NIDCR Oral History Project

Interview with Michael Collins

July 9, 2024

KD: This is an interview with Dr. Michael T. Collins for the NIDCR Oral History Project. Today is July 9, 2024, and I'm Kenneth Durr. Dr. Collins, welcome.

MC: Thank you, Ken.

KD: I'm intrigued by your beginnings. You did undergrad work at Catholic University. Are you a DC native?

MC: I am. I was born and raised in Washington, DC. Went to high school and university here as well.

KD: And you had a music background. I'm always intrigued by how people move from early enthusiasms into their later careers. Tell me about how that happened.

MC: Well, I went to high school here in Washington, DC. I went to Saint Johns in northwest Washington, and I was drawn to, captivated, excelled in both science and music. I was drawn to both of them. And when it came to applying to university, the decision was would I study science or would I study music? Of course, I was 18 at the time, a bit dreamy-eyed maybe, and I chose, over my father's objections, to study music at Catholic University, which had an excellent music program.

And so that's how I got into music. And I loved it, I enjoyed it very much, I was pretty good at it, and went out to make a living, trying to make a living playing music, which, as you probably know is a very difficult career. And after a while, I was, okay, the music thing isn't working out very well, what should I do? And the only other thing that I had really been drawn to was science and medicine, as I said, and so at that time, after undergraduate, I was 29, I think, at the time, I said, "Well, let me try premed and see if that works out for me."

Because although I had been at Catholic University for six years, I had no premed background whatsoever. I went back to the University of Maryland College Park and took a couple of premed classes. I found that I did quite well, and I really liked it, and at that point I made the decision, okay, I'm going to go to medical school.

So I continued undergraduate work and finished undergraduate work at University of Maryland College Park and started in graduate school there while I was applying to medical school, and ended up getting accepted to a number of medical schools and decided to go to the University of Maryland in Baltimore at the ripe old age at that time of 31. So I started medical school at 31 years old, and that's how I got my start in medicine.

KD: And from medicine you developed an interest in research. Tell me how that came up.

MC: That was interesting. Like every premed applying to medical school, I wanted to get some research experience. And living in this area, a friend of a friend introduced me to someone at NIH. The initial position was in the NIAAA, National Institute of Alcoholism and Alcohol Abuse. And I was volunteering in the evenings, on the weekends, in the laboratory of Bob Eskay and I just fell in love with the work. I just thought it was fascinating. The opportunity to explore, to go somewhere where no one else has gone before, as they say in *Star Trek*, is really something, and I loved it.

While I was there, I got observed by a researcher in the NIMH, Larry Tamarkin, and Larry offered me a job in NIMH in his section and I took on this parttime job, working with Larry, and this really further cemented my desire to do research.

In fact, when I started medical school, my initial intention was to do like many physician scientists do, go to medical school and go straight to the laboratory and not get involved in clinical care at all. And that was my initial intention, until I started medical school and endocrine fellowship training and fell in love with the patient care, and the combination of science and medicine. It just drew me to it and that's where I went.

KD: So you became an endocrine fellow. Was this at NICHD?

MC: Yes. The NIH has an amazing program, the NIH Inter-Institute Endocrine Training Program. Currently, it involves the NIDCR, the NIDDK, and NICHD. And it's really an amazing program. It's trained some of the best physician scientists in endocrinology in the world, and I was fortunate enough to get a position there. And in fact, it was one of my early experiences there that really first cemented my love for translational research, and further, it directed the sub-sub specialty work that I would go into.

I was a first-year fellow in the endocrine training program, and each week we would be assigned patients to care for that week, and the patient that I was assigned to care for was a gentleman from New York City who had parathyroid carcinoma, very rare form of hypercalcemia, a parathyroid disease. I, of course, had never seen parathyroid carcinoma before. I was fascinated to help take care of this man. And he came and he was in really bad shape. I mean, his calcium was really high, we couldn't get it down by all he means that we knew. He was not a candidate for surgery. He had metastatic disease all throughout his neck. This guy was destined to die.

And I learned from the head of the training program at that time, Monica Skarulis, that there was a molecule, and drug in development, that had the potential to help this man. It was an agonist of the calcium sensing receptor, and theoretically, if his parathyroid tissue worked like it should, this would shut down parathyroid hormone secretion and allow us to treat this man.

It was 1998, before the internet, and the only way I got ahold of these people at NPS Pharmaceuticals in Salt Lake City, Utah, was to call long-distance information. And I long-distance information, I cold-called them, I eventually got connected to a man there, Ed Nemeth. Ed is one of the people who co-discovered the calcium sensing receptor with Ed Brown, who by the way was a former Endocrine Training Fellow at that time at Harvard, and those two, NPS Pharmaceuticals and Ed, share the patent for the calcium sensor receptor. And it was Ed and NPS

Pharmaceuticals that developed small molecules that were agonists and antagonists of the calcium sensor receptor.

So things were much easier doing clinical research in 1998, and literally within days we had started this patient on this drug, the first time this drug had ever been used in a patient, and it was really nothing short of miraculous. His parathyroid hormone level came down almost immediately; his blood calcium came down. This poor guy, who had been obtunded for months, woke up and communicated and in a couple weeks walked out of the hospital and we treated him with this drug for five years.

He, unfortunately, met his demise as a result of a car accident, but it saved his life and I was completely hooked on this concept of translational research. And further, I was hooked on the idea of mineral metabolism, calcium phosphate, and bone disease, and that's really how I got started. That molecule, incidentally, eventually became the drug cinacalcet. It was bought by Amgen Pharmaceutical and was a billion-dollar blockbuster drug for them. And the opportunity to have been involved in that in the very first stages, it just cemented what I wanted to do for my career.

KD: You talked about the inter-NIH program. Did you get a chance to work with people from other institutes? Did this give you a perspective on a broader NIH?

MC: Yes, very much so. And that's one of the beauties of the program. It not only involved—I was in child health at the time, and I told you it involved people from other institutes. In fact, the people that I worked with on this project were from NIDDK. It was Alan Spiegel, Steven Marks, Lee Weinstein, Monica Skarulis. So it not only involved other institutes, I was training. I was trained in internal medicine and training as an adult endocrinologist, but we'd also had the opportunity to see pediatric patients as well because it was conjoined with the pediatric endocrine training program as well, which was in the NICHD. So it was an amazing experience to not only see all kinds of pathology from childhood to adulthood, but to work with amazing people across the NIH.

And it was, incidentally, experiences at that time, too, that played an important role in what I did later in my career, caring for and studying patients with McCune-Albright syndrome and fibrous dysplasia. We would see these patients on the ward at the NIH, and the focus of the child health research at that time was taking care of their precocious puberty, their endocrine problems, hyperthyroidism, growth hormone excess. And what was interesting about it and the challenge to me—well, there were many challenges; these were incredibly complicated patients with multi-system diseases interacting with each other.

But the one thing that wasn't happening with those patients is their bone disease wasn't being taken care of, and we just didn't have the expertise in the intramural program at that time and it was really through the amazing efforts of Pam Robey, who was a cell biologist, that we in the NIDCR got started in a clinical program in fibrous dysplasia and McCune-Albright syndrome. It was Alan Spiegel who brought bone samples from patients with McCune-Albright to Pam, and Pam and her collaborator, Paolo Bianco, quickly reasoned out that this bone disease is a disease of the skeletal stem cells. This mutation that causes McCune-Albright syndrome, if it exists in a

bone cell, it causes this disease, fibrous dysplasia. And so they were very interested in starting a clinical program.

As I said, Pam was a cell biologist, Paolo Bianco, who was in Rome, was a pathologist, and another collaborator was Shlomo Weintraub, who was a pediatric orthopedic surgeon. So they really needed a physician, a clinician, to help them get these studies started. As I said, I'd been interested in bone and mineral homeostasis and had looked for someone on the NIH campus to work with for this.

But I wanted to learn the basics, the cell biology of bone, and I looked around the campus and really the only person on the campus with a program, and that was Pam Robey. I was in child health. I went to my boss at the time and said, "You know, I'd really like to work in Pam's lab for a little while, three, six months, maybe something like that, because I really feel if I'm going to do bone I really need to learn the basics of bone biology and bone cell biology." And I'm blanking on her name—Carolyn Bondi. So Carolyn Bondi was my boss. I went to Carolyn and said, "Dr. Bondi, I'd really like to work in Pam Robey's lab for a little bit."

Carolyn said, "No, I don't think you need to." I said, "No, I really think I need to." "No." "Yeah, I really think I'd like to do this." And Carolyn Bondi, God bless her, acquiesced and let me go work with Pam for six months.

Well, six months turned into 25 years that I have stayed in the NIDCR. And the way it played out is I was there learning how to grow bone cells and that sort of thing, and Pam came to me and said, "Look, we're going to start this study. We'd like to start this study in fibrous dysplasia, McCune-Albright syndrome, a clinical study."

And I had seen these patients as a fellow, and I had recognized that there was nothing we could do for these patients in terms of their bone disease. And my first reaction was, "Oh my God, fibrous dysplasia, why would you …" And then it dawned on me that this was an incredible opportunity. Because I knew we could get these patients here. I knew with the translational expertise in the NIDCR and across the NIH that this was an incredible opportunity.

So Pam, Paolo, Shlomo and I put together three clinical protocols. One was a natural history protocol; the other was a medical treatment protocol with the drug alendronate. Why alendronate? Because it was the only thing we had. If the only tool you have is a hammer, everything looks like a nail. So that's what we did, we started these patients on it. No, there was a rationale for it.

And then we tried to start also and studied a few patients with an autologous bone marrow skeletal stem cell transplantation study that, unfortunately, as things do, didn't go anywhere. But anyway, that's how I got started in 1998 with fibrous dysplasia/McCune-Albright syndrome in the NIDCR.

KD: And the most common reference—you talked about three protocols—the one I've read the most about is the natural history study that seems to have been a benchmark. Tell me about why a natural history study, what that entails.

MC: Natural history studies for rare diseases are absolutely critical. When I trained as a fellow, I was exposed to what were essentially natural history studies, although they weren't called that, in both NICHD and NIDDK. They had cohorts of patients with rare diseases that they brought to the NIH on a regular basis and did a very thorough evaluation of them and then collected that information positively, and this is what I had seen and been exposed to, and this is what we developed in the NIDCR. And with the time and the perspective that we had at the time, it was really a brilliant idea.

We did an incredibly thorough evaluation of these patients. We did ophthalmology, audiology, imaging, physical therapy, ENT. It was really an incredible protocol. And that protocol has been ongoing since 1998 to the present. And in rare diseases in particular, what the field has learned is that when you develop treatments for these rare diseases, oftentimes you can't really have a really good placebo-controlled study. The numbers are too small; the action of the drug may be too long; and it's really against the natural history of the disease that you measure the efficacy of your drug. This is critical for research in rare diseases, and this is something we do really well at the NIH.

KD: Yes, so essentially you're really taking a 360 degree look at all these patients and tracking them over a long period of time.

MC: Yes, that's right.

KD: And you did some medical protocols early on. How did those work out?

MC: Well, first of all, they were very challenging. We did the first-ever placebo-controlled study in fibrous dysplasia with the drug alendronate. Why alendronate? Because it was a drug that had some potential to address some of the underlying pathophysiology of fibrous dysplasia. And in fact, it was at that time the only class of drugs that made any sense to try in fibrous dysplasia.

So we were ambitious. It was a randomized, double-blind placebo-controlled study, and it took well over five years to recruit. And I actually try and forget the actual number, but I think it took about 10 years before we actually completed the study and published a paper on it. And it was essentially a negative study, which you can imagine was very disappointing, and it was disappointing. But the fact was that over that period of time we learned so many things. We learned so much about the patients and what they wanted and what they needed. We learned so much about the pathophysiology of the disease.

And we learned a lot about how to conduct and not to conduct clinical trials in rare diseases. And that really has made a huge difference in what we do today in some of the work being carried out in fibrous dysplasia by the person who is the head of the program right now, Dr. Alison Boyce.

KD: You published on some of those lessons, things like the lesions show up generally very early in life, right? Was that the first one?

MC: Yes. After we had seen enough patients, and after we had collected enough longitudinal data, we were able to retrospectively go back and look at the disease in the patients. It had been our clinical sense from seeing the patients and talking to the patients that it was really in

childhood where the disease took off, and that once they reached adulthood, young adulthood, they were done developing new lesions of fibrous dysplasia. The damage was done, so to speak, but it was in childhood that they accrued these lesions.

So this is really a critical point. We were able to map out quite accurately when and where the fibrous dysplasia lesions arose in these patients. And again, it's this historical data that allows you to design a prospective study now with a drug that you think will prevent the progression of the disease. And this is exactly what Alison Boyce is doing with denosumab in pediatric patients with fibrous dysplasia. And it's this historical data against which efficacy will be measured for the ability for this drug to prevent new lesions.

KD: There was also a lot of concern about the optic nerve and the effect of fibrous dysplasia on treatment. And one of your early insights involved in that. Tell me about that.

MC: Yes. As we were starting the work, I think I read every paper that had ever been published on fibrous dysplasia, and what emerged as a major issue for the patients was the optic nerve. The place in the skull where fibrous dysplasia is most commonly found is the skull base, and the optic nerve passes through the skull base. And the literature was rife with—in the surgical literature in particular—that when the optic nerve is surrounded by fibrous dysplasia that these patients will progress to develop blindness, and that it's important early on to intervene surgically to try and decompress the optic nerve to save these patients from going blind. And this is what the literature said over and over.

But after a period of time, that was not our observation. We saw many patients who were adults now who had their optic nerve completely encased with fibrous dysplasia. From what we could tell, it had been that way for years, and they weren't going blind. So what Janice Lee, who came to the NIH after completing her training in oral maxillofacial surgery, Janice and I were seeing the patients together, and we said, "Look, this just isn't happening. These patients aren't going blind."

And so we did a study, a retrospective, cross-sectional study of patients in the cohort at that time, and showed very clearly that the vast majority of patients did not go blind. There was not any age-related progression in this—so in other words, it wasn't that they had this in childhood and they needed surgery. They progressed into adulthood without any blindness. And in fact, what we found is the patients who did go blind and did the worst were the ones who had had these prophylactic optic nerve decompressions.

And so we were able to say pretty definitively that prophylactic optic nerve decompression in craniofacial fibrous dysplasia is contraindicated. And this was a big deal. It was published in the *New England Journal*. It was our first *New England Journal* paper. And it was the application of objective criteria to a surgical technique that I think made it so attractive to the *New England Journal*.

And it had the effect, we hope, because we've really beat the drum and tried to get this message out there as much as we can, we actually think it's probably saved a lot of patients from unnecessary and unwarranted and dangerous optic nerve decompressions.

KD: You were officially the Director of this natural history study, is that right?

MC: That's right. Pam Robey was the Principal Investigator when it started in 1998, and I think I took over when I became a staff clinician in 1999.

KD: Tell me how you split up the work. You were brought in to be the clinical guy, to see the patients, that sort of thing. What was Pam Robey doing, other people in the labs at NIDCR?

MC: Well, what Pam and her colleagues, in particular Paolo Bianco, did is they did a lot of work with the cells from the patients with fibrous dysplasia and made a number of really important observations. First of all, they were able to very definitively say that fibrous dysplasia is a skeletal stem cell disease; that cells that harbor this Gs alpha mutation become the pathologic cells. They were also able to show that the development of fibrous dysplasia required both normal and abnormal cells, which is a very interesting phenomenon. In other words, if 100 percent of the cells had this mutation—and they did this in mouse models—you wouldn't get fibrous dysplasia. It's only when you mix these cells with non-mutation-bearing cells that you develop fibrous dysplasia.

This was a really important observation and something that we really to this day haven't figured out completely, but it was a critical observation that continues to drive the research to this day. So they did a lot of the cell biology work. Paolo Bianco eventually went on to make a mouse model of fibrous dysplasia that was very useful in better understanding the disease as well.

Again, we remained in pretty much constant communication, both the bench scientists and the clinical scientists, and it was exactly this sort of bench-to-bedside translational research that we do so well at NIH that has allowed our understanding of the disease to progress and the development of new therapies, which is coming on now, and even better therapies in the future.

KD: At this point, you're pretty well ensconced in NIDCR. It wasn't a three-month or a six-month sabbatical. Tell me about the culture. You'd seen other parts of NIH, so tell me about the Dental Institute, your impressions of it, how it worked, how it was different or the same as other institutes.

MC: Well, you know it was a funny thing. I was here, an endocrinologist interested in bone, and I was going to work in the Dental Institute. People said, "The Dental Institute? Why?" Well, what people didn't know is the NIDCR had been, even before I arrived, for decades a leader in bone research. There had been, under John Termine, who was Pam Robey's boss, a bone research branch. So important bone research had been going on at the basic level at NIDCR for a long time.

And it was Pam who brought to the Institute a clinical program and a translational program. And what evolved from that or what came out of that that was very interesting is the NIDCR ended up being tremendously supportive of the clinical research that we started in 1998, and I would say, having colleagues in other institutes, I would say what the NIDCR was probably even in many ways more supportive of clinical translational research than some of the other institutes. They funded us quite generously up to and including the present, so I think the NIDCR has done an amazing job.

Janice Lee, who worked with me in 1998, left NIH, went to UCSF, she rose to become a professor at UCSF. She came back to be Clinical Director at NIDCR and it was really under her leadership that the clinical research program at NIDCR even got better. And I think it is really a model across the Institute, and in fact, other institutes not infrequently come to us for guidance to see how we do it. How do we fund the infrastructure that's necessary for this? We've been very successful at public/private partnership and collaborating with industry and using that funding to support some of the translational and clinical trials we've been doing at the NIDCR. So really, I think the NIDCR is a real model for how to do this across the Institute.

KD: Was this a full-time job? Were you spending all your time on the natural history study? Because at some point, you start setting up your own lab.

MC: One of the important things that came out of the study of fibrous dysplasia, and this is a phenomenon that occurs all the time, is how research in this rare disease informed a broader aspect of biology and physiology, and in this case, mineral homeostasis. When we first started the studies, we knew that some patients had low blood phosphorus. We didn't know why, we didn't know how that occurred, but we knew that occurred. We didn't know the frequency at which it occurred. And so that's one of the things from the start we set to figure out.

And we did that from the start by collecting all the materials that we would need to figure that out later—the blood, the urine, imaging, that sort of thing. When we entered into this, we figured that the cause of this was the Gs alpha mutation in the kidney, that the Gs alpha mutation in the kidney was causing the kidney to spill phosphorous into the urine, and that was the cause of the low blood phosphorous or the hypophosphatemia.

And so one of the studies I did, completed in 2001, in trying to figure this out, was the following: If the cause of the low blood phosphorous was the mutation in the kidney, those patients should have high levels of a molecule called cyclic AMP in the urine. This is what happens in other forms of hypophosphatemia that's caused by parathyroid hormone which works through G alpha S.

In 2001, again, we did a retrospective cross-sectional study looking at patients, those with low blood phosphorous, and those without. And what we observed was the fact that these patients did not have high levels of nephrogenous cyclic AMP in the urine, they had normal cyclic AMP, and this said to us, ah, this must be something else.

And the something else at that time, in the year 2000, the hormone FGF23 was discovered. FGF23, fibroblast growth factor 23 was a hormone that was discovered to be present in high levels in the blood in patients with little tumors called tumor-induced osteomalacia. So it appeared that these little tumors made high levels of FGF23 and this FGF23 is what caused loss of phosphate in the urine. And so we hypothesized, I wonder if it's FGF23 coming from the fibrous dysplasia that is the cause of this. And that ended up being the case.

So that was in 2001 that we published the first paper, and in 2003 we were able to show quite definitively that FGF23 was high in the blood of patients, that its level in the blood correlated with the amount of fibrous dysplasia they had, so the more fibrous dysplasia, the higher the

FGF23, the lower the blood phosphorous. We were able to get specimens of fibrous dysplasia from patients and able to stain them, looking for FGF23, and they had sky-high levels of FGF23 in the bone of fibrous dysplasia.

Interestingly, everybody has FGF23 in their blood, and it wasn't clear to anyone at the time what's the source of this, where does it come from? Does it come from an endocrine organ or where? And we were able to show at that time, in 2003, that in fact normal bone also stained for FGF23 and we were able to posit that bone was the physiologic source of FGF23, which is really quite a breakthrough in the field. And this is subsequently confirmed by a number of other laboratories that bone is the physiologic source of FGF23, the pathologic bone in fibrous dysplasia makes even higher levels of FGF23, and now this part of the story was finally revealed after this work.

KD: It's intriguing, too, the small tumors, the role of these small tumors. I think around 2000, maybe shortly thereafter, you started to make some really big findings in actually treating these people and removing these tumors. Tell me about that.

MC: This is another one of these fascinating rare diseases that we are able to study at the NIH and recruit these patients. So we worked very actively to recruit patients with tumor-induced osteomalacia to the NIH, and over a number of years were able to recruit what came to be the world's largest cohort of patients with tumor-induced osteomalacia.

We were interested in them because they had high levels of FGF23. And we were also interested in finding ways to identify these tumors, remove them, and cure these patients. It's one of those conditions in medicine where if you find the tumor and you completely cut it out, the patient's cured for life. It's an incredibly satisfying thing to do. These tumors are really small, though; they're the size of a pea. And they can be anywhere from the head to the toes, so finding them is very difficult.

So we developed a protocol for finding these tumors, which was a combination of a number of nuclear medicine studies with collaborators in the NIH Radiology and Nuclear Medicine department. We used selective venous sampling with collaborators in the NIH radiology department as well. And we developed I think what has become the hallmark of how to find tumors with TIO.

At the same time, part of the reason for wanting to see these patients was I was beginning to develop a program, a broader program that was more about mineral homeostasis, so phosphate, calcium, FGF23, parathyroid hormone, and how all of this worked together. And these patients with TIO became a really interesting model of which to study this.

We were able to figure out the half-life of FGF23 in the blood with patients. We were able to study the interaction between parathyroid hormone in FGF23 in regulating phosphate and calcium. And it really, I think, has made a significant contribution to the field of mineral homeostasis, this translational work that we did.

KD: Had you set up the skeletal clinical studies section at this point?

MC: Yes. At that point I became independent, a tenure-track investigator in NIDCR. It went through a number of names. It settled in Skeletal Disorders and Mineral Homeostasis Section. I was independent at that time, and at that time the work had expanded beyond fibrous dysplasia to include tumor-induced osteomalacia. We were also interested in the role that parathyroid hormone played, so we extended the work into patients with disorders of PTH, in particular, hypoparathyroidism.

Patients with hypoparathyroidism are patients who lack parathyroid hormone, and this offered a model in which to study independently of the effects of parathyroid hormone, the effects of FGF23 on patients. So we included a cohort of patients with hypoparathyroidism as well.

KD: And your lab, are spending all your time in Building 10? Is it very much like bench science? Explain to me what it's like to have this clinical studies lab.

MC: Clinical studies translational research is very challenging. Clinical research is very challenging. There is, appropriately, a lot of oversight, a lot of rules, a lot of things you have to do. So we bring patients to the Clinical Center, we care for patients in the Clinical Center, study for patients in the Clinical Center in Building 10.

The laboratory is in Building 30. We use model diseases to study this. We use cells from patients, we use cell lines, we use animal models. We have animal models of fibrous dysplasia, animal models of another disorder of FGF23 that we identified called cutaneous skeletal hypophosphatemia syndrome. And it's this constellation of disorders that come together to inform the integrated physiology and pathophysiology of these diseases that have really advanced our understanding of this.

So there's a lot of walking back and forth between Building 10 and Building 30. It's really challenging work, but it's very rewarding as well. There's nothing like when a mother of a patient calls you up and says, "I think my child has this disease," she tells you the story, and you say, "I think you're right." And she says, "Well, we don't have anybody here that can take care of it. We don't have insurance." And we can say, "Don't worry, we can take care of you," and bring them to the NIH Clinical Center and care for them. It's the most rewarding thing that I think a physician can do in medicine, and we get this over and over. It's tremendously rewarding work.

KD: Now typically, do the patients like the hypothetical patient you mentioned, would they come in every few weeks, every few months? How did that work?

MC: Again, because of the incredible resource that the NIH Clinical Center is, we're able to design the care for the patient per their need. A patient that's complicated may need—we've had patients come and stay for literally over a month as an inpatient while we try to figure out what's going on, try to figure out a care plan for them.

The typical patient with one of these disorders who's in a natural history study will come once a year and stay for a week. That's how it generally works. Again, the more complicated, the more challenging patient may need to stay longer. A patient who's not so complicated may stay shorter. And some patients we may see every few months; some patients we may see only every few

years. It's the flexibility that these natural history studies and the resources that the NIH Clinical Center afford us that allow us to study these patients in this manner.

KD: You've talked about a lot of different interests developing. The whole idea of mineral homeostasis is fascinating, you're looking at all these variables, I guess, and everything has to be in balance. And it appears that your research can go in all kinds of directions.

MC: Yes.

KD: At some point, you stepped down from the natural history study. You turned it over to somebody else. When was that and why was that?

MC: I don't remember the year, do you?

KD: No, but I've got it written down somewhere.

MC: The work was expanding, as you can see. It included a number of diseases, a number of molecules, a number of hormones, a number of different animal models. It was really becoming too much for a single person to handle. And fortunately, someone who had worked with me since she was a Fellow was Dr. Alison Boyce. And she took over and Principal Investigator of the natural history study and all of the studies in fibrous dysplasia and McCune-Albright syndrome.

So that afforded me the ability to broaden my focus and work on other matters. It offered to Alison an opportunity to become a tenure-track investigator, which she has, and she's doing an amazing job. And it was a win-win-win situation. A win for me, a win for Alison, and most importantly, a win for the patients. Because we were able to really significantly expand the other studies, especially in tumor-induced osteomalacia. We identified this new disorder called cutaneous skeletal hypophosphatemia syndrome. We expanded the studies in hypoparathyroidism. And the NIDCR now really is recognized world-over for this translational research that we do here in Bethesda.

KD: Moving into the 2000s, I want to talk about some of the research that you've done more recently. Does it all stem from this FGF23 and mineral homeostasis, or have you gone—

MC: It does. A lot of the work that I'm currently doing grew out of that. It grew out of the study of tumor-induced osteomalacia and FGF23. Some of the important work that we did is we were able, with collaborators in China, to identify that it was translocations between fibronectin and FGFR1, fibroblast growth factor receptor 1, that underlie the pathophysiology of tumor-induced osteomalacia. And this suggested, or I should say this confirmed what had been suggested was that it was FGFR1 signaling through which FGF23 was doing its deeds.

And so again we embarked on a public/private partnership with a small company in California called BridgeBio. They had acquired from Novartis a molecule, infigratinib, which is an inhibitor of FGFR1, and we posited whether or not this could be a potential treatment for tumor-induced osteomalacia. And again it was a patient in dire straits who informed this work.

We had a patient with widely metastatic tumor-induced osteomalacia. He had tumors all over his body. His phosphorous was incredibly low. He was incredibly sick, and we weren't able to

adequately treat him with medicines that existed at the time. And so we posited perhaps an FGFR1 inhibitor, infigratinib, might treat this patient.

So we did a single-patient compassionate use study in this man, and it, too, like the patient with parathyroid carcinoma, was really dramatic. Within days, his FGF23 levels came down, his blood phosphorous came up, and even more excitingly is that these tumors that he had had throughout his body that could be picked up on PET scan seemed to melt away.

And in fact, we had biopsied one of these tumors before treatment. It was clearly a carcinoma. Under treatment with infigratinib, it seemed to calcify. Tumors calcify a lot of times, and that's not a big deal, but we biopsied it. It had not only calcified; it had turned to lamellar bone. So these cancer cells had transformed into a benign cell under the treatment with infigratinib. We said, "Ah! This might be a treatment for not only this man with metastatic disease, but for other patients with tumor-induced osteomalacia."

Interestingly, though, and what became a problem with this drug, is that man with the metastatic disease began to experience what ultimately became intolerable side effects with this drug. This drug is a tyrosine kinase inhibitor, which are notorious for their side-effect profile. And it eventually reached the point that he was more miserable on the drug than he was with the disease, and after five years of treatment, we withdrew the drug and he died, unfortunately. But nonetheless, he was able to see his daughter graduate from high school; he had been able to go back and play tennis. It really had, at least for five years, transformed his life.

But based on that experience, we did a small study of patients with tumor-induced osteomalacia with this drug, infigratinib, and as predicted, it lowered the FGF23, it raised the blood phosphorous. But again, the side-effect profile was too much, and this was not the sort of thing that was going to sustain these patients. What we had hoped the drug would do, based on what it did in the first patient, transform the carcinoma to a benign disease, it did not do in these patients with TIO. When we stopped the drug, the TIO came back.

So in some ways that was a failed study, but in other ways that was very informative. We will eventually have much more specific with much less side effects inhibitors of FGFR1, and that molecule, when it comes along, will be a treatment for these patients with tumor-induced osteomalacia as well.

KD: Who's going to find that molecule? Is that going to come out of NIH labs? Is it going to come out of the private sector?

MC: Probably the private sector. For someone who studies rare diseases, the last decade has been a boon for us. The private sector industry is now interested in these rare diseases where they weren't before. They have deep pockets to pursue this. The methodologies for developing small molecules, the methodologies for in silico study of proteins has changed. The ability to identify inhibitors and agonists of small molecules in silico that can then be tested clinically has tremendously advanced.

So this will probably come out of industry, but the important thing is when industry does find these molecules, and again the progress that has been made is incredible, it still requires treating

patients in a very careful, a very meticulous way, and a good place to start with these things oftentimes is these rare diseases. These patients, they have a single mutation often that's causing this disease; they're very clean in a way. They are often in dire straits, as I mentioned before. They offer a wonderful population to test some of these drugs. And that's what we've been able to do.

And a great example of that is another project that we had, again this is with this company BridgeBio in San Francisco. Based on our suggestion that antagonists of the calcium sensor receptors—so I talked to you before about the agonists of the calcium sensor receptors—this class of molecules, again originally discovered by Ed Nemeth, were antagonists of the calcium sensor receptor. We knew early on that these molecules, these drugs, had the potential to treat patients with another rare disorder that we study at NIH called autosomal dominant hypocalcemia type I. It's a rare disease of hypoparathyroidism caused by gain of function mutation in the calcium sensor receptor, and theoretically, a calcilytic, an antagonist of the calcium sensor receptor, could treat these patients.

We brought this idea to BridgeBio, and BridgeBio went out and did their homework. They found one of these molecules that was sitting on the shelf of a company in Japan and they—I should say first of all that many companies developed drugs in this class, calcilytics. They had the notion that this molecule might be able to treat osteoporosis. You take a pill, it raises parathyroid hormone, and you can treat osteoporosis that way.

Many companies developed them, some of them went as far as Phase III studies, they all failed in the clinic. So there were a lot of companies who have these molecules sitting on their shelf, and so BridgeBio tracked down one of these molecules that was a terrible molecule for osteoporosis, but the best molecule for ADH1. And so we did a Phase II study of patients with ADH1 at the NIH Clinical Center. It worked incredibly well. Some of the most beautiful data I've ever generated in my life. We were able to publish this in the *New England Journal*. And now BridgeBio is conducting a multi-center international Phase III study and this drug looks like it will hopefully be approved for ADH1.

KD: Is that encaleret?

MC: Yes. That's encaleret. The interesting part of this, too, is a really sweet side effect of this research is you begin to get a better sense of human mineral physiology, how the body works. And so based on what we did in patients with ADH1, we also hypothesized that this drug, by its effects on the kidney in patients with what's called post-surgical hypoparathyroidism—

So there is a group of patients who not infrequently have all four of their parathyroid glands usually inadvertently resected during thyroid surgery. These patients have no more parathyroid hormone. They have this condition called hypoparathyroidism. And we postulated that the use of this drug, encaleret, in these patients could also have its effect at the kidney, allow the kidney to hold onto calcium and increase blood calcium, and this could be a potential treatments with patients with post-surgical hypoparathyroidism.

And right now, with my junior colleague Iris Hartley, who is the Principal Investigator of this study, Iris is conducting a study of encaleret in patients with post-surgical hypoparathyroidism. And the preliminary data, which we just presented at the Endocrine Society meeting, looks very, very promising. And this Phase II study in patients with post-surgical hypoparathyroidism will finish within the year, and if it continues as it does, hopefully this will turn into a Phase III study and it will be the first molecularly targeted oral drug for patients with post-surgical hypoparathyroidism.

KD: Any other scientific accomplishments, things that your lab has done over the years, that we haven't talked about?

MC: Let me think.

KD: You mentioned denosumab.

MC: Yes. Another line of work that grew naturally out of the study of patients with fibrous dysplasia. We had known for a long time that these patients had very high levels of bone turnover that not only did they have dysfunctional bone-forming osteoblasts, for the high levels of bone breakdown that they had, they must have something wrong with their osteoclasts as well. Osteoclasts are the cells that break down bone.

And we were able to show that, from biopsies of patients with fibrous dysplasia, that in fact there were very high levels of osteoclasts in some of these patients, especially the younger patients. And it really made sense, because osteoclasts are regulated by a pathway called a RANK RANK ligand pathway. RANK ligand in bone-forming osteoblasts, under normal physiologic conditions, is stimulated by parathyroid hormone. Parathyroid hormone works through the pathway that's altered in McCune-Albright syndrome, the G alpha S pathway, and independent of parathyroid hormone, patients with fibrous dysplasia on their bone-forming cells have very high levels of RANK ligand.

This stimulates, in some cases, massive formation of bone-forming osteoclasts. So the disease sets up this vicious cycle of bone formation and resorption, formation, resorption, but the bone that's being made is pathologic. It's not strong. But nonetheless, this signal, this RANK RANK ligand pathway, was probably critical in the pathophysiology of fibrous dysplasia.

I told you that early on the only hammer we had were these anti-resorptive drugs like alendronate, but what had happened in the meantime is Amgen had developed a monoclonal antibody against RANK ligand that interfered with this RANK RANK ligand interaction, and here again Alison Boyce and I postulated that this could be a potential treatment for fibrous dysplasia. This was around the time when Alison became the Principal Investigator of the natural history study, and so she also became the Principal Investigator of this study with denosumab to treat patients with fibrous dysplasia. And it really had dramatic effects.

This was also published recently in the *New England Journal* because it was so impressive. It had a tremendous effect on turning down bone turnover, relieving pain. It really seemed to have effects at the basic pathophysiology of the disease of converting the pathologic fibrous dysplasia

into something more like normal bone. And this is the study that I mentioned that Alison continued into pediatric patients with the hope of preventing the formation of fibrous dysplasia.

So the identification of the importance of the RANK RANK ligand pathway was, I think, one of the important findings of my group. And then taking that to the clinic with denosumab has really been the icing on the cake for it.

KD: What kind of skills do you have in your group? Have you brought in immunologists, folks like that that can have special expertise in some of these pathways, things you're talking about?

MC: As you point out, these are complicated conditions, and it requires a lot of different sorts of expertise. The primary expertise, of course, is in bone. And again, it was Pam Robey, Paolo Bianco who did some of the pioneering work. We additionally did work to identify the RANK RANK ligand pathway.

One of the people in my group who has really been instrumental in this work is Luis Fernandez De Castro. Luis, coincidentally, trained, did a postdoc under Pam Robey. He came to work with me. He's a bone cell biologist. He has really done fantastic work in fibrous dysplasia and cutaneous skeletal hypophosphatemia syndrome. He's really a leader in the field. Luis recently was awarded a Stadtman Scholar. Hopefully, he will become a tenure-track Investigator. Hopefully in the NIDCR, but at least in the NIH. So Luis is a bone cell biologist who's really important.

The work that we do in the Clinical Center requires a lot of collaborators. We have the skull base work with the optic nerve. We've had an amazing collaborator in the NEI for many years, Ed Fitzgibbons, who just retired, by the way, so he had a great career with the NEI.

We have a great collaborator in Jeff Kim, an otolaryngologist who works in—what's the in institute that does the … I can't think of it. Anyway, we have a tremendous otolaryngologist who we've worked with for years. We've had tremendous support from physical therapists and occupational therapists in the NIH Clinical Center. We've had collaborations with people in nuclear medicine and radiology, John Butman, Clara Chen, Bob Oxyburi. It really has been an incredible team that's really been necessary to do this work over the years.

And it's because of a place like the NIH Clinical Center, where we have access to these people who not only can do the work, but are as fascinated by the work and drawn to the work as much as we are, it's really incredibly rewarding to work with people like that to crack the code on some of these diseases, to define the care, to figure things out.

KD: It sounds like a lot of your work is keeping these contacts intact, and making more contacts, and just setting up networks of people to work with.

MC: Yes. I would say that a big part of this is finding collaborators in the NIH, nurturing and maintaining those collaborations. It's also, at least for the last decade, involved significant public/private partnerships, identifying partners in the private sector who will work with us. And that's a challenge also.

KD: Why?

MC: Because especially the big pharma companies are much more difficult to work with. They know how it should be done; they know what needs to be done; they want to dictate how things are done. But they don't. They don't understand these rare diseases, and they don't necessarily have such an interest in it. It's been the small biopharmaceutical companies who have entered into the pharmaceutical field that have really been a joy to work with.

BridgeBio Pharmaceutical in San Francisco, Ultragenyx in California as well. We've also ultimately been able to work nicely with Amgen as things have gone on over the years. But there's a lot of small biopharmaceutical companies now who are interested in doing this work and begin to recognize the potential for information that can be gained by treating patients with rare diseases, often monogenic rare diseases, with these molecules that they develop.

So yes, it's a large network of intramural, extramural collaborators. My research group is not that large, maybe 10 people or so, including scientists and nurses, but yes, there's a lot of balls in the air to keep this thing going.

KD: And you've told some great stories about accomplishments, maybe not curing people but making big strides in treatment. And I'm interested in that you appear to have been the first winner of the Constellation Award from the Fibrous Dysplasia Foundation. Is that right?

MC: That's right. And you speak about something that we haven't spoken about yet that is also incredibly important and incredibly satisfying, and that is working with the patient support groups. This is a modern phenomenon as well. When we first started the studies in fibrous dysplasia, it was really sort of pre-internet. Then eventually there was a website, FDsupportonline. The father of a girl with fibrous dysplasia created this.

This led to the establishment of the Fibrous Dysplasia Foundation. One of our patients, Charlie Harles, who eventually passed away from a probably unrelated condition. Charlie was an amazing guy. Charlie had pretty bad fibrous dysplasia, and from very early in childhood had had fracture after fracture and was fairly debilitated by it. Charlie went on to become a lawyer with a specialty in disabilities. He was involved in the writing of the Americans with Disabilities Act. He was dedicated to the field. Charlie lived in Washington. He was a consultant, a lobbyist.

Charlie became one of our early patients at the NIH and immediately Charlie recognized the importance of a support group for patients. As we would bring patients to the NIH Clinical Center, week after week from all over the country, from all over the world, Charlie would come and visit them. And once he had a key cohort of patients, he would have little parties at his house on Capitol Hill, and the fibrous dysplasia support group was born.

And this has been a tremendous boon for patients with the disease. It's a resource of camaraderie. Most patients with these rare diseases have never met another patient with the same condition, and when they finally meet other people with it, it's incredibly rewarding to them. They are not alone anymore; they're not the only person in the world with this; they meet someone who's gone through the same hardships they've gone through and now they have hope of bonding together and developing ways and supporting the research to improve the care for themselves and others.

So Charlie started the Fibrous Dysplasia Foundation. It's continued to this day. It's morphed into what is now the FDMAS Alliance, a much larger professional organization. I've been involved with that group since the very beginning. I've been on the medical advisory committee, the scientific advisory committee, and now the board of directors. That led to the creation of an international consortium of patient support groups with fibrous dysplasia, the International Consortium of FDMAS, which I've been involved with since the beginning, too.

And so early on, in appreciation for the work that I did supporting them and helping them, I got their premier award, which is called a Constellation Award. And I really value this. I really value the work that I do with these patients, and I value the rewards that I get from this. It's incredibly rewarding being able to play a role in the progress of the treatment and the care for patients with this one disease.

KD: Tell me about the support you've had over the years from NIDCR. There have been times when the Institute has gone through changes in focus. Have you experienced that? Has there been any change in the attention that you're getting from NIDCR or what you're able to do?

MC: The NIDCR, from the very beginning in 1998 with the studies that Pam set up until the present, has remained incredibly supportive of the bone research program. It's always been our assertion that teeth are a mineralized tissue. They are sort of a specialized bone. And without the bone to put the teeth in, you don't have teeth. Mineralized tissue is mineralized tissue, and what we learn about bone we learn about teeth. And so probably because of that, the NIDCR has been, all along, very supportive.

We always worry a little bit about the fact that you can make the argument that this is not relevant to the mission, and I can very strongly make the argument that it absolutely is, that teeth are a mineralized tissue and we need to understand mineralized tissue, and what we learn about teeth informs us about bones, and what we learn about bones informs us about teeth. So I feel really, really fortunate that all along the NIDCR has remained very supportive of a bone research program. And that appears to be the case going forward, and they are supporting now Alison Boyce and Kelly roscoe and Luis Fernandez de Castro and hopefully the bone research program in the NIDCR will continue for many, many more years because it really, I think, has made really important contributions to the field.

KD: Tell me about some of the people that you've worked with, both mentors and people that you've mentored. When we were talking earlier, you mentioned Allen Spiegel. You got to work with him?

MC: Yes. I got to work with Allen Spiegel. He was one of the coauthors on our first paper on treating the man with parathyroid carcinoma. Allen Spiegel, at that time, was the Scientific Director of NIDDK. The person who worked under him who I worked with closely on this project was Stephen Marks. He was there. In Steve Mark's branch was Lee Weinstein. Lee Weinstein was one of the people who, when he was in Allen Spiegel's lab, discovered that it was mutations in Gs alpha that caused McCune-Albright syndrome. These three have always been important supporters and mentors over the years.

And then, of course, when I first came to NIDCR to work with Pam Robey, she afforded me an amazing opportunity to be involved in her research, so Pam has been an important supporter over the years. Ed Nemeth, who discovered the calcimimetics and calcilytics, I've worked with closely over the years with the early calcimimetic studies and continue to the present in these studies in calcilytics.

Two other people who were part of my tenure-track mentoring committee, was Les Biesecker in the genome institute here at NIH. Les is in the Genome Institute. Les is someone I've always been impressed by. He is a translational scientist, and I approached him early on about being on my mentoring committee, and he agreed, and he's remained a staunch supporter ever since.

Another person outside of the NIH who was very important in my development was John Potts at Massachusetts General Hospital, the head of the endocrine unit there. John had actually done his early training here at the NIH in what would probably be considered a precursor to the inter-institute training program. So John was at NIH and left for Mass General and has been a giant in the field of mineral homeostasis and parathyroid hormone biology, and he was on my mentoring committee and has been supportive over the years as well.

And I think it was in part the feeling of indebtedness that I had for these people who helped me that mentoring others has always been front and center one of the most important and also one of the most rewarding aspects of my career. It's something that I've taken very seriously. I actually think it started when I was studying in my internal medicine training program at the University of Maryland. I stayed on to become a chief resident, which is really a mentoring role. I came back; I became involved in the inter-institute endocrine training program. I was Deputy Director there. I really loved that, helping the trainees.

I've also been involved for a number of years, and found very rewarding being involved with the MRSP, the Medical Research Scholars Program, which was previously the CRTP, the Clinical Research Training Program. So I've been involved in this mentoring programs, and I've spent a lot of time mentoring the people who work for me. I take great joy out of seeing them succeed—Alison, Kelly Roscoe, Luis—it's incredibly rewarding to me to see them succeed and to think that I was able to share both my knowledge and resources to help promote their careers.

Because at the end of the day, when we're gone and we've retired, and we've moved on, and our papers have become passé, what will live on as a representation of our work is the people who we mentored. And I feel very fortunate to have mentored a number of people not only here at the NIH, around the world. Pablo Florenzano, who's rising through the ranks at the University of Chile is Santiago. Diana Ojero, who's in Barcelona. So it's been this network of mentees around the world that continue to be a great source of joy for me.

KD: Is there anything that we haven't talked about that we need to cover?

MC: I don't think so. There's a couple of funny stories that came up that probably should not enter into this, but I'll share them.

KD: I love funny stories. Let's do 'em.

MC: One of my really important experiences during my music training that led me away from considering music as my career is I was studying music at the Catholic University here in Washington. We had an incredible music training program there. My teacher was David Flowers, who was a trumpet player in the National Symphony Orchestra.

And there was a circus that came through town. It was called Circus Americana. And Circus Americana was in need of trumpet players, so they contacted Dave Flowers and said, "Hey, you have any guys who might be willing to join the circus?" And so Dave contacted me and a good friend of mine who also played trumpet, Vince McCool, and Vince and I looked at each other, it was the summertime, we said, "What the hell!" We auditioned and got a job in the circus and went on the road with the circus.

That lasted through the summer. That was quite an experience. That was really a rough gig if you will. We had a traveling show and we had a show at Busch Gardens. The show at Busch Gardens, we worked seven days a week, we played seven shows a day, playing the same stuff over and over and over in the hot sun. That convinced me I didn't want that.

The traveling show, which we also went to, would travel by school bus from town to town. If we were lucky, we would stay in some cheap hotel. Often, we stayed on the basement floor of a church in a sleeping bag. That was a pretty brutal existence. That said to me maybe music isn't the way to go.

I had another experience, too. While I was playing music, and trying to make a living playing music, and teaching lessons and all of this stuff, I had gotten married and I had a child, and I had to have a day job, as many musicians did, so I had a day job at the Safeway, which actually was a great job because it had healthcare benefits for my family, it paid pretty well.

And it was looking like the music thing wasn't going to work out and I was considering a day job, so I did two things. First of all, I took an aptitude test to figure out what I was going to be good at, and it said that I would be good as an insurance salesman. So I said, what the hell! So I bought a blue blazer and a white shirt, and I interviewed with some insurance companies, and they were quite excited about hiring me. And I said, there's no way, I can't do that, so I bagged the insurance company idea.

But then the other thing I did is I was working at the Safeway part time, and I said, "Well, maybe I could go into management training and I could become a store manager and a district manager. It's not so bad."

So I applied for the management training program at Safeway, and they completely blew me off. So that actually was the turning point where I said, "Screw these guys. I'm going back to school." And that's when I went back and took the premed courses, so thank God they denied me entrance into the Safeway management training program because we wouldn't be here now if they had and my life would have taken a completely different course.

KD: Yes, and the benefits to science would not have happened. Or somebody else would have stepped in, I guess, but it's great that it worked out the way it did.

MC: I have one other thing that as I was toying all this over that I thought about. You had talked about early on this sort of relationship between music and science, music and medicine. And in thinking about that, the first time that I really became aware of that was in my organic chemistry class. And in organic chemistry, one of the things that you're often charged with is creating a molecule. You want to end up with this molecule. How do you do that? What are the synthesis steps that can get you to that molecule? And you start with this, and there are very prescribed steps that you go to get to that molecule through that synthesis.

And that struck me as incredibly parallel to music theory. In music theory, when you want to end up you're writing something in the key of C, for example, and you're going in C, and you make diversions to other keys, but you need to come back to C to come home to give resolution to the piece of music.

And again, there's a number of fairly prescribed steps in music theory that you have to go through to get back to C. And it really struck me as the same thing as in organic chemistry. And in science, too, you start with the end. You have a vision of something, you have a hypothesis of how it's going to end up, and in clinical medicine, the patient who walks through, the experiment is done, the patient is representing what has been done. And then the question is, How did you get there? What were the steps that preceded this?

And it's the same thing in music theory or in organic chemistry. You work backwards from the end product in the case of clinical medicine/translational medicine, and you see how the physiology, the pathophysiology worked to end up where you wanted, and you unravel the puzzle. And that's what's been an amazing driving force for me throughout this. And it's the same thing in medicine. How do you get back to C? You have to go through F and G first.

KD: The circle of fifths, that whole thing.

MC: That's right, exactly. Music harmony is amazing. Bach wrote the rules and then broke the rules.

KD: Well, this has been a great talk. I really appreciate your taking the time today.

MC: Well, thank you, Ken. It's really been fun. This is a really good time for me to look back at the work I've done and been able to take joy and satisfaction in it and helping patients and helping trainees and sharing the word.

KD: Terrific.