RICHARD GRACELY ORAL HISTORY INTERVIEW
December 18, 1998
Interviewer: Marcia Meldrum

MM: It's December 18th, 1998, and we're sitting in the NIH History Office, recording an interview with Dr. Richard Gracely.[1] We want to start out with just vital statistics. Tell me about where you were born, when you were born, how you grew up, how big your family was, that kind of thing, what your dad did?

RG: OK. I was born January 23rd, 1949, in Hamilton, Ohio, a small town, manufacturing town in between Cincinnati and Dayton, Ohio. I was the first of five children. I was actually followed in 11 months by a sister and then twin sisters. For most of my life, I had three sisters and myself, in a little tiny two-bedroom Cape Cod tract of many similar [houses]. My father was an engineer for General Electric, would go down there every day, and he was an engineer. He suddenly had this family, and then we thought we needed a bigger house, because he always said that he actually converted the attic of the house, a bedroom for my three sisters. He ultimately bought a lot in a very nice neighborhood in the town and then decided he wanted to build his own house. During these plans, my mother became pregnant again, and this is going to be the fourth sister. I was ready to leave, but it turned out to be a brother who is 13 years younger than me. So now there were five children in this little two-bedroom Cape Cod, and then we did build a house.

I'm perhaps giving you more than you asked for. But it was very interesting. Actually, for me, I was 13. You know, we started out with this thickly wooded lot, and we would survey it together, which means he would sit there with a transit[2] and say, "Son, see that tree over there. Take this tape and walk straight to that tree," and I would be, with a machete, working through sticker bushes, cut and bleeding, while he'd be drinking a can of beer, and then we would do all this. We surveyed it and then we actually cleared the lot, which means I was chopping down trees and trying to chop off my feet and otherwise clearing this whole thing by hand. And then they dug a big hole of excavation. They made a mistake, and so he actually dropped me off in this hole in this morning on his way to work with an old [sandwich] cooler for bread and water and some bologna – no mustard. "Dad, you know, how about some Twinkies or something?" And I would sit there and dig and expand this hole till suppertime, when he picked me up again. And then there were other jobs. Then there was, after the foundation was poured, the walls go in first, there were 600 tons, 60 tons of pea gravel put in one corner, so he gave me a wheelbarrow and a rake and a shovel and he said, "Spread this out eight inches thick." And that's the worst job, because when you shovel pea gravel, you put your shovel into it and pour it out, it all rolls down, so it's like nothing ever changes.

MM: Oh my gosh, like Sisyphus.[3]

RG: Yes. It's pulling that boulder up the mountain. That was pretty bad. Then we went on, progressed to wiring the house, putting up the roof. I did – we only hired very few subcontractors, so I had to do all these things. After four years after toiling on this, it was a magnificent five-bedroom monster. We lived in it one year.

MM: You built it yourself.

RG: Yeah. And then we lived in it one year and he got a job in Philadelphia. We lived in it for one more year without him and then we moved to Philadelphia. So we lived in it basically – he lived in it one year, we lived in it two years.
Then I moved from Ohio, which at the time, the middle '60s, was kind of an oppressive place to live in a way, you realized later, a very caste system. People tend to have their noses in their neighbors' yard, and the relatively freedom of Philadelphia was actually very exciting for both myself and I realized also for my parents. So we lived in the Philadelphia suburbs and I finished [high school]. We moved at Christmas break my junior year of high school. So I had like six weeks of being the new kid in school, then one senior year in Philadelphia, and so that was my high school experience, and that was kind of fun, actually. I was ready to leave Ohio. I didn't know why, but I realize now it was a very, very different social scene, a different kind of life than being in the Midwest, so it was good.
There were three social systems in high school in Ohio at that time. The stars were the athletes who wore letter sweaters, and then there were the nerdy students, and then there were the hoodlums. And actually sort of, I was in all three. I played football and I was one of the best students in the school. Of 500, I was like in the top two or three always. Actually, I should say I turned my life around. I was a lousy student and then I got in trouble with somebody and I was grounded until I got on honor roll, and then during eighth grade, I suddenly realized that if you get really good grades, you can get away with anything. So my grades shot right up to the top of the class, and I was always in the top two or three of those 500 ever after. But I also was running around with some rowdy elements too and got in a lot of trouble. But there was nothing [very serious].

Then when we moved to Philadelphia, nobody cared about sports, so the athletes were not the stars. The good students and the hoodlums kind of merged in this leftist intelligentsia class, so that was a more comfortable place to be in. But I still played sports, but it was a very different scene.

MM: Yes, I know. It all sounds really familiar. I grew up in Indiana.

RG: Yeah, OK, similar. Actually, my parents didn't even want to go back. It's very funny. I was really amazed that they just – I could see that, you know. Where they lived in the Philadelphia area, nobody really cared what anybody else did. That was the biggest thing, I think. So it wasn't so much it was conservative. For example, I lived in Takoma Park [Maryland] here for years, where there's a big Seventh Day Adventist presence, but they just keep to themselves. They don't seem to proselytize. So that was a good thing for me, I think. Then I graduated from there and went on to school at Brown [University in Providence, RI]. Why I wanted to go to Brown only, I think when I was in Ohio, is because another football player friend went and it seemed like a neat place. I didn't have a clue of where to go or why I should go anywhere. But I did end up there. And was very good in math in high school, I won all these tests and scholarships and things and went in as a math major, and that didn't last very long. I know that's the next stage, going to the university.

MM: So let's talk about that. So what was your thinking about math and science during this period? What were your career ambitions?

RG: It was definitely medicine. Actually, back in high school, which actually is another little interesting [and] very important story, which I skipped, I wanted to be a doctor. I always wanted to be a doctor; I was really excited about medicine. I was really high – good grades in biology and mathematics, physics. I got sort of the top of my high school in all of those areas. I was [great on] achievement tests.

I actually was an orderly in an ER, [at] Bryn Mawr Hospital, Bryn Mawr, Pennsylvania, where Marilyn Monroe was born. I worked there nights and weekends. I was on the floor in the ER, sometimes worked double shifts, and I worked there for a year and a half. As a matter of fact, I got a job within half a year of moving there, and for the whole year I worked in this hospital. But I was getting paid $1.60 an hour, and finally I just needed more money. They refused to give me any kind of raise, so I finally quit and got a job working on a road-construction crew. I was putting in sewer pipes in an older neighborhood. This is after graduating; I made this switch in the summer after graduating from high school. I was going to go to Brown in the fall, so I was going to spend the summer working this road crew.

Six weeks after I started, it was just a comedy of errors, but a friend of mine driving a pick-up truck came around the corner, and the end result is I ended up being run over by the truck. My legs were run over by the truck, and, actually, I'm not going to describe the details of how it happened, for whatever reason. Let's just say it was both my fault and his fault, but in any case, probably more my fault. I ended up with two broken legs. But the accident was a very amazing experience, because I wasn't – just basically my legs and my hands – he ran over my hands too and didn't run over the rest of my body, but the force of throwing my body down by the wheels sort of broke both my ankles and messed my knees up. I'm laying there in pain, screaming. I mean, I didn't know what was wrong. I kind of went into shock. The top of my body was in a yard and my legs were in the street, and my back was arched, so I really couldn't see my feet. When I finally looked down at my boots, and the tip of the left boot was against my shin, and then the right boot – I was laying on my back – was sort of pointed to the right flat on the ground. And I said, "My God, the thing knocked the boots off my feet." Then I got up and said, "Oh my goodness, they're still tied on." This guy gave me a cigarette to smoke, and I [had a scruffy] beard, and I was full of dirt because I'd been digging and stuff. And then the ambulance came and they said, "You've got to put out that cigarette. There's oxygen here." So I put it out against the side of the oxygen tank and it broke. I'm still holding it in my mouth. I got taken into the very same ER that I used to work in, where I knew everybody. Everybody's, "Oh!" So that was really hilarious. So they said, "We told you you shouldn't have left." So I ended up being in the same hospital I worked in, knew everybody, and that was a very interesting experience. That was a very interesting experience. I was in a wheelchair for several months. I didn't do any walking without crutches or anything for almost five months, I think. So that first semester I didn't go to Brown University. I went to Villanova [University],[4] a local school. Friends from high school who were afraid to leave town and the high school area would drive me to Villanova, and they had wheelchair access. That was a whole interesting thing we might want to go into, but I spent one semester at Villanova and then I did arrive at Brown for the second semester with orthopedic shoes on, still not walking very well.

Also, socially, it was an interesting time because a lot of the social groups had been formed and I was a stranger. I didn't come in with the freshman class. But, more importantly, I missed – most of the pre-med courses were year courses, so I couldn't take any of those. So I took these ridiculous courses that first half semester, and then starting in my sophomore year, when I finally made some [friends], socially, and got into this really neat, kind of the neatest social club. It was a fraternity, but it was national. At the same time, I had to take all the pre-med courses at once, and also I was socially getting involved finally with people I really liked, and so I was burning the candle at both ends. I [took] physics, math and biology and chemistry, everything at the same time. And I did a movie, I did independent study in art, and the result is that I scored above the median of my peers, which were nothing but people at 800 on the Board [exam]s in chemistry, being the chemistry majors or pre-meds, and I scored better than them, these people. But, because Brown was so ridiculously grade curved, I would get Cs on a lot of my things. Even though I was above the top half of that student class, that wasn't enough. And I was so, whatever. So most of my pre-med courses, I didn't do that well in. After that year, I ended up getting As and Bs pretty much, working really hard. I got very interested in psychology. At the same time,

some of my friends, who really weren't that bright, who were getting Ds in the courses, would bail out and go to Harvard in summer school and get As for the same work. So the end result was, at the end of my undergraduate time, I didn't get into medical school right away. And that was a real – that was very depressing.

At the same time, I had made a lot of friends in the Psychology Department, and a professor there, John Corbit,[5] who was a physiological psychologist, who I really liked, said, "Why don't you just come work with me? I'll let you be my graduate student. I really like you, and if you like, I will make arrangements." Another professor in biology said, "I'll make arrangements for you to get into medical school next year." So I had arrangements, and basically it was credible because I started psychology. Brown only had five graduate students [in psychology] that year, and I became number six, and I kind of got shoehorned in without ever applying. When I entered, there was already a group of professors who were sort of annoyed. My advisor was the youngest full professor ever there to get tenure, and he just sort of pushed me on to the department. But I also had this idea that I was going to do it for one year and then go to medical school. And that was already arranged. The place I had acceptance worked out there, so that was my plan.

MM: So where were you going to go? To Brown still?

RG: No. Medical school… Brown, I went to Brown in psychology. And also, they have a policy to never accept an undergraduate [to medical school], so I was in the Brown Psychology Department. I was going to go to the University of Oregon and work with a guy named [William] Montagna,[6] who did monkey work and skin work, and I had worked with a guy, [Walter C.] Quevedo, I had done independent study with doing some skin stuff. My honors thesis was in human genetics; it actually was in rodent genetics, and I just enjoyed that. I did work in it, but I just dropped it then. So I had this early interest in genetics. So I started graduate school and I just really liked it. I liked it a lot. And also, financially, my parents I think were stretched thin to get me to Brown in the first place, so I was actually financially independent now and I had student loans or whatever. I was actually making a little, $280 a month or something. I didn't know how I was ever going to pay for med school. So I ended up, after the first year, staying the second year and getting a Master's. And there again – there were sort of two camps in the department, but most of the professors, I think, really preferred that I leave after my Master's. But then I worked for some of those professors. There became a time where I could continue, and there was a big meeting and I basically was allowed to stay to get my Ph.D. But there was still this sort of lingering feeling about me by certain unnamed people.

MM: Were you the only student? I'm sorry. You said there were only six students. You mean in the Department.

RG: That year, so it's a very small – And I changed. I did physiological – I did this guy's research the first year also. I had a progression [experiment], physiological studies in monkeys on thermoregulation, so it involved motivation, it involved making them too hot or too cold, and then they would –

MM: So they would do different [behaviors].

RG: They were pressed [to respond to] either changes in the air [or] temperature changes. We had these little pipes of water running through the hypothalamus. That was the idea. This guy Corbett had done this work in rats, and now we're going to try it in monkeys. They would work for these different rewards. Temperature is very nice because both your reward and your motivation [are] the same units of temperature. It's very elegant. But we had trouble. I was working with squirrel monkeys, and we had

troubles getting them trained, and sometimes they were very fragile, sometimes they'd get infections and die. And not much came out of that. The next year, my advisor went for a year's sabbatical, so I shifted gears. I went up from physiology, I went to animal behavior with Russ Church,[7] who's a very well-known animal behaviorist in terms of punishment. So his whole expertise was in negative reinforcement, you know, shocking rats basically and looking at escape and avoidance behavior. So my master's was actually in the whole aspect of shocking rats and the behavioral thing. I had all this animal experience and it was always on the negative side. But then I just became interested in human things. I still wasn't going to medical school yet. I was still pursuing this. So every year I switched, and so I [worked with Church] for a year, but then I decided I wanted to do human work, so this very nice Norwegian, Trygg Engen,[8] who's from Norway but he's been in the department a long time, a human psychophysicist, became my third advisor the third year, and I wanted to do pain work.

I decided I wanted to do something that's medically relevant. I didn't want to do something that was academic. I still had this sort of [plan that] I was going to go to medical school someday. So I arranged to do my thesis, after I got through this hurdle of being permitted to do a thesis, at a local hospital, which is Miriam Hospital [affiliated with Brown], and this is prior to the behavioral medicine program at Brown University, which really began [after that]. I was one of the first students ever to have any work outside of the Department. I was [living] down the street and I would go to this hospital every day. That work actually progressed kind of slowly. It was getting going, but I had troubles getting patients. I set up this lab.

MM: And what were you getting patients to do? Was this the pain measurement, or was this something else?

RG: Yeah. I was doing pain measurement. Well, we were doing a couple of things. I was doing a signal-detection[9] study because I was very interested in pain measurement, so I was reading up on all the signal-detection literature, which has some bearing for some issues in pain. One of the exciting fields of pain was the whole signal-detection controversy that erupted years ago.[10] But I was also looking at evoked potentials.[11] I was going to do some evoked potentials and some conditioned emotional responses. I had this idea that – and probably it would still be valid today – that if you looked at a GSR response in a normal person, you get these nice big responses [and then they would begin to] habituate.

MM: Galvanic skin response.[12]

RG: Yes.

MM: Remember, not everybody is going to know.

RG: Galvanic skin response. And the idea is this. It's kind of like Pavlov's dog with a bell and meat powder, but in this case you have tones that you pair with electrical shocks, and then you give the tones alone and we have an electroencephalograph [so] we're measuring this change in electrical skin resistance. Actually what you do is get almost a microperspiration in this response and it lowers your resistance. And the idea is that in normals, [the change] would be pretty big because they're really not that anxious. But in patients who sort of have a lot of pain, their sympathetic activity rises up partway to the ceiling, so if you measure their response, it's reduced because it's already halfway up to the ceiling anyway and it can only go up so far. So if you measure the spontaneous fluctuations, which are usually big, versus their little ones, the ratio is that they're evoked, and these spontaneous fluctuations are due to pain, that they would be bigger than the evoked responses. Well, in a normal, they'd be the opposite, so that was my thesis I was setting up. I'd run a few people, and I was also working on signal detection of a few other pain-related things.

So at the time I'm doing this, I'm also rebuilding a wooden sailboat, which I still have, a Cape Cod cat boat, a really nice sailboat, which all the – everybody at Brown University, the professors had boats. So the boat thing didn't bother them, they said, but a grad student shouldn't have a wooden boat. A grad student should have a fiberglass boat, because wooden boats are too much work. And actually they were right. That boat is still too much work.

But, in any case, I'm building this boat and I'm working on my thesis. It's a great summer. And a letter arrives, actually, at the beginning of the summer, from Ron Dubner.[13] Two letters were sent, one to my advisor saying I have this job for a PhD in psychology and pain, talking about the program. He was just getting here to NIH. This is the spring of '74. One was sent to the Department. And I don't know if this should be in the history, but it was just a fascinating thing for me. So [Trygg Engen, my advisor] said, "Look, this is the perfect job for you. I'm going to write you a letter recommending you for this job." I said, "But I'm not a PhD." He said, "But you're interested in this area, and next year you would be, so big deal. This is your area. This is perfect for you." So he wrote this wonderful letter, which I could never even have written for myself.

Then there was a sign up in the common rooms of the Psychology Department there saying, "If anyone's interested in this job, please see the chairman and I'll write you a letter." So I walk into the chairman and I said, "I'd be interested in this letter." But he was one of the old guard who never liked my being shoehorned in in the first place, you know, and he sat down and really just sort of was very dismissive of me. He said, "How could you?" He said he can't believe I had the chutzpah to come in there and even ask him. He said, "You're not a PhD. This is a job for a PhD." He says, "I have two excellent candidates here, and they're actually both animal people that have been left over from the year before." They were sort of animal people, and the reason they were there was because they couldn't get a job. And he said, "But both have published; you haven't published. They have an excellent chance of getting this job. I've written letters for them. I'm very confident one of them will get the job and I won't waste my time writing one for you because you don't have a prayer." He just basically told me to leave his office. And I got the job anyway. Bottom line is, I got the job.

MM: Because of Engen's letter.

RG: Yeah, partly because of Engen's letter, but also, Engen was right. I came down for an interview with Ron Dubner, and what was important to Ron was that you were interested in the field. I had read all the literature on pain measurement, and amazingly, Ron Dubner had too. The one thing about Ron was, all through the years, until near the end, when it got really big, he would be your best collaborator and colleague because he was right up on the issues as much as you were. There was nobody else I could talk to. And yet he was up on all these other issues too. He was truly amazing. So we had this tremendous talk, because it turns out he could never talk to anybody about measurement like he could talk to me. We just meshed so wonderfully on the issues and what I wanted to do, and he was just excited. I got excited. So it was very exciting being here. Then the next day he said, "Yeah, I'd like you to come." Then he said, "Look, Rick, I know that you probably want to finish your thesis at Brown. You've got it going." He didn't know that my output hadn't been that great because it really was hard getting patients and getting it going there, and I was also building a sailboat. And he said, "I would like you to not do your thesis there, just basically throw all that away," which he didn't realize wasn't that much to throw away, "and start over again here and do your thesis here. What do you think?" I pretended to think for a moment. I said, "OK, sure, I'll sacrifice my little bit of data I have there and come here," so that was the arrangement in the beginning of the summer. He wanted me to come sooner, but I really wanted to stay [at Brown over] the summer. So I ended up coming and starting in November, and it took a long time to get going. So November of 1975. The Department was just

flabbergasted. So basically I got a four-day-a-week job here, civil service, paid civil service rates, to do my thesis work here. I did start over. I had a protocol written in 1975 which lasted for 20 years. I ran 2,000 subjects on pain measurement. I mean, there've been longer ones at NIH, but I wrote this classical protocol which is very interesting.

MM: Now that would be something I'd like to see.

RG: Ron came to review it and said it was just too grandiose, I'd never get it done, but we did do everything there we said that we did. But it went beyond it. So I wrote this protocol, and I actually finished my dissertation work in '76, but it wasn't awarded till '77, at the end of the academic year. So it took an extra year for me of the four-year program, but I did finally get my PhD. I would go back, had this old '64 Cadillac Fleetwood. I would drive up to Rhode Island and I would meet with my committee, and in a sense it was like wonderful because here's what I'm doing, I would get the OK all along, so at the very end, they had agreed to everything up to this point, and it was really a moot point. So I was a student. Ron also said, "Look, Rick," and actually my advisor said the same thing, "Don't make this the best thing you've ever done, your thesis." My advisor would say, "It's just to get you a union card." Ron insisted that I write up my work for publication before I ever did the thesis, and that's what we did. The thesis became my – my first three publications were basically my dissertation. So I got my degree there and then I was here. Also, another thing that was interesting, as I was never a staff Fellow, I was one of these people who went through this loophole that I was in civil service, and now I had a Ph.D. I ultimately just got converted into a full-time civil [service job], and so I avoided that whole issue as well. I think after I got in, the administration realized their error and quickly closed that loophole. But it was closed soon after. So then here I was with a permanent job at NIH and a new Ph.D.

MM: So did you sail your sailboat down the coast?

RG: No. I brought it down on a trailer. I wanted to, but there wasn't time. It's not a very fast little boat. But I brought that down the next year and sailed it a lot.

MM: Well, I have a bunch of questions. One question is, did you feel, now, having made all this change, I mean, did you feel regretful that you hadn't gone to medical school, or – I mean, I think you were jazzed about this pain work. It sounds really exciting.

RG: Well, there are always times now that I regret it, but in fact, you know, maybe it's just the ego to having an MD and what you could do with an MD. Here, I always have to have another MD to help me. But, on the other hand, you know, many honest physicians – I remember Yolanda Roth,[14] a surgeon here, saying, "Rick, you did the right thing." She said, "Medical school just, if you have creativity and ideas, it's an occupational hazard. It just stomps it out of you." She said, "You just are trained to memorize and regurgitate, and it's really no place – You seem to have ideas and stuff, so you really don't need it." And to that extent, it was probably true. I mean, I've known many, many physicians, and actually dentists as well, in this Institute or here [at NIH] because they don't want to pursue what their degree trained them for, although it does give them some license to do things that I have to get somebody else to help me. An interesting example was, again, as a graduate student, I was still going to go to medical school. I took the Brown neuroanatomy course that medical students have to take, although at Brown University it wasn't one semester, it was actually two semesters long, and they call it neuroscience, [although] it's neuroanatomy. It's all the head and neck anatomy, and it was really extensive. There were like 100 medical students and there were seven of us graduate students. So the final exam – and this is actually really interesting and it speaks to your point – was the standard neuroanatomy exam, which is lots of brains with toothpicks in the gross structures with little numbers, and you walk around

your sheet, you know, [you have] 200 lines to fill in. You go, OK, "Number four," and you write in what that structure is. Then you look through a lot of microscopes and there's little pointers with numbers, and so on. So on a microscopic level, you're filling all these things out as well. So you have 200 of those. Then they had one question at the end, and the question was, "You're recording from a dorsal root ganglion." Devise an experiment" – I guess it's in an animal. They didn't say what the animal is – "Devise an experiment to show whether you're in a sensory [nerve cell]." You've got a nerve. You hit a cell. Is it a sensory cell or a motor cell? And if it's a motor, is there an alpha or gamma motor neuron?[15] And if it's sensory, is it a motor spindle neuron or a muscle spindle neuron or a tendon? Devise an experiment." It depends what kind of equipment [you use]. You [could] devise like 20 different ways to do it. Can you sacrifice the animal? Well, then you can just cut. You know if it's a sensory neuron, you can just cut the tendon and yank on each side, or you can just yank on the whole thing and then you know that the spindle muscle will relax while the other one will be stretched; and you did all these things. You have a timer available. [You have a mouse or a rat. So we all did this thing. So the grades came back. All the medical students got like basically 100 on the regurgitation, and all seven of us just sort of got like 73. We just barely hung in there by our fingernails. On the thinking question, all of the graduate students got 100 and all the medical students got zero, every one of them. They all said it wasn't in the book.

MM: I believe that.

RG: That was very telling. I realized how hard these guys worked and what they had to do, their tactics for studying. Yeah, they don't have a chance. So there is that aspect of it. I mean, science – it worked for me. In other words, I kind of always was a creative-idea person, and that's not enough. You actually have to give ideas that work out or whatever, and there's no guarantee, and I wouldn't recommend it for my children. But in my case it was OK. And certainly, then you're with bright physicians who give up the idea of a lot of money, whatever, to work in this environment as well, so it's OK.

MM: Yeah. That's what I always value about this field, being able to talk to bright people.

RG: One other thing. You always want to – You like people, so you want to be a doctor and work with people, instead of being able to do science. Well, then you realize, no, in science, you going to have to work with people, while if you're a physician, you have all these – I mean, in the best case you have very nice people who are dressed up in their Sunday best to see you, and you play sort of God, and in the worst case it's much worse than that. I actually had a private psychology practice for a number of years where I saw a lot of patients, so I got a taste of that, and I've retired from that as well. OK, so that answers that, I think.

MM: Yeah, pretty much. So tell me, you were interested in pain from the beginning, before you came here. So tell me about what interested you about it, and then sort of how you began thinking about pain measurement. I'd sort of like to explore how your ideas about measurement developed sort of before you met Ron and after you met Ron.

RG: OK. I think I can answer that. Well, there are two things about pain. One of them is it's medically relevant. I didn't want to just – I think the model for many people in psychology was to emulate the professors. OK? So I'm going to do laboratory experiments as well, and I'm going to be in academia and I'm going to do experiments in college on sophomores, which is academically kind of dry. I didn't want to do that. I wanted to do something that was kind of medically relevant. So there was still that desire, I think, is one.

Secondly, if you look, Brown University had a fellow there named Lorrin Riggs.[16] He was an eminent scientist in vision, I mean, and a neat man, just a tremendous guy. And most of the work there was in vision. You ended up reading a lot of vision studies. If you look at the vision studies in the '40s and '50s, they're very elegant. They're almost like calligraphy, very simple, kind of clean and neat. But the field has grown so that it allows [experiments] to become very nitpicky in a way, and so it's just an overly researched field. At the time, pain was very interesting because like nobody had done anything in it really. There was very little work in it. Actually, one of the problems with it now, I think, is it's also becoming so extensive. I really appreciated how you can do neat little things that were done in vision. The same with hearing. Most of these studies. Actually, my interest [turned to] pain basically, because not much work had been done in it. Pain was sort of like the frontier, one of the last frontiers. So that's one issue. I think pain – both it was medical and it was basically virgin turf, you know. Another issue is that I had been involved in motivation. I had done work with monkeys being cold and hot; I had done animals escaping electric shock. I was in human psychophysics, and looking at intensity and the unpleasantness of things, you know. So I got this idea of not only measuring like with smell and taste, which my advisor had done. Not only do you measure the intensity of sensation, you measure how good or bad it is. [With] both temperature and the chemical senses, taste and olfaction, there is a goodness and badness.

I hooked up with a good friend there. I was involved in some studies in his thesis; his name is George Mauer, and we were friends – we both had the same advisor – where he was looking at taste, temperature, and smell. He did a study, and this guy Bob Mayer, actually Mauer and Mayer, did one study where we did psychophysics, and I was involved in his eye studies where he sat people in tanks of cold water, and I did this to lower the body temperature. You actually kind of shiver and lose the will to live. And then we had them rate the intensities of other water samples. We immersed their hand in these little buckets. We also had a psychophysics wheel where we had them rate the unpleasantness. I was one of the subjects in this. Then in another experiment, which I was a subject for, we got on a bicycle and we would get people hot by wearing a lot of clothes and exercising on a bicycle. We had these [measurements of] core temperature rectally, these little probes. Then with the chemical sensor study, we had people be really hungry or really full, and they would rate the intensity and unpleasantness of sugar solutions. In all cases, we showed that the pleasantness or unpleasantness would shift depending on internal state; and the intensity judgments would not change. OK? There's a word hedonic, which implies both pleasantness or unpleasantness (of sensation), so I was involved in hedonic cycle physics before I got involved in pain, or at the same time I got involved in pain work.

MM: Has that work been published?

RG: Yes. I have some reviews that refer to it and actually describe the work, at least the one I can show you. So I'm thinking intensity, unpleasantness right away. And there was a little bit of that in pain, but not much at the time that I became in pain. They talked about the affective component, the reaction component. But some people would measure pleasantness, unpleasantness, or some people would measure intensity, but nobody really looked at those two things. And [Ken] Casey and [Ron] Melzack[17] talked about the – And the McGill stuff[18] came out, actually, too. So there was stuff about it, but nobody really thought of it as just two real dimensions. And that's what my thesis was about. And, actually, [Bernard] Tursky[19] had done it too. Tursky had taken Melzack's and [Warren] Torgerson's words and developed this [descriptor] scaling word system; he had an affective dimension, but he called it a value dimension. The dimensions were kind of strange, you know, and he had like severe and excruciating as sensory words, where to me they have affective connotations. But he had done some work on this, and I really got involved. And he's a political scientist, so I went to visit him. So I really got excited about that. Then I basically took his scaling method, which I thought was sophisticated, but I changed the words a little bit and let these two dimensions of pain. And, actually, I think I can – in

terms of intensity and pleasantness, I'm the one [who] called it unpleasantness, I didn't call it affect. And I think, if we go back, I'm the one who coined that term first.

MM: Well, I haven't seen it before you. I reviewed most of the measurement literature.

RG: Yeah, yeah. I call it unpleasantness in my thesis, and actually, my two pain descriptor papers[20] were most of my thesis. You know, there's more, actually. And I give an affective ratio, too, which is also in my thesis. So my thesis was developing these words, and I did this scaling of affect, or I thought it was, with a tranquilizer, which I later found out a placebo did the same thing. I think pain gets less unpleasant with a tranquilizer, or maybe both placebos and tranquilizers are equally efficacious. I was able to modify the unpleasantness.

MM: Without modifying the intensity.

RG: Yeah. Then the first major study after my thesis is where we did fentanyl and made people nauseous, and we were actually to make these, to modify the intensity and make the unpleasantness stay the same or go up, in a sense, in comparison to placebo.[21] So that was wild, you know.

MM: That's really neat.

RG: That's another thing about my career. I was published, you know, I peaked early. I was published in *Science*, and that's a whole story behind how that got into *Science*, too, that's very interesting. So that was a direct follow-through from this earlier hedonics psychophysics work, that there's two separate dimensions and you have to measure them separately and they're both important. And, again, you can change internal state, make people nauseous, and you get a shift and a change in the affective rating while intensity ratings wouldn't necessarily change.

MM: So tell me a little bit about the mechanics of how this worked out. I mean, you told me once that you sort of selected the words; you sort of made the words up.

RG: Well, we had the original words by Melzack and Torgerson. But there weren't enough of them. And then we sat around the table one day and Patsy McGrath[22] was there too. We had a bunch of words, and we decided, "Well, let's try all these," you know. So we did a study on those, and they were my thesis, and they were published in this *Pain* paper. But then we did a second set of words. Oh, and actually, Patsy wanted [to include] "salient". I said, "Well, that's too big a word," so we put in "clear-cut". But I never liked it because that's a probability word of whether it's really distinct versus how intense it is. I wanted some different dimension. So in the second set, I took that out.

MM: It can be clear-cut without being intense.

RG: Yeah. And then the original affective words were just a bunch of affective words: terrible, frightening, whatever. But the second set – and there should have been a third set and there never was a third set, but there was always planned to be a third set. The second set was, I'd been reading this work by Cliff in '59.[23] He had a paper, I think, in *Psychology Review* about how adverbs multiply adjectives. So this whole idea is that adverbs had a multiplier, and then adjectives had a certain value. So I was very interested in testing that. So what I did was I took four words or five words, adjectives, and I added "slightly" and "very" and "extremely," and I had nothing, and then I can't remember – Maybe I just had those words, but I'm sure I had another adjective. No, I just had those. I had "slightly," "very," and no adverb modifier, a list of four or five adjectives for both the affect, and the affective ones were

"unpleasant," "annoying," which are very similar, it turns out, "distressing," and "intolerable." OK? So I had this little mix of those words. So I wanted to verify Cliff's thing, and to some extent I did. So that's why I chose those words. They were published in – they were the second part of the thesis, and it's one I used for the *Science* article, and I just never bothered to change them ever since. But there's always been some issue about the different dimensions of distress. Some of the words refer to the sensation, like unpleasant, some refer to your reaction to it, like intolerable or what it's doing to you, you know, and, actually, unpleasant and irritating are very different. Unpleasant refers to sensation; irritating says it's making a behavioral consequence. So I was always aware of little nuances. But, again, one thing working with Ron, you know, things are going faster. We're piling studies on top of studies, and right then we started to immediately go into the work on placebo effect and other things.

MM: Yeah. Obviously, that would be the next interesting thing.

RG: And, you know, I never – There was such pressure to get on and do work [on new problems and keep up with] what's going on that you never – To some extent, I tried to go back and tie up these loose ends, but sometimes you just had to move forward.

MM: OK. Tell me about this third scale. What would that have been like?

RG: It would have had, it would have been equidistant. There would have been words – Well, I really had a scale of just using the word "unpleasant". I developed a list of like 12 adverbs.

MM: To modify unpleasant.

RG: Yeah. I did scales, and I developed these.

MM: How about the random-staircase study?

RG: No, no. That's totally different. But I had this scale "painfulness." I had a [third] scale of painfulness. And those adverbs. I published it and it [was reviewed and there were] major revisions required. I never finished it. I did one with pleasantness and unpleasantness. So I used the same adverbs to modify painfulness, pleasantness, or unpleasantness. It turns out the adverb values were the same in all three studies. So I really did multiply adjectives. But, see, the fear is there that a person could – We'll have to go back to what I think is useful about words. But my fear was that people could just ignore the adjective. If all the adjectives were the same, they could ignore the adjective and just look at the adverb and measure intensity instead of unpleasantness. OK?

MM: Oh, yeah.

RG: Because that's giving an ordinal thing. Then the second word doesn't matter.

MM: Carried to the one, two, three, four.

RG: And I found – And the adverbs we chose were really fun, because some were very American English, like "extremely" and "rather," and some were very British sounding, "rather," "quite," "decidedly," "unusually," you know, so that was kind of fun. And then I looked at these in the study –

MM: You wonder if there's a difference between "rather" and "quite." I guess there is a difference. But never mind, go ahead.

RG: Well, I found that, for instance, in my subjects, there was much more agreement across people on the American ones than the English ones. But the English ones were tighter. Once somebody pegged the meaning for [a word], that was pretty locked in. So within people, they were pretty solid, but they varied between people, so I showed all that in this little study, so that was fun. But to explain this concern I had – I don't know if we want to do that now.

MM: Yes.

RG: OK. Well, one thing about words is, if you have a – Most, almost all in the world, responses to pain is scaling our response space, a visual analog scale, a category scale. It can be bounded or can go on forever, and that's an important distinction. But it's a response space. But if it's bounded like a 10-point, numbers one to 10, a visual analog scale, or a list of adjectives, there are two issues. One is, if they get to use it multiple times, they'll tend to want to spread the responses out all over the scale. And if you want to be sophisticated about it, they want to make the response distributions pretty much [rectangular] with a little – It doesn't go right to the ends. They'll avoid the ends. [The scale] slopes at the ends. That's what they want to do. OK? So almost all the biases – The biases aren't described as this need to make a rectangular response distribution. Parducci[24] talked about stimulus spacing effects, stimulus frequency effects. So if you bunch up all the stimuli at one end, you know, if you give a lot of low stimuli in a small range, say, from 45 degrees to 47 degrees, in little steps, they're going to use the highest response [in the rectangle] to describe the 47. And then if you give them [up to] 50, then things change. OK. So there is this bias in almost all scales.

The second issue about scales is what dimensions are described. You know, if you just have a space, even if it's words, take off your glasses and treat it like a space, and so you don't have to attend. Even though I want you to measure something that might be hard for you, if you have something easier like intensity, just rate that instead. Or if you're suffering in pain and you want to communicate your suffering, even if the intensity scale you use to [do it] – Well, the whole idea of doing randomized words is that you avoided the spatial thing; that people had to make the choice by the meaning of the word, which should avoid these biases of spreading your responses amongst a [visual] space. Secondly, as far as looking at different dimensions, we help them tune in to that dimension.

MM: I see. Whereas you give them different groups, one grouped under intensity, one grouped under affect.

RG: Well, that's another thing, is if you – I mean, so you're having people tune in. Now if you can do a study where you look at the different dimensions – I did different groups, too, because you're always concerned that somebody might have a look-up table in their head. Hey, every time I call something unpleasant, I'm going to say it's moderate, and if it's distressing, I'm going to say it's intense. And so you're always concerned that they [will attach their own meanings]. Why not? So the most conservative way to do it is to use randomized words in separate groups. The other in the continuum is to ask people, to have two scales the same. Give me a VAS scale of intensity and unpleasantness for the same stimulus and the same time. OK? And then there's different ways in between those two extremes. So I was always most conservative. And I never denied that you could train people to do it simultaneously, VAS scales, or some scales don't help you tune in. But I think it takes a lot of training. I think people vary that way. I know [the conservative] way always works. I think one of the issues between myself and Price's work^ has always been that. I know Don can get people to make these distinctions in his hands. The question is, can other people do it, and how easy can that [be manipulated]? And no one will ever know, probably, really, whether that's true or not. So, anyway, I was really careful to not allow that kind of contamination to happen. But I think that's fascinating in that

way. I think it's more difficult with patients, they don't like it, and you lose probably sensitivity. You lose something because of that. But, on the other hand, it really is effective in discriminating dimensions. So if I had a scale with McGill, I would make it different. Other people have done that. I wouldn't organize it in the categories and the structure. I would just put it on a bunch of cards and throw them in the air or shuffle them and ask people to rate, make ratings about it.

MM: OK. Now, clarify something for me. You talk in your papers about the method of limits and the method of constant stimuli. Can you just explain those?

RG: Sure. The method of limits is classically is, say – these are both methods for determining a threshold. OK? In the method of limits, you would start out below the threshold and go up in steps and ask for either two or three responses: yes, no, or yes, no, undecided. And you would march up until you cross that boundary, and the responses went from no to yes or from no, undecided, to yes. Actually, it would be no or yes. Forget the undecided. But it could be, you could do an undecided. No/yes. Then you would start above and come down and do that, and you alternate ascending [and] descending trials. If you're good, you wouldn't always start the trials at the same place. You would start randomly so there wouldn't be a thing they'd respond to [in anticipating] the third stimulus. And the fact that you went in two directions, there were classical errors of anticipation or habituation that you would respond early or late, and so these would all balance out. So that's about the limits. It's a very good – You know, for certain kinds of thresholds, it's a very decent procedure. One of the problems in pain, which we'll probably get to next time or maybe this time, is that it's always modified. These are modified by the limits [if you] do descending trials only, and there are some issues with that. So you immediately lose the control built in of coming in ascending as well, so it actually destroys it. It's no longer – The whole idea of it was to go both directions.

The method of constant stimuli is very similar to a psychophysical scaling experiment, but it's done around the threshold. You pick a bunch of stimuli and you give them multiple times. Now, this is where they can have one "yes, I feel it," "no, I don't," or "I'm not sure." And you can [vary it with] two or three response methods. And so you pick these stimuli, and then you plot the probability of, if it's just yes/no, you can plot the probability of the yes or the no, and you get this function that comes down. And when the stimuli are very high, the probability is 100 percent; if it's very low, it's 0 percent, and then you can take as your threshold the 50 percent level or sometimes the 75 percent level. You get sort of a function. Actually, it's called an Ogive, and it's actually cumulative. It's a Gaussian distribution, so it's a cumulative Gaussian distribution.[25] So if you take the derivative of it, it becomes a Gaussian curve. So, but you think of it, just taking a scaling experiment where you give random stimuli, you know, in a range, fixed stimuli, and just move them down, and the response instead becomes responses of intensity, becomes responses of a discrete yes/no or yes/no/maybe. Maybe is good, but maybe is a problem because a lot of people just give maybe all the time. But you still can look at the yes/no. You still look at the yes/no. Now the yes/no is becoming independent, so you have to plot all three. You could look at some function of both of those. There's been some criticism of that. That [can be biased] as well. Depending on how you choose your stimuli, you have to know in advance kind of where it is so that it's in the middle of that. And if you choose your stimuli to be high or low, you can distort it. OK? And, of course, you can always iterate. You could go through a series of procedures where you get one [response relative to another] one, and it would keep shifting, but that's the criticism of it. But it has a lot of psychophysical controls built in.

MM: Yeah. I mean, that was one of the things that impressed me, is that you tried to build controls into your work as much as possible.

RG: Yeah.

MM: And not just construct an experiment to say, OK, look what we've shown, but always to fall back on validity, [to have] an internal check for validity. And I don't know how common it is in psychology. I guess that's my own ignorance.

RG: Well, I think today, you know, I was actually – I'm now doing functional imaging, getting ahead to the end, and the people who are [following that] are just amazed. I'm doing a lot of the a analysis on my own without talking to somebody, which – this is a loose association – but I think you can only be naïve once, it's very valuable to try out your own ideas, because as soon as you talk to somebody, they're going to tell you to do it this way. And I actually got a lot of compliments from people. I'm going now to meetings with people who've been doing it for years, and in some ways I'm ahead of them. I'm trying to look at all these little how it can go wrong, how can it go right, you know, getting an intuitive feel for it. But that's for a later date. But the psychophysicists are always concerned about this, so I think that psychophysical training really carried over to this. Now, a lot of psychophysical questions are useless for pain. They're not – you can't just apply them blindly because there is always [a question] about the shape of the function while pain is really how high is the function, and they didn't really have good methods for dealing with that. You can't just measure pain and really get a lot of meaning out of it unless you anchor the judgment some way. So our discussion of threshold can go down two paths. One is talking about that. The other is talking about a continuation of threshold measures. All these threshold measures give me stimuli. Now if you introduce a blank stimulus into the mix, then you get into this whole field of sensory decision theory and of something called two alternative forced choice.

MM: Which is?

RG: How you do it is I'm going to – OK, close your eyes. I'm maybe going to give you something now for number one, or now for number two. [Touches MM's arm] When did you feel it? During number one or number two? Give me a forced choice?

MM: Oh, two.

RG: OK. That's it. Or I'm going to stimulate you here or there. Okay? When did you feel it, in your left arm or your right arm?

MM: Oh.

RG: OK, so that's it. You can do it in time or you can do it in space. Forced choice. Now, you get a measure that's uncontaminated by bias, like, in signal detection, it's equivalent to D prime. But instead of measuring the bias like in sensory decision theory, it's just eliminated. There's only one parameter, but it's bias-free. It's like D prime. So you don't get the second parameter, but it really doesn't matter. It's free of that parameter. But that's another intellectual thing about the whole – We could go down that path. We'd need to spend half an hour on that. And then there's the idea of going back to the other [problem of pain] threshold scaling, and I don't know which way to go.

MM: Well, I think both of these are interesting. Talk to me a little bit more about this. I think I go to the original set of work that you did. You had these groups of subjects, and you have them rank and order the words using hand grips, button presses, and other kinds of analog measurement. And they did this multiple times, so they created their own ranks and values for the words. Then the same subjects were exposed to electrical and cold stimuli, painful stimuli, which actually continues to amaze me that you got

people to do this. And then they chose the same words that they had already assigned values to, but this time they were presented in randomized lists?

RG: Yeah. They used words to measure stimuli. And they also made comparisons cross-matching to the stimuli as well. Yes.

MM: But then you went on to do a variety of other kinds of scaling projects, one of which is double random staircases and multiple random staircases.

RG: Right, and the DDS scale [Descriptor Differential Scale] is another one.

MM: The DDS scale. And so I'm just wondering, where are we going with all this? I mean, what kind of dimensions are we exploring here? You want to talk about that for a while?

RG: Well, going back to the first thing, the way I did the words is, I followed up from what Tursky did, and he followed up from a book by Smitty Stevens, S.S. [Stanley Smith] Stevens. I mean, these methods were evolved by Stevens, and there's two things that are notable. One is how you get validity information from something that has no physical metric, value words, just like pain has no independent measure, so words are very similar to pain, and you can't, you know – And the way you do it is, you scale the words by two different completely independent methods that are theoretically equal, and then you plot these against each other, and it turns out it's a perfect correlation of 1.0. It's like .999999. And it's like, wow, I did it two different ways, and they come out exactly the same. So that gives you some confidence, [that] actually people are paying attention and doing it. Otherwise, they'd be all over the place. The way we actually did it – there's a method called, there's something called regression bias, which, I mean, this gets really picayune, but if you – You could draw lines, links, make VAS scale responses, say, to numbers. Or I could give you different lines and you could do numbers. Well, when you do that, one should be the opposite of the other when you plot the data, and it isn't. There's a bias where you always shrink the response dimension. OK? So if you did these two things and inverted one, they wouldn't agree. The one would be lower. You always shrink the dimension you're responding. They call it regression bias in the literature. And this method I [used when I] did the words, eliminated regression bias as well. So what people would do is they would make a response to two different sets of stimuli. One would be line lengths and the other would be words. But then you express the two stimuli in relation to each other. And so by coming to the response and back again, you've canceled out the effect of the response, whether it's time duration or hand grip, which are centric within and between people, you also cancel out [the bias]. You [get to the point where the] regression bias is the same. You reduce it, if not eliminate it. So that's getting really technical. But the method – There were a couple of reasons for the method. And what you do now is, so you've always have a psychophysical function relating your response, whether it's hand grip or time duration or anything else, to line lengths. Then you can, along your Y axis of, say, hand-grip force, you have four different words come out. Well, you just use that function and convert it back to line lengths. And you've gone through the regression biasings twice, and now you have it in terms of line lengths, which is a common unit. And now you call it – I call it relative magnitude. And then you do it with a whole 'nother response, and now you've got something else [of that relative] magnitude, that both should be equivalent, and you plot them and they are. So that technology was actually Smitty Stevens' [method]. There were a couple of ways to get rid of regression biases. That was one way: common response to two stimuli. Another way is two responses to the same stimulus, and you could also work it out that way. And we've never really much done that with pain, but that's also possible.

People now have shortcuts where they have people take VAS responses to the words and use them, and that actually works very well, but it doesn't correct this regression bias. And maybe we need to correct for regression bias. Maybe it's just being too conservative then. It seems to work well without it. But at the time – Make the best scale you can, you know. And it may not matter. Maybe just taking mean ranks, which turns out to be equivalent to these ratios, if you just give people cards, index cards, for the words, they arrange in order, and you have code numbers written on the back; you just write down the code orders, there's your scale. That works probably just as well and takes a second.

MM: Quick and dirty.

RG: Yeah. Maybe we didn't need to do all this.

MM: Well, it was extensive.

RG: Yeah, it was, yeah.

MM: So tell me about the random staircase.

RG: Well, one of the problems with this traditional psychophysical thing is you pick a fixed stimulus, and you want to pick the same sort of stimuli for the whole group of subjects. Well, for some subjects, those things are too intense, and others are not intense enough. That's one problem. Another problem is, is that most psychophysics deals with static dimensions, you know, what's the relationship between intensity and response to a stimulus range. They don't measure the effect of an intervention that might change sensitivity. Now, in the pain world, we want to know, (a) we want to assess change in sensitivity to an analgesic. We want to measure analgesia. So as soon as you change things, now your whole range is changed. All the stimuli aren't as intense anymore. People are getting cues that something's happened. So now it's a dynamic situation where there's a change in response, and how you deal with that. OK. Actually, prior to the random staircase, I did this other thing called artificial analgesia, which I never published, and now other people are using it. But I have an abstract. And, again, it's just, why this happened. There's a lot of things I never publish because Ron was always, "Let's do this, let's do this, let's do this," you know.

Given this dynamic situation, when you change sensitivity, you have a scale and you're worried about how well that scale works anyway. Now, is the scale the same afterwards? Does it, if you do a step change in sensitivity, does the scale give you a step change? And I did this paradigm which, I thought it was really cute, where I faked it. I had – everybody had an IV in, and then I gave people an intervention. And there was a placebo group that got the saline and the same stimuli. Well, the active group also got saline, but it reduced the intensity of the stimuli. So they got a lower stimulus and things felt less. So now if you think of the black box, I know exactly how much intensity has changed. Now, how do the words follow it? And it turns out my words followed it without any thing, but a six-point category scale; you can see people persisted, then they'd change it, and they moved, and it moved back to exactly the bias you would expect. And I still haven't written it up.

MM: That's wonderful.

RG: I have it. I've talked about it in chapters. I have it in abstract. So I called it artificial analgesia, and I know some people who've done it as well. My friends in Montreal copied it, and I think Don Price recently has done something with this as well. But that was the idea. Now we get a dynamic situation: How do they follow the step change? And the randomized words did very well, better than anything

else. OK. That's the whole problem with pain now. Traditional psychophysical. Now we have to measure the height of something in absolute terms, and, again, I think words are anchored. We haven't discussed that much. Every word response is an anchor to a subjective level versus a VAS scale,[26] like, what does a four mean, and can that be shifted? Secondly, you want to measure a change in that response. Well, when you change sensitivity, now the range changes. People know something happened. So the multi-random – And plus, there's other issues. Doing conventional scaling, you don't really get measures of – You can block a stimuli, you can get kind of gross measures over time, but you really can't look at temporal effects, change in sensitivity over time.

MM: Yes. That's very hard to do.

RG: And then there's this problem of choosing the right stimulus, and for some people, it's going to be too much or too little. And, finally, the response dimensions in humans of psychological magnitude, which, you know, biologists always sort of mistrusted and didn't understand, it was too abstract for them. So the random staircase was designed to deal with all of these problems. Quite modestly, it's like five different issues. OK? So the idea was to take a – It was based on an original work by (Tom N.) Cornsweet, who developed a double-random staircase. A simple staircase is, you know, you give a stimulus and they feel it. OK, lower it for pain. It still hurts. Lower it. Now it doesn't hurt. Raise it. So you titrate it. And then you can also lower it by big steps, and every time they come around and change a response from feeling it to not feeling it, and you reverse the direction of a stimulus, you can make it smaller steps and kind of hone in pretty quickly. And, actually, that's a principle of intervening in a serial system, is geometric reductions. Come in halfway and then go to half of that, and it's the most efficient way to get somewhere.

MM: OK. Fractionally.

RG: Yeah. So that existed. But Cornsweet pointed out, both birds and animals can understand the rule that every time, you know, the change from one stimulus to the next is contingent on the response. People aren't fools, and probably pigeons aren't either.

So we developed the double-random staircase where you have two of these going on simultaneously. They're completely independent. You basically flip a coin each trial to [determine] which [staircase] are you on, this one or that one, and the response to the one you're on determines the response it's going to give the next time it's chosen by the coin flip. It might be the next trial, it might be further down the road, and you just flip between these. So I thought that was kind of cool. What I did is I applied that to superficial pain response, because I realized even a threshold is just a judgment, in this case whether pain is there or not. Well, you can apply this to other judgments. So I developed staircases where you could have a staircase in between two levels, like moderate versus intense, for instance. So when I first developed this, most versions [I used] were three double-staircases, and the doubles are nice because if the person is doing it, they should superimpose on each other over time. I had one at a threshold level, and I had one at a moderate level and one at an intense level, and these things would titrate. Instead of flipping a coin, I rolled the dice. I had six staircases now. I randomly choose between one each time. And I had another version. Well, actually, I had 16 independent ones, all between different response intervals. The nice thing about that was, choosing stimulus intensity doesn't matter. Just start everybody at the same thing and everybody will hone in to it. Everybody gets the same subjective level. OK? So that problem was solved. Give an intervention? Well, if the responses go down, the computer will just increase intensities to get the same responses again, so they have the same subjective feeling. They might notice a transient change, but they're still going to have the same subjective feeling.

The unit now, instead of being, in terms of psychological magnitude, is units of stimulus intensity. The units come out in degrees centigrade, so you can compare it across subjects, across trials, [and] across experiments. It's very solid. You can say this person's intense response was 49.2 degrees centigrade. It has internal consistency check built in because of the doubles, but even without the doubles, they also parallel each other. They shouldn't overlap, these lines. You can do analysis of variance of the data to show that they're all at separate levels, so you know people are attending. They can still have little biases in them, but attending. If they're not attending at all, [the responses] seem to perform a random walk. It's very efficient. Almost all the stimuli contribute to the analysis, because it does have this increment that hones right in. And, actually, the size of that shows how well they discriminate. It also tracks over time. It provides a record like a strip chart recorder so you can give interventions. You can see how the sensitivity changes, you can see when it starts, when it stops, so it automatically does that as well. In addition, a conventional psychophysical paradigm where we pick a bunch of fixed stimuli and [track] the response, computerized annotations of those really are just computerized [replications of] you can do on a piece of paper. But to do the double random staircase mainly is very, very difficult. So it's another generation of computerized use where you really need the computer, and so it's a very interactive thing with the computer. And I think it has the most – In some ways it's the most bias-free methods, because there's none of these range effects.

MM: OK. Now, does this – I don't know if this is what you wanted to talk about earlier, but at one point you said there is a certain softness in the scale, especially towards the bottom end and towards the higher end, particularly in terms of unpleasantness. It seems to me that would be true. As you rise to a certain level of intensity, it becomes more and more difficult to sort of differentiate between horrible, horrible, and most horrible.

RG: Yeah. Well, this response –

MM: Or am I just reading too much into this?

RG: No, that's correct, what you're saying. There's also – I was also referring to an independent thing, which is, no matter what your rating – I mean, it could be political attitudes – people tend to avoid the ends as much. Now, in pain, people may in fact, patients may go to the top, and that may not be true, that may not be true. I have scales of different spacing. I have some where I have the middle as moderate, so you have a middle notch way down near the bottom. I've shown that sensitivity depends on the spacing. They've [varied the levels] in the middle, so the scale is very sensitive to most of the things we do in the laboratory. But if you have moderate sort of near the bottom and you spread out the top descriptors, it's more sensitive to the most intense stimuli. So there are ways. You can have scales that are most sensitive to a particular range of painful sensation, and, actually, the DDS scale, which we can talk about in the future, is really designed to deal with that problem. It has lots of subscales that are differentially sensitive for different ranges of pain. So, yeah, those are both issues, I think. And I think also, once you get, if you're really suffering from a lot of pain, who wants to scale anything anyway, you know? I mean, I'm not sure I want to.

MM: Exactly. I mean, I didn't want to get into -- OK. I have one question, which is – and I'm sure you're aware of this – one of the problems with verbal scales is we're really depending on a common educational level, and that common facility with the English language. There's no reason, I suppose, why scales can't be constructed in Italian or Greek or any other language. Aren't we essentially trying to achieve something which is a sort of universal scale, or are we just trying to achieve a universal method? What do you think? That's one question.

RG: OK. I think verbal scales probably wouldn't be the universal scale. And I'm not going to stand behind them for all reasons. I'm not wedded to them. I think they may be, in certain cultures and situations, the best tools to address another question, which might be mechanisms or efficacy of a drug or what's going on in a specific group of people. As a universal pain clinical-measurement tool, they're probably are going to be problems of translation between cultures, people's educational level, what have you. They probably wouldn't be the best universal scale. If your goal of your study is to measure across everybody, just use sort of a gross yardstick, actually, I think the best, once we get a good scale for children on a verbal scale, a really good one, that would be – with pictures and animated, make cartoons and things – that'll probably be the best adult cross-cultural scale as well. It will be the universal scale. So, no, they're not probably best for that. But they might be more sensitive if the question you're asking isn't comparing across cultures, but whether a drug works or whether, or looking at a mechanism. So it's different. I think some [researchers] have tried to say, look, you know, we've got to look at the goal of the measurement, and there's different scenarios. A medical legal determination, does this person get disability or not, is a different kind of measurement tool than, does this drug produce a significant analgesia in a post-surgical model, for instance, and there's no reason to believe the same tool would be the best for each. Don't know necessarily which ones are the best, but conceptually, there should be different tools for different purposes. Words, yeah. And I think there's a lot of – I think when you use them, probably, maybe the VAS scale or some other kind of spatial scale might be the very most sensitive in certain situations. Don't really know.

MM: So do you want to talk more about the differential-descriptor scale {DDS}?

RG: Well, I think I got to it on the multi-random staircase. I think it's… Yeah. And there's other things. We started to talk about problems with scaling, and the paradigms like which I've invented and never really used, like have people – Well, I told you about these different regression-bias things. You could have people using a hand grip to rate pain stimuli and rate words, and they're intermittently interspersed, and that's a neat technique that has – I think some people tried to do something like that, but I always wanted to do it as well. The DDS scale – In most clinical scaling, you just get one point, OK? Measure pain, OK, we're done – while in psychophysical studies, you repeat them over and over and over again. But if you think of – There are many psychophysical studies where you have a subjective standard. You give the stimulus, boom. Here's the standard stimulus. It's a 10. Now, what is this stimulus [relative to the standard]? OK? So you're making multiple comparisons from, between your stimuli and a standard. OK? But there are multiple comparisons, and this reduces a lot of the random error that's always present.

What we do with the DDS scale is turn that around and say, OK, now we've only got one pain we're measuring, clinical pain. Well, let's get multiple standards and get multiple judgments to multiple standards, and it should be just the same, and we again reduce the random error involved. That's the whole principle of it. So what people do, they're basically given every one of these 12 words of the dimension and then asked to rate it, their pain in relation to that word, and the first idea, which is a simple category scale, +10/-10. I actually have a computerized version which I never did anything with. It's really neat. It's a manometer sort of display, which avoids biases too, because you don't want one to be fixed because then [that becomes an anchor]. So as one goes down, the other one goes up, so [the subjects are] constantly having to readjust in the biases, and that's something I still want to pursue. I just haven't had the time, even though I'm interested. But I have the program; I wrote the programs myself to do this. So I used to just put these things out with a piece of paper with 10 spaces to the left, 10 to the right, and all on one page, and that was kind of hard. A group in San Diego, Doctor and Slater and Atkinson and a few other people,[27] have actually developed a better method where they do one word at a time, and there are actually boxes that go up and down and people check these boxes. So there are other,

more user-friendly methods than the original method. But the concept is really neat. Warren Torgerson, who, he's this very bright guy, you know, at Hopkins who is very clever, I mean, he wrote his book[28] when he was in his late twenties, I think, and very clever, and really was the intellectual force behind the McGill Pain Questionnaire. He loved the DDS scale, and it turns out that you could – What happens when people use this is they scale the words – they scale the words at the same time they're using the words of the scale thing to get both measures out at the same time. And you can use it and you have a built-in internal consistency check. You can look at – I mean, every subscale gives you – theoretically has an offset built into it, so you get the same number out. So you get 12 responses and they all should be the same because they're computed from the subscale. And you can look at the variance to show how good people are [in reporting their responses]. The variance says how good or bad somebody is. And then the mean value shows the level of their pain. And then there's another. I don't want to give this away because I still haven't done it yet. But I will give it away. Somebody should do this. It's also true that if you have a real intense pain, and I'm going to ask somebody to say how great or less is this very intense pain to weak, you know, as they hit the ceiling. But if I say, how great or less is this to intense, OK, that intense scale might give a better measure than the one that's a way off. So there may be, if certain pains are greater than these words and certain less, maybe the scale where the pain you're measuring is right in the middle is the most sensitive for that pain. I give a drug, that's the one that's going to change the best, while the ones on the ends are the least sensitive. So even though you've given 12 scales, you could pick the group, the four that are closest to the middle before the intervention, and they will be the most sensitive. So you have that kind of capability. And that would be very – That can be computerized, interactive, and which ones you picked [would] depend on the person and the drug at the time, and it would be computerized and independent. It wouldn't be a cut-and-fixed way to do it. So it gives that possibility as well.

Again, I've never pushed the scale. I'm not in a situation to do clinical trials with it, though whether this group in San Diego actually finished a clinical trial, was published in *Pain* this summer where they used – the DDS scale was their main measure. They've liked it, and it's better than [my work]. They in fact have shown that it's more sensitive than all of their alternatives. But it was just sort of that principle.

MM: That it's better than the alternatives. That's great.

RG: And then you talked about how you measure, you know, the idea of how you separate the real intense pains of the scale. As I said, the DDS scale has that little feature to it.

MM: It's, I think, more flexible than the McGill.

RG: Another thing is, the McGill Pain Questionnaire, and actually, the short McGill is another version of it addresses this problem. It's very vulnerable to people. Some people might be very verbose and pick a lot of words. Some people might pick very few. But DDS and other versions of McGill force people to make these many responses, so they eliminate that problem or reduce it.

MM: Can you sort of talk about what the DDS is good for? I have an idea about this, but I want you to, as compared to the McGill, I mean, in terms of clinical uses and experimental uses.

RG: Well, I think the McGill – I always find them very complementary. First of all, most of [the McGill] is quality, so it really helps to distinguish qualitative differences between different kinds of pain syndromes and how certain interventions may change those qualities as well. So it really emphasizes what's different between different [pain] syndromes. Although the overall value might indicate magnitude, and does, there's always been a problem with it. The scoring scheme adds together the intensities within a quality and the number of qualities, and it sort of confounds those to some degree. But I always thought

of it as a way – And it's been used very well to show, discriminate this kind of [difference], like a reversible versus an irreversible pulpitis, which is probably one of the closest examples.

MM: Pulpitis?

RG: Yeah, pulpitis, the one study[29] where [they showed] the difference between one that is reversible and irreversible, distinguished the qualitative difference between those two. And they're so closely aligned, that's kind of a neat thing. I mean, plus or minus the difference between a headache and a sunburn is no big deal, but these things are very close together. The idea of a sensory dimension of unpleasantness; these are dimensions that are common to all pain experience, so they cut across the different conventions. And you ask questions, how unpleasant is the intensity of a certain pain, with cancer, whatever. You can do these effective ratios. So [the DDS is] sort of universal for everything, while [the McGill] is really distinctly, you know, what are the differences. And it has a problem about that, and also the word-choosing behavior built into it as well. But then the results of multidimensional scaling in general, you know, there's always the people saying, "Look, I've, *a priori*, picked these dimensions," and they've let people pick their own. OK?

MM: It's much more individual.

RG: Clark and Janal[30] – these are good friends – they've always coming out and saying these things I have are archaic, and just are forcing people to think in these dimensions, where they are free to choose them. And one answer is that one of the purposes of their methods is to discover the dimensions, and the ones they use are based partly on those discoveries, and so now I've used them. In fact, they have such strong historical precedents. Intensity and unpleasantness are involved in other sensory systems, and they go back in pain, back to Aristotle and Plato. I mean, everybody agrees that these are the dimensions. Most of the work, the discovery things, come out with these dimensions. OK? And so it's kind of circular. You can't – these things are based on discovery, basically, and they go ahead and use them. And then there's other things about multidimensional [scales]. I mean, it's a field you would have to get into, and I was very fortunate to have Warren Torgerson sort of help me along with [learning it]

MM: When do you start working with him?

RG: Oh, gosh. One of his graduate students did her thesis with me, Donna Kwilosz,[31] and it was on the DDS scale [and clinical pain assessment], so [that was] in the '80s, and I haven't talked to him much recently. You know, he's been ill. But I would fly my little airplane up, and instead of meeting in his office, he has a gorgeous farm north of Baltimore. I would fly my little airplane up to this tiny little airstrip, and he'd pick me up in his old car and we'd drive to his farm, and they had these neat horses. His wife and he – he was a farmer/gardener, she was a horse person, and they each have their own – not their own rooms in the house, they had their own little buildings. She had the tack room and her stables for horses. He had like a greenhouse, and he had like a room in there he sat, you know, and he had orchards and stuff. And we would talk about stuff and drink coffee, and then he would load me up with garbage bags and paper bags full of apples and stuff. I mean, he'd always like be filling my plane with all this produce as a gift. You know, I'd spend a wonderful day with him and I'd fly back here. And I have this old antique airplane, so it was just a wonderful time. This is an example I've used many times in my talks. We're talking about factor-analysis studies of the McGill Pain Questionnaire and others. He says, "Rick, you know, people just don't get it. They just confuse semantic and associative meaning." And I said, "What?" "Semantic and associative meaning." I said, and I kind of looked quizzical, "I think I'm following you, Warren." "OK, so let me give you an example, Rick." He says, "What does butter go with, margarine or with bread?" He said, "Butter and margarine are semantic

meaning, but butter and bread is associative meaning." He says, "The McGill Pain Questionnaire is constructed with semantic meanings, like qualities. Butter and margarine are grouped together. But when you do a factor analysis of what that patient fills out, you get butter with bread. You get deep and shooting versus burning and whatever, superficial." And so he said, "You will never," he said, "It doesn't tell you anything about the scale, and everybody does it and they get these factors, and then they go back and they say, "Well, that validates the scale, [legitimates] the scale." It doesn't really say anything about the scale. It says something about some parameter you're measuring about the syndrome. And they want to say, he said, "You could do a food," you know, "You could get people to rate foods, and you'll get cheeseburgers and fries, but you won't get the major food groups." And he said, "Now, there are ways you can get it," he said, "but no one really appreciates – I mean, I'm not saying there's a universal rule, but it's very close to universal and you have to be very – it's not a hundred percent true, but it's almost a hundred percent true that basically these have nothing to do with each other."

Then I wrote a little editorial[32] in *Pain* once about – this is one of the issues I address. I addressed all the issues in one little editorial, but Dennis Turk[33] had basically said, "Look, in the McGill, if you look at the affective intensity measures, they're very highly correlated and should make one measure." He misses the point that if you think of the affective system as a gain that goes up or down based on intensity, it's always going to follow intensity correlated, but it shifts [with] relative intensity. So if you look at the ratio of affective given intensity, that's independent. That's not correlated, and that's the one you want to measure. And then [take the] example of height and weight, and that's going to probably be correlated. But you don't eliminate that because you get body style or body type out of that. So I think that, again, all these multivariate people said it doesn't matter. Well, they really are misleading people because [it definitely] matters. So that was just [insightful of Torgerson]. So he was neat, just a wonderful, sort of a best [mentor].

MM: It's quite fascinating, and particularly interesting that you thought about doing a third scale at some point.

RG: The third scale would use words that are similar in their meaning of whether they're a person's response to something or [to a difference in] the stimulus. And if they weren't single words, they would use some adverbs when they had to, to fill it out. OK? That would be the answer. So there would be one about pleasantness or aversiveness of a stimulus, there would be one about your response to it, your emotional response, a frightening, for instance, a fear response, irritating, or is it at most mildly bothering you? It's "annoying" and "irritating" are both very similar, where the connotation may be not allowing you to focus attention on something else, taking a little bit of your attention; [but] "distressing" has a suffering kind of component to it. So there really aren't that many dimensions, but you can think of your response to something or characterizing something itself, and we'd separate those out and use whatever means you could, adverbs if you had to, to get a decent interspaced scale.

MM: I think that's really interesting. It's quick. I mean, your work sort of demonstrates that people can in fact discriminate consistently between these different aspects of pain. It's not just some sort of monolithic horrific experience that they're not able to verbalize, which I think is where a lot of the cultural literature on pain sort of falls apart. They say, well, pain is indescribable, it cannot be shared, it's ineffable. We can't really, you know, there's no way – But it does seem to indicate there are ways of communicating in a fairly rigorous fashion, and that relatively normal people can do this.

RG: Yes. I mean, think about it. Why do people go to doctors? [Pain is] a human experience. And when you have it, I mean, the people who have it are the ones who articulate it so beautifully because they're trying to convince people they have it because nobody – sometimes their credibility is at stake, some

people don't believe them. Yeah, it's with you all the time. You have time to think about it and describe it. We talk about why would somebody with severe pain want to measure pain. On the one hand, they don't want to be bothered; on the other hand, they're so familiar with it that they're able to make fine gradations. That [can be shown with the right] experimental design.

MM: Yeah, that they're able to talk about it. You were talking earlier about fentanyl,[34] which I guess was the first time [intensity was reduced] in [an opioid] drug study. So this was a new finding.

RG: Yeah. Well, also, the opiate, you know, the whole idea – OK. Yeah, fentanyl… Well, if you read all the – Read Goodman and Gilman[35] up to that time, that fentanyl study. It was a classical Beecher[36] notion, which is still probably right in some ways. Narcotics did not change intensity of sensation; they just changed the reaction component, how much it bothered you. The pain was there, but it doesn't bother me anymore. OK? And so there are two important things that I think about that fentanyl study. One is that we showed there was a significant reduction in the intensity of pain sensation. It was reduced by 40 percent, I think. And so we showed that it does attenuate the sensation, and at that time, that was human evidence that was converging with animal physiological studies. I mean, everyone agrees now.

Part 2 of Interview

MM: Dr. Gracely, good afternoon.

RG: I guess where we left off – and thanks for giving me the opportunity to rehearse what I was going to say; I don't know if it'll make a difference – was about the effects of what we call narcotics, opiates, or the term opioids. As we were saying, beginning to talk about last time, that up about to 1980 or so, the dogma or conventional wisdom was that opioids produced analgesia, not by reducing the intensity of pain sensation, but by reducing its unpleasant emotional component or its reaction component, and I think this followed from the influential writings of Henry K. Beecher. So one of the first studies I did after developing these scales of sensory intensity and unpleasantness, we performed a simple double-blind study of administering the very strong, fast-acting narcotic fentanyl or a placebo to groups of normal volunteers. And each volunteer rated seven different intensities of electrical tooth-pulp stimulation ranging from their own personal threshold of tolerance six times. That was 42 stimuli. And they did this both before and after a double-blind infusion of fentanyl or placebo. The dose of fentanyl was 1.1 micrograms per kilogram, which is a funny dose. It really meant that we gave half of a .1 milliliter vial to a 100-pound person, a whole thing to a 200-pound person, and we weighed people and did whatever in between. One section of subjects, actually two of the groups, used sensory intensity verbal descriptors to rate their pain sensations, and these were presented on a randomized list which is freshly randomized for each subject. Another two groups, one of these pairs of groups that received either the drug or placebo, the other section of subjects used unpleasantness descriptors, also randomized in a list before then, to rate the unpleasantness of the pain sensations. Anyway, the result was very interesting in that if you looked at the sensory intensity descriptors, a placebo had no effect while fentanyl significantly reduced the intensity of the pain sensations. Sensations described as mild prior to the drug were described as very faint or nonexistent afterwards, and sensations described as strong pain were now described as mild pain after the drug. And because the things were scaled on a ratio method, you could actually say that the sensations reduced by about 40 percent.

If you look at the unpleasantness responses, in the placebo group, the unpleasantness responses actually were reduced over time, and perhaps because people got used to stimuli. But in the group that received fentanyl, there was no reduction. So in comparison to placebo, fentanyl actually increased the unpleasantness. And I omitted to say the first time, and also now, that when we gave the [injections], we sort of accentuated the unpleasantness of this experience by ambulating the patients. They received the

injection in one room and got up and had to walk to another room, and so they all complained of nausea. Some had an emesis basin next to them, on their shoulder, assuming they might vomit. So we had two different scales. So the [finding is that] there is a reduction in sensory intensity. Secondly, the outcome of the study can depend on the dimension used to assess it. This study does not say that usually the fentanyl increases unpleasantness. Most conditions with people in pain, it probably reduces it. But under this sort of contrived condition, I think the unpleasant result just shows that it says something about scaling, that these are really dimensions, and this is a situation in which the dimensions worked in opposite directions. Maybe in other situations, they may just move in the same direction but not to the same extent. So that was sort of the first publication after my thesis, and actually it's the fentanyl story. But that was actually published in *Science*. Then, after we published it, we realized, one of the issues about this study is that it's very clear to somebody, everybody involved, who gets the active drug, because it's a profound experience to the subjects. So we replicated the study, and the only change was that we had, instead of giving an actual placebo instead of fentanyl, everybody got a masking drug first. In our hands, we found that diazepam [Valium][37] really didn't do much to these scales. If anything, it acted just like placebo. It didn't change intensity, and unpleasantness is reduced after diazepam. So we gave everybody diazepam first during the study, and then we gave them either double-blind fentanyl or placebo; the placebo is just saline, and that was very interesting. It was very hard for anybody to tell that they got fentanyl. As a matter of fact, even the surgeon couldn't tell. So everybody experienced – The fentanyl effect – and I've shown slides before of a woman getting it – the diazepam effect, rather. And these people had been up all night, they were about to have their wisdom teeth taken out. All these subjects – this is before an oral surgery, so they're anxious, they haven't slept, they're stressed out, and we do this because they're going to get the drugs anyway, there are no unnecessary venipunctures. It's an interesting group of subjects because they're not volunteering; their parents are volunteering them so that they can get the surgery for free. When you give them a benzodiazepine, they get this euphoric, disinhibition response. They're sort of giddy and laughing and whatever, and it's a very strong effect. And then underneath that, it's very hard to see the effect of the fentanyl. Anyway, we reported that in *Anesthesia and Analgesia*,[38] and we got exactly the same effect, and the purpose of that paper was controlling for the detection of active drugs, which was an issue that we later – which was sort of a design feature we put ultimately in our clinical trials in conjunction with Mitchell Max on chronic pain patients. So those were sort of initial experimental studies with fentanyl. And then we replicated those subsequently with nitrous oxide – not that many, you know. The point was, I mean, once it was demonstrated – then fentanyl ultimately was used as a model to test other aspects of scaling methods.

MM: Did you want to comment on placebos and any observations you've made about the effects of placebos? I mean, the placebo effect is talked about a lot nowadays. People are advocating for placebo, using placebos interspersed with active drugs to alleviate the side effects of active drugs. Dr. Robert Ader has talked about that.[39] And there's a lot of discussion about whether or not placebos could actually – I'm assuming we're talking here about how inert placebos could be turned into an effective pain therapy by producing some kind of subjective reduction of unpleasantness. I'm just wondering if you have any thoughts about that.

RG: I have lots of thoughts about that. I mean, they could be objective pain therapy by reducing unpleasantness, or they can actually produce physiological changes. I mean, the belief that you have an active thing can actually cause physiological changes that go beyond just the palliative reduction of unpleasantness. It could actually change physiological systems. And I think if you go outside of the pain field into other medical systems where placebos are used, I mean, [in] things physically measurable, like asthma or whatever, you find improvement with placebo. It's not just changing how people describe their symptoms; it's that people actually get better. So, I mean, I think what placebos do can be more than just changing the report of your experience or your perceived unpleasantness, although

unpleasantness could change. You could have affective physiological changes where you accurately report a change that something doesn't bother you as much as it did before.

MM: Right. But what you're talking about essentially is the perception of receiving an effective medication will create centrally modulated – What do I want to say here? Central modulation of perception? Is that what we're talking about?

RG: Right. It would be more than – Yeah. Well, there's a lot to talk about placebos. I mean, I think I'd like to talk about – what is changed in placebo, and right now you can think of, there's pain perceptions [that] change in many different levels in the system from, you know, the spinal level to the supraspinal level; in the brain, both intensity and unpleasantness can change, and you can also change your language descriptor of it, sort of a response-bias effect. In certain syndromes, perhaps like migraine headache and others, maybe placebos act not by producing analgesia, but they actually remove the stimulus. If you have a tension, a headache, and the tension goes away, it hasn't been analgesia. You've actually cured the cause; you've changed the cause. I mean, even drugs for migraines don't attenuate the migraine pain; they prevent the attacks from happening. Once they are full-blown, you really can't modulate them very well. So there's lots of things that placebos can do. How they do it – I think it's interesting. You know, obviously, soon after the discovery of endogenous opioid systems, you know, it's one of the big phases in pain research, was the use of narcotic antagonist naloxone[40] to infer endorphin activity by assuming – You assume, hey, endorphins are present; we'll inject naloxone, we'll antagonize the endogenous opioids, pain should go up. So you see naloxone-produced hyperalgesia was sort of taken as a sign of endogenous activity. And then there were the really landmark studies by [Jon] Levine and [Howard] Fields[41] using post-surgical pain,[42] and they apparently showed that you can give a placebo and pain goes down; you give naloxone, the pain goes back up. Well – this is, you know, the public was waiting for this. I mean, this was reported in, I think, news magazines and newspapers, and it's such a popular finding and it still persists to this day in all the literature, that placebo has an endorphin effect, which it may. It may. But you realize that placebos can do so many things in medicine. It's, I think, saying that placebo analgesia is due to endorphins is a very strong thing, because it eliminates other possible [mechanisms] and perhaps it wouldn't be endorphins. Interesting. Our first big placebo study, we sort of kind of replicated all the conditions Levine and Fields did, but we added one more that they didn't include in the original design. When they gave – I mean, you can distinguish between the action of naloxone, which blocks opiate receptors, the physiological action. There's also a psychological effect of having a drug administered which produces the placebo effect, and you can give placebo or saline or fentanyl. But the problem with their study is they had no treatment, and then they had the administration of saline and they had the administration of naloxone. Well, those had different physiological effects, but they both had a placebo effect. They can never tell what naloxone would do alone without the placebo effect, so you have to administer it without the subject knowing they're getting it. Then you can really manipulate a 2x2 design, the action of the drug and the knowledge whether you received the drug or not, and that's exactly what we did.

So we had like a hidden [control] and we were the first people to do this.[43] We had the IV line in, and before the subject rated – Again, these were all surgery subjects after their wisdom teeth had been taken out now. They're rating oral-surgery pain. And then they rated [their pain] for a while, about an hour, and then we came in, and before we came in the room, we actually administered naloxone or placebo to the patient as a first infusion. So when you administer naloxone, you block all their opioid systems. Then we turned around and gave them no treatment or placebo, and, also, we had to give them fentanyl in some people because – which we'll talk about later – to make sure they had a good placebo effect. You had to be – people had to have the possibility the real drug would be given. And then what we found – So if we plotted these – Forget the fentanyl now for the results. People either had naloxone on

board or not, and they had placebo or no treatment. If you graphed it, it was two parallel lines, that the given placebo reduced pain either when the opioid system is working or when we had blocked it, and the amount it reduced it was the same. And naloxone had an effect whether – it had an effect in each case. In the no-treatment condition, it increased the pain just as much as in the placebo condition. So this, in a classical [study design of] two main effects with no interaction, it shows that there are two independent mechanisms, that there was probably endorphins released – not after this pill, but after the trauma and the anxiety and the tissue damage and the pain of oral surgery, which is reasonable. And we actually have since shown that, that there is endogenous release after, not oral surgery, but most surgeries, and then when you give naloxone, you reduce that and your pain is increased. So our point – we just added this fourth point, and that was our interpretation, and we point out that the Levine and Fields studies really couldn't distinguish between these alternatives. I mean, there's a sense like, you know, either a person – I don't know. I'm trying to think of – I can't think of a good metaphor now for this kind of design, but they really couldn't tell if it was one effect or if it was two independent effects operating independently. In our hands, it was two, and I don't think there's ever been a clinical study to show that it's ever been one. So we said that. We didn't rule out that placebos could not be mediated by endorphins. We just said, in our hands, they were not. And I don't know of any evidence in the clinical situation where they are. There is evidence, you know, Grevert and Goldstein [reported on an] experimental [study].[44] They went through a contrived thing to kind of show it was, and maybe it can be. But I'm not sure, in oral-surgery models, that it has to be. But it's funny. So that was our first study. And I still stand behind it. I think it would be replicated if we did it again today. But getting back to the necessity to use fentanyl, we did – at the beginning of that, we did a study where we told subjects they could get any of these drugs, fentanyl, which might decrease their pain; placebo, which might decrease or have no effect; and naloxone, which might have no effect or actually increase it. But we told the guy giving it, "Listen, we're not allowed to give fentanyl yet, so just tell the subjects – It's in the consent form. Just tell them it'll be a possibility, but we can't really give it." So we did that for a while. Then later on we said, "Oh, listen, fentanyl is now a possibility," and then we started including it as a possibility, and you would see that fentanyl produced an effect. Then we measured the placebo effect of those two conditions, and the placebo effect was significantly stronger when fentanyl was a possibility than when fentanyl wasn't a possibility. And this is consistent with the ideas that a drug is always half as active as – a placebo is half as active as the drug it's being compared to. If you give them morphine, the placebo effect is very powerful. If a placebo is compared to aspirin, the placebo effect in comparison to aspirin is a lot less powerful. So it's very reasonable. But in this case, it was just the clinician's knowledge of the range of possible treatments, so it could be a possible influence per se. And I think that gets to the action of placebo. The recommendation to use placebo alternating with active drugs, well, that may work, but it seems to be that the clinician's faith in the efficacy of the treatment they're giving is a very important variable. And if they know the placebo is given half the time, it may not work as well. Now, if their secretary snuck in placebos half the time and they didn't know it, it might be very effective. But to knowingly do it, they might – maybe they have the charisma and they can pull it off, and a good con artist, but it may, in fact, it may not work for that reason.

MM: Or if they have very strong effects in the treatment, then it will work.

RG: Yeah. I think that – and that's a fascinating topic, that the belief, you know. And also the study we describe. You know, most of the focus on placebo is on the expectations of the person receiving it, but this focuses onto the expectations or the knowledge of the person giving it, so it's probably those two independent factors, and there probably is a third interaction term, which is the relationship between those two people, whether they like each other, whether they click as personalities. I mean, some of the stuff you probably can't even measure. But it's a social dynamic of somebody administering the drug. There might be variables such as providing a good explanation for what they have, providing

explanation for the effectiveness of what they're going to get. If the patient notices side effects, it probably makes them think, "Ah, this is the real medication," what have you. And there are a couple threads to go from there. One is that, with Mitchell Max, we did a study once where we gave patients, chronic pain patients, a single dose of a bunch of different drugs, including placebo. It was clonidine, ibuprofen, codeine, and placebo, and when we looked at the analgesia for those who reported side effects and those who did not, and three of the four groups, including two active drug groups and a placebo group, there was much more analgesia if they also felt a side effect. And there are several possible explanations, but the one I like the best is that, you know, these people are probably – I mean, I would feel a little insecure about my ability to rate pain and get a drug, so I would use any cue available to give the right response, the appropriate response, and not look like a fool. And so they think, "Oh, I feel something," and they say to themselves, "Oh, that must be – I must have the drug," and then somehow that influences their responses. So that's, I think, one issue. The other is just this, given that we know the placebo effect probably operates in all active treatments, then the poor placebo doesn't – It's not the right word. We don't have a word in the language that, in fact, there is something in the treatment situation that benefits the efficacy of it, which is independent of whatever you're doing; that is, part of the personality or whatever. Certainly, there are many treatments that don't involve giving anything to a patient, which are successful, I mean, going back to even witch doctors and what have you. And I think that's a fascinating topic. It's an interesting story. I was on the program committee for the Vienna IASP meeting,[45] and they wanted to – there was really some interest in having a plenary session on chiropractic medicine. And I went, "Whoa! Before we like start giving every alternative medicine the day in the sun, maybe we should first get an idea of what this thing does that we're trying to talk about, the power of just suggestion or whatever in the absence of any manipulation, because that's the baseline. Until we know what that is, how can we evaluate these therapies?" I said, "On one hand, you have evidence-based medicine, where it's very hard to show that anything works, but then you can always conduct studies to show that anything works on the continuum." So ultimately, everybody thought that was a great idea, and they said, "Well, that's great. You do it."

So I have to give a plenary on this topic, and I'm trying to read about it. And some people talk about it, but there's really no literature on it. Actually, the only real literature addresses the old story about audio analgesia,[46] you know, when that was just –they basically started that when [it was assumed that analgesia] depended on the charisma of the operator. So it's something – I think it's very important, and we don't realize – I think it's very difficult to assess it. But we have to get some handle on how can we measure it, manipulate it, this magic. You know, there's no term. I went through the dictionary and the thesaurus, and the best English word I could find was actually – well, it's not even English; this is Greek – was panacea, you know, the idea of a universal remedy, healing.

MM: And chiropractic frequently sort of presents itself in that sense.

RG: Yes. But then there's obviously a lot of groups that support this, and then also now there's, on the Internet, you can find groups like Quack Watch, which are very – and will document chiropractic disasters. But, anyway, so panacea. But I don't like that word, but maybe that's the whole idea of this universal healing power.

MM: It's a complicated issue, and yet we know it exists, and we also use it very actively. I think most doctors use it in treatment if they can figure out how to latch onto it. And especially in pain, as opposed to chicken pox. I mean, don't you think this really complicates all of the experimental studies that you do in a sense? Or do you really feel confident about your ability to statistically account for the placebo effect?

RG: No. I think it does influence almost everything you do. It's very difficult in many situations. Well, acupuncture is a classic example. It's very difficult in acupuncture to get a true placebo. If you can do sham acupuncture at different points, well, you know, if you have a skilled acupuncturist doing it, they know these different points act differently. Or so then you say, well, maybe you push – They have them now where they put the needle through a hole in a sheet, a pinhole in a sheet, and there's a body part on the other side. They know what they're doing. But they say they can tell they're right. I mean, that's the kind – But right away you've destroyed [the benefits of the interaction]/ Maybe as you've – Then what you do, you show the treatment isn't very successful. I mean, there probably are ways to get around it, but it is very difficult, you know, the social psychology.

And it's also the – I mean, I also looked at the thesaurus. I've been looking at meanings; I'm pulling the thesaurus off the shelf. But it talks about, has meaning in the beginning; I don't know if I'll find it. Somewhere in here [opens the thesaurus] is healing. It refers to the healing arts. And so right away, the art of healing, you know. And it probably is an art, and so I'm not prepared [to talk about it]. But it is in here. I will find it later. But that talks about the healing art. And can you study that art, or is it just art? Can it be studied by Western techniques? I don't know.

MM: It's kind of mystifying.

RG: Yeah.

MM: The very phrase.

RG: So that's a whole area of discussion, I think.

MM: OK. Well, let's – What are the things which are interesting you most in the last few years? I think you've probably moved on in a lot of ways.

RG: Well, I mean, before I get – what happened with the scaling method we talked about is I developed this multi-random staircase.

MM: Right. We talked about that.

RG: Yeah. We talked about that. Good, OK. Well, I think –

MM: I think we were about up to 1990.

RG: Yeah. Well, I think that's when we started really [working with] pain patients. I mean, I'd done mechanisms of deep-brain stimulation and that's something that we never really got enough patients to publish. Then the placebo effect. And then there was work with [47]Gary [Bennett], his idea to start studying these chronic pain conditions, which were a fascinating puzzle at that time. And no one really – There was just, the whole idea of mechanical hyperalgesia was a puzzling finding. You know, at the time, light touch producing pain, there was a paper by the [Jose Ochoa and Erik Torebjork] group, saying this is due to sensitized C fibers,[48] and so we started –

MM: Yeah, peripheral.

RG: Yeah. And we started seeing some of these patients, doing sensory testing on them, and we didn't know where we were going. We just wanted to like learn about them. Then we finally got the courage to do

electrical stimuli in some of them, and we really showed that this – We weren't the first, but we were one of the first to show that this mechanical hyperalgesia was really mediated by A-beta fibers. And then we did all sorts of things. The electrical stimuli were interesting because they bypass the receptor and they activate the axon behind the receptor directly, and they activate the touch fibers at detection because they're the most sensitive to it. As you increase intensity, the first thing you feel is tactile, and no matter whether the receptor is fatigued, sensitized, or what have you. So when you do light brushing, your C fibers could be sensitized, so now you're activating Cs as well as A-beta. So we found that we could look at, get a detection threshold [for touch and then] raise up the pain threshold, and in [normal] skin, these were the same. The pain threshold, as soon as you felt it, it would hurt. So there was like one line of evidence. Then we also did blocks and anesthetic blocks and tourniquet blocks and other lines of evidence as well, and reaction times, showing that these things were maybe in the range. So that was like a really interesting finding. But the most interesting finding was that, it was working with Gary, and it was funny; I mean, I remember I was arguing over this day after day that this thing, there was like a C-fiber loop, I called it at the time. We had done this earlier work with Marvin Hoffert in '84. We published this paper on somebody with neuropathic pain, and we found that we – We were doing nerve blocks in two different major nerve territories in the leg, the sural nerve distribution and the peroneal distribution.[49] And this patient had allodynia in these distributions, and we did a block of one nerve territory and we limited the allodynia in the other nerve territory. And we could not figure out what this was about. And actually, if you read the paper, it's obvious we had no clue. You know, we just sort of stumbled around, and we didn't know what it was.[50] So one of the neat things we did with this series of studies is we actually found really small painful areas in these patients, and we injected them with just a few cc's of local [anesthesia], just a minute amount infiltrated superficially under the skin, and every – all the symptoms of these patients would disappear dramatically for the duration of the block. So that was the most profound, probably, result we'll ever have in our lives, you know. And I remember the very first time we did it. We were actually in the recovery room, in case we had to medicate this patient, and actually, we did it and we got the effect, and then we did all the sensory testing, although in this case the sensory testing, it was like we didn't know what. We couldn't quantify stimuli because like the warm thing was a tuning fork dipped in my cup of coffee, you know, and she had coffee dripping down her arm, and we had ice. We had all kinds of things, room-temperature metal objects, you know. Then we got more sophisticated and used all our sensory stimulators and did it in our laboratory after that. So that was just a fascinating result, and there were a lot of spinoff results. Some of them we haven't fully pursued.

MM: So these were kind of exploratory studies?

RG: Yeah. We just – patients would come in and stay here for a week, and they'd come in every day and we would just do injections, and the kind of studies where, yeah, totally, almost treat them like an animal. We would do something and then see what happened and figure out what to do next. There was no rigid protocol, you know, and notes were written on the back of brown paper bags and paper towels and the back of our hands. And we got more sophisticated as time went on, but it was just really exciting. And then we published this paper in '92 where we put this model forward, and now everybody accepts it.[51] But at the time, I think Jim Campbell[52] was thinking along the same lines, but really, very few people were thinking about this.

MM: That was the model where peripheral input maintains alterations in central processing.

RG: Yes.

MM: I thought that was a very interesting paper.

RG: Yeah. And we actually figured this out in the late '80s, you know, and so now it's whatever. Still, what we did, I mean, a lot of experimental work in animals and in humans, but in terms of the clinical populations, I mean, very – I mean, I know lots of people replicated it, but no one else has really written about it, you know.

MM: No, I haven't seen very much.

RG: And so it was kind of neat where we demonstrated this whole mechanism, not in a normal volunteer, but we actually did it in patients.

MM: And these were patients with neuropathy, diabetic neuropathy?

RG: Yeah. Well, they were [diagnosed with] reflex sympathetic dystrophy.[53] They had allodynia and they had spontaneous pain, evoked pain after an injury over widespread areas of their arms or legs. Actually, we had one arm and three legs, I think. And then we had other interesting findings. And then this model said that, in all cases, you know, that this altered central processing – we called it abnormal central processing. Our first figures – they're around here somewhere – but we realized after a while, we changed it to "altered", because the central processing probably isn't "abnormal" at all. It's altered central processing. It's initiated and maintained, those two separate things, which we also made that distinction, by persistent input from peripheral receptors. And in a normal situation, if I can depart from our study for a second, Pat Wall wrote that gorgeous editorial in '79 about a dog being hit by a car, and certainly there are two aspects of pain.[54] One is, you know, fleeing the scene, yelping and screaming, and then the dog lies in the bushes, not moving, so it's recuperation, you know, protecting the injured part and not moving, maximizing its chance in the healing process. It's really recuperation.Well, probably the abnormal spinal processes, like allodynia and stuff, are for recuperation. After you have a long-term injury, they produce an overall tenderness and sensitivity outside the area in an effort to keep the animal still, so healing will take place. So what's weird isn't the fact that they're there, but the fact that this input doesn't go away. The persistent input should be transient; it should go away. Once everything's healed, it should go away, but it remains. And our models show that probably it remains for lots of different reasons, like there was a commonality here, the common and final pathway of peripheral input that maintains altered central processing, but there's probably lots of ways of getting that input. It could be from a neuroma, it can be due to a sympathetic activity, you know, the idea of synthetically maintained pain, receptors at the injury site, or it can be a true nociception, like inflammation or a wound that doesn't heal. But all of these could produce a focal input and produce –

MM: It's all essentially based on continued peripheral input.

RG: Right.

MM: No actual tissue irritation persists?.

RG: Well, no. It could be the nerves. The tissue could be fine. It could be just a damaged nerve. I mean, it would be tissue irritation of the nerve itself, but the rest of your body can be fine. The nerve can be sending ghost images.I mean, one analogy I wrote about is like you're hanging a picture on your wall and you drive a nail through the wires of your burglar alarm, and the alarm goes off, but your window is still closed. OK. So you're feeling pain. And that's what neuropathic pain is. It's damage to the pain afferent signaling system, but not necessarily to the body. So instead of signaling damage, it's just going off.

MM: OK. But the damage is in the afferents. Then there is altered central perception. It's a realistic response.

RG: The pathology is in the persistent – Yeah. But I guess the point is the central sensitization, or whatever we call it now, and neuropathic pain are independent concepts. But you can get the persistent input from neuropathic sources or from nociceptor (sensory receptors responding to damage) sources, and the result is the same. And we tended in the early days, they considered neuropathic and this altered processing in the same thought. They are really independent processes. And, you know, it was fun because Gary worked with the animals, and we collaborated. I was in humans. We spent a year thinking about writing this paper, and we both had remarked that this is sort of one of the neatest intellectual things we've ever done, and enjoyable things.

MM: Right. Very exciting, and a major problem.

.

RG: Yeah. Now, I'm not sure we helped people, but we certainly said, this is the target. And certainly I have to – I've spoken that I think a lot of people have designed therapies to try to change the altered central processing and make it more normal, but if you follow our work, it almost leads to the point, to the idea that that isn't the way to go, that that will be difficult to do, and that's actually not pathological in the first place. The pathology is the persistent input, and you should target what's going on in the periphery. But the thing is, there's multiple things to target, and some of that work is not as exciting as dealing centrally. Like we still don't know how to cure a neuroma, you know, and we cut them out and you get a new one. I mean, some people think they can; but that's still a major problem for some of these patients.

MM: Yeah, it's complicated. It's easier sometimes to go where you think you can make a difference or at least demonstrate a clear result with a study. So, did you stop working on that essentially because Gary left?

RG: No. I would have stayed – I'm still kind of working in that area. I didn't have access – Can we pause for a second? Anyway, I followed up this work in a couple of ways. One is that, one really interesting, beautiful thing about doing these studies in patients is they usually had an affected extremity that was unilateral, like they had an arm or a leg, and we had like the contralateral control. And so I've done two things. One is, there's a similar clinical condition in women called vulvodynia, which is usually burning pain in the vulvar vestibule. It's usually not unilateral, it's symmetrical. It's on the midline. And this is a terrible condition. Once I learned about this – Maria Turner,[55] who is a wonderful person in this hospital [the NIH Clinical Research Center] who's won teaching awards and stuff, sought me out to see some of these patients with her. I was a little leery at first, and we actually – There were some very charming funny times about these studies. But, so anyway, we devised a testing protocol where we devised over 20 areas that we would stimulate with a little cotton wisp. And she'd bring these patients in, and I'd be at the head of the patient, holding my scales, and we'd stimulate these 20 areas. And I didn't know what areas they were. We had them letter coded, and I would write down responses. Then we looked at the responses and we found there were several areas that [were] very sensitive to touch, and were the same kind of focal areas that we had seen in these RSD patients. And immediately, you know, given I had just come from that study, and rigid thinking, whatever, went, "Hey, if the only tool you have is a hammer, you tend to treat everything like a nail." So I said, "Let's inject, let's anesthetize these focal areas." And these turned out to be the openings to the major vestibular ducts, the Bartholin's glands and the Skene's ducts,[56] and there's this sort of like a little box arrangement. And so we put in a tenth of a cc (cubic centimeter) in each one of these spots in one patient, and magically, almost all her symptoms immediately disappeared. I mean, she could – And then we'd stimulate these areas again. So

we actually did this. We did six subjects, and we were slow in writing it up. We presented the work, and now we have to write it

But so the idea is that this is the same syndrome. There is irritation at the opening to the glands, maintaining this central process accounting for it. I mean, the allodynia – even touching the pubic hair was painful. The pain would spread to the inner thighs. Sex was impossible. One of Kevorkian's[57] clients apparently was one of these women with this who committed suicide. I mean, there's no posture that's comfortable. And the only real fix has been a major surgical resection of that entire area, which women have done. And probably when they do that, they seal off these ducts, which probably cause the irritation. So that is a natural extension of this work. Again, it's targeting – this is probably where the pathology is. And it's very interesting that the most pain that disappears is along the midline. If you think of these four areas as each spreading allodynia, they kind of combine and overlap along the midline. So that study. And then we did sort of a [auxiliary study with] placebo controls and got a very nice result, so we now are talking about gearing up and getting ready to replicate it, where you have the design set in a much more controlled way, which we really wouldn't necessarily use placebos, because it's very difficult to do with these patients. They wouldn't come back. But we would actually do things like double-blind, give very short- or long-acting local anesthetics, and then have them take diaries to measure how long [before the pain] comes back and other ways of controlling it where we still give them some relief. But that was a problem. There were things in the midline, although we still had normal skin to test. Then, lately I've been really interested in the problem of fibromyalgia, which now here we have no control area of skin. It's total body pain, all over the place. And, of course, there's a credibility issue. You know, some people think these people [fibromyalgia patients] don't have anything at all. Some recent findings about elevated substance P levels in the cerebrospinal fluid, I think, really help them, that there is something really there, although I don't think it's a single entity. It's probably many. There are probably many disparate syndromes that have a common feature of tenderness, the mechanical [hyperalgesia], you know –

MM: Oh, yeah. You mean, the term describes multiple etiologies.

RG: Yeah, probably it's not a [single condition]. So I had a chance to collaborate – Oh, for years I've been talking to a rheumatologist at Georgetown, Dan Clauw,[58] who's been very active in this field. He actually was one of the people studying Gulf War syndrome,[59] and basically his hypothesis is that what you see in there is the same symptoms in a normal population with the same frequencies, or maybe stress has exacerbated them a little bit. Fibromyalgia is defined is by increasing pressure stimulus, which, as a psychophysicist, has a real psychological compound in it. You can give orderly data [that looks] sensitive, even if you have an artificial limb that you're pushing against. So one of the studies [on which] I consulted with him and designed is looking at a whole multitude of all of our psychophysical things, multi-random staircase, scaling, whatever, and give these people everything and do more than one modality. And we've actually just completed – we're writing up an abstract for the Vienna meeting, and we've completed some of that work. And we actually find that there's sensitivity shown in all measures. It isn't psychological. There really seems to be a consistent sensitivity across modalities and methods, and it's the same no matter what method you use. Even the most sophisticated methods we have show the exact same level of sensitivity as a simple clinical procedure. I mean, the methods were different. I mean, when you do a clinical procedure, the threshold is biased because of delays in reaction times, but the difference between the normal population and the patients was preserved over all the methods. So that's one.[60] and then the other aspect of the study which also is a major change for me is, for years I've avoided anything high tech. We've always been [using] chewing gum and injections and heat and verbal scales, and the way you measure pain is ask people. So I finally have succumbed to getting involved in the high-tech stuff, which is brain imaging. I've been involved in some early PET

studies[61] with Mike Iadarola,[62] and I had the opportunity to sort of design and run my own with the help of Bob Coghill,[63] which is something we can talk about that, the result of that PET study. That's something to put over here on the shelf. And now I'm doing functional MRI.[64] I'm learning that because it's just really fascinating because it's a methodology that's very new. There is no really right or wrong way to do it yet. People are developing it, and it's more difficult to do than PET, and it's like an infant science compared to PET, which is much more mature. And that's just really fun to be part of that, this community of people, and also to, you know, each person can really work out and explore themselves and what it's doing.

One of the studies I'm looking at is pressure pain, and instead of heat, pressure is actually very useful [as a stimulus] because I can give it repeatedly at the same spot. And, secondly, we just had a clinical study where we were looking at pressure pain in patients with fibromyalgia, so trying to see in a clinical study if we can not only characterize the response to pressure, but see if it's different in these groups. As of right now, it's only half over, but there's some evidence – Certainly, things are different. Whether they'll persist and be stable, we don't know, but clearly there are significant differences between the populations at this time. So that's been really sort of fun, and that's what these things are. This cost $2,000; that cost $50,000. So these workstations just run all the time doing these analyses.

MM: So, tell me a little bit more. I'd like to know a little bit more about both of these, actually.

RG: The PET.

MM: Yeah, and the fibromyalgia. I mean, the fibromyalgia describes a variety of different problems, probably. But we're talking about this kind of generalized sensitivity that can really stretch all over the body; it's not localized in any one particular place.

RG: Right. There's this idea that there's these tender points, and tender-point counts, and really what we're – It's our working hypothesis that the sensitivity is not just from finding these tender points, but it's everywhere. And, actually, in our studies, we've just conveniently used pressure on the thumbnail, on the thumb. A little thumbscrew is our stimulus, so we just don't even – Other people are looking at tender points, so we're just using that as our measure. All the psychophysical procedures I've described have been applied there and we see differences. We're doing it for imaging, as well because the thumb has a nice representation in the brain, so it's a big area. It has more representation than the entire arm. It's a good spot, is another reason.

MM: It's very sensitive.

RG: Yeah.

MM: That's great. So do you have a hypothesis, or are you exploring?

RG: Well, it's kind of like this is a new field of study. The idea is that we're giving -- Well, first of all, looking at, just characterizing what's this response to pressure using functional MRI. Now, there've only been a couple of people who have done maybe one study like that, or maybe two, but nobody's really done much with pressure in any PET or MRI [study]. There has been some recent stuff [using] MRIs. So in our own hands, what can we reliably do with pressure? And it's very fascinating. We can get, you know, I can show you individuals where we get a significant result in a person in 10 minutes versus a group of people [after some] hours in a PET study. In just 10 minutes. So we're trying to characterize that. And you find there's variability amongst people. I mean, PET [studies] never really

look at the variability amongst people. There's tremendous variability. And so we're trying to get a handle on that as well. The kind of interesting [finding] is that, to produce, to squeeze the thumb to produce intense pain in a person, you need a lot of pressure, say, 10 pounds. Let's say 10 pounds. Actually, for some people, it's exactly 10 pounds. While to get the same amount of intense pain in a patient, you only need four pounds. So what we're doing is – OK. We're going to give four pounds to a patient to produce intense pain. Now we're going to give a normal volunteer 10 pounds to produce intense pain, or we're going to give him four pounds, which is the same intensity, and then just look at the brain response of those. What does a normal [brain show]? Does the patient match the same intensity or the same experience? And the more their response matches the same experience, then there is this sensitization. There's some abnormal processing where they have increased tenderness. There's evidence for it. If the four pounds matches four pounds, then there really is no evidence.
So it's just kind of like, which way does this thing, these two conditions in normals – Now, I've got to assume that I can even separate those apart. Maybe I can't, but it looks like we can. And then like, which way, where does the patient fall? So the hypothesis – There is no hypothesis. It's just a measurement, so it can't go wrong. And it can all fall apart if we don't get anything in between the patient and the normal volunteers. But, if not, we'll try to work something else out.
But it's also – fMRI has never been used for anything clinical. There's no clinical utility yet. It's an experimental method. And so what's interesting about this study is that it might be one of the first examples of the clinical utility of actually characterizing patients in a way that – I don't know. And that might be almost like your holy grail in pain that I, you know – It would be pretty amazing if this was that good a cut, but it's where we're focusing.

MM: Yeah. That's a good way of putting it. Wouldn't it be a very expensive way also, expensive to do this on pain patients routinely?

RG: Yes. Very good point. Well, I think – One of my talks has always been, when people think about pain measurement, they don't think about the purpose of pain measurement. Well, one of the purposes might be medical-legal determinations, and where you have to make a decision about somebody that's going to be very expensive to someone [involving disability payments], perhaps there are certain situations in which the cost of this – And it's ambiguous enough that – Whatever. But, again, I don't think there's any evidence on a case-by-case base that this can do it. But I mean, actually, even PET can do single individual subjects now too, but FMRI really can do individual subjects. It's hardly been explored, but it would be very interesting to look at, can this make distinctions amongst people that hold up? And FMRI has certain advantages over PET methods, and there are still some things that PET can do that FMRI can't do. But both of them are very – can only look at certain aspects of brain processing.

MM: Yeah. Can you make that distinction for me?

RG: Well, let's compare it to like the evoked potential of something, which we have trouble localizing. It looks at the very primary response that happens in milliseconds and shows how things move around. OK? A PET study looks at processing that happens over a minute. It has to be focal in one area in one minute. Now, the [neural activity] could have been bouncing around a lot, but it has to – They're very different things. FMRI, instead of minutes, can reduce that to seconds. But, still, a lot could go wrong in one second. EEG [electroencephalographic] methods can look at the very first seconds, but they have to look at synchronous activity. The activity has to be in phase and go in and out together, you know, very fast time scales.

MM: Well, EEG is pretty one-dimensional, really, isn't it?

RG: Well, no. They have ways they can put [electrodes] all over the head and they can actually model in three dimensions the signal, where it's coming from, or with these magnetic systems to measure magnetic things. The modeling is similar in both. But [it can be on a very] fast time scale, but it has to be synchronous. PET and FMRI don't have to be synchronous, but [the activity] has to be focal and it has to be sustained for a period of time of either seconds or minutes to be observed. So fast, asynchronous activity right now that happens in a few seconds probably can't be imaged by anything, you know, except these optical methods where you have to like take the top of your head off and put a camera on, which we're [experimentally] doing now both in humans and in monkeys.

MM: Really? But surely the humans are quite ill.

RG: Yeah, oral surgery. They don't do it in normal volunteers. Right.
But there are distinctions between the methods. I mean, [in] functional MRI, you have to do something kind of that you can turn on and off many times. So if you can study – We've done PET studies that kept [on going], where you just measure and then give the stimulus and it lasts a long time. It would be difficult to do that in an MRI study because the scanner, the signal is very small and the scanner drifts, can drift over time and sensitivity, and that drift can be greater than your signal, so you always have to kind of go back and forth between the two conditions to correct for that. But, you know, it's very off the topic, but one of the things I like about fMRI is kind of an analogy with pain. When I first got into pain, I'm sure we talked about this our first meeting – it was such a wide-open field and little was known about it. It was kind of fun to work in it because you could do very neat, simple things, and now it's a lot more elaborate and there's a lot more knowledge base. It's hard for any one person to know it all and do it all. In FMRI, the situation is growing, but it's still kind of like in its beginnings, so it's kind of fun to get involved with something in the beginning and go with it.

MM: I kind of see where it's going. Are other people using MRIs in pain? I haven't heard too much.

RG: It's funny. Five years, six years ago, [no one was] using PET, and now there's a lot of PET studies. Last year, [at the] Neuroscience and APS[65] [meetings], there was maybe two or so, and now there are many. So it's gone up an order of magnitude in the past year. PETs are very expensive and they're far and few between; but almost every medical hospital has an MRI machine, and many of them, they have to be adapted. You know, you have to get an accessory pack to do functional MRI usually, but it's attainable, and so a lot of people are doing it. And then the PET studies are exciting in that there's a rigid protocol, there's a cyclotron, radioactivity is coming up, you have a rigid sequence. If you slip up on one of your scans, everything is usually ruined. That's exciting. Well, FMRI is so much more flexible. You can stop it and start it over again; you can do people day after day after day, one person, you know. You can do some things that you can't do with a PET. And there's no radiation. But I don't know. There are critics of these fields too. I mean, the brain imaging – the idea, there were these first-generation studies where you showed activations, and this is the response to pain. Now what are you going to do? And I think people are starting to do more involved things. They're starting to show [neural] networks and how things are connected together. They're starting to show the effects of attention on cognitive manipulations. So I think all these fields are going up to another level.

MM: I can see how it would really allow you a lot more flexibility and a lot more dimensions than some of the studies that have been done before. Electrophysiological recording, which is such a very old and well-established technique, but really has – You know, you have to give a specific stimulus and see if anything will happen. In whichever area, you're always working in a single area.

RG: It's funny you bring that up. One of the puzzles about pain is the wide dynamic-range neuron, that you can activate it with lightly brushing the skin and it doesn't hurt; you get high activity in it, but it's not painful. You can also activate it by noxious things, and the same level of activity now produces pain. Well, how does it know the difference? And that's an amazing puzzle. And probably, you know, one of the examples from the electrophysiologist's view is, looking at one neuron at a time, is there a difference in patterning? There's information in the pattern of the pulses, not just their frequency, but the way they're clumped together. And I know Fred Lenz,[66] who I've been collaborating with at Hopkins, looks at that in patients. But probably also, there's tremendous information available in the pattern of these over the population, and that's one thing that a single neuron at a time – Well, the needle can't tell you, while perhaps some of these other methods can give you an idea.

MM: Comparative data.

RG: Yeah. But I'm not sure that anything we've talked about can do it yet either, but certainly that information is there.

MM: Accumulation of data.

RG: Yeah. And comparing across populations and patterning differences. So some of these optical imaging methods where you look, there's sort of like a series of resolutions, you know, with PET being one example and probably single-unit recording on the other. But there are these optical methods where you can actually look at a lot of activity in real time and see [several] populations of neurons [and look at] their interaction.

MM: You seem to know more and more, and yet somehow it doesn't make it any less clear. Pain is still such a mysterious thing. I was just at this talk. Alan Feingold gave a talk on the gene work. There was this guy in the second row. I don't know where he was from, but he kept asking – I'm sure he's a distinguished, eminent scientist. He kept saying, "I don't know anything about pain." It was very clear. I mean, he was asking elementary questions.

RG: It's fascinating.

MM: It's still fascinating.

RG: Yeah. It's a puzzle. It's very hard to measure it, and even though I'm doing imaging, I still think asking people [about pain] is probably one of the best ways. And, you know, the knowledge, it's more than just an academic discipline. It really can benefit people who are suffering. I think once you have something severe, that you've had some sort of intractable pain or something that's persisted for a length of time, you empathize with that situation.

MM: Yeah. You can really get a sense of what it's like. That really helps. I've been watching Elisa [Rosier][67] do PET studies, and is there a correlation between reported verbal pain scores and observed brain activity on PET or MRI?

RG: Yes. Actually, that group, Elisa and Bob [Coghill] and Mike [Iadarola], have just actually published and are working, doing studies where they actually give different levels, and they find a correlation in the activity of certain structures.[68] So that, you know, there seems to be evidence for that. I think it's interesting that you – Why would the brain care about the magnitude of a pain stimulus? I mean, I'm going to be doing that work as well, but you have to wonder, why does the brain care? Maybe one of the

reasons the brain cares is, again, those first few seconds, an animal in the wild steps onto a hot rock that's been basking in the sun, and immediately you have to make a decision, do you stop or keep going. So there's a magnitude of pain, the rate at which a foot is getting heated. You have to immediately know. I think it's probably one of the more natural things. Or you step on something that has some degree of sharpness, the edge of a rock, which may injure you or not, and you need to adjust, which has a major interaction with the motor systems, you know, which I think is also interesting. What are the pain issues in the wild? And when you think about that and the modulation of pain, what is pain and the modulation of pain in the wild? And [the athlete] study, I was able to do with Wendy Sternberg[69] at Haverford, which – I don't know if we talked about that last time or not.

MM: No. I'd like to hear about it.

RG: We just published that this year.[70] We did a study with competing athletes where we measured pain sensitivity in athletes before, way before the competition day, immediately after competing, and then a day or so later. And we had this hypothesis that it was the competition that, you know, we were looking at the anecdotal evidence from the Anzio Beachhead, the Anzio Beachhead, Beecher,[71] the idea that all the stuff that wasn't so much – You know, there's obviously stuff on athletes being fit or physically exercising producing analgesia. And some of that work was that athletes show analgesia. They're more analgesic because they're fit. But what we looked at is like a competitive interaction, which would be more like a situation in the wild with an animal in which analgesia systems might come into play. When you're fleeing from a predator, you know, and you're a little hurt, it's best to just ignore it, you know, just like playing football on a broken ankle or something.

So we designed a study where we had a cognitive sport that wasn't that exerting, which is fencing. We had a physiologically stressing sport, which wasn't that competitive, we thought, which was track. And then we had basketball, which is both. And we did all these measurements and we assumed we'd see a difference. Well, we kind of really didn't. In some ways we did, but it turns out that all these things are both stressing and competitive. The track runners say that they compete against the clock, and fencers say, "Look, we're not in that great shape, and we get really exhausted doing this." But we did find similarities and differences amongst the athletes, and it was published in *Pain* this past year. That was really fun. And people said, "What are you doing involved in this?" But, I mean, you're involved in it because this is a very natural, this is really – why would you have these analgesic systems? And so, it was an opportunity for Wendy and I – I mean, she'd been an animal worker – for me to collaborate [with her] and also get on a university campus and work with students. It was really fun.

So we're doing a new one this year where we kind of replicate it, but we're trying to find some activities that are very competitive and that have no athletic situation at all. We were thinking of playing chess, but now we're going to use some video game competitions with people who are equally skilled. And then we're also going to have people who are just doing aerobic exercise on a treadmill where there really is no competition. So we're trying to broaden things and then still have like track and basketball players, and then refine some of our techniques as well. So we're at phase two, which we're just beginning.

MM: I think that's really important. My sister is an athlete, and she goes to this sports medicine clinic. She swims, she skis, you name it. If they'll let her do it, she'll do it. And they put a lot of emphasis in her programs on sort of functioning in such a way during competition that the pain won't bother you. I mean, they teach you to be analgesic – at least that's what they claim that they're doing. And yet, at the same time, being, we hope, responsible physicians, they want to teach you not to ignore pain, which is

actually potentially dangerous. So it's very interesting. I talked to her about this because I did think she was putting too much pressure on her body. She's like that. She does rough-water swims to Alcatraz.

RG: Oh, I see. She's macho.

MM: She says, "Yes, but I know when I'm doing too much." And if we could find a way to sort of harness that ability or figure out what was going on there, I think that would be really fascinating.

RG: Yeah. I'm going to try to show you a Web page here while we talk. So that's really interesting. And we're talking about physiology stuff, but I think the idea of a natural placebo and treatment things and these natural conditions that evoke analgesia, I think are also just really – That's the interesting thing about pain. You can be really biological, and yet it has [these subjective components that you can't ignore]. You know, it encompasses so many different disciplines and it's really fun to be involved there, and you can choose to work in more than one of these at the same time.

MM: Yeah. Well, it's good to have talked to someone who's still excited about it.

RG: After all these years, yeah.

MM: I think it's fascinating. I've only been studying this for a couple of years.

RG: So it's good we brought that up, because that was one of my other major avenues, which I'm now doing more, is these natural situations where – I mean, because one example is, I mean, well, what I'm thinking of while I'm doing the imaging: Why would pain activate certain structures? Why is pain important to an animal? And, certainly, fleeing is one. No. One is being injured, the dog hit by the car, that whole system of escape and then recuperation. But the other is fleeing. Well, two is like say you sprain your ankle, which Dan [Clauw] and I are all interested in. We're interested in the motor system, and that the intensity of pain really matters. If you have to run on a hurt foot, you make a certain compromise in your gait that exactly attenuates for it, and this is done automatically. So probably these other systems are very tuned into magnitude of pain, and that's probably what cares about the magnitude more than anything else. We don't know. And then there are these situations – So that's not going to be modulated now. It's just you're making a compromise, and I want to get from here to there, and yet I don't want to really – And how important is it for me to get to there? I mean, it could be so important that I don't care if I trash my ankle for the rest of my life. I'll live. Or it's not that important and I still want to limp a little, or I'm not going to move. So there are those situations. And then there are situations where analgesic systems come into play as well. I talked about the PET study I did. This kind of relates too, in that lots of -- These are kind of caveat studies, and I'm trying to look at some of them. coming at the PET things. I've been doing a lot of them. What are some of the issues of PET studies? One is that, you know, that they have a certain cognitive sameness, that a person is laying there on the table, and then they're about to be hurt for a minute or so, and then after the minute is up, the hurt will go away. So imagine if you're in that situation, you have apprehension and anticipatory anxiety, and then there's actually the event itself, which you know will be short-lived, you know you can stop, you know you can pull on certain coping strategies, it's all predictable, and you know it's going to end. And one possibility is that a lot of the activations you see are due to these cognitive factors, because we know that, in other areas of inquiry, cognition can produce activations of the same magnitude. So it's not unreasonable to think they'd also work in pain studies.

The PET study we did recently is we did heat in subjects, like everybody else does, and then we did a tourniquet stress task where you cut off the blood flow and exercise the hand, and you have this pain that

goes for about 20 minutes or 25 minutes, slowly rising, and the subjects have this pain. And during this painful experience, three scans came and went, but there's nothing unique about the scans at all. There was nothing, no impending episode of pain associated with the scan. The pain was just rising. And we did a very good job of rating the intensity and unpleasantness of pain, and at the end this pain was as intense and more unpleasant than painful heat. And yet the brain activation was very minimal, hardly any at all, and very different than what you see with heat.

MM: Yeah, because there isn't a cognitive element.

RG: Well, that's the most outrageous interpretation. It could be true, but a lot of people won't like that. There's other interpretations, you know, inferring neural activity from blood flow, and maybe they become uncoupled in this situation. There's also the idea that, [as] we observed in patients, there's actually a quiet thalamus. There's actually less activity. Perhaps this transition from acute pain to chronic pain response exists, occurs in as fast as 20 minutes, occurs very quickly, you know, and that fast. There are lots of different [possible] interpretations. But it's very interesting.

MM: Yeah. That's very interesting.

RG: At least different kinds of pains can show a very different signal, different responses in a PET situation. Another thing about PET is that you're not supposed to move. So it's very –

MM: That would be very hard.

RG: Well, it's a very artificial situation to lay there and get hurt and not move, and so I think a lot of the activity we always see is bracing and trying not to move in that situation as well, and the same will be – Movement in functional MRI is really bad. You can't move your head at all, and unfortunately, most of our subjects do, so we have to deal with this big movement problem. But that's also an issue as well.

MM: This is something that's always sort of bugged me about pain studies from the beginning, about experimental pain work, and, of course, Beecher talked about this as well, is that you put someone in an experimental situation, they're going to think through the situation while it's happening. You know, they have expectations and they also have certain assumptions about duration.

RG: Yes.

MM: And that no matter what you do, you can't – that's not going to replicate, even in a chronic-pain patient where you're giving that chronic-pain patient pressure on the thumb or whatever. They know that's a different situation. And there's a kind of a baseline cognition which is going to treat that pain differently.

RG: Right. And I've been an experimental pain person all my life. I've always objected to that.

MM: You know all about this.

RG: Right. Well, the thing is that there are multiple goals of pain assessment. One of them is to duplicate a clinical-pain experience, but that's just one of many, many goals. You know, there are multiple goals: There's looking at mechanisms of pain in populations that can be useful; there's looking at certain components to the pain experience; you can use pain with a patient to help get a better measure of their pain and diagnose them; there's lots of other – looking at kinetics of analgesic systems. So there are lots

of purposes, and duplicating clinical pain is only one of them. And to some degree you can, to some degree you can't, but for the parts that you can, there's a lot of utility. But I think there's lots of utility for experimental pain without having to exactly duplicate the clinical-pain experience.

MM: No, of course not. You wouldn't want to do that. It would be interesting. You could sort of isolate that cognitive area and say, OK, we know that this part of the brain here – I'm sorry; I'm talking very simplistically.

RG: Well, but any kind of thing – You know, you get right into pain experience. Any kind of unpleasantness you feel, whether it be pain or nausea or dizziness or dysphoria or tinnitus, you know, if you know it's going to last for a short amount of time or you don't have any idea of what it means or how long it's going to last, there is a cognitive difference that you can't – I mean, unpredictability, uncertainty, is a major part for pain patients' experience, other pain patients, [and] other patients' experience as well. Pain patients are additionally burdened by credibility. At least [if] people have a disease that's, you know, life-threatening, whatever, [there is] something they can show. The pain patients often have nothing. Nobody believes them.

MM: Right, right. Obviously, that's something which frustrates pain people a lot. It persists.

RG: Yeah. I mean, sometimes we talk about it. I was a psychologist seeing pain patients for many, many years. So the whole issue of seeing pain patients as a clinician, where I'm a psychologist, where I'm not going to do any intervention, I'm just going to talk to them and help them, really is – I mean, I think it's very useful for me. I had sort of one leg – You know, I wasn't completely in the ivory tower. I had one foot in the real world and seeing some of these people. I think it's very difficult to study what you do with those people, but certainly there – I mean, right away, if you have pain, you're irritable; many aspects of your life have been altered bit by bit by bit, many facets of your life. Together, each one isn't so important, but the ensemble of all those is very powerful. It's like little pieces of wax make up a ball, and then when you have to train people, you have to instruct patients, this is true, because they stop socializing as much. And you have to say, "Look, being with these friends, it's not necessary for you to put a smile on your face [like] when you didn't hurt." They don't sleep well; they don't do activities they used to do. Well, [for] many of the people, [these] are sort of [ordinary], sexually stereotyped activities – a woman, cooking or laundry; a man fixing a light bulb or mowing the grass. It just kills them that they can't do these things that they define themselves with. Sense of humor is one of the first things that goes. The biggest one is probably sleep. But all these together are devastating. And then what happens is these people have got to fight harder, and then they've got compensation systems that are unpleasant to deal with. They wish they had like a broken arm or a foot amputated or something so you could see. A cane or a brace is really cool because you've got an outward, visible sign. There are so many psychosocial aspects of chronic pain. And then any clinician who sees them for a while is good with them, but also gets burnt out, and so they have the medical establishment responding to them. I'm not saying anything new here.

MM: No. But tell me what you – I mean, there's the Fordycean approach,[72] which, you know, you can sort of teach them to, I guess, teach them to function, modify their behavior. And not everybody – I've been reading some literature lately which essentially says you're really not being fair here, you're telling the patient they have to do something, that it's their problem, they have to change, they have to make the pain go away.

RG: You're not helping the patient, you're only helping the person that has to live with the patient.

MM: Right. And it sounds like, I mean, just by being a psychologist, that you've more or less come to believe that neuropathic pain and chronic pain by and large has an organic cause at the root of it.

RG: Oh, yeah. I mean, even [thinking as] a scientist. You have to. The idea of malingering as a concept, I mean, it's such a small percentage that you ruin it for everybody. You've got to assume, give everybody the benefit of the doubt.

MM: I would believe that. But you can also argue there's a kind of cognitive alteration that, after perhaps a long period of extended pain, the person comes to actually believe that mild touch is pain even though the nervous system is not reacting.

RG: Right, right, and the body can do that for sure. We have – there's lots of examples that we haven't even talked about where people, instead of the suggestion to reduce pain, the suggestion to increase pain is very effective. That's for sure. And, actually, in some of these things, back pain is a social disease. It's a function of the worker compensation systems in the society. So how I think about Fordyce

MM: Just a question, thinking about it as a psychologist. OK, go ahead.

RG: Well, I mean, I think it's an issue of, it's like *The Trial*. I mean, patients are trapped in a system right now that's pretty awful. It's like Kafka's trial.[73] You know, I talk about uncertainty and credibility and whatever. A guy gets arrested, doesn't know why, doesn't know how to find out. They get involved in a system that's just, they can't see the end of it, they don't know what they have, often; they get different diagnoses from different doctors; they don't know what the future's going to bring; very similar issues. So, to deal with these people, you have to deal with that psychosocial [dimension], what you've created in these people. And it's the same thing – a totalitarian state could give its people the same kind of feeling. So that's so far removed from neurons. But certainly, chronic pain treatment must consider all those factors. One of those things I would do – So I was always the – You ask people how they feel, you know. [You induce] behavior so that you see what they do. And I would say, well, the stoic gets punished in that system.

But the Fordyce model, I mean, I also understand it and agree with it in many ways. For instance, my compensation system would be, OK, you can get paid well if you've been hurt, but you can't stay at home on the couch, you can't stay home with your sweetie. You have to – As a matter of fact, the hell with rehabilitation, the hell with training. You've got to come into this room that just has folding metal chairs and old high school cafeteria tables and nothing in it. You have to punch in. You don't want to go to work, you have to go to this room instead. You punch in and you just sit there all day long.

MM: Oh, my lord.

RG: You're not allowed to have books or TV, nothing. And you get your full salary. You go there and you can get your full salary, and you can talk to people, but you can't play cards. You've just got to sit there, and then you punch out. That would be my simplistic answer, and you'd get full salary. Or you get, say, two-thirds of your salary. You get like, in the good compensation systems, in Scandinavia and stuff, you would get that, but you couldn't – I mean, there are things you're avoiding from work, and there's also the reinforcers you get for being at home. So immediately, that would take away all the reinforcers for getting at home, and also, you wouldn't be able to watch TV and soap operas. You wouldn't be able to do any of the things that you're going to do laying around. And you can lay down. Maybe there'll be couches; you can lay on couches if you want. But you couldn't, you know –

MM: Well, if you let them lay on couches, they'll probably all just sleep.

RG: Yeah. You're not allowed to sleep. You've got to be alert. If you're asleep, you don't get paid. So that's my – And so, you know, would you sign up for a company [where] they say, "Here's our compensation system. If you're injured, once you're out of the hospital, you've got to show up here every day, even if you're wheeled in, and if you don't show up, you don't get paid." All you've got to do is show up and you'll be fine. So that's – I mean, I've never published it anywhere. I want to publish this somewhere. It's my own idea. It's very simple and not that expensive.

MM: No. You're paying them anyway.

RG: Yeah.

MM: That could be very effective. Well, we have to sort of start winding this up. We're sort of running to the end. Was there anything else? What else haven't I asked you about?

RG: Oh, and I brought this up just because.

MM: We're looking at this Web site from Haverford. It says, "Haverford athletes are the subject of research on pain and competition stress."

RG: And it starts out, "Gymnast Kerri Strug's remarkable performance[74] in the '96 summer Olympics in Atlanta," so we're talking about here running on a broken ankle, you know, the whole idea of running. That's an example I wanted to [show you].

MM: Great image.

RG: Yeah. Where to begin? I think, clearly, it's been very exciting being in a field, and especially I had the opportunity to – you know, I showed up here in '74, to really be in on the inception of the field, when John Bonica was sort of a younger guy and used to put me in headlocks, and to grow with the field and see it expand like this, and also, I mean, there aren't that many frontiers left in a sense. This is a field that covered a whole medical area, so many facets, and to see it grow to the place it is today. And I think that many battles have been won in terms of recognizing pain as a disease state, as an entity, and in the treatment of pain. It's gotten much more complex. We know a lot more. We still haven't solved many problems. What's also fascinating about the thing is it encompasses molecular biology all the way up to psychotherapy, spiritual things, or discussions of psychological issues like we just talked about, and so to be in the field, you can partake of these multiple disciplines. Going to meetings are very exciting because they're much more fun. People aren't just one discipline. There are so many different disciplines, there's a more buoyant air about it, although it's a very serious business. I mean, I don't want to make light of it. Again, I guess as an academic psychologist, instead of studying pigeon behavior or something, I think this has direct benefits, and then you can help people suffering with pain as well. And the field is certainly – You know, I think it's gone from a recognition that people do have pain that now that we can give people who don't have malignant pain opioids,[75] and that's one thing we haven't talked about. We should have included that. You know, I think right now the society is very pro-opioid, and all my psychologist friends are like really very upset by this, opioids being used. And on the one hand, the fact that you can give opioids to people without pain and relieve their pain is an extension of the battle we've all fought, that pain should be recognized and fully treated. It's always been undertreated. And the people who give opioids use that as an argument. But then, on the other hand, these are people who have tremendous drug-company resources behind them and are getting lots

of money to do it, so you wonder about the ethics of that. And then I wonder why – But if they can help people, why are the psychologists so upset? And, actually, I had to give a talk in Australia last year. I was in Tasmania and Australia, and a third to a fourth of the world's legal opium supply is cultivated in Tasmania. So, you know, they had a meeting on "Pain and the Poppy," was the title of their meeting. And I think the answer it comes down to, the problem in this country is that people who give opioids to patients indiscriminately, those who are failures, they are basically dumped onto a multidisciplinary pain clinic or psychologist, where they come in and monopolize most of the resources of the psychologists. So the person giving it, he gets to reap all the rewards and successes, but he never gets punished for the failures, and somebody else gets the problem, the failures, and they don't get any benefit of the rewards. So the answer is to, you have to interconnect these things and put the treatment – the glorifying and the successes and the punishment for the failures have to be in the same institutional system. It can be the same clinician, the same clinic, the same hospital, the same insurance company, but whoever's giving it also has to take, be responsible for the failures. And that will create the necessary conditions – this is like signal detection theory – that the person getting it will become much more astute and discriminating who they give it to automatically. And that would satisfy all the psychologists. As a matter of fact, then that person can hire psychologists for huge salaries to take care of these people and give them the resources, and that would, I think, solve that problem.

MM: Yeah. That really sort of goes back to the point that clinics should have pain people on their staff, people who are responsible for pain; whereas most people get, their pain is treated by almost anybody, the GP or the oncologist or the rheumatologist, and not that most of those people aren't really good people, but most of them really don't know – they don't understand pain as a whole problem.

RG: Right, they don't. And HMOs, what HMOs are doing now, they're taking multidisciplinary pain clinics and ripping them apart, and then having their own psychologists on staff [handle the pain patients]. They might have procedure people, like anesthesiologists, who'll do their stuff, but the social aspects and the physical therapy, they do in-house and it's a huge mistake. It's almost like it's regressed from what the heyday once was.

MM: In a way, it has, but it gets to where it seems like an uncomfortable evolutionary process. I hope that's what it is, and it's going to eventually [evolve into something more effective]. Because I don't know that the pain field – We can't go back to the way we were, with people sort of ignoring pain altogether. We have about 60 seconds. So, what about working at NIH? Do you think that was the right career choice overall, as opposed to being, I don't know, in academia or in private practice, completely in private practice?

RG: Oh, for me, yeah, it was definitely the right choice. I mean, I'm sort of an idea person. Actually, the experience with Ron was a very wonderful experience. I mean, we were sort of family in many ways. I mean, we all acted out together and we went on adventures together. It was something I really treasure with our whole group. And basically, I think in some ways that's history now. I mean, I don't know what our future will be, but it won't be like it was in the past. But being at NIH and being with this group and seeing it evolve over the years and a bunch of individuals has been a very, very special job situation for me. And I have no regrets. I would have done it the same way if I had to do it over again.

MM: OK. We're going to sign off now, and it's possible we may come back, if I have other questions, but in the meantime, we're going to sign off. It's ten to five.

END OF INTERVIEW

[1] Richard H. Gracely, PhD, left NIDCR in 2002 for the University of Michigan School of Medicine, where he was Professor of Internal Medicine (Rheumatology) as of 2015 and actively involved in pain research.
[2] A transit is used in surveying to measure both horizontal and vertical angles.
[3] In Greek mythology, Sisyphus, for his hubris and deceit, was condemned by Zeus to endlessly roll a large boulder up a steep hill, only to have it roll back down again.
[4] Villanova is a Catholic university in northwest Philadelphia, founded in 1842.
[5] John D. Corbit, Jr. (1920-1973) was a physiological psychologist at Brown, known for his work on emotion and motivation.
[6] Italian-American biologist William Montagna (1913-1994) initiated the Montagna Symposium on the Biology of Skin at Brown in 1950 and moved it to Oregon Health Sciences University in 1965, when he became Director of the Oregon Regional Primate Research Center. His younger colleague Walter C. Quevedo, Jr. (1930-2010) remained at Brown throughout his career, from 1961 until his retirement in 2002.
[7] Russell M. Church has been Professor of Psychology at Brown since 1955, where his research has focused on the ability of animals and humans to discriminate time intervals, and adjust their behavior to the temporal constraints of tasks.
[8] Trygg Engen (1926-2009) is considered the founder of the psychological study of olfaction. He was Professor of Psychology at Brown from 1965 until his retirement in 1991.
[9] Signal detection theory in psychophysics seeks to explain how organisms differentiate information-laden patterns, the sensory stimulus or signal, from random patterns, or noise.
[10] See for example Jones B. Signal detection theory and pain research. *Pain* 1979 Dec; 7: 305-312.
[11] Evoked potentials are electrical potentials recorded from human or animal nerves following presentation of a stimulus.
[12] GSR, or galvanic skin response, is a measure of the electrical conductance of skin.
[13] 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.
[14] Yolanda Roth is an orthopedic surgeon at the Washington DC VA Medical Center as of 2015.
[15] Alpha motor neurons are the large neurons of the brainstem and spinal cord that innervate skeletal muscle fibers; gamma motor neurons innervate muscle spindles, the sensory receptors within muscles that detect muscle length.
[16] Lorrin A. Riggs (1912-2008) was a member of the Brown University faculty throughout his career; he was first appointed there in 1938 and retired in 1977 as the L. Herbert Ballou University Professor and Edgar J. Marston Professor of Psychology. He was internationally known for his research on the mechanisms of vision.
[17] In 1968 Ronald Melzack and Kenneth Casey described pain in terms of its three dimensions: "sensory-discriminative" (sense of the intensity, location, quality and duration of the pain), "affective-motivational" (unpleasantness and urge to escape the unpleasantness), and "cognitive-evaluative" (cognitions such as appraisal, cultural values, distraction and hypnotic suggestion). They proposed that pain intensity and unpleasantness are not simply determined by the magnitude of the painful stimulus, but are modified by cognitive and affective information.
Ronald Melzack (1929-), emeritus professor of psychology at McGill University as of 2015, has been one of the leading theorists of the pain field for 50 years; he developed the gate control model with Patrick Wall in 1965 and the McGill Pain Questionnaire (see note 18) with Warren Torgerson in 1971, among other significant achievements. Warren S. Torgerson (1924-1999) was professor of psychology at Johns Hopkins from 1964 until his retirement in 1997. Dr. Kenneth L. Casey (1935-) worked with Melzack as a postdoctoral fellow at McGill; as of 2015, he is professor emeritus of neurology at the University of Michigan in Ann Arbor.
[18] The McGill Pain Questionnaire, first published in 1971 by Ronald Melzack and Warren Torgerson, is the classic verbal descriptor pain scale. Patients select seven words from a list of 77, divided into 20 groups, to describe to their clinicians the intensity and quality of pain they are experiencing. (There are also shorter lists). The McGill has been applied to many pain conditions and translated into several languages besides English. See Melzack R, Torgerson WS. On the language of pain. *Anesthesiology* 1971 Jan; 34: 50-59.
[19] Bernard Tursky (1918-2002) began his career as a technical engineer at MIT. His skill and innovative ability in developing and programming experimental equipment led to recognition as a researcher and an eventual appointment as professor of political science, psychology and psychiatry and behavioral science at SUNY Stony Brook in the 1970s. He retired from SUNY in 1985. His Pain Perception Profile was first presented in 1973; it incorporated three dimensions: intensity, sensory quality and unpleasantness, but was superseded in clinical practice by the McGill Pain Questionnaire which was simpler to administer. See Jamner LD, Tursky B. Discrimination between intensity and affective pain descriptors: A psychophysiological evaluation. *Pain* 1987 Aug; 30: 271-283.
[20] Gracely RH, McGrath P and Dubner R. Ratio scales of sensory and affective verbal pain descriptors. . *Pain* 1978 Jun; 5: 5-18; Gracely RH, McGrath P and Dubner R. Validity and sensitivity of ratio scales of sensory and affective verbal pain descriptors: manipulation of affect by diazepam. *Pain* 1978 Jun; 5: 19-29.
[21] Gracely RH, Dubner R and McGrath PA. Narcotic analgesia; fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations. *Science* 1979 Mar 23; 203: 1261-1263.
[22] As of 2015, Patricia McGrath is Professor of Psychology at York University and Director of the Divisional Centre of Pain Management and Pain Research at the Hospital for Sick Children in Toronto, ON.

[23] See Cliff N. Adverbs as multipliers. *Psychological Review* 1959 Jan; 6: 27-44. As of 2015, Norman Cliff is emeritus professor of psychology at the University of Southern California.
[24] Allen Parducci is professor emeritus of psychology at UCLA as of 2015.
[25] The normal (or Gaussian) distribution, named after the 19th century mathematician Friedrich Gauss and also called the "bell curve," shows the probability that any data point will fall between any two real limits, as the curve approaches zero on either side. An Ogive curve (S-shaped) is the graphic representation of a cumulative frequency distribution for a given set of data.
[26] Patients specify their perceived level of pain on the VAS, or visual analog scale, by indicating a position along a continuous line between two end-points ("no pain" and "worst imaginable pain").
[27] See: Doctor JN, Slater MA and Atkinson JH. The Descriptor Differential Scale of Pain Intensity: an evaluation of item and scale properties. *Pain* 1995 May; 61: 251-260.
[28] Torgerson WS. *Theory and methods of psychological scaling.* Wiley, 1958.
[29] Grushka M and Sessle BJ. Applicability of the McGill Pain Questionnaire to the differentiation of "toothache" pain. *Pain* 1984 May; 19: 49-57. Pulpitis refers to inflammation of the tooth pulp.
[30] W. Crawford Clark and Malvin N. Janal of Columbia University and the New York State Psychiatric Institute. Clark is considered a leader of American psychophysics.
[31] Donna M. Kwilosz is a Clinical Psychologist in the Interdisciplinary Pain Clinic of the Department of Neurosurgery at the University of New Mexico.
[32] Gracely RH. Evaluation of multi-dimensional pain scales. *Pain* 1992 Mar; 48: 297-300.
[33] Dennis C. Turk held the John and Emma Bonica Endowed Chair in Anesthesiology and Pain Research at the University of Washington as of 2015. He was an original member of the International Association for the Study of Pain (IASP) and a pioneer of the use of cognitive-behavioral therapy in pain management.
[34] See note 21. Fentanyl is a synthetic opioid analgesic that acts rapidly and is highly potent.
[35] *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. The12th edition was published in 2011.
[36] [36] 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.
[37] Diazepam is a benzodiazepine tranquillizer widely used to treat mild anxiety syndromes, insomnia, panic attacks and other disorders. First marketed as Valium by Hoffmann-LaRoche in 1963, it was one of the bestselling drugs in the US from 1969-1982 and remains the most well-known and frequently used of its class.
[38] Gracely RH, Dubner R and McGrath PA. Fentanyl reduces the intensity of painful tooth pulp sensations; controlling for detection of active drugs. *Anesthesia and Analgesia* 1982 Sep; 61: 751-755.
[39] Robert Ader (1932-2011) was an American psychologist and cofounder of the field of psychoneuroimmunology, which studies the links between the brain, behavior and the immune system. He was Director of the Division of Behavioral and Psychosocial Medicine at the University of Rochester until he retired in 2011, a few months before his death. For his work on placebos, see Ader R. The placebo effect: If it's all in your head, does that mean you only think you feel better? *Advances in Mind-Body Medicine* 2000 Winter; 16: 7-11.
[40] Naloxone is the primary opioid antagonist and will also block the action of endogenous endorphins.
[41] As of 2015, Jon D. Levine was Professor of Medicine in the Divisions of Rheumatology and Clinical Pharmacology, and Clinical Pharmacology and Experimental Therapeutics at the University of California San Francisco; and Howard L. Fields was Professor of Neurology and Director of the Wheeler Center for the Neurobiology of Addiction at UCSF. Both are recognized as leading researchers in the field of pain.
[42] See Levine JD, Gordon NC and Fields HL. The mechanism of placebo analgesia. *Lancet* 1978 Sep 23; 2: 654-657.
[43] See Gracely RH, Dubner R, Wolskee PJ and Deeter WR. Placebo and naloxone can alter post-surgical pain by separate mechanisms. *Nature* 1983 Nov 17-23;306: 264-265.
[44] Goldstein A and Grevert P. Placebo analgesia, endorphins, and naloxone. *Lancet* 1978 Dec 23-30; 2: 1385. Avram Goldstein (1919-2012) was Professor of Pharmacology and founder of the Department at Stanford University; Priscilla Grevert was also a Professor in that department.
[45] The International Association for the Study of Pain (IASP) holds World Congresses every three years (since 2008, every two years) which bring thousands of pain researchers from all over the world together. The Ninth World Congress was held in Vienna, Austria, in 1999.
[46] Audio analgesia uses white noise or music, without medications, to relieve pain; it has been employed in dental procedures, during labor and with dying patients, with inconclusive results. It was initially reported effective in dental pain in 1959; see Gardner WJ and Licklider JC. Auditory analgesia in dental operations. *Journal of the American Dental Association* 1959; 59: 1144–1149.
[47] Gary J. Bennett, PhD, was a researcher in the Neurobiology and Anesthesiology Branch at NIDCR 1978-96; as of 2015, he was Canada Senior Research Chair in the Department of Anesthesia and Faculty of Dentistry at McGill University. He is perhaps best known for his paper with Gracely on neurotoxicity (see note 51).

[48] Jose Ochoa and his colleague Martha Cline were working at Oregon Health Sciences University in Portland and Erik Torebjork at the University Hospital in Uppsala, Sweden. See Cline MA, Ochoa JL and Torebjork E. Chronic hyperalgesia and skin warming caused by sensitized C nociceptors. *Brain* 1989 Jun; 112 (Pt 3): 621-647. C fibers are the small unmyelinated nerve fibers believed to be the primary transmitters of pain sensation.
[49] The sural nerve distribution in the leg includes collateral branches of the tibial and common fibular nerves. The peroneal nerve distribution is a branch of the sciatic nerve and supplies movement and sensation to the lower leg, foot and toes.
[50] Hoffert MJ, Greenberg RP, Wolskee PJ, Gracely RH, Wirdzek PR, Vinayakom K and Dubner R. Abnormal and collateral innervations of sympathetic and peripheral sensory fields associated with a case of causalgia. *Pain* 1984 Sep; 20: 1-12..
[51] Gracely RH, Lynch SA and Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. *Pain* 1992 Nov; 51: 175-194.
[52] James Campbell as of 2015 was Professor of Neurosurgery at the Johns Hopkins School of Medicine and a noted researcher on the neurobiology of pain.
[53] Reflex sympathetic dystrophy, or RSD, is characterized by persistent severe and disabling pain without apparent organic damage, usually in an extremity. Originally recognized as causalgia following high-speed bullet wounds by S. Weir Mitchell during the Civil War, the major causalgias were grouped with similar disorders in the 1940s under the term reflex sympathetic dystrophy. In 1993, these conditions were renamed Complex Regional Pain Syndrome (CRPS).
[54] Wall PD. On the relation of injury to pain: The John J. Bonica lecture. *Pain* 1979 Jun; 6: 253-264.
[55] As of 2015, Maria L. Turner, MD, was a Scientist Emeritus in the Dermatology Branch of the Center for Cancer Research at the National Cancer Institute.
[56] The two tiny Bartholin's glands, located near the vaginal opening, secrete mucus to lubricate the vagina. Skene's ducts, or glands, are located in the vaginal wall and also secrete liquid which may contribute to vaginal orgasms.
[57] Jacob "Jack" Kevorkian (1928-2011) was an American pathologist and right-to-die activist, who became notorious after he claimed to have assisted some 130 patients to commit suicide to avoid natural deaths which they believed would be painful and lingering.
[58] Daniel J. Clauw, MD, as of 2015 is Professor of Anesthesiology, Medicine (Rheumatology) and Psychiatry at the University of Michigan and serves as Director of the Chronic Pain and Fatigue Research Center.
[59] Gulf War syndrome is a chronic multi-symptom disorder which has affected some 250,000 Gulf War veterans and civilian workers. Multiple causes have been suggested, including combat stress and exposure to various toxins. The primary treatments are psychological.
[60] See Petzke F, Clauw DJ, Ambrose K, Khine A and Gracely RH. Increased pain sensitivity in fibromyalgia: Effects of stimulus type and mode of presentation. *Pain* 2003 Oct; 105: 403-413.
[61] PET, or positron emission tomography, was developed at Washington University St. Louis in the 1970s. The technology produces a three-dimensional image of functional processes in the body, by introducing a position-emitting radionuclide (tracer) within a biologically active molecule into the system to be studied. The tracer emits gamma rays which can be detected and imaged by a computer.
[62] Michael J. Iadarola, PhD, was Chief of the Neurobiology and Pain Therapeutics Section at NIDCR as of 2015.
[63] Robert C. Coghill, PhD, was Professor of Neurobiology and Anatomy at Wake Forest School of Medicine in North Carolina as of 2015. He was a frequent NIDCR collaborator during this period.
[64] Functional magnetic resonance imaging, or fMRI, uses the change in magnetization between oxygen-rich and oxygen-poor blood (dHb, or differential hemoglobin) to detect changes in blood flow and thus in activity in the brain. It was developed through the work of several researchers in the early 1990s.
[65] American Pain Society, founded in 1977.
[66] Frederick A. Lenz, MD, was Professor of Functional Neurosurgery at Johns Hopkins School of Medicine as of 2015.
[67] Elisa M. Rosier, MD, was a pediatrician practicing in Ketchikan, Alaska, as of 2015.
[68] See Rosier EM, Iadarola MJ and Coghill RC. Reproducibility of pain measurement and pain perception. *Pain* 2002 Jul; 98: 205-216.
[69] Wendy Sternberg, PhD, was dean of Academic Departments and Programs at Union College in Schenectady, NY, her alma mater, as of 2015. She was a member of the Psychology Department at Haverford from 1995 to 2013.
[70] Sternberg WF, Bailin D, Grant M and Gracely RH. Competition alters the perception of noxious stimuli in male and female athletes. 1998 May; 76: 231-238.
[71] Henry Beecher's observations that wounded soldiers on the Anzio beachhead in Italy in 1943 reported less pain and requested less analgesia than he expected were central to his theory of the "reaction component," the centrality of cognitive and affective context to the clinical experience of pain. See Beecher HK. Pain in men wounded in battle. *Annals of Surgery* 1946 Jan; 123: 96-105.
[72] Psychologist Wilbert E. Fordyce (1923-2009) developed the original behavioral modification therapy for chronic pain patients at the University of Washington in the late 1960s, demonstrating that patients would respond to social rewards – attention and praise – with increased activity and self-management of pain. See Fordyce WE, Fowler RS and Delateur B. An application of behavioral modification technique to a problem of chronic pain. *Behaviour Research and Therapy* 1968 Feb; 6: 105-107.
[73] In Franz Kafka's classic *The Trial* (1925), Josef K. is arrested, prosecuted and finally executed at the will of an unseen, unknowable authority, without ever being told what his crime actually was.

[74] Kerri Strug was a member of the "Magnificent Seven" US women's gymnastics team that won the gold medal in the Team All-Around at the 1996 Atlanta Olympics; she participated in the vault despite having injured her ankle and later had to be carried to the podium by her coach.

[75] The controversy over the use of opioid drugs for chronic pain continued into the second decade of the 21st century. Originally strong opioid doses were offered only to patients with acute injuries or at the very end of life; this practice began to change with the introduction in 1986 of the World Health Organization's Analgesic Ladder for Cancer Pain, which advocated titrating dosage to the patient's need. A number of pain management specialists, including Kathleen Foley and Russell Portenoy, in the United States, championed similar liberal opioid practices for patients with severe chronic pain. However, the abuse of Oxycontin, Vicodin and similar prescription opioids, which came to widespread national attention in the 1990s, forced many advocates, including even Portenoy, to retreat. As of 2015, the question remained open and contentious. For some historical background, see Meldrum ML. The ladder and the clock: cancer pain and public policy at the end of the twentieth century. *Journal of Pain and Symptom Management* 2005 Jan; 29: 41-54.