The fire department couldn't go in to put out the fire until they found somebody to come and turn off the power. This was at the time when NIH was going through A1 or A4, I can't remember what, but they were replacing non-governmental employees with contractors, so it took them two hours to find

somebody to turn off the power. Meanwhile, billowing, billowing. And 5,000 cages of mice were on the fifth floor and the smoke was coming up right through the elevator shaft.

So they finally got that turned off and I called Larry Tabak on my BlackBerry, which is dying because it's not charged, and he was refereeing a basketball game. That was Larry Tabak's form of getting exercise, he would be a referee on Sundays and run up and down the court. And so we get the fire department in, they finally turn it off, and he calls everybody that we can think of to get people to come to the building so we can create a human chain to pass the 5,000 cages of mice because the building was out of power and it was 16 degrees and it was not inhabitable in the building. Only people with face masks on were going in the building filled with smoke.

So they put fans on the staircases and cleared out the smoke and we passed down the cages. We finished at 3 o'clock in the morning. We were lucky because over in Building 13 they had just cleared out a couple of rooms because they were going to be renovated, so they took our mice over to that room. And Building 13 is a veterinary building to begin with, so they had the staff that could handle it.

We had trucks and racks. They brought the trucks over. We had the racks wrapped in cellophane to try and protect the mice in some way. They would take the racks over to Building 13, unload, come back and stuff like that.

And then the building was condemned, and I had to find space for close to 300 people to sit while they were remediating the building. No power. We had over 100 minus-80-degree freezers that were powerless, not to mention the minus-20s and the minus-4 degrees and stuff like that. We arranged for 200 pounds of dry ice to be delivered in the morning and the evenings. I was allowed to let 20 people in the building, five from each floor, come in and pack the minus-80

freezers and the minus-20 freezers with dry ice to prevent total loss. All of the incubators were gone. We eventually had to dump all the cells and things like that. The 4-degree freezers were toast, and everything was gone.

This went on for 3 and 1/2 months before we were able to get back into the building. It was quite an experience.

KD:

Not something you ever would have expected.

PR:

I called it baptism by fire.

KD:

I'm surprised I hadn't heard about the fire at Building 30, but I'm glad I did. Is there anything else that we should talk about that we haven't discussed?

PR:

We did a lot of things while I was acting. I believe in complete transparency, so during our Branch Chiefs meeting I would tell them everything that I had learned from Scientific Directors and things like that. Some people thought I was being a little bit too open in terms of animal facilities and who has how many cages and all that kind of stuff.

It's not that we all have equal amounts of everything. Why would I give so-and-so 300 cages of mice if he doesn't use mice? You balance it with who needs what to do the work that they're doing. And we get reviewed by the Board of Scientific Counselors every four years and

adjustments are made and things like that. They are advisory to the Director and to the Scientific Director.

KD:

Did that full transparency work?

PR:

Some people didn't like it, and it was not continued.

KD:

Anything else we haven't talked about?

PR:

No, I think those were the major things.

KD:

I want to wrap up with some thoughts about NIDCR, how it's changed over the years that you've been here. As an institute overall, certainly from the perspective of the intramural program, has there been some sort of trajectory? Has there been some sort of evolution that you can point to?

PR:

When I first came to the Institute, there were several areas that were very unique to the Institute. There was pain, there was salivary gland, there was connective tissue, which encompassed bones and teeth. I used to say bones and teeth R Us. There has been a major shift away from pain, away from matrix and bones and teeth into salivary gland. And I think that I understand why. Salivary

gland is very dental institute specific. But I think that we've lost a little bit of the balance that we used to have.

I've seen the Institute Directors valiantly try to raise the profile of the Institute and I think that we have in some respects, but I think that more needs to be done in that area. The Directors inevitably are much more interested in the extramural program than the intramural program, and that they should make more to-do about the value of the intramural program and what we bring to the table.

KD:

This has been a great talk. I appreciate the candid discussion. I've learned some things that I didn't know, which is really, really useful. I'm glad we've got this information down. Any last thoughts?

PR:

The basic bottom line is that the people here, I've always enjoyed my colleagues. Especially when we were a branch, my colleagues were just terrific. Larry Fisher, Marian Young, then Mike Collins. We brought Mike Collins into the fold and also Eva Mezey.

KD:

Thank you very much. This has been a great talk.

PR:

I hope you find something useful. It's been an interesting place to work. I'm not thinking of leaving any time soon. I hope for the best, I do.

KD:

Thank you so much.

PR:

Okay, take care.