

ORAL HISTORY INTERVIEW

RAYMOND DIONNE, 1998

Interview by: Marcia Meldrum, Stetten Fellow

MM: Today is Monday, December 21st, and we're here in Dr. Raymond Dionne's office at the National Institutes of Health, at the National Institute of Dental and Craniofacial Research, and it's 2:10 in the afternoon. Good afternoon, Dr. Dionne.

RD: Hello.

MM: To start the interview, I'd like to start with vital statistics, where you were born, where you grew up, how big your family was, that kind of thing, and sort of move from that through your early education and so forth.

RD: OK, all right. Providence, Rhode Island. I must have been born in Providence, raised in Providence, for sure. [I was born there] December 25th, 1946, and then stayed there, went to some grammar school that's long since forgotten, high school at some local school, and then moved to East Providence somewhere along the way and graduated from East Providence High School. Then after that, I went to college at the University of Connecticut, ironically enough, so that I could get far, far away from the small environment of Rhode Island. And 60 miles later, I was in Storrs, Connecticut, and that's where I went and got my BA.

MM: That's a big step up.

RD: It was. Ooh, man. Had a whole different state. Rhode Island gave you that small mentality, so doing something like that was considered to be a big [deal]. You know, I was the only guy in my class, I think, who went outside of [the state]. Then, after four years of doing that, I went to dental school at Georgetown [University in Washington, DC] and graduated from there in 1972.

MM: OK, that's good. Stop there.

RD: I jumped too far.

MM: Yeah. So your family was how big?

RD: It depends how you define it. I had three sisters, and I was the oldest boy, and then my mother died, my father remarried and started a second litter, as we called it, had another girl, and then she died eventually. He remarried a third time, and she came with two sisters, two daughters, so that made two stepsisters of sorts. And then, being the mean woman that she was, she clearly outlived him, and she's still around. And so I have, depending on how you keep score, three full sisters, one half-sister, and two stepsisters.

MM: My lord. And you're the only boy.

RD: Yes, yes. I'm carrying the burden for the family. And it's getting tough. You see, I've had to take in new work [joking] to make ends meet.

MM: OK. And can you tell me when you thought you might go into dentistry and what kind of your career ambitions were in high school and so forth, and what led to this choice of career?

RD: It's almost embarrassing, because I'd have to go back to a time when I was so naïve that it is embarrassing to ever admit having been like that. But somewhere along the way – There was one practical reason why. I went to college as an engineer, and my choice of career was that my father was an engineer and I was having no problem getting A's in all the math courses when I was in high school. And then I took a mechanical drawing course, which they billed as being some sort of a prelude to engineering, but, of course, that was a joke to think that drawing pretty little blueprints was really anything like engineering. So based on those false assumptions, I went off to college and was going to be an engineer. And they had that old thing where they said, look around at the guy on the right of you and the guy on the left of you, only one of you will be left at the end. I bailed out at the end of the first year, when I realized that math was actually very hard when you did it at the college level, and calculus was a foreign language even to today. And then I took physics for engineers and staggered to a C, and I said, "This can't be my future. I hate doing this, and it's damn hard."

So that's when I started looking for a career alternative, and right about that time was getting somewhat idealistic, so I thought maybe I'd go out and do something that would help mankind, as the cliché would go, but I was a little fuzzy about how I would do that. So I went into just being a biology major, and as time wore on, I was trying to decide whether I should be a clinician or go into research. I even flirted with the idea of maybe becoming a social worker or something like that. But then things really became crystal clear to me, because it was during the Vietnam War and I was subject to the draft. I went home one summer, and they called me in for a draft physical. And I said, "But, but you don't understand. I'm in college." And they said, "Sooner or later, you'll be all through with college, and we want to be able to process you as quickly as possible." And it turns out that Rhode Island was having trouble filling the draft quota, so they were prescreening people while they were still in college. So I saw my future coming, so I decided that going someplace that involved a deferment maybe was in order. So that became, do dental school first, and then you could always go into research or do something more worthwhile later on. So I backed in the door that way, into dental school, and applied to five dental schools and went for interviews in February and March. And guess which one was the warmest one of the bunch? It was the one in DC, because all the rest of them were in New England or in New York City, which was pretty frightening for a kid from Providence, Rhode Island, who had to go down for an interview. So I ended up going to Georgetown based on the weakest of reasons: it was warm and it looked like a manageable-sized city. So I ended up going there.

MM: So you wound up at Georgetown.

RD: Yeah.

MM: So no burning desire to solve people's teeth problems?

RD: If I did, it would have been snuffed out by the educational process, that's for sure, because it turns out that, unbeknownst to me, Georgetown was the last of – not the last, but certainly the worst example of a school that strictly trained you to be a technician. And the intellectual part happened by accident. To save money, they combine the medical school and the dental school classes, so you got the same lectures, took the same exams, and they just graded you on a different curve. So I got two years of real good basic science training, but at the same time I was getting two years of an introduction of what dental school or dentistry was going to be like. The first lecture we ever had was on plaster, and you might not appreciate the importance of plaster, but it turns out you make all your models out of plaster. So they wanted us to really know plaster inside and out, so we got about an hour's lecture on plaster, and then we went to the lab and, for an experiment, we mixed up a batch of plaster, stuck a thermometer in it, and took its temperature for four hours. And at the end, we grafted out. And we had a group discussion, a hundred of us with our chunks of plaster and our little thermometers and everything, and he said, "Well, what happened?" and we said, "Well, the temperature went up, hit a peak, and then went back down." And he said, "That's good. And when did that happen?" Well, we said, "When the plaster was setting." He says, "What's that an example of?" And we said – they had just taught us – that's an example of an exothermic reaction. It gives off heat. And he said, "Very good." He said, "We can clean up and go home now." And we go, "What? This was it?" And worse yet, he said, "Yeah, that was it. That was the purpose of this thing. We wanted you to get familiar with plaster and teach you this important principle that plaster gives off heat when it sets." Then he said, "All right, now what you have to do is take your thermometer out of the plaster, clean up, and you can go home." So we all grab our thermometers and we pull and we pull, and we snapped off a hundred thermometers. There were a hundred people in the class. And –

MM: Mercury all over the place.

RD: Yeah. He said, "Oh, I forgot to tell you, you should have put Vaseline on it first." So we learned a lot of valuable things about what education was going to be like at Georgetown. So, needless to say, by the end of the year, everybody was looking for another career, but they were stuck with the fact that they were in dental school, and the drawback was you had to borrow money to go to dental school, and if you dropped out before you graduated, you owed all that money. So you got entrapped, and in no time at all we all ended up staggering to the finish line, with the exception of a few people who decided to bail out along the way.

But I started doing pharmacology research. I was desperate, by my second year, for something that was a little more intellectual than that. I mean, at best, someone once characterized dentistry as making small holes in teeth and filling them back up. It seemed humorous at the time, but now, of course, I recognized that's exactly what it was, and we would have been doomed to doing that. So I ended up, on the basis of that, doing pharmacology, and it was a young department. We had a chairman who was in his, probably, late 30s, and all the faculty members, as a consequence, were mostly young people that he'd recruited. So it looked very exciting by comparison with all the old departments that had kind of a lot of old fogies, probably guys my age.

So I did pharmacology research, and that was very exciting, because now, suddenly, you're doing something that was seemingly important, very intellectually challenging, and had a little beginning, middle, and end to it and stuff like that, and you were always learning new techniques. So I got bitten by the bug. And, actually, the first project that I did ended up – no, the second project I did ended up getting a good paper in a good journal. The first one I did was a total failure, and I just flailed for a whole summer trying to get this project that never worked. So that was a good example, too, of what research can be like. So, in any case, I decided to just suffer through dental school and go into research when I got all through.

MM: Was Bill Beaver¹ there then?

RD: He was. He was on the faculty. He was a fairly unexciting guy to be around because he had got his lectures worked out about 10 years before that, and his research was very repetitive. And, as a consequence, he didn't strike anybody as being too dynamic a fellow. In fact, the story on him was, one year he put a little sign up on his door that said, "Dr. Beaver is on sabbatical, and he can be reached at..." and it had his home number. And someone came along and wrote next to this little thing, "Which year?" because he was so undynamic and never around that much that it was questionable whether he'd been on sabbatical the year before, the present year, or maybe he was going to go on sabbatical next year.

MM: It was kind of a permanent sabbatical.

RD: Yeah. In fact, he wrote up some papers once and submitted them to the *Journal of Pharmacology*, I think it was, and they were technically very clean, and they got rejected on the basis of the fact that everybody knew that was true. In fact, you could look up in Goodman and Gilman,² the standard textbook, and see that information. And he said, "Yes, but ask the author of the chapter who gave him that information," and it turns out it was Bill Beaver, based on unpublished observations like 10 years before. So on the basis of the fact that it was already in the textbooks but it had never actually been verified or printed, they accepted him and they published him that way. So he didn't attract a lot of graduate students to speak of.

MM: No. That's interesting.

RD: Yeah. So I went from being in cardiovascular research to going into a group that was doing CNS [central nervous system] pharmacology primarily, looking at stuff for seizures, and I did that for a good year or more with them, and that was kind of exciting. But we ended up, in the end, rediscovering [that] barbituric acid³ was an anticonvulsant, because we were studying a very complex form that had been modified and was going to be the new drug for seizures. We would give it to animals; we tested them in three different animal models, collected all these blood samples, brain samples, and looked at the correlation between the activity we saw and the metabolites that were forming. In the end, the only metabolite that made any sense was the last one, which was nothing more than pure barbituric acid. And we said, if that's true, then we've just rediscovered mankind's oldest anticonvulsant. So that was the end of that line of research. Unfortunately, right about that time, the two people that were working together, one was like an associate professor and the other one was supposed to be his assistant, but he was actually on the faculty as an assistant professor, had a spat that became one that couldn't be repaired. So eventually the associate professor kind of retreated to the Neurology Department at the hospital and stopped coming by, and eventually left the institution. And the assistant professor stayed in the Pharmacology Department, but he must have been told it was time to look for another job, because it wasn't more than another 60 days when he disappeared and took a job elsewhere. And I actually ended up with this huge laboratory with all this equipment as a graduate student, and I was the only one in there. I kept staggering forward, trying to do the research, but I was ill-equipped for it. So the only way to resolve it, finally, was they said, "Well, it's going to be ridiculous for you to be here. You're only partway through the PhD program. You're going nowhere. All this research you did is not going to account for anything," because not only was it not very exciting, you don't even have a mentor anymore. So rather than start all the way from scratch, they offered me the option of finishing up with a Master's. And about that time – I was now about five and a half, six years into graduate school and was getting mighty tired of it, idealistic or not. So I took the Master's option and was able to finish up just in a few months. And right about the time I thought I was out the door and maybe was going to put science in the rearview mirror, I saw an ad in *Science* magazine for a fellowship at the Medical College of Virginia [MCV, in Richmond, Virginia, now part of VCU, Virginia Commonwealth University] where you could go down there and learn how to do pain research. And I said, "Well, that's what I've been trying to tell these guys for the last couple years I want to do." It was just a choice of doing it with Beaver, which looked pretty unexciting, so I thought [instead of] doing it with these guys who looked pretty sharp, who were doing all the neurology stuff, that would approximate it. Now I realized that none of this was going in the direction I wanted, but here's an alternative. So I was able to interview for that position and get accepted into it because they were looking for people just like me who had a dental degree or a medical degree and wanted to do pain research.

I ended up going down there, and that was like just a pivotal educational experience. Everything was in a warm, nurturing environment, unlike the last two I had been in or the one I'd been in for the last 20 years, for that matter, and they wanted you to succeed, and, by and large, they would do whatever it took to make you succeed. So I was able to get into the PhD program, I was able to do a project that was in my area of interest, and I was

able to get it done. And before I was completely done, there was this job that opened up at NIH where someone was leaving, they wanted someone to fill his position, and they were looking for a dentist who had advanced training in pain. So I applied for the job. I got it, but the drawback was they wanted me right away, and I was probably still four to six months from finishing my PhD. So I faked it by doing a first draft, showing it to everybody on my committee. They said, "It looks fine as long as you promise to finish it up shortly." And so I disappeared and came up here and got the job and started working away. And then about nine months later, I got a nasty letter from my thesis advisor saying, "We have repeatedly warned you. We have told you you'd better finish up. If you don't finish up by the end of this semester, forget it."

MM: That's pretty heavy.

RD: I said, "Wait a minute. This warm, nurturing guy who would never harm a fly just told me he's about ready to crush me if I don't do what I'm supposed to do." So I quickly shifted around and started spending [my time as] a scientist by day and a graduate student by night until I finished it up. And I was retelling the story recently to somebody about how it was to be working on a certain day by noontime, and I was still racing down Route 95 at noontime, and knowing that the guy went to lunch from 12 to 1 and if somehow I could magically get it on his desk before he came back from lunch, I wouldn't violate this [deadline]. And that's exactly what I did, was around a quarter to one, roll in the door, throw it on his desk, and run out before he caught me, and then defended it a couple of weeks later and went on from there.

MM: Wow. That's a good story.

RD: Yeah. Well, it's kind of analogous. Everything since then, though, I'm always kind of racing in at the last minute, throwing something on the desk, which isn't the best thing they've ever seen, but it's usually good enough to get the job done. So whatever, that's how I kind of got into pain.

MM: So tell me about this. Now, you said when you said the position offered at that time or the fellowship offered at MCV, they were talking about pain research, and you already had the interest in pain, although you hadn't been really inspired. And apparently, the sort of line in the official Dental Institute history is, everybody – all the dentists were passionately concerned about pain and anxiety, and you've written this yourself in some papers. So how did you get into pain? What was interesting to you?

RD: Well, actually, what happened was, when I was – What caught me was the fact that when I finished up dental school, I wanted to make some money, mainly so I could pay back some of my educational loans. So I got a job in a clinic over in Northeast [DC]. If you were a member of a certain union, you got to go there and get your dental work done, and you got your medical work done as well. And this kind of was nifty to me, because I had mentioned earlier that I was going to save the world. I just wasn't sure how I was going to do it. So suddenly now, I was here in a situation with this lower socioeconomic group that had access to free dental care, so I figured, "Well, geez, this is perfect. I'll fix up all

their teeth. They'll live happily ever after and I'll just feel so good about the whole thing."

So I went over there and started working, and I spent most of my time drinking coffee and reading the sports page with all the rest of the dentists in the back because the patients never came in. And yet, when they came in, they were usually just a wreck. They needed to have teeth extracted and everything, and I couldn't comprehend why we were giving away free dentistry for them, because it was all paid for by their union dues, and no one was coming in. And slowly, I thought I had discovered some important truth, that patients were so afraid of coming to the dentist that they stayed away until the pain from the neglect got to be worse, and then they would, of course, overcome their anxiety because they were in such discomfort and come in. It turns out that once I started looking at the literature, this was hardly a revelation, that many people had made that observation ahead of time, but I said, "Well, what's missing here, then, is some way of making dentistry painless enough that patients won't always be frightened to come in," because it wouldn't do any good if we had great dental materials or we had preventive techniques or we could prevent gum disease by having them come in. It was doing us no good if they never showed up until it was already too late to do anything except extract their tooth. So I said I wanted to go into doing work with techniques that allowed you to overcome the pain and anxiety associated with dentistry. And it turns out that was relatively new, because at that time there was only two alternatives. You either gave someone local anesthetic and they either tolerated it or they didn't; or you put them to sleep, and that was very dangerous. And there was not much in the middle. There was this fuzzy stuff about IV sedation, but that was something that only real pros could do, and there was nothing that a regular dentist could do. It was almost always just oral surgeons, and they only had one trick to offer, and that was to take the teeth out. So I said, "Well, that's where the work needs to be done," and all the stuff – I had enough scientific training at that point in time to recognize that the studies that I looked at in this area were poorly done, usually just case series where someone did a hundred cases and said, "This technique works in my hands and it's safe, so let's go ahead and use it." So I said on the basis of that, there's got to be more done, and that's what I wanted [to do]. So that's what I ended up doing when I went down to MCV, was I teamed up with some people and we said, "Let's study this field;" and they said, "Well, what are the methods you would use?" "I don't know." I looked in the literature, and the only methods I could find that had been studied at all were some psychomotor techniques for looking at the effects of drugs on driving, and they were pretty crude. Although one time I asserted I thought they were probably good for testing, I was quickly corrected by people who knew better and said that you could have drugs that didn't cause an impairment in these tests, but still [caused] enough impairment that someone's driving would not be any good, so I had to do better than that. And then it was, how do you assess anxiety and its relief? Well, there were some scales for pain, but not much for anxiety, so I had to adapt them, and then finally said, "Well, you've got to just show this method works before you do anything," and the way you do that, very often, is to do an increasing series of doses of drug compared to placebo, and if you can show that there's some sort of linear increase in the effect as you give more drug and it separates from placebo, then that makes sense. So that's what I ended up doing as my first study.

MM: That was your project.

RD: Yeah. And then once I had shown that I could do that, and I did all the stuff you've got to do to make it look scientific – measured blood levels and had a nauseating amount of extra measures that in the end weren't worth anything, but at least I did them. And then I did a second study where I studied two techniques, one of which was drug alone, Valium, or Valium plus a narcotic, and showed that in the eyes of the patient, you really couldn't tell the difference between the two; yet the clinicians always said the narcotic made it better. So that was the beginning of a series of studies where I was able to demonstrate that that's probably true most times, that the drugs – you sedate someone real well, you give them a local anesthetic, the procedure is enjoyable enough that an hour or two later or the next day, they just know that they were sedated and they got through it, not that they got three drugs or two drugs or one drug and whatever. So that was enough to parlay it into a PhD, that and 72 credits and comprehensive exams and four years of work and stuff like that to get the degree. And that gave me my ticket out of Richmond and up to here.

MM: OK. So you talked a little bit about how nurturing the environment was in Virginia. Were there any people in particular that you enjoyed working with?

RD: Yeah. There were two people. I mean, there were some people that were particularly good, and there were others that I remember for being particularly the opposite.

MM: Either way.

RD: Yeah. The two people that really made a difference were – actually, three if I generalize. One was my thesis advisor, a guy named Bill Dewey,⁴ and he was someone who had joined the faculty maybe three or four years before I got there and had a fairly humble beginning. I think he was someone's technician who decided to go into graduate school and he'd gotten his master's, he'd gotten his PhD, and he just worked extremely hard and had already got to the point where he was like an associate professor when I got there. And actually once, right before I left, I saw his CV being printed out on a mag card,⁵ those old things that take forever, so that's just typing away. And I'm talking to the secretary and I said, "What's that?" She said, "That's Dr. Dewey's revised CV." So we chatted. We did some stuff. The mag card just kept going and going. And finally I said, "Is that still his CV?" She said, "Yeah." So I went over and looked at it, and it was typing in reference 243. And I said, "How many more does he have?" And she said, "Oh, he's only up to 260," or something like that. I said, "He's only been in research for about 10 years. How could he possibly have that many?" Well, what it was is he approached everybody the same way. He made sure that they did well and got through the graduate program, got a job later on, everything. People used to be standing outside his room, you know, Kleenexes and tears in their eyes because it was another bashed graduate student who needed Dr. Dewey to fix their boo-boo. And, as a consequence, everybody would make sure that they put his name on their paper, and he had like 10 or

12 grad students at a time, so all he had to do was stay in his office and field emotional problems, and he was getting 20 publications a year, it looked like.

MM: Good deal.

RD: Yeah. And then he did research to boot.

MM: It really pays off.

RD: Yeah. And then he had his own postdoctoral fellows. So he had a lab of his own, plus he had all the grad students he was taking good care of. So he was the kind of guy that made sure.

He even taught me tricks, like when you were going to go have a meeting with the dissertation committee, I'd show him all I had, and then he'd say, "Well, where are we on this?" and I would try to articulate and he'd say, "No, that doesn't make sense to me. Tell me, what has this shown?" And then I'd try to explain it to him. He'd write it down in simple language what he understood. And then he finally said, "What are you going to do next?" and I would explain to him. He said, "That doesn't make any sense. Explain it to me again." And finally I'd get it through to him or he'd get it through to me what I had to say. Then finally he'd say, "Well, what are we going to get out of this meeting?" "I don't know. We're just going to have a meeting, you know." He said, "No, no, no. We have to have an objective for this meeting. We have to have an agenda, our personal agenda that we're shooting for." I'd say, "OK, an agenda, all right," and then we'd go into the meeting and he'd make sure that it happened that way, that even though the meeting might go for two hours and go all over the place, in the end they agreed or disagreed that what I concluded was true. They agreed or disagreed with my plan, and they disagreed with what had happened, where we were, how many courses might have to be taken, how many more patients, where we're going. And so not only was he very benevolent, but also very businesslike in getting the job done.

MM: Yeah, good for him.

RD: Yeah. So he was a tremendous influence. And now it turned out, less directly but of the same vein, was the department chairman, a guy named Lou Harris⁶, who was another guy who had started out from a very humble beginning as being [Henry K.] Beecher's⁷ technician back at Harvard way back when, and he eventually decided he was bright enough. I don't know, maybe he looked at the rest of the people and said, "Well, shit, if they can do it, so can I!" And so he went off and got his Ph.D., and he ended up down at the University of North Carolina and had built up a good reputation, and then got selected to be chairman at MCV; and, again, was one of these guys who was, you know, when you first talked to him, he was almost shy and quiet and didn't really dazzle you, but when the chips were down, he came alive.

I remember one time there was going to be a little television interview, and he was supposed to give a little something. Right before the interview, he was kind of quiet and

not saying much – and he was short. And then, all of a sudden, when it came time for the interview, man, suddenly he got like real tall, booming voice, you know, and he just starts, boom, talking right to the camera, talking right to the interviewer, whoever, so he had a good ability to say it right, do it, and he knew the facts, and he had made some important contributions up to that point. Now that he was department chairman, he wanted to make sure that everything; first of all, that it was a very productive department was doing good work, and also that everybody was doing well.

And the only drawback to all that was that there was the old guard who had been there before he came, and they were only too willing to snipe at him whenever they could and cause a lot of intramural warfare. And then there was a parallel group. There was like three divisions in Pharmacology – CNS, toxicology, and the other one was cardiovascular-renal – and they [each] had their own little agenda as well.

So it was a three-part department, with him being the head of one division and running the whole department. So he put a lot of effort into making sure that the amount of warfare that went on was minimal, the damage to the graduate students was minimal, and the department as a whole looked good.

I think the last time I was down there, they had moved into a new building, and I think part of the department had stayed behind in the old building, which was ancient, and part of that had moved into the new building, so I think maybe that was a way of keeping the warfare to a minimum.

And then there was Dave Mayer,⁸ who was down there at the time, and he was very new out of graduate school, and he was doing a lot of hot stuff. And although I didn't work with him that much, I was always inspired by the stuff he was reporting, the fact that he was achieving excellence in doing pain research, where up to that point in time it was the rare individual who got [it right].

And a lot of this important pain research wasn't really even considered pain research. It was pharmacology or it was physiology or it was clinical stuff or something like that, but it wasn't really pain research, and he was one of the – That whole program was one of the first times I saw everything pulled together to be called pain research. And what was nice is they, right from the beginning, adopted the model of having some basic research, some clinical research, and then having everybody interfacing. Now, it didn't work that well because, except for the pivotal people, a lot of the other players weren't as strong. When they were looking for people to populate, to fill the program with postdocs, they got the grant first and then they figured out how they were going to do it second. So it was a motley crew: someone like me, who was a dentist with a vague idea about doing pain research; there was some guy who had finished his PhD, who wasn't really sure what he wanted to do, so they snapped him up as a postdoc; and then there was some guy who had been on a faculty at a dental school for like 15 years and wanted to do a sabbatical, so they brought him in because they thought he knew a little bit about pain research.

Then there was a fourth strange guy who had been in engineering and then had gone into something that was like a PhD in biomedical engineering, and then he showed up as a

postdoc, and he worked with Dave Mayer. His name was George Wilcox.⁹ And George later went on to actually do extremely well as a researcher. But at the time, no one could figure out what to make of this guy who was an engineer, who claimed he was a physiologist one day, claimed he was a pharmacologist another day. In fact, he had about four CVs, and depending on which job he was applying for, he would trot out one of the CVs.

MM: Yeah, good for him.

RD: He would change them around. He was always going to people, "What do you think I should do here? How would I shape it to make it look like I'm a pharmacologist today?" And he eventually got a job at the University of Minnesota, in the Pharmacology Department, and I said, "That's great, George. That's fantastic. I mean, that's a real good pharmacology department." He says, "Yeah, Ray, but there's one problem." I said, "What's that?" He says, "I've never taken a pharmacology course in my life." I said, "Oh, that's right. I forgot." I said, "What are you going to do?" He said, "I'm going to buy a copy of Goodman and Gilman and stay one chapter ahead of the class." And that's what he did. The first year, they realized he was a bit of a liability, so I think they made him just a tutor in the medical class, and he just would basically go to the lectures, read the chapter, and, being bright enough, he would know instantly more than the medical students knew, so when they came and asked him questions, he would try to explain it as best he knew. By the second year, he was giving lectures, and by the fifth year, I think he was in charge of the program, teaching at the university.

MM: Oh. On-the-job training.

RD: Yeah, running the whole show. And then he did a lot of good research So that was our group. So as a consequence, it was a motley crew. No one person was doing the same thing, and that would be ideal if we were all big experts and we contributed equally, but it was a heterogeneous group. So, I mean, in the end, everybody got something out of it, went their different ways afterwards. George went on to be a good basic researcher; I went on to do clinical research; the Ph.D. postdoc I think ended up going into education somewhere within the Virginia school system; and the guy on sabbatical decided he was going to change careers and go into something else, and I ran into him years later, and he had done this like maybe three times in his life, I discovered. So he just had a short attention span. You know, whatever was appealing to him at the time, that became his new thing and he would acquire transient expertise in it, do a few things in it, become seemingly a master of it, and then start looking for some new challenge. So he was at one point an oral surgery resident, he was going to be a prosthodontist, then he was going to be a periodontist, then he was going to be a perio-prosthodontist specialist, but that led him into occlusion, and occlusion led him into pain, and then after he'd been with us for a while, he decided to go into orthodontics, because that's another way of treating occlusion.¹⁰ The last time I heard, he was on the faculty of Ohio State, and he was like appointed to four departments, but he was already looking over there because he thought maybe the grass looked a little greener over there. He was going to learn something else. So who knows what he is [now]. And he was ran a

trucking firm on the side. He came from a blue-collar background and he had bought trucks, and he had like a small fleet of semis running around the country. Every once in a while, he'd have to leave because a business problem came up and he'd have to go, because they were on strike and he had to do a delivery, or a truck broke down and he'd take off to go [fix] it. So an interesting character.

MM: Certainly not your stereotypical scientist.

RD: No, not at all.

MM: That's great.

RD: So that's what happened.

MM: That was MCV.

RD: Yeah.

MM: OK. So tell me a little bit more about this. You came here [to NIDR], and there are a couple of things I'm sort of interested in where they came from. One of them is the third-molar-extraction model¹¹ and where that came from, who developed it, whether you came and found them using it here. Because when Ed Driscoll¹² started working, he was using full-mouth extractions. He was taking out everybody's teeth.

RD: Yeah. Well, that, of course, was in the 1950s, and that's what was going on then. You were more likely to be doing full-mouth than you were worrying about the third molars, and if the third molars were there, you took care of them along the way.

MM: Right.

RD: But it turns out that when I was at Georgetown, one of the things I did see was [that] Steve Cooper and Bill Beaver were – Steve was a fresh-out-of-dental-school person who wanted to get fame and fortune as well as a PhD, and after he had gone to a number of programs and looked around, it looked like Beaver was the best bet. Then, when he went to Beaver and said he wanted to do pain research, the question arose, “Well, how would we do it?” because all the stuff we normally do is people who have had their gallbladder out or people who have cancer pain. Those were the two models pretty much, general surgery or cancer. So Beaver said, “Well, what's going on in dentistry that would be a good model for pain?” and Steve, without too much thought, said, “Well, extractions are the worst thing.” And they eventually evolved to the point where, for Steve's dissertation project, he would try to validate the use of third-molar removal as a pain model. He had to study a couple of doses of an active drug, compare it to placebo, show that it worked, and then he did a couple of – that was aspirin, I think. Then he did a couple of doses of acetaminophen compared to placebo and showed that worked. And then he looked at the combination of aspirin plus codeine and showed additive effects. So that was enough to say that he had demonstrated that this was an important analgesic [model], a new way of

assessing pain. But at the time, everybody dismissed it because they said, “Well, it’s still just dental pain, it’s not the big thing. It’s not the big pain.”

MM: Really?

RD: Yeah. But we were fortunate that the first year he got out, he was able to stay at Georgetown as an instructor. He wasn’t even an assistant professor, just an instructor, I believe, in the dental school. So he set up a little unit to study various new analgesics using a pain model. Right about that time, there was this new drug called ibuprofen that was available in Europe, coming to the US, and they were trying to get it approved primarily for rheumatoid arthritis, but they recognized that there was a big market for pain medicines in the US, and they thought they would try it for some types of things. Well, they figured it wasn’t good enough, wouldn’t be up in the big leagues with morphine, so it probably wouldn’t be worth trying for cancer pain, wouldn’t be worth trying for post-surgery pain.

So someone suggested, well, there’s this new kid on the block down at Georgetown who works with the old pro Beaver. Maybe you might want to test it for this type of pain, dental pain, and that would be an indication that you might be able to get it approved. So they got together, and Steve told him how much it would cost to run a study like that, and they hemmed and hawed and finally agreed to do the study and went ahead and tested the drug compared to aspirin, and it turned out to be much better than aspirin both in terms of peak effect, duration of action, and side-effect liability. So that was like the first demonstration of an NSAID having an effect on acute pain that I was aware of. So that got a lot of attention.

So, at about that same time, I was down at MCV now, and I talked to Steve and I said, “Well, it would be nice to do some of these oral-surgery studies down at MCV, and Steve, being a little bit of a businessman, was doing the math and realizing that if he had two sites going, that means he’d probably have twice as much money coming through his hands, and that means there’d be a little residue left over. I mean, I’m probably putting the words [into his mouth], but he got a big reputation of being a businessman. So he said, “Well, yeah, that makes sense to me, and then eventually he had like probably a dozen sites or half a dozen sites at one point. So the first thing we looked at was this question that, well, ibuprofen looked good. By maybe two hours, it looked a little better than aspirin; by three and four hours, it looked much better. It had a slow onset, and we didn’t know what that meant, but we quickly reasoned that if we just gave the drug earlier, it would be working when you needed it. And the only drawback was, no one had ever done a study that way. Everybody had always waited for pain onset, and we were going to try to prevent pain. So we conjured up the study that we would give the drug ahead of surgery because we thought that not only would it get the drug absorbed and be working when you needed it; we knew from the little physiology that was available at the time that when neurons got sensitized due to (people were saying) prostaglandin E-2,¹³ then that would cause more pain for longer periods of time afterwards. So we said, “We can block that phenomenon from happening by giving it before surgery, before the

prostaglandin could get made, before the nerve endings could be sensitized, blah-blah-blah.” At the very least, we’d have good drug levels by the post-surgical period. So we did that study, and it was a terrible failure, and we didn’t see any difference between the groups, couldn’t figure out what the hell was going on, because we gave it ahead of time, and then when they developed post-op pain, we gave them their second dose. And the only real measure we had was what happened for the second dose, and all the treatments looked alike. And we said, “This doesn’t make any sense.” I had lots of time to think about it, though, because I was driving back and forth to Richmond, to DC, because I maintained my residence in DC because that’s where my wife was.

So one Friday night, I’m literally driving home in my old Volkswagen, and I said, “I’ve got it! We’re doing it wrong. We should be measuring how long it takes before that second dose is required. That’s the measure of whether the first dose works.” And we didn’t have any hourly data. It would have been nice if we’d been getting the data every 15 minutes or every hour. Then we could have just looked to see, was there a difference between pre-treatment and no pre-treatment, and the answer would have been yes. But the only thing we had was how long it took before they requested it, and that was just a piece of information we just coincidentally [collected]. We wrote down when the surgery ended; we wrote down when they got the drug, so it was like, “Ooh, ooh. I want to turn around and go back.” But it was Friday, and I said, “What the hell, I can probably wait till Monday.”

So I went back on Monday, and by like noontime on Monday, I had all the data analyzed, and it was clear that there was a huge difference. Pre-treatment postponed when [the request for the second dose] was, and then the pain they reported at that point was less, but it was still enough to cause them to want to take the pill. So I said, “That’s great.” I printed it up, I showed everybody. I went around, and not one person would believe me. Everybody said, “Well, that’s just retrospective data drudge.” I said, “That’s true, but look at this. This is unbelievable!”

And I can still remember the guy who was the big oral surgeon guru within the dental school, head of the Perio[dontal] Department, and they were doing [epidemiological] research, so that, by definition, made him the big research expert, and he later on went on to be dean and then dean of another school and stuff like that. And he looked at me and said, “Ray, no one’s going to believe you. The methods, you made them up,” you know, and everything. He said, “You’re going to have to do another study to convince anybody.” I said, “Another study? God!” At the time I didn’t realize [that] clinical research went slow.

So we went ahead and started another study, and by this point in time I was getting close to the time I was going to leave MCV. So I started the study but never was there to actually see it finished. But I had everybody else collecting the data for me, everybody had been trained. And, sure as heck, on that one, it was clear-cut that you gave the drug ahead of time, and if you recorded the hourly or the half-hourly [pain level], whatever we did it, you could see a huge difference between the groups. Then you gave the second dose, and sure, if you gave a second dose and everybody was having varying amounts of pain, but it worked, everybody kind of went back to looking like normal. So we had to redesign the study to show the differences on the second dose as well. But that was a

paper that eventually got published in the *Journal of Clinical Pharmacology*,¹⁴ and I always point back as one of those papers that was important. I'm glad I did it and everything.

That got me going, so by the time I came here, then the people around here said, "Well, we believe you, but there's a lot of other questions you haven't answered." So that basically was the first two or three years of my research, was doing all these small studies to answer a lot of the questions, and eventually I was able to show that it was... They said, "Well, suppose you gave any drug ahead of time? How do you know it's anti-inflammatory? How do you know it has an effect on sensitization? What is this? You don't even know what sensitization is. That's a physiologic term. You're not measuring nerve endings. You're not doing nerve recordings." I said, "Well, you don't do those on humans, I don't think." So I eventually squelched all their skepticism by doing a series of studies that eventually showed it [ibuprofen] was better than just any old drug ahead of time. And the only question I never answered was, well, what happened if you gave it post-operatively, before the pain occurred? How do you know that it wouldn't be just as good?" And I said, "Well, you don't have to because we've already in a sense done that." On some of the studies where we waited for pain onset to occur, then we gave them another dose of Motrin, sure, they got pain relief, but they had that two- to three-hour period when they had more pain, and then it took a while for the drug to work because the Motrin is slow, so we know that's not true.

Well, one of the guys who was with me at the time [and] did some of the studies, was an oral surgeon, and he left and he went down to Medical College of Georgia, and the first study he did was giving it immediately before surgery versus immediately after surgery, and they looked the same. So I dismissed it on the grounds that he hadn't shown that he could separate – But he didn't have any placebos. He just had either pre-treatment or post-treatment, and it was the same. I said, "Well, this guy is a good surgeon and he's been trained with me, but he still hasn't done the right study." And I always had a good technical excuse why that wasn't true. Well, it turned out, it was true. The pre-treatment stuff wasn't so important, it turns out, until just the last couple of years. We finally figured out what was going on there, and it had to do with the fact that, while all that stuff happens during surgery is true and you block it, it's what happens two hours later on when cyclooxygenase-2 gets formed, and then you get all the prostaglandins being formed. That seems to be the key event that results in all the pain.

MM: Yeah. And also, the surgical pain. But isn't it – I mean, it seems to me that most of the literature says that pre-operative treatment reduces anxiety ahead of time and does not – Isn't that basically – doesn't that contribute to post-operative pain? I mean – I'm probably hypothesizing.

RD: Well, no. The anxiety associated with the procedure presumably would heighten your pain, and when patients are anxious, they're going to be more reactive, and when they're having pain, they're going to be more anxious. But in this case, we always had a control for that, but, in fact, everybody got sedative drug ahead of time. They were getting something like Valium. So everybody was having an equal procedure. But we did a

series of studies looking at that whole question, and it turns out, if you got a placebo and had a miserable experience, but then after surgery, things didn't bother you because you were numb and you weren't having any pain, or you were practically flaccid because you'd gotten near-general anesthesia, but then later on you come out of it and you're still numb, the anxiety levels look the same post-operatively.

MM: Really?

RD: You could see the big difference. You know, everybody starts here. Pre-operatively, they're like that. And then if you don't have anything, you shoot way up, the other group stays flat or maybe drops down a little bit, but then post-operatively, it's all the same again. But then later on, once the anesthesia wears off, as the pain goes up, so does the anxiety level. The catecholamines get released, beta-endorphin gets released, the body is saying, "Jesus, I've got to do something about this," and whatever. But in this particular case, because we controlled the anxiety, then we controlled the post-operative pain initially, and it was only when the local anesthetic wore off, which was then two hours post-surgery to four or five hours, you saw the big difference between the groups, and that would seem to be due to the fact that there was a difference in the alleged effects of the pre-treatment, but in reality it was just the fact that if you got the drug on board before and suppressed some of the formation of the cyclo-oxygenase-2,¹⁵ that left less prostaglandin.

MM: Prostaglandin makes the difference.

RD: And that was the big thing. So it wouldn't have been a career. It got me my job here, got me in the front door, and it got me a permanent position. But where I blew it is I never really recognized that all this pain input in the post-operative period was contributing to the so-called central sensitization that results in greater pain at later time points. But that's okay because no one else had even – That phenomenon, nobody knew about it. It wasn't until the '80s that people even started, the late '80s, that people started talking about that. So I never recognized that there was something important going on at that point that was probably contributing to later time points as well. But there was still some [importance] to it, and to this day, depending on – I knew I was onto something because there was a phenomenon of some kind.

I thought I had, again, discovered [something important], but someone pointed out to me that there's three phases in coming up with something new. The first phase is, it's wrong. No one believes you. The second phase is, well, it's true, but it's not important. And the third phase is, we always knew that was true. And sure as hell, after I had published about four or five papers on this, then people started coming out the woodwork and saying, "Well, I've always told people to take aspirin before oral surgery!"

[One scientist] was interviewed by *The Washington Post*, and he proceeded to tell them how he had discovered this whole phenomenon of pre-treatment with Motrin, and he had discovered it just a year before. Fortunately, that was about 1988, so I was able to point out, when someone asked me about it, that my first paper on the thing was published in

1978, so he was rediscovering an old truth, if nothing else. So, in any case, that was the pre-treatment story, and it turns out it would have been –

MM: Interesting. It took quite a long time for the real story to come out.

RD: Yeah. I mean, we started doing those first studies probably in '76 or something like that. We got the first publication out in '78. And to this day, when people have gone back and looked at that, they've said, "Well, it wasn't the most convincing piece of work." I've said, "Well, no, it wasn't the most convincing, but it was a significant finding." here was a clear difference between pre-treatment, [where people] went four hours [without complaining of pain], people who didn't get pre-treated went two hours, and that coincided with when the anesthesia wore off, and that was as clear as you could do when you had a study that went back and kind of retrospectively discovered. Unfortunately, the second series of studies took so long to get done. A lot of those publications didn't come out till like the early '80s, so then it was a lot of distance between the two. But if you were to do an archeological dig, I could make the case for having published a paper in '78 that showed that analgesic pre-treatment made sense.

MM: OK. So tell me a little bit now about when you first came to NIH, what the Institute was like then. And Driscoll had been doing this for – he was still around?

RD: Yeah. He was actually the person who hired me. It was November of '78 that I came here, the day after the Marine Corps Marathon, because I could barely walk as a consequence of having run the marathon the day before. Ron Dubner¹⁶ was the [Neurobiology and Anesthesiology] Branch chief, and Driscoll at that point was section chief. Even though at one point he had been running the show, they had at some point in time decided it was going to be more of a basic [science]-oriented group, and Ron had gone from being a junior person to finally being appointed Branch chief, and had at that point built it up pretty nicely. It wasn't as big as it became later on, but he had probably 15 or 20 people that were here. Driscoll was still doing things that weren't that far removed from what he had been doing probably in his early career, which is, of course, probably a frightening analogy that I should consider, because he had started doing outpatient studies in the '60s, and now it was the late '70s, and the studies were pretty similar. There was a lot of talk. We had a lot of friction because he always wanted to do things that would be useful for the guys out there in practice. And I said, "Well, that doesn't remove you from the obligation to do them scientifically correct," and like a smart-ass, I would then proceed to tell him how to do it scientifically correct. And he was a gentleman enough that he would listen to me, and then if it looked like we were going to really get into a big disagreement about it, he would figure out a way to divert me or temper the meeting or something like that. So I picked up the mantle from what my predecessor had been doing, a guy named Steve Gelfman, who had left to go to oral surgery training, and was trying to finish the studies they were doing as well as get my own study started as well as finish doing the dissertation on the side, and it got to be a little schizophrenic because I was doing the sedation studies, I was getting the analgesic study started, I was in a laboratory learning how to measure beta-endorphin, working with Candace Pert,¹⁷ which was something that

Ron wanted me to do, and then I was trying to write up my dissertation and do other things like that. So I was putting in long hours. In fact, it got to be a crisis where one night I came staggering home for the twentieth night around midnight, and my wife blew her stack and said, "I thought this was only going to be while you were in graduate school. You keep doing this. It's been a year now since you finished up," so then it was, "It's only going to be till I get the dissertation defended," and then right after that it was, I was... Yeah, that's the old [dissertation].

MM: Sorry. I interrupted you. Go ahead.

RD: So finally we agreed that I would start working more reasonable hours after I did that. But it worked out OK in that I helped Driscoll finish up two or three studies. He tried to get me to write up some of the studies that had been kicking around for a while, where he was guilty, as we all are, of running patients, collecting a lot of data, kind of getting it analyzed, but never quite getting it written up.

And there was also a tradition at the time – this was before data analysis got really sophisticated – of there being a computer section, but they kind of just provided you with the infrastructure, and you still had to go over there and learn how to enter it and how to analyze it. Driscoll was coming from the pre-computer era, so he didn't have the foggiest idea what to do. Steve Gelfman was a guy who had just done some clinical training and was trying to decide whether he wanted to be a researcher or do something else, and he was having trouble doing it.

So by the time I got there, they had a lot of stuff that had never quite been published, and they wanted me to analyze it. And one of them was a study that 500 patients in it, and they had collected EKGs the old-fashioned way, on paper, for about a half-hour on every one of these patients, and it filled the room. There was a laboratory, double-module laboratory space, and all the cabinets were filled with these damn things, and they wanted me to analyze the stuff after the fact, and I pulled some of them down and I looked at it and realized this was going to be like monumental to take all the stuff and measure it in all these little minute increments, and then enter it into the data and then get the heart rate entered, then do the respiration rate. Then I think they might have had CO₂ or something like that.

MM: Oh, my lord.

RD: And do all this stuff, and then make a story out of it. It was going to be impossible. Hundreds of patients per group. So I convinced them that it would be better to do a kind of pilot study, I called it, where we would randomly select from this mountain of data 20 or 25 in each of the drug groups, analyze that, and then if we saw something interesting, we could always go back and do the rest. So I was trying to do that as my way of escaping from this project. Driscoll thought that was a great idea, so that's what I ended up doing.

And it turned out to have some significant findings, which eventually led me to continue one of the studies they were doing, because we could also measure cardiac output non-invasively. What happened was in the first study, you could see hints that there was some cardiovascular depression from some of these techniques that they were using. So here we had a way of actually measuring cardiac output and stroke volume and stuff non-invasively. So we did a second, continued a study they were doing and demonstrated that some of the sedative regimen did have some depression that was of significance, so that became a second line of research we pursued. And fortunately, after I finished the mega pilot study, I convinced them that we had probably learned as much as we could from this.

So then he pulls out another pile of data that was even older that was like about a thousand patients' worth of data, and he wanted me to do something with that. Right about that time he retired, and I was able to convince the next [Section Head], Dubner, who had no interest in this type of research, that maybe we should forget about this. So we waited a while and eventually Driscoll – I can't remember how we worked it, but he agreed it was okay to throw away the old archives. The amusing thing –

MM: He did?

RD: Well, it was a killer. That was his life's work getting thrown away. I mean, he had stuff. He had done some surveys in the early '70s on anesthesia morbidity and mortality, and he still had the raw data from that. This must have all happened while he was still around, but he let me get rid of a lot of the old stuff. And I would do it, like I would get his permission and I would do a little bit each day. Then, when I finally got to the point where I had done all that and he hadn't noticed it happening, then I would ask him about some new pile I had found. And he'd hem and he'd haw, and finally after a few days, he'd come back and say, "Well, I guess it's OK to throw it away." So then I'd slowly throw that away. So I did this, and finally I got to the point where I had cleaned out all the shelves that were just a monument. We could have published *The Washington Post* for a week with all the paper that had been recycled. Then I'm working my way across the top shelf, and that's when I came across the old surveys and stuff like that.

Finally I got to the back of the room, and there were three jars in the back of the room, and they were filled with teeth. On top, they said "1949, 1950, and 1951," and I said, "Ed, what the hell are these?" And I actually unscrewed the top and almost passed out and fell off the ladder because they were so foul-smelling. He looked at them and said, "I don't know. They were in the lab when I moved in. The guy who had it before me had left it behind, so I just put them up there in case he ever wanted them." So he had saved several hundred putrefied teeth that had been, who knows what purpose. So I said, "Do you think it's OK to throw those away?" And then the question was, where would you possibly throw something like that away, because this was before people were really concerned.

MM: Biohazards!

RD: Yeah, before people called biohazards, biohazards. So we did eventually throw it away, and finally, that was the end of the Eddie Driscoll archives. Then the last thing I did with them was –

MM: Oh, how distressing to an archivist!

RD: Yeah. So then we did a couple of papers using the non-invasive measurement technique and were able to make a case about the fact that some of the sedative techniques were actually causing a fair amount of depression, significant respiratory depression, and published it, and I thought that was the end of the problem. Once you identified that these things were toxic, people would stop using them. Nothing happened. I couldn't believe it.

I remember I started asking people, and they would say, "In my hands, it works, and I've never had a problem." And I said, "Well, how would you know if you never monitored?" This was before anybody monitored. And they said, "Well, you know, the patients get up and they leave at the end." And I said, "Well, you know, what would happen if, say, one in 10,000 patients did not get up and leave at the end? Wouldn't you think that was important?" He says, "Yeah." I said, "Well, how many do you think you've done in your life?" He said, "Two thousand or three thousand." I said, "Well, then, you don't know if this is safe. You don't know if tomorrow you're going to kill someone with this technique." And I said, "Where do you think these reports come in the literature, [about] people dying in the dental office due to respiratory depression?"

Well, I was really the lone – In fact, I always used to talk about, in classic pharmacology terms, that we're going to evaluate the efficacy and the toxicity of this drug and determine what the benefit-to-risk ratio is. I came to the conclusion that some of these sedative techniques had an unfavorable benefit-to-risk ratio. Man, talk about how people get pissed off at you! I'd go to these meetings and I'd present this stuff, and they'd take turns getting up to criticize me.

MM: Because they'd been using the stuff all along.

RD: Yeah. So eventually I realized that I had to talk about the efficacy and safety of the techniques. At least if I was talking about two positive parameters, that made people a little more comfortable. And then if I reached a conclusion that was negative, I could still talk in terms of the better technique and being safer, and equally efficacious but safer, rather than talk about the one they were using is toxic.

But it was still a voice crying in the darkness, until finally in the mid-'80s the public caught on, and they had a Consensus Conference here which was aimed at the efficacy and safety of sedatives. And I was far enough along that I helped plan the conference. I was a speaker at it, and then I was shrewd enough to say that this is important, we've got to get this out. So I was able to get someone to pay for us to publish it as a monograph with Elsevier, which was a pretty big name in medical publishing at the time. I got to be one of the co-authors of it along with Danny Laskin.¹⁸ And still, it had minimal impact. In fact, the Consensus Panel reached a conclusion that all the treatments that were used in

a hospital for anesthesia or sedation were equally as appropriate for a dentist to use in his office. And then they said that dental anesthesia has a remarkable record of safety, but later on in the report they said, “However, there’s no data to support that.” So at the conference, when they were revealing all this, there was a lot of skepticism by the reporters who were there to be the public’s, you know, the recipient of this good news. And so, as a consequence, it didn’t have the impact they thought, which would be to say “Everything’s OK, don’t worry about it.” And eventually this resulted in more deaths. Finally what happened was a guy whose daughter died in the oral surgeon’s office out in California got did a video. The video led to changes in the Dental Practice Acts,¹⁹ and that eventually resulted in some change in that area. So now, if anything, it’s worse, because we didn’t do anything as a profession, and now legislators are telling dentists what is safe and what’s effective, even to the point of saying, in the state of Ohio, you can’t use anything that has like barbiturates, because that is a general anesthetic by definition, and if it’s a general anesthetic by definition, you can’t use it for –

MM: Dentists can’t use this.

RD: Can’t use it. So it’s come around full circle, but the worst part about is, it’s the politicians who are making the judgments, not the profession.

MM: Reactive regulation.

RD: Well, they can only react. If someone says this is a general anesthetic, “Oh, dentists are using general anesthetic? That’s illegal! We passed that law last year.” So now we’ve got to pass a law that says that barbiturates are really doing stuff like that. They’ve even gotten to the point where now they have laws in some – Well, in all the states, there are some regulations about nitrous oxide, but in some states, they even act like this is a dangerous drug. It’s only dangerous in the sense that if you have a mechanical problem with the plumbing that causes things to be reversed, you could do some harm that way. So that was another one of those little revelations that the field doesn’t follow the science necessarily, and that it really takes something of the nature of a regulatory change to have any impact on clinical practice, or else you’ve just got to wait for all the old people to die off and the new ones to be better educated. But, unfortunately, the guys who are doing the educating are usually of the old school of thought, or the ones who have at least risen to prominence by embracing the old way of looking at things. So it’s a very slow, tedious, frustrating process.

MM: Yeah, it is. It’s extremely frustrating. So do you have that sense that not much has changed in dental anesthesia/analgesia unless practitioners are forced to change by legislation?

RD: Well, I can only look at two areas, and one is the anesthesia stuff, where things have improved drastically because legislation forced it. The area where things haven’t improved is the treatment of chronic facial pain, where the way it used to be done was you tried this, you tried that; if it didn’t work, then sooner or later you ended up in a surgeon’s office, and he would do the surgery, and things always got worse from that.

Then after a while, you were always being treated for the consequences of the surgery. And the effect of all that was that people ended up very debilitated.

One group of patients we're studying right now ended up having these implants put into their joints that turned out to be totally stupid. The material broke down and caused all kinds of problems, and the conclusion of the surgeons was not that the surgical procedure didn't work because of this, it was just that they didn't pick the right material and they just had to find the right way of mechanically fixing this joint and everything would be OK. They've gone on to total joint implants, and the only thing that saved them then was the FDA said, "Stop. You can't use any of these things until we figure out what's going on." So now they've said it's OK to use two of them [the implants], one of which is an old one that was around, grandfathered in, and another one is a new one that's gone through some degree of proof.

But the tradition of ignorance leading the field still continues, because the FDA recently had a hearing to look at these devices that are used to make diagnosis on patients, and they're based on totally fallacious assumptions. The science is actually probably 180 degrees in reverse. There's never been any good evidence that these things do anything; yet they'll do these magical measurements on patients and say, "We have to change your bite by a millimeter," or "We have to relocate your teeth back or forward," or whatever. And on the basis of this, they then go and do all these irreversible treatments, which always have a little bit of iatrogenic [damage] possibility associated with them because you're doing so much. But then they kind of lock patients in to having this idea that it's a mechanical problem that's causing their pain, and this treatment they did didn't quite work, because after a while they still had the same problem. So then they go seeking more mechanical treatments, and that leads to surgery and whatever. So it's going to be one that someone or something tragic is going to have to happen, even of bigger magnitude, to point out to people that this ain't the way to do it before it'll change. Or else there'll be a new generation coming along and, by some divine process, [they] will see things the way they appear to be emerging scientifically and they'll go about it in a different fashion. Unfortunately, it's not something like tooth decay or tuberculosis that's liable to go away because of a miracle cure. It's always going to be something that's going to require little increments of improvement, little attempts at conservative treatment. It could be something like psychiatric treatments which, sure, once every generation, some big treatment comes along that makes it seem like people get better, but, by and large, it's still talk therapy and a lot of ignorance out there.

MM: Yeah. That's really scary. I had the impression that things might have not actually – that this information might not really leak down to the general community as a whole, but that it would still, that there was improvement.

RD: It depends where people go to school, because there are places – If you go to the University of Washington or maybe out in San Francisco, UCLA, the word has gotten out there, and actually, I guess, maybe Friction at Minnesota.²⁰ But even then, I mean, you can – A lot of the implants got put in right in the Minnesota area, and that's why they're doing a study now of these implant patients, because there were oral surgeons running in

parallel with the guys who were being conservative, doing the cases and causing all the problems.

MM: Probably, a lot of my impression does come from UCLA.

RD: So you've been in an enlightened environment for quite a while, so you thought everybody was like that.

MM: No. But it did seem that there was wider attention to the problem. But what do I know? OK. So now you're at NIH and you're working – Well, tell me a little bit about what you do to assay beta-endorphins, then. You worked for a while with Candace Pert.

RD: Yeah, I did that for probably a lot of time, for about two years, working with her and her husband, Agu. At the time, the methods for measuring beta-endorphin were pretty crude. We ended up doing – there were actually like radio receptor assays where the original thing that Pert and Snyder had developed was to isolate the receptor, and then you looked for the amount of occupancy of this receptor using radioactivity. So you didn't know what exactly the receptor was; you just knew the magic formula that allowed you to get a bunch of receptor in the thing, and then you allocated it out. So, presumably, if all the wells that you were measuring had approximately the same amount of receptor, and then you had these unknowns that you were plugging in there, and then in the end you put some radioactivity that was a known thing that should act with those receptors, if the receptor was still with this unknown, then having a standard curve and everything, you would infer there was a lot, some quantity of the unknown endogenous thing. And if you had a lot of binding, then that would tell you that there was nothing in there and there was lots of room for the exogenous radio-labeled stuff to light up.

MM: Sure.

RD: So then when you counted all the samples, created a standard curve, you could talk about occupancy of endogenous ligand. You don't know where it's coming from, but if the source of your stuff was cerebrospinal fluid and you had reason to believe that that was only beta-endorphin, then you would say it must be the amount of beta-endorphin or whatever.

But it turned out it was a very screwy assay to reproduce. It was very sensitive to technique, and I could take the same set of samples and spend 18 hours one day doing this elaborate preparation and getting all the stuff and setting up the assay and then letting it incubate, and then finally, around midnight, filtering them through the big filter and then putting them into the counters and come back the next day and look at the results and say, "Yes, the assay worked. I have a nice linear thing. But, damn, those samples don't look the same as they did last week when I tested the same samples." So it was really hard to make a story out of it.

So after a lot of time, [we] got a couple of studies out, papers out; I did a study with Agu, primarily, on electro-acupuncture where we demonstrate a certain amount of decrease of

endogenous opiates in one part of the brain associated with the stimulation, and I believe there was an increase in the cerebrospinal fluid, although that was a little more subtle. So we said yes, acupuncture must be releasing beta-endorphins. But it was called electro-acupuncture, and it looked a tad nonspecific to me. You were just using high frequency to stimulate these animals, and it had to be stressful. So the fact that it did look a little different from the control group didn't surprise me, but I didn't think it was so specific for acupuncture as it was for some kind of stress analgesic.

MM: Endorphin response to stress.

RD: Yeah. So, we were getting frustrated. Someone appeared from across the street, [from] USUHS, the Uniformed Services University of the Health Sciences, and he had developed a radio immunoassay that looked real good for measuring beta-endorphin, and he wanted to collaborate with someone over here that was doing pain research, so we jumped on it, and I started working with him. He was a guy named Greg Mueller.²¹ We were able to quickly get to the point where we could much more reliably measure the stuff, and then you had a little bit more of an inference that you thought it was –

MM: Sort of like to get an antigenic response?

RD: Well, let me see if I can think about how you would say it worked. So if you had a radio immunoassay, you had an antibody for what you were trying to measure. So in this case, you knew you were trying to measure beta-endorphin. So you took some authentic beta-endorphin or whatever you thought was authentic beta-endorphin at the time, injected it into rabbits, and eventually the rabbits would develop an antibody for what you were giving it. And through some fashion of testing to make sure it was what you wanted and then diluting it out, you'd eventually end up with a concentration of antibody that was optimal for these assays. So you would then put your standards in there, so you'd say, "All right, I've got beta-endorphin a little bit, a medium amount, a high amount," and then you'd react it with the antibody, and then that would allow you to then make some inference as to how much of the actual endorphin was there.

Then you took your unknowns, handled them the same way, but then once you drew a standard curve and said it matches up here, and according to my approximation, that should be 20 picograms per mil of beta-endorphin. So that worked a lot smoother than the stuff had worked with the radio-receptor assay. So we quickly did a series of studies to show that it didn't look like it was the beta-endorphin that was getting released when you stimulated humans – this was actually humans – in the vicinity of the periaqueductal gray [PAG].²² It turned out that it looked like something completely different. It turned out that it was actually the dye that was being injected into the patients to allow you to do the procedure, because on one group of patients, when we put the electrode in, we just, for the sake of conservatism, took a sample before we turned the stimulator on. And then we collected samples over time, and when we analyzed them or whatever, it looked like the highest level was before the stimulator had been turned on, and then just kept dropping off. And then we had this group of patients that had a catheter in place, for reasons I can't remember how it was justified. But we were able to then go back the next

day, get a baseline, and then have them turn on the stimulator, and it was just flat line, nothing happened.

So you could argue a lot of things because it's a negative study, but the fact that we were able to see this increase that was seemingly only associated with the dye made us very suspicious. Put the dye into the assay. It looked just like beta-endorphin because it had lots of iodine in there, the antibody. The tracer, when we were doing the assays, required high iodine 125, so that was interacting with not only the antibody reaction and was apparently actually interfering with the whole process of, when you have radioactivity interacting with the medium it's in, it lets off light, and you're actually measuring light. Well, this was interfering with that process, and there was some third phenomenon whereby it was mimicking the effects of the authentic beta-endorphin. So we published on the basis of that and said, however, it might be – we thought it might be that stress might be part of the story. But we really were suspicious then, and so we ended up publishing it on the basis of that, saying it was really the dye. That was the thing.²³ So we followed up on it, and we were halfway through a second study where we had a cleaner group of patients who had the implants, had been in for a while, still had the catheters in, and the surgeon we were working with out of UCLA, Ron; he might actually be listed as a minor author on that one; I can't remember.

MM: Yeah. Was that Ron Young?

RD: Ron Young, yeah. He was the surgeon at the time. He had a group of patients who we brought back in, and he actually would take a baseline sample, and then turn the stimulator on, and then collect serial samples and then ship them to me. We were doing that study and I can't remember what the results were, because what happened was, right about that time, it was a [Neurobiology and Anesthesiology] Branch review, and I presented our findings to date and then described the study we were doing, and the question arose, was that ethical? And I said, "Well, we never really thought about it, to tell you the truth. We're just getting the samples and we're just testing them." And they said, "Well, has this study been approved by your IRB?" and we said, "Well, no. It's being done at UCLA." And they said, "Well, shouldn't it be approved by your IRB?" Well, no one at the time knew. No one had – this was like before any of the regulations had been passed saying that anybody who participates in a clinical study, still has to have it approved by their IRB, the whole study. So it finally went on and on and on, to the point where at the end, the guy who was asking all the questions said that my answers were no better than that of a Nazi war criminal during the Nuremberg hearings. And I said, "Whoa!"

So I saw my career flashing before my eyes, because that was about '84 or something like that, and I hadn't quite made it up to the point of having a permanent appointment. I was just a candidate who was looking good up till that minute. And the consequence was we couldn't defend it on ethical grounds. Clearly there was a possible risk of reinfection, and you were talking about messing around right up there, even though the cannula was let down to the point where the action was. So, and there were also some questions about how would you ever get backflow if you were measuring from where we were

measuring, and we sure weren't going to start tapping in here just to measure beta-endorphin. So we stopped the study, so we never got to follow up to see whether, under ideal circumstances, in patients who weren't having any surgical stress, weren't having any dye injected, could you see any release?

We got into a little spat with one of the authors who had published the original paper, saying that it was all beta-endorphin release, where we pointed out that, the way their paper was written, it appeared that their measurements were baseline, following stimulation, and then later, and they had no control sample after the thing was given. And they said, "Oh, no, you didn't understand it," or "That's not what we meant when we wrote it that way. We did it another way," or whatever. But the whole thing died off after a while because it didn't work. So it got to be an academic point. If it didn't work and it was a risky procedure and there was always the problem that if you're sticking an electrode down in through someone's brain, even under ideal circumstances, you're going to nick a blood vessel on them. In fact, I think for every one of the case series, we quietly let it be known that they had had a serious complication and that, given the fact that it wasn't working, that was enough reason to stop there.

MM: Better to stop it.

RD: So the positive reports continued for about four or five years. But it was basically one surgeon who, if you looked at his table, even though he kept changing the titles of the articles, reporting all this great new success, the ones that showed beta-endorphin were always the same patients. They were the same numbers, the same initials, and he was still doing it for at least five years later on, claiming that he had the answer or whatever. And the other guy who was doing it down in Louisiana, I think it was, he eventually stopped bragging about it and stopped coming to the meetings, and I haven't heard what he's doing now or whatever.

MM: That's a very interesting story.

RD: Yeah.

MM: But can you explain this just a little bit more, particularly for lay people. Does this mean that stimulation of the PAG does not cause beta-endorphins, does not generate secretion of beta-endorphins?

RD: It turns out that the PAG is the place in humans, I mean in animals, where the original research was done. That's where Dave Mayer was putting the old electrode.

MM: Yes, I know this very well.

RD: Yeah. And that worked, no question. And that seemed to be producing the release of beta-endorphin, although I'd have to go back and look at those papers now in light of modern technology and the number of subject animals and stuff like that, because if it was the old radio-receptor assay, you could have taken the data on the good day and said,

“Yes, that shows beta-endorphin release.” Those studies were done prior to when we had done our studies. It wasn’t even our protocol to use. What happened in humans, though, was you couldn’t put the electrode in the same spot. It was too aversive. So you had to put it someplace a little bit more lateral, and the name of that slips my mind right now. And in that particular location, it just wasn’t that effective as an analgesic-producing thing, and there’s always the possibility that it was activating descending processes that were going down the spinal cord. But this release of beta-endorphin locally, which was then going to somehow or other bathe the brain in beta-endorphin, didn’t seem to hold up based on the studies that were published, in humans anyway. I think that’s probably why the technique wasn’t effective.

If you could have stuck the electrode down in the PAG, it would have been great, except the heart rate would have been about 250. In fact, the way you kind of figured out where you were with these things is you put the electrode in and you had multiple little leads that you could hook up to, and I can remember being in the OR with this guy [neurosurgeon Richard P.] Greenberg, and he hooked up lead A, and the guy’s heart rate went like way up, so he turned it off right away and slowly the heart rate came back down again. So we decided, well, that’s not the right place. So then we went to another spot. It went up a little bit. Then he finally found a spot where the heart rate didn’t jump up, and then he left it on and the patient said, “Oh, yes, yes, I can feel it. I’m getting much better,” you know. These are people that had been in the OR for three hours screwed into a stereotactic apparatus and getting Valium, and you’re supposed to be trusting their report. So, not too surprisingly – And it was a report of like, “We know this works. Just tell us which one works,” that kind of stuff. So I think with almost all those patients, over time, they had them removed, because suddenly it stopped working. Whatever the time action of the placebo response was after such a massive thing, it eventually stopped working and we would have them removed. So after the near massacre of the Nazi war criminal, I lost interest in that whole line of research, and we never got – Subsequently, we got a protocol approved. In fact, the original protocol wasn’t even mine. I just came along when the question was measuring the beta-endorphin. They probably ran through at least 50 patients trying to find out whether, under carefully controlled conditions, they could demonstrate that it worked, and the answer was, “We don’t know,” because after 50 or 60 patients, the study tapered off, and then eventually just hung on the books for a couple of years and then disappeared about 10 years after it had been started. And there was never a publication that came out of it, so we really could never hang our hat. The only thing that came out of it was this thing here, and that was strictly an observation that had to do with the stuff.

But that did lead us into a whole series of studies with this guy Greg Mueller, and Ken Hargreaves,²⁴ who was a dental student at the time, who turned out to be extremely talented and very ambitious, hard-working. So we started doing studies. After he finished dental school, he ended up coming here to do a postdoctoral fellowship, and then that led to doing a PhD at USUHS in physiology with Greg Mueller. And he did an exhaustive series of animal studies, and we did some clinical studies in parallel, which seemed to indicate that beta-endorphin gets released into the bloodstream during surgical stress, oral surgery, and that if you gave Naloxone,²⁵ you increased the amount of beta-

endorphin that got released, and patients reported more discomfort during the procedure. And then if you gave something that blocked the stress during surgery, the beta-endorphin level stayed low. So if you gave them Valium – And then post-operatively, if there was no pain, then everything dropped off, and then when they started to develop pain, it went way up.

So we eventually harnessed that information to try to do two things, one of which was to decrease the amount of beta-endorphin that was available by giving a steroid, and it had been well known that if you give a steroid, that acts to feed back on the pituitary to inhibit the release of beta-endorphin, because it turns out that beta-endorphin gets released when ACTH²⁶ gets released from the pituitary. And that then causes the adrenals to push more steroid out into the system. But if you have steroid, that feeds back into the pituitary to turn off the secretion. Well, if you just give the steroid exogenously, that blocks the beta-endorphin in ACTH, so you get a dramatic decrease. Well, the only problem is the steroids are anti-inflammatory in their own right. And in the oral surgery model, that may or may not show up as analgesic.

So we took the normal dose of steroid and said, “Let’s give one-tenth of that, and we’ll see how that works.” Well, it turns out, that still had a slight amount of analgesic activity. Even though it decreased the beta-endorphin levels way down, it was still having its own effect. And we wanted to systematically – We started with 10. I think we dropped down to five, and then we kept going down. So then we tried going down even further, and eventually we got to the point where I think it was one-tenth of a milligram of dexamethasone blocked the release of beta-endorphin still, but didn’t seem to have any activity of its own. And sure as heck, over the first two or three hours, patients reported greater amounts of pain in the group that had received the low dose. The middle dose, they actually had no difference, and the higher dose, they had a little bit of an analgesic effect. So we said while there’s obviously a pharmacologic effect of the drug, and then there’s its physiologic effect to suppress beta-endorphin, and if you suppress beta-endorphin, then you had more pain. So that suggests that this pituitary release of beta-endorphin is something to do with pain.

The other alternative would have been to give Naloxone, but that would have been blocking endogenous opiates everywhere up and down the system, and there was always some suspicion that it had its own little hyperalgesic effect of its own, so this was a better way of doing it. And we were, of course, privy to all that stuff because Rick Gracely and Dubner were doing all their stuff with Naloxone here, so we knew that Naloxone maybe wasn’t the thing to test this hypothesis. And then the opposite approach was, can we raise the beta-endorphin levels by giving a hormone that would cause its release, and that way we’d be mimicking the normal system. So we gave CRH, corticotropin-releasing hormone,²⁷ and that resulted in a whopping release in beta-endorphin and, at later time points, an analgesic effect. The only problem was that we were bothered by the fact that we wanted to give the CRH early enough to have the beta-endorphin release happen before pain, because we didn’t think it would be something like an analgesic thing, and plus we knew the body was already secreting beta-endorphin once you had a lot of pain. So we gave it about a half hour after surgery, and then we got this big bolus of beta-

endorphin, but then, by the time the anesthesia wore off, that's where we saw the difference in the amount of pain they were having. And we said, "Well, there's two possibilities," one of which is you've got to get the beta-endorphin released, it's got to get to its site of action, and then it has some kind of effect to block the pain as it would normally start to occur. Or maybe the CRH has an effect of its own. Hargreaves eventually went on to do a bunch of animal experiments that seemed to suggest that the CRH had an analgesic effect of its own, so it was maybe not a clear demonstration of the beta-endorphin effect. But taken in the context of the series of studies we did at the time, it seemed to be a tidy story that you get release. If you block that release, that results in more pain. If you block that release post-operatively, that causes more pain. And if you give something that increases the release of beta-endorphin, that causes less pain. So it was a consistent little story. So eventually we said, "All right, that's a tidy little package. Let's move on to something else."

MM: OK. So you were sort of doing this in conjunction with running dental studies of analgesics and ibuprofen.

RD: Yeah, I kept the dental studies of the sedative combos going for a long time, probably like 10 years, and then kept the analgesic studies going. Got away from the pre-treatment question eventually, and then started looking at novel analgesic drugs to see what they did, and have always kind of had that thing going where I've had two or three separate types of lines of research.

Eventually dropped the sedation stuff when it got to the point where I got criticized at one of my reviews for doing too many things not very well, and it was suggested that if I just did one or two things better, I would be a more valuable employee to the NIH. So the sedation stuff was the easiest one to give up, and I pretty much have stayed away from that with the exception of an occasional dabble where I would do a study here or collaborate with someone, stuff like that.

MM: But do you think that that is sort of pretty well established by now, I mean the clear effects of sedation in dental procedures?

RD: Well, I mean, in the minds of those people that read the papers and are willing to adopt a different viewpoint, then yes, but I think in reality still, it's the regulatory process that led the field. So I only served to confirm what people either find true or to be ignored if it's not what they find true. And we did actually do a large study to try to wrap all that up. It was a thousand-patient study that was done on a contract. Unfortunately, it was only presented as an abstract and then included in a kind of review article one time. I never actually got the primary paper out. But that did seem to indicate that patients note it doesn't make that much difference to them. It seems to make more difference to the operator. But they're the ones that take the risk in terms of respiratory depression and cardiovascular effects, so I always argue one drug is probably the best, two at the most, but you pay a tradeoff, and it's probably not worth it. And now, because it's been so well regulated, it's primarily guys doing oral sedation or doing IV sedation but sticking to just

one drug usually, so I think it's improved. Maybe there was some minor contribution of science to the change, but in any case it's a much safer thing for patients.

Although there is supposedly going to be an article, I mean a television show, in January that's going to get at this whole issue of sedation and anesthesia. It's another one of these "Deaths in the Dental Office" types of things. I'll have to wait until I see it to find out whether they're on to something, [or] it's more yellow journalism.

For a long time, there's been concern that pediatric dentists were being a little bit cavalier in the drugs they used and maybe not as careful about monitoring as they should, and I think this program is supposed to be aimed at kids rather than adults. So if that's true, then that will open up a new [or] reopen the old box again. But –

MM: Yeah. I think several times in the literature, you state that general anesthetics or using two drugs can really help the dentist because then the patient is not able to protest very much.

RD: Yeah.

MM: But is very cooperative. High marks for cooperativity.

RD: Yes, yes. Unconsciousness is equated with cooperativity.

MM: But that's not actually necessary if what you're trying to do is relieve pain and anxiety.

RD: Yeah.

MM: I thought that was a very interesting point.

RD: With the emphasis being on safety.

MM: Yeah, especially safety.

RD: Yeah. But it's actually – I mean, it rears its head even now, because there's a group that's trying to get a specialty established in anesthesia for dentistry, and they want to have it such that you could have, in those cases where you need to have a second person there to actually give the anesthesia and monitor it, that and the fact there's a group of people that exists that can do that; and, secondly, to do the research that's never been done; and then to teach other dentists how to do it intelligently and safely. Unfortunately, the oral surgeons are violently opposed to this because their little niche in the dental world is they're the only ones who can give anesthesia and sedation.

So that if you suddenly have these other people doing it, then that takes away a lot of their business, and God forbid people might go out and have fillings done rather than have their teeth extracted or something like that, and then where the hell would we be? You know, we'd [not] have all these fancy offices.

So they are opposed to it, and it's been voted down twice, the last time by only like one vote, and the oral surgeons have already voted something like \$4 million to fight it this year. The way they do it is they make contributions to all the candidates for political office. I never realized they have political action committees. They collect money, they run campaigns, they have hospitality suites. When you show up at the ADA [American Dental Association] meeting, if you're a voting delegate, you'll be showered with all kinds of gifts from these various candidates for the offices and things like that. And then they cut deals. So the last time they cut a deal with the orthodontists and said, "You have no interest in this one way or the other. If you vote with us, we'll vote for you on something later on." So on the basis of this they were able to get it rejected.

Last time was actually so crass. The first time they did it was in New Orleans, and they had a hearing, and it had passed all the criteria. The ADA has very carefully worked out a way to avoid this and has lots of due process. So they had gone through a due process, and on the basis of this, the specialty made it to the final vote, second from the final vote. The final vote is on the house. Before that, they have a so-called reference committee because there are so many things that have to be decided upon, they have to sort them out the day before. So this was like the only major issue to be decided. And when we got to the room, it was filled, and it was filled with oral surgeons who had managed to get themselves lined up behind every mike, sitting in every chair, and they stood up one after another and said the same thing over.

MM: A filibuster.

RD: It was. Finally the guy who was chairing the session said, "I don't want to hear it again. If you don't have anything else to say new, sit down." So the guy would say, "I'm Dr. So-and-So. I've been in practice for 20 years, and it's my belief –" He'd go, "No, that's enough of that." Finally he got to the point where the rest of us got to stand up, and we would say – And then at that point, the guy said, "You've got one minute to make your case." I'd say, "I'd like to report the results of approximately 10 studies that show the safety issues with this." "You've got one minute. You'd better wrap it up." So, needless to say, the people who had the alternative viewpoint weren't heard real well. So they set up a new set of criteria, a new process, it went all the way through, and this time I think, again, at the reference committee, there wasn't – The oral surgeons didn't want to look as heavy-handed as they did the time before, so they were actually mildly diplomatic about the whole thing, because they figured they'd already bought all the votes ahead of time. So they just sat there en masse and didn't say much while we all stood up and said, "Here's the evidence, here's the evidence, here's the evidence." And the committee said, "That's very nice. We vote against the specialty." So then they were able to force it to come up on the floor, and it just lost by one or two votes on the floor.

MM: Oh, well.

RD: So one would think that in a logical world, you could finally, this time, possibly get it through. But the oral surgeons are saying, "Over our dead bodies!" and they're going to do every political shenanigan. Because last time it even got to the point where one of the

rules was that if you had something like this, you could go to the caucuses. Again, I never would have thought about it, but each state has its own caucus. So the groups that were in favor of the specialty went to all the caucuses, went to as many as they could, and after they had started to make their case with the delegates who had never heard this stuff before, because they just knew that their buddies, the oral surgeons, said, "Vote no," they quickly decided no more caucuses. They weren't going to let these people go because they were having too much influence on changing the perception of the people and whatever, that kind of stuff. So right in the middle of the whole process, they changed the thing. So it'll be one more thing.

We're not talking – It's the oral surgeons' self-interest pitted against the presumed self-interest of these anesthesiologists, but there's only like 30 or 40 of them left in the whole country. They're all busy, they're all successful, and they're spending tens of thousands of dollars.

END OF PART ONE

MM: Okay. We're starting the second phase of our interview with Dr. Ray Dionne, and today is December the 30th. It's just about 3:00, and we're again in his office at the Clinical Center at NIH. Good afternoon.

OK. We talked a lot – we actually covered quite a lot of ground in the last session. And before we go on to more recent events, there are a couple of questions which interest me in particular, and one of them is the question of pain measurement and what kinds of different scales you use to assess people's pain. And why don't you just sort of comment on what you've found the most useful. I know the research team usually uses the algometer, pulling the red slide in and out.

RD: Yeah.

MM: But in the clinic, they mostly are using verbal scales or numerical scales.

RD: Yeah. Actually, the person to talk to about that is Rick Gracely because that's been his interest.

MM: Right. But I want everybody's perspective.

RD: Yeah. Well, my perspective is, one, the simpler it is, the better, and if you can get away with one thing rather than two, that's good too. And I started out with, at a time, doing analgesic studies when the standard was those four-point category scales: no pain, mild pain, moderate pain, and severe. Then pain relief was measured the opposite, you know: a little relief, some relief, lots of relief; and then complete relief, or something like that. The statisticians always had a lot of problems with that because it lacked a lot of the properties you would want of a scale. And even the people who say you're trying to approximate a human perception, it doesn't work that way, because you don't know if moderate is twice light and half of severe and stuff like that, and you don't know where the continuum breaks.

So the visual analog scale²⁸ developed as an alternative to that, and at least it had the functions of being continuous, and other than being anchored on either end, people could put the marks wherever they thought they fit, and then you would look for changes from those marks as things changed over time, and stuff like that. But even that still left a lot to be desired, at least in the minds of some people. So then they developed more and more sophisticated scales.

When I came here, I embraced them all. The first study I did here, I had nine analgesic scales I did in parallel so that every subject, “How much pain are you having now?” “Moderate,” 50 percent; slightly intense, on and on and on down the list. And what I discovered very quickly, that was too many scales to give anybody because they can’t begin to do them all without getting very bored. But the other problem was that I learned what probably everybody else knew to be true, and that’s that everybody used the scales a little differently, so that when you started making generalizations about someone filled out a category, I mean, one of these very elaborate scales, and got a score of 3.8 or something like that, that didn’t necessarily [equate].

The next person that came along and checked at 3.8 might be having twice as much pain or half as much pain, and people were always stumbling on the words. And the more elaborate the scale is, the more they stumbled. After I did enough of them, I finally got to the point where I had people take the scales and kind of rank order them themselves. So rather than taking, say, Rick’s 13 words and assuming that this word had a value of 0.8 and that had a value of 2-point whatever, and they were some ratio of each other, that only works in an idealized world doing experimental pain where you carefully select the subjects, you throw out those who don’t behave by the rules you’ve established ahead of time, and then you have 10 perfect subjects, and that’s representative of those 10 subjects. That’s all. In fact, a friend of mine, Ken Hargreaves, was a subject, was screened to be a subject in one of those studies like that, and he was rejected because he wasn’t good enough. So here’s a guy who was otherwise a normal-functioning person who could see, could hear, but he wasn’t good enough to do the pain scales quite right. When I had the patients doing it themselves, they quickly started, I learned, kind of group[ing] them. They would take all the words that were at the low end and kind of use them interchangeably. And then they had all the words that were kind of in the middle and they used them interchangeably. Then the words at the high end, they used them interchangeably. And then if you added in a none [no pain], you’d have a four-point category scale again. So I said, what the hell. Why am I wasting my time with this? So everybody uses the category scale, and that’s one that you can relate back to the old docs. The people that say it’s much better still will let you get by with the visual analog scale. And then if you throw in one of the fancy ones, you cover your bases with those people. So I started using three of them at a time. And over time, I found that I could never really get much mileage out of all three of them in a paper, so I will often collect all three, report on them, but only highlight the one that fits my bias, which becomes the best-scale-of-the-day type of stuff. And people can obviously look at the paper, read it, and draw their own conclusions, but if all three scales are consistent –

So the problem is, yeah, they're not giving you any absolute ranking and they're probably not good for going from patient to patient and saying, "He's got a 50, she's got a 50, therefore they're having the same pain." So you look for changes within a subject, and if you're looking at drugs, that's easy because you're often looking at changes over time. You give a drug and it goes away. So if one person is using half the scale, at least they're still consistent within themselves. Then the other thing is, when you're doing group comparisons, you just take lots and lots of patients and throw them into the same situation. So you've got 25 people in one group getting the same drug, using the same scale, so all that variability – the highs, the mediums, the lows – kind of collapse together and you get useful data. So it's a not very sophisticated [system]. It's one that's gone from the simplistic approach to the most sophisticated approach and back to the simplistic approach, and it works and it gets published, so I stick with it at this point.

MM: OK. And I wanted to ask you to sort of talk about your perspective on the ethics of pain research, not trying to get into discussions of being a Nazi war criminal, which I think is way off the scale here. But, I mean, what we're asking people to do essentially is suffer pain so that we can learn sometimes rather narrow questions about different drugs.

RD: Yeah. I mean, very often – All the patients who are willing to participate in one of our studies, they sign a consent form that says, "You will not benefit from this research. However, others in the future may." That's the strongest endorsement we ever make on this whole thing. So you're right. People are agreeing to participate with little to no hope of advantage. But in reality, the way it works is, on many of the studies where we're looking at something and standard treatment is our reference, we're telling them there's a chance you're going to be even better off than standard treatment. And with, say, the preemptive treatments or the preoperative treatments, still, that is not a standard approach. So if we do something that compares standard treatment to something that may be better than standard treatment, we're offering them the possibility of getting more pain relief, less discomfort.

The other side of the equation is that still, the people in practice, especially for this model, which is a fairly innocuous one because it's a one-time-only thing, the pain is most intense for one day, and all you've got to do is get some pain medicine into them and it usually diminishes pretty quickly, will be, in a private practice setting, you'll have the procedure done, they'll be given a prescription to go fill on their way home. They get it filled just about the time they're starting to develop a lot of pain. They swallow and they wait an hour or two before it starts to work.

MM: And they have to suffer through that.

RD: Yeah. We keep them here, they develop pain, we give them a pill to swallow, and then it either works, or an hour later they're asking to be re-medicated. And then we give them something IV that works right away. So in many cases, I think that if they get into the right treatment group, they're better off. If they get into the control group, they're no worse off than they would be, and we have rapid treatment to deal with it. Plus by keeping them here, any other problems they have associated with the surgical procedure,

the other drugs, anything else, they've got a million-dollar situation with the nurse standing right beside them, a physician a few steps away, dentists in the building, and then, if you ever should have a true emergency and you press the button, you'll get run over by all the people that come charging in to help you out. So by and large, I think they're equal to or better off than they would be in a private-practice setting.

Now, with the chronic pain people, that's probably less true, but, unfortunately for us, the only people that get referred to us for chronic pain studies are the ones who failed everything else. So they show up on our doorstep as they can only get better. Unfortunately, in many cases, they've also had enough iatrogenic problems superimposed on their original pain that not only are they not going to get better, they're kind of stuck in a rut. That's unfortunate. They're never going to improve that much. And we see that with these TMJ patients²⁹ who have had multiple surgeries. By the time they come here, they're not suffering from a little bit of an arthritic joint. They're suffering from 10 failed surgeries.

MM: Right.

RD: And the best athlete in the world, if he's had 10 surgeries on his knee, is not going to run the 100-yard dash real fast. He's going to hobble in. And that's what we end up with. So if we were in a real therapeutic situation, we would work on the patient's pain behavior, lower their expectations, I guess, and try to have them get by with that type of stuff. But in this situation, we evaluate them. If there's still some chance that they're suitable for study, we put them on the study, but with the expectation that they may not get any improvement. But at least we haven't done any harm to them over that period of time.

MM: So how much work do you do with chronic pain patients? Those are probably – I don't know if this is your area of expertise?

RD: Well, it's not my area of expertise, but we still do some work in that area. The studies we talked about earlier where we were doing this deep-brain stimulation stuff, that was really – everybody else was treating them [and] I was just involved in the technical end. But we eventually got involved with patients who had what's called temporomandibular disorders, and I have done more failed studies than good studies, but that's not exactly always a failure in the scientific sense, because if we look at some treatment that people are using on the outside and we find that it doesn't work, then we provide some people that are intelligent enough to read it and think about it with a basis for saying, "Well, I'm not going to expose my patients to risk if there's no benefit associated with it." So we've done a lot of those. But I try to stay as much away from the hands-on part of that as possible because it's very labor intensive, takes a lot of time. You've got to screen a lot of patients to get one on the study, and then you've got to spend a lot of time with that one patient to get one data point. And if I did that over and over again, I would be so out of the loop scientifically. As it is, I struggle to maintain any kind of credibility with the few things I read, which are usually things I have to read that day to write an article, that kind of stuff, you know.

MM: Yes, it's difficult.

RD: Well, we're going to make a bigger attempt at that. That's going to be my swan song here, and NIH is doing chronic facial-pain patients, and I'll either do some contribution [to] my field, at the end of my career, or I will fail like many other people have. But at least I'm at the stage now where I can afford the luxury of doing it. Otherwise, I would never have been able to get by.

MM: So is there a way to see this problem which is different from the way other people view it?

RD: Well, certainly the problem associated with dentists treating it has been the classic "I'm under the lamppost and I found," because that's not where the key is, but that's where I could see. So you go to a guy who does oral surgery, and he's going to see it as a surgical problem. In fact it's that one patient in a hundred that benefits from a surgical treatment, then they're going to get better. But the other 99 people are going to be harmed, likely. If it's someone who at times has been, you know, people thought it was all due to the way the bite came together, the way the lower jaw related to the upper jaw or the muscles and spasm, anxiety of causing muscle spasms, stuff like that. I think now it's reasonable to assume that there's a biologic process going on that is either due to overuse or some lower capacity for dealing with the stress on the joint, that results in over-injury on kind of a microscopic level, [so] that it just gets repeated and repeated. Eventually it leads to inflammation. The inflammation leads to various responses that then cause either resolution of the problem, which is good, because then you can hopefully just manage the patient while the acute phase is going on and then they get back to normal, or there's going to be some changes that occur, either plastic changes in the central nervous system or just localized changes where the disk has been moved and sure, it hurts like hell, but after a while the tissue stretches, the inflammation dies down, and you just have a person who has a chronically dislocated joint or a dislocated disk. So it's like me with running. I used to run like a fanatic, and every time I got an injury, it never quite went away before I discovered that that was part of the [process]. And now I'm convinced I'm just a composite of every athletic injury I've ever had in my life, and they're all just waiting right below the surface, and all I have to do is lift one weight. I mean, there's one exercise I do that I can know that when I get to 120 pounds on that exercise, I'm going to get injured the next week, because at 122 ½, I pull a muscle, and it happens all the time. I could sneak up on that weight for a year and it's going to be the same thing. I cross that little threshold and I'm injured. So with some of these things, there's that kind of variability in the population. The guy beside me can do 150 [pounds], someone else behind me does 80.

So these injuries do occur, so there's a case of trying to come up with an intelligent treatment philosophy based on the knowledge that some of the changes are reversible and have to be managed, but somehow you've got to be able to identify that. Some of them are going to be progressive, and it would be nice to identify those and say, "All right, this is a progressive thing, and we know that inflammatory mediator Z is what's probably

contributing to the progression at this point in time, so let's get the antidote to mediator Z in there and block it." And then there are others that are just going to go on to injury or have already been injured, you know. Someone gets slugged in the jaw. Maybe they've already started cascading down the thing.

I don't know if I mentioned it last time, but one of these patients we had had her jaw broken when she was a child; but [she] was in an abusive household, and the mother didn't want to expose the husband to any more criticism or criminal actions, so they kept it quiet. So she healed up a broken jaw. And since then, she's always had problems associated with her jaw that led to surgery. Then the surgery led to replacement of the joints, which has now led to more misery. So some of those people, you could say, "All right, well, let's just limit the damage that's associated with the treatment rather than make it worse and worse by aggressively treating something that's probably already been traumatized to the point where it's never going to be back to normal." So, rather than trying to take a guy who's wearing a prosthetic limb and turn him into a marathoner, you be grateful that they can still walk.

So that's kind of vague and doesn't really lend itself to me standing up in front of a bunch of clinicians and saying, when a patient comes in with this set of symptoms, they have this and you treat them this way; when they come in with that set of symptoms, they have something else and you treat them that way. So I don't have a lot of success when I do that kind of presentation. So the only thing I can tell them is to introduce doubt into their mind that they know the answer, because they haven't pursued the methods of answering the question; hold up a lot of examples of things that I know appear to be true, but didn't hold up when you inspected them; and then say, based on this limited knowledge, here is how you should proceed to treat patients. And in the absence of a lot of proof, you should actually tell these patients that these are investigational treatments at best and that you don't know for sure whether they work, and at least let them make the judgment. That's when the dialogue usually breaks down, because when you try to convince someone that something he's using that he knows to be true, like the pile of 80 pages there in the corner, the guy says the proof of his assertions is logic, and then he proceeds to put his opinion down as the definition of logic, and then goes, "Therefore, I have proven my assertion." And you read the letter and you say, "This poor man, he hasn't got a clue," and then he says, "This is my life's work of 37 years, which I am calling to your attention so that you can sanction it as an official NIH view," and you go, "Huh?" Right, you know. But [if] you try to talk to a guy like that and say, "Hey, throw it all away and let's start with a blank slate again," you don't have much success. That's why people are saying, all right, let's try to do something that limits the damage that the clinicians are doing out there who are ignorant about biology, shall we say; [let's] try to train the new generation coming up. But the drawback is that most of us are not really up to doing the training. It's the old philosophy that's still there, training the people.

MM: Right. I was wondering if you've had much more chance to work with Dan Laskin.

RD: A couple of times, yeah.

MM: Because he was president of the ADA for a while. Isn't that right?

RD: I know he's been president of the Oral Surgery Association. He may have been president of the Anesthesia Society as well at one point. I can't remember, though.

MM: Because we were talking last week about the difficulty, the oral surgeons essentially blocking progress in terms of introducing good methods of anesthesia or actually preventing dentists from doing anesthesia altogether and introducing a new class of dental anesthesiologists. And I was just wondering. I mean, Dan's been working with us for a long time, hasn't he?

RD: Yeah. Now, he's the exception to the rule by any means, and he's been, as a result, while he's respected within the oral surgery community and he holds prestigious positions, he's also been subject to a lot of nasty comments through the years. And, in fact, some of them had to do with TMJ. When he first started doing his stuff 25 years ago with Charlie Greene,³⁰ they came up with these conclusions that at least part of the problem associated with temporomandibular joint was people who were very anxious, who allegedly had high mobility, did a lot of muscle activity. This led to the pain, led to the joint dysfunction, stuff like that. And they counseled a do-no-harm philosophy based on that. They were just highly criticized because the people who wanted to say that there was something physically wrong that can be corrected either surgically or dentally wanted to have that dogma persist.

I can remember one time there was a guy who hosted a party one time, a reception, at a meeting strictly for the purposes of rallying support against Laskin, because he was of the mindset that it was all a surgical defect, and all you had to do was go in and fix the disk and the joint, and Laskin had been preaching this heresy and he was going to prove him wrong. So he went ahead and tried to organize some kind of counter-movement, and the only thing that happened was I'm sure he got a lot of people to go along with him while they did more and more surgeries, but then eventually that all blew up in their face. Laskin may not have been completely right about it being a psychological problem, but certainly it wasn't – The alternative solution had more harm and no greater efficacy associated with it. With the anesthesia stuff, I suspect he's been a little bit of an apologist for the oral surgeons, because whenever he was in a position to try to influence thought, he always tried to kind of say that everything's OK the way it is, and it should just kind of keep it going, it'll be all right. And that was OK if there was no harm going on. But the whole reason the controversy existed because there was a perception of harm, and he kept saying, "No, it's OK." But, of course, that was when he was a little bit older and more, probably, sensitive to having been a rebel early in his life.

But certainly, every time I've ever heard him speak, he's either sounded very intelligent or very experienced. It's just that sometimes his opinion is one that I agree with and sometimes it's one that I don't agree with. So what does that say about me if I find I am not in agreement with a voice of reason and intelligence, and still can recognize that and then proceed as if the problem lies with that?

- MM: OK. Well, I'm actually going to interview him in February. I've been reading some of his stuff and it's fairly interesting.
- RD: Well, he's an excellent editorial writer, I've noticed through the years, because when I was trying to edit a journal for seven years, I was always envious of the fact that every month he could have a well-written editorial in this thing [*The Journal of Oral and Maxillofacial Surgery*].
- MM: I know.
- RD: I don't think I wrote two editorials in the whole time I had the journal, you know. I never felt I had anything worth saying quite that well.
- MM: Some people have a real facility for it. OK, so, can we talk a little bit about working here at NIH and what you think the advantages are of being here? You seem to like it here.
- RD: You would think. Either that or I'm really stupid for having stayed for 20 years. Well, the big reason that everybody always says that it's a great environment is that it's usually pretty close to the alleged, the proverbial cutting edge, you know, that anything that is taken for granted on the outside is usually subject to reexamination here, often found wanting, and then any new methods that are coming along are usually readily available here. And then when someone does something that ties field B with field Y and allows for an overlap, then you can usually quickly pick up on that and go with a situation like this. Plus there's the time constraints on your time unlike where they are anywhere else, where you are expected to do a certain amount of administrative stuff; there's always a little bit of patient-care stuff, but even that is always geared towards the research mission. The bulk of your time is, in fact, aimed at getting research done. Now, the converse of that is true, is, Ken [Hargreaves], when he was here, we both agreed that if we did everything that was asked of us, we could probably almost fill a 40-hour week without getting around to doing the research. So we decided we had to be a little more selective about what we actually followed through with, and what happens first is you stop going to a lot of seminars that you would otherwise like to go to, and you start ducking meetings left and right. Then you try to avoid any reports or assignments, like the one I've got stuck in the corner there, and you hope that they go away. And then you try to get to be very guarded with your time and start trying to find times when you can lock the door for two hours or not answer the phone and stuff like that. In fact, the ideal circumstance I had was, for about a five-year period, I had my office on the bridge that joins the old building and the new building, and it was just this little single cubbyhole. And not only was I not – I was the only person in it. There were very [few] other people around me because it was just a corridor that connected two buildings. And the phone rang at the front desk, and we had a little switch and we could flip it off so it didn't even ring in our office. So you could go in there, lock the door, turn off the phone, and just have an – And that was before e-mail became so prolific. So you just wouldn't be interrupted for two or three hours at a time. And the best concentrated work I ever did was in those periods. There were also lots of times when I drifted off to sleep and the banging on the door, I thought was the alarm clock as I came to. But here, where there's

always someone around, the e-mail comes in a lot, the phone rings a lot, and now I have more administrative duties, 10 minutes, 15 minutes at a time [gets lost].

So you get the ability to usually concentrate your time towards research, to lock in large amounts of your effort, and also to pick your mission. You can say, all right, I think looking at some animal model that might be predictive of pain in humans is worth studying, and once I've studied every possible factor associated with it, I might be able to make some assertion that I can take to humans and actually test. Or I can take someone else's basic science observation, test it, the hypothesis in humans, and find out what's going on. And the only limitation is, while you can be very creative in animals, you are extremely limited to what you can do in humans, but the relevance is a lot greater.

MM: It's a lot more important.

RD: Yeah. I mean, I can remember when people were just ranting and raving about, I think, kappa-opioid analgesics³¹ as the new hot thing. We got a hold of one that was a kappa opioid and we tested it in man, and it worked a little bit, caused a lot of side effects, and I said, "Well, why waste any more time on that issue if that is that specific?" There was another time when we looked at a prostaglandin receptor antagonist, and this was supposed to be really good for blocking the receptors that the prostaglandins interact with, and we tested it and it didn't work at all. And I said, "That's hard to believe," so I never really embraced that as a truth and just said it's probably a bad drug. And, in fact, I was at a meeting about a month ago and the guy was talking about prostanoid receptor antagonists, and he brought this one up. And he said the problem with this one, well, it wasn't a good drug. It wasn't as good as they said for what it was supposed to do, and, as a consequence, it's easy to imagine why it didn't work. So, whereas no one has ever come up with a good, clean kappa-opioid and said, "Ah-hah, it does work without causing all these psychotic mimetic effects." But there are lots of people in the lab still going crazy trying to tease out, find that part of the kappa receptor that's going to do the good stuff and not the bad stuff. And there was a whole history of narcotics that was written about how people spend 50 years trying to find the good part of the opioid drug to avoid the bad part of it, and in the 50 years they just have a lot of drugs that look just like morphine.

MM: Right. And acted pretty much the same.

RD: Yeah, yeah. They were qualitatively the same, you know, so it was like, how do we ever – how could we have been so stupid?

MM: It's a good idea on paper, you would think.

RD: Yeah.

MM: Somebody did anyway.

- RD: Well, what was the killer there was, the way you screened for new drugs was to come up with an analgesic model or two you could test, and the way they validated the model was to take a drug they knew that works. So they validated their models with morphine, and then they went screening for new drugs that looked like morphine. And in the end, they turned out to be like morphine, and everybody said, “How could that have happened? Damn!” So the desire arose to, let’s look at things that don’t look like morphine, and that’ll be our criteria. That’s how Pentasa³² seemed to develop basically as a drug, because they went looking for something that was different. While it didn’t turn out to be the perfect drug, at least it was a step in the right direction. It was less of an abuse potential, less of a respiratory depressant effect, I think, and as a result, it was a little bit of a cleaner drug.
- MM: Now, speaking of which – this is a minor question, but I’ve noticed that a lot of your studies seem to endorse Flurbiprofen.³³ I’m just wondering. It seems to, if I’m reading your accounts correctly, it seems to be superior in terms of efficacy and safety to other NSAIDs. Or am I just sort of – just happened to read a lot of studies with Flurbiprofen.
- RD: Well, we have used it a lot. We’re probably – this is probably the world’s epicenter for Flurbiprofen use in research.
- MM: Actually, I’d not heard of it being used very much. Of course, it’s now available over the counter, which may or may not mean anything.
- RD: Yeah. Well, what it was is, when I first came here, I had done a couple of studies with ibuprofen. I was looking for something new to study. Flurbiprofen was the next drug coming down the pike, and it appeared, on the basis of the pre-clinical and clinical stuff, to be clearly more potent, but that doesn’t mean much unless you get some other advantage. But it also appeared to have this greater efficacy without having greater toxicity associated with it. And, as a consequence, I went and tested it, both as an example of the NSAIDs but also to see if it was in fact as good as it was. Then, when we always had success with it, I always said it’s just that. It’s partly attributable to this drug, but partly a factor of the class of the NSAIDs. Then, after we got a lot of experience with it, it was like, why bother using something that’s new that might have all the problems of the new NSAIDs, but you don’t want to just be using ibuprofen because people recognize that, if it’s just an over-the-counter drug, well, it’s probably not that effective, they would think.
- MM: I see.
- RD: So by using this drug, you had the advantage of a drug that was a prescription, it wasn’t as well known, we knew it worked real well, and it didn’t have the liabilities of the new NSAIDs; and in the ‘80s they were coming and going about every two years. One would go on the market, you know, people would develop problems, and it would disappear. So it’s been good to us, and it’s still being good to us. This is data we just analyzed yesterday, looking at giving the Flurbiprofen – I think I probably mentioned this down below – at the extraction site.

MM: Right, right.

RD: And what we've been able to determine is there's a placebo response, and when we get to the highest dose, we're getting about a doubling of the amount of time it takes before anybody says they're having any pain. And if you look at the hourly pain intensity, placebo gets up to about 60 percent of maximum on a visual analog scale, and the patients who were getting the Flurbiprofen are having less pain, and in the highest group they're in the range of mild pain. So if this can be generalized by the time we do a bigger study and we can show this has lower drug levels, doesn't cause any localized problems, then we could say we could always prevent pain by this little strategy of squirting the drug in locally.

MM: Yeah, I observed that upstairs. One of the patients, [nurse] Janet Rowan, was working with her—when was this? Two or three weeks ago.

RD: Yeah, because we've only done it over the last month or so. So now what we'll have to do is see if it has any prophylactic effect on interfering with processes that might contribute to more pain at later time points. But that'll be a harder study to do. This was actually just to see if it worked at all in this formulation, because sometimes you waste an awful lot of time chasing after questions only to discover there's something wrong with the formulation.

MM: OK. Three or four more questions.

RD: OK.

MM: Let's see. Well, I guess we sort of stopped last time somewhere around 1985, about the time of the Conference for Anesthesia and Sedation in the Dental Office. I wanted you to talk a little bit more about what you've been working on since then. You talked a little bit about the study that showed that the critical event was the formation of cyclooxygenase post-surgery, and I wonder if you could talk a little bit more about that research and about how you actually established –

RD: Let's see. Well, I mean, I probably have talked about things that we did here versus things that happened in the field and kind of got rid of them altogether, because, really, until I read about them in the newspaper, I didn't know cyclo-oxygenase-1 from cyclo-oxygenase-2. Now that it's obvious that that's going on, it's being formed, we looked at the studies as we've done them and said that this is suggestive.

MM: Some sort of evidence supported that.

RD: Yeah. So it's not like we're blazing the trail there. But we are saying that, yes, it's probably important clinically, and then the question is, to be answered, is, if you can block that formation, are you going to get an analgesic effect over time? There was always the possibility that all that stuff is unrelated to pain, but the fact that the selective

cyclo-oxygenase-2 inhibitors are analgesic in man supports that concept that that's where the action is, because there's always been concern that you have so many effects of these drugs. Even though you've designed them to be narrow for one thing doesn't mean, when you throw them in the physiologic milieu, they don't have other effects. But now that you've designed something that's specific for interfering with this thing and it's analgesic in man and doesn't have a lot of other effects, that makes sense. But whether that's an acute effect or whether that results in other things downstream not happening, because the way these mediators work is you'll have a wave of something immediately, and then there'll be another something else and another something else later on. In that four days, when compound Z is causing the pain, if you had blocked compound A on the day of surgery and prevented the cascade or attenuated the cascade, would that have lowered the pain later on? So that's where we'd like to go with this kind of research in the future.

In fact, when I was home at Christmas, I was thinking, the future is now. It's time to do those studies while there's still importance and do them quickly, so I'm going to try to conjure up some quick protocols. But there are so many things to do, because there's the gene-therapy study, there's the genetic study, and then the preemptive study. And there's the studies we're doing which we have to finish. There's this micro-crystal study and all these other things. But what I would hope to do this year is to take advantage of the fact that we're kind of past the point where we've suffered through our review, we've got all the papers out, so I'm hoping that we've got kind of a good group of people; you wax and wane sometimes in terms of how productive you can be based on who you have working with you, and right now I've got an optimum crew, so I'm hoping that we can be real productive over the next year or two.

MM: OK. Tell me about what you think is the most interesting stuff you've found in the last 10 years.

RD: I don't know. Nothing jumps right out at me, so that means either nothing is all that interesting or else I've done so many interesting things that –

MM: Endless.

RD: Yeah. Well, I like my stories simple, and I would still think the fact that you can show that having an effect on the nociceptive input during surgery has an effect on pain that occurs 48 hours later, to me is pretty amazing. And then to find that it's more related to the post-operative pain and inflammation rather than that intense barrage that occurs during surgery, I find pretty interesting as well. So I think that then makes this whole concept of looking at using the oral-surgery model to study what happens in the post-operative period and try and block that much more important and much more generalizable. So I find that pretty exciting and I'd like to pursue that as much as we can.

MM: So it really kind of justifies the whole sequence of studies that you've been doing along the way.

RD: Yeah, kind of. So it's gratifying as well as startling, you know. We once had some data we presented, and it was based on some work someone else had done, but we just used it in a classic clinical situation and reported that, oh, by the way, it turns out that this was true. And one of the guys around the table got this big smile on his face and he says, "You mean it was really true?" as if he made it up and he was pleased to find out it was true and said that. I couldn't quite figure out where he was coming from, but sometimes you get that sense. You know, you do all this work, you keep saying, oh, it's got to be important because of this and that, and then, boom, it actually turns out to be [significant]. You say, "Wow, that's amazing." Of course, you've got to have that kind of optimistic viewpoint, because once the reviewers send back an alternative viewpoint, and if you took their viewpoint seriously, you'd stop.

MM: Yeah. It's pretty demoralizing.

RD: Yeah. You'd find another field in a hurry.

MM: OK. So tell me about all these... I mean, you seem to have, constantly, new studies or new possibilities for studies if you stick around. You have to get all these reviewed before you put them into action?³⁴

RD: Yeah, but less so than you think. There is a process for doing any clinical protocol that has to have it approved to show that it's, first of all, scientifically sound, that it's safe, and that you're not going to be abusing the patients. But once you get past the process of doing that, you know, and how to do it, you can usually get most ethical studies approved. So then it's really a question of picking between the scientific questions, and it used to be, when you had a strong, authoritarian Branch chief, a lot of those decisions were made for you. Even though you still had the ability to say, "I want to pursue A or B," sometimes choice C was eliminated for you, or, "I really want you to do A, so I'll let you do B if you do A as well or if you do A first," that kind of stuff. But now we have a little more freedom to pursue it, so we can go do it that way. So then it's a question of just making your own intellectual best guess, and sometimes that works out real well and other times you waste time.

I did this thing recently where we did two studies where we showed that the preemptive analgesic effect seemed to be important. Then we did an effect with dextromethorphan, which supposedly was blocking the mechanism whereby this hyperalgesia occurs. And then I became infatuated with the idea that, well, if this works and morphine works and people say you put the two together and you get an additive effect, let's pursue it. We wasted an exhaustive amount of patients only to find out that it was like adding two grains of sand together and getting an effect of four and not getting a shovelful of sand. It was just such a small effect. And that's the second time I've actually had that happen to me, and on both occasions it was based on observations people made using experimental pain in extremely small numbers of subjects that smelled a little bit, almost too selected, you know. So it kind of made me realize that maybe I've got to be a little bit more cautious about pursuing every one of these little leads based on not only the

strength and the generalizability, but also maybe the people that published the preceding papers, that kind of stuff.

MM: So when you try to do a study, how many patients do you think – I mean, are you aiming for hundreds of patients?

RD: It depends on how many parallel [groups you need]. If I can do a study in 20 patients, I'd be immensely happy. In fact, in the good old days, I used to design the studies to be crossover studies within a patient,³⁵ and 20 patients was plenty to do a study. But it really gets to be very contrived because you can only look at one comparator and one experimental treatment, and you can't do much with different doses and stuff like that. So now we'll say, all right, we'll design the question to include the minimum of the standard treatment of the placebo, the treatment that we know works, and then one or two doses of the investigational treatment. Well, [you can] easily get up to four or five groups of patients that way, and when you do them between groups, then you know you need about 30 subjects to make it work. Then it's suddenly 120 or 150, and that looks like a six-month to an eight-month study. So that gets to be unpleasant to think that you'll go that long without getting it reinforced. So then you start trying to whittle it down and whittle it down, so somewhere between 75 and 100 kind of is the maximum size study you want to do to make sure you're not chasing after something that doesn't pan out in the end, yet you're not stopping short or you don't have enough control groups and that you can't interpret it. Because that's always very frustrating when you finish a study and it didn't turn out the way you planned it, and you left out that one control group to be economical, and now you don't know what happened or what the answer is.

MM: So you don't use crossover studies. A lot of the early studies were crossover studies.

RD: Yeah. The oral surgery model has the inherent limitation that you can only do that once, and then if you have four treatments, there are designs called incomplete block crossover, so you'd have, I think, four subjects in a block, and one would get treatment A first and then another one would get treatment B first, another one would get C first, another one would get D. You'd cross them all over, and at the end you would have a perfect comparison of one block, and then you'd repeat another block, and maybe by the time, after 15 blocks, you have a nice comparison. But one of the problems is that the first dose is the one that's randomized, and then for any given subject, the second dose isn't. So people say there are some limitations of that. And then, worse yet, if things don't work out exactly the way you predicted it, that these two treatments, A and B, C and D, are also going to be somewhat similar to each other in terms of efficacy, then you might end up with a comparison like this, and then you really can't compare across because one subject down here is being compared to one up there, and one here is being compared to one there, and it gets to be a statistical nightmare and people start to really complain a lot. So I've done the complete crossovers where it's just two treatment [groups], and I've done the incomplete block crossovers, had them not work, and then tried to say, "Well, these were just parallel groups," and then everybody says, "Well, they're not really parallel groups." So then you're back to using the first dose, and if you're back to using the first dose on parallel groups, it's just a non-crossover study again, and then you've

got – you know, it’s a mess. So if you have some condition that’s going to be continuous in a patient, then that patient can be crossed over and you can learn a lot, and that’s where some of the chronic pain studies do exactly that. But if you’re looking in the oral-surgery model, it gets to be very constraining to do that kind of stuff. And then there’s always the issue of the washout and carry it over and all that crazy stuff like that.

MM: I sort of asked you about NIDR and working here, and then we went someplace else. In terms of working with the sort of mix of people that have been here, people working on genetic studies and molecular biology and things, like Mike, and then other people working on what Ron was doing, which is supraspinal pain mechanisms. I mean, is this a useful kind of mix? Has it been intellectually provocative, or how would you characterize it?

RD: Yeah. It’s been an excellent mix because of the fact that it allowed you to have the – every question was examined from a different perspective. And you were always kind of thinking a little bit beyond your normal paradigm of how you viewed the world, because you had everybody else looking at it and telling you how it looked from their point of view. The only drawback is, it was hard to assemble the critical mass, because very often what makes a lot of progress on some little area, there’s a lot of people working very intently on it. And that’s the thing I probably miss the most here. There’s only been brief periods of time where I’ve been focused in on one or two questions with enough people to really address it aggressively, come up with a black-and-white answer, or at least a dark shade of gray, and then move on to the next question in the series and keep on going till you reach the logical conclusion. And the problem was that, because it was such a diverse group, there were just a fixed amount of resources, and up until the last few years NIH wasn’t set up to necessarily reward those people that are working hard and producing a lot of papers. It was kind of always a decision to be made by the prince of the kingdom, who was the Branch chief, and he allocated the resources how he saw fit. So you could be very industrious and not necessarily get the rewards that go with it. Now there’s an external mechanism that allows that to happen, and it seems to be sorting things out in that there’s not necessarily going to always be someone who does the supraspinal mechanisms. There’s not always going to be someone who does the cellular stuff and someone who does the molecular, someone who does the clinical. It’s going to be the survivors who will be doing what they do well, and then they may or may not be allowed to grow very big and then have their own little feudal kingdoms, or someone else might come in and say, “Well, that’s nice, but we don’t need any of those things anymore. What we really need is someone who’s looking at the molecular genetics of pain and rapidly translating what happens when some gene gets expressed and then does this, and that’s where we should concentrate all our efforts,” and there’s always logic for that too.

The other thing, though, of course, is the infrastructure has been built now. You know, it was only in the ‘70s when [John] Bonica³⁶ recognized the vast wasteland that pain research was, started trying to mark out the parameters of a discipline, so it matured during the ‘80s. And now, ironically, we look back at things that were done 10 or 15 years ago and say how archaic. But, in reality, you had to do those first before you got to

the next step, and maybe there's some historical pearl that everybody recognizes when they look at a field, but to me, we couldn't have done clinical trials without some ability to measure the pain; you couldn't have done it without some ability to have a good model.

You couldn't have done the clinical trials without someone doing the animal research that gave you the insights to do the clinical trials and stuff like that. So now we're at a stage where the technology is vastly improved, the questions can be addressed in a much better fashion. But if they invented the molecular biology of pain today and didn't have the infrastructure in place, we'd still turn around and say, "Hey, we need a model to study this in humans. We need an animal model. We've got to be able to measure it," you know. "What's going on here?" you know, that kind of stuff. So as long as everybody's comfortable with the idea that they're standing on the shoulders of giants, or at least a lot of short people, then it's OK.

MM: What else should I ask about? What am I not hitting on? I remember we talked about the work you did with Ken Hargreaves, on dexamethasone studies.

RD: Yeah.

MM: OK. I guess I'd like to go back a little, because I think, for the benefit of myself as well as for future people who might listen to the tape, I still want to get a better understanding of this kind of chemical cascade that occurs during pain. And I'm not quite sure that I could lay this out in any clear fashion. I know that when people experience pain, there's an endogenous production of beta-endorphins – at least we seem to think that there is – and that there's a cascade of chemical messengers that seem to both sensitize the nerves to pain as well as attempt to modulate the pain. Am I expressing this right?

RD: Well, I'm not sure whether we have a good handle on it, and if we do, it's one that I don't.

MM: Well, I've seen some beautiful diagrams.

RD: Yeah. Well, diagrams are easy to put together because we only deal with the stuff we know for sure, and [then we] kind of leave the rest out. Certainly, it seems that when there's a tissue injury going on in the periphery, that you get a cascade that gets initiated, like you talk about, that is primarily due to the cell that has gotten injured, releasing chemicals, such as arachidonic acid³⁷ leading to the prostaglandins, thromboxins, and leukotrienes, and that seems to be an attempt by the body to start the healing process, and part of the healing process is to immobilize or stop using the injured site. So pain becomes therapeutic in the sense that it keeps you from using [the injured limb or part]. Those chemicals also then help initiate the inflammatory response, which seems like it would be undesirable, but in reality, it's an attempt, again, to repair the damage, bring in the cells that are going to heal things up, but at the same time keep you from damaging it any further by making it painful.

So rather than, if you're an athlete and you get injured and it hurts too much to play, you're not going to keep playing on it; whereas if there wasn't pain, you'd probably play until the leg falls off, and you'd get a great lot of peer review or peer reinforcement for that. You just wouldn't play the next game, or it would be a year before you healed up. But then this input goes into the nervous system, and the body then has another attempt, which is to try to keep functioning despite the fact this message is coming in. So it kind of relays and amplifies it up to higher sites. But at the same time, there's an attempt at higher sites to say it's kind of, I guess, the equivalent of the ego, id, and superego trying to balance each other out, and in this case the body says, "All right, so it hurts, but we've got to get the hell out of here because we're in trouble." So then the message starts to be: let's send down some descending messages to inhibit the pain, let's do some hormonal things to inhibit pain, and that's where the endorphin release probably starts to happen. But also, it appears to be some participation in the events that are occurring by the fact that you get release of things like substance P³⁸ that only seem to be there to cause pain. And I don't know if we clearly understand why that's happening, but our guess is that that's part of the attempt to limit the use of the injured thing by making it too painful to keep on doing it.

Then there's probably just some malfunctioning of things that weren't necessarily designed to either be producing pain or produce analgesia, so that likely [if you] have an injury that's going to cause some anxiety for the organism, then that causes the release of epinephrine, norepinephrine from the adrenal gland. Well, that only would be – that's not really pain-related, but it certainly does fit in with the fight-or-flight type of syndrome and things like that. So part of the problem there is, then, also dealing with these other phenomena that are associated with the pain but necessarily aren't part of the normal pain process. And then again, in a teleologic sense, it's good to be geared up and have your catecholamines³⁹ secreting so you can run for cover. But it ain't doing us a lot of good if we're trying to treat someone and they're scared to death, and we can't get to do the treatment because they're afraid of the pain or afraid of the therapy we're going to give them to decrease the pain, that's going to eventually allow us to treat them and stuff like that, so it gets to be a complex process.

MM: Yeah, it does.

RD: Yeah. So the endorphin is probably a sign of pain, yet it's actually an analgesic mechanism. So when we see it and we say their endorphins have been elevated, it may be because they're hurting or it may be because the body is taking its physiologic step to decrease the amount of pain they're experiencing. At any given time point, when you look at it, you can look at a thing that has a time course that looks like this, and you take a slice across it and you might get a confusing story.

MM: Actually, that's pretty clear.

RD: Oh.

MM: In terms of explaining it to people who have not, who think about pain as strictly a neural response, which I think is still what mostly people see it as.

RD: Well, at the simplest level, it is, because you don't necessarily need a very complicated response. If you just get close to putting your hand on the stove, you feel it and you pull back. But then when you sizzled it, then it gets to be a more complicated thing, so, yeah, the simple neurologic part of it is kind of like a preventive, protective mechanism, but then once there's some injury that has occurred, then there's the reparative process, which requires immobilization as part of it – swelling to clean up a lot of stuff and bring in more cells and things like that. So in the long run, it all seems to make sense. And, in fact, it's almost like a myth of the field, but there was a study done way back when [showing] that if you inhibit inflammation in some situations, you get far less survival than if you allow it to maintain attack, because it's performing a function that's useful. I can't remember what – It was published in *Science*. They did – I think it was probably, give some kind of like a lipopolysaccharide that produces kind of a systemic inflammation, and in some of the animals, you inhibit the inflammation, and then you look at the number that survived, and the ones who had the inflammation inhibited were probably less swollen and in less pain as their body were overwhelmed by this septic process that had been initiated and would have been fought better by having an inflammation there. So I guess that's why you feed the fever, starve the cold.

MM: Laudable pus.

RD: Yes, right.

MM: Those old docs were right anyway. OK. Sort of another trope in the pain field is the individuation of pain, that each person responds to it differently based on a whole cascade of cognitive and affective factors. Do you observe this? I mean, when you look patients, do you see patients reacting differently?

RD: Yeah. It's the biggest factor there is, because we can do studies where we know we give them something that relieves pain, like morphine. I mean, I always thought morphine was it. You gave someone 10 mg of morphine and they're out of pain. And the first time we did a study where we were using morphine – and I can't remember what the highest dose was, but it was more than 10 mg – and some people didn't get any better, and other people did real well. And it almost didn't make any difference what we gave them, because some of the people who got the placebo shot did real well for about 30 minutes to an hour before they started to say, "Hey, that didn't work," and other people, you'd give them all the morphine you'd dare give them, and they'd just be blinking right back at you, "That didn't help me. I'm still dying, doc."

And the same thing, to a lesser extent, is true with Toradol,⁴⁰ because Toradol just happens to be given in such a dose beyond what's probably needed that if someone went back and redid the studies now, they'd probably conclude that 15 mg of Toradol is what should be released, and initially it was released in 60 mg. So it's pretty rare not to get it work. And if you give 30 mg IV versus giving it IM like you used to be, it's like you

expect everybody to get better now, at least for a while. And yet, when you give it to them, that fixed dose that you think works all the time, it's really the bell-shaped curve, and you've got most of the people are getting an effect and some get a little too much, and then there are some that absolutely have no response to it. And it's not always just a surgical procedure or the amount of pain they're experiencing. There's some just inherent variability that's huge going on there, and that's why we'd like to do more research on the genetics of pain. Even though it's going to be looking for a needle in a haystack, we've got some idea that there's a difference in the way people respond.

One simplistic possibility is that someone might mobilize more endogenous opiate things to block it, or there might be some reason why they manifest less inflammation or toxicity associated with the injury, or it might be all at the higher cognitive functions, that they just take that level of pain and read it as no pain or less pain or escape or relief, you know, all the various stories that have been told. So that's probably the biggest factor, and that'll be the next generation's interesting story to tell, will be how they identify what those factors are and how you then block them to get drugs. And it's going to probably be as crude as Von Euler in the '30s finding some strange substance in the semen and calling it – I think it had something to do with the prostate, and that led to prostaglandin; and then in the '70s, people were screening for things that inhibited this because they now recognize that that might be analgesic, and still it was going to be really an anti-inflammatory, and then when they gave it in an analgesic situation, it worked. Everybody was like, "Oh, that's unbelievable!"

So somebody right now is doing some genetic study that's identifying some screwball thing, unknown gene or a gene that releases something that we didn't know had anything to do with pain, and yet it seems to be related to variability. So once we're convinced that's true, then we start finding out what it does and then we start finding out what happens if we either augment it or block it. And then once we find out that that's important, then, depending on which direction it's going, then they'll start making up thousands of little molecules just like it and see which one's the best for either blocking or augmenting the response you're getting, and then that leads itself to finding a non-peptide that looks like that to then having a drug you give. And then, with great hoopla and expectation, the next wonder drug will come along, and it'll work. It just won't work as well as everybody thinks it is, because it'll be one of 20 factors or a hundred factors or something like that.

MM: OK. So I'll ask you again, is there anything else we should talk about? Anything in the last few years that's really sort of come to your attention that's been interesting?

RD: Well, I guess I have a bias that clinical research is a lot more important than people give it credit for, and I recognize that without basic research, without R&D, there is no clinical research. But I think without clinical research, there is no impact to all the stuff that comes before. It's nice to think that we do all this stuff for, to build that little pyramid of knowledge that, at the peak, is the one thing that's useful. But I think you need more of the people doing the good applied research to figure out what works and what doesn't work, at the very least to get feedback to the smart guys that are doing the research at the

bottom that's building that body of knowledge. And I think it's been belatedly recognized to be important, and yet, still, it's mostly lip service being given to it. Everybody's beating their breast, saying, "Yes, we've got to reinvigorate clinical research. We have a crisis in clinical research. But, boy, I'd much rather have a guy who can do molecular biology in the laboratory than I would rather have one of those guys who does clinical research." I think it's going to take – something's got to happen to really change that way, and I'm not sure whether we want to wait 10 years while people trickle through programs that are just being created now, to finally get their feet wet three to five years from now, to finally contribute something 10 years from now, but it may be the only choice we have.

MM: Is it hard to recruit people?

RD: No. It's hard for them to survive once they get out. You've really got to take the – you've got to be first. Someone gets reinforced with, you know, they've got to be a long-distance runner. You're never going to run the hundred-yard dash in clinical research and, at the end, have solved the question or feel like you've accomplished something. And you almost have to do it by ignoring the fact that everybody around you is doing the hundred-yard dash or the 440 and getting a lot of applause while you're plodding forward towards the finish line, you know. It's really a slow and difficult process.

MM: A high degree of frustration.

RD: Yeah. And a lot of times you go three miles, only to find that that was the wrong turn, so then you've got to run back three miles and go off the other way. And you can do that in a laboratory a lot quicker because there's always a hundred more rats you can order next week and then quickly find out what's going on. But if it's six months' or a year's worth of clinical research that just led you up a blind alley, then you've really got a problem. So I think clinical research is probably more important than it ever was. It's still somewhat neglected, and if there isn't something that happens that reverses it and truly makes it – Clinical research, I've seen a lot of people come along lately who talk the talk but then really try not to walk the walk. They say it's important and they say, "Yeah, I'm going to do clinical research, but meanwhile I'm going to go into my laboratory and finish up this experiment. I'm going to hustle down to the library and read some stuff, and we'll take that first-year fellow and let him do the patient stuff. As long as he gets those samples back to my lab, where I can really do some clinical research on them, everything's okay."

MM: It doesn't work.

RD: It ain't gonna work.

MM: Have you been encouraged by all this movement toward evidence-based medicine?

RD: Only in the sense that, why did it take that long? I mean, I thought that's what we were doing 20 years ago when we started saying, does this drug relieve pain? I mean, I

thought that's what Beecher did before. That was his contribution to the whole thing, was not only as a pain researcher, but saying it has to be based on evidence, you know. If the placebo response is 30 to 50 percent of what you're getting, and the analgesics don't really work more than 50 to 60 or 70 percent of the time, half of your effect is make believe, and yet how can you just give prescriptions to patients and make generalizations on whether they work or not? So I'm horrified to think that it took this long, but the problem is that then, when people say, "All right," at least the academics say, "I believe it," then they go back and look at the database to examine the questions, and there's nothing there.

MM: There's no evidence.

RD: Which is why you need more clinical researchers to do more good studies so that they'll have more evidence that then you can make intelligent judgments on. And right now it seems like we're skipping that step.

It was almost like when I first came into the field in the early '70s, there was a perception then that we needed more good basic researchers to really do good basic research, and then that would trickle down to being better dental care and better medical care, if you did good basic research. And all those people that came through that had great hopes of doing that all got sucked up into being deans and administrators, because they were the leaders of tomorrow because they were the ones who had these unique credentials. Well, they didn't accomplish anything by being in an administrative suite somewhere. And then when they emerged on the other side of their 20-year academic or administrative career, you don't go charging into the research environment at the age of 50 or 55 and get anything done.

So I'm afraid what's going to happen is we're going to have a lot of people that are going to come along, you know, beat on their breast, it's important that we do evidence-based care, and they'll have the capacity for doing it, and yet they'll quickly become the people on the talk circuit, the ones that write the textbooks, the ones that become the deans who actually then keep that database small because no one's actually doing it. Maybe that's human nature, but, still, it's kind of frustrating to see it.

MM: The other problem is that clinical studies are so expensive. I mean, they tend to be expensive. They take a long time.

RD: Yeah. They can be in some circumstances. But if you go to like a dental school that's treating 50,000 patients a year and you don't know which of those restorative materials is truly better than another one, well, you can do a clinical trial almost for nothing if you set up a design and go out and try to answer those questions.

And so if you're a TMD person and you're the only school in the state that's getting all those patients, rather than just taking some treatment that's already in the books and memorizing it and giving it to every patient who comes through, why don't you say, "All right, all those who fail those treatments, then I'm going to try to do an experiment on those, and I might only get 50 a year, but if I do that for the next 20 years, I'm going to

have 50 studies to publish or 20 studies I will have published?" I would have done that job anyway, but I would have contributed much more to the next generation by doing it in a controlled fashion. So that's what would be nice if we did it that way.

MM: Yeah, it would be nice if we did it that way. I mean, this is the same story that people were talking about in the '60s, when the FDA started saying, "We need better evidence for drugs." So they started looking at the literature and there wasn't any.

RD: Yeah. It took them, unfortunately, almost five to 10 years before they came up with some guidelines that said these drugs are probably effective, we'll leave them like they are; these drugs are probably ineffective, and we're going to get them off the market. And then there's all these; we don't know whether they work or not, and we're going to give everybody a few years to show proof or get them off the market. Ten years went by before they pulled some of the drugs off the market, and in some cases the research still hadn't been done. I mean, I was involved with one where I testified, and that drug had been five to 10 years past the point where the FDA had said, "Put up or shut up," and they didn't bother putting up because they just kept marketing the same old thing, and then finally the FDA came along and said, "Listen, it's gonna be gone now." They pulled it right off the [market].

MM: Actually, the DESI ⁴¹s still going on. They're still closing out the results of the study they did in the 1960s, trying to establish if X drug has any evidence at all to show that it's any good for anything. I don't know, the last time I looked, [there were] 10 or 20 cases that they were working on.

RD: Really.

MM: Yeah.

RD: It's amazing.

MM: Well, the wheels of government grind exceedingly small and take forever.

RD: Yes, yes. Proof right here.

MM: Well, I guess that's all I have to ask right now.

RD: OK. Well, thanks for asking. It was a lot of fun.

MM: Yeah, it was. OK. So we're completing this interview at five after four.

END OF INTERVIEW

ENDNOTES

¹ William T. Beaver pioneered the comparative study of analgesics in the 1950s, working with Raymond Houde and Ada Rogers at Memorial Sloan-Kettering. He joined the Pharmacology Department at Georgetown in 1968 and was for many years a consultant to the FDA on analgesic drugs.

² *The Pharmacological Basis of Therapeutics*, edited by Louis S. Goodman and Alfred Gilman of Yale University, was first published in 1941 and is considered the standard reference work in the field. The 12th edition was published in 2011.

³ Barbituric acid, discovered by Adolf von Baeyer (who named it after Saint Barbara) in 1864, is the parent compound of the barbiturate sedative drugs.

⁴ William L. Dewey was Professor and Chair of Pharmacology at Virginia Commonwealth University in Richmond as of 2014. His research focused on drugs of abuse.

⁵ The mag cards of the 1960s and 1970s were early word processors that read data off magnetic cards (similar to credit cards). The IBM Mag Card II had an 8,000 character memory, corrections capability and a card reader able to handle a pack of 50 magnetic cards. The machines were very popular in business and academia until replaced by PCs in the 1980s.

⁶ Louis S. Harris was Professor of Pharmacology at Virginia Commonwealth University in Richmond as of 2013. His research focused on the relationship between chemical and biochemical factors and pharmacological actions of drugs affecting the central nervous system.

⁷ Henry Knowles Beecher (1904-1976) was a pioneering American anesthesiologist who made significant contributions in pharmacology, analgesia, medical ethics, as well as his own field, during his 40-year career at Harvard University Medical School and Massachusetts General Hospital. His analgesia studies of the 1950s elaborated the concepts of “the reaction component” and the placebo effect.

⁸ David J. Mayer is best known as the lead author of a 1971 study documenting endogenous analgesia in the rat brain. (Mayer DJ, Wolfle TL, Akil H, Carder B and Liebeskind JC. Analgesia from electrical stimulation in the brainstem of the rat. *Science* 1971 Dec 24; 174: 1351-1354.) This work is discussed further below. Dr. Mayer continued his pain research at the Medical College of Virginia for 30 years.

⁹ Dr. George L. Wilcox is now Professor of Pharmacology and Neuroscience at the University of Minnesota Medical School.

¹⁰ Periodontics is the study of the diseases of the supporting structures of the teeth, including the gums, the alveolar bone, cementum around the root, and the periodontal ligament. Prosthodontics is the dental specialty that focuses on the design and creation of prosthetics to replace missing teeth and other dental structures. Orthodontics refers to the study and treatment of malocclusion, or improperly fitting teeth bites.

¹¹ The third-molar-extraction model refers to the use of wisdom tooth, or third molar, extractions as a model for the study of dental pain and analgesia.

¹² Edward Driscoll, as Chief of NIDR's Oral Medicine and Surgery Section, began conducting studies of dental anesthesia in 1957. His aims were: to establish the necessary baseline physiological data; to evaluate the effects of stress on the dental patient; and to find the best methods of alleviation. With his associates, he performed full mouth extractions on more than 1200 patients, and collected readings for pulse, blood pressure, respiration, arterial oxygen levels, EEG, and EKG. See: http://history.nih.gov/exhibits/pain/docs/page_02.html.

¹³ The lipid compound prostaglandin E-2 excites autonomic neurotransmitters, as well as inducing uterine contractions in pregnant women and stimulating other types of physiologic activity.

¹⁴ Dionne RA, Campbell RA, Cooper SA, Hall DL, Buckingham B. Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. *Journal of Clinical Pharmacology* 1983 Jan; 23: 37-43.

¹⁵ Cyclo-oxygenase 2, or COX-2, is an enzyme that acts to stimulate the production of prostaglandins and similar compounds, causing pain and inflammation among other effects.

¹⁶ Ronald Dubner (1934 -) was Branch Chief of Neurobiology and Anesthesiology, later Pain and Neurosensory Mechanisms, from 1974 to 1996. He pioneered studies of pain in behaving animals and has been a leader in pain research throughout his career. See: http://history.nih.gov/exhibits/pain/docs/page_05.html. Since 1996, Dubner has been Professor of Pain and Neural Sciences at the University of Maryland School of Dentistry.

¹⁷ Candace B. Pert (1946-2013) was an American neuroscientist best known for her co-discovery of the opiate receptor, the cellular binding site for endorphins in the brain, while completing her graduate work with Solomon Snyder at Johns Hopkins in 1972. Her research in her later career focused on the neuropeptides and their role in the immune system; she also wrote extensively on holistic and alternative medicine. She was a section chief at NIMH from 1983 to 1987, when she left to found a private biotechnology laboratory.

¹⁸ Daniel Laskin (1925 -) is one of the leaders in the field of oral and maxillofacial surgery and the long-time editor of the *Journal of Oral and Maxillofacial Surgery*. He has been a faculty member at the Medical College of Virginia since 1984.

¹⁹ <http://www.dbc.ca.gov/lawsregs/laws.shtml> .

²⁰ Dr. James Friction as of 2014 was Professor Emeritus of Diagnostic and Biological Sciences at the University of Minnesota School of Dentistry.

²¹ As of 2014, Gregory Mueller was Acting Associate Dean of Graduate Education at USUHS.

²² The periaqueductal gray in the midbrain is the primary cortical control center for pain modulation. This was the area identified by Mayer and colleagues in 1971 (see note 8).

²³ See: Pert A, Dionne R, Ng L, Bragin E, Moody TW and Pert CB. Alterations in rat central nervous system endorphins following transauricular electroacupuncture. *Brain Research* 1981 Nov; 224: 83-93; and Dionne RA, Mueller GP, Young RF, Greenberg RP, Hargreaves KM, Gracely R and Dubner R. Contrast medium causes the apparent increase in [beta]-endorphin levels in human cerebrospinal fluid following brain stimulation. *Pain* 1984 Dec; 20: 313-321.

²⁴ Dr. Kenneth M. Hargreaves is Professor and Chair of the Department of Endodontics, and Professor of Pharmacology, Physiology, and Surgery at The University of Texas Health Science Center at San Antonio as of 2014.

²⁵ Naloxone is the primary opioid antagonist and will also block the action of endogenous endorphins.

²⁶ Adrenocorticotrophic hormone (ACTH) is a polypeptide hormone produced by the pituitary gland. ACTH is often produced in response to stress, and acts by stimulating the production and release of the corticosteroids.

²⁷ CRH, or corticotropin-releasing hormone, is the precursor of ACTH and is produced by the hypothalamus.

²⁸ Patients specify their perceived level of pain on the visual analog scale by indicating a position along a continuous line between two end-points (“no pain” and “worst imaginable pain”).

²⁹ TMJ, or temporomandibular joint syndrome, more correctly TMD, or temporomandibular disorder, is a painful condition in which the muscles moving the jaw and connecting the jaw to the skull become stiff, painful and dysfunctional. TMD often becomes chronic and intractable.

³⁰ Dr. Charles S. Greene was Director of Orofacial Pain Studies at UIC College of Dentistry as of 2012. He is a nationally recognized authority on TMD.

³¹ The kappa-opioid receptor is one of four related receptors that bind opioid compounds in the brain and are hypothesized to be natural addiction control mechanisms. KOR agonists are analgesic, but also cause side-effects, including dysphoria.

³² Pentasa is a controlled-release brand-name formulation of mesalamine, an anti-inflammatory aminosalicylate.

³³ Flurbiprofen is an NSAID compound marketed as Ansaid by Pfizer and mostly prescribed for arthritis.

³⁴ Dextromethorphan is an NMDA-receptor antagonist, most widely used as a cough suppressant as in the OTC drug Robitussin. It is a dissociative hallucinogen at high dosages.

³⁵ The same patient would take both the experimental and control drugs according to a randomized protocol and act as his/her own control. This was the methodology used by Houde and Rogers in their analgesic studies.

³⁶ John J. Bonica (1917-1994), widely recognized as the founder of the pain field, was Chair of Anesthesiology at the University of Washington for much of his career. He edited the first edition of *The Management of Pain* in 1953, founded a multidisciplinary pain clinic at UW and convened an International Pain Symposium in Issaquah, Washington, in 1973, which catalyzed the formation of the International Association for the Study of Pain.

³⁷ Arachidonic acid is a polyunsaturated fatty acid and a key inflammatory intermediate; it is also involved in cellular signaling as a second messenger and may act as a vasodilator.

³⁸ Substance P is a peptide neurotransmitter, discovered in 1931, that appears to play a key role in the sensory perception of pain.

³⁹ The common catecholamines are epinephrine (adrenalin), norepinephrine and dynorphin.

⁴⁰ Toradol is the Syntex brand name for the NSAID ketorolac, indicated for short-term management of moderate to severe pain.

⁴¹ The FDA began the Drug Efficacy Study (DES) in 1966, after the passage of the 1926 Kefauver-Harris Amendments to the Food and Drug Act empowered the agency to mandate the efficacy, as well as the safety, of marketed drug. Nine expert panels were formed to review drugs on the market prior to 1962 and determine whether there was sufficient evidence to support their efficacy. After the panels completed their work in 1969, the DESI phase (Drug Efficacy Study Implementation) began, as the FDA sought to remove more than 1000 drugs with insufficient proof of efficacy from the market in the face of determined opposition from manufacturers. Although many such drugs have since been discontinued, proceedings against some products were still pending as of 2014.