Mitchell Max
ORAL HISTORY INTERVIEW
Conducted by Marcia Meldrum
March 1999

Meldrum: Good morning. It's now 10:35 on March 3rd, 1999, and we're in Dr. Mitchell Max's office at the Clinical Center of the National Institutes of Health, beginning our oral history interview with him. Would you say hello so that I can make sure you're recording?

Max: Hello. How does it sound?

Meldrum: It sounds just fine. OK. So I'd like to start, then, by just talking a little bit about when you, as you were thinking about your education and career plans when you were growing up, what made you make the choices that led you into medicine and into research?

Max: Well, first I went into medicine because from the time I was eight or nine years old, I was fascinated by reading anatomy and physiology books; and also, my father strongly encouraged me. He had been a child of the Depression and worried every night for hours about how his business was going to go, and he just said, "You've got to be a doctor. You should be out and be a big specialist out in private practice because they're in control and they're not beholden to anybody."

Meldrum: Right.

Max: Of course, when I decided to go into research and not be a big specialist out in the suburbs, he was concerned, but he eventually saw the wisdom of that.

Meldrum: OK. So you did pretty well in school, I take it. Did you enjoy science?

Max: Sure.

Meldrum: And courses of that kind. Go on.

Max: I went to Yale College and I majored in chemistry and studied a lot of other things. And then I went to medical school at Harvard, and I really loved the neuroscience course. The first year was so fascinating, how the brain was put together and worked and I got a chance to be at a little seminar for students with the great Norman Geschwind,[1] who elucidated how the cerebral cortex works, and language and cognition. And I worked one summer as a tutor for the junior students in the neurosciences.

But then when I got to the clinic, my plans to become a neurologist got temporarily derailed, because I found at the time the neurologists had nothing to offer the patients. They were generally – this is at a time in the early 1970s. They had patients with hopeless diseases like severe stroke or multiple sclerosis or cerebral vascular disease, and they would sit in a little conference room and talk about the variety of lesions and pathophysiology, and there was very little that they offered for the patients. There really weren't models like that.

On the other hand, I was exposed to a lot of very charismatic internists who had many treatments, and I decided I wanted to become a general internist. I actually went on to do a whole residency in internal medicine, focusing on primary care with a marvelous mentor, a fellow named Matthew Budd, who later became chief of behavioral medicine at Harvard Community Health Plan,[2] who just said, "Send me all the long-suffering patients. We'll find a way to help them." I worked with him on doing group therapy for people with intractable illnesses and [using] hypnosis and meditation and behavior therapy and a variety of things.

Meldrum: So you were becoming interested in people with chronic disease.

Max: Yes. So I was very interested in people with chronic disease. However, I found that I didn't quite have – I don't think I ever had the heart that he had. I couldn't get anybody to stop smoking and lose weight, and just in terms of healing people because of my great love for humanity, it just didn't seem sufficient. Back then, medicine was still pulled towards the scientific model. General internal medicine, health services research, which now are big things, were just getting launched.

So the pull to be a specialist came back, and I almost did an arthritis fellowship, but the last rotation of my medicine residency was in neurology at the University of Chicago, when, paradoxically, the whole neurology department had quit in a territorial dispute, so they called back a former professor, Professor Douglas Buchanan,[3] who was a 75-year-old Scot, one of the founders of pediatric neurology. And he was such a marvelous clinician. I saw him in the clinic with patients with severe childhood retardation and their families he had known for 30 years and he showed that you could be a neurologist and put all the love and healing of the best clinicians that I had seen. So he sort of put together the patient care and the technical aspect of it. I finally had a good role model for a neurologist and I applied to a few programs and I got into the Cornell program, which was one of the leading research programs at the time.

Meldrum: Let me just go back for a second. Dr. Budd was at Harvard, is that right?

Max: At Harvard, yes. He had been on the faculty, but he had started off as an academic gastroenterologist, but then grew more interested in issues of somatization and patient suffering. He actually eventually developed some ways to treat patients in groups that many of the big corporations have used throughout the country. He's recently left. He was with Harvard Community Health Plan for about 25 years and now he's on his own.

Meldrum: OK. So you worked with him while you were still at Harvard.

Max: As a student. I worked with him as a student and I came back for a senior residency in medicine.

Meldrum: OK. So that was like the first course. When you say senior resident, does that mean you were a resident or a clinical fellow?

Max: No. I worked with him for a month as a medical student, and then I did two years of residency at the University of Chicago, and my final year of medicine residency, I worked at Harvard.

Meldrum: So then you came back to the Harvard program.

Max: To work with him, yes.

Meldrum: OK, I got it.

Max: But then I went off and did neurology instead of staying in internal medicine.

Meldrum: Right. I see. But you had two role models, then, that sort of directed you towards this –

Max: Well, I've had lots of role models, but Douglas Buchanan was this marvelous old neurologist. Actually, by the time I got there, he was still diagnosing a large proportion of the patients as having tertiary syphilis.[4]

Meldrum: Oh, my goodness. Wow!

Max: But his heart was there.

Meldrum: In the right place, yeah. I see. That really happened. You don't think about tertiary syphilis as a very common diagnosis for years. OK. So this is 1978. You came to Cornell, to Memorial Sloan-Kettering Hospital.[5]

Max: Yes. And I took part in a very rigorous neurology residency, and after a few years the question arose of what I wanted to do with myself. I was torn. One interest I had was in how the cortex functions in language and higher thought, back to my studies with Geschwind as a student, and there was a good group there led by Michael Gazzaniga.[6] Unfortunately, the first month of my residency, I had a fascinating patient to present to him. I had spent days working out his deficit, and on the day of the presentation, he had another stroke, and this was all wiped out. And somehow my interaction with that group never got off the ground.

Meldrum: Yeah.

Max: But we needed to find something to do because the alternative, in your senior residency year and later on, was to be part of Fred Plum's group[7] studying stupor and coma, which is nice to know about, but it didn't really inspire me.

Meldrum: Not very lively patients.

Max: So I was looking around for something to do, and then at the beginning of my second year, I saw a young faculty member over at Memorial Sloan-Kettering Cancer Center going on rounds, seeing patients with pain, and she was this lovely, caring woman who reminded me of the second grade teacher I've had a crush on ever since. I stopped her and I said, "What are you doing?" She said, "Well, I'm Dr. Foley,[8] and I'm the pain consultant for the whole cancer hospital, and we're doing research on how the brain and neurotransmitters and pain work." And I said, "Well, would there be any possibility of doing research with you my third year or staying on as a fellow?" and she said, "Absolutely!" At the time, she had just accepted her first fellow; she was a junior faculty member, and so I signed up. You know, that combined all of my interest to bring in the science of the brain and the care of people with chronic illness and a terrific person. So I turned out to be her third fellow.

Meldrum: Wow, that's great. So it really was sort of a personal meeting that brought you into this.

Max: Oh, sure.

Meldrum: And you had not previously thought much about pain.

Max: Well, actually, I started to think about pain a few months previously. Howard Fields had visited from the University of California at San Francisco and given a fascinating lecture about the work that Allan Basbaum[9] and [he] had been doing to work out the anatomy of the descending pain modulating systems. It sounded like something just ready to be explored, and, actually, my first 10 years at NIH, I've been working out some of the pharmacological implications of that model.

Meldrum: So you were aware of this?

Max: Yes.

Meldrum: But you had not thought of it as a career choice.

Max: Well, I didn't know anybody who was doing it, and I saw Howard presenting the basic science. And then when I met Kathy, she said this is actually something that a neurologist can do and not just take people with coma and pinch them very hard.

Max: And squirt ice-cold water in their ears.

Meldrum: OK. I see. That's great. So tell me about Sloan Kettering, then. I mean, it's a key place in the development of pain medicine and of analgesic trials as well.

Max: Well, Kathy had a remarkable mentorship style. She saw patients with you, and she saw lots of her own patients, so she showed you that care of the patient was going all the way and looking at every piece of evidence and looking freshly and not trusting any diagnosis and leaving no stone unturned. So she was a great clinical model. In terms of science, she gave people a lot of independence and ability to do things on their own. I showed up at the beginning of my fellowship, and Tony Yaksh[10] had recently discovered that small doses of spinal opioids in animals and in a few patients gave long-lasting and profound relief of pain. Kathy at the time was collaborating with several clinical pharmacology groups, one led by Chuck Inturrisi, who's still a very distinguished pharmacologist on the faculty there, and Bob Kaiko,[11] who later went on to lead a lot of the science at Purdue Frederick [on controlled-release] morphine.[12] And she gave me a sheaf of reprints and she said, "Here's something that Tony Yaksh has discovered. We want to start giving some of these drugs. I've got some beta-endorphin, which I've just given inside patients' ventricles. We have some beta-endorphin in the freezer. And this is very peculiar that this analgesic lasts so long. So why don't you work out a project where you will treat the intractable patients with spinal narcotics and work out the pharmacokinetics with myself, Chuck Inturrisi and Bob Kaiko." So she said, "Here's your project for two years." Actually, I started this as a senior resident, and that was the main thing that I worked on.

I also did a few things. There was a study of the kinetics of intravenous heroin infusion, and I later started a project with intrathecal DADL enkephalin[13] that Dwight Moulin[14] later completed to show that delta opioids may have some contribution to pain relief spinally, though this is a mixed agonist. So that was one of the main projects. So she really gave me a big chunk of space to develop it. And when I'd say, "Well, how am I going to do it?" her response would be, "You're smart. You'll figure it out." And then I'd come back every, you know, three or four weeks and show her what I'd done, and she would either make a few criticisms or guide me to something or say, "That's great." So she really fostered a sense of independence but gave me lots of support [and] helped me write a few grants to

support my fellowship.

The other remarkable thing about Kathy at the time that it took me a long time to get was, she didn't seem to be doing the things you're supposed to do in the academic rat race. I believe at the time I started my fellowship, she wasn't tenured yet. And I thought what you really needed to do was to just stay at your desk, decline a lot of work for the benefit of the world as an assistant professor, and get out as many papers as you could and snub everybody else. But what she was doing – every week, she was accepting an invitation to go to a different city in the country and the world to speak about cancer pain syndromes and the treatment of cancer pain and to help out one or another cause or colleague. And I just said to myself and to colleagues, I said, "You know, she's really not going to get ahead this way because she's not playing the game."

It was only after being with her for close to two years that I got it, that she saw this opening. You know, she has a strategic vision that very few people in the field have had, and she just saw something new and she saw exactly what's necessary to create a new field, to create a career track. And, you know, when I started, she just hadn't done it yet, she was just getting started, and in retrospect, it's easy to see. Then when I finally got it, I mean, ever since then, I've tried to talk to her every couple of months and get her ideas about what was next on the horizon. And she's continued to be a marvelously supportive mentor.

Meldrum: That's really great. So tell me about the pharmacokinetics part and explain for the benefit of the people who might be listening to this tape who don't know exactly why this is important, what we're talking about here, why it's important to figure out where [and] how the drug metabolizes within the body.

Max: The problem with all the drugs we have for pain is that they have both pain-relieving effects and side effects, and they're really pretty close. If you give most people enough of a – narcotics, opioids are still the best pain relievers we have. But if you give most people enough to relieve their pain, an awful lot of them will be sleepy or nauseated or constipated and so on. So the way to get pain relief without side effects with any drug which has a so-called narrow therapeutic ratio is to try to exactly adjust how much there is and give just the exact amount you need to relieve pain or to treat the disease and no more. And you need to get that drug right near the site where it's having its good effects and hopefully have small amounts at other sites. So in order to understand how to get the right level of drug, how much you need at the good site and how much you need at the bad sites to reduce side effects, you need to do studies and find out whether it's the drug you give or the [by]product that's made in the liver or the kidney that causes pain relief or side effects, and how long it stays in the brain or in the blood, and where it goes.

So this science of pharmacokinetics, of the time course of drugs, was extensively investigated. It was developed largely by Bernard Brodie[15] at the NIH in the

'40s and '50s, and it was applied to analgesics rather intensively in the '60s and early '70s. And he found that there's a certain level of narcotic you need to reach pain relief and a certain amount to reach side effects, and the traditional way of giving the drug was to give injections into the muscle, which would, for about an hour, give very high levels in the brain at various sites and give lots of side effects – it made people sleepy – then two hours later, they'd be in pain again. So it would be better if you just gave just the right amount to give pain relief, but not the excess to produce side effects.

So a lot of these kinetic studies tried to find out what level you needed and how to get that and resulted in inventions such as patient-controlled analgesia [PCA], which have revolutionized postoperative care. [This research] produced sustained-release morphine and other preparations of opioids, which has now made it possible for patients with cancer to sleep through the night and work without being interrupted. I was working on the kinetics of spinal opioids because Tony Yaksh and colleagues initially observed that pain relief [lasted] up to 72 hours after one shot of intrathecal lumbar morphine. It appeared shorter with other drugs. So we did the studies, and sure enough, we found that morphine is not lipid soluble, can't pass through membranes very easily, so when you put it in the spinal fluid, it sits there for three days before levels drop too low; while if you take lipid-soluble drugs like methadone, we found that this rapidly gets up into the bloodstream, the little capillaries in the spinal cord, and in the meninges, so pain relief is very short-lived. And others worked on this as well, and so these understandings of the time course of drug action have been used to shape the way spinal opioids are given as well as lots of other drugs.

Meldrum: OK. So, clearly, Kathy Foley was a major influence on you. Now, she had been trained by Ray Houde.[16]

Max: She learned some things from Ray, and she was also a student of Fred Plum and particularly of Jerome Posner,[17] who was the chief at Memorial Sloan-Kettering for many years in neurology, and he developed the field of neuro-oncology. She was really a student of his in working out the details of many clinical syndromes, and a lot of her early work was to describe cancer pain syndromes and who may occur, who's at risk, how you treat them. So that was a big influence on her.

But I think she was also very influenced by the pharmacologists that she worked with, Gavril Pasternak,[18] who came after her to Memorial Sloan-Kettering, as well as Chuck Inturrisi and Bob Kaiko and others.

Meldrum: OK. I was just wondering because Ray and Ada Rogers[19] are kind of important in pain history, if you have any impressions about them specifically.

Max: Oh, well, Ada was a remarkable person. I met her on my rounds; when I was seeing the neurology consults, she was seeing the pain consults. And she was just a force, this warm, middle-aged beautiful Italian woman who had come to make people better and would tell the doctors what to do. She had clearly been around the block, and she let the residents and fellows know it in a very nice and charming way. And she taught me a huge amount about doing studies. She really ran that operation, had at the time about four or five nurses working for her. And I also learned a lot from Ray Houde and Stan Wallenstein,[20] who was his partner, and everything was really the three of them all along. I would just go to their offices and they would give me all their reprints and they would sit for an hour anytime I wanted to and tell me how different methods were developed. I planned most of my studies with Kathy, but an early trip would be to talk to Ray and Stan and Ada and get their thoughts on it.

Meldrum: Now, cancer patients – Let's see. Where do you want to go from here? Do you want to tell me some more about Sloan-Kettering? I guess the next question I would ask is, you made the choice to come here. How did that develop? And also, you seemed to be moving, then, from working with long-term cancer patients to working with neuropathic pain, which is a different kind of pain presenting different kinds of problems, although – Well, you tell me.

Max: Your question is how I ended up at NIH.

Meldrum: That's part of the question.

Max: The issue was, after I did two years of fellowship with Kathy, I needed a job, and she didn't have a job for me. She said she'd love to, she just didn't have a job yet. It was a few years later, when Richard Payne[21] finished his fellowship, that was the first time she was allowed to have a second pain doctor, and that slot later on, Russ Portenoy[22] came back to fill that, and Catherine Elliott[23] made a third. But she didn't have a job and I needed a job, and I started looking around. I looked at one private-practice job with Arthur Taub,[24] who was one of the early pioneers of pain research and treatments in New Haven, Connecticut.

But then this lead came when I was presenting my findings about spinal opioids at the [IASP] World Congress on Pain in 1981 at Edinburgh.[25] I was at my poster, and Gavril Pasternak, who was a faculty member at Memorial Sloan-Kettering, he had come there after playing a part in the discovery of the opioid receptor with Sol Snyder,[26] and he's continued that, the work on opioid receptors, ever since. He came up to me and he said, "Mitchell, there's somebody who wants to meet you." Previously, Gavril had fixed me up with his beautiful sister, who I was mad about but she wouldn't have me. So I said, "Gavril, do you have another sister for me?" And he said, "No.

That was my only sister." He said, "But the person I want you to meet is Ron Dubner,[27] and he has an absolutely fantastic operation down at Bethesda. They really do things right. They found ways to measure pain so you can sort out the good, the patients who are good pain assessors from the bad pain assessors, and they have the basic science and the clinical science and it would be a great place to go, and they need a clinician just like you." It turned out they had tried to recruit him and he was very happy where he was.

So I went and met Ron Dubner, and he was a remarkably lively individual. At the meeting, he said, "We've got to have you come down," and I made a few trips down, and I gave a talk and interviewed with the whole group. They were about to open up a whole floor of the new NIH Outpatient Clinic, and they had just gotten a great review from their Board of Scientific Counselors. At the time, the clinical operation was just Ray Dionne[28] and Rick Gracely,[29] [who were] doing these devilishly clever studies of the placebo response and of analgesia and pain measurements, and a room or two in the dental clinic. And they had a big basic science program. At the site visit, I said, "This is a great program, but what a shame that you're confining this clinical expertise to just dental pain. Why not hire a physician and reach out to the rest of the institutes and develop a more general medical program?" and it just seemed like a fantastic job. After a little bit of haggling with Ron, we came to an agreement, and I moved here. I came here January 1983, a few months before the clinic opened.

Meldrum: And so you have sort of carte blanche developed this program as you saw fit. There was never any suggestion, for instance, that you should spend your time thinking about dentistry.

Max: Oh no, no suggestion that I work on dental pain at all because there were plenty of dentists around. There were Ron Dubner and Ray Dionne and Gary Duncan[30] and a variety of other dentists. No. They wanted me to look at general, other kinds of medical pain. I think Ron had a much different management style from Kathy Foley. I never heard Ron say, "You're smart, you'll figure out how to do it." He did want his protégés, you know, all of his postdocs at the time, to come up with the ideas, and one would say, "What do you think we should study?" He said, "That's your job to decide." Once I came up with an idea and a design, he would then come back at me with all his ideas. And the way he taught was you had to quickly learn everything that's been written about methodology to try to defend your own positions against his onslaught. It still probably wouldn't do you as much good as he'd like, but he really took a tremendous interest in the details of everybody's clinical program. It's amazing how much energy he put into it and how much he knew about everybody's program, whether it was molecular biology or some clinical problem that he had never encountered before or pain psychology or

measurement. So he was a real hands-on, detail-oriented mentor.

Meldrum: Manager, yeah. That's very interesting. So how did you frame your problems when you first started here?

Max: Well, I was interested in a few things. One interest was to continue my work in cancer pain. And I worked out a few protocols. Actually, Ray Dionne had had a protocol. I came when actually there were a few protocols that were already written or had gotten – They had to write protocols to show they deserved a floor of the clinic.

Meldrum: Yeah, right.

Max: For instance, Ray had developed a protocol to treat cancer pain, and I tried to get that going, but it turned out that the NIH Clinical Center had a much smaller population, as big as NCI was then, than Memorial Sloan-Kettering or M.D. Anderson[31] with a big private practice. Most people come from far away and get blasted with chemotherapy and go back, and we actually have tried three separate times in the past 16 years to get a clinical trial program going with the Cancer Institute, but you need 80 patients a year with the same [diagnosis], and they just don't have that number. It's really a Phase 1[32] place. They want to take 20 patients with one thing, try and do therapy and work out the biology. You know, you really need a Phase 3 place with hundreds and hundreds of patients in each protocol, like a Memorial Sloan-Kettering program, to do that. So that was a disappointment, and I really have done very little cancer-pain research since I've been here.

But another issue was neuropathic pain, and Marvin Hoffert,[33] who had been a basic-science postdoc here, but was also a neurologist, had written a protocol to study diabetic neuropathy with amitriptyline.[34] And that was so cumbersome, as it always is when a newcomer in the field writes his first protocol There was absolutely no enrollment. I looked at that, and in reviewing it, I knew from my past work that there was absolutely nothing known about the pharmacology of neuropathic pain in terms of controlled clinical trials except the one the year before. In 1982, Peter Watson[35] [had] published the first really nicely done controlled trial in neuropathic pain showing that amitriptyline helped post-herpetic neuralgia[36] in non-depressed patients. I've always loved Peter's work and I took a lot of the features of his work as a model, and Rick Gracely and the others in the group worked with me to develop some other features, such as using active placebos so people wouldn't obviously guess that they knew they had a drug rather than an inert placebo.

Meldrum: Right. So you tried to pick a substance that mimicked the effects, some of the

effects of the drug, or the active substances.

Max: Yes. And I'm still concerned to this day that we might start using a drug that has no effects on pain apart from some cognitive biasing of people just because it has some harmful side effects that make it just an inert placebo.

Meldrum: Sure.

Max: We're still really at the level of getting about 20 percent pain relief, so there haven't been many of the drugs we've looked at, besides amitriptyline and the other tricyclics, for which we have that level of proof. But anyway, Rick and I worked out a measurement scale based on the descriptors he had used and a variety of other methods. But we looked at neuropathic pain, and there really were almost no controlled clinical trials, and we just looked at the rat data. I thought of all the different classes of drugs that had been shown to relieve pain in animals, and we came up with opioids and tricyclics and benzodiazepines, because they worked through GABA-ergic systems,[37] and clonidine, which has an adrenergic effect, and ibuprofen. We just took this list and we said, "Let's throw these all at people with diabetic neuropathy and post-herpetic neuralgia," because those are very easily obtained, diagnosed, common conditions where, unlike chronic back pain, much less of the variance is due to economic and psychological factors. And we had a psychiatrist. Bruce Smoller[38] was involved from the very beginning to characterize patients and verity that we weren't just having effects of drugs on mood.

Meldrum: Yes, exactly. Not just cheering them up, in other words.

Max: So I generated a series of three or four different neuropathic pain clinical trials, and the cancer pain trials, the systemic drug trials, and the intrathecal drug trials never got off the ground. We had a whole bunch of other ideas, but generally, you know, usually most clinical-trial ideas don't work and they crash [when] the drug is proved toxic in early developments. But the neuropathic pain trials came out very sweetly, and that was the main track that we continued, particularly after Gary Bennett[39] got very interested in that.

Gary started coming over to the clinic and looking at some of our patients, and he was –He'd started off as a psychologist, and he was always very interested in patients and started to examine in detail patients with post-herpetic neuralgia and got a dissecting microscope and looked at their skin, and we marked patients up and started taking skin biopsies. Things really took off after about three or four years, when Gary serendipitously discovered a rat model of neuropathic pain.[40] Then he was generating hypotheses that we could directly test in patients.

Meldrum: Sure, that's great.

Max: And that collaboration interaction was, you know, the great treat of my years thus far at NIH.

Meldrum: Yeah. It's sort of an exciting thing, everything coming together and everybody being able to contribute. That's really great.
OK, so tell me a little bit – the patients you recruited through the Diabetes Institute or –

Max: No, very few, very few. We started out, when I got here, I just called up – For diabetes, I called up every endocrinologist in the area. For shingles, I called up every neurologist in the area, spoke at the derm societies, put ads in the paper. Eventually, there's a national Patient Diabetes Society. At NIH, we can fly people in from all around the country, so a large proportion of our patients were from far away. Enrolling patients has always been the difficult thing for any study of chronic pain, certainly, anywhere.

Meldrum: Right. And the patients – You have a variety of designs. I mean, you used crossover designs and you used parallel studies. Do you want to talk –

Max: No. Mostly we used crossover designs. Because pain is something that usually you don't cure by giving any medication. When you stop the pain medication in chronic pain, the pain comes back. There's so much mechanistic variability in patients that a crossover study aids tremendously in being able to take each patient or a subgroup of patients and try to sort out, does the drug work in people with burning pain or does it work in brief pain or does it work in patients of a certain type, with a certain physical exam? And in a single center, if the limit is how many patients I or my fellow can see in a couple of years before getting totally burnt out, and that's really like about 60 or 80 patients for a study, that's equivalent to four or five in a crossover. A crossover gives you the power of four or five times as many patients as a parallel design. So while we've sometimes done some parallel analyses of, say, first treatment period, if we got a weird second-period effect, we've done all of the studies in chronic pain as crossovers. That was something that Ray Houde really clung to because he was one of the first people to recognize the importance of heterogeneity. He stuck to the crossover design and insisted that pain could be different things in many people at a time when his colleague and rival, Beecher, was saying pain is pain no matter what it's from.

Meldrum: Right. One should be able to have some sort of standard baseline.

Max: And this lumper or splitter controversy[41] is still a key unanswered scientific question.

Meldrum: Sure. That's good. And in terms of measuring the pain, which I think is a

very interesting question, you were using Gracely's scale, the 13-word descriptor scale on intensity. Right?

Max: We started off using his scale for intensity and pain unpleasantness, and we used both of them for the first generation of studies. And if I had two main outcome scales, it meant that every analysis of a co-variate I did, I had to do for both scales, and it took me an extra month of analysis. All the results came out exactly the same with the unpleasantness and the pain-intensity scale, and from that time on I never looked at the unpleasantness scale again. And we used a bunch of other scales. You know, I did some informal comparisons that [showed that] Gracely's intensity scale, actually both of [his] scales looked much more sensitive in the first generation of studies that we did then, the McGill[42] once or category descriptor scales taken once. But we never did a fair comparison because we were taking the average of multiple ratings. And I think a lot of the increase in sensitivity we got was from doing multiple points. So it's apples to oranges, and I think it's still an open question in chronic pain, which is the best scale.

Meldrum: Which is the preferable one to use, yeah. OK. And the question I guess I'm getting down to here is, in terms of patient compliance and cooperation with all this, I mean, for a lot of these drugs, the patients essentially took them home and the nurses called them up to collect their responses].

Max: Right. Oh, we always had fantastic nurses. We gave the nurses a lot of autonomy and training and participation with the research. You know, I've worked closely with nurses, including a few of them, Mary Culnane and Susan Schafer and Elaine Robinovitz and Susan Booher and Susan Parada and Joanne Muir; and they've called the patients every day and nursed them through, and we would have dropout rates over a three- or four-month study of 20 percent or so. We've had 80 percent completion rates, which is pretty good.

Meldrum: Yeah, yeah, it is really good. You've made the distinction several times in articles between explanatory studies and pragmatic studies.

Max: Yes.

Meldrum: Yeah. It seems to me that you were looking at these as explanatory studies, but you tell me.

Max: Well, it's really a hybrid. This is a concept that was developed by two French researchers named Schwartz and Lellouche in the late '60s,[43] and they said clinical trials may be said to be aimed at one of two ideal goals at the extremes. One is to establish some biological principle in humans that you could then apply to lots of other things, like is morphine an analgesic in

human beings. If you study it in dental extraction pain, you don't want to go around and, say, just sell morphine to dentists. You want to say, therefore, give morphine to everybody who has pain. So the other type of pragmatic study is just trying to understand what to do for that patient group. So you may want to study cancer chemotherapy just in patients with a certain kind of tumor to tell doctors what to do with that, and there'll be many design choices that will be different depending upon which aim you have.
I think our aims fell in the middle. On one hand, we hoped that diabetic neuropathy and post-herpetic neuralgia would be models.

Max: Explanatory. OK. Anyway, diabetic neuropathy and post-herpetic neuralgia might make up, say, 10 percent of patients with neuropathic pain. So in one sense we were trying to crystallize some principles that would apply to other neuropathic pain. On the other hand, we weren't targeting one specific mechanism. It wasn't the extreme of an explanatory study, so it was a hybrid. We wanted to tell doctors how to treat patients with these disorders but also have some principles about neuropathic pain, too.

Meldrum: OK, because there's a lot of work that you did trying to determine the specific neurotransmitter process that was involved. I think at one point you were talking primarily about norepinephrine reuptake blockers.

Max: Right: That's why we – So an explanatory study to try to make the point about which neurotransmitter was right for tricyclic action. That's assuming the Basbaum-Fields model[44] is true and it's the monoamine inhibitory action in the spinal cord that's important. And, as you know, amitriptyline and other tricyclics block reuptake of both of those transmitters so they stay out in the synapse and inhibit longer, though others now think that – John Hunter[45] is propounding an effect of tricyclics on sodium channels.

So maybe they don't work through monoamines at all. But anyway, there's still a consistent story in the clinic, so we try to look at the mixed drugs and the most selective agents we had at the time, desipramine for norepinephrine and fluoxetine for serotonin, and to see if we could preserve all of the pain-relieving action with those selective blockers, and we couldn't. We could preserve most of the effect with the norepinephrine reuptake blocker. Fluoxetine did nothing.

The Danes, Søren Sindrup and Lars Gram and colleagues,[46] and Peter Watson, have had rather similar results. The Danes have been a little less discouraged with serotonin than Watson and our group. They find a little effect. They think that desipramine and, for instance, paroxetine, have similar effects, but we all agree that the mixed reuptake blockers, these dirty drugs, are still the champions.

Meldrum: Yeah. But we don't know exactly why that is, or we can't –

Max: Well, it might be monoamines plus many of the other effects they have. It may

be the sodium channel effect.

Meldrum: Mm-hmm, OK. I've noticed several times the observation that some things seem to work for some patients and some things seem to work for more patients, but nothing really seems to work for all patients all the time.

Max: Oh, that's true, that's true. Even opiate analgesics are – You know, after 16 years of working towards alternatives to opiate analgesics, the data is now coming in from Peter Watson on post-herpetic neuralgia. And actually, we're working with Srinivasa Raja[47] and colleagues at Hopkins on a post-herpetic neuralgia study, and so far, the opioids are clobbering the tricyclic antidepressants. And they're probably better than gabapentin.[48] They're probably still the champion drugs, and even they don't work in all patients with pain.

Meldrum: Like in, there are patients who take opioids and they basically show no pain relief?

Max: Oh, there are plenty of patients. Dwight Moulin published a series of about 30 patients with mostly musculoskeletal-type pain and didn't find very much.

Meldrum: Just sit there. But we really don't know why this is. Are we attributing this to mechanism, differences in pain mechanisms, or are we totally in the dark?

Max: Well, you can say there must be a difference in pain mechanism. I mean, it may be a difference in metabolism of opioids. You know, for instance, there's a little bit of data that you need to be able to metabolize codeine to morphine with the 2D6 P450 liver isoenzyme.[49] And you need to make morphine analgesia out of codeine, and there's less evidence for any of the other narcotics, but maybe people metabolize narcotics differently. Maybe they have different mixes of receptors. Maybe pain from certain tissues is less opioid-responsive than other tissues. Maybe some patients have more side effects from the drugs or are less tolerant. It's not clear. Maybe, you know, there may be some processes that overcome opioid analgesia, such as the stimulation of protein kinase C that Dave Mayer[50] and Jianren Mao[51] and others have talked about.

Meldrum: OK. I guess one of the reasons I'm asking this is because there has been, you know, there's a continual question about the importance of central processing and then when Gary developed the chronic constriction model and targeted the phenomenon of spontaneous discharge – now, let me see if I've got this right – the basic idea here is that the spontaneous discharge, this continuous peripheral input, eventually leads to abnormal central processing. Am I right about this?

Max: Yes. Just about every kind of pain condition that is not just a central nervous system injury involves a peripheral component. It's a sensitization or at least an ectopic discharge of the peripheral afferent and includes some component of central sensitization.

Meldrum: So isn't there a possibility, then, that there can be a central – I mean, patients have, obviously, different cognitive and experiential histories, cognitive approaches to pain. Different patients have different approaches to their own pain modulation, and this can affect their reactions to drugs.

Max: Oh, absolutely true. I mean, I've been talking mainly about the first neuron, the peripheral afferent, and the second neuron in the pain pathway in the spinal cord. You're referring to the trillions of neurons that we have upstairs that obviously mediate the vast differences in emotional, behavioral [and] cognitive responses to life. A lot of those [52]experiences will then change modulation, change actually the rate of firing of even the second neuron in the chain, as Gary Duncan and Cathy Bushnell and Ron Dubner and others showed a long time ago here.

Meldrum: OK. So, with the development of Gary's model, then, he talks about the importance of the NMDA receptors[53] in mediating this process, setting up the central sensitization. And clearly, when he talks about discovering neuropathic pain and post-herpetic neuralgia, it was very exciting. So you want to talk a little bit more about that and about if there are new directions that you thought you were going, how you were able to feed into his model or –

Max: Oh, sure. Well, actually, there were models of neuropathic pain before Gary. There had been the autotomy model that Pat Wall[54] and many others had worked on. This, people argued about whether the animals really had pain. Bill Sweet[55] argued that if the only sign is scratching and biting the paw, kids with insensitivity to pain will do the same thing, then maybe they don't have pain. And when Gary found that the rats that he had, whose sciatic nerves he had constricted seemed to jump and flinch to cold and to pressure and to touch, he immediately jumped on it.

So, anyway, there had already been the autotomy model in use, but Gary recognized that his rats were behaving, were much more convincing to him that they had pain than the autotomy rats had been. Very shortly thereafter, other people developed models such as [Ze'ev] Seltzer[56] and Jean-Marie Besson[57] and Dennis Coombs and Joyce DeLeo[58]. But Gary really jumped on this, and, remember, he was so excited about it, he made us all come and look at these rats. Then he started not only working out the mechanisms, but doing drug studies, and it made our clinical program tremendously exciting.
Until then, it had been this really isolated backwater where I would do a study and it would take – I'd wait two or three years and get the answer and then present it to the whole group, and they'd say, "Uh-huh. What are you going to do next?" and then I'd do the next study and it would be another two years. M.A. Ruda[59] might make some comment about the anatomy of the monoamine pathways. But now suddenly a large proportion of the people in the basic lab were working on animal models of neuropathic pain, and every week there was

some phenomena, either some observation we made in the clinic with a drug or with an exam, or at that time Rick Gracely and Sue Lynch[60] started to examine patients with reflex sympathetic dystrophy with Gary, and finding some very fascinating, [they did] some quantitative sensory testing.

So every week there was interchange between the basic and clinical scientists, and when Gary highlighted the importance of central sensitization, we developed another tool. We went to the Adelaide World Congress on pain [in 1990] and Gary and I shared a room there and we went to Eric Torebjork's[61] lecture, and he showed that he was able to inject capsaicin[62] into human skin and show microneurographically that he had produced central sensitization in humans. And I said to Gary, "Why don't we use that to produce central sensitization so we could use it as a model for drugs?" and we all jumped on it. Rick Gracely and colleagues looked at that for looking at pain mechanisms, and we focused on it as a model for drugs. So it became a very exciting time, you know, a really hot four or five years in the lab.

Meldrum: That sounds really exciting. Now, capsaicin, as I understand it – Torebjork was using it to test drugs? Is that what he was doing?

Max: He was using it for mechanisms. This had been something that Don Simone [in Oregon][63] had worked on extensively along with Bob LaMotte [at Yale][64] and Jose Ochoa [in Oregon][65] or with Bill Willis's group[66] and with Linda Sorkin[67] [at Galveston], and so Don had worked out the dose response in humans and some of the mechanisms, and there'd be a long history. I've worked with capsaicin before because it's such a fascinating excitant. But then Torebjork worked on the neural mechanisms and he injected it into a patient's foot right at the receptive area, the receptive field of neurons that he had already had an electrode stimulating.

Meldrum: So it could be very targeted.

Max: It could be very targeted, and he showed that injecting capsaicin changed the receptive properties. It changed patients' pain report so that a very faint stimulus that was only stimulating A-beta fibers and was bypassing the peripheral receptor. He was sticking it in the nerve, in the peroneal nerve. Now just stimulating A-beta fibers in the leg gave rise to burning pain, where before the capsaicin it had only given rise to a feeling of a little bit of a tingle. So, therefore, this had to be processing by the central nervous system, so therefore the central nervous system had for a transient period become sensitized.

Meldrum: Right, right.

Max: And it looked just like the results that Gary was getting in his rats.

Meldrum: The constriction model. That's great. That's exciting. OK. So tell me a little bit, then, about the trial that you developed out of this.

Max: We'd done a series of studies with capsaicin as a model for the study of glutamate- blocking drugs, and other labs – I think they had the same idea at similar times, and we might have been the first or one of the first to publish drug studies. But we did a series of studies where we gave ketamine[68] to patients with reflex sympathetic dystrophy,[69] or now it's called complex regional pain syndrome, and simultaneously – In both studies we gave ketamine or an opioid or a placebo under double-blind conditions to patients in one study and to normal volunteers who got capsaicin in another study. Karen Park,[70] who's now at George Washington, found that ketamine reduced pain by about half in the model, and Michael Byas-Smith[71] and I found that in patients it reduced pain by about half, just at the time people were becoming a little catatonic. So it wasn't a great drug.
Then Navil Sethna[72] used that model to study a combination of ketamine and opioids and studied a wide variety of doses, because normal volunteers will put up with this. If you have a pain model, an experimental model with patients, you want to wait until you have your final best choice. Navil found that the opioid-NMDA blocker interaction seemed to be just additive. And then Christine Sang,[73] who's now at Massachusetts General, used the capsaicin model to show an effect of an AMPA/kainite[74] blocker. We speculate now it's a Lilly drug that it's through the glu-R5 receptor, but we're very excited about that, and we've got to replicate it. We're going to find out today if the same drug works in postoperative pain.

Meldrum: Wow!

Max: And then Rick Gracely and Sang and others have worked with Gary and myself and others to look at various mechanistic aspects of the capsaicin model. You know, Bob Coghill and Mike Iadarola[75] studied the effect of capsaicin on PET scanning. So we all gave each other a lot of injections of chili pepper.

Meldrum: I know. They've been offering this to me occasionally. I may have to do this before I leave.

Max: Yeah. Now I've gotten a little sick of injecting chili pepper into people, and the past couple of years I'm much more interested in studying patients with real disease, because I worry that this model may just be an artificial model and I want a bigger dose of reality.

Meldrum: Yeah. It's an interesting question. Capsaicin, I know, hurts, but it's only a

temporary thing. It's not something that people think it's going to go on and on, and they suffer a lot less anxiety [than with clinical pain]. So, on balance on all these very, very interesting studies, do we – Yet you said earlier that we really, opioids are still our drug of choice.

Max: Well, in our program here, we've come across three or four classes of drugs that we showed for the first time or sort of tied for the first that they really work in people with chronic pain like the norepinephrine-specific tricyclics. We got some effect with systemic clonidine,[76] similar to Jim Eisenach's results [at Wake Forest] with epidural clonidine[77]. We found in now a third trial in diabetic neuropathy and now in some patients, I think, with chronic facial neuralgia, that high- dose dextromethorphan,[78] an NMDA blocker, will relieve pain. But we're getting reduction in pain of 20 or 30 percent, and that's the same result that people found with gabapentin. In the post-herpetic studies with opioids, Watson is getting about 40 percent relief. So we're only getting modest levels of pain reduction with doses of drugs that have lots of side effects. This is similar with mexiletine,[79] a sodium channel blocker. It's really just a 20-25 percent reduction in pain compared to the amount of pain people have at the end of six weeks of a placebo. So we need to do better. Maybe it'll be through combinations of drugs, maybe it'll be through finding the magic bullet. You know, we hope that the kainate blockers may be or a glu-R5 blocker will be the best group of drugs yet, but I'm very skeptical. I mean, until I've seen a couple of trials and proof that this isn't just side effects, it always seems too good to be true.

Meldrum: OK. So let's go back, then. Let's put trials aside for a while and just go back. Very, very early, very soon after you came here, you became involved in the WHO [World Health Organization] cancer pain effort.

Max: Yes.

Meldrum: And so, could you tell me about how that came about? I know Kathy was involved from a very early stage.

Max: Well, this is just my understanding of how things happened. I gather just about everything in current pain treatment and research started with John Bonica,[80] and Bonica, for 50 years, was meeting with everybody, cajoling and twisting their arms, and enrolling people, converting them to be interested in pain, and holding meetings. And one of his converts was a marvelous anesthesiologist from Milan named Vittorio Ventafridda,[81] [who] was particularly interested in cancer pain. He was the pain doctor at the National Cancer Institute in Milan. And he had a wealthy patron, I think, named Floriani, whose Foundation[82] set up a series of meetings about cancer pain to which they invited people from all

around the world. They discovered that, just like Italy, in India, in China, in South America, in most countries in Europe, in fact, it was really hard to get opioids for patients because there existed strong drug-control bureaucracies in just about every country. Narcotics control was worldwide, and pain-relief advocacy was almost nonexistent. None of the governments had anything.

So towards the end of my fellowship, Kathy came back from a meeting in Italy,[83] and by that time I had understood what she was up to in going to all these meetings, you know, just trying to make something happen, and she was dissatisfied that in the end, there would be a reward in this world or the world to come, and she said, "This is amazing. I just came back from a meeting of a handful of cancer experts, and they said most cancer patients in the world can't get morphine." And I said to her, "Kathy, that sounds awfully peculiar. Don't you think that the companies that are selling morphine would want to give a lot of money to fix that? So it seems, so if it's just a matter of getting laws changed to still crack down on drug abusers but to make drugs more available, what's going on there? You know, what's holding it up and what's the plan?" She said it really wasn't clear from the meeting what the plan is or why things won't happen.

But she said, "You know, you're really right. I think the drug companies will do something." She said, "But I'm not immediately going to do anything next month, but if you want to talk to somebody, there's this great guy Jan Stjernswärd" [84] – It was a Swede who was the head of the World Health Organization cancer unit [and was] ready to be a leader in that. So we talked a few more times. I was just in the process of moving down to NIH, and the next time I saw her I got Stjernswärd's address.

It was funny. I was just taking a course at that time from a Chilean philosopher who had been a student at Berkeley of John Searle and John Austin,[85] very interested in the Language and Speech Acts. They said that when nothing's happening, if you make a request or if you promise to do something, if the language isn't talking, there are these acts where you can actually change reality. So I said, you know, I was taking this course and it sounded pretty interesting in making things happen, and I had never really done anything big in the world. I had just been in an ivory tower, been a resident. I thought, “Let me try this experiment,” and I wrote a letter to Stjernswärd. I said, “I don’t understand what’s going on with why nothing’s happening to try to change these laws." I said, “If you’ll just meet with me and tell me what’s going on, what are the barriers, what are the next steps, I promise to within one year raise $100,000 for this program.” And I thought that was a reasonable bet, that if there were any kind of plan to go ahead, I could probably go to some rich people [or to] a drug company and get the money.
So I wrote this letter. Kathy sad it sounded like a good idea. A week later, I got a call from Ken Stanley, who was a Harvard-trained epidemiologist and statistician, who was Stjernswärd’s right-hand man, and he said, “I must come

and visit you." And a week later, he was in my office, and I just told him that I hadn't done any international medicine stuff, but I had a lot of freedom here at NIH and it just seemed obvious that I could try to get something together. So he said, "Well, this is fantastic. You've got to come to Geneva." So he sent me a ticket to be a [WHO] consultant and flew me out, and I spent, oh, a week with them, talking, in Geneva. They said, "Here's what's happening. We have this World Congress on Pain coming up and we have a meeting of an expert panel that Kathy is going to be chair of, and how we go about doing this…" We just talked and I found out who was involved, and I visited with Vittorio Ventafridda. I just said, "Well, I think I'll help you write your speech to address the key concerns of the international pain people at the second meeting I've gone to. They love to get involved. Why don't we set up a booth so we can get the people at the meeting. They can come over and be involved, and I'll sit at it, and find somebody else to sit at it. Now I know what you're doing, we can try to raise some money."

So I went home and we helped, and Jan had had his speech. In some of these courses, I met a pharmacist named Noreen Tijo, who was very interested in world hunger, but she was also interested in big pharmacy questions. She was an administrator at the Tulane pharmacy. And she volunteered to come out to the meeting on her own steam. So we went to the Seattle World Congress on Pain [in 1984] and set up a little booth. I made up a big sign, WHO Meeting, and just printed up a bunch of forms, saying, "I will promise to do this, that, or the other thing, and commit myself to do something like get everybody opioids by the year 2000," something like that. And they put their name, address, fax number – we didn't have e-mail then. I spent a lot of time at that booth, and Jan gave a very nice speech and Kathy gave a speech.

A lot of the big shots in IASP started coming over to the booth. For instance, Charlie Cleeland[86] came over. He said, "I'm a professor of neurology and I'm going on a sabbatical next year and I want to do something about this." I said, "Well, great, sounds terrific. Maybe it's wide open," because Ron Dubner said, you know, "I want you to do research. You've spent enough time doing world health. Your job is to go to all the talks and do research study. It's clear [this opioid project] is not going to be my job. Why don't you go?" I introduced him to Vittorio Ventafridda, and Charlie then became the research leader of the program from that time on. And Rick Heidrich[87] came over and said, "What could I do?" He was starting a little newsletter for pain called *PRN*, which he later teamed with Russ Portenoy to make *The Journal of Pain and Symptom Management.* I said, "Well, we've got all these responses of what people are doing, so I'll sort of write up what everybody says they're going to do, and you can publish this." Then I guess I went to this meeting, and helped Kathy, and I guess it was probably Twycross[88] – Robert Twycross was the editor – put it together.

I guess the other main thing I did was – I'd promised the money, so I asked around, "Where can we get some money?" My wife was a real estate developer, and one of her friends gave a few thousand dollars for the pediatric pain piece,

and Neil McDonald[89] raised about $6,000 or $10,000. Finally I got Cathy and Jan – Cathy eventually contacted the Sacklers[90] and got the Sacklers together with Jan Stjernswärd, and Jan said, "'What I need is somebody to do this." Finally after – it took about three years to raise this $100,000, but it was just by getting Jan together with the Sacklers, and the Sacklers gave $100,000. We hired Noreen Tijo, who since then had come to about three of these meetings on her own expense, and it was finally – I guess it was the 1987 World Congress [in Hamburg, Germany] where I was the WHO liaison, and by that time Noreen was on the staff and Charlie was taking the lead, and it was clear – I had just gotten married and I didn't want to move to Geneva and do this, and people thought Noreen would do a good job.

Charlie had said, "Do you want to sort of do the research, take the research lead?" and I said, "No. I need to learn how to become a pain scientist. It's for a full professor to do, and I'm a beginning guy." So he went ahead and took that on. So after about '87, I had a very peripheral role in it, but I guess I sort of helped Cathy give that a shove and maybe moved it ahead a year or two quicker than it might have otherwise.

Meldrum: So, most of the people that were involved in this, Takeda from Japan[91] and the guys from India, they were essentially volunteers.

Max: They were volunteers, and somehow they had been, people like Takeda – I think a lot of those were at the first 1982 Floriani Foundation meeting that Vittorio had organized. I don't know where [their interest] came from. That was John Bonica's work. I just got involved in '83 and '84.

Meldrum: OK. And the WHO analgesic ladder?[92] Do you have some perspective? I mean, it seems a fairly simple concept. It doesn't seem to have – It was based on current knowledge at the time.

Max: Right.

Meldrum: It talked about, yes, if new methods are developed, we'll look at those later, but this is the basic stuff that you have to do.

Max: Yeah. I think it was largely put together for political, not only for teaching purposes, but for political purposes, because, as you know, grade 1 [the first rung of the ladder] was non-opioids; grade 2 were the weak opioids in combination; and grade 3 were strong opioids such as morphine, which were highly controlled, and they were the ones that weren't available in most countries.

Meldrum: Right.

Max: And by formulating it like that, you could draw a map, as Charlie Cleeland later

did and David Joranson[93] has done, and you could say your country, your ministry of health, does not have step-3 opioids, and Charlie made a measure.

Meldrum: So you march up the ladder.

Max: So you march up the ladder, and then Charlie went into the Chinese Ministry of Health and they said, "We decree this. We have step 3." I think, you know, there have been some critics of this that say it isn't validated enough, or now the division between step 2 and step 3 is blurring, but it was a very commonsense, a very simple formulation that has worked.

Meldrum: And I don't know if you want to comment on this one or not, but, I mean, there was this major campaign, and, you know, looking at your various reports, I mean, people were really off and running with this, or at least trying to do so, trying to put pressure on governments to change policies, and setting up demonstration programs which in many cases appear to have a lot of visibility.

Max: Yes.

Meldrum: It seems like in some ways we've been talking about this issue for the last 20 years. And yet, you know, there's still a perception among a lot of people, particularly among the terminally ill, that they're undermedicated, that there's not enough opioid use, that there's still a certain amount of patient reluctance and physician reluctance. I think this has changed somewhat in the last two years since the APS made its end-of-life statement.[94] I mean, that's just a perception.

Max: Well, what you've raised, Marcia, is one of the big challenges and mysteries of pain treatment that we've known since the '60s and '70s, how to give excellent relief with opioids, sometimes spinal [or] local anesthetics [or] anti-inflammatory drugs, to opioid-responsive pains, particularly those patients with cancer and just about every postoperative pain patient; yet some people still have a lot of pain.

One issue we talked about with the World Health Organization was legal barriers, and there's been a lot of progress on that. In the United States, certainly David Joranson has been leading the way to educate every state board, and many of them have created intractable pain laws, and David and colleagues have developed model legislation. And so, you know, there's been a big thawing in the legal area.

But there are other issues [related to] how you change clinician practice. I must say, around the world, there are some places like China, where there's been a

major change [in opioid policy] because Cleeland got the Ministers to change it. But in India, one of the places the WHO program started, there's been just a glacial pace of change, and Joranson is going over there now to try to find out why nothing [has] happened in 15 year and try to move things along. But the issue is why, once we know how to relieve pain, it doesn't happen. And this really is a bit of a mystery through medicine, how you get people to use best practices. With just about any problem you look at, any known effect of treatment, it's spottily applied. And there are only the beginnings of research on how to fix it.

We in the pain community have made some efforts towards doing it. I think one movement that the American Pain Society has a lot to do with has been using quality improvement mechanisms to do that; an opening for that began, I guess, in about 1987. Ron Dubner was the [APS] president, and Wayne Evans, who was a pharmacologist, now deceased, in the Midwest, wrote to Ron and said, "There are now these Quality Assurance committees. Maybe we could use those to improve pain relief, set up a committee." Ron called me and said, "What should we do?" I said, "Well, here are some names of people that have written about it." At the time, Marilee Donovan[95] had just written a fantastic paper looking at 500 patients. She was at the time in Chicago. She had found that of about 500 patients in a big Chicago hospital, half of them had excruciating pain. It was only occasionally documented in the charts. They had to wait a long time for medicine.[96] I was running into the same thing, seeing the pain consults at Memorial Sloan-Kettering and here at NIH. So we got together a committee of Marilee and Wayne and Charlie Cleeland and Russ Portenoy and a few other people, and we brainstormed for a while. We tried to come up with something short, how we might fix it. In the end, we came up with four or five simple points that we published in around 1990, [and] that we presented at the World Pain Congress in Adelaide [in 1990]. We just said, "We'll put pain on the charts." Just promise the patient that we'll give you attentive relief, or come after us; and measure the time that it takes [the patient] to get an analgesic; and make sure that it's convenient to relieve pain."

The whole analysis was, rather than demonizing the Commission[97], saying they don't care, rather than saying they're callous, [that] surgeons or oncologists or internists are callous sons of bitches who don't care about pain, which is sort of our natural righteous tendency, if we just said, "Gee, medicine is based on structure" – You'll notice that the oncologists really care. They work 15 hours a day to shrink the tumor and on any given day, they didn't want to spend two hours reading the latest literature on how to use morphine. They really thought their job was to shrink the tumor, and when it got more complex, pain wasn't first on their list.

And it was really a remarkable – I had a remarkable experience trying to get pain higher on the agenda here at NIH. There's a marvelous pediatric pain researcher named Angela Meisner,[98] who worked to do some of the first studies of opioid infusions in kids here at NCI. She was a rather lowly fellow. And

when her outside fellowship expired and she had done marvelous work, they said that her work wasn't high enough priority to get renewed. Instead they'd do one more chemotherapy protocol to treat advanced bone cancer. We were just aghast, how they could choose, you know, how these oncologists could choose to not fund relieving pain in kids when they're not going to cure all cancers for many, many years to come. "Oh, maybe the head of the Cancer Institute is a mean person."

But then my eyes were opened when I had a talk with one of the former Fellows. There was a guy who had been the most caring oncologist who called pain consults on lots of patients, and we talked about the details of pain management. Then he graduated and grew up to become the assistant to the NCI director of cancer treatment for the whole country. I went to him and I said, "You know, we're having a horrible time. NCI is not making this a high priority, and I'm just amazed. How can you do that?" And he thought for a second and here this very humane clinician said, "Well, I can understand that. Our job is really to try to treat and understand the tumor, and cancer really only causes pain when the tumor enlarges and hits a nerve." He said, "I think it's probably the Neurology Institute's job to take care of it."

Suddenly, here was a guy who was the nicest clinician you could ever want, and he was spouting this insanity. And for me, it struck me that it was what some of my social science colleagues were talking about in that it was this historical discourse, that this discourse of medicine being concerned with structure, that had, it was like aliens seized the brains, and this man was in the grip of his discourse where their first priority was [not] to relieve pain. And the more I read, you know, when I read about the history of hospitals, you know, Foucault talking about the birth of the clinic, then Rosenberg writing about the history of hospitals,[99] and then Cabot, in the early 1900s at Harvard, was saying how terrible it is that we don't care about patients, we should care about the patient more,[100] he was spitting in the wind. He was going – they were going against this discourse of structural disease. So you need to find a way not to demonize the docs but to say we need to fix the system. It's not your fault, it's the discourse. And for me, they wrote about this in an *Annals of Internal Medicine* article in about 1990,[101] is improving pain, something like improving pain through education is not enough, and that's why we got so interested in the quality improvement movement. That's why I've got to say this has not been a panacea, so we articulated this with Marilee Donovan, a bunch of other nursing professors, Chris Miaskowski[102] and Sandra Ward[103] and the nurses at Memorial Sloan-Kettering like Nessa Coyle[104] and Dr. [Marilyn] Bookbinder,[105] and they put pain on the charts. Slowly it lets you target pain and, over years, improve it. By itself, it hasn't dramatically reduced. Just putting pain on the charts hasn't reduced pain, unless you put in a lot of effort and you can get unit-by-unit changes in pain. But so far it's been catching on, and the AHCPR guidelines on pain seized [attention], when they got organized. Ada Jacox[106] called me up and said, "You want to help me start these AHCPR panels?" She

had gotten pain first on the list for the AHCPR,[107] and I said, you know, "It's still my job to do research. I really want to not spend a lot of time on these policy things." But she said, "Let's further develop these American Pain Society draft guidelines," and Dan Carr,[108] Rich Payne, and Ada and Chris Miaskowski just carried this on. And now the VA Hospital has seized on putting pain on the charts.

Meldrum: Yes, and that's really important.

Max: So we'll see. We'll see if this is something that makes a difference. There are a whole lot of issues, payment and –

Meldrum: Yes. There's really no reimbursement for pain treatment, still. But I think it does make a difference having pain on the charts. How are we doing?

Max: Like two minutes.

Meldrum: Two more minutes. OK. So, are you saying, though, that you think, then, that the legal restrictions on narcotics use have largely been addressed, at least at the government level?

Max: No. The national governments, national laws, according to David Joranson and others, are not [yet sufficiently open toward opioids for chronic pain]. Bob Angarola,[109] who had a huge impact before his untimely death, went over to Europe and flipped the narcotics hierarchy of WHO to be more open. But on a national [US] level, there aren't a lot of terrible laws, though the DEA [Drug Enforcement Administration] [has been leaning toward stricter enforcement].

Part Two

Meldrum: So far, so good. It's Wednesday, May 19th. It's just after 10 in the morning, and we're starting the second part of our interview with Dr. Mitchell Max in his office at the Clinical Center. Good morning, Dr. Max.

Max: Good morning, Dr. Meldrum.

Meldrum: Thank you. Now, you were beginning to talk about the DEA. And you want to go on from there? We were talking about –

Max: Well, in a number of projects when colleagues and I were working with the WHO cancer pain relief program and trying to make opioids more available for cancer pain in the US through state cancer-pain initiatives, we repeatedly looked at the laws and what were the legal impediments to prescribing opioids. I'm not an expert in this. I got what I know from people like David

Joranson and the late Bob Angarola. But they repeatedly, and others, confirmed this, said that there really isn't a problem with the text of the international and national U.S. laws about prescribing opioids, because on those levels, they all contain text that says nothing that should keep opioids from being prescribed for people who need it for pain.

There are some difficulties with some of the state legislation. I believe that Joranson has worked through the State Uniform Controlled Substances Act.[110] There's a mechanism to change laws in all the states, and he's made some progress on that. A big impediment has been the way regulations have been informally enforced in the states by the medical boards, which tend to be very old physicians, often semi-retired physicians, who review cases of prescribing where doctors will give somebody with chronic low-back pain who need to work for a living or a longshoreman. You know, I've defended a number of physicians who prescribe for a longshoreman who, on six Percocet[111] a day, could unload the boats, get through the day, and support his family. If he didn't have them, he couldn't work; and they would throw the book at doctors for that kind of prescribing. So there's been a big push through Joranson and others to try to educate the people in the state level to change their criteria, because there are a number of people who will benefit. That's an evolving thing, and there will be some people who will abuse drugs, and physicians who will go through the loopholes.You know, this will forever be a problem. It's just the balance needs to move towards the judgment of the physician in allowing some patients to get opioids. But that's a whole 'nother story. I think David Musto[112] has written about the way the pendulum has been swinging, and we've got to help it swing back the other way, but not to do it in a Pollyannish way.

I think you asked me about the DEA. The DEA has a small group of people. They really don't have a force to handle medical prescribing throughout the country. There, the national laws again have the caveat that they should not hurt patients who need pain relief, and I think any conversation I've had with a high-level DEA official, in any of those conversations, the DEA official says, "Yes, we want to help people with cancer." In various laws that have come up before the Congress, the DEA has generally advocated additional controls, monitoring, which most of the pain people thought would serve to act as a barrier to pain patients getting it. The DEA has had its priorities. Its top priority is being able to track and reduce drug abuse, and some have felt that this goes too far. And, you know, as a government employee, I need to be circumspect about criticizing others.

Meldrum: Mm-hmm. Well, I think part of what you say is kind of a spectral effect in that the DEA has one mission; but I've occasionally heard people speaking on the news saying essentially they aren't prescribing or are trying to reinforce certain

regulations because they think the DEA is after them or that pharmacists are afraid of the DEA.

Max: Well, they are afraid of the DEA. And I think, you know, there are some cases where the DEA has acted in ways that would be an impediment. On the other hand, there has been published – It's referenced in one of Joranson's pieces – the DEA administrator came out with a directive. It was either that or there was an administrative law ruling that was very positive towards the treatment of pain. But that's really something that's outside my expertise. I really should leave that to other people.

Meldrum: Recently – I mean, this seems to have been a very good year. In February, the VA announced that it was going to have everyone assess pain, and recently the JCAH has started including pain assessment in its standards.

Max: Yeah. JCAHO [Joint Commission on Accreditation of Health care Organizations, formerly the Joint Commission on Accreditation of Hospitals] is what they call it now.

Meldrum: JCAHO, yes. Do you want to comment on that? Do you think it's going to make – Well, you tell me.

Max: OK. The JCAHO and the VA, to my understanding, really are implementing the spirit and many of the details of the American Pain Society quality improvement guidelines, which also were the AHCPR guideline. Essentially to make pain visible, as I wrote about in 1990, to just have it on the charts, to make pain something that's checked and pain relief recorded and something that's trackable.

The research thus far, which has been done mainly by nurse researchers like Christine Miaskowski and Sandra Ward and Marilyn Bookbinder and others, has suggested that just putting pain on the charts in a nursing station, just tracking it, is not enough to dramatically reduce the level of pain in a hospital. That it's a necessary but not sufficient step for solving the problem; that once they have those readings, the next step is the needed institutional commitment to then identify, here's a ward where there's lots of pain after urological surgery, to then call in physicians, nurses, to do bedside teaching, and there they can get targeted dramatic reductions in pain. So it's an essential intermediate step. But just monitoring pain, which is a big piece of what these two systems are [doing], isn't enough. I think those two systems have additional steps. But we haven't solved the problem. There's not a hospital in the country where pain experts are satisfied that they've been able to get all the clinicians to take care of the patients like they would. And so we think this is wonderful, but whether or not it's a big part of the solution remains to be seen.

Meldrum: What do you think a good pain service in a hospital would be like? How would you structure it? Say you had carte blanche and you could do anything you wanted, and the clinicians were going to do, the clinicians would do what you told them to.

Max: Well, the most important thing is that – and this has been shown again and again at Memorial Sloan-Kettering and the University of Wisconsin – one needs commitments from the top, from the head of the hospital and the major services, that their services there, internists and surgeons, nurses, will make it a priority to work with the pain experts to do what's necessary. So you need buy-in from the top. You need to monitor pain, how to be visible, where the problem is. The hospital is only a very small piece of it.

Now, one of the main areas of frontiers of pain management is the home, the nursing home after the patient gets discharged; you need transition, you need ways of working there. Most of the research done so far, and our standards, were really developed with the hospital in mind because that's where the academics have been, so we need to reach beyond that. But, you know, given you need institutional buy-in from the top, you need to monitor pain, you need pain experts who will week by week come to the bedside and teach the young clinicians to make them feel like they, like this is one of their great skills, to be role models. You need a way to get these internists or surgeons in training to be interested in paying attention, and a lot of the hospitals are saying [that] a pizza goes a long way. So I think that's all we know thus far.

Meldrum: The pain expert should be on call or should do regular rounds in the wards. What do you think? The pain consultants.

Max: Well, we're building a service here. The new service here will have the pain [consultant] making rounds every day anyplace where patients are at high risk of being in pain, like surgery, cancer wards. They should be on call. They should have regular teaching rounds. They have at Memorial Sloan-Kettering, I believe, there's one fellow or faculty member assigned to each patient care unit to be their liaison [and] special teacher.

Meldrum: OK. So you have the service in place. We talked last time about the fact that we still don't have a really good next step beyond the opiates. I mean, we have some drugs that work in some cases, but the opiates are still our first line of defense.

Max: All the two classes – the opioids and the drugs in the aspirin, NSAID, acetaminophen class, so those two classes are the mainstay of therapy. And then we have a bunch of very mediocre treatments proven effective for certain types of neuropathic pain. And that's all that's proven up till now. Industry has jumped in and there are many, many compounds that appear

exciting in the laboratory and that are in clinical trials, and we'll see what comes of them.

Meldrum: Now, I'm just wondering where you thought the next step might be. I wrote down here. You did some work with acupuncture.

Max: We did work with acupuncture. We did a large trial with acupuncture. That is a rather controversial literature whether acupuncture does anything for chronic pain, because the studies were all small and poorly controlled. We did a large study with 125 patients with HIV-related neuropathy in each group, and [125] patients who got real standardized acupuncture with the points that a number of acupuncturists had recommended, and 125 got treatment with the points that the acupuncturists thought were the least likely to help, and there was no difference in pain after 14 weeks of treatment between the groups. But once we published it, many other acupuncturists who weren't involved said, "Well, of course, you picked the wrong disease. Acupuncture doesn't work for nerve injury," or they said, "You picked the wrong points." So the jury remains out on acupuncturing chronic pain. That isn't a particular area of my expertise.

I think that biological solutions, particular drug treatments, are going to be the next step. I think we have developed opioids and the aspirin-like drugs hundreds of years ago just by picking the plants around us, without having any idea of the design of the nervous system. And now we really have our hands on the blueprints of the nervous system. We know where almost all the neurotransmitters are. We know how to find them. We're close to having the whole human genome, and we have methods for identifying genes that get turned on and off and then looking at the protein products. I think we're going to be able to figure out how the system works, and there's a great possibility of throwing in very smart drugs to derail the process. Many scientists are saying that it's been hard to get drugs into the central nervous system to reduce pain without interfering with so many of the important functions, like cognitive functions, like all the five or six groups of drugs that work for neuropathic pain thus far impair consciousness or some other vital CNS function. So many pharmaceutical companies are saying, "What if we get a drug that won't even get into the brain that just works on nerve endings, or the nerve as it courses through the body before it gets into the nervous system? That won't make people sleepy or psychotic or any of the other wonderful things." And that's a great target. The peripheral nerves mediating pain are much different from the nerves that don't mediate pain but take care of motor function and fine sensory function, and there are many potential molecular targets such as the newly discovered capsaicin family of receptors and many other markers on the surface of these small neurons. So that's a great target. But I think in general, you know, we've been working

on glutamate systems, and it may be that that will provide an entree.

Meldrum: OK. So we're really talking about trying to look at cellular mechanisms and molecular mechanisms. I mean, that's ultimately where you think some solution, new solutions will come from.

Max: Absolutely. I would be astounded if we can't come up with something that's just as good as morphine and less toxic. And it might take 10 years, it might take 20 years. The rate people are going, I mean, now that we have good animal models and a lot [of options]: just about every drug company sees they can make a lot of money if they do this right.

Meldrum: Yeah. It's definitely going to tum the comer. You've heard Robert Ader[113] talk about placebo treatments? And he's proposed more than one idea. The one that I heard the talk on was where he suggested that we alternate a randomly interspersed placebo treatments with opioid treatments, thereby reducing toxicity but getting essentially the same analgesic effect. Do you think manipulating the placebo effect is really a useful possible therapy?

Max: Well, I would strongly – if what Ader is saying is to fool the patient and give them placebos, I would not – he's not a physician, but if he were, I would tell all my friends and relatives to stay clear of his office. I think the placebo effect has the funny quality that if you try to cash in on it by taking away what you know is the powerful therapy, you deflate the placebo effect. So I've read Ader's arguments, and maybe I've missed the point.

Meldrum: Maybe I missed the point too.

Max: My immediate reaction was that it's a very wrong headed idea, but, you know, he's a very bright person and maybe I just, maybe just missed it.

Meldrum: You talked a little bit about NCI last time and about some of the problems or some of the reluctance to really look at pain at NCI. And you've done some consulting with some of the other institutes?

Max: No, no. I really don't recall what I said. I might have said that we were mad. We were upset at NCI. Or, you know, you could look at their budget figures and I think they were giving a third of a percent of their budget to pain and the Dental Institute was giving 7 percent. So what do you want to know?

Meldrum: I was just wondering about some of the other institutes, if you had found other people around campus who were interested in pain in different -- You've talked on your CV about consulting at NIAMS and NICHD and...

Max: I mean, there are many people at NCI who are champions of pain, have a big,

even a small percentage of their budget is a lot of money, and they have some terrific people who are championing pain. Now, I've been working recently in a little informal action group to promote palliative medicine research at NIH, you know, broadly – most of these are extramural offices [that is, managing NIH research grants to universities and other outside groups], in general, and the leaders of this group. Leadership has been coming from one of the main NIAID [National Institute of Allergies and Infectious Diseases] program officers; the head of the AIDS program is the champion. The National Institute of Nursing Research is very active. You know, a lot of Institutes have some interest in pain. But I'd just as soon not –

Meldrum: No, I'm sorry.

Max: You can just go. Yeah. You can go look at the budget figures.

Meldrum: I wasn't intending to do that. I was just wondering if you'd done any interesting work with any of the others.

Max: Oh, collaborations. Well, we did. I've done two AIDS trials with NIAID, the acupuncture study and another study, and the AIDS clinical trial group did a reasonably large clinical trial of several drugs in HIV neuropathy and found that amitriptyline and mexiletine, a sodium channel blocker, didn't do too much. But they have an ongoing series of studies in AIDS neuropathy.
You know, I'm working on a Web-based pain-and-symptom clinical research textbook and getting a lot of advice from the Nursing Institute, as well as some advice from the National Library of Medicine. We're collaborating with Hopkins on some NINDS-supported programs. You know, we've also worked in our own intramural research. We've had some collaboration from the biological psychiatry groups in the National Institute of Alcohol Abuse [and Alcoholism] and NIMH [National Institute of Mental Health].

Meldrum: Did you ever think about going into academia or leaving NIH or going somewhere else?

Max: Oh, a little bit. I mean, there have been a few times when I've looked at jobs at universities and I've looked at jobs in industry and I've looked at jobs in the FDA.

Meldrum: Yeah. I mean, with your interest in clinical trials, you virtually wrote the book. You did write the book, one of the books anyway.

Max: Yeah. Right now, I mean, a number of institute directors have declared that they intend to build a large multi-institute pain research program, and it's very interesting to stick around for a few more years and see if anything happens or not.

Meldrum: I'm just wondering about, you know, you seem to actually be – I mean, this is

a great place for you because I think it's given you kind of a national status [and] an ability to have a lot of impact. I'm just wondering if you miss teaching or something like that.

Max: Well, I teach. I teach a few fellows that I have working personally for me. I teach in courses. I mean, I teach a lot through writing. And what this place gives is a chance to polish one's research manuscripts and write chapters. I mean, it's like my clinical colleagues, Ray Dionne and Rick Gracely, write a lot of the key chapters on pain, for Ray for the dental textbooks of many stripes, and Rick, as you know, writes a lot of the main chapter textbooks on pain measurement and pain psychology and that's a place you can really – Dubner's emphasis was on methodology, and we all had a lot of time to examine and compare various methods and debate them, and that's something that we can share.

Meldrum: Talking about methodology, do you have a sense that analgesic trials are being conducted well outside of NIH and Sloan-Kettering? There's a lot of talk about meta-analysis, the Cochrane Collaboration[114] and so forth.

Max: Well, the problem with meta-analysis in the pain field is that there are almost no primary trials in the areas of interest. Alejandro Jadad,[115] who is one of the leaders of this, has compiled a database of, say, 15,000 published papers, and almost all in acute pain situations. There are very few – I don't know if it's a thousand or what the number is – there are relatively few in chronic pain and even fewer with some of the newer kinds of agents of rather low quality, and most of the meta-analyses in those areas are garbage in, garbage out. In acute pain, we know opioids and NSAIDs work, and meta-analyses don't really help us very much.

Meldrum: They don't add much.

Max: So I think you have to do a decent job of meta-analysis to keep up with the state of the art and justify what you do. But the main problem is there are so few interesting clinical trials. Now, I don't recall if we talked – Did we talk about the bunching of clinical trials and chronic pain?

Meldrum: I don't think so.

Max: OK. Well, this is very important. As a historian, this may be of particular interest. Well, anyway, I can pull this up if you want. But if you go to any of the pain or pharmacology meetings and look at the clinical trials presented, or if you do a search of the NIH research grants, you'll find that studies in chronic pain are all bunched into just a few areas, and most of the areas of medicine are not covered. It's a funny thing. And if you look at the membership of the IASP, you'll find that the

areas where there are maybe a dozen trials a year carried out or there may be 10 to 20 NIH research grants are those where John Bonica, who singlehandedly founded the field, had friends. So there are 10 or 20 grants and lots of clinical trials in neuropathic pain because there are a lot of neurologists who are interested. So that's pain, neuropathic pain and headache, a lot of postoperative pain, a lot of back pain, because there are psychologists and anesthesiologists from the pain clinic, cancer pain, and dental pain and chronic facial pain. Those were the main groups that Bonica was able to enlist. And the membership [patterns have] continued – membership in the APS [and] of the International Association for the Study of Pain, is mostly anesthesiologists and psychologists who work in pain clinics and a sprinkling of neurologists and oncologists.

On the other hand, if you look for some of the most common complaints of people who walk into a doctor's office, among the top 20 are chest pain, belly pain, muscle pain, and when I looked a few years ago, there were one or two NIH clinical research grants, almost no clinical trials [for these types of pain]. There are almost no representatives of most of the medical and surgical sub-specialties who come to the American Pain Society or the International Association for the Study of Pain. You'll find almost no urologists, no cardiologists. You know, chronic pain in heart disease after you've done all the bypasses may cost $10 or $20 billion a year in this country in disability, and we're doing the most outlandish things like, for half a million dollars, you can get a machine that will put a lot of laser-bored holes in the ventricle and has a high mortality, and they're doing this for pain after everything else fails. There's very little study of the pain physiology and treating the pain as a symptom, very few cardiologists, gastroenterologists, GI surgeons, and many of those other specialties, even not too many rheumatologists. So there's a wonderful body of scientific knowledge and methods in basic and clinical pain research, but it's only circulated among a relatively few specialties. So we're leaving out most of the parts of the body, so that's a big problem.

And thus far, industry isn't going to handle that because industry tends to be conservative in some ways. You've got to justify to the business guys at a meeting. You've got to justify how likely you are to have a return. And people jumped into neuropathic pain. Now every company is doing neuropathic pain after Gary Bennett and Yi-Kuan Xie found rat models where you could patent a drug and where we and Peter Watson and Soren Sindrup showed that you could take 20 or 30 or 40 patients in a clinical trial, diabetic neuropathy, and get a replicable result. We all got very replicable results with the same methods. So you could say, OK, we're going to spend $5 million on a program and we'll have a result, positive or negative, in two years. If you want to go into GI pain or cardiac pain, there's no track record for clinical trials, so it's very uncertain. So industry tends to want to wait until there's at least some academic trailblazing.

So NIH needs to support something in the universities. A problem is that the watchword at NIH is investigator-initiated proposals. They really don't want to have a welfare program to identify an area and fund it even if poor proposals

come in. But the problem is, they're not going to get excellent proposals in cardiac pain if none of the cardiologists have been exposed and gone to the meetings and seen the opportunities. So there's an emergency. We've got to step in. Most of the pain in most of the parts of the body is falling between the cracks. So we need to find some way of getting the pain-trained anesthesiologists and psychologists to hook up with the specialists in the rest of the body.

Another thing is there are some other issues that industry isn't going to really handle, like drug combinations. We found so far in our clinical trials and those of others in neuropathic pain, the best individual drug, like opioids or tricyclics or gabapentin or NMDA antagonists, will reduce pain on the average of about 20 or 30 percent above the placebo effect. And that isn't enough, and people will get side effects. So they're, on the average they're grumpily satisfied, but it isn't fantastic. And it may be that blocking one channel in the brain just isn't going to be enough, and I think the basic scientists agree that probably we're going to need to combine several different drugs just like they've done in hypertension and bad infections and cancer and AIDS.

But drug companies are rarely interested in looking at combinations because it's very cumbersome to get approval; they have to own most of the drugs. They're going after single drugs, and I think government agencies like the NIH and similar agencies in other countries are going to need to fund drug-combination studies or studies in conditions that are uncommon enough that they don't represent the $300-million-a-year market that a drug company is going to want. So I think research, training, to reach out to other specialties, more, a much bigger volume of clinical trials, so when you ask about the quality – I guess your initial question was, what's the quality of clinical trials. It isn't even the quality of clinical trials. It's that they aren't being done in most of the chronic pain conditions. The major problem is, in pain, is chronic pain of its various types. And we actually don't know now, is chronic pain mostly one thing? So can you do a study, like they do now, they do studies in dental surgery or osteoarthritis. If it works in that, will it work in cardiac pain and bladder pain and uterine pain and GI pain? Or are those separate physiological disorders that are going to need different classes of drugs? And there are several traditions in this. Did I give you my 1994 article, "Divergent Traditions in Clinical Trials"?[116]

Meldrum: Yes, yes, I have that one.

Max: OK. What I've argued is there's a tradition of lumpers and splitters in pain, that the clinical trialists, from Henry Beecher and Lou Lasagna,[117] from the late '40s and early '50s, said that pain is pretty much one thing, and you could use any of the models, any kind of simple pain model like surgical pain, to represent all human pain, and so they're great generalizers. On the other hand, the Bonica tradition, Bonica really exhaustingly described each pain type and was fascinated by the differences between them and got a bunch of basic scientists who were interested in

the anatomical differences and the neurochemical differences. And the tendency of us academics, those who follow from them, to get grants, you want to have a lot of different, separate niches that you can be an expert in and get a grant. And so our tradition has been to say that there are many different kinds of pain with different mechanisms, and there are some clear distinctions like some of the anatomical changes after you injure a nerve, like the nerve develops new sprouts which are not present [de novo]. That said, there have been many claims made for individual kinds of pain that have not held up, like there was a very radical claim that neuropathic pain does not respond to opioids based on one small, very unconvincing study. There are now many good studies that refute that and say, well, maybe opioids reduce neuropathic pain a little less than they'll reduce pain from tumor or bone. Russ Portenoy's group has shown maybe it's some 75 percent effective. But still, the opioids beat everything else in a condition like neuropathic pain, like post-herpetic neuralgia so far.
So the lumpers may win out in the end. But the point I'm getting to is, for rational drug development – I'll give you an abstract that I presented at this biomarkers meeting.

Meldrum: Yes, I'd like to see that.

Max: That we don't know now, in drug development, whether we need to do studies in 15 different pain models or whether we can just do two and generalize, and this is a very important issue. Now, I think the FDA is just beginning to address this, and they have no idea because there isn't a track record of anything besides NSAID-Iike drugs and acetaminophen and opioids. They don't know what a claim structure should be, how to set up the rules and incentives for companies to pick models. You know, it would be great if two models predicted everything, but I think we need to spend the next 10 years with 10 different classes of drugs and do lots of models and see what the pattern of generalization is.

Meldrum: OK. Now, that's really helpful.

Max: Yeah. There are some things, for instance, like now people are saying, there are some arguments that visceral pain is different, like Bill Willis's group is showing that pain from the viscera in the pelvis is largely transmitted by the dorsal column post-synaptic tract, and you cut that and sigmoid colon pain goes away. And this is a lot different from other kinds of pain. And Jerry Gebhart[118] is showing a particular sensitivity of inflamed colon pain to peripheral opioids, suggesting visceral pain may be different in some ways. But we'll see. These are claims of academics who want to create their niche. And there are apparently different peptide patterns from viscera than from joints and skin. But we'll see.

On the other hand, there are some mechanisms, like no matter where the pain is coming from, any viscous or skin or joints, peripheral sensitization occurs in inflammation [and] central sensitization occurs whether it's inflammation or nerve injury. So there are a lot of common pathways that a drug like

gabapentin [can work on], which seems to block every kind of central sensitization, as do these nicotinic frog-skin toxin analogs.[119]

Meldrum: Yeah, OK. So it's really still kind of wide open.

Max: Right.

Meldrum: OK. And you're saying that industry is sort of looking at some areas, and there's some possibility for government to stimulate grants. But you seem to be saying it's really going to have to come from individual people who are willing to go into this field or are willing to sort of carve out new niches for themselves.

Max: Oh, absolutely! I think the key thing is to get new people from different backgrounds into the field. I mean, we desperately need the young rheumatologists, gastroenterologists, urologists, cardiologists, people in new areas of disease that aren't the usual suspects at the pain meetings, to team up with pain basic scientists, with pain clinicians, medical psychologists, and submit good grant proposals. So I think something's got to come. Either these people from new areas aren't going to know about it unless the pain people reach out to them and unless either government or industry sprinkles some money, puts some incentives on it. You know, the problem is, the big scandal is we're really – The trainees and protégés of friends of John Bonica are all huddled in a small group of specialties.

Meldrum: Yeah. It became sort of an exclusive little club.

Max: Well, I don't think we're trying to be exclusive.

Meldrum: No, I know, but, you know, it's natural.

Max: Yeah. For instance, I'm trying to push my fellows, when they go out to universities, into going and teaming up with clinicians from different areas, like Christine Sang, who was with us for three years. Now she's at Mass[achusetts] General. She went out to the spinal cord injury hospital at Harvard and got a grant for that, and I think they would, pushing my fellows, they would do marvelously to hook up with cardiologists or rheumatologists or what have you.

Meldrum: One of the questions I was going to ask you was, you probably have a lot of applications of people who want to come and work as a fellow with you. Is there something in particular you look for in fellows?

Max: I look for people – Some of my most successful fellows didn't have any real prior research experience. I just want someone who has been taking care of patients with

chronic pain and has found that frustrating enough that they want to spend a lot of their time, maybe they want to spend a number of years in relative poverty, studying hard things like statistics and epidemiology, and hook up the new knowledge in basic science to the treatment of patients. So I'd look for people who are thoughtful clinicians.

Meldrum: OK. And so, looking back over, what, you've been here about –

Max: Sixteen and a half years.

Meldrum: And, you know, we've talked about a lot of things you've done. Are there any particular experiences that sort of stand out or were particularly exciting to you?

Max: Oh, well, there were a lot of experiences that were really exciting. I guess if I want to talk about our intramural program, I think a very exciting time was my collaboration with Gary Bennett. You know, it was actually a group of Gary, myself, Rick Gracely, and Gary's lab people, and Gary – When I first got here, you know, Gary was very interested in coming over and seeing the patients, and he got interested in the clinical manifestations of neuropathic pain. And once he had a rat model, things really took off. He came up with a discovery every month and wanted to apply it to patients. So Rick and I were constantly in discussions about how to test these things, and it was just a wonderful time. The three of us got an awful lot done. I think Rick, I'm sure, has talked to you about his discovery of A-beta-mediated pain, and I think a lot of our studies have – The capsaicin model is a model for testing drugs that work on central sensitization, and our studies of glutamate antagonists came out of that work, which, you know, really arose in Gary's bench studies. So that was a terrific time, and, you know, I miss him.

I mean, it was also enormously exciting to work with Kathy Foley and Jan Stjernswärd on founding the – well, actually giving a big kick to the World Health Organization Cancer Pain Program. It was really exciting to produce the pain textbook. I'm having just a fantastic time now. You know, I have one project, which is to expand the methodological research, to expand the teaching that we've done about pain clinical trials to the other symptoms, and that's another thing. I don't know if we've talked about it. There's now a perceived research breakdown in the country. This was stimulated in a funny way by Kevorkian.[120]

Meldrum: Oh, yeah.

Max: Did we talk about this at all, palliative medicine?

Meldrum: Not with you, I haven't.

Max: Yeah. Well, I mean, the other exciting thing is, I think I just mentioned, I've got a

_____ $1.6 million NIDCR contract to produce a Web-based symptom-research textbook, and exactly what that is, I don't know. We're finding out. I feel like one of my heroes, Duke Ellington;[121] he just got together people who could really play their horn very well, and just gave a little instruction, so what came out – We've got a lot of terrific people who are working on it, and we'll see what emerges from that. But this is a strategic opening that I think was first picked up by Kathy Foley. For a long time, it appeared to some of us, like it appeared to Kathy, that the field of pain was viewed by the leaders of medicine as a backwater, as a little niche of the anesthesiologists. And she had started to see, before the rest of us, that pain was going to come to the forefront because of Kevorkian and the controversy and public interest in physician-assisted suicide, that suddenly when Kevorkian, in his somewhat demented way – this is just my opinion – Kevorkian was clawing back in a strange way to one of the fundamental commitments of medicine, to provide comfort, in a way that I don't agree with. But it elicited…

And then there are many more responsible [physicians] who are advocating physician-assisted suicide. But Kathy saw the mainstream medicine people were saying, "We don't want to kill our patients or help them commit suicide. The answer is not that. The answer is better pain control." And suddenly, better pain control, better control of symptoms at the end of life. And suddenly the leaders of medicine have become champions of pain control, and rather than this be a backwater, Cathy heard them coming to her and quoting her own work, and they didn't know that she had written all these things. She suddenly saw 10 years ago that this was coming, and that's when she worked with George Soros[122] to get a foundation to move this along. But recently, there's an Institute of Medicine report that was addressing what is needed, and if you're saying, if the leaders of medicine are saying, "We need to do a better job controlling symptoms," the gap is [that] there's very little physiologically-based research on any of the symptoms apart from pain. This became clear when the Institute of Medicine invited representatives of all the NIH Institutes to describe their portfolios. And there was a modest-sized portfolio in many Institutes on pain at the bench, in the clinic. But when one asked about shortness of breath, the head of the panel, Chris Cassel,[123] said to the people from the breathing-related institutes, "What have you got in animals or in people, on neural mechanisms of the shortness of breath, measurement of shortness of breath?" They could think of very little.

Meldrum: Oh, wow.

Max: And there has been a lot of industry research on acute vomiting from chemotherapy, in the first 24 hours after chemotherapy, because these gave rise to a big market. Some of the best-selling drugs are Ondansetron [Zofran][124] and other anti-emetics. But there's nothing for the chronic nausea of cancer patients, very little known about that, very little work done on that. And fatigue and many of the other symptoms, there's almost no biomedical research

base.

The funny thing is that the field of palliative medicine came out of a clinical tradition, came out of the hospices, so there are a lot of expert clinicians; but these are not people who stand at the bench or work closely with bench scientists and write grants and do controlled clinical trials. So, I mean, people like Russ Portenoy and Eduardo Bruera[125] are trying to found a biomedically-based field. But where we came in with this textbook, as I saw that the missing piece is research training to get the basic scientists, and particularly to get the clinical investigators in cardiology, in neurology, in pulmonology, to start writing grants not only for doing pain studies, but also studies of the physiology and treatment of the symptoms in their field. So whatever we say for pain, that's much farther along than anything else, and I think the chapter which I helped to write in the Institute of Medicine report says pain can be a model.

The innervation, the anatomy of sensation, is very similar for all the symptoms. We know that pain starts with a small, unmyelinated neuron [that] synapses into the spinal cord. The second neuron goes to areas that say in the brain, "Emergency, pain is bad, this is awful, get away, stop it, kill the fly, don't go on the hot rocks," to the very fundamental emotional aversive centers like the hypothalamus and centers in the brainstem and periaqueductal gray[126] and the limbic system. And, similarly, shortness of breath is very aversive. It's an emergency. Nausea. They may be very, very similar, so I think the basic scientists as well as the clinicians can piggyback on all the discoveries in pain, like wind-up in pain.[127] Who knows if there's wind-up in shortness of breath? There may be a lot of the same mechanisms.

So I've been arguing that to develop an NIH program on the physiology of pain is a little narrow. Why don't you, while you're at it, have a program looking at the physiology of symptoms, and a comparison of those, whether you're looking at PET scans, measurement, [or] clinical trials; [research] would benefit from the interaction.

Meldrum: Right, right.

Max: So those are, if you want prophetic statements where things should be going, I mean, the whole – I think I would like, you know, four or five hobby horses that I think I've given to you so far, like the multiple models for clinical trials, getting people outside Bonica's friends, combination studies, extending the physiology of symptoms.

Meldrum: Yeah. With the population aging, as they keep hammering and as everybody in television keeps talking about, but it's true. I mean, we're going to have a lot

many older people. And it looks like the number of people we're going to be able to keep alive longer in rather extreme conditions of life is just astronomical.

Max: And being alive is going to feel terrible. I think that's what we need, someone going on TV and saying the odds [are that] with the new developments in medical technology, you're likely to be alive well past 80, and it will be terrible unless you start promoting physiologically-based symptom research.

Meldrum: I think we'll probably need a catchier title than that, but that's excellent. Have you worked at all with any of the patient groups, Chronic Pain Support Association or any of those groups?

Max: Well, I'm pretty active in a group called the Neuropathy Association that's a support group based in New York. Norman Latov,[128] a distinguished neurologist at Columbia, started it, and it's very well-funded. It's to educate people with all different kinds of neuropathy, and we've been working on – I just developed a piece of neuropathic pain. Haven't worked a lot with the other patient groups.

Meldrum: I don't know. They have a certain level of activity, but they actually seem to be very quiet to me in terms of what I would have thought. I thought by this time they'd be out of the woodwork yelling. But they seem to be rather low key. Maybe if you're in pain, that's all you can be. I don't know. But I have had that impression from the pain clinics. In pain clinics, the patients tend to be quite vocal, and I guess it's just a difference in setting. OK. Well, I've about come to the end of my questions. Any important thing you think we should say?

Max: I'm not going to say my list of great contributions. I'm going to go off the record. My big contributions were giving – I think I accelerated the WHO cancer pain program a couple of years. You know, it would have happened anyway. It was just sort of sitting there. That's part of being in NIH. I could take five hours a week when things were difficult and work on that. You know, I was able to work in areas like QI, when the nurses had done the best research, but I hadn't done any research. I mean, but I could sort of talk to them and write, and no one was doing it. I could move it forward. So I guess the WHO, the APS QI stuff, the textbook, our particular program in clinical trials, which I think I already said that

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Bennett and I are convinced, and I think there's a lot of evidence, that our work – I mean, we got the two medals the same time, and that was a thrill to be recognized. That, having the animal model and the clinical trials, got the

industry spending 50 times the money we had for it. And the American Pain Society principles was something that made a lot of money for APS, and maybe they put it on the boards. It's a handy thing. Now we'll see where we go with the Web-based symptom textbook, and if I can get pain human genetics going, we'll see.

Meldrum: Well, that's clearly a big frontier.

Max: So I think I covered my favorite things.

Meldrum: OK. Because we can always come back later.

Max: Yeah.

Meldrum: OK. We're going to conclude the interview now. It's just 11 o'clock on May 19th. Thank you.

Max: OK.

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[1] Norman Geschwind (1926-1984) was a leading American behavioral neurologist. He spent his early career at Boston University and then served as Professor of Neurology at Harvard from 1969 until his death.

[2] Dr. Matthew Budd as of 2015 is a retired Assistant Professor of Medicine at Harvard, who practiced internal medicine and gastroenterology at the Harvard Community Health Plan, a University-based HMO founded in 1969, for thirty years.

[3] Dr. Douglas Buchanan (1901-1983) joined the faculty of the University of Chicago School of Medicine in 1931. He had major influence on the development of the field of pediatric neurology, especially the diagnosis of childhood brain tumors and infantile spasms.

[4] Patients with untreated syphilis may develop sudden and dramatic psychotic symptoms in the late stages of the disease, 10 to 30 years after infection, indicating that the disease has attacked the brain. Patients with such symptoms, often called GPI, or general paresis of the insane, were thought to have mental disorders, prior to the discovery of the spirochete that causes syphilis. Due to early treatment, this condition is now rare in most developed countries.

[5] Memorial Sloan-Kettering Cancer Center traces its history to the founding of the New York Cancer Hospital in 1884. This institution became the Memorial Hospital for the Treatment of Cancer and Allied Diseases in 1916 and was moved to its present site, on land donated by John D. Rockefeller, Jr., in 1936. The Sloan-Kettering Cancer Research Center, founded in 1948 by two General Motors executives, was built adjacent to Memorial Hospital in 1948 and the two merged into one corporate entity in 1960. MSK is the largest and oldest private cancer research and treatment center in the world.

[6] Michael S. Gazzaniga (1939 -) is a leading American cognitive neuroscientist, probably best known for his split-brain studies with Roger Sperry in the 1960s. As of 2015, he was professor of psychology at University of California Santa Barbara.

[7] Fred Plum (1924-2010) was an American neurologist best known for his extensive research on consciousness and the comatose state. He introduced the terms “permanent vegetative state” and “locked-in syndrome” into the medical and popular vocabulary. He was the co-author, with his longtime collaborator, Jerome B. Posner, of *The Diagnosis of Stupor and Coma* in 1966 and an advocate of advance health care directives. Plum served as chair of neurology at the University of Washington and later at Weill-Cornell Medical College in New York.

[8] Kathleen M. Foley (1944 -) has been a leading advocate for intelligent use of opioids to relieve pain in cancer and chronic pain patients. She has spent her career as a neurologist at Memorial Sloan-Kettering Cancer Center, where she helped to establish the Pain and Palliative Care Service in the early 1980s and served as its head until 1998. As

of 2015, Dr. Foley was professor of neurology, neuroscience and clinical pharmacology at Weill Medical College of Cornell University, as well as Chair of the Society of Memorial Sloan-Kettering Cancer Center in Pain Research and medical director of the National Public Health Palliative Care Initiative of the Open Society Institute.

[9] As of 2015, Howard L. Fields was Professor of Neurology and Director of the Wheeler Center for the Neurobiology of Addiction at the University of California San Francisco; and Allan Basbaum was Chair of Anatomy at UCSF. Both are recognized as leading researchers in the field of pain.

[10] Tony L. Yaksh, as of 2015, was Professor of Anesthesiology and Pharmacology at the University of California San Diego.

[11] As of 2015, Charles E. Inturrisi was Professor of Pharmacology at Weill-Cornell Medical College. Robert Kaiko, who was for 28 years associate medical director and medical director of clinical research at Purdue Pharma (formerly the Purdue Frederick Company), in 2014 joined Cytogel Pharma as a scientific and clinical advisor. Both men are pioneers in research on the pharmacokinetics and pharmacodynamics of the opioids and other analgesics.

[12] Controlled-release opioid formulations release continuing dosages into the body over a period of time; they are designed to maintain adequate analgesia, while preventing the development of patient dependence and addiction.

[13] DADL enkephalin (or DADLE) is a synthetic opioid peptide and opioid receptor agonist, binding to the delta and mu receptors. It has analgesic properties and may also have protective effects against long-term loss of dopamine transporters and in the event of brain injury.

[14] Dwight E. Moulin as of 2015 was Professor of Clinical Neurological Sciences and Oncology and held the Earl Russell Chair in Pain Research at Western University in London, Ontario. He is a leading pain researcher.

[15] Bernard B. Brodie (1907-1989) was a leading American researcher on drug metabolism and drug therapy and is widely considered the founder of modern pharmacology. His most well-known findings were his determination that animal and human responses to drugs are essentially the same and his demonstration of the roles played by norepinephrine and serotonin in the brain. After beginning his career at NYU, Brodie founded and served as Chief of the Laboratory of Chemical Pharmacology at the National Heart Institute at NIH until his retirement in 1970.

[16] Raymond W. Houde (1916-2006) pioneered the scientific evaluation of analgesics for more than twenty years at Memorial-Sloan-Kettering, working with Ada Rogers and Stanley Wallenstein. He developed the idea of the patient as "his own control" in cross-over studies.

[17] Jerome B. Posner as of 2015 holds the George Cotzias Chair of Neuro-Oncology and is Professor of Neurology and Neuroscience at Weill-Cornell Medical College. He was a longtime collaborator of Fred Plum (see note 7).

[18] Gavril Pasternak holds the Anne Burnett Tandy Chair in Neurology at Memorial Sloan-Kettering Cancer Center and heads the Laboratory of Molecular Neuropharmacology there as of 2015.

[19] Ada G. Rogers, RN, was a Research Associate and clinical coordinator of the pain research studies led by Ray Houde (see note 16) at Memorial Sloan-Kettering Cancer Center. As of 2015, she had retired and was living in New York.

[20] Stanley L. Wallenstein (1920-1996) was trained as a psychologist. He joined Dr. Ray Houde's analgesic research team (see note 16) in 1951 as a Fellow and became a Research Associate and active participant in trial design and analysis. He retired in 1991, but continued to be active as a consultant.

[21] Following his Fellowship at Memorial Sloan-Kettering, Richard Payne, MD, (1951-) served as Chief of Pain and Symptom Management at Anderson Cancer Center in Texas 1992-1998 and then succeeded Kathleen Foley (see note 8) as Head of Pain and Palliative Care at MSK 1998-2004. As of 2015, he was Professor of Medicine and Divinity at Duke University Divinity School and the Esther Colliflower Director of the Duke Institute on Care at the End of Life.

[22] Russell K. Portenoy, MD, as of 2015, is founding Chair of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York and Professor of Neurology at Albert Einstein College of Medicine. A leading advocate of liberalizing opioid use in chronic pain since the 1980s, he retreated slightly from this position in the early 2010s, but remained a controversial figure in pain management. See: http://www.wsj.com/articles/SB10001424127887324478304578173342657044604 .

[23] As of 2015, Mary Catherine Elliott, MD, was a Pain and Rehabilitation Medicine specialist in Melbourne, Florida.

[24] Arthur Taub (1932 -), MD, was a Clinical Professor of Anesthesiology and Neurology at Yale University School of Medicine at the time of his retirement in 2000. As of 2013, he continued to be active in research.

[25] The International Association for the Study of Pain (IASP) was founded in 1973. It held World Congresses every three years from 1975 through 2008, and every two years from 2008 thereafter.
[26] Solomon Snyder (1938 -), PhD, is an American neuroscientist best known for his isolation and characterization of the endogenous opioid receptors in the 1970s. As of 2015, he was University Distinguished Professor of Neuroscience, Pharmacology, and Psychiatry at Johns Hopkins School of Medicine.
[27] Ronald Dubner (1934 -), DDS, PhD, 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.
[28] Raymond Dionne, DDS, PhD, is a leading researcher in dental analgesia studies; he succeeded Ron Dubner as Branch Chief of Pain and Neurosensory Mechanisms at NIDCR in 1996 and was named Scientific Director of Intramural Research at the National Institute of Nursing Research in 2005. As of 2015, he was Professor of Pharmacology and Toxicology at East Carolina University in Greenville, NC. For more information, see his oral history interview at: http://history.nih.gov/archives/downloads/raymonddionne.pdf .
[29] 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; 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.
[30] As of 2015, Gary Duncan was Professor of Stomatology and a member of the Dental Faculty and the GRSNC (Groupe de recherche sur le système nerveux central) at the Université de Montréal in Quebec.
[31] M. D. Anderson Cancer Center was established by the Texas State Legislature in 1941, with a state appropriation and matching grant from the M. D. Anderson Foundation established by banker and cotton broker Monroe Dunaway Anderson (1873-1939). The Cancer Center saw its first patients during World War II, moved to its present site in Houston in 1954 and has become one of the leading cancer research and treatment centers in the world.
[32] Phase 1 clinical trials are done in small numbers of subjects to determine toxicity, side effects and dosages; Phase 3 trials are normally large randomized controlled studies in which the new drug is tested against established drugs and/or placebo.
[33] As of 2015, Marvin Hoffert, MD, was a neurologist in Charlotte, North Carolina.
[34] Amitryptiline is the most widely used tricyclic antidepressant, developed by Merck in 1960 and approved by the FDA in 1961. It is used to treat various types of neuropathic and neuralgic pain as well as psychiatric disorders because of its inhibitive and agonist effects on neurotransmitters.
[35] As of 2015, C. Peter N. Watson was Professor of Medicine at the University of Toronto. For the paper, see: Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L and Warsh J. Amitryptiline versus placebo in postherpetic neuralgia. *Neurology* 1982 June; 32: 671-673.
[36] Post-herpetic neuralgia is nerve pain due to damage caused by the varicella zoster virus (chicken pox), commonly referred to as shingles. It is usually self-limiting, but the pain can be severe.
[37] That is they work by activating or promoting the release and availability of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the nervous system, which acts to reduce excitation. Adrenergic drugs work by stimulating the sympathetic nervous system to release the epinephrines, as in times of stress.
[38] Bruce Smoller, MD, as of 2015, was Chair of Pathology and Laboratory Medicine at the University of Rochester School of Medicine.
[39]Gary J. Bennett, PhD, was a researcher in the Neurobiology and Anesthesiology Branch at NIDCR 1978-96; as of 2015, he was Canada Senior Research Chair in the Department of Anesthesia and Faculty of Dentistry at McGill University. He is perhaps best known for his paper with Gracely on neurotoxicity (see note 29).
[40] The chronic constriction rat model was developed by tying a loose ligature around the rat's sciatic nerve. 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: 87-107.

[41] The lumper/splitter issue is discussed further in this interview; see below. See also Max MB. Divergent traditions in analgesic clinical trials. *Clinical Pharmacology and Therapeutics* 1994 Sep; 56: 237-241.
[42] 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.
[43] Daniel Schwartz and Joseph Lellouche were statisticians. See Schwartz D and Lellouche J. Explanatory and pragmatic attitudes in therapeutical trials. *Journal of Chronic Diseases* 1967 Aug; 20: 637-648.
[44] See Basbaum AI and Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annual Review of Neuroscience* 1984; 7: 309-338.
[45] At the time of the interview, John C. Hunter was a researcher at Roche Bioscience. As of 2015, he was Vice-President and Head of Pharmacology at Merck. See Jett MF, McGuirk J, Waligora D and Hunter JC. The effects of mexiletine, desipramine and fluoxetine in rat models involving central sensitization. *Pain* 1997 Jan; 69: 161-169.
[46] As of 2015, Søren H. Sindrup, MD, was Professor of Neurology at the University of Southern Denmark in Odense; Lars F. Gram, PhD, was Professor of Clinical Pharmacology at that institution, but as of 2015, had moved to Odense University. See Sindrup SH, Brøsen K and Gram LF. Antidepressants in pain treatment: Antidepressant or analgesic effect? *Clinical Neuropharmacology* 1992; 15 Suppl 1 Pt A: 636A-637A.
[47] As of 2015, Srinivasa Raja, MD, was Professor of Anesthesiology, Neurology, and Critical Care Medicine, and Director of Pain Medicine and Pain Research at Johns Hopkins School of Medicine.
[48] Gabapentin was initially synthesized to mimic the endogenous action of GABA, but is believed to be somewhat different in its effects, interacting with different receptors in the brain. It is used as an analgesic and anti-seizure medication.
[49] Cytochrome P450 2D6 is one of the enzymes encoded by the CYP2D6 gene. CYP2D6 and its enzyme products are responsible for the metabolism and elimination of about 25% of clinical drugs; individuals' ability to metabolize and benefit from specific drugs may differ because of genotypic or phenotypic variances. CYP2D6 is expressed in the liver and also in the nervous system.
[50] David J. Mayer, PhD, is best known as the lead author of a 1971 study documenting endogenous analgesia in the rat brain. (Mayer DJ, Wolfle TL, Akil H, Carder B and Liebeskind JC. Analgesia from electrical stimulation in the brainstem of the rat. *Science* 1971 Dec 24; 174: 1351-1354.) Dr. Mayer continued his pain research at the Medical College of Virginia for 30 years.
[51] Mao J, Price DD and Mayer D. Thermal hyperalgesia in association with the development of morphine tolerance in rats: Roles of excitatory amino acid receptors and protein kinase C. *The Journal of Neuroscience* 1994 Apr; 14: 2301-2312. As of 2015, Jianren Mao, PhD, was Vice-Chair for Research in the Department of Anesthesia, Critical Care and Pain Medicine at Harvard University School of Medicine and Director of the Translational Center for Pain Research at Massachusetts General Hospital.
[52] As of 2015, M. Catherine Bushnell, PhD, was Scientific Director of Intramural Research and Senior Investigator in the Pain and Integrative Neuroscience Branch (PAIN), at the National Center for Complementary and Integrative Health at NIH.
[53] The N-methyl-D-aspartate, or NMDA, receptor is a highly specific glutamate receptor that plays a significant role in controlling memory and synaptic plasticity.
[54] Patrick D. Wall (1925-2001), DM, was a leading British neuroscientist and pain researcher, best-known for his development of the gate control theory with Ronald Melzack in 1965. See: Melzack R and Wall PD. Pain mechanisms: A new theory. *Science* 1965 Nov 19; 150: 971-979. For more on Wall, see: http://www.oxforddnb.com/view/article/76148?docPos=8 .
[55] William H. Sweet, MD, DSc, (1910-2001), was Professor of Surgery at Harvard University School of Medicine and Chief of the Neurosurgery Service at Massachusetts General Hospital 1961-77. He developed the original PET scan technology in 1953 and the most frequently used surgical procedure for the treatment of trigeminal neuralgia; but is perhaps best known for his classic 1969 book with James C. White, *Pain and the Neurosurgeon: A Forty-Year Experience.*
[56] Seltzer Z, Dubner R and Shir Y. A novel behavioral model of neuropathic pain disorders produced in rats by

partial sciatic nerve injury. *Pain* 1990 Nov; 43: 205-218. 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.

[57] Butler SH, Godefroy F, Besson JM and Weil-Fugazza J. A limited arthritic model for chronic pain studies in the rat. *Pain* 1992 Jan; 48: 73-81. Jean-Marie Besson (1938-2014) was one of the leaders of European pain research. He was director of the Pharmacological Neurophysiology Research Unit at INSERM in Paris from 1976 and was known for his elucidation of the action of opiates at the spinal cord level and demonstration of the analgesic potential of deep brain stimulation.

[58] See DeLeo JA, Coombs DW, Willenbring S, Colburn RW, Fromm C, Wagner R and Twitchell BB. Characterization of a neuropathic pain model: Sciatic cryoneurolysis in the rat. *Pain* 1994 Jan; 56: 9-16. Joyce DeLeo, PhD, as of 2015 was the Given Professor of Pharmacology at Dartmouth Medical School. Dennis Coombs, MD, was an Anesthesiologist in the Department of Surgery at Dartmouth-Hitchcock Medical Center.

[59] Mary Ann 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.

[60] See note 29.

[61] Erik Torebjork, MD, PhD, was Professor of Clinical Neurophysiology at University Hospital in Uppsala, Sweden.

[62] Capsaicin is a chemical obtained from plants of the chili family, which produces a burning effect in animal and human tissues.

[63] 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.

[64] As of 2015, Robert H. LaMotte, PhD, was Professor of Anesthesiology and of Neurobiology at the Yale School of Medicine.

[65] As of 2015, Jose Ochoa, MD, PhD, DSc, was Director of the Oregon Nerve Center in Portland and Clinical Professor of Neurology and Neurosurgery at the Oregon Health Sciences University.

[66] 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 made many contributions to the understanding of pain mechanisms.

[67] Linda S. Sorkin, PhD, as of 2015 was Professor of Anesthesia at the University of California San Diego, where her research laboratory studies the pharmacological changes in the spinal cord following peripheral injury which alter sensory processing and pain perception.

[68] Ketamine is an NMDA-receptor antagonist that produces sedation and pain relief, while not affecting normal autonomic reflex activity; it is most often used to begin and maintain anesthesia.

[69] Reflex sympathetic dystrophy, or RSD, is characterized by persistent severe and disabling pain without apparent organic damage, usually in an extremity. Originally recognized as causalgia following high-speed bullet wounds by S. Weir Mitchell during the Civil War, the major causalgias were grouped with similar disorders in the 1940s under the term reflex sympathetic dystrophy. In 1993, these conditions were renamed Complex Regional Pain Syndrome (CRPS).

[70] As of 2015, Karen M. Park, MD, was practicing at the Michigan Pain Institute in Ypsilanti.

[71] As of 2015, Michael G. Byas-Smith, MD, was Medical Director of the Adler Center for Caring, a palliative care center and hospice in Northern Virginia.

[72] As of 2015, Navil Sethna, MC, ChB, was an anesthesiologist and pain medicine specialist at Boston Children's Hospital, and Associate Professor of Anesthesia at Harvard Medical School.

[73] As of 2015, Christine N. Sang, MD, MPH, was Director of Translational Pain Research at Brigham-Women's Hospital in Boston, and Assistant Professor of Anesthesia at Harvard Medical School.

[74] AMPA receptors and kainate receptors are both non-NMDA receptors that bind to glutamate in the nervous system. AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors mediate fast synaptic transmission, while kainate receptors are less well-defined, and may play a role in synaptic plasticity.

[75] Michael J. Iadarola, PhD, was Chief of the Neurobiology and Pain Therapeutics Section at NIDCR as of 2015; Robert C. Coghill, PhD, was Professor of Neurobiology and Anatomy at Wake Forest School of Medicine in North

Carolina as of 2015. Coghill was a frequent NIDCR collaborator during the period of the interview.
[76] Clonidine is an adrenergic agonist that acts on the central sympathetic nervous system. It has been used for many years to treat hypertension, ADHD, anxiety and some pain disorders.
[77] Eisenach JC, DuPen S, Dubois M, Miguel R and Allin D. Epidural clonidine analgesia for intractable cancer pain. *Pain* 1995 Jun; 61: 391-399. James C. Eisenach, MD, as of 2015 was Professor of Anesthesiology, Physiology and Pharmacology at Wake Forest College of Medicine in North Carolina; and editor of *Anesthesiology.*
[78] Dextromethorphan, a morphine derivative, is an active ingredient in many over-the-counter medicines as a cough suppressant and pain reliever.
[79] Mexiletine is an anti-arrhythmia medicine also used to treat intractable pain. As of 2015, it was not available as a licensed drug in the US.
[80] John J. Bonica (1917-1994), widely recognized as the founder of the pain field, was Chair of Anesthesiology at the University of Washington for much of his career. He edited the first edition of *The Management of Pain* in 1953, founded a multidisciplinary pain clinic at UW and convened an International Pain Symposium in Issaquah, Washington, in 1973, which catalyzed the formation of the International Association for the Study of Pain.
[81] Vittorio Ventafridda (1927-2008) was for many years Chief of Anesthesiology at the Instituto Nazionale dei Tumori in Milan, Italy, and later Director of the Palliative Care Unit. He was a leader in the pain and palliative care fields, a founding member of the International Association for the Study of Pain, and played a major role in the development and promulgation of the WHO Analgesic Ladder for Cancer Pain.
[82] Ventafridda co-founded the Floriani Foundation with telecommunications industry leader Virgilio Floriani in 1977; the Foundation funded many palliative care and research programs and gave early support to the development of the WHO Analgesic Ladder.
[83] This was probably the first of several meetings Ventafridda and Jan Stjernswärd (see note 84) organized at the Villa D'Este outside Milan, in October, 1982.
[84] Swedish oncologist Jan Stjernswärd (1936 -) became head of the World Health Organization's Cancer Unit in 1980 and began planning a major Cancer Pain Relief Initiative, which bore fruit as the WHO analgesic pain ladder. The ladder is a simple graphic metaphor for titrating pain medication to the patient's needs. The ladder was published in the WHO booklet, *Cancer Pain Relief,* in 1986, written by Stjernswärd and Robert Twycross; it would be translated into 28 languages and adopted worldwide. Stjernswärd continued his efforts to improve cancer care throughout his term as Director of the Cancer Unit, which ended in 1996, and as of 2015, was still active in global efforts in this field.
[85] John R. Searle (1932 -) as of 2015 was Slusser Professor of Philosophy at UC Berkeley, and is well-known for his work on the philosophy of language and of mind. John Langshaw Austin (1911-1960) was a British philosopher who developed the theory of speech acts, which argued that people use speech to do things, to act, not simply to make assertions.
[86] As of 2015, Charles S. Cleeland, PhD, McCullough Professor of Cancer Research and Professor of Medicine in the Department of Symptom Control and Palliative Care at the MD Anderson Cancer Center, affiliated with the University of Texas; he served also as Director of the Pain Research Group, and Director of the PAHO/WHO Collaborating Center in Supportive Cancer Care.
[87] George Heidrich, RN, MA, usually called "Rick," as of 2015 was a home health practitioner in Madison, Wisconsin and still active in the pain field.
[88] Robert Twycross, MRCP (1941 -), is a British physician and important leader in the palliative care field. He demonstrated the effective use of diamorphine (heroin) and other opiates in the care of dying patients at St. Christopher's Hospice in London in the 1970s, as a Research Fellow working with Dr. Cicely Saunders. He later became Medical Director of Michael Sobell House in Oxford and co-wrote *Cancer Pain Relief,* the WHO booklet which introduced the Analgesic Pain Ladder (see note 84), with Jan Stjernswärd in 1986. Twycross retired from active practice in 2001, but has continued to write and publish.
[89] As of 2015, Neil MacDonald is Professor of Palliative Medicine and Founding Director of the McGill Cancer Nutrition - Rehabilitation Program in the Department of Oncology at McGill University.
[90] The Sackler brothers (Arthur M. (1913-1987), Mortimer D. (1916-2010), and Raymond (1920 -), are three physician-entrepreneur brothers who have had significant impact on medical education and pharmaceutical manufacturing and marketing in the US. They purchased the small Purdue Frederick Company in 1952 and built it

into the powerhouse Purdue Pharma, weathering the Oxycontin crisis of the 2000s. Arthur Sackler founded the *Medical Tribune* in 1960 and turned it into an important medical and pharmaceutical opinion-shaping journal. The Sacklers have also been major philanthropists, endowing medical schools and museums in the US and abroad.

[91] Dr. Fumikazu Takeda was a neurosurgeon at the Saitama Cancer Center and Saitama Medical School in Saitama, Japan. He was one of the many physicians who participated in the field testing of the WHO analgesic ladder (see note 84).

[92] See note 84.

[93] David Joranson, MSSW, a Wisconsin social worker, co-founded the National Association of State Controlled Substances Authorities and the Wisconsin Cancer Pain Initiative, and helped to design a White House Conference on prescription drug misuse, abuse and diversion. In 1996, he founded and became the first Director of the Pain and Policy Studies Group (PPSG) at the University of Wisconsin-Madison, which developed the first systematic approach to evaluate and improve "balance" in federal and state drug control policies in order to prevent diversion and drug abuse from interfering in legitimate medical practice and patient care with opioid drugs. Joranson retired as director of PPSG in 2012, but continues work on special projects.

[94] The American Pain Society was founded in 1977. Its current guidelines on analgesia in cancer pain and in chronic non-cancer pain are available on its website at: americanpainsociety.org .

[95] Marilee Donovan, RN, was a pioneer in pain management at Kaiser-Permanente. As of 2015, she had retired and was living in Washington State, where she was active in promoting horsemanship.

[96] Donovan M, Dillon P and McGuire L. Incidence and characteristics of pain in a sample of medical-surgical inpatients. *Pain* 1987 Jul; 30: 69-78.

[97] That is, the Joint Commission on Accreditation of Healthcare Organizations, known as JCAHO, or simply "The Joint Commission," founded in 1951, which accredits and certifies more than 20,500 health care organizations and programs in the United States.

[98] As of 2015, Angela Meisner was an Epidemiologist in the Division of Epidemiology and Biostatistics at the University of New Mexico Cancer Center.

[99] Michel Foucault (1926-84), *The Birth of the Clinic: An Archeology of Medical Perception.* New York: Pantheon Books, 1973; Charles E. Rosenberg (1936 -), *The Care of Strangers: The Rise of America's Hospital System.* New York: Basic Books, 1987.

[100] Richard C. Cabot (1868-1939), an American physician and hematologist, pioneered the concept of social work in the outpatient department at Massachusetts General Hospital in 1905, hiring the first medical social worker and paying for the position himself. See RC Cabot, *Social Service and the Art of Healing.* New York: Moffatt, Yard and Company, 1909.

[101] Probably Von Roenn JH, Cleeland CS, Gonin R, Hatfield AK and Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. *Annals of Internal Medicine* 1993 Jul 15; 119: 121-126.

[102] Christine Miaskowski, RN, PHD, FAAN, was Professor of Physiological Nursing at the University of California San Francisco as of 2015 and a highly respected pain researcher.

[103] Sandra E. Ward, RN, PHD, FAAN, was Professor of Nursing at the University of Wisconsin-Madison as of 2015.

[104] Nessa Coyle, NP, PhD, as of 2015 was a nurse-practitioner on the Palliative Medicine Service at Memorial-Sloan-Kettering Cancer Center, with special training in the care of symptomatic advanced cancer patients and their families, and in end-of- life care.

[105] Marilyn Bookbinder, PhD, as of 2015 was Adjunct Associate Professor of Health Policy and Management at the NYU Wagner Graduate School of Public Service and Director of Quality and Performance Improvement at the Metropolitan Jewish Health System's (MJHS) Institute for Innovation in Palliative Care.

[106] Ada Jacox, RN, PHD, FAAN, has been a leader in the professionalization of nursing, nursing research and pain management and education throughout her career. As of 2015, she was Professor of Nursing and a research consultant at the University of Virginia.

[107] AHCPR, the Agency for Health Care Practice and Research within the US Public Health Service, was founded in 1989 and became AHRQ, the Agency for Healthcare Research and Quality in 1999. AHCPR published 19 clinical practice guidelines between 1992 and 1996, which are archived on its website at http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/archive.html . However,

pharmaceutical companies and others protested when some guidelines recommended reductions in the use of drugs and other conservative measures. More recently, AHRQ has become a clearinghouse for such guidelines published by different agencies and professional organizations. The Clinical Practice Guidelines for Cancer Pain Management were published as Jacox A, Carr D and Payne R. New Clinical-Practice Guidelines for the Management of Pain in Patients with Cancer. *New England Journal of Medicine* 1994; 330: 651-655.

[108] Daniel Carr, MD, MA, was Professor of Public Health and Community Medicine and Program Director of Pain, Research Education & Policy at Tufts University School of Medicine as of 2015.

[109] Robert T. Angarola, JD, (1946-1996), served as legal adviser to the International Narcotics Control Board, General Counsel to the White House Office of Drug Abuse Policy and Assistant Director of White House Domestic Policy Staff in the Carter Administration. As a Washington lawyer, he wrote and spoke extensively on drug and alcohol abuse, and on pain and drug policy issues.

[110] The State Uniform Controlled Substances Act, which has been adopted by all states, follows the Federal Comprehensive Drug Abuse Prevention and Control Act of 1970 in developing schedules to define controlled substances and restrictions on their manufacture, sale and use. The State Act was drafted in 1969 and disseminated by the National Conference of Commissioners on Uniform State Laws.

[111] Percocet is the trade name for an oxycodone/acetaminophen combination drug, marketed by Endo Pharmaceuticals and approved by the FDA in 1976. Percocet has been widely used for the relief of severe pain, but concerns over its abuse and addiction potential led to calls for reduction in prescriptions in the 2000s.

[112] See David Musto, *The American Disease: Origins of Narcotic Control.* 3rd edition. New York: Oxford University Press, 1999.

[113] Robert Ader (1932-2011) was an American psychologist and cofounder of the field of psychoneuroimmunology, which studies the links between the brain, behavior and the immune system. He was Director of the Division of Behavioral and Psychosocial Medicine at the University of Rochester until he retired in 2011, a few months before his death. For his work on placebos, see Ader R. The placebo effect: If it's all in your head, does that mean you only think you feel better? *Advances in Mind-Body Medicine* 2000 Winter; 16: 7-11.

[114] The Cochrane Collaboration is a global independent network of researchers, professionals, patients and providers that review, evaluate and disseminate the available evidence on health care products and practices to inform therapeutic choices. The Collaboration is named for British medical researcher Archie L. Cochrane (1909-1988), who in his very influential book, *Effectiveness and Efficiency: Random Reflections on Health Services* (1972), he stressed the importance and reliability of randomized controlled trial evidence as the basis for therapeutic practices. The first Cochrane Centre to review and evaluate evidence opened in Oxford in 1992 and The Cochrane Collaboration, a scheme to coordinate such efforts around the world, was founded the following year in 1993.

[115] Alejandro Jadad Bechara (1963 -) is a Columbian-born Canadian physician and Founder of the Centre for Global eHealth Innovation at the University of Toronto. As of 2015, he was Professor and Canada Research Chair of eHealth Innovation at the University.

[116] See note 41.

[117] Henry Knowles Beecher (1904-1976) was a pioneering American anesthesiologist who made significant contributions in pharmacology, analgesia, medical ethics, as well as his own field, during his 40-year career at Harvard University Medical School and Massachusetts General Hospital. His analgesia studies of the 1950s elaborated the concepts of "the reaction component" and the placebo effect. Louis C. Lasagna (1923-2003), who worked with Beecher as a Fellow, later became an internationally recognized expert on clinical pharmacology and proponent of controlled clinical trials to test the effectiveness of drugs. He held several academic posts and completed his career as dean of the Sackler School of Graduate Biomedical Sciences at Tufts University.

[118] As of 2015, Gerald Gebhart, PhD, was Professor of Anesthesiology, Medicine, Neurobiology and Pharmacology and Director of the Center for Pain Research at the University of Pittsburgh.

[119] In 1976, researcher John Daly at the National Institute of Diabetes and Digestive and Kidney Diseases isolated a toxin from the skin of an Ecuadorean "poison dart" tree frog that resembled nicotine in structure and was found to be a powerful non-addictive analgesic. This substance was named epibatidine. At therapeutic doses, epibatidine unfortunately has high toxicity, causing hypertension, paralysis and possibly death. Work as of 2015 was continuing to try to identify a less toxic derivative.

[120] Jacob "Jack" Kevorkian (1928-2011) was an American pathologist and right-to-die activist, who became

notorious after he claimed to have assisted some 130 patients to commit suicide to avoid natural deaths which they believed would be painful and lingering.

[121] Edward Kennedy "Duke" Ellington (1899-1974) was an African-American pianist, composer, recording artist and bandleader. He had a significant influence on the development and popularity of jazz throughout his career. Ellington's Cotton Club Orchestra initially formed in Harlem in the 1920s and played under his leadership until his death.

[122] George Soros (1930 -) is a Hungarian-American business investor and philanthropist who, as of 2011, had given more than $8 billion to human rights, public health and education causes. His donations played a significant role in easing the transition of Eastern European countries from communism to capitalism in the 1980s and 1990s. As of 2015, Soros remains the guiding head of the Open Society Foundations, which he founded in 1984. He founded the Project on Death in America with Kathleen Foley in 1994.

[123] Christine K. Cassel, MD, is a leading American expert on geriatric medicine, medical ethics and quality of care. As of 2015, she was the President and CEO of the National Quality Forum, a Washington-based organization that seeks to facilitate the improvement of health and healthcare quality through measurement and national collaboration. Dr. Cassell is also a member of President Obama's Council of Advisors on Science and Technology.

[124] Ondansetron was developed by Glaxo-Smith-Kline in the 1980s and approved by the FDA in 1992 as Zofran. It is a serotonin receptor antagonist used to reduce nausea and vomiting caused by cancer chemotherapy and radiotherapy. As of 2015, it was available as a generic drug.

[125] As of 2015, Eduardo Bruera, MD, an Argentinian-born physician was of Palliative Care and Rehabilitation Medicine at the University of Texas MD Anderson Cancer Center in Houston.

[126] The periaqueductal gray in the midbrain is the primary cortical control center for pain modulation. This was the area where Mayer and colleagues found endogenous analgesia in 1971 (see note 50).

[127] Wind-up refers to exaggerated neural responses to stimuli.

[128] As of 2015, Norman Latov, MD, was Professor of Neurology and Neuroscience, and Director of the Peripheral Neuropathy Clinical and Research Center at Weill Cornell Medical College in New York.