ORAL HISTORY INTERVIEW
GARY BENNETT
1999
Conducted by Marcia Meldrum

Part I

MM: OK. Good afternoon. Today is the ninth of February, and we're in Dr. Bennett's apartment- Dr. Gary Bennett's apartment in Philadelphia, with an absolutely beautiful view of Philadelphia--which could easily distract us, but we'll try not to be distracted. Can you turn on your microphone and say hello so we can see if it's working?

GB: OK. Here I am. Hello.

MM: OK. I'd like to start by asking you to tell me just a little bit about your family and how you grew up in New Jersey.

GB: That's right, yes. Yeah, born and raised in New Jersey on the Jersey shore, about sixty miles south of New York Harbor. Um, an undistinguished educational career –

MM: [laughs]

GB: I went to university at New Jersey State University, which was Rutgers University,[1] at that an all-male school.

MM: Oh, really?

GB: They didn't go coed until the year after I left. The women's college was Douglas College on the other side of town. But it turned out to be an excellent school, and I did fairly well there, majoring –

MM: You were a psychology major there?

GB: Two false starts. A false start as a history major, a topic that I still love, and then an Italian major. I was the only non-Italian kid in New Jersey studying Italian. And then realizing that one couldn't make a living doing that, I developed an interest in psychology and graduated with a bachelor's degree in psychology, heavily oriented toward what was then called experimental psychology, which eventually of course merged with neurophysiology and neuroanatomy and became neuroscience.

MM: Right. Was this – you started out in history; had you had an interest in laboratory science before this?

GB: No, none whatsoever.

MM: It developed in college?

GB: It developed, the clinical psychology, which is pretty close to literature, if you look at it carefully – [laughs]

MM: [laughs]

GB: And I found that unsatisfying as an explanation because of its nonscientific basis, and then got into the experimental psychology side of it.

MM: Mm-hm. And was there any particular work that interested you while you were in college? Or professors who influenced you?

GB: My undergraduate work and my early graduate school work were on memory, a topic that still interests me also. I stay current with it, and it's remarkable – so that was what, twenty-five years ago or more – there's been practically no significant advance in the entire field during all that time.

MM: [laughs]

GB: It's still a very mysterious kind of topic. But that's what I was looking at in the beginning.

MM: That's an interesting topic.

GB: Well, it is. It's still a mystery.

MM: I took this course at NIH this fall with a professor – Well, he's working on several things, but he was particularly interested – this is where he sort of lit up and started talking about long-term potentiation, which is a factor of memory, I gather.

GB: Likely to be, although I've never been a hundred percent convinced that that's true. After all, it is a phenomenon that was first discovered in snails, who I don't think remember a hell of a lot. It's a plasticity of behavior, there's no question about that. But whether a more complicated version of that allows me to remember what my grandmother's face looked like is I think very debatable. My interest in memory began while reading Wilder Penfield's description[2] –

MM: Ah, right.

GB: -- of stimulating cortex in awake epileptics undergoing surgery. And I've always had a bit of a – not highly developed, but a bit of an eidetic memory myself, good memory for scenes

and such. And so the patients' descriptions sounded like my memory, and I thought that was, you know, exactly what memory was like. If you're almost just unbelievably rich in detailed memory of things, and then we don't access it very well – most of us don't access it very well – but all that information is stored in there. And you add up all that information every hour, every day for twenty, thirty years, and the amount of information is utterly staggering. And how is that possible?

MM: Amazing.

GB: How is that possible? And I still don't think we have the faintest idea, and I would bet that long-term potentiation is going to be no more than a very small part of the story.

MM: That's really interesting. So you graduated about 1970.

GB: Right. And one of my professors who I'd been working with as an undergraduate, Mike Eaton, actually at the time he was a graduate student; he had gotten a job as a new professor in Virginia Commonwealth University,[3] which is the state university of Virginia – the University of Virginia is private – and he had gotten a job in the psychology department there, and he invited me down to do my graduate work with him. And so for the first time in my life I went further south than Cape May, New Jersey. In those days the south had an ill reputation which was well deserved. I'll never forget my first day, driving into Richmond, Virginia, with my wife and a car full of stuff, and driving down one of the main streets on the outskirts of town past a shopping center, and there was a Ku Klux Klan rally going on in the parking lot.

MM: Oh, God.

GB: I was utterly shocked. I almost turned around and drove home. It turned out that that was not a typical proceeding; [laughs] it was an awfully odd thing, even for Richmond. But to see it on the first day –

MM: I know. That would be really appalling.

GB: – just didn't set me off well. It was appalling, yeah. So I settled in. And for the first, approximately the first year of graduate school I continued to work on memory problems. And then I got drafted.

MM: Oh, yes, of course.

GB: In those days the draft was a lottery, of course, that went by your birthday.[4] And then everyone with that birthday was further broken down into subgroups based on the first letter of your last name. My birthday and the letter Bs were the very last people to be drafted in the nine years of the war.

MM: Oh, my Lord. [laughs]

GB: I was one of the very last, probably one of the last few hundred people drafted that year. And then I had to figure out what to do. I was opposed to the war in Vietnam; I thought it was an illegitimate war, and I had decided that if I was drafted, I was going to resist going into the army. So you had three choices: you could become a Canadian, you could go to jail, or you could file for conscientious objector status. I thought running away to Canada was cowardly, and so I prepared an extensive reading list, in case I went to jail – [laughs]

MM: [laughs]

GB: And I filed for – It was a wonderful reading list; I still have it. I wish – I'm slowly working my way down it! [laughs] I had all the classics, you know; I'm just now up to Anatole France.[5] So I filed for conscientious objector status, which was very difficult to achieve, especially if you weren't a member of a religious organization like the Quakers, for example, that had a history of being [pacifist]. But I made my case and my presentation to the draft board, and for reasons that escape me still, they said, "OK, you're a conscientious objector." And then they allowed you to suggest places where you might work. A conscientious objector, strictly speaking, is drafted and has to do alternative civilian service. They don't go to boot camp, and they don't get paid, either, by the way. But you are under their [the Army's] control. But they did give you a choice. So most fellows wound up doing bedpan duty in VA hospitals.

But I had heard of a fellow across town, [at] the sister campus across town, the Medical College of Virginia, which was amalgamated into Virginia Commonwealth University but had a separate campus. I knew a fellow over there named John Rosecrans,[6] who was a pharmacologist studying opiate drugs, in particular the stimulus properties of opiate drugs and addiction. He wasn't a pain guy at all; he was interested in opiate euphoria and in addiction. And heroin addiction was a legitimate problem for the United States Army in Vietnam. So I said, "Sure; let me be a research assistant studying the problems of opiate addiction." And they said yeah. So I worked in John's lab for two years on that.

MM: Was he able to pay, or was this all gratis?

GB: I would have done it gratis, but fortunately he was able to pay me a modest predoctoral salary. And so it worked out very, very well. I learned a lot of pharmacology, a subject I didn't know anything about. And learned a lot about opiates, although in a kind of odd way – completely divorced from analgesia; it's just the other face of opiates. So two years is up, and I'm still a graduate student; I was a part-time student while doing my alternative service, but after the two years is up, I'm back in graduate school and need a dissertation project. I didn't know quite what to do. And then I met Dave Mayer[7] and Don Price.[8]

MM: Ah! The plot thickens.

GB: Yeah. That was a real turning point for me. I was walking through Sanger Hall – we were in another building – to make a delivery of something to someone, and walking down the hallway, and I just happened to peer into a laboratory as I walked by, and it was just this extraordinary sight. Mayer was sitting in a kind of rocking chair in front of this enormous bank of loudspeakers and amplifiers and oscilloscope screens, calmly, elegantly smoking a cigarette as he twirled – you could still smoke in your lab in those days – as he twirled knobs. And to his right, Don Price is in a big Faraday cage.[9] Now, in those days amplifiers had very poor common mode rejection, so electromagnetic radiation from elevator motors, power lines, typewriters, that kind of stuff got amplified along with your neural signal. You had to screen all that stuff out. And so you built a big cage, a big closet or small room, out of metal screening. The best was brass, even though it was very expensive. Very fine, like a window screen, double layered, and your experiment and your amplifiers and everything were inside. All the electronic equipment that needed a power cord, they were outside. So that's why the equipment's out there, the experiment's in this big, glistening bronze cage, and Don Price is in there just cursing like a sailor at the top of his lungs.

MM: [laughs]

GB: He was preparing a monkey for neurorecordings – actually, the recordings became a famous and important paper in *Brain Research*[10] – but something had gone wrong with the surgery and he was angry. He was just cursing up and down. And Mayer's just ignoring him completely, smoking a cigarette. And it was so bizarre that I was compelled to go in, look at these two strangers, and say, "Hi! What's going on?" [laughs]

MM: [laughs]

GB: That's exactly how it happened. You couldn't walk by. You couldn't ignore it! It was just too bizarre. It was Felliniesque.[11] It was just unbelievable. I mean, Price--when Donald gets angry he gesticulates a lot, you know, and the monkey's on the table with tubes coming out of everything, and Mayer's smoking a cigarette. It's just an extraordinary sight. So I went in. And so they started to tell me what they were doing, and it was fascinating, and I hung around. And about an hour later the experiment finally gets under way, and I'm looking at what's going on, and Mayer looks at his watch and says, "Oh, it's lunchtime. Don, let's go get some lunch. Gary, you stay here and do the experiment, OK?"

MM: [laughs]

GB: Well, it didn't look that hard; I mean, the surgery was already done; the rest of the experiment's pretty easy, so I said, "Sure." I stayed there for an hour and fooled around and did it until they came back from lunch.

MM: So your first experience was this kind of recording.

GB: My first experience in electrophysiology. Everything prior to that had been behavioral

psychology, you know – why rats turn left, that kind of nonsense. And why rats turn left after you inject them with a given drug. [laughs] Behavioral pharmacology. Yes, that was it, and it fascinated me. Putting nerve cell activity on an oscilloscope and putting it through a loudspeaker so you can hear it, and being able to change what that nerve cell does by where or how you touch the animal's foot – that's pretty exciting. I still think that's pretty exciting, actually, but it was really exciting then, too. So I came back next time they did an experiment and the time after that, and asked David if I could be his graduate student and do my dissertation work with him, and he said yeah, which I did. David, of course, had been one of the first people involved in the electrical stimulation-evoked analgesia, stimulation of the periaqueductal gray matter.[12] The initial demonstration was by a guy named [David] Reynolds,[13] who never followed it up, never, I don't think, recognized the importance of what he had shown. But Mayer picked up on it, and he and another graduate student at the time, Huda Akil,[14] who were both graduate students of John Liebeskind's[15] in the department of psychology at UCLA, started working on it. And David [Mayer] had characterized it in behavioral terms very carefully; he'd done the anatomy to determine what part of the brain you had to stimulate, and then he had done the brilliant and wonderful experiment to see what naloxone[16] would do.

MM: Yeah.

GB: Not an obvious thing to do, I guess; in hindsight it looks obvious, but at the time I don't think it was obvious. Naloxone was an opiate analgesia, and what did that have to do with your electrodes? But of course once you saw that the electrically evoked analgesia was reversed by naloxone, you knew that you had tied two things together. You tied electrical stimulation, analgesia, and opiate pharmacology together, and you had the obvious conclusion that the electrical stimulation was releasing morphine or something very similar to it. And that was a wonderful observation. So he was pursuing that work, and I joined him on that, and what was my dissertation research? What was I doing? Oh, after fooling around for a little bit on unproductive experiments, we decided to look and see if we could stimulate the periaqueductal gray and record from spinal cord dorsal horn neurons that were responding to painful stimuli and see if that stimulation was modulating their activity. It didn't <u>have</u> to be in the spinal cord; that stimulation could have been modulating the activity anywhere in the central nervous system. But we thought, let's start at the beginning, down in the spinal cord, and see if the first neuron in the chain is modulated. And so I would implant rats, test the efficacy of my electrodes in behavioral experiments to guarantee that the phenomenon was there, and then go into an electrophysiological experiment where I exposed the lumbar spinal cord, go into the lumbar, the dorsal horn, find a pain-responsive neuron, characterize what it did before and after electrical stimulation, and that was my PhD dissertation. Oh, and it worked, by the way! [laughs]

MM: Amazing!

GB: It did indeed block the activity, the pain-evoked activity of the spinal cord neurons. So, those were good years; those were fun years.

MM: So obviously you were enjoying this work.

GB: Well, I enjoyed it tremendously. It's strange; electrophysiology is difficult and strange work. There was a belief that the best recordings were obtained at night. And, actually, I believe that's true, and the primary reason, I believe, is the stability of the [animal] preparation. If you take a micro-electrode, you have to get really close to the nerve cell before you can see its activity clearly. And you get just a little bit closer and you can puncture the cell and it dies. So, maintaining stability of a preparation, which is breathing, his chest is going up and down, his pulse is pulsing up and down, was quite difficult. And buildings move. You don't realize it, but if you put your ear down to a table and listen carefully, buildings move. They bounce –

MM: Sure. Vibrations.

GB: Every time an elevator comes to a stop, boom, the building moves; the floor moves up and down. Every gust of wind makes a building move a little bit, and then it comes back and oscillates. And footsteps, and jumping up and down, like that, and outside traffic; trucks rumbling by outside. So at nighttime there's no one walking around, traffic is decreased, the elevators aren't going up and down, things are more stable. And it's also why there was a great tendency in those days for an electrophysiology lab to always be in the basements of buildings, because they moved least. In fact – I know this distinctly – it was over twenty years before I had an office that wasn't in the basement of a building. So you worked at night. It was tedious and difficult work. You often – the experiment would go – once you set up and prepared the animal, which takes a great deal of time, you keep it alive, you keep it running for as long as you possibly can, so the experiments would usually start around eight or nine o'clock in the morning with preparation and often wouldn't end until three, four, five o'clock in the morning. But I found that enjoyable.

MM: So it was quite rigorous.

GB: It was, yeah. It still is. In Galveston, when they prepared monkeys in Bill Willis' laboratory,[17] which is easier to keep alive under anesthesia for an extended period of time because it's a bigger animal, their experiments would last two or three days, and they'd do it in relay teams. That's how hard it can be. [laughs] But I would keep it all night long and pretty much did it by myself, but I enjoyed that.

MM: This is a really silly question. A monkey or large animal is easier to keep alive than rats?

GB: Absolutely. The area is larger. Primary problem is controlling respiration. Go off just a little bit, and the animal deteriorates. Yeah, the animals – actually, once you get bigger than a rat, once you get up into something the size of a cat, it turns out to be relatively easy. Rats are pretty hard. Mice are almost impossible.

MM: Yeah. So one of the things I've been talking about with different people is why you use certain models, and there's obviously a certain amount of increased pressure these days to use rats because people don't care much about rats, and they care more about other animals.

GB: Well, that's certainly true. Expense also played a role in some of my decisions. Monkeys became – when India prohibited the exportation of rhesus monkeys, [in the] early '70s, for religious reasons, because it violates Hindu ideas about animals – they had allowed them to be exported, but it was understood that they would be used only in biomedical research for the good of man, and they thought that was religiously acceptable. And then the Department of Defense got some of those monkeys, did neutron bomb-related experiments. I mean, this is really true.

MM: I believe it.

GB: The Armed Forces Research Institute,[18] right across the street from me. I know the guy who did it, bomb-related research, using some of those monkeys. And India heard about it and became incensed and simply cut them off. For many years. For years you couldn't get a rhesus monkey. You had to switch to a related species called a cynomolgus monkey,[19] which I think they were coming from Thailand or the Philippines, someplace in Southeast Asia. So monkeys became fantastically expensive. And even cats became fantastically expensive. By the time I gave up using cats, cats were costing about $350 apiece, for an alley cat. That's incredible. And monkeys were four or five thousand dollars. But there are other reasons.

MM: Sure. Anyway, that was sort of a side issue. So you were very interested in doing this work, and were you beginning to think about pain as a problem, or was it more the interesting nature of the nervous system?

GB: At that time my interest in pain was completely divorced from its clinical significance. It was an intellectual puzzle in sensory neurophysiology. If you're going to try to figure out how the mind and the brain work in a scientific way, you can start on the input side, sensation, you can start in the middle, cognition, you can start on the output side, motor behavior. I thought motor behavior was kind of boring and that cognition was unapproachably difficult. So, like many other people, we started on the input side. Pain was an interesting one for several reasons. It's evolutionarily primitive, which is important, and that links it tightly to emotion and motivation, which were interests of mine because I was a psychologist. That's not necessarily true for vision or audition, for example. So you've got sensory neurophysiology, a tractable problem that also gave you access to the emotional/motivational side of neural processes. And it was tough, and it was mysterious.

It turned out that the primitiveness of it was also a drawback. The cells were often small or very small; an unmyelinated C-fiber nociceptor[20] is the second smallest axon in the nervous system. The olfactory nerve, which is another primitive system, is just a little bit thinner, a little bit smaller. But next to that, that's as small as they get, which is a tremendous technical

challenge. It was a technical challenge – still is, but it was an insurmountable technical challenge until the late '70s. They were just too small to do; you couldn't get an electrode near them; you couldn't do much. Even the microscopy is terrible. An axon one tenth of a micron in diameter is just about at the limit of resolution of a light microscope. So you can't even see it clearly unless you use an electron microscope, which is a pain in the neck; it's hard to do.

MM: I would think it would be difficult. [laughs]

GB: [laughs] It really is.

MM: And to do a procedure that way would be impossible.

GB: Well, impossible, yeah. So, that was my interest. Intellectually challenging, still related to psychology in the broad sense. I didn't know anything about clinical pain states; I knew opiate pharmacology, and I quickly picked up the only missing piece, which was the analgesia stuff, which I hadn't gotten yet, but that was easy to pick up. But that was my interest. For many, many years my interest was on that side. And I think that characterized the pain field. I don't think it was just me; it was very, very characteristic of the whole pain field. How that started, why that was true, for a subject that has such utterly obvious clinical importance, [laughs] why it should be divorced from its clinical importance for so many years, is kind of odd. I don't know quite why that happened, but it did. It didn't change until the late '70s, early '80s, I think, when the clinical relevance, clinical applicability became a much more prominent part of the whole story.

So it was scientific work, intellectual challenge – what kept everybody, kept us all going, were the great payoffs. So Mayer does a study that predicts that the body makes its own morphine, and sure enough, five years later Kosterlitz comes up,[21] and there it is. That's pretty impressive. Of course, I remember that remark. Mayer had gone to a meeting – I forget what the meeting was – but had come back and gotten me and Donald [Price] and one or two of the other graduate students and said, "Come on into the office," and sat us down and just said, "They found it." [laughs]

MM: [laughs]

GB: And that was such an exciting – I remember that moment very clearly. It was such an exciting, wonderful moment. We all knew it was there. It was inescapable; it had to be there. But to actually find it makes you feel pretty good – or hear that they found it.

MM: Exactly what sort of thing it was.

GB: Right. And then of course we were all enormously confused because they didn't find one; they had to go find two. What was that all about? And then just a few months later, endorphin comes on the scene, and now there's three, and things are getting murky; then

dynorphin; then there's four. And I don't even know how many there are now. I gave up keeping track of it now. Kind of ruined the story because there are so many of them, I think. [laughs] But it was there. And that was exciting. And of course what was also exciting was that they were the first obvious, clear-cut polypeptide neurotransmitters.

MM: Really!

GB: Sure. Everything before that was a monoamine [single peptide]. But now you get small proteins being neurotransmitters. And of course that whole field is now an enormous part of neuroscience. But endorphin and enkephalin were the beginning of that. I don't know if that was officially the beginning; there may have been one or two before. But that was the one that made an impact because you knew what it did; you knew where the receptors were, where the actions were, and you had all this enormous pharmacology that you could play with it. You had naloxone, you had morphine, you had all that stuff. You had addiction and tolerance. You could just go to town with these peptides, these small peptides, and figure out what they did, which was very exciting.

MM: Yeah. So it really opened up whole new areas of research.

GB: Whole new areas, whole new areas.

MM: A lot of them.

GB: Yeah. And then, interestingly, the second polypeptide neurotransmitter which entered neuroscience in a big and important way was also a pain peptide, dynorphin. Now, who knows? That's another thing I don't keep track of any more – how many polypeptide neurotransmitters are there now?

MM: [laughs] I don't know, either!

GB: I'd take a guess that there are fifty. There might be fifty. But the first ones were related to pain. It's interesting.

MM: Yes. That was the first time it was characterized. OK. So, you were at VCU, or actually at this time MCV; you were still getting your degree.

GB: MCV was a part of VCU, yeah.

MM: Working with Dave and working with Don.

GB: Dave and Don, yup. Wonderful guys to work with. Taught me a lot.

MM: OK. And at some point you started thinking about what you might do next.

GB: Right. Then I needed a job, yeah. I was graduating and needed a job. And two things conspired to take me to Washington. First, Donald [Price] was leaving or had recently left VCU to join NIH in the Neurobiology and Anesthesiology Branch in the National Institute of Dental Research under Ron Dubner.[22] And my wife had just graduated from law school and gotten an opportunity to be a fellow in the Department of Justice. So, me coming to Washington looked pretty like an obvious thing to do. Donald was here and I'd always loved working with him, and we persuaded Dubner that that was a good idea, too. So I came here on an NIH postdoctoral fellowship. Oddly, Donald left very shortly thereafter [laughs] to pursue his interests in psychology in Georgia someplace, University of Georgia, Georgia State, something like that. So I never did get a chance to work with Donald at NIH, but that was how I got there and one of the reasons I went there.

MM: So had you definitely decided that research was what you wanted to do, rather than looking for an academic position at that point?

GB: In those days, one did a postdoc.

MM: That's right.

GB: That was the ladder. And that was pretty much my intention, to do a two-year NIH postdoctoral fellowship and then go get a real job. That was the plan, the usual way things proceeded in those days. So I joined NIH, which turned out to be – well, NAB turned out to be a marvelous, marvelous place. Other young people who were there were M.A. Ruda,[23] a neuroanatomist who trained at the University of Pennsylvania, Don was there of course, and Dubner. And Steve Gobel,[24] who was the finest anatomist, neuroanatomist that I've ever met to this day, who taught me anatomy, taught me how to use a microscope, who taught me what I was <u>seeing</u> in a microscope – the tricks of looking at sections throughout their depth and reconstructing it in your mind, and how to do all that, how to connect the dots. Not an obvious thing to do. And I was just terribly, terribly fortunate to have Steve to show me how to do that. We decided, after a few preliminary experiments left and right, messing about, that we were going to check out this new gate control theory of Melzack and Wall.[25] A very attractive theory; accounted for numerous clinical observations. Very tricky in one little respect: everything interesting in the theory happened in the substantia gelatinosa, which no one had ever studied or been able to record from. [laughs] So the key to this theory was in this mysterious place, terra incognita.

MM: OK. This is a relatively small area, am I right about this?

GB: Yes and no. If you cut – the spinal cord's a long tube. If you cut a cross section of it, it's the top of the spinal gray matter, it's a relatively thin band. However, that thin band extends from the conus [medullaris] to the trigeminal, so it's very, very long. And if you added up its whole volume, it's actually a pretty big structure. But in any cross section, it's a thin layer.

MM: OK. And this was like 1978?

GB: Roughly there, yeah, or a year after.

MM: Or 1979. So, the gate control theory's been around for thirteen years. I know quite a few people have tried to poke holes in it, or thought about it.

GB: Yeah, quite a few people have tried to poke holes in it in terms of clinical observations. Everyone who tried to check out the neurophysiology had failed. And they were failing because the cells in the substantia gelatinosa are extremely small; the axons that enervate them, the pain fibers, are small, and the cells they synapse upon are extremely small. If you recorded from a cell with a typical older electrode, a piece of tungsten wire sharpened to a tip and insulated by coating it in varnish except for the tip, a little pin essentially, you recorded the activity of the nerve cell that you were in. And then to know where that cell was, you passed electric current, burned a small hole in the tissue, sacrificed the animal, sliced the tissue, and [tried to] find this little burn mark that you left behind.

MM: Oh, my gosh.

GB: Well, it was known that that wasn't a terribly accurate way, that you could make an error of plus or minus fifty or a hundred microns. Now, in the substantia gelatinosa of a cat, which was the animal that we were working with at that time, for reasons – remind me to get back to it – the thickness of the substantial gelatinosa was only about seventy-five microns; above it was lamina [layer] one, below it were lamina three and four. So the margin of error of your burn mark could take you in or out of the substantial gelatinosa with no problem whatsoever. In addition, it was known that dendrites [branches] of deeper cells and dendrites of cells in lamina one penetrated through the stretched gelatinosa. So you couldn't be sure that you were recording from a cell body that lived in the substantia gelatinosa or a dendrite of another cell in another location that was passing through. So that's where it was.

So people were just failing left and right, failing miserably, giving up. And then Don Price had an idea, and this was the first thing that I worked on when I was at NIH; they were just finishing the experiments, and I came in on the tail end of it. He thought that if you could identify a lamina one cell, which you could do because their axons projected to the thalamus,[26] so you could antidromically activate the cell,[27] unequivocally identify it as a spinal thalamic lamina one cell, and then look at the cell right underneath it in the substantia gelatinosa; so they studied pairs. The lamina one cell, and they just blew through that; they just wanted to establish that it was indeed lamina one, and then what was right underneath it, because that had to be a substantial gelatinosa cell.

MM: Oh, that's very clever.

GB: It was a clever idea. And they had had a little bit of success with it. The problem is that that's just really, really hard, [laughs] to pick up two cells in the same electrode track, with

one being less than fifty microns below the one on top, and to hold it long enough to make sense out of what it did was just fantastically difficult. I don't even remember – yeah, they did publish that work.[28] I think they wound up with maybe fifteen pairs – I'd have to look it up. Then Don was gone. So I'm there, and two other postdocs had recently joined the laboratory – Haruhide Hayashi, from Tokyo,[29] and Mohamed Abdelmoumene, who was from Algiers but who had been studying in Paris.[30] So there are the three of us, wondering what to do next; Don's gone, and I ran across a paper by a guy named Steve Kitai,[31] who was studying neurons in the retrorubral nucleus.

The retrorubral nucleus is also a place where you have some pretty small cells, and identifying what kind of cells you're looking at has related problems. And he had used a new way to manufacture glass pipette microelectrodes. Now, taking a hollow glass tube, heating it, pulling it apart so it comes to a sharp point, and still has a hole in the bottom, was an old technique. And you filled the tube with salt water, it would conduct electricity, you'd stick a wire in the other end, and you had an electrode with the glass as an insulator. But to get a really small pipette had proven to be extremely difficult or impossible. Two guys named Brown and Flaming[32] had developed a method to get submicron tips involved – heating it, heating the glass tube in the middle, having powerful magnets on either end of the tube that would pull it apart, and then having a little trigger so at the moment of separation a blast of dry air, cool, dry air, would blow out over the tip. And that gave you a tiny, tiny tip without a wispy hair, which was useless at the end, a whisker which was too soft.

So they had developed a method to do this; the machine was available. It didn't cost too much in those days, two thousand dollars. And Kitai had gone one step further, and instead of filling the micropipette – because the tip is so small, by the way, you can record from small things because the exposure is small – but he had filled it not just with salt water but with salt water that contained DAB (diaminobenzidine). So you could record from the cell outside of it, and then puncture it, inject HRP [horseradish peroxidase] into the neuron, and then develop the tissue histochemically. And not only see where that cell was but see the cell – the anatomical detail that was revealed was as good – in many cases, distinctly better than the Golgi stain.[33]

MM: So the peroxide –

GB: Yeah, I'll tell you in a second. Previously, Golgi stains were the very best that you could do. But Golgi stains cells capriciously; you can't pick which one you want to stain. And it doesn't stain them all, but it stains bunches of them, and eventually they get tangled and you don't know who's who. So Golgi stains allows you this beautiful picture of the cell, but intracellular HRP staining was even better. So you were going to ask how does HRP work?

MM: I was just asking, yeah.

GB: The method had been developed in another context; I forget what it is.

MM: It sounds like such an odd compound. [laughs]

GB: It is, isn't it? Yeah. Well, peroxidase is an enzyme that cleaves peroxide, hydrogen peroxide; [these are] fairly common in nature. And this one had been studied and isolated from horseradish, because it turns out for some reason that I don't know to this day, horseradish contains an enormous amount of this enzyme. It's a rich source of this enzyme.

MM: [laughs] How interesting!

GB: I looked up the original paper on the isolation of this enzyme, and it's a very entertaining paper.[34] The guys started out and they said, "We went out and we got a hundred pounds of horseradish" – I'm not making that up – "and we started to grind them up. And very quickly we realized that we would have to do this outdoors." [laughs]

MM: [laughs]

GB: So, they go outdoors with this hundred pounds of horseradishes, grind them up, and you can imagine the tears coming out of their eyes as they do this, right? And the stench. [laughs] And they were the first to isolate horseradish peroxidase. So it's a peroxidase. So, if you add hydrogen peroxide, where the enzyme is, it cleaves it, you get a molecule of water, H_2O, and an atom of oxygen, which is of course extremely chemically reactive. If simultaneously in the bath, you have a substance which oxidizes, it rapidly attaches itself to that oxygen and oxidizes. So the trick was you got a substance that was soluble in water in its nonoxidized state, but insoluble in water in its oxidized state. And at the time – there are now much better ones – but at the time that was diaminobenzidine, DAB, light brown and soluble in water, and black and insoluble when it was in its oxidized form. So you just ran the tissue through a solution that contained hydrogen peroxide plus DAB, and wherever the enzyme was you'd get this incredible deposit of black oxidized DAB, which allowed you to see the smallest possible detail.

I'll never forget looking at my first intracellularly stained cell. The detail was just astonishing. And the background was perfectly clean, unlike Golgi stain, because you've only stained that one cell. So you see it in extraordinary detail. We found out, for example, that spinal cord dorsal neurons would have dendrites that would span the distance of, say, three millimeters, an enormously long distance. And [with] Golgi stains, you could never follow them out to the end. You never knew how far they went, really. But it was the first time we ever had a good picture of how big dendritic trees were; it stained the axons beautifully, the axon collaterals, the boutons, the presynaptic elements, the spines, the spine necks, just gorgeous.[35]

MM: Did you see the vesicles?

GB: No, because they're too small. They're below the limits of resolution of the light microscope. But if you had a really thin structure that stained just faint gray, you could

sometimes see the mitochondria.[36]

MM: Oh, wow! How exciting.

GB: Because they didn't pick up the stain. They didn't pick up the stain; they had a membrane that excluded the peroxidase. So you'd see it in negative relief, and the mitochondria are just barely big enough to see in a light microscope. Now, of course, I see this picture, this article about him successfully doing this in a cell about as big as a substantia gelatinosa cell, and the anatomy is spectacular, and I'd been looking at spectacular gelatinosa anatomy because that's what Steve Gobel did with his Golgi stains. He was the first person, really, since Cajal[37] to do careful and extensive studies of Golgi staining in the spinal cord and in the substantia gelatinosa. And he had an enormous amount of beautiful new data of different anatomical subtypes; he knew a little bit about – well, he knew a great deal about dendrite trees, a little bit about their axons, so if anybody knew anything about the substantia gelatinosa, this mysterious place, Gobel knew the anatomy. Nobody knew the physiology yet, but Gobel knew the anatomy. But here was a method where I could get the physiology, prove conclusively that it was a substantia gelatinosa cell, and have an anatomical preparation which I could then go and prepare the Golgi staining. The Golgi work that Gobel had done.

MM: That's great.

GB: So I ran around with this paper by Kitai and got all excited and said, "Here's how to do this," and Hayashi and Abdelmoumene shook their heads and looked at me and were skeptical, and I pushed ahead and I got Dubner to buy me a Brown and Flaming electrode puller and gave it a shot, gave it a shot. Actually, we started out doing the work in monkeys. That became very expensive because we failed for quite some time. [laughs] And we eventually realized that Gobel's work was predominantly in the – So we failed for about a month, I guess. So the experiment goes like this. You prepare the animal, you stick the electrode in there, you record from your cell, then you try to pierce the cell, you try to pass HRP in it, you sit around, waiting for the HRP to diffuse throughout the cell for as long as you can stand it, and then you sacrifice the animal. The next day you slice the tissue, and you wind up with, I don't know, about twenty slices, long, thin slices of spinal cord, reacted in this mixture of hydrogen peroxide and DAB, mount it, dry it, clear it, cover slip it, [put it on a slide,] and then you can see whether you failed or not.

MM: If there really is an image.

GB: If you've done anything, right? So for a month all we got were either we got nothing whatsoever or these diffuse blobs of HRP that were contained inside of a cell. And eventually we figured out what was going on. So when you're getting ready to pass HRP, you have to throw a switch that disconnects the electrode from the amplifier and allows you to pass current through the electrode. Nowadays there's an integrated circuit where you don't have to turn out the amplifier. But in those days you had to turn it off, or else you blew

the amplifier when you passed current through it. So we'd throw that switch, turn on the current source, which would deliver I think it was something like five nanoamps, five billionths of a current, and let that go, and then after a minute or so reconnect the amplifier, see if you're still inside the cell, switch, pass, switch, pass. What we were doing, it turns out, we were throwing the switch with the current source set to begin to deliver five nanoamps right away. So all of a sudden five nanoamps of current start passing through the electrode tip. Turns out that that causes the tip to move. And we were either popping out of the cell or slicing the cell open or passing through it and poking the other side so that it would leak like crazy. What we eventually learned was that we had to turn, switch out the amplifier, turn on the current source at zero, and then very slowly increase the amount of current up to five billionths of an amp.

MM: Wow! [laughs] That's one billionth at a time.

GB: Well, yeah, that's the way it went. And then we succeeded, so that you're sitting there and you're going through the sections and you're used to seeing nothing, absolutely nothing, because you didn't even count on seeing the sections, because they were just transparent. You were looking at nothing. [laughs] And then one day you're looking at nothing, you're looking at nothing, and boom! There is a nerve cell stained to absolute perfection.

MM: Gosh.

GB: All of it. Everything. The axon, the collateral synaptic bouton, just a breathtaking thing to see. Really wonderful. And right away we were seeing the major morphological cell types that Gobel had discerned, that we were getting – we confirmed him right away. We got an even better picture of the anatomy. He had excellent pictures of the anatomy; we had even better pictures of the anatomy. And we knew what they did, their electrophysiology. So we would take these sections – well, eventually we stopped clearing them and cover slipping them in the ordinary way and started clearing and cover slipping them in glycerine, which doesn't harden them, which is reversible; you can just wash it out so you can take the tissue after you've looked at it, you can take the glycerin out, rehydrate it, and then Steve Gobel can do electron microscopy of it.

So we would just – to verify and study the anatomy, we would look at these cells on a camera lucida device.[38] And because the stains were so perfect and so detailed, we could reconstruct the cell and the tree in its entirety. And we did it at a maximum resolution of a hundred nanometers. That's subjective; the highest, the best you can get on the best German microscope money can buy, and we would draw the whole cell. And at that magnification you filled up a great big sheet of drawing paper really quickly, so you would go to another page and in the end you'd tape these all together, and you'd have a complete picture. We wound up with some cells with pictures that were six feet long.

MM: My God. That's incredible! [laughs]

GB: Well, when you blow stuff up, you have magnification, it gets big; it's hard to draw! And we had pictures that were over six feet long. And we encountered the problem, well, how do you, we produce that and publish a picture like that? How do you take a picture of that? How do you take a picture of a picture six feet long? We found a photography shop in Washington [DC] that did aerial photography, an old CIA guy who had learned his trade in the CIA and set up his own shop to do aerial photography, and the camera was actually a small room. The film, big sheets of film, three-by-three [or] four-by-four sheets of film, would be in a frame, and in front of the film there'd be a lens, and these were hung from rails on the ceiling. So he'd mount our picture against the four walls of the room, walk between the film and the lens, grab these things, and walk backwards and forwards [laughs] until it was in focus, and get out from in between, flash the light, and take a picture.

MM: [laughs] Oh, my Lord.

GB: Extraordinary stuff, just extraordinary stuff. Nowadays you'd trace it into a computer and get a computer-generated image, but we couldn't do that. So it would take days of extraordinary work to document the morphology.

MM: For one picture.

GB: But it was a picture like no one else had ever gotten before. I think we had the best early studies of neuroanatomy, neuronal anatomy in general that had ever been done up to that point. And quickly people started to do it with all kinds of cells, of course. But we had some of the best early stuff. We were probably some of the very first people to actually see a neuron in its entirety, out to the very, very tiniest, just almost the tip. We were probably the first.

MM: That's fantastic.

GB: And then we succeeded in taking a lot of that stuff to the electron microscopic level. Gobel had studied a lot of normal EM material, the new lay of the land; now he could look at the lay of the land, but the cell that we were studying, a dendrite or its axon, was black. You could see DAB [diaminobenzidene] in the electron microscope as well. So he could figure out which elements he was seeing belonged to the dendrite or the spine or the axon. Actually, with our drawings, he could tell which profile was <u>that</u> dendrite or <u>that</u> axonal cell; that was the level of precision that we had then. It was cool. Yeah, we worked on that very hard for about two years, I think. And we published the physiology and light microscopy in a big paper and then a companion paper on the electron microscopy by Steve, back to back in the *Journal of Comparative Neurology*.[39]

MM: Wow. That's really exciting.

GB: Yeah. Those were exciting days. Great fun, too. Hayashi and Abdelmoumene were just wonderful guys, you know, great guys to work with, hardworking, brilliant, fun guys.

Gobel, the expert on anatomy, guiding us, you know, Dubner, being the quality control guy, demanding extraordinary quality and precision in everything, which at the time we resented and then in hindsight we thanked him for it. Great, great times.

MM: Sounds exciting. What exactly did this say about the role of the substantia gelatinosa, if any?

GB: It showed that the details, the anatomical, physiological connectivity details of the gate control theory were unequivocally wrong. [laughs] And it confirmed – Gobel had an idea that he called the stalked cell, actually, was feeding information from the substantia gelatinosa to the overlying lamina one, known to be important because there are spinal tract neurons that live there. And we confirmed that. We could see the axon much better; we could see the varicosities, we could demonstrate the electron microscope where he couldn't, and in fact that, those varicosities were synapsing right onto lamina one cells. So that the stalked cell was a relay cell out of the substantia gelatinosa. But prior to that it was thought that the substantia gelatinosa was an entirely self-contained system. The input from the periphery, the output from penetrating dendrites, but that the cells of the substantia gelatinosa interacted only within the substantia gelatinosa. But with the stalked cell that wasn't true, because its axon went out.

MM: Right. It projects.

GB: It projected outward to the lamina one and the spinal tract neurons. We identified the second major cell type, morphological cell type that he had found, an islet cell; the name is also from Cajal, who saw it first. And we saw that this was the cell whose axons remained within the substantia gelatinosa, interacting with other islet cells and with the stalked cell dendrites. And with these dendrites that penetrated from below. So the original story wasn't entirely wrong, but it wasn't entirely right, either. But the idea that touch fibers were synapsing on the dendrites of the substantia gelatinosa neurons was not true, because their dendrites didn't leave the substantia gelatinosa, and the axons didn't penetrate up. So, the details of [the gate control theory] – I mean, in general, the summary of the clinical observations was correct, but the detailed anatomy structure [of the] circuit that everyone was trying to prove wrong or right was wrong. And we still don't have a good substitute; we don't really know exactly what a right-looking diagram would be; I think I could come close, based on a lot of separate studies. But we did know that in detail that was wrong. So, one of the thrilling parts about those years, Pat Wall would visit all the time –

MM: [laughs] I was wondering when we would hear about him.

GB: Because Dubner had been a postdoc with him in London, and when he came over he'd make the rounds, you know. So, the first time he comes over, we had gotten some data. So he would ensconce himself in the conference room in front of Dubner's office, and we would go in there one or two at a time and present our results. So I go in there with Hayashi and Abdelmoumene, and in the first place he's sitting there and he's rolling a cigarette. In those

days, you didn't see people roll cigarettes. You saw them roll marijuana cigarettes, [laughs] but you didn't see tobacco cigarettes. So my first remark to Pat Wall when I first met him, "Are those cigarettes?" [laughs] And he responded, "I'm afraid so." [laughs] So we go in there and we say, "Well, we know what gelatinosa neurons do." He immediately gets this skeptical look on his face, and with a flourish Hayashi takes this great, big roll of paper and rolls it out, and there's six feet of neuron! And we had his attention! He loved it, of course. And that was fun; that was fun. But a great moment. "There it is; that's what they do." It was fun.

MM: Did he appreciate that? He is such an iconoclast, I'm sure he would appreciate it.

GB: Pat loves a beautiful fact more than anything in the world.

MM: Right. That's right.

GB: And here was six feet of beautiful fact. And he knew what he was looking at. There was no resentment whatsoever; he was absolutely delighted, wanted to hear all about it. We spoke for hours. Other people might not have reacted that way, but with Pat, that's just the way he was. Now, if you didn't have the evidence, he wasn't going to put up with your crap, OK? But if you had the evidence, he wanted it; that was the name of the game. [laughs]

MM: That's really exciting. OK. I don't know exactly where we are in time right now, but you've clearly been there longer than a postdoc.

GB: Oh, yeah, right. Well, I'm in the middle of the good stuff; the two years is up. I don't want to go anywhere. I'm in the middle of getting divorced from my first wife. I was happy. I mean, NIH in those days was the ivory tower. It was wonderful. They gave you all the money you needed for your experiments. You didn't have to write grants. It was against the law to write grants. You worked for the government; you were an employee of the Executive Branch. The money was just there. Anything you wanted. I have to admit that when I ordered equipment or supplies at that time, I literally never even looked at what it cost. Didn't matter. And you had no responsibilities for teaching or committee work or anything. Now, the downside was that they paid you almost nothing. The salaries were low.

I used to point out to people when I was a young staff fellow, that the guy who drove the bus that I came on in early in the morning made more money than I did because I knew what bus drivers in DC made, and he did make more money than I made. So the salaries were terrible, but it was just fun. It was just fun. And I don't know, beginning five or six years ago, that changed dramatically. Everything except the low pay, which is still true. [laughs] Well, you see, it's civil service. NIH scientists, almost all of them, they're like postal workers. I mean, it's the same principle. See, it doesn't matter how well you do; you can't get rewarded. God Himself can't get you a raise; you're a civil service employee. It's all longevity, how long you're there. But it was great; I didn't want to go. So Ron Dubner had

me appointed as a staff fellow, and then I just, I don't know, the most potent factor in human behavior is inertia, right? So there I was, things were doing well, I'm happy in the lab, I just stayed. And I wound up staying for seventeen years, I think, which went very quickly.

MM: OK. The work that I looked at that seemed to rise to the surface was with the dorsal column postsynaptic neurons.

GB: They were fun.

MM: I don't know if there's something in between them and the substantia gelatinosa that you want to talk about, but there was a lot of work that you published.

GB: That's pretty much where we went. We didn't think there was much more future in substantia gelatinosa, no obvious things to do in substantia gelatinosa, so we went to the next cell, the output cell, transmission cell. Well, we knew that the spinal tract cells were being studied by Bill Willis' laboratory, a powerhouse, brilliant laboratory; we didn't want to jump into competition with them. We knew that Alan Brown in Scotland[40] was working on the spinal reticular tract. We knew that the spinal reticular tract neurons were tough and tricky, and we knew that they were really involved. But there was this other cell whose very existence wasn't well known, and that was the dorsal column postsynaptic tract cell.

The classic understanding of the dorsal column tract is that the primary afferent A-beta low-threshold mechanoreceptor comes into the spinal cord and branches. One branch goes into the dorsal horn and enervates spinal cord neurons. The other branch travels up and down in the dorsal columns, with the upward-going one being longest, going all the way up to the dorsal column nuclei, the medulla, synapsing there, what is that tract called – oh, my God! [laughs] – the lemniscus, the medial lemniscus, going from the dorsal column nucleus to the thalamus, from the thalamus to the spinal sensory cortex, and that's the sensory pathway for touch, for proprioception. A few workers had discovered, most particularly Denise Petit in France,[41] had found electrophysiological techniques that some of the axons in the dorsal column weren't primary afferent touch fibers, but were actually coming from spinal cord dorsal horn cells. And it looked like, according to her experiments, that some of them may be pain responsive cells. So the initial reaction when you hear something like that that goes against the established wisdom was, "OK, maybe there are six of them as an aberrant thing; it doesn't really mean anything."

MM: A mutation or something.

GB: Well, we decided to do an experiment. Linda Watkins,[42] a graduate student who followed me in Dave Mayer's lab, was doing something clever. She was taking HRP and incorporating it into a polyacrylamide gel, and then she would dry the gel, and then you would get these little hard pieces of Jell-O-like stuff that would contain HRP. And she said you could make a little slit at some interesting place in the nervous system, stick this little piece of gel in there, you would rehydrate, and gradually release its HRP in a restricted area,

and the axons that you had cut would take up the HRP, transport it, and you'd get a retrograde signal. Now, that didn't give you as much anatomical detail as an intracellular stain, but you could see out into the primary and sometimes the secondary dendrite. And she had done some lovely experiments that I knew about because I'm still talking to those people.

So, just on a lark, I asked her for a couple of pieces of the stuff, take it home, go in, make a small slit in the dorsal columns up here in the high thoracic spinal cord, stuff it in there, sew the animal back up, three days later sacrifice it, go back in the lumbar spinal cord and see how many of these Petit cells are there really? And the very first cat we did worked beautifully, and the very first time we looked at it we knew that these were incredibly numerous. This wasn't an aberrant, minor population at all. In fact, the density of cells was comparable to when you did the experiment for the spinal thalamic tract or the spinal cervical tract. They were just as numerous as these other well-known ascending populations. So we did a bunch of studies on those things.

MM: OK. A bunch of dumb questions. These are postsynaptic cells because they're getting input from other dorsal cells, is that what we're saying?

GB: From the primary afferent. The nomenclature isn't intuitively obvious. What was thought to be there was a primary afferent neuron that came from the periphery, branched and ascended, without synapsing on anybody, OK?

MM: I got that. OK.

GB: These were cells that were collecting synaptic input from the spinal cord gray matter and sending *their* axons. So they were postsynaptic with respect to the primary afferent input.

MM: I got it.

GB: Not intuitively obvious, you're quite right.

MM: OK. And they appear to be – I mean, they're not, like, clumped together? They were intertwined with the primary afferent.

GB: Intertwined?

MM: Well, where were they? [laughs]

GB: Well, you really didn't know. They were discovered electrophysiologically, which gave you plus or minus a hundred micron burn on a few cells – twenty cells, that's a big deal in an electrophysiological experiment. And they looked like they were in the base of the dorsal horn, the base of the spinal cord. With the staining experiment, you stained thousands of the cells and could establish their location unequivocally. And in the cat, we found that they

formed a really lovely band. If, instead of cutting the spinal cord crosswise, you cut it lengthwise, it was a stripe of cells, a very striking strip or stripe of cells in deep lamina four. The monkey was slightly different, but very clear-cut anatomical distinction about where they were. And then we went and we did the single-cell physiology, collaborated both with antidromic identification with intracellular HRP and synaptic connections and all.

Counted them – we wound up counting them because Glenn Geisler[43] had taunted me once; I was presenting this material, I think it was, in Washington and he was in Tampa or Minnesota, and he had been studying the spinal and cervical thalamic tract. And I made the comment that these cells look at least as numerous as the well-known cells, and he raised his hand and he said, "Well, how many *are* there?" And I looked at him and I said, "I haven't counted them; you crazy?" [laughs]

MM: [laughs]

GB: But he had, you see! He had counted the spinal thalamic tract, and he knew that the cat lumbar segment contained – I don't know what it is – seven thousand spinal thalamic – So he had all these numbers. He knew. So that annoyed me because he had caught me being lazy. So, we went and counted them. [laughs] And they are only slightly less numerous than spinal thalamic tract neurons and about as numerous as spinal cortical neurons. So we counted them. [laughs] Actually, Bill [Guo-Wei] Lu counted them, a fellow from China I was working with at the time. But we did that; we counted them. [laughs]

MM: Is there a particular reason you were working with cats?

GB: Again, we had switched out of monkey to cat in order to study substantia gelatinosa and Gobel's anatomy. And when we moved to dorsal columns, we stayed with the cat because that was what we had used before.

MM: OK.

GB: It turns out, by the way, that the cat is the least appropriate animal for pain studies in the spinal cord.

MM: Oh, yeah? Tell me about that.

GB: The structure, in terms of anatomical arrangement of cells and dendrites and axons and such in the spinal cord, especially in the thalamus, people and rats and monkeys are very, very similar, and the cat stands out as distinctive – not completely different, but you can obviously tell they're not quite the same. So, if I had it to do over again, I wouldn't have done the cat. It's not a typical mammal. Rats are a better choice. Rats are just little people. [laughs]

MM: [laughs] In some respects, anyway. OK. So, I've got a paper here from 1983, in which at

one point you make a statement. You say, "The DCPS [dorsal column postsynaptic] neurons constitute a projection system capable of signaling innocuous and tissue-damaging mechanical stimuli and therefore may play a role in the modulation of touch and pain perception." So I wondered if you wanted to talk a little bit about the evidence for that.

GB: Well, we were confused, I guess is the best word for it, by the fact that these cells, which were responding to painful input, [that these] dorsal column postsynaptic neurons were synapsing in a place that didn't seem to have anything to do with pain. They were synapsing in the dorsal column nuclei, which was then thought to be exclusively touch-associated. And it wasn't apparent to me, until I learned more about the dorsal column nuclei, there are two kinds of cells in the dorsal column nuclei, one cell called the tufted cell because its dendrites come out the top and form this pretty little tuft, receive input only from the primary afferent touch fibers [and] send their axons from the medial lemniscus up to the thalamus. So that's the classic pattern.

But there's another cell called the multipolar cell, just as numerous. These cells receive their input from the primary afferent touch fibers *and* the dorsal column postsynaptic tract cells. But we knew that much. But what we didn't know is where the multipolar neurons sent their axons. Now, we now know that they're incredible and send their axons to half a dozen places – back down to the spinal cord, into the cerebellum, into the brain stem core – now known to include the periaqueductal gray, which is important – and the reticular formation, [the gigantocellular reticular cells, all kinds of different places. But we didn't know that then. So we had a dead end. We had this pain-responsive system, very numerous, must be important, making a synapse in a touch nucleus. And so we wrote this silly sentence that you just read to me there. [laughs]

MM: [laughs] OK. So, at this point you're just sort of gathering observations and trying to see if this –

GB: That's as far as we could take it. We couldn't get it out of the dorsal column nuclei. We didn't know enough.

MM: OK.

GB: It hasn't gotten much further than that in the years since, actually.

MM: No? I didn't think so.

GB: No, it hasn't.

MM: Yeah. OK. This brings me to 1988 and the development of the chronic constriction model.

GB: Yeah, it was about that time, it was about that time. Or the year before, in '87.

MM: Yeah, it was published in '88.[44]

GB: So how did that come about? A new postdoc – not a postdoc; a new visiting fellow, visiting scientist, had come to the lab, Xie Yi-Kuan, from Beijing, and he and I were going to work together. And I was finishing up a project looking at dorsal column postsynaptic tract cells, actually, and didn't quite know what to do next. I knew I couldn't go much further in the dorsal column cells; there wasn't any obvious place to go. And what were we going to do next? And Xie Yi-Kuan is very anxious to start doing some experiments, and I don't know what to tell him. I don't know what to do. And then a paper, an old paper, caught my eye, by Bill Calvin and his colleagues about echo spikes.[45] So the story goes like this: If you have an axon that has a spot of demyelination, a small segment of demyelination, an impulse will pass through it, but because the myelin sheath is absent, all that bare axonal membrane will act as a capacitor and it will store charge. And as soon as the axon recovers from its refractory period, there will be enough charge left to treat another action potential. And they call this the echo potential. I always thought that a burp potential was a much better word for it.

MM: Wow! [she laughs]

GB: It is, if you think about it! [he laughs] In the lab I always call it a burp. But they called it an echo potential. And because it's arriving at mid-axon level, it'll travel in both directions. Now, the clinical -- not the clinical -- the consequences for sensation are very likely to be nil. One axon goes -- one impulse goes through, burp; you get a second impulse going up. But the backwards-propagating impulse will collide with the next one coming up. When an antidromic and an orthodromic impulse could meet, they collide, they obliterate one another and neither passes and nothing happens. It's called collision, is the technical term for it.
It's a good name for it. Well, on the oscilloscope[46] you can see them collide. And then, poof, nothing is left. So the sum total of impulses is not changed. You have one extra going up but you subtract one, the next one coming up, and the amount of information getting to the central nervous system is zero. But Calvin had shown that in some cases, these axons wouldn't just burp but would start discharging in an epileptic way, very high frequency.
And I thought that what might be happening is that in their experimental preparation, some of their axons might have had multiple segments of demyelination. So now the impulse passes, you get a burp, it comes to the next segment of demyelination, and that is repeated. So one gives you two, gives you four, gives you eight, gives you sixteen; pretty soon you're off to the races and you have a high-frequency discharge, a chain reaction type of thing. So I thought that might be happening. And I knew that demyelinating axons were important,[47] and [that] nerve injury evoked pain; I knew that much about the clinical situation.

So it was a Saturday; we were in there doing something on Saturday, and I said, "Xie Yi-Kuan, I have an idea." And I explained my thoughts to him. "Let's give it a try. Go get a couple of rats. Let's see what happens." So the technique that Calvin had used actually goes back to Ramon y Cajal – everything goes back to Ramon y Cajal! [he laughs] He'd shown that if you take a ligature and tie it loosely around a dorsal root, that underneath the ligature

would develop segmental demyelination. So I wanted multiple sites of demyelination, and the roots weren't long enough. So I went out to the longest nerve in the body, the sciatic nerve, and picked the number four out of thin air, and tied four loosely constrictive ligatures around the sciatic nerve. People always ask me why I used chromic gut suture in my model. It's because we reached up on the shelf and came down with chromic gut.

And four was just a number. Four was the number that I could fit in there reasonably easily. So we did two animals, went home, and came back on that Monday morning and went to check the animals. Something fascinating was obviously going on with these animals. They were obviously not normal. They're limping, or actually hopping, refusing to let that foot touch the ground. You went in and you touched their foot and they went crazy. They let you know right away that they didn't want you to do that. And I knew that this was important.

If the ligatures had completely interrupted the nerve – I'd done that; I'd done sciatic transsections, so I knew what that looked like. That was a foot that had a flaccid paralysis, that flip-flopped back and forth, and the animal ignored it. After ten days or so they started this self-mutilation stuff, but for the first few days they just ignored it; it was this floppy, paralyzed, insensate foot. And this one didn't look anything at all like that. So the fact that they didn't want me to touch it and they wouldn't let it touch anything else, they just walked around or sat around, and I don't know if you've ever seen these rats; but it's really a striking thing. It's just striking. You just know in your heart that they don't want that foot to touch anything. Of course, I'd seen the pictures of neuropathy patients, holding their hands up in these protective positions, and I knew it looked like that right away.

Within the next day, I noticed the feet started to get this characteristic distorted posture, too; rats' toes are usually widely separated and slightly arched because they walk on the tips of the toes, and these guys had their toes together, strongly flexed, and their foot – paw, rather – turned outwards in inversion. And that looked almost exactly like the pictures of causalgia patients, except in causalgia,[48] because the human muscle and tendon arrangement is different from the rat, it's almost always an inversion. But in the rat, with that exception, it looked like the pictures I'd seen in Bonica[49] and everyplace else. So I was pretty convinced that we had animals with abnormal pain sensation.

Then we got lucky a second time, and the luck was that a week prior, Ken Hargreaves[50] had had our technician, or our electronics guy, Fred Brown, had had him make the first paw-flick apparatus. So Hargreaves was studying inflammatory-invoked pain, injecting the paw with a little bit of adjuvant or something, and usually you tested the tail, but he didn't want to do that because he wanted the other foot as a control. So he had the idea that you could modify the tail flick by having the animal stand on glass and shining a hot light through it. When he told me, I didn't think that would work, but fortunately he was smart enough to ignore what I thought and went ahead and did it. So they had this apparatus that they had been using for a week with great success. It was wonderful because, you know, the essence of new experiments and doing new science and stuff is all puttering, OK? Actually, when I

changed labs and set up my lab here in Philadelphia, I had this tremendous insight. In everybody's lab, you go to anybody's lab, and they have a junk drawer. And this is old equipment, bits and pieces of equipment, bits and pieces of tubing and wiring and junk and crap. And that junk drawer is one of the most important things in the entire laboratory. Because when you're puttering, when you're making the first paw-flick apparatus, you don't go out and spend six thousand dollars; you get some tape and some wire and some paper clips and putty and you put something together! You go to the junk drawer and making something, OK?

So this initial paw-flick apparatus was, like, the top of it was a cabinet door, a glass cabinet door that they'd yanked off one of the cabinets in the laboratory [he laughs] and put on four legs, and Fred had taken a projector bulb and made some electronics and encased it in a little aluminum box that he'd gotten from Radio Shack for seventy-nine cents, and just hooked it up. And the wires are hanging out and dangling and probably dangerous. But the damned thing worked! [he laughs] And it worked beautifully. Actually, there are now three commercially available versions of it, and none of them work better than that original one made out of a cabinet door.

So I knew that was there; I knew it was working well, and I thought I had a rat with an abnormal foot. So we went to Ken and said, "Let's do this. Let's use your machine, throw them on, and measure their pain thresholds to heat and demonstrate it." Yeah, no question about it; they have hyperalgesia.

Now, previously, the only pain model for nerve injury was [Patrick] Wall's anesthesia dolorosa model.[51] You cut the nerves to the feet, and after a few days the animal begins to mutilate itself, chew on its toes and stuff. And the rationale was that he was experiencing spontaneous pain from this amputation in continuity – amputated at the nerves, but it was like phantom pain when the thing was still attached because you'd cut the nerves. That was the model; that's all there was. Right away everyone realized that there were two problems with that story. Patients with nerves cut to an extremity didn't chew off their fingers and toes, and how could you be sure that's why the animal was biting its toes? And the answer to that, of course, is impossible. There's no way you can be sure.

MM: Because he doesn't have the ability to express his feelings.

GB: You can't read its mind. You can't read the rat's mind. He won't talk to you, and you can't read their mind. So you can never, ever, as a matter of principle, you can never, ever be sure. It's likely, it's probable, but you can never be sure, and people don't do it [self-mutilate]. And now it turns out that some people do do it, especially if they're very young or mentally retarded and they get their nerves cut, they do the same thing. There are three or four cases in the literature now that suggest that.

But here we had a pain model where some of the fibers, at least, were still connected up to their peripheral receptors. So we didn't – although the animal had behavior that suggested

that he had spontaneous pain and hyperalgesia, I didn't have to rely on that. I could measure his pain responses to controlled stimuli. That was the value of the model. I didn't have to take anything on anybody's word for it; you could measure his pain threshold in seconds and see that it was abnormal. So we did that, and then we started devising other ways to test his pain threshold. And we came up with the idea of having the animal stand on a metal floor, and underneath the metal floor we were circulating ice water, so it was cold, and we set it at a temperature where a normal animal would just stand there and look bored, but these animals would stand there and whenever their foot touched this cold floor, in a second or so they'd pull it up and shake it and act like it hurt.

So we could measure the frequency of these withdrawals, the duration of the withdrawals, how big the withdrawal was, and show that the animal had abnormal pain responses to cold. And then we came up with the idea of having the animal – well, we didn't come up with that idea; somebody else did – the way to test mechanical pain thresholds at the time was with a device called a Randall-Selitto method.[52] The animal's foot goes down on a pedestal, and on top of it is a cone-shaped stylus, which is driven into the foot with slowly increasing pressure until the animal jerks his foot or says uncle. A Randall-Selitto device. So we got one of those; I think we had to buy it or we borrowed it from somebody, and didn't like it. It turns out that we weren't using it properly.

Well, we were using it properly, but we weren't habituating the animals carefully enough. You have to really train them to be calm in this situation before you can get reliable data because the animal doesn't like the entire situation – being held, wrapped up in a towel and his foot resting on this thing; he didn't like it at all. But we didn't know that. We didn't have any experience. So, initially we couldn't demonstrate any abnormality. But then somebody else – who was that? Ze'ev Seltzer[53] had the idea that you could have the animal stand on a screen floor, which you would take up in the air so you could come underneath the animal and touch the bottom of his foot with von Frey hairs.[54]

MM: Right. So he's just walking around.

GB: Well, you put a cage, an inverted cage, over him so he can't run far, and you put him up there every day for three or four days until he's thoroughly familiar and bored and not frightened; then he just stands there. Actually, they very often roll over on their sides and go to sleep, so you have to wake them up to test them. That's a nice sign; it means they're not stressed.

MM: [she laughs] Yes. Very calm rats.

GB: Calm rats, right. Actually, that's important. A rat that's under stress, a rat that's afraid, adopts a species-specific technique. He freezes because things that eat rats trigger on movement. You've ever seen a cat step on a mouse that it's chasing because until it moves, the cat doesn't even really see it. That's true for almost everything that hunts. Well, it's not true for snakes, but for most things that hunt. So whenever a rat is frightened, it freezes, and

you want it to move; you want it to move its paw. You don't want them to be in this freeze posture. So it is important that they be very thoroughly habituated. It turned out that was one of the benefits of my training as an undergraduate in psychology: I knew how to do behavioral experiments with rats. I knew all about the natural history of the behavior of rats, what it took, how to do it, and that came in very handy when we started to do these experiments.

So Ze'ev determined that – the Von Frey hair method, which works beautifully; Michael Tal, an Israeli,[55] came and worked with me eventually, and we did a pin-prick test, which also works beautifully. Jin Mo Chung and his colleagues[56] developed a better cold test. Having them stand on a cold metal floor, there's a confound. The environment is cold, and that could have, probably does have, effects. So he developed this method where you just squirt a little acetone onto the foot, nail polish remover. When it evaporates, it produces a mild cooling sensation which is not painful normally but which these animals responded to as pain.

So eventually we had the full battery – we developed some; we stole some from other people – a full battery to test a variety of abnormal pain sensations, all of which the rat had. At this point, something really interesting happened. We were ready to write this up; this was the first publication on the method. We said, "OK, the animals have – well, they always have heat hyperanalgesia, they always have cold allodynia;[57] well, how often does that happen in the patients? Let's go compare this now to the patients."

And here is when I started to get interested in the patients. Nowhere in the literature in the world is there any indication of how often that happens in a man. I understood the syndrome better in the rat better than anybody had ever understood it. They were talking about neuropathic pain as this general, unitary concept; some people, some very smart people – like [Ulf] Lindblom,[58] for example, and [Willem] Noordenbos[59] – knew that there were specifically different kinds of abnormal pain sensations, but nobody else was really paying attention, and no one had quantified it. So because no one had quantified it, what turned out – [laughs] I don't know if this is embarrassing or not – I would be asked by audiences, what kind of patients does my rat model model?

MM: Well, that was a good question.

GB: And I could say, "Anyone! Anyone. Choose anyone you want." Because you don't know what your patient really has, so it might be just like the rats! [laughs]

MM: [she laughs]

GB: That's less true today, but it took ten years before we started to get the information. Don Price did some of it, and [Rick] Gracely did some,[60] and other people have done it, where we're starting for the very first time to get an exact picture of exactly what kind of abnormal pain these patients do have. It turned out that these rats looked like some of the patients but

not all of them, and we don't know why, da-dum, da-dum, da-dum. But that was an interesting discovery.

MM: That is interesting! Gosh.

GB: So, knowing that no one knew exactly what the patients had, and wanting to know that to compare it to what I was getting in the animal, then all of a sudden I needed neuropathic pain patients. We would get an occasional trigeminal neuralgia patient[61] because we were in Dental Research, at the Institute, but we didn't get a large number of those patients. And then we got hooked up with Bob Schwartzman here in Philadelphia; how did that happen? Let's pause for a minute –

MM: OK.

GB: So I find myself in need of patients to look at. And if I remember this correctly, Bob Schwartzman, a neurologist with an extensive practice of RSD patients,[62] introduces himself to me at some meeting and says, "I've read your paper, your rat paper; it looks really good. It looks like – "

[TAPE 2]

MM: OK. We're starting tape 2 of our interview with Dr. Gary Bennett, and we were just talking about Dr. Bob Schwartzman and how he assisted your observations of neuropathic pain patients.

GB: Yeah. So Bob invited me up; and Rick Gracely and Sue Lynch, a young neurologist who had just joined the division, and I came up here, on the day that he had his once-a-week RSD clinic. Another extraordinary moment that I'll never forget, walking into the waiting room of his clinic that day, and there were twenty RSD patients. That's probably ten to twenty times more than an average physician would see in an entire career, and there they were, all sitting there. And Bob was incredibly generous, allowing us to watch his exam of the patient, showing what he had seen, what he had found, et cetera, et cetera, and we went back up there several times. And when we got particularly good patients – that is, patients who did not appear to be too complicated, who hadn't had too many failed surgeries, and who agreed to help us out – they would come down to NIH.

And that's when we started our clinical study of RSD patients, which was just fantastically fun – also terrible! [he laughs] Terrible because it was the first time I had been exposed to how bad this is. When it's bad, and it often is -- when it's severe, and it often is, I don't know how these people live. I don't know how they don't kill themselves. The pain is terribly severe, they can't avoid it, it's there all the time, they've had it for years, and the courage of just continuing on with life that these people had, still does have, a very powerful impression on me. And the occasional patient who commits suicide is not a mystery. The mystery is why more of them don't, I think. Because back then there were

practically no drugs.

MM: No treatment, yeah.

GB: Nothing was doing any good for these people. So we were studying them.

MM: In the early '90s?

GB: Yeah.

MM: Which is not that long ago.

GB: No. So we're studying them, and the point of view of studying them, we started out by just doing to them what we'd been doing to the rats. [he laughs] Cooling, Von Frey, heat, da-dum, da-dum, da-dum.

MM: And quantifying their responses.

GB: Quantifying it and seeing the pluses and minuses, mapping it out. We would spend a whole day, the three of us, just studying the hell out of a patient. It got to the point where we were doing so many things so rapidly to these patients that we started videotaping it. Originally, two of us would work on the patient, one at the patient's side, the other doing instruments and equipment, with the other person sitting in the corner and acting as recording secretary.

We found out that the recording secretary couldn't keep up with it, and we started videotaping this stuff and then going back and, at our leisure and carefully, doing the notes off the videotapes, so that we didn't miss anything. That was especially true when we started with our local anesthetic block experiments, because then things were happening very quickly, things were changing minute by minute. Very exciting time. Everyone would break for lunch, the patient would go have lunch, and we'd go and grab a sandwich and sit around and try and figure out what we'd just seen and what we want to see next, and after lunch we'd go back and do it again until five o'clock. And some of these wonderful patients would come back two, three, four, five times for us.

MM: It's really extraordinary, the willingness of the patients to participate in this.

GB: Well, it is, because we're hurting them. The whole point of everything we do [he laughs] is to hurt these people. Of course we try to minimize it; we tried to be as gentle and as careful as we could, and of course the patient could stop us and very often did say, "You just have to stop for a while," you know. But yeah, these people demonstrated courage, real courage. No question about it. And then after a while we thought we were starting to get a feel for what these patients actually had. They had a mixture of stuff, but we could see the components of the mixture. We started to get a feel for it. And we started trying to make

sense out of what was going on.

And we were stuck there probably for almost a year, continuing to see people, debating stuff back and forth; it was intellectually an extraordinarily challenging time, exciting time. Rick and I, who were good friends and who were further along in this than Sue was, but Sue also, just had unending discussions, arguments, diagrams drawn on scrap paper, scratching our heads, going to get papers, talking about papers, "What the hell is going on? What's going on? What is this? How could this be true?" And then eventually Gracely had an idea. And he told me about it one day, and I don't remember – either I didn't get it or I didn't think it sounded right, and I told him no. And he was persistent. And the next day he comes back at me again – I remember this very well. And the third day we're at lunch, and he's still hammering away at this cockamamie idea. And he grabs his sandwich bag, and sketches out what he thinks is going on. And I look at it, on a brown paper sandwich bag, his lunch bag. And the moment I saw the diagram it was like a Zen moment, you know, "Yeah, that's right! So that's what you've been saying all this time!" He had it pinned on his wall for many years. I don't know if he still does.

MM: I don't remember seeing it.

GB: It probably fell off and he threw it away. But funny, he'd been yelling at me, talking, discussing it, I just wouldn't get it, wouldn't buy it, wouldn't pay attention. I don't know what was wrong with me. But the instant I saw the diagram I knew it was true. And so that's the pain paper --the Gracely, Lynch, and Bennett pain paper,[63] where we propose that what's wrong with at least some of these patients is that there's a persistent C-fiber pain input from any one of a variety of causes which causes central hyperexcitability so that any input is exaggerated in terms of its readout. And at the same time, when this diagram gets drawn on the lunch bag, the Zen moment is true, and then right away another orgasm, another Zen moment, within less than five seconds –I'm sure it was bang-bang – because I immediately realized that the central hyperexcitability that Gracely was drawing for me was [Clifford] Woolf's[64] NMDA-mediated phenomenon. It all came together for me.

MM: Oh! I don't think I've gotten to that paper yet. Go ahead.

GB: Well, he and Pat [Wall] had shown that C-fiber input caused exaggerated withdrawal reflex in a decerebrated rat,[65] so we all had that in our pocket; we all knew that. And I just reviewed the Woolf and [Stephen] Thompson paper where Clifford had gone on and shown that this central sensitization was due to activity at the NMDA receptor.[66] When I reviewed that paper, I knew it was a brilliant and important paper, but I didn't connect it to my own projects and my own thought at the time. I connected it to the previous Woolf and Wall demonstration, which was electrophysiology in an animal without a head – you know, just electrophysiology stuff, and in retrospect the connection is perfectly obvious. But in retrospect everything is pretty obvious. But I see the diagram, boom, I know it's true. Right away, boom, NMDA, gotta be! Which was true. [he laughs] Which was at least a big piece of the truth. So that was a lovely day, too; that was a lovely day, too.

MM: That's great.

GB: Isn't it an interesting comment on how science works? Remember in school they teach you that you patiently collect facts, sift them, organize them, outline them, generate a hypothesis, test it. That's bull! It happens because you're having a shouting conversation in a cafeteria and somebody scrawls something on a paper bag. *That's* how science works. [he laughs] Or you're trying to make echo spikes, and you end up making an animal that limps. That's how science actually works.

MM: Yeah. I hear that a lot.

GB: Oh, it is. And that's why it's fun, of course. If you were just collecting facts and organizing them, that sounds boring.

MM: It sounds extremely dull.

GB: Doesn't that sound boring? Who could think of anything more boring than that? But nobody does that – nobody worth their salt does that. So, that led to a –

MM: Explain this for the sake of the tape a little bit more. What happens is that a lot of the A-beta and A-delta fibers are essentially deafferented.

GB: Yeah. The key point, it turns out – So the previous generation's work on the problem had looked at the injured nerve, either from missile or bullet wounds or whatever it was, and had tried to find some particular pattern of nerve damage that gave rise to the pain. And that culminated in Noordenbos' theory that it was a relative loss of A-beta touch fibers, or just proportionately large loss of A-beta touch fibers, whose input normally inhibited pain sensation, that disinhibited [pain, leading to a chronic pain disorder] – and that was it. And actually that statement is the core of the gate control theory. Melzack and Wall certainly elucidated it in important ways. The core idea is Noordenbos.

It turns out that that's not true, that there is no particular pattern of nerve injury; *any* pattern of nerve injury can give you neuropathic pain. And it's because the damage to the A-beta touch fibers – our belief now is that the damage to the A-beta touch fibers and to the A-delta fibers is contributory, but not essentially more important, that the key is the damage to the pain fibers. Damaged pain fibers begin to send abnormal extraneous input into the central nervous system. When their axons are damaged, they begin to discharge spontaneously; normally they're silent. They acquire an exquisite mechanical sensitivity. Now, a C-fiber axon normally has almost no mechanical sensitivity. We're not talking about its receptor, but the axon. So, if you tap your ulnar nerve at your funny bone, you have to whack it really hard before you feel anything, and you feel something when you activate the fibers. And for it to give you a burning sensation from activation of C-fibers, you'd have to whack it really hard.

But an injured C-fiber axon, which is attempting to regenerate into a sprout, is so sensitive that the pulsations from a nearby artery will make it discharge. Exquisitely tender, which is a problem in stump neuroma, which is why guys have trouble with their prostheses. If their prosthesis pushes on those C-fibers, the hyperalgesia is just too painful to bear. So spontaneous activity, exquisite mechanical sensitivity, and they acquire an excitatory response to norepinephrine and adrenaline and dynorphin, which is almost certainly an important link in the sympathetic part of the story.

MM: So the individual attempting to deal with the stress of the situation, or under stress –

GB: Well, the pain itself – It's a vicious cycle. It *is* a Livingston vicious cycle.[67]

MM: So there will be more norepinephrine and more adrenaline.

GB: More pain, exactly. That's part of it. Plus any time it moves, it hurts, and it's discharging spontaneously; as far as we can tell, it discharges for no reason whatsoever, just literally spontaneously. So all this extra C-fiber input is going into the spinal cord and releasing glutamate, acting at NMDA receptors, and causing central hyperexcitability – that is, the cell who receives that input is now having an exaggerated response to <u>all</u> of its inputs. Normal pain fiber input, normal touch fiber input, abnormal input from damaged touch fibers, abnormal input from damaged A-delta fibers, all these inputs. And we know there are lots and lots – It's the rule, it's not the exception; it's the rule that spinal cord pain neurons receive convergent input from multiple different kinds of pain fibers. The exception is important, but we don't have to – These are the wide dynamic range neurons that I'm talking about. And that that's it. And that when we, when Gracely and Lynch and I would temporarily block what we thought was a little neuroma[68] and see the entire pain syndrome disappear right in front of our eyes for two hours until the lidocaine wore off, that what we had done was temporarily turn off that sustaining C-fiber input.

So that's the – you could almost call it the standard model that we're working with today. It has to be true at least in part; it's obviously not entirely true. There are obviously important holes in it, but it was the first reasonable, testable, useful theory. For example, it predicts that NMDA receptor blockers will block neuropathic pain and have little or no effect on normal pain. That was true. That's a good prediction. With a little bit of luck, there may be a medicine that comes out of that prediction. And it predicted several other things that have turned out to be true. So that's been very, very exciting.

MM: Now, at one point you said the nerve was attempting to regenerate and sending out messages.

GB: A cut axon will attempt to regenerate.

MM: But the pain persists. The nerve in fact does not regenerate, or becomes a distorted version

of itself?

GB: It doesn't successfully regenerate. Successful regeneration is pretty hard. The little sprout at the end of the regenerating axon moves, looks very much like an amoeba, as you remember from high school, OK? And it's crawling, literally crawling, and when it encounters areas where the nerve's been damaged, it encounters scar tissue, fibrosis. And it can't get through or around. Or if the nerve's been completely severed, it comes up to the stump, which is covered with scar tissue, and they just crawl around until they look like a ball of worms or a ball of spaghetti.

MM: OK. That's a very vivid description.

GB: If you cut the nerves off clean, get rid of the scar tissue, carefully sew them end to end, then they've got a decent chance to successfully regenerate all the way out to their original target. And the evidence is that once they've accomplished that successful regeneration, they stop discharging spontaneously, they're no longer exquisitely mechanically sensitive, and they lose their positive reinforcement, so they don't feel anything anymore. That probably happens very, very commonly with burns, by the way. Because to successfully re-innervate regrown skin is such a short trip, there's no neuropathic pain because re-innervation happens quickly and there it’s a matter of course. And, oddly enough, burns are almost never a cause of painful neuropathy.

MM: Yeah, that's really astonishing.

GB: Of all the traumatic causes, burns are almost never --and I've gone to burn doctors; I've made it a point to talk to burn doctors because I thought that was odd, and they confirm it. They don't know – orthopedic surgeons know about this stuff because they see it all the time – not really commonly, but they see it. Burn doctors never see this neuropathic stuff. Interesting.

MM: That's really interesting. OK. What you're describing here is, it seems to be essentially a peripheral and a pathway phenomenon. I mean, we've talked about – there's a response to the release of neurotransmitters, but it's not centrally created –

GB: The central argument, one of the arguments that had gone on for a hundred years is, is the pathophysiology in the peripheral nervous system or the central nervous system? And this hypothesis says very clearly, it's in both. And it's an interaction between the two, and that's why it's so damned complicated. [he laughs] It's essentially in both places. That's a very, very key point. It's a good point for therapy; it means you have two targets.

MM: Two places where you can intervene.

GB: And if you're real smart, you might try getting them both at the same time, which is useful – something that we're pursuing now. So it solved that problem, and that's right. As I said,

there are certainly holes in it. The biggest hole that bothers me the most is the missing neuropathic grandmother. [he laughs] Now, there must be several million grandmoms out there with severe arthritis, constant C-pain input from their joints, and they never have hyperalgesia and allodynia. I mean, we'd know it, OK? If there were several million grandmothers with allodynia out there, we'd know it. They're not there. It doesn't happen. Maybe this hypothesis we're talking about doesn't work in old people. I don't know. Maybe it doesn't work if the pain develops really, really slowly and gradually; I don't know. But the arthritis observation strikes me as a significant problem.

Also, you don't see this much anymore but I have some personal experience with it, gout in young people. Here's an acute inflammation of a joint that's fantastically painful, but cutaneous allodynia and hyperalgesia? No. I've had several attacks of gout, and I've never experienced it. It's sore, and if I move that joint it hurts terribly. But the skin is not, as far as I can tell, hypersensitive. So the age factor doesn't count there, the onset factor doesn't count there. Gout has a rapid onset. We know in the cat that joint nociceptors are indeed capable of generating an NMDA-mediated central hyperexcitability. So it's not something peculiar about the pain fibers that innervate the joint. There's something missing; there's something not quite right, and I don't know what it is. And the other hole, the other serious problem with the hypothesis -- I've been meaning to write this up; this isn't in the literature any place. This is just what guys talk about at the bar after the meetings, right? The other hole in the story is the capsaicin[69] story, the intradermal capsaicin injection in normal volunteers.

MM: Right. I was going to ask you about that.

GB: That seems to be a brilliant confirmation of the hypothesis, and in many respects it <u>is</u> a brilliant confirmation, but there's one big problem. There is never a dynamic mechanical allodynia in the capsaicin model. Hair movement doesn't move them. Gentle touching of the skin, yes. That's static mechanical allodynia. But hair movement, no. And these experiments are usually done on the molar surface of the forearm or the dorsal area of the foot, two areas that aren't particularly hairy, although at least for me there's some hair there. And I noticed right away that hair movement didn't hurt when you injected capsaicin into yourself. Hair movement in the patients, when it's present, is a terrible, enormous phenomenon.

MM: Oh, yes, that's awful.

GB: You quickly learn that you have to take your necktie and stick it in your shirt so it doesn't flop against the skin, because they'll go crazy. And we examined some patients where their dynamic mechanical allodynia was so terribly severe that we had to wear face masks when we stimulated them because our breath on the hairs was painful. When we started to do capsaicin, with Mitchell Max,[70] after the lead from Don Simone [at Oregon] and Bob LaMotte [at Yale],[71] I noticed immediately the hair movement. I went to look for hair movement, and it wasn't painful. And then we started doing dorsal forearm, where it's very

hairy, and confirmed that the hair movement just doesn't do it.

So why not? It's present in the patients; the central hyperexcitability in animals can be demonstrated by moving hairs, A-beta touch input from hair follicles, but in the capsaicin model, it's absolutely not there. That's a hole in the story that bothers me. And there are a couple of other little ones. But, you know, a good theory doesn't have to explain everything; it just has to explain more than you were able to explain before. And we had nothing that made any sense that had any evidence behind it before. This one has made some successful predictions, it's useful, clearly not completely right, not the whole story, but it's clearly, for the first time, on the right road. Before, we didn't know which tree to bark up.

Part II

MM: Good morning. It's February the tenth, and we're resuming our interview with Dr. Gary Bennett. We broke yesterday and had dinner last night, so now we're extremely rested [laughs] and ready to get back to interviewing. OK. I wanted to ask just a little bit more about your sort of experience of moving from experimental work into observations of clinical pain patients. You talked about that a little bit yesterday. I mean, the impression I had was that this was the first time you had really been thinking about pain as a clinical entity.

GB: Yes, it's true. So it started out that I had the observations of what kinds of abnormal pain sensations were present in the rats, and wanted to know what patients they matched and discovered that no one had that information for patients, and so that I'd have to go out and start generating it myself. Then we started to look at RSD patients referred to us from Bob Schwartzman's clinic in Philadelphia, and we got into this program of trying to understand what might be causing it, based on some local anesthetic injections and other experiments that we were doing with those patients. And that was the Gracely hypothesis that we discussed yesterday.

In the meantime, I discovered that clinical pain was a truly fascinating topic. I've been doing it ever since, so more and more and more. One of the reasons I left NIH was the relative difficulty of doing that kind of work at NIH. NIH doesn't have a general admissions hospital. If you're hurt on the job, they take you to the hospital across the street. All the patients are referred [to NIH] to participate in studies. And we were asking for referrals for our studies in pain patients, and there's a very, very strong tendency, when you're at the National Institutes of Health, to be referred the hardest of the hardest patients. With typical disease, there'd be no sense to send it to the, quote, experts – God knows we weren't [laughs], but people think of us as experts – there's no sense to send typical, ordinary disease to us, and that's what I didn't know; that's what I missed. It's very difficult to learn anything scientifically from the hardest of the hardest patients. They're just too complicated, too many things have been done to them. It's just too tough.

So I needed to see more ordinary disease, and that was difficult or impossible at NIH, and that was one of the reasons why I left. And I've spent roughly half my time on human research. Quantitative sensory testing, continuing the effort to understand what kinds of abnormal pain sensations they have, doing some work with a scanning laser Doppler instrument now,[72] trying to get an understanding of the sympathetic nervous system's role in the pain of some of these patients, a topic which I still view as the most puzzling and confusing issue in the field today, I think.

And I'm doing clinical drug trials, which are also fun and which are almost impossible to do at NIH. Congress passed something – what was it now, almost twenty years ago, fifteen years ago, I guess it was –something called the Technology Transfer Improvements Act.[73] And it made technology transfer almost impossible to do. There's a clause in there that says that if any work is done by a government laboratory, and it doesn't matter how significant that work is, a ten thousand dollar experiment to satisfy my personal curiosity with a drug that the company has spent twenty million dollars to develop, it doesn't matter how significant or insignificant the work – the fact that the work, any work, is done in a government laboratory gives the government the right to determine or participate in the determination of the product pricing. Now, I think a drug company executive would have to be criminally incompetent to act like that.

MM: [laughs] Right.

GB: And in fact they're not incompetent because they don't sign those contracts, so that stopped it and made it almost impossible to do that work. So that was frustrating. I would test compounds in the rats, and a week later I'd know if it worked or not, and I'd want to go see if it would work in people. And I couldn't do it. Otherwise, I had to sit and watch other people do it in other institutions; I found that extremely frustrating. So that's another reason why I left NIH. But, yes, so now half the time with patients, half the time with rats.

MM: I remember from your talk in October, you seemed to have such a – I was so impressed with it that I thought you were a clinician. [laughs] I thought you must be a clinician, that you had such empathy with the patients with diabetic neuropathy and postherpetic neuralgia.[74] So these are patients you've recently come to encounter? Were they among the first group that you met through Dr. Schwartzman?

GB: The first patients I saw were all referred, RSD patients or causalgia patients. And then some diabetics and postherpetic neuralgia patients started to come through NIH because Mitchell Max was doing the drug trials, not industry sponsored, NIH sponsored. So I saw some there. And when I would visit friends, I would go out on rounds, go into the wards, and meet more and more of these patients. They're fascinating in a terrible kind of way. I mean, they just have this awful, awful problem, so much difficulty getting any relief at all. So many of them get no relief.

Physicians who do pain medicine I have a lot of respect for, because you're dealing with people who need help desperately, who are insistent that they have to have help. I mean, if

you're in pain, you want help. And there's just very little that a physician, no matter how skillful, can do for many of these patients. That's a tough position for a physician to be in, and after all, physicians become physicians because they want to make people better. And here they are, spending all their day taking care of patients who they know they can't really make very better, in many cases. Very, very tough.

My role is a much, much easier one; I just go in and ask questions and poke, prod, and do experiments, and I have no responsibility for that patient's care; I have no responsibility for finding relief for that patient – at least not that particular patient; I mean, I hope in the future to help others. But Mrs. Smith, who's coming in for my experiment, knows that she can't count on me the next day when her pain flares up and she's, you know, about to go out the window. But she's not going to call me; she's going to call the physician. That puts me in a really enviable position. I can study the patient, I can empathize as much as I want; I don't have any responsibilities. The people who have the responsibility have a tough, tough job.

MM: OK. Now, when you started looking at clinical patients, you were already a member of IASP and APS?[75]

GB: I don't even recall. I've been a member of IASP for a long, long time.

MM: That's what I thought.

GB: I never got around to joining the APS until I think [laughs] about fifteen years ago or so. I don't know why.

MM: Well, it's only about twenty years old.

GB: Yeah. I used to go to the meetings without being a member. It was just a silly oversight; I never meant to. It was just odd.

MM: It was just more that – I mean you'd commented at one point off tape that you thought the societies had done a worthwhile thing in bringing together basic scientists and clinicians.

GB: No question. But for the first few years that I was in the field, I wasn't interested in the patients – not really. I was, my premier professional meeting was the Society for Neuroscience,[76] which has now become markedly less important, [still something I participate in], but markedly less important.

MM: OK. One thing I'm personally interested in is pain assessment, and you've been doing a lot more with that – I mean, we talked a little bit about how difficult it is to assess pain sometimes in animals and some of the different things you observed in the rats. But I was wondering about your thoughts on pain assessment in humans, about the relative value of the tools that you have available to you.

GB: Well, I'm not an expert in that; when I have to do that, I get Don Price and Rick Gracely involved.

MM: Well, that's always good!

GB: That's how I do that! [laughs] Those are the guys who know how to do that. The tools that we use are relatively crude but adequate. The analogy I always like to make is that the tools that we use are fundamentally similar to the tools that an optometrist uses to get a good prescription.

MM: Oh, I see.

GB: "Can you read that line? Is this lens – Which is clearer, A or B?" He switches the lens, OK? So he's measuring subjective sensation of visual acuity. And you're not always sure which is clearer, A or B; you're not always sure whether you see the third line or not, OK? You're guessing sometimes, you're making it up, you're tired, you're not paying attention. And he keeps asking you, "Which is better, A or B?" And it's an obviously imprecise, messy kind of thing. However, you almost always come out of the office with a perfectly good pair of glasses. Maybe not perfect, but perfectly adequate. Psychophysical testing of subjective sensations. And I think we do the same thing with pain with approximately the same kind of success.

MM: That's a very good analogy.

GB: Well, it's a perfect analogy because there's absolutely no difference between the two situations. Every medical student, and young doctor, fellow, intern – who are even worse than medical students because they think they know something – always have this belief – God knows where they get it from – they have this belief that you can't measure subjective sensation. I just shake my glasses at them. [laughs] "What are you talking about?" I mean, the most common medical test used today is the psychophysical test, subjective sensation, Snell's eye chart.[77] That's the most commonly used medical test used today. And there's nothing significantly different between Snell's eye chart and a one-to-ten VAS [visual analog] scale.

MM: Well, what about the MPQ [McGill Pain Questionnaire] and some of Rick's scales? The verbal scales.

GB: The Minnesota test? Waste of time. Inappropriately used for pain patients. Never validated for pain patients, never intended for pain patients. I am firmly opposed and appalled by its uses.

MM: You're thinking about the MMPI.

GB: I am.

MM: I'm sorry. The Minnesota Multiphasic Personality Inventory,[78] clarifying for the tape, which is essentially –

GB: [It assumes that the] chronic pain patient is overly concerned with his bodily symptoms and has hysteria. That's intellectual horse shit. I mean, that's just ridiculous. But you meant something else.

MM: I meant the McGill.[79]

GB: Ah, the McGill. Uh [pauses], never been overly impressed with it. Seems to be to be more of a vocabulary test.

MM: Ah!

GB: I don't think there are a majority of people have a sophisticated enough vocabulary to understand the distinctions between the words. Some of them, there isn't any distinction between the words, but they're on there. I think it pulls out the obvious, that when skin hurts it tends to burn, and when muscle and bones hurt, they tend to ache. The intensity word scale, I think it's ten points, is superior [to the quality scale]; I think the McGill is a noble experiment, intelligently done, beautifully done, but that in the end I don't think it got us anything. I don't use it in my clinical assessment of patients.

MM: No, I've noticed that despite the variety of tools being out there, the visual analog scales[80] still seem to be the most widely used. Of course, they're easy to use.

GB: They're easy to use, and they're good enough; they let you do what you want to.

MM: OK. There was a paper that interested me on up-regulation and dynorphins, I guess in the rat model in particular. There was a question about whether or not this showed some kind of sensitivity to the modulation of touch or pain.

GB: Yeah. That's an interesting story, although it's one that dead ended pretty quickly.

MM: You should know that the historians love that. [laughs]

GB: Science is full of fascinating dead ends. Eventually they get unblocked and it's pushed forward, but it's interesting to see how it gets there. Sometimes it takes a long time to get to a dead end; sometimes it happens very quickly. So the story began with Mike Iadarola[81] and this is work that we were doing with NIH. And Mike had shown that there was a fantastic up-regulation of dynorphin in the spinal cord dorsal horn in animals with an inflamed foot, one of their hind feet inflamed. Extraordinary up-regulation; the peptide increased something like four hundred percent, I mean, [that's] one of the largest

biochemical changes that you can measure. He's working down the hall and we'd talk every day, so he had a young visiting fellow with him from Rome, a guy, Gaetano Draisci,[82] and we were talking and we said, "Let's look and see what happens with the chronic constriction [CCI] rats. Let's see what the story is." Sure enough, on the side of the nerve injury, tremendous up-regulation. Not as large as inflammatory response, but still I think it was a hundred and fifty percent, two hundred percent. And we went on to show that not only did the peptide go up but the messenger RNA was activated; identification of the peptide was with antiserum, [so] there's always a question about the certainly of your identification. So you do the mRNA to confirm – I don't remember if Mike did that or if Gaetano did that, but somebody did that; we confirmed that. And we did the sections, stained the sections to see the increase, and there were just beautiful, beautiful pictures of obvious, dramatic increases in dynorphin content and neurons in lamina five, in lamina one, and in lamina two.

Interestingly, we compared the CCI with a bunch of other nerve injuries and complete sciatic transsection, a complete crush of the sciatic nerve, and we did something else – I don't remember what it was. And they did not evoke the change in dynorphin. There was something peculiar amongst the nerve injuries about the CCI. We knew that in both the inflammatory case and the CCI case, that there was also a dramatic and very rapid induction of activity in the C-fos chain[83], which Steve Hunt had shown earlier to be evocable by pain.[84] And that's an early change that's very, very early in a cascade of changes; it's a master control switch that once it's thrown, there's an enormous downstream of many, many other changes, which at the time we didn't know what they were.
So there was an obvious guess that the cells that were lining up with C-fos, which were in approximately the same places, were also the ones who were having the dynorphin gene up-regulated. And M. A. Ruda did – I think she worked with Mike on this, or she might have done it independently – an absolutely lovely, lovely double labeling study showing that, yes, the cells that have the C-fos activation were also up-regulating dynorphin.[85] So we had this whole story. And that story, [since] 1991, 1992, hasn't moved an inch since then. Dynorphin is tough to work with because there's not a lot of pharmacology that you can play around with; dynorphin peptide itself, when injected into the spinal cord, causes a bizarre paralysis that's obviously not physiological, and we don't understand what that's all about.

MM: Sure. That doesn't usually happen.

GB: One assumes that the dynorphin is up-regulated as a compensatory endogenous opioid suppression of pain, so that the pain you see is sort of a tip-of-the-iceberg phenomenon because the endogenous system is suppressing most of it but can't get all of it, which is why the patient or the rat complains of pain. That's what one presumes. But that, at the moment, is still a naked presumption; there's really no evidence, plus or minus, about what this enormous increase means, what it does. Nobody knows. Pretty interesting. Someday maybe we'll figure that one out. But at the moment, nobody knows.

MM: A couple of people commented to me that there seems to be such a lot of physiological responses in pain and pain modulation, a lot of which we don't see – we're not too clear on what happens why. And they're wondering if this is some kind of evolutionarily developed overcompensation, or duplicated system [laughs] of some kind.

GB: This would be for endogenous inhibition?

MM: Yes. Endogenous inhibition.

GB: Sure. That idea's been around for a long time. I've never thought it made any sense whatever. Two lines of reasoning. The first is I experience endogenous analgesia very infrequently in my life; I don't know about you. It doesn't happen in [arthritis, for example]. When I was a kid and I was playing football and running around and doing all that stuff, it didn't happen a lot then, either. So there's all this multiplicative circuitry to give me endogenous analgesia once in my life, three times in my life. So I think that's implausible in the extreme.

So the other line of evidence is that the pain subsequent to tissue injury has to be suppressed in a Darwinian sense so that the organism can fight or flee from the source of the tissue injury. But that's what that was for. I always thought that was pretty nonsense, too. Any injury, especially any severe injury, in a Darwinian sense, is almost always fatal. Deer who break their legs don't survive, period. Any serious injury, internal or external, to a wild animal results in that animal's death, almost invariably. It's tough out there. It's a tough jungle, OK? And the weak and injured are somebody's dinner, almost always. And I just can't believe that there's this enormous endogenous system present to give wild animals hospice [care] so they can recover and rejoin the Darwinian struggle. I don't think that happens. I don't think that makes any sense either. How infrequently you see wild animals with healed major injuries is indicative of this.

So I don't think the several systems have been identified, and how many are there now, three, four, five, six? I don't even keep count any more. First of all, I don't think that their job, in the physiological sense, is pain control. And a story, an analogy that I have in my classroom lectures is Gary fixing his old TV when he was a graduate student. The vertical hold was off, and the picture would roll and roll and roll. And I discovered that if you bang hard on the front right-hand corner of that TV, it would stop rolling and fix it. Now this was a perfectly acceptable therapy. I did it time after time after time. It was independently replicable. I could tell somebody else to go bang it on the front right-hand corner and it would fix the TV –

MM: Ah. [laughs] It wasn't a magic touch.

GB: All right? But was the right-hand corner there so that the TV's vertical role could be fixed? Was I really *fixing* anything? No. It was just a complicated machinery that responded in this predictable, but not ordained or planned or logical, way to a certain activation. So I

view the pain control circuitry – both the pain encoding and the pain decoding circuitries – as at least as complicated as our TV. And when we bang on one of them, by sticking an electrode in there and zapping it and we get a predictable response, that doesn't mean that response is the *purpose* of that system any more than the purpose of the top front right corner of my TV was to prevent vertical roll, OK? It's reproducible, it's true; it's real, but it's not the actual function of that system. So what *is* the function of all these interactive systems? And I don't know. And if I knew that, I think I would know a great deal more than anybody in the world about the relationship between sensory excitation and conscious perception. And I don't know that, and neither does anybody else.

So my feeling is that it has something to do with the essence of consciousness, and I don't understand that and neither does anyone else, but I don't think that they are simple, endogenous pain control systems; I think it's far more complex than that. Although they work, and they do control pain; I mean, that is certainly true. I don't think that's their purpose; I don't think that's what they're there for.

MM: Hmm. OK. In 1996, then, you made the decision to move to Allegheny. Was there anything else about NIH, about your work there, the PET studies, that you would like to comment on?

GB: Well, I really had a relatively minor role in those studies. That was Mike Iadarola and Bob Coghill, predominantly.[86] I was just on the sidelines, being a cheerleader and helping, for most of those.

MM: OK. So let's talk a little more about your decision to move here. I think you sort of mentioned earlier some of the compelling reasons that you decided it was time to leave NIH.

GB: Yeah, there were a number of reasons. It was a difficult decision. We've talked about some of them. Probably the overriding reason was that NIH isn't what it used to be, as I said yesterday. NIH, when I first went there, it really was the ivory tower. It was wonderful. It was perfect. I think it was one of the best things any government has ever done in the history of man. Wonderful, wonderful institution. And then, just like the golden goose, they screwed it up. They cut off the money; money became harder and harder to get for research. Congress started to micromanage its affairs. The paperwork started to become extraordinary. During my ten years at NIH, animal care and use protocols evolved from a one-page form to a twenty-seven-page form. I was on the committee, and I fought it every step of the way, but didn't have a chance. It got so you couldn't do anything.

Then the government, or the Congress, rather, started to insult us regularly. The prohibition against accepting honoraria for delivering a lecture. So this was a law that was passed because a senator was caught stealing. So they passed a law. It means I can't get a hundred-dollar honorarium, but the senators continue to steal. Prohibition against travel, how difficult that became. I had to consult with a drug company; the drug company wanted me to come out and deliver a seminar, talk to them about their research plans. All of a sudden I

had to have a contract between that company that went to the NIH lawyers – NIH also started getting more and more lawyers, which paralleled the decline in the institution – and the company would have to sign this contract, which they would sometimes want to negotiate with the government, about intellectual property rights and on and on and on, all this nonsense, which would take three to four months to accomplish. I counted the signatures that were required for Gary to go give a lecture at a drug company: Seventeen signatures were required for me to give a lecture. I'm not making that up. I mean, it was utterly ridiculous.

And it just started – while all this is becoming worse and worse and worse, the pay is not getting any better! [laughs] The deal always was that they wouldn't pay you very much, but they'd let you play; they'd let you do what you wanted to do. Now they weren't letting you do what you wanted to do, and they weren't paying much, either. I don't think it's an accident that people go crazy at the post office. I think it's the natural end stage of what bureaucracy does to people. And I found myself starting to go postal. I was angry; I found myself being angry every day. And life was just too short for that. I had to get away. And it was the right decision. The outside world has its problems and its bureaucracy, too; yeah, sure, it does. But it's not *that* crazy. It's not like that.

MM: [laughs] And so what brought you to Allegheny?

GB: Bob Schwartzman offered me a job.

MM: Oh, that's a good reason!

GB: Yeah. He knew I was unhappy, knew there were problems at NIH. He had moved from Thomas Jefferson[87] – at that time it was Hahnemann University, then it became Allegheny; now it's back to Hahnemann.[88] He had just come over, and he had a pot of money to build up a [program], and he took some of that money and offered me a job.

MM: And so you built up a new laboratory? Tell me about what you've been doing in Allegheny.

GB: Yeah. I built up clinical and basic research testing laboratories, got an NIH grant, as I said last night, and doing pretty much what I wanted desperately what I wanted to do at NIH: continue my animal research, but have a much broader ability to do clinical research, clinical trials, consult with industry, which I do extensively now, which I view as a really important part of my job. No matter what I discover in the laboratory, I can't make a drug on the pharmacist's shelf; the drug companies can do that, and they want to make money at it, which is OK by me, and that's the system. But if they want to make a medicine available that will help people, I'm happy to work with that, and I do a great deal of that. That's very satisfactory, actually, especially since some of the drugs have made it to the market and are actually helping people. SNX 111 will be out there soon.

MM: OK. Let's talk about those.

GB: Very, very, very rewarding. Talk about which? SNX-111?

MM: Yeah.

GB: SNX-111 is pretty cool. So I don't know if you know the story; do you want to hear the story?

MM: Well, the tape wants to hear the story.

GB: OK. [laughs] So there's a young Filipino biochemist named Baldomero Olivera,[89] and he's trained in the U.S. and he goes back to his native Philippines and is trying to figure out what the hell he's going to do. Well, in the Philippines ten or twelve people every year die when they step on one of these poisonous cone snails. There are – In the Indo-Pacific Ocean, I think there are something like three, four hundred different species of cone snail. When I was a kid I used to collect seashells – not just what you'd find on the beach, but go to shops and look at catalogues. And I had an extensive collection of seashells. They're very beautiful. I have them still; they're in the office. They're particularly beautiful seashells.

MM: Cone-shaped?

GB: They're cone shaped; hence the name. And most of those cone snails lead ordinary slug lives and crawl around eating algae off the rocks. But a few species have adopted the habit of eating fish, which is a wonderful biological problem. How does something as slow as a slug catch and eat a fish? And they've solved the problem in two ways. First, they fish; they go fishing. They have a long stinger that they wave in the water; it looks like a worm, and the little fish comes up to investigate it. And they don't wait for the fish to put it in its mouth; they're active hunters. When it gets close enough, the whip it around and sting the fish underneath its gill covers, which injects the toxin directly into the cardiopulmonary circulation. So that's one half of the problem; they put the poison into the fish. They've killed the fish. The other problem that they face is that if that fish swims three feet away before it dies, by the time the snail gets there, somebody's going to have stolen the fish. So they've developed a very complex venom with multiple ingredients, the net effect of which is to cause the fish to literally drop dead on the spot. So the cone snail is [right there] when the fish goes. Just lovely, lovely biology. I really like that. [laughs]

So Olivera decided that he would study the venom of these cone snails. And as with all animal venoms, they're complex mixtures of different toxins. The cone snail venoms turned out to be unlike anything else that had been discovered before. They were a very large family of small polypeptides, twenty to thirty amino acids that had the unusual property of having multiple disulfide bridges, which, so whenever there are pairs of cytosines in the polypeptide chains, they link together with a sulfide bond, which tends to take the strand of polypeptides, the strand of amino acid, and fold it over itself. These tiny polypeptides in the snails had up to three cytosine pairs. So this chain of amino acids was tying itself up into a

really bizarre little knotlike structure, just unlike anything we'd seen before. [Olivera] subsequently went to the University of Utah, and he's still there; he's doing beautiful groundbreaking work on these components. Some of them, it turned out, were acting on voltage-gated calcium channels [in the nerve membrane], and they would have different patterns of activity, and they were now used to identify different subtypes of calcium channels which previously we didn't really understand, but now we have the pharmacology to pull that out.

One of the toxins which was from – It was called G6A – G is for the map cone, the pattern on its shell looks like a map; it's a lovely shell. And 6A refers to *conus geographus* where it came off the column when he separated the venom. So G6A had a unique property of affecting calcium channels in nervous tissue, but not the calcium channels in cardiovascular muscle, which are a different type. So that channel in nerve tissue is now called the N-type, although N was a designation that was applied to it before it was found to be neuronal specific.

MM: Oh, well! [laughs]

GB: Well, just like Substance P;[90] P stands for pain, although it didn't come out that way. P stands for powder.

MM: Oh, really? I didn't know that!

GB: Powder, yeah. Typical German exuberance in naming stuff, right? [laughs] Substance P. So the calcium channel was of interest because it was only [affected in] the nervous system. So some of the people in his laboratory and he formed a company called Neurex,[91] out in San Francisco, to start trying to commercialize the stuff, and the people out there thought that it was known that calcium channel blockers that had no specificity for subtypes, that were broad spectrum, had some record of activity for controlling neuropathic pain. Drugs like nifedipine and nimodipine. But they weren't particularly useful because the dose that relieves the neuropathic pain was the dose where you started to get unacceptable cardiovascular side effects. But with an N-type specific drug, you automatically avoid the cardiovascular side effects. So they were very anxious to test this compound. We spoke back and forth a while, and I wasn't particularly interested until I attended one of their Society for Neuroscience presentations, where they had – this was a slide presentation – they had prepared an iodinated version of G6A, which they had made synthetically and were calling SNX-111, and done the autoradiography on a slice of spinal cord. [It was] one of those moments that gets etched in your mind, I'm sitting in the middle of the room and this slide comes up, a cross section of spinal cord, stained autoradiographically with SNX-111, and it's all in lamina one and two. And I stood up straight out of my chair.

MM: Wow.

GB: Literally. I literally stood up to get a closer look at this because I knew immediately that if

you had a drug that bound only in laminae one and two, that was really likely to be a useful drug. It was like a site-specific lidocaine[92] – instead of producing, getting rid of all sensation, just getting rid of pain, and leave touch behind. So once I saw that, I became very interested in testing their substance, and a Chinese postdoc was with me at the time, Xiao Wen-Hua,[93] and I applied it to the site of nerve injury and got really, really excellent results with it. Annika Malmberg and Tony Yaksh applied it intrathecally to the top of the spinal cord and got excellent results with it.[94] And now it's in either Phase II or Phase III trials.[95] It was initially tested in patients who were just unbelievably difficult – late-stage cancer patients who had failed the most aggressive opioid regimen that we can do. They had pumps applied on top of their spinal cords, were receiving massive amounts of morphine directly onto their spinal cords, and even that wasn't controlling their pain. And several of those patients took SNX-111 and within hours said, "The pain is all gone."

MM: My word.

GB: That's impressive, really impressive. If you can help that patient, that's really something. The side effects have turned out to be very much of a problem with SNX-111, and I'm not certain what the therapeutic index is going to wind up to be. But there's the inherent problem that it's a small protein, which means you can't take it as a pill, and an intrathecal pump, the pump alone, to have the machine and the surgery implanted, costs fifteen thousand dollars. That's pretty expensive medicine. But I suspect that it'll be useful, used for a while at least in dire cases. I mean, remember, these are the cases where they would do stuff like frontal lobotomies for pain. That's where that patient was. You fail aggressive maximum morphine on your spinal cord, and if you're going to do anything else, the next step is you start chopping the nervous system. And twenty years ago that would sometimes proceed to frontal lobotomy. So having even an expensive drug that works for that patient is good and important. But it's not going to be an enormous number of people, but it will help people who are in terrible, terrible trouble.

By the way, an interesting thing is happening in medicine that pertains to chronic pain and chronic neuropathic pain, too. Keeping all these people alive longer. Terminal cancer patients suffering from the terrible pain of late-stage cancer live longer than they used to. His pain ordeal is longer than it used to be. The life expectancy of a diabetic is now normal, a remarkable statistic. But that means that with more older diabetics, we'll have more chronic painful diabetic neuropathy. Elderly people are getting more and more elderly, so when they get their postherpetic neuralgia in their sixties, they're not going to die at seventy; they're going to die at seventy-three, on average. Everything that prolongs the life of the elderly or the seriously ill also prolongs the ordeal of those that will develop a chronic pain syndrome associated with that, a kind of an odd tradeoff.

MM: Live longer and suffer.

GB: Yeah. Well, for some people, I'm afraid that's what it boils down to. So SNX-111 is out there; it's going to be FDA-approved almost certainly sometime soon. Many drug

companies are pursuing a non-protein anti-calcium channel blocker, something you can take in a pill, and they'll succeed eventually. And then we'll have I think a really useful medicine, if we can figure out the side effect stuff, which is some very odd side effects, completely unexpected. Rotary nystagmus [laughs]

MM: I don't even know what that is!

GB: Your eyes spin around in their orbits. [laughs]

MM: Ooh! [laughs]

GB: An ordinary nystagmus is when they beat horizontally and shift back and forth uncontrollably, but in this, your eyes go around in a circle. It turned out to be an utterly unacceptable side effect because every time you open up your eyes you want to vomit, and we have no drug to stop that. We have no way to control that side effect. It's not life threatening at all, but it turned out to be utterly unacceptable and completely unprecedented. And then some other things that are turning up. It suppresses the resting sympathetic tone.[96]

MM: Are these very high rates? I mean, are we talking about ten percent of patients have these, or fifty percent? Or a hundred percent?

GB: We don't have good figures. When you start out with end-stage cancer patients, as you test them, you encounter a variety of unique problems. And one of those is understanding the side effects. These people have multiple organ failure to begin with. I mean, these people are dying. And it's difficult in the extreme to tell if the strange and crazy things that happen to them are due to the fact that they're dying and they have multiple organ failures or if it's your drug. So, talking incidence, you just can't do that with those patients; it doesn't make any sense. But some of the other side effects that pertain to – the rotary nystagmus doesn't happen even when you're dying from cancer, at least not usually.

MM: No. [laughs] One can only imagine.

GB: Yeah, a bizarre thing. So, that's been very satisfying. So the animal work in the CCI rat that Yaksh's lab did and that my lab did prompted that company to go to clinical trials, and it succeeded –

MM: That was a critical role.

GB: And it's helping people.

MM: That's great.

GB: And that's happened twice more in my laboratory. There's a very, very good epilepsy research group at NIH, Mike Rogawski[97], who we would talk to all the time, and he was

telling us about a new antiepileptic drug that had strangely been developed jointly with a small drug company called Carter-Wallace, I think it is, and the United States government acting jointly, something which is very, very odd. And it was called Felbamate.[98] And it was wonderfully successful. It was working in epilepsies that were refractory to the old anticonvulsants. It was working for partial complex seizures, which are very difficult to control, and it was effective in a really vicious epilepsy of childhood called Lennox-Gastaut syndrome,[99] which affects young children, and they quickly progress to status epilepticus and die, that's resistant to the other anticonvulsants. And Felbamate was working in that. So they had thought that the mechanism of actions for Felbamate were a weak degree of NMDA receptor block, and we knew that was good for pain, a weak degree of sodium channel block, and we had reasons that that would also be good for pain, and a potentiation gabanergic release,[100] which sounded like a good idea, too. So we threw that into the rats, and to this day that's the best drug we've ever given the rats. Felbamate made the rats look normal.

MM: My gosh.

GB: And no other drug has even come close to the efficacy. Well, gabapentin comes close, but it's clearly not as good as Felbamate. We were thrilled. I was working with a Japanese fellow who had come over here, Yoshiki Imamura,[101] and we worked very, very hard to do the animal work because we wanted to get to people immediately. We started telling people about this and they started trying it on their patients, and we were getting back glowing reports. Schwartzman was having excellent luck with it; other people were having wonderful luck with it. We were very excited. We thought we had a cure. And then on the very day that we did the last animal experiment, collected the last time point, the last piece of data, we get a letter from the FDA saying that Felbamate is killing people. In preclinical testing, it had had a superb record, just fantastically safe. But it was increasing the incidence of aplastic anemia and hepatic failure, which are bad side effects because they don't go away; you die. [laughs] That's not a rash; that's the bad stuff. And I think before it was all over, I think thirteen people in America died.

It was never withdrawn from the market because of Lennox-Gastaut syndrome, where the kid's going to die anyhow and he'll take a one in five thousand chance of getting aplastic anemia; it's his only chance. But it was obviously not going to ever be tried on pain patients who were otherwise healthy patients. So that was just crushing, really crushing. But we had demonstrated efficacy in the rat and at least on anecdotal – we never could do the controlled clinical trials, but at least on anecdotal data, we had another medicine that worked.
Then we hear about yet another new antiepileptic drug, gabapentin.[102] And gabapentin also was effective in partial complex seizures; it was effective in epilepsies that weren't responsive to the older drugs, and we – though actually it was just a dead spot in the lab. We didn't have anything going on at the moment, so when we heard about this new antiepileptic, it was pretty much, "What the hell? Let's give it a try. We don't have anything better to do right now." And [collaborated] in these experiments as well. And gabapentin worked really, really well. We received a note from a physician, I think he was in Ohio,

what's his name? I'm blocking on it, but I'll think of it in a moment.

MM: You can always add it to the tape later.

GB: Yeah. He had given it to three or four RSD patients, and he had written to me, telling me--I get these letters all the time--telling me how wonderful it was. As I said, it was a dead time in the lab and although I would ordinarily ignore that kind of stuff, I decided, "What the hell? We'll try it." And it worked, and it worked really, really well. We presented our rat results at an American Pain Society meeting, where the poster was really well attended. Parke-Davis, the guys who were making gabapentin, heard about this and became very excited. They went out, and they've done the controlled double-blind clinical trials; they're just recently finished and getting ready for publication, and it does work – not in everybody, but it does work. The funny thing is that gabapentin is probably the most commonly prescribed drug for neuropathic pain in the United States today, and Parke Davis sells more of it for pain than they do for epilepsy. And that was due to the rats. The rats did that.

MM: That's great.

GB: People believe rats. They believe rats more than they believe patients. They do! You know, it's a good model; the rats were clearly better; you don't have to worry about it. All the variables that mess up the human trial, it convinced people.

MM: No subjectivity.

GB: Most importantly, it convinced the drug company to make this investment to make this effort. So that's three drugs that the CCI drugs brought to the market which are going to help a lot of people. And then lastly, work that wasn't done in my laboratory – We did some of it, but we were kind of late getting in, and that was the NMDA receptor blockers. Marshall Devor[103] was the first guy to do that, and subsequently it's been done by very, very many people. The model, the Gracely model, would predict that it would work in painful neuropathy, and when it's tested in rats with painful neuropathy, those drugs work beautifully, without having any effect on normal pain sensation. And then we tried to translate that into the clinic, we ran into serious side effect problems. NMDA receptor blockers make you stupid, they seriously interfere with your thinking ability, and that's a problem. Everyone, however, agreed in both the rat and in the patient, that it works. There's no question that it blocks the pain. The efficacy is there. But there's a serious side effect problem, a serious therapeutic index problem, which numerous people are trying to solve, and with a little bit of luck we will solve that. Then we'll have a fourth class, an entirely new class of medicines for the treatment of neuropathic pain. And the rats played key roles in all four, and I'm very proud of that and very pleased, and that makes it fun to go to work every day, when you do stuff like that.

MM: Yeah, I think this is interesting, to see this sort of direct line of achievement from this working on the rat model and studying the physiology of the injury reaction.

GB: My animal research is split like that. Half, about half, is just basic mechanism kind of stuff, neurophysiology, neurochemistry and so on, just basic science. And the other half of the animal effort is throwing drugs at them and seeing what sticks. I can test a drug for two weeks for five hundred bucks. So far the rats have been perfect predictors of what will work in the clinic, what will have efficacy. And so we've had four positive hits. Boy, that's not bad at all! [laughs]

MM: No, I think that's actually very good!

GB: You're a lucky fellow to get one per career; we've got four already.

MM: I keep thinking of Paul Ehrlich and his six hundred and six.[104]

GB: Yeah, there you go. Well, we've had our failures; but we only tell you about the positives.

MM: [laughs] We're leaving them behind.

GB: But we're working on that. We're still working on that.

MM: Now, all this work with the drug companies, you've been more active in the clinical trial process, developing the drug for market, and you were talking a little bit off tape about how the FDA [Food and Drug Administration] played a not necessarily positive role in all of this.

GB: Well, yeah. [laughs] So what shall I say? I'm not a fan of the FDA in general, and those sections, those departments of the FDA that deal with analgesics, I think have seriously dropped the ball in the last seven or eight years. Prior to the development of the rat model, they were concerned with post-op pain, opiates, and minor everyday aches and pains. They had done well; of course, that's an old story – from the very first days of the FDA they were dealing with those. And I don't know the early history, but by the '60s and '70s, certainly by the '80s, they knew how to deal with those classes of drugs. They had reasonable rules, reasonable ideas, it was OK. They were doing a good job. But then we started telling them this was coming down the pike; we've got neuropathic pain, we've got chronic pain, we have entirely new drug classes never before considered as pain medicine.

MM: Morphine and ibuprofen don't work on neuropathic pain.

GB: Doesn't work. And, you know, you've got to get ready for this, right? And Mitchell Max was a leader at this. He took it upon himself to go say, "Look, let me help you. Let's work together; let's be prepared for this. I mean, we all want to get medicines to the people. Come on; let's go. All right, this is what's going to happen." And the FDA has done nothing.

MM: Really?

GB: Sat on its hands. Solved each problem, each drug application as it comes, patchwork, craziness, no thought, no consultation, or at least not paying any attention to any consultation that was offered them. They didn't have to search for it; people went to them and were sincerely eager – not industry people, other government people, [laughs] and [the FDA] ignored them, brushed them off. Blew them away. And I think they have set back this program of bringing new medicines to chronic neuropathic pain patients for no good reason, and I think they should be ashamed of themselves.

MM: You also talked a little bit about the processes that set up now, we go from Phase I to Phase II to Phase III trials, that being rather cumbersome.

GB: I think it is cumbersome, and I think the logic of it is fundamentally and obviously flawed. The primary job of the FDA should be to establish safety. That should be their number one job. You can't positively establish safety in a small number of people because many severe side effects are relatively rare events – one in five thousand, one in ten thousand. And when you do thirty college sophomores, you're not approaching that problem.

Now, if it's a really, really lethal drug, yeah, you'll pick it up anyway, [laughs] you'll pick it up in the animals and you'll pick it up in the first few people. And occasionally you do pick that up. But in the vast majority of cases, you shouldn't do more than that thirty patients. That should be it, because it's not reasonable to expect to learn anything more until very large numbers of people are exposed to the drug. And that doesn't happen until after approval. So I think the emphasis on safety – initial safety screening, yes, of course, obviously. But that they overemphasize preapproval safety and should take that money and effort and make it into post-marketing surveillance of the drug. Because when it gets out – thalidomide is a perfect example – liver cells could grow and thrive in a petri dish full of thalidomide. They actually did grow in a petri dish full of thalidomide. It wasn't until fifty or sixty thousand people get the drug that you see that there's a one in five thousand chance of getting liver failure from the drug. There's just no way known to do that, except post-marketing surveillance. People, when I complain that all that effort should be in the post-marketing thing, complain that that makes the buying public the guinea pigs. That's absolutely right. And that's unavoidable. And that's not pleasant, it's not fun, but there isn't anything else you can do.

MM: It's not necessarily politically viable.

GB: No. Politicians want to be able to tell voters that the world is completely safe. And a moment's reflection will tell anybody that that's simply not true. One would like it to be true, but liking it to be true doesn't make it to be true. So the analogy I gave you last night, when the FAA [Federal Aviation Administration] proposes a new engineering safety standard for Boeing 747s, they don't put it on thirty jets and fly them around for three years; they make the change, it goes out there on service, and thirty million airplane passengers test that rule. And if something goes wrong, if there's a crash or a mishap, the post-introductory

surveillance is severe. They jump right on it, you learn a lot, you fix it, and that's a grim, grim business, but there is no other way to do it. So do it and do it well. And the FDA does that very well, even though every once in a while something awful happens.

MM: And you lose a lot of people.

GB: Can't be avoided. Unless you want to fly 747s for fifteen years empty, it's just not going to happen. [laughs]

MM: [laughs] One can only imagine!

GB: It's just not going to happen.

MM: OK.

GB: So more post-marketing surveillance, less emphasis on efficacy. I don't think the FDA is well suited at all to make pronouncements about efficacy. The marketplace, the medical marketplace, clinical experience and independent clinical investigations, they establish efficacy. What the FDA is doing establishing efficacy is beyond me. You know, snake oil won't last in the market very long.

MM: No. But historically there have been numerous instances, and actually my dissertation was on Darvon. You remember Darvon?

GB: Yes.

MM: Darvon was one of the best-selling drugs in the country for years, although the clinical trial evidence, such as it was, kept continually showing that it really wasn't very impressive as an analgesic. Tended to make patients feel good, and as you know there have been at least a number of other instances in which drugs have been commercially successful but not really necessarily more efficacious than other drugs, perhaps more expensive than other drugs –

GB: The better-than-what's-out-there rule is another rule that drives me crazy. It's based on a fundamental misunderstanding of statistics and what statistics mean when applied to the individual. Take two hundred people, give a hundred of them Drug A, a hundred of them Drug B, with B being the new drug, and showing that you have equal efficacy, that does not mean that B isn't a valuable drug, even if it's five times more expensive, because you're looking at group averages. When it comes to medicine, group averages don't really mean much at all. What matters is what happens to Mrs. Smith when she takes Drug A and Drug B. We see time and time again that many people fail to respond well to an effective medicine and respond beautifully when we switch them to something that ought to be equivalent. And we don't know why that is, but that's a really, really common clinical occurrence; that happens every single day. So why shouldn't Drug B be there even if it's no more effective on average for the person who won't respond to A, but will in fact respond to

B very, very often? So, that rule is utter nonsense, complete nonsense. And then you wind up with, you know, what has that rule given us? The new streptokinase inhibitor,[105] right, where they tested thousands of patients in two groups, showed superiority in, what was it, 0.8 percent? And that got their approval.

MM: [laughs] Yes, that's not much.

GB: Absolute nonsense, absolute nonsense.

MM: OK. If we're ready to go on –

GB: Oh, no, let me tell you about the combinations. That's the other one that drives me crazy.

MM: Oh, yes, let's talk about that. I love that. This is great.

GB: The FDA regulations are that the combination drug, even if both components – let's say there are two components – even if both components are approved drugs, the combination has to start at the bottom of the ladder and work its way up, like anything else. Now there are lots and lots of medical conditions that we nowadays treat routinely and effectively with combination therapy. High blood pressure' everyone takes two, three, four high blood pressure medicines. Epilepsy; very commonly epilepsy patients are managed with two or three antiepileptics. It's just straightforward stuff. Drug companies are looking at combining interesting stuff, like a little gabapentin with a little NMDA receptor blocker; sounds like a nice idea, doesn't it? [It could be] effective. Everyone talks about it, but drug companies refuse to invest in that. Because they're going to have to go to the FDA as if these two approved drugs, when we put them in a pill together, is an entirely new thing. There's no logic to that

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Everybody takes drugs in combination with other active ingredients. So, if I introduce a drug, do I have to prove that it won't interact with broccoli? That it won't interact with grapefruit? Grapefruit's a great example, by the way, because lots of drugs do indeed interact seriously with grapefruit! [laughs] But everyone takes pills in combination with other chemicals every single day, so why not just ignore that? [laughs] Do that post-marketing surveillance, but why make the company go through those hoops? For what logical or reasonable purpose? There's absolutely no logic or reason whatsoever beyond that. And it prevents, actually prevents, the development of potentially useful combination drugs. I've wanted to test combination drugs myself for years; I can't get anybody to support it.

MM: Wow. I'm just wondering if the pharmaceutical companies will benefit because then they're able to sell two drugs instead of one combination drug.

GB: Well, if they have a uniquely effective combination, they should be able to do very well. But they just don't want to do it because of the extraordinary cost involved. They don't want

to start – especially with two proven drugs, because the patent lives are running out, the generics are out there; they're afraid someone will make their own generic combination; there's just no -- It doesn't make any business sense. If they could do it for a million bucks, they'd think about it. But if it's going to cost them twenty, it's just a bad business move.

MM: Right. OK. Anything else?

GB: No, that's the end of my rant on the FDA.

MM: That was great. OK. Recently you've been involved in a group that's interested in developing a new taxonomy, a mechanism-based taxonomy of pain, and there was a group editorial that was published about a year ago in *Pain* on the subject, and I think you said it's still in the formative stages. I just thought you could talk to me a little bit about your thinking on this and also how the group got together, or what you remember about it.

GB: Yeah. That's an interesting and important development. I think it also stems very largely from the work on the rats. Before 1987, '86, there was a general conception that neuropathic pain was a unitary phenomenon, a single thing. There had been reports, notably by Noordenbos and Lindblom, showing that that in fact wasn't true and that different patients had different kinds of abnormal pain sensations in different combinations. Some had dynamic mechanical allodynia; some didn't. Some had heat hyperanalgesia; some didn't. Some had cold hyperanalgesia, some didn't. All these different kinds of abnormalities would mix and match in different combinations that had nothing to do with the patient's diagnosis. And we rapidly showed that this was true in the rats as well; they had several different kinds of abnormal pain sensations. What really drove the importance of that home was some of our early drug work where we found that some drugs were brilliantly effective against some of the symptoms in the rat and completely ineffective against other symptoms in the very same rat. That's true for gabapentin, for instance. I think there's now six drugs, or drug classes, where that differential symptom sensitivity has been shown.

What that means is several things. First, it means that the different kinds of abnormal pain sensations have at least partly different pathophysiological mechanisms, because they respond differently to drugs. It means that polyneuropathy, where a patient who has polysymptoms is going to need polypharmacy, because some drugs are likely to affect one symptom and not another, and the object of the exercise is to make *all* the pain go away. That's why we add on epileptics, because the object is *zero* seizures. The fact that we reduce seizures by ninety percent is not considered satisfactory; we add on drugs until the seizure incidence is zero. And that's what we're going to do with pain. We want zero pain. And we're going to have to add on drugs. And before we can start to do any of this nonsense, we're going to have to start paying attention in the patients as to what exactly is wrong with them. We have to describe what's wrong with them more carefully. It should not be adequate today, it should not be allowed today, for a patient to walk out of a doctor's office with a diagnosis of, quote, neuropathic pain, with no other specification. He should walk out of the office saying, "This patient has dynamic mechanical allodynia and cold allodynia,

heat hyperanalgesia is not a problem; he has spontaneous proximal [where the affected limb joins the body] pain"; those are his symptoms. That's also subsumed under the rubric of neuropathic pain, but that rubric by itself is no longer very meaningful.

So, to make this point, I've been making this point for quite some time, both in reports of our drug trials in the animals and in my talks with drug companies and such, and in a talk at the FDA. Somehow, I'm not quite sure how, Burroughs Wellcome[106] became interested in this. Burroughs Wellcome is working on developing neuropathic pain drugs, and I think they realized that this was likely to be true and likely to be important, and that they would wind up perhaps with a drug that was effective not against neuropathic pain in a general sense, but that was brilliantly effective against mechanical allodynia. Well, before you can prove that your drug has done that, you have to measure that specifically and know that it's present. So how would you go about that? How could you do it? And so on. Was it reasonable? Was there consensus amongst pain specialists that that was reasonable, or was Bennett talking out of his hat? [laughs]

So they funded a small meeting that was held at the Waldorf Astoria and chaired by Clifford Woolf, who had recently moved from the University College, London to Harvard. A few doctors [and] a few basic scientists sat down for two days and just talked about this. A very interesting meeting. Immediate total acceptance of the concept as being true. That took five minutes. I thought that would be a big debate; that took five minutes. Everyone recognized, yes, this is true; this is just really obviously true. Can we prove it's important yet? Well, no, we haven't, but you can't prove it's important until you count it and measure it and identify it first. And that hadn't been done. The second point which I thought would be contentious, would it be reasonable to go the FDA with a drug not for disease, like postherpetic neuralgia or RSD or painful diabetic neuropathy, but to go to the FDA with a drug like, for example, dynamic mechanical allodynia? Would that be reasonable? Again, I thought that would be contentious, but that was five minutes. "Yes. Sure." And then we quickly got down to multiple symptoms, multiple pathophysiological mechanisms; how many mechanisms are there?

Part 3

MM: OK. We're starting Tape Three.

GB: So we spent the two days of the meeting coming up with a draft list of how many mechanisms are there, and how can they be identified with reasonably useful precision – not perfect, but reasonable precision – in patients? And we wrote it up. Subsequently, the American Pain Society received an open-ended grant, a no-strings-attached grant from a wealthy philanthropist in California, and they organized and I chaired this meeting out in the Napa Valley. This time I recruited – well, Clifford was there again, but mostly I tried to get other people, other physicians with extensive bedside experience. The best and the brightest young physicians who were seeing these patients. We spent two days out there discussing this further. What's the list? Can we come up with a list that we can all agree upon at the

moment of how many mechanisms are there? And can we get some sort of roughly standard idea of how we're going to test to see if they're present? And that went fairly well. And the report is sitting in my briefcase, and I haven't written it up yet, but I will sometime soon. And then we're going to have a symposium devoted to this subject at the IASP meeting in Vienna [in 1999].[107]

So I think some time fairly soon we will have a general consensus of what the list is and how to test for it, and then one would hope that drug companies would use that list and that series of tests so that when they did their drug trials, they weren't just asking the patient, after they take the pill, "How is your pain?" Which is probably a very silly question. He doesn't have *a* pain, he has multiple pains, and he doesn't go around testing them all the time; he goes around trying to avoid them all the time. So I wonder how often in the past a patient has said, "I'm twenty percent better," and the company is disappointed. But what has actually happened is that the drug has completely eliminated one of his pains, but he's got other pains remaining. I wonder how often that's happened. Maybe we'll find out.

MM: So really, this would be a better way of pain assessment than doing the VAS scales and subjective reports.

GB: Well, you do multiple tests.

MM: I mean, you have to do that, too.

GB: Well, you apply standard cold stimulus, and you [ask them for] an idea as to how much did that hurt? You do a standardized latent brush stimulus across allodynic skin and you say, "How much did *that* hurt?" *Those* are the numbers. Not a sit there and do some sort of mysterious arithmetic in your head and come up with one single VAS [score], which is what we're doing now.

MM: Separating them out.

GB: Yeah, separating them out. With luck, that will be a really major advent that we'll see come to fruition in the next year or two, with a little bit of luck. Man, that's been fun.

MM: OK. I have some sort of general questions. One of the things that interested – well, I mean, this happens to everybody – but you have worked with a number of fellows and postdocs over the years, many of them coming from other countries, and so I have two questions. One is, what do you look for if someone comes and says, "I'd like to work with you"? Do you take them on faith, or are there some things that you look for in a new collaborator or a new student or fellow? That's one question. And the second question, then, is, are many of these people going back to their home countries? Is science becoming more international, as you perceive it? You have a significant number of interactions with people around the world.

GB: Yeah. I think science has always been international. It's now more international because of E-mail and the Internet. That makes us – I routinely interact with colleagues in Israel, Germany, Japan on a weekly or better basis with – It's just no trouble at all. You type in a message and send it off. It's wonderful. Wonderful.

MM: Right. I know.

GB: Whereas it used to be by mail, and once in a while you spend twenty bucks on a long-distance phone call but not too often [laughs], but now what was commonplace has now become both commonplace and remarkably, wonderfully easy. Science is a worldwide thing; pain medicine is a worldwide thing. And that's a wonderful part of the job, actually. How do I select fellows? My experience is quite unlike most others, I suspect, because I was at NIH rather than at a university. NIH is not a degree-granting institution, so we didn't have doctoral students. Or med students working for the summer or something like that. We didn't have any of that. Our manpower came from visiting scientists and visiting fellows. And postdoctoral fellows wouldn't be Americans; the visiting fellows and visiting scientists came from overseas. A government-supported program that's really a fine, fine program. No better way to promote peace between nations than to have the doctors and the scientists go back and forth. Those are the ties that count.

So we had – often it would be relatively older people, late twenties, early thirties, rather than early twenties for a Ph.D. student. How were they selected? Mostly contact networks, recommendations. A guy who'd been over there five years before had his best student, and they would send their best students over. The result was that we had truly remarkable people, just great, great people. They had succeeded in their own countries; they were the best in their own countries; that's how they got the opportunity to come to NIH, and they were just uniformly superb quality. Because of the NAB's contacts, we happened to get a very large number of Japanese students, and the Japanese would go home. They came over and they did their work, and when they went back, they joined the university. In the early days we had a few people coming over from the People's Republic of China, and in the early days there weren't a lot of--

MM: Did Xie Yi-Kuan come from there?

GB: Xie Yi-Kuan and Lu Guo-Wei; and in those days they weren't allowed to bring their families with them.

MM: I remember that.

GB: And there was a good reason for that. I mean, their families were hostages. And so those fellows went home. Nowadays, Chinese postdocs come to the universities, and they don't want to go home.

MM: Right. They want to stay.

GB: They can't do their work at home. But in those days, they had to. Some of those, you know, when I was working with Xie Yi-Kuan, that was the Cultural Revolution time. I wouldn't send, I wouldn't mail envelopes. There was a period for about a year and a half when I wouldn't send correspondence to Xie Yi-Kuan, because to receive a letter stamped from a United States government department could have put him in jail. I mean, it was a crazy time over there. The fact that I was sending him reprints would not have made any difference. [laughs] If he got an official – that would just be ridiculous. That was so out of bounds that I didn't even bother to do that. We would communicate, people would visit, and there would be this underground correspondence stuff, always in suitcases, never through the mail. That went on for quite some time. So that was difficult. A few Europeans would come to the lab. I was always surprised we never had any South Americans; I don't know why. We never had any connections with Mexico or South America. Mostly Japanese and Chinese. It was just, you know, patterns of referral.

MM: Right. If one of your current fellows came – say, someone who's just starting a career who has a background in psychology or physiology and says that he'd like to pursue a career in pain, would you give him any particular advice or suggestions?

GB: As a researcher? As a non-physician researcher?

MM: Yeah.

GB: I would tell him that it's a fascinating field and important field, and I think it's one of the hottest fields in neuroscience today. I think it's largely outside of the molecular genetics boom, which I personally view as one of its strengths. [laughs] But that means that even though it's hot and it's good, it's not the most easily granted area of work, but I think its grants importance is getting better and has a chance of approaching, becoming adequate, in a couple of years. It's still sub-adequate. I would encourage them to do it. I wouldn't pretend that it's easy; it can be very difficult. It's not like going into molecular biology, where there are tons and tons of jobs, tons and tons of opportunities. That's not the same; that's not the same. But, still, it's a good way to spend your day.

MM: [laughs] OK. At some point I usually ask people what they think their greatest contribution has been.

GB: Oh, God, I don't know; it's so philosophical.

MM: Yeah.

GB: I got really lucky and developed really useful rat models; I guess I would say that.

MM: I thought that might be true. OK. So do you want to talk a little bit about the more recent work that you've been doing or been involved in?

GB: Well, yeah, the stuff that's currently going on in the laboratory I'm very excited about. An Israeli doctor, his name is Eli Eliav,[108] [worked with me] my last year at NIH, and then when I came here in the beginning; we're working on a model of experimental inflammation of the nerve, neuritis. When a nerve is injured, there is structural damage to the component cells and an inflammatory reaction; the inflammatory reaction involves mobilization of the immune system. I don't think that's generally recognized. Everyone knows that infection mobilizes the immune system, but the immune system is also involved in cleaning up the debris of a sterile injury. So we asked the question of what were the respective roles of the structural damage in the immune-mediated inflammatory response? In a CCI animal, they're present together. So we developed a method to inflame the nerve without causing structural damage to the nerve. Turned out to be very simple. We wrapped the nerve in a piece of sponge, soaked it with an inflammatory stimulus like capsaicin, and we get not only an inflammation outside the nerve, but we also get an endoneural inflammation, a neuritis, and the animal developed abnormal pain sensations in their hind paw. We're very excited about that and it's allowing us to probe the role of the immune system, which now appears likely to be, very important, at least in the onset; it's certainly not going to describe, I think, many chronic problems, but it may be an essential early event in the genesis of the chronic problems. And we're doing a great deal of that, and that's been great fun because I've had to learn immunology.

MM: Wow! A new field!

GB: You go out, you buy a textbook in immunology, and you start reading it! [laughs] It's been fun. So we're doing a lot in immunology. And the other thing that's very new – we'll be presenting the abstract at the IASP meeting – an oncology nurse at the University of Pennsylvania named Rosemary Polomano was struck by the pain syndrome produced by Taxol chemotherapy. Taxol, you might remember, was first isolated from the bark of the Pacific yew tree, and there was a problem because there weren't enough yews, and then someone devised a way to extract it from the needles of the common European yew tree, and now it's readily available. It's rapidly becoming the first-line chemotherapeutic drug for most of the truly significant and frequent cancers – ovarian, breast, prostate. It looks pretty soon like lung cancer, too.

So it's going to be the A-Number One drug. It has three bad side effects. It suppresses the bone marrow, it damages the kidney, and it damages the nerves. The kidney damage, it turns out, is very easily controlled. You just have the patient drink eight big glasses of water a day, and it flushes the kidneys and you avoid the toxicity. The anemia turns out to be relatively easy to control because you take another drug, a colony growth-stimulating factor that causes the residual marrow to go into overdrive and makes up for the deficit. So that's not a particular problem. The uncontrollable side effect now is nerve damage. And it's a painful neuropathy which can be severe, uncontrollable by morphine, and has limited the doses that are used and can cause the course of chemotherapy to be stopped. Now, when you're in the middle of a course of chemotherapy and you're watching the tumor shrink,

stopping is something you do not want to do. But this neuropathy makes it stop. Makes it stop, makes them wait six to eight weeks for the nerve to recover before they can go in there and try something else. And, again, sitting on your thumbs is not what you want to do. You want to aggressively go after the tumor. So, if we can figure out what was producing this pain syndrome and this neuropathy with Taxol, we could give more drug, give it more often, and perhaps actually save lives.

There had been some animal work showing that you could damage the hell out of rat nerves by giving them Taxol, but you produced a syndrome of anesthesia and paralysis that didn't match what was present in the clinic. Well, Rosemary came to work with me, and we started playing around with it, and we found that the trick was that everyone was using doses that were probably about ten times too high in rats. If you went down real low with the dose, and you were really skillful at measuring pain sensation in rats, which is what we did for a living, you could pick up painful peripheral neuropathy in rats from Taxol without paralysis and anesthesia. And that's the clinical syndrome. So we got it now. We've got the model; we can reproducibly reproduce this in every animal who receives these low-dose regimens of Taxol. And we're very excited about that, and we're going to pursue that on a two-pronged approach.[109] Basic science. Why does that hurt? Why does that nerve get damaged? And, B, let's throw some drugs on it and see what makes it stop. And that's where we are with that. Very excited about that. That could also have real immediate clinical impact, so we're very excited about that.

MM: Yeah. And it's very positive for cancer patients.

GB: Yeah.

MM: That's great.

GB: So that's what we're doing today. That's what I'll do when I go to the lab this afternoon [laughs].

MM: You have a reason to get up in the morning.

GB: Well, it's still fun, you know? It's still fun. That's right. I get up every day – almost every day [laughs] – I want to go to work. My father was a very intelligent man who never had an opportunity to get a college education who wound up in a job that he hated, supporting his family, and I remember him going to work every day and hating his work. And I'm a very lucky fellow that I don't have to do that.

MM: Right. Yeah. I think that's very rare, but hopefully not as rare as it used to be.

GB: Hopefully; hopefully. I consider myself very lucky.

MM: But a great gift. OK. Anything else that you would like to say?

GB: Oh, I don't know. I think I'm going to be talked out.

MM: OK. Well, I think it's probably about time. It's now ten past eleven, and we're ending this interview. Thank you very much.

GB: Thank you, Marcia.

END OF INTERVIEW

Notes

[1] Originally founded as Queens College in 1766 and named after William Rutgers in 1825, Rutgers was designated the State University of New Jersey in 1945. The University became coeducational in 1970.
[2] Wilder Penfield (1871-1976) was a Canadian neurosurgeon at the Montreal Neurosurgical Institute who became famous in the early 1950s when, operating on conscious epileptic patients, he stimulated the temporal lobes with electrical probes and elicited specific detailed memories. He also used this method to map the sensory and motor cortexes.
[3] Virginia Commonwealth University (VCU) was founded as a medical school in Richmond, Virginia, in 1838 and became the Medical College of Virginia (MCV) in 1854. A merger with another professional school in 1917 led to its renaming and redevelopment as a research university.
[4] The draft lottery was instituted by President Richard Nixon and was in force 1969-73, during the last years of the Vietnam War. There were two lotteries in 1970 and 1971. The numbers issued in 1972 were never pulled and the draft legislation was allowed to expire at the end of June, 1973.
[5] Anatole France (1844-1924) was a French novelist and poet, honored by the Nobel Prize in 1921.
[6] John A. Rosecrans, as of 2015, was Professor Emeritus of Pharmacology and Toxicology at VCU.
[7] David J. Mayer is perhaps best known as the lead author of a 1971 study documenting endogenous analgesia in the rat brain, written when he was a postdoctoral fellow at UCLA. (Mayer DJ, Wolfle TL, Akil H, Carder B and Liebeskind JC. Analgesia from electrical stimulation in the brainstem of the rat. *Science* 1971 Dec 24; 174: 1351-1354.) Dr. Mayer continued his pain research at the Medical College of Virginia for 30 years.
[8] As of 2015, Donald D. Price, PhD, was Professor Emeritus of Oral and Maxillofacial Surgery in the Division of Neuroscience at the University of Florida.
[9] A Faraday cage, invented by Michael Faraday (1791-1867) in 1836, is any enclosure made of conductive material to block external static and non-static electric fields by channeling electricity along and around, but not through, the walls of the "cage", providing constant voltage on all sides.
[10] Price DD and Mayer DJ. Physiological laminae of the dorsal horn of *M. Mulatta. Brain Research* 1974 Oct; 79: 321-325.
[11] Felliniesque, refers to the somewhat surreal quality of the films of Italian director Federico Fellini (1920-1993).
[12] The periaqueductal gray in the midbrain is the primary cortical control center for pain modulation. This was the area identified by Mayer and colleagues in 1971 (see note 7).
[13] The article referred to is Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science* 1969 Apr 25; 164 (3878): 444-445.
[14] Huda Akil, as of 2015, was Co-Director and Research Professor of the Molecular and Behavioral Neurosciences Institute and Distinguished University Professor and Quarton Professor of Neurosciences in the Department of Psychiatry at the University of Michigan. She is one of the leading researchers in the neurobiology of emotions.
[15] John C. Liebeskind (1935-1997), professor of physiological psychology at UCLA, was a founding

member of the IASP and the APS. He is perhaps best known for his work on stress and stimulation-produced analgesia (see note 3), and also for his demonstration that persistent pain *is* harmful, in the stress it places on the immune system and other endogenous systems (see Liebeskind JC. Pain can kill. *Pain* 1991 Jan; 44(1): 3-4). He was also the founder of the Liebeskind History of Pain Collection at UCLA.

[16] Naloxone is a pure opioid antagonist that is used to counter the effects of opioids in case of overdose.

[17] William D. Willis, MD, PhD, was Professor and Chairman of the Department of Anatomy & Neurosciences at the University of Texas Medical Branch in Galveston 1996-2003; as of 2015, he was Professor Emeritus of Neuroscience and Cell Biology. His lab has made many contributions to the understanding of pain mechanisms.

[18] Presumably the Armed Forces Radiobiology Research Institute in Bethesda, Maryland, chartered in 1961.

[19] The long-tailed or crab-eating macaque. The Rhesus monkey is also a macaque.

[20] The nerve fiber that responds specifically to pain.

[21] Hans W. Kosterlitz (1903-1996) and John Hughes at the University of Aberdeen identified the first endogenous opioids, which they called enkephalins, in the brain in 1957. See Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA and Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 1975 Dec 18; 258: 577-579.

[22] 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.

[23] Mary Ann [M.A.] Ruda, PhD, was the Head of the Cellular Neuroscience Section of the Pain and Neurosensory Mechanisms Branch at NIDCR until her retirement in about 2006; her laboratory carried out significant research in tracing synaptic pathways, and in elucidating the biochemical basis of gender differences in pain and of the effects of pain on neonatal development.

[24] Stephen Gobel, DDS, did extensive neuroanatomy work at NIDCR. He later became a Scientific Review Administrator at NIH.

[25] Ronald Melzack (1929-), emeritus professor of psychology at McGill University as of 2015, and an important theorist of the pain field, and Patrick D. Wall (1925-2001), DM, a leading British neuroscientist and pain researcher, are best-known for their development of the gate control theory in 1965. The theory postulated a "gate" in the substantia gelatinosa cells of the spinal cord, where pain signals from the periphery were blocked or relayed on to the brain. See: Melzack R and Wall PD. Pain mechanisms: A new theory. *Science* 1965 Nov 19; 150: 971-979. For more on Melzack, see: https://publications.mcgill.ca/headway/magazine/the-king-of-understanding-pain-qa-with-ronald-melzack/ .

[26] The thalamus is the brain structure between the midbrain and the cortex responsible for relaying sensory and motor information to the cortex.

[27] Antidromically activate: that is, activate the spinal cell from the thalamus, whereas the normal physiological pathway would be the reverse.

[28] See: Price DD, Hayashi H, Dubner R and Ruda MA. Functional relationships between neurons of marginal and substantia gelatinosa layers of primate dorsal horn. *Journal of Neurophysiology* 1979 Nov; 42 (6):1590-1608.

[29] Haruhide Hayashi was a researcher at NIDCR in the late 1970s and early 1980s. He later returned to Japan and as of 2011, was on the faculty of the Tohoku University Graduate School of Dentistry in Sendai.

[30] Mohammed Abdelmoumene later served as deputy director of the World Health Organization.

[31]Stephen T. Kitai was Professor of Neurosurgery at the University of Tennessee Health Sciences Center in Memphis.

[32] Kenneth T. Brown and Dale G. Flaming were working in the Department of Physiology at the University of California San Francisco.

[33] The Golgi stain is a classic method for staining tissue with silver nitrate so that the cellular structure and can be more clearly visualized under the microscope. It was developed in 1873 by the Italian physician and microscopist Camillo Golgi (1843-1926), who shared the Nobel Prize [with Santiago Ramon y Cajal] for his work in 1906.
[34] For historical perspective on HRP, see Veitch N. Horseradish peroxidase: A modern view of a classic enzyme. *Phytochemistry* 2004 Feb; 65: 249-259. According to Veitch, the initial isolation was in 1904.
[35] The axons are the extended projections of the neurons with dendritic branches. The axon terminals, where the synaptic release of neurotransmitters occurs, are also called synaptic boutons.
[36] The vesicles are the small sacs that store neurotransmitter at the boutons; mitochondria are membrane-encased organelles within the cell.
[37]Santiago Ramon y Cajal (1852-1934)is considered one of the greatest microscopists of all time and a pioneer of modern neuroscience for his studies of neurons in the brain and central nervous system. He used and later improved on Golgi's silver stains. Cajal shared the Nobel Prize with Golgi in 1906.
[38] A camera lucida is an optical device used by artists that superimposes an image of the object on the drawing surface.
[39] Bennett GJ, Abdelmoumene M, Hayashi H and Dubner R. Physiology and morphology of substantia gelatinosa neurons intracellularly stained with horseradish peroxidase. *Journal of Comparative Neurology* 1980 Dec 15; 194(4): 809-827; Gobel S, Falls WM, Bennett GJ, Abdelmoumene M, Hayashi H and Humphrey E.
An EM analysis of the synaptic connections of horseradish peroxidase-filled stalked cells and islet cells in the substantia gelatinosa of adult cat spinal cord. *Journal of Comparative Neurology* 1980 Dec 15; 194(4): 781-807.
[40] As of 2012, Alan G. Brown was Professor of Veterinary Physiology at the University of Edinburgh.
[41] Denise Angaut-Petit was a researcher at the CNRS Laboratoire de Neurobiologie Cellulaire et Moléculaire, in Gif-sur-Yvette, France.
[42] As of 2015, Linda R. Watkins was Professor of Psychology at the University of Colorado in Boulder; she has continued her research on pain.
[43] As of 2015, Glenn J. Geisler, Jr., was Professor of Neuroscience at the University of Minnesota.
[44]See: Bennett GJ and Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 1988 Apr; 33(1): 87-107.
[45] Calvin WH. Synaptic potential summation and repetitive firing mechanisms: Input-output theory for the recruitment of neurons into epileptic bursting firing patterns. *Brain Research* 1972 Apr 14; 39(1): 71-94. William Calvin (1939 -), as of 2015, was Professor Emeritus of Psychiatry and Behavioral Sciences at the University of Washington. He is a well-known popularizer of evolutionary biology and neuroscience.
[46]An oscilloscope is used to varying signal voltages over time.
[47] The small C-nerve fibers that are dedicated to pain sensation are demyelinated and for that reason have very slow conduction.
[48] Causalgia, literally "burning pain," was first described by Silas Weir Mitchell in the early 1870s. The patient has suffered from a nerve injury or other injury which appears to have resolved but left him with a persistent intolerable burning sensation, usually in a hand, foot, or limb. Causalgia and causalgia-like pain disorders were later named reflex sympathetic dystrophy, or RSD, and then in the 1990s again renamed Chronic Regional Pain Syndrome (CRPS).
[49] John J. Bonica (1917-1994), widely recognized as the founder of the pain field, was Chair of Anesthesiology at the University of Washington for much of his career. The book Bennett refers to here is *Bonica's Management of Pain*; Bonica published the first edition in 1953. He also founded a multidisciplinary pain clinic at UW and convened an International Pain Symposium in Issaquah, Washington, in 1973, which catalyzed the formation of the International Association for the Study of Pain.
[50] Dr. Kenneth M. Hargreaves is Professor and Chair of the Department of Endodontics, and Professor of Pharmacology, Physiology, and Surgery at The University of Texas Health Science Center at San Antonio as of 2014.

[51] See: Wall PD, Devor M, Inbal R, Scadding JW, Schonfeld D, Seltzer Z and Tomkiewicz MM. Autotomy following peripheral nerve lesions: experimental anaesthesia dolorosa. *Pain* 1979 Oct; 7(2): 103-111.
[52] Lowell O. Randall and J. J. Selitto at Hoffmann-LaRoche developed the paw pressure test for the measurement of pain and analgesia in 1957.
[53] As of 2005, Ze'ev Seltzer, DMD, was Professor of Dentistry and Physiology at the University of Toronto and affiliated with the UT Centre for the Study of Pain and Program in Neuroscience.
[54] Austrian physiologist Maximilian von Frey (1852-1932) used very fine calibrated filaments, or hairs, to localize pain and touch sensation on areas of skin; he developed this method in 1896.
[55] As of 2015, Michael Tal was Professor of Anatomy and Developmental Biology and Director of the Center for Pain Research at the Hebrew University of Jerusalem.
[56] Jin Mo Chung was working at the University of Texas Medical Branch (William Willis' laboratory) in Galveston, where, as of 2015, he was Professor and Interim Chair of Neuroscience and Cell Biology.
[57] Hyperalgesia is severe pain response to a mild pain stimulus; allodynia is pain response to an innocuous stimulus.
[58] Ulf Lindblom as of 2015 was Professor Emeritus of Neurology at the Karolinska Institute in Stockholm, Sweden. Lindblom was a founding member of the International Association for the Study of Pain (IASP) in 1973, a founder of both the Scandinavian Association for the Study of Pain in 1976 and the European Federation of Chapters of IASP (EFIC) in 1993.
[59] Willem Noordenbos (1910-1990), a Dutch surgeon, published his medical thesis, *Pain,* in 1959, a short but germinal work that heavily influenced Melzack and Wall (see note 25), as well as other researchers.
[60] Richard H. Gracely, PhD, is a psychologist best-known for his work on the Differential Descriptor Scale, a pain measurement tool, and for his paper with Gary Bennett on the development of neurotoxicity in chronic pain, based on the chronic constriction rat model; see Gracely RH, Lynch SA and Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. *Pain* 1992 Nov; 51: 175-194. After 20 years as a researcher and Section Chief at NIDCR, Gracely moved in 2002 to the University of Michigan School of Medicine, where he was Professor of Internal Medicine (Rheumatology) as of 2015 and actively involved in pain research.
[61] A chronic facial pain condition based on a disorder of the trigeminal nerve.
[62] Reflex sympathetic dystrophy; see note 48.
[63] See note 59.
[64] Clifford J. Woolf as of 2015 was professor of neurology and neurobiology at Harvard Medical School and director of the F.M. Kirby Neurobiology Center at Children's Hospital Boston. His research with Patrick Wall was done at University College London.
[65] Woolf CJ and Wall PD. Chronic peripheral nerve section diminishes the primary afferent A-fibre mediated inhibition of rat dorsal horn neurones. *Brain Research* 1982 Jun 17; 242(1): 77-85.
[66] See: Woolf CJ and Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991 Mar; 44(3): 293-299. NMDA, N-methyl-D-aspartic acid, is an amino acid which mimics the action of glutamate, the neurotransmitter which normally binds to the NMDA receptor. Overactivity of these receptors can trigger various neurotoxic reactions.
[67] William K. Livingston (1892-1966) was an Oregon neurosurgeon and pain researcher, a pioneer in the field before World War II. After the war, he organized a pain clinic at the University of Oregon where the young Ronald Melzack worked as a fellow. Livingston imagined chronic pain as created by a feedback loop, or "vicious circle" in the nervous system in his 1943 book, *Pain Mechanisms.*
[68] A neuroma is any neural growth.
[69] Capsaicin is a chemical obtained from plants of the chili family, which produces a burning effect in animal and human tissues.
[70] Mitchell B. Max, MD (1949-2008), was medical director of the Pain Research Clinic of the Neurosensory and Anesthesiology Branch at NIDCR from 1983 to 2005 and Director of the Clinical Pain Research Section 2005 to 2007. In 2007, having developed an interest in pain genetics, he moved to the University of Pittsburgh as Director of the Molecular Epidemiology of Pain Program there.

[71] As of 2015, Donald A. Simone, PhD, was Professor and Interim Chair of the Department of Diagnostic and Biological Sciences at the University of Minnesota; and Robert H. LaMotte, PhD, was Professor of Anesthesiology and of Neurobiology at the Yale School of Medicine.
[72] The laser Doppler instrument measures non-contact surface vibrations.
[73] The Technology Transfer Improvements Act was passed in 1991.
[74] Diabetic neuropathy is functional pain thought to be caused by diabetic damage to the nerves or to the blood vessels supplying the nerves; the patient may also suffer dizziness, weakness, numbness, and other symptoms. Postherpetic neuralgia is neural pain, usually on the skin, caused by the varicella zoster virus (responsible for chicken pox), and commonly referred to as shingles.
[75] [75] The International Association of Pain, or IASP, was founded in 1973, following a seminal meeting of pain researchers in Issaquah, Washington, and the journal *Pain* began publication in 1975. The First IASP World Congress was held in Florence, Italy, that same year. The American Pain Society, or APS, was founded through the merger of several regional pain groups in 1977.
[76] The Society for Neuroscience was founded in 1969, by a subcommittee formed by the National Academy of Sciences; its first meeting, with 1300 attendees, was held in Washington, DC, in 1971. Today SfN has nearly 40,000 members and some 30,000 attend its annual meetings. For more on the history of SfN, see: http://www.sfn.org/about/history-of-sfn .
[77] The Snellen eye chart, using 10-12 lines of progressively smaller letters generated on a standard grid, was the most commonly used measure of visual acuity into the 21st century. It was developed in 1862 by the Dutch ophthalmologist Hermann Snellen(1834-1908).
[78] The Minnesota Multiphasic Personality Inventory is considered the gold standard in personality testing, used to measure psychopathology and personality structure. The original version, with more than 500 items, was developed in 1939 by Starke R. Hathaway, PhD, and J. C. McKinley, MD, at the University of Minnesota and published in 1942. The most recent version, published in 2008, is a less redundant measure with 338 items.
[79] 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. A number of other verbal scales, such as Richard Gracely's Differential Descriptor Scale, have been developed as variations on the same model.
[80] Visual analog scales used points on a line or graphic illustrations (e.g., faces) to assist the patient to rate his/her pain from 0 (no pain) to 10 (worst possible pain).
[81] Michael J. Iadarola, PhD, was Chief of the Neurobiology and Pain Therapeutics Section at NIDCR as of 2015.
[82] Gaetano Draisci as of 2015 was Professor of Medicine and Surgery at the Catholic University of the Sacred Heart in Rome. See Draisci G, Kajander KC, Dubner R, Bennett GJ and Iadarola MJ. Up-regulation of opioid gene expression in spinal cord evoked by experimental nerve injuries and inflammation. *Brain Research* 1991 Sep 27; 560 (1-2): 186-192.
[83] C-fos is a proto-oncogene.
[84] See Munglani R and Hunt SP. Molecular biology of pain. *British Journal of Anaesthesia* 1995 Aug; 75(2): 186-192. Stephen P. Hunt, PhD, was working in the Laboratory of Molecular Biology at Cambridge University at the time of the article. As of 2015, he was Professor of Molecular Neuroscience at University College London.
[85] See: Noguchi K, Kowalski K, Traub R, Solodkin A, Iadarola MJ and Ruda MA. Dynorphin expression and Fos-like immunoreactivity following inflammation induced hyperalgesia are colocalized in spinal cord neurons. *Brain Research Molecular Brain Research* 1991 Jun; 10 (3): 227-233. For M.A. Ruda, see note 23.
[86] 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, and

was involved in the PET studies. 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.

[87] Thomas Jefferson University is a private health sciences university in Philadelphia, originally founded in 1825.

[88] Hahnemann Medical College of Pennsylvania was founded in Philadelphia as a homeopathic medical school in 1848. It became Hahnemann University in 1982 and merged with the Women's Medical College of Pennsylvania (founded in 1850) in 1993, as MCP Hahnemann University School of Medicine (briefly renamed Allegheny 1996-1998). In 1998, Drexel University took over management of Hahnemann, which was renamed Drexel University College of Medicine in 2002.

[89] As of 2015, Baldomero Olivera was Distinguished Professor of Biology at the University of Utah.

[90] A tachykinin peptide neurotransmitter, associated with inflammation and pain.

[91] For more information see: http://www.biotext.com/Neurex.pdf .

[92] A local anesthetic commonly used in dentistry and minor surgery.

[93] As of 2015, Xiao Wen-Hua was a member of the Department of Anesthesia and the Alan Edwards Centre for Research on Pain at McGill University.

[94] See: Malmberg AB, Yaksh TL. Effect of continuous intrathecal infusion of omega-conopeptides, N-type calcium-channel blockers, on behavior and antinociception in the formalin and hot-plate tests in rats. *Pain* 1995 Jan; 60(1): 83-90. This work was done at the University of California San Diego, where Tony Yaksh, a leading pain researcher, was Distinguished Professor of Anesthesiology and Pharmacology and Co-Director of the Pain and Symptom Management Core of the UCSD Regional Cancer Center as of 2015. Annika Malmberg was a researcher in the Department of Neuroscience at the biotech firm Amgen in Cambridge, MA.

[95] That is, trials with human subjects to compile data for FDA approval. Phase I trials give ascending subclinical doses to healthy volunteers to screen for toxicity. Phase II trials are usually done with 100-300 patients to determine the effective dose; Phase III trials are large-scale randomized controlled trials with 1000 or more patients, to determine the drug's relative efficacy to comparable medications or to placebo.

[96] That is, the resting muscle tension sustained by the sympathetic nervous system.

[97] As of 2015, Michael A. Rogawski, MD, PhD, was Professor and Chair of Neurology at the University of California Davis.

[98] Felbamate was approved by the FDA in 1993, but removed from the market the following year after ten cases of aplastic anemia developed in patients taking the drug. There were also cases of acute liver failure. It was re-approved for patients with severe epilepsy, where the benefits outweigh the risks, within two months. It is marketed by MedPointe, which acquired Carter-Wallace in 2001.

[99] Lennox-Gastaut syndrome, a childhood-onset disorder involving multiple daily seizures, was described in 1960 by the American neurologist William Gordon Lennox (1884-1960) and further by the French neurologist Henri Gastaux (1915-1995).

[100] That is, it activates the release of gamma-aminobutyric acid, or GABA, the chief inhibitory neurotransmitter in the nervous system.

[101] As of 2015, Yoshiki Imamura was on the faculty of the Nihon University School of Dentistry in Japan.

[102] Gabapentin, marketed as Neurontin [by Parke-Davis], is a structural analogue of GABA. It was approved in 1993 as an anticonvulsant and is extensively used for the treatment of neuropathic pain and migraine.

[103] Marshall Devor, PhD, a leader in the international pain field, was chairman of the Department of Cell and Animal Biology at the Institute of Life Sciences of the Hebrew University of Jerusalem as of 2015.

[104] Paul Ehrlich (1854-1915) was a pioneering German scientist who established many of the early principles of chemotherapy and immunology, the work for which he won the Nobel Prize in 1908. In the early 1900s he and his Japanese colleague, Sahachiro Hata, embarked on a painstaking testing of one chemical after another to find the "magic bullet" cure for syphilis. In 1909, they succeeded with

Salvarsan, compound number 606.

[105] Streptokinase is an enzyme secreted by several types of streptococcus bacteria that interacts with and binds blood platelets.

[106] Burroughs Wellcome was founded in London in 1880 by two American pharmacists, Henry Wellcome and Silas Burroughs. The company launched several important drugs, including acyclovir for the treatment of herpes zoster. In 1995, it merged with Glaxo, Inc., as Glaxo Wellcome, which then merged with Smith Kline Beecham in 2000 to become Glaxo-Smith-Kline, or GSK. As of 2014, GSK was the sixth largest pharmaceutical firm in the world.

[107] For the follow-up on this project, see Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell C, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR and Weinstein SM. Advances in Neuropathic Pain: Diagnosis, Mechanisms, and Treatment Recommendations. *Archives of Neurology* 2003 Nov; 60(11): 1524-1534.

[108] As of 2015, Eli Eliav, DMD, MSc, PhD, was Director of the Eastman Institute for Oral Health at the University of Rochester Medical Center.

[109] See Polomano RC and Bennett GJ. Chemotherapy-evoked painful peripheral neuropathy. *Pain Medicine* 2001 Mar; 2(1): 8-14. As of 2015, Rosemary Polomano, RN, PhD, was Professor of Pain Practice at the University of Pennsylvania School of Nursing.