LOUIS LASAGNA INTERVIEW

TAPE ONE, SIDE ONE

MARCIA MELDRUM: Good morning.

LOUIS LASAGNA: Good morning. [he laughs]

MELDRUM: It's Friday, September the eighth, 1995. We're here in the Dean's office at the Sackler School of Graduate Medical Biomedical Sciences, right?

LASAGNA: Right.

MELDRUM: In Boston, talking to Dr. Louis Lasagna, and I'm Marcia Meldrum, the interviewer. Dr. Lasagna, I'd like to begin by asking you to tell us a little bit about how your career got started, about what led you to choose medicine and particularly a specialty in pharmacology.

LASAGNA: Well, I think as a kid I always considered only several careers. One was being a teacher; the other was being a lawyer, and the other one was being a physician. And I think I was attracted to the physician, primarily because of the romantic aspects of Dr. Kildare movies where he always seemed to be doing good, surrounded by gorgeous nurses [he laughs], and so forth, and it looked like it would be a career that would be enjoyable as well as useful. Pharmacology became an interest of mine because, of all the basic sciences I had at Columbia College of Physicians and Surgeons, pharmacology seemed to me the one that was the closest to the bedside. And I also sensed, correctly in retrospect, that a lot of what was being done in the way of research left a lot to be desired. And it seemed to me wonderful if one could get to use drugs in an optimal fashion. So that's how I got started.

MELDRUM: And you trained initially at Rutgers and then at Columbia?

LASAGNA: I took my bachelor's degree at Rutgers and then went to Columbia Medical School.

MELDRUM: Any particular reason for choosing Columbia?

LASAGNA: I think it was because I was born in New York and I enjoyed being in New York, and I thought on those occasions when I had some free time and I'd want to go to the theater or what have you, that would be the place to be. [he laughs] The only other place I considered was Philadelphia. Got admitted to both of those, and I decided to go to New York.

MELDRUM: I see. And then you did your residency at --

LASAGNA: [he coughs] I did my internship at Mount Sinai Hospital in New York and then I went to a hospital called [Moses] Maimonides --

MELDRUM: Ah, yeah, I remember that.

LASAGNA: In Brooklyn. I was the assistant resident in medicine, then chief resident in medicine. Then, there I went to [Johns] Hopkins to do post-doc because my boss, a man named David Seegal, S-E-E-G-A-L, had worked with some of the folks during the war on the malaria project and told me that if I wanted to become a clinical pharmacologist, I should go to Hopkins because I was starting a new year. And so I went down there, interviewed for the job, got it, spent two years there and then went to work with [Henry Knowles] Beecher for two years before going back to Hopkins. The way that came about was that -- maybe my best friend, or at least one of my two best friends in high school and college was a man originally named Arthur Katz, who then became Arthur Keats.

MELDRUM: Oh, really? [she laughs]

LASAGNA: K-E-A-T-S. And I met him one day on the boardwalk in Atlantic City during the so-called spring meetings and he told me about this exciting stuff they were doing, which was trying to quantify subjective measurements, and the more I heard about it, the more excited I became. So he introduced me to his boss, Harry Beecher, who then proceeded to get me assigned to them to carry, help carry out, an Army project. I wouldn't be -- [microphone feedback] I owed the Armed Forces some time because I'd gone to medical school in the B-12 program with the Navy and then I switched over [when] the war ended to the Public Health Service and was planning to go to the NIH to spend my time there. But Beecher got the Army to request that I be detailed to work on this cloak-and-dagger project.

Beecher was a very dramatic character. He'd come back, for example, in this instance from Europe with stories about how the Russians were building not one but two factories beyond the Urals to manufacture LSD [lysergic acid diethylamide], which would then be popped into the drinks of our diplomats and generals and so forth and help the enemy take over the world. And so he got a contract to work on whether hallucinogenic or other drugs might allow one to probe into the secrets of one's mind. So there were silly experiments like getting volunteers to come and telling them, "Now, under no circumstances should you tell us your mother's maiden name, or your whatever," and then we'd give them a drug and then we'd ask them a number of questions, and one of them would be, "What is your mother's maiden name?" [he laughs] It was silly, and I ended up not doing anything with that. It was all done by a psychologist named [John M.] von Felsinger with whom I published, but it got me there; it was a cloak-and-dagger project [he laughs].

We used to send reports to the Pentagon using an armed courier who would come with a briefcase [he laughs] handcuffed to his arm, with a sidearm. And it was kind of silly. But it got me there, and while there, I was able to work on pain and sleep and subjective response. It was really very exciting because it was the opening up of the subjective response quantification. Prior to that, people had said, "Well, how can you study pain? It's all so sort of subjective and you can't make any sense out of it." And Beecher led the way, and you know, and then that was followed by measuring anxiety and depression and all the things that we take for granted today, but which were not taken for granted in those days.

MELDRUM: Which had not been done previously.

LASAGNA: Yeah.

MELDRUM: Okay. So maybe we could talk a little bit about that.

LASAGNA: Yeah.

MELDRUM: I've certainly heard many stories about Harry Beecher. He was a very dramatic man to work with. Arthur Keats was also there --

LASAGNA: Yeah.

MELDRUM: And --

LASAGNA: Well, he left when I – before I got there.

MELDRUM: I see.

LASAGNA: So I sort of succeeded him, in a way.

MELDRUM: You sort of followed Keats.

LASAGNA: But Keats played a key role. Have you interviewed Keats?

MELDRUM: No, but we want to.

LASAGNA: Yeah. He played a key role, I am sure, in working out the details of the original approach. There was also a woman named Denton --

MELDRUM: Jane Denton.

LASAGNA: Jane Denton. And she preceded Keats, I think, or they were there simultaneously. I don't think I ever met her. Beecher was a big enthusiast, as I recall, for the notion that pain resulted from the sort of physiologic perception of noxious stimuli attacking the body, and then there would be a reaction to those perceptions, and that together, those two things together constituted the pain experience. And he wrote this article about how soldiers on the Anzio beachhead, when they were wounded, seemed not to want pain relief or ask for it the way civilians would, and Beecher's dramatic explanation for that was, "Well, it was for them a ticket home away from the front." So it wasn't an ill; it was a good and that was sort of typical of Beecher's flair for the dramatic.

When he got into the informed consent business, for example, despite the fact that we never got consent from anybody – he sent me the draft -- I had sent him some references because he tended to read the anesthesia literature and not much else. So when he sent me the draft, I said, "You know, Harry, it has [not] been traditional for people to talk about informed consent in

manuscripts." I said, "Maybe some of these folks actually asked for consent, got it, and then just didn't put it in the manuscript." And he said, "No, if they got it and didn't put it in the manuscript, it's as bad as if they didn't get it at all," which, you know, [he laughs] persuaded me that Harry didn't want to interfere with a good story by [he laughs] inserting the truth. We had the advantage of working statistically with Fred[erick] Mosteller; he's still around. Have you interviewed him?

MELDRUM: Mm-hmm. Yeah, we're planning to interview him also.

LASAGNA: Yeah. Fred was then, as now, capable of being underestimated because he came on like a Midwest farmboy. And beneath this farmboy exterior was this [he laughs] steel trap of a brain. But he kept us honest with regard to statistical analyses. He was on partial pay from Beecher and was a paid consultant.

MELDRUM: Right.

LASAGNA: I guess the only thing I published with him was that placebo paper.

MELDRUM: The placebo paper, yeah. Now, when you arrived, that was in 1952?

LASAGNA: Mm-hmm.

MELDRUM: They'd already begun working with the crossover method?

LASAGNA: Yeah, you know, I don't --

MELDRUM: You don't remember?

LASAGNA: I remember that we did a lot with crossover.

MELDRUM: Oh! [she laughs]

LASAGNA: I seem to remember that we weren't using crossover because unlike [Raymond W.] Houde's work, Houde with [Stanley L.] Wallenstein's work at Memorial, where they had patients with chronic pain – [we had] post-operative pain, because it was rapidly disappearing; and so crossover seemed to, at least intellectually, to be less attractive and it's interesting that with the passage of time, mostly it's noncrossover studies these days.

MELDRUM: Yeah.

LASAGNA: And the theory was attractive in that the same person's evaluation of pain ought to have some utility in improving the precision and the efficiency of your studies. But I don't remember that we did a lot of crossover. I do remember that we didn't do randomized stuff. I would, for example, alternate. I would put the patient, Number One, on Drug A and Patient Number Two --

MELDRUM: Number Two.

LASAGNA: -- on Drug B. And we, as I say, we never got consent. We just had technicians interviewing them. We assuaged our guilt somewhat by saying that, "Well, our patients were better monitored than those who were not in our studies, and if they weren't getting adequate relief, they could ask for something and get it." Whereas traditionally, in hospitals, you had an order written for Q3H or Q4H [every three hours or every four hours], and God forbid you should get another dose before [he laughs] the time elapsed.

MELDRUM: Between times, yeah. For sure.

LASAGNA: The blinding was done in the pharmacy, as I remember, and the materials were usually prepared at the Massachusetts General Hospital pharmacy.

MELDRUM: So I mean, you sort of selected the patients you wanted that were coming out of post-op, or --

LASAGNA: Yeah, I would go see them ahead of their surgery, as I remember and write orders for them.

MELDRUM: Okay. When you saw them, did you explain the study to them?

LASAGNA: No. No.

MELDRUM: Or you just said, "We're going to be giving you – "

LASAGNA: We were completely insensitive to the notion that people should be asked [he laughs] about participating in the study.

MELDRUM: Mm-hmm.

LASAGNA: And it wasn't, you know, it wasn't really that we thought about the downside of asking them, you know. "Maybe some of them will say no," and so forth. We were just so insensitive to the ethics of it. And I think this was sort of traditional. We were doing what everybody else did. And in retrospect it's – I'm ashamed of it.

MELDRUM: Well –

LASAGNA: But –

MELDRUM: Thinking has changed a lot –

LASAGNA: Yeah.

MELDRUM: Since that time.

LASAGNA: Yeah. Yeah. It just wasn't, you know, at that level of consciousness.

MELDRUM: You were operating on a different ethic.

LASAGNA: Yeah. Yeah.

MELDRUM: A sort of experimental –

LASAGNA: Beecher would also say [he laughs] that our patients got treated better than the patients on the private service, because as you looked at how much morphine they got, they got much more than our patients did. And he used to say it wasn't right that the rich should get treated better than the poor, but they shouldn't be treated worse than the poor. Let's just say that no wonder they had captious appetites and so forth. They had nausea and vomiting from too much morphine.

MELDRUM: Okay. So there wasn't really an opportunity to use crossover because the patients were in the hospital for a short time and after the operation their pain would begin to decrease naturally.

LASAGNA: Right. Right.

MELDRUM: At least we hope so. So tell me a little bit then about the techniques they were using to sort of counter subjectivity.

LASAGNA: Well, you never counter subjectivity; you're attempting to quantify it.

MELDRUM: Okay.

LASAGNA: You know, we'd ask patients to describe their pain and give it some level of mild, moderate, or severe. And then we'd go back periodically – when I say "we," the technicians would – and ask the questions again. We'd ask about relief of pain: "Have you had--" "Is your pain any better?" I can't remember exactly what we were using in those days, but they were fairly primitive questions like that. And then we would measure pain relief on the basis of these changes in scores, arbitrarily giving severe pain a number and moderate pain a lesser number, and so forth.

And I think it was shortly after I left there, that I did a study which I think I published in maybe the *Annals of the New York Academy of Sciences*, I remember, where I went and asked patients, where they would put severe, moderate, slight, very severe on this -- on a scale from zero to ten or zero to a hundred. And I also asked them, what would they be most grateful for, a drop from very severe to severe, severe to moderate, moderate to slight, slight to zero. And the results were all over the map. Mostly people were grateful for a drop from severe to moderate, but there would be some who would say, "No, the mild to zero would be the best," because complete disappearance of pain was desideratum. And also they put their marks on the scale in different places. So that convinced me that you were always going to be stuck with individual judgments about how bad something was and where they would mark a scale and so forth.

MELDRUM: Yes, that's very interesting.

LASAGNA: With the passage of time, things have obviously gotten more complicated, in the sense that in those days we studied pain in patients that were available to us on an in-patient basis, because we realized that there would be problems on an out-patient basis in getting the measurements done and getting the medications taken correctly and so forth. So there was a lot of, I think, wishful thinking that if you studied post-operative pain and cancer pain, for example, you could generalize to all kinds of pain. And with the passage of time we realized that that was really a primitive notion, and with the advent of drugs, for example, that are much better than the old drugs for treating dysmenorrhea, we realized that that class of pain doesn't respond the way other classes of pain do.

Headache is obviously a complicated business; migraine and non-migraine and so forth. And it's a pity in some ways that some of these things weren't studied earlier. Headache, for example, didn't get around to being studied for years after we started in pain and that was largely because, as I say, if you were going to do it in the hospital, you went to the surgical service because that's where the pain was. And then, later on, we developed the – well, I shouldn't say "we" – people in the dental field developed the post-dental surgery for impacted wisdom teeth [an experimental model] which has turned out to be very useful, too. So it's gotten more complicated, and it's interesting these days, if you want to get an over-the-counter drug, with claims for different kinds of pain, you've really got to study the different kinds of pain. The FDA [Food and Drug Administration] will not let you say "good for anything." If you want to claim that it's good for dysmenorrhea, you've got to study dysmenorrhea.

MELDRUM: You have to do the study in dysmenorrhea, yeah. Um, but ambulatory studies have their own problems.

LASAGNA: Yes, they do. Yeah. And a former colleague of mine and student of mine, Mike Weintraub, heads the OTC [over-the-counter drugs] division at the FDA now; and he's moving towards asking them to get more naturalistic studies of over-the-counter drugs, you know, what happens in real life when you have people without any screening, with whatever, and they take these medications. And it's a pity that we don't have more naturalistic studies, because the clinical trials, randomized clinical trial, while wonderful for giving you reliable information on whether you have a drug that's worth studying, is such a hothouse approach to life with, you know, screened patients and informed consent and fairly expert researchers – and then the drug is marketed. Everything changes. You have unscreened patients, physicians of varying talents and experience, multiple drugs often being involved, multiple diseases –

MELDRUM: Yeah. Yeah. That gets very complicated.

LASAGNA: Every reason in the world why the performance might be different from what you'd seen in the hothouse.

MELDRUM: In the real world. Yeah.

LASAGNA: The randomized, controlled clinical trial was just beginning to get rolling in the late forties in Britain with the streptomycin trials, and then, later on, Beecher was a big advocate for that. I'd gotten interested in that also, because when I was a medical student I'd read the Cornell Conferences on Therapy, which were edited by a man named Harry Gold, who was a pioneer in this area as well. And I became interested in placebo reaction and the importance of blinding and so forth.

Walter Modell, who was the first editor of *Clinical Pharmacology and Therapeutics*, and I were, I think, the key witnesses during the sixties leading up to the Kefauver-Harris Amendments, the Food and Drug Act of 1962, in pushing for randomized controlled trials as being a necessity if you're going to approve a drug. And in retrospect, I don't feel sorry about that, but in recent years I spent a lot of my time trying to convince people that the world doesn't begin and end with randomized controlled clinical trials; and that [Austin] Bradford-Hill, the statistician who was the sort of statistical father of controlled trials, back in the forties in Britain, said about thirty years ago, "The controlled clinical trial doesn't tell the doctor what he'd like to know, which is, what does this patient require for optimal therapy, and what does that one? Don't tell me on an average; don't tell me about the herd phenomenon; tell me about the individuals in the herd." And we still do a dreadful job of that.

MELDRUM: Yeah.

LASAGNA: And the goal of therapeutics ought to be individualization, not homogenization and yet we've done very little in that regard.

MELDRUM: Right. And so you think the RCT, the increased use of RCTs, does tend toward this homogenization of treatment?

LASAGNA: Yeah. I think it makes people say, "Well, the important thing is for us to show that on average, if a hundred patients get treated with this drug and a hundred patients get treated with a placebo, the patients treated with the placebo, on average, are better off. And that's all we need, provided there's a significant difference, I mean a biologically significant difference as opposed to a statistically significant one, that's all we need to know." And that just isn't good enough. And the trouble is that up until now, that's been enough to get a drug on the market. You don't have to do any more than that.

MELDRUM: Yeah. Yeah. Let's, let's go back just a little bit –

LASAGNA: Yeah.

MELDRUM: And talk more about the placebo response. Certainly you noted this response –

LASAGNA: Yes. Yes.

MELDRUM: And there was at least one or two very interesting papers came out, which noted that some people responded to placebos almost all the time, and some other people responded [she laughs] some of the time, inconsistent placebo reactors.

LASAGNA: Yeah. Yeah, I think when we published that first paper, I was looking for ways of discriminating between people who would respond and people who would not. And I do believe there is something in that notion, that is, that people aren't all susceptible to the suggestibility that's involved in placebo response. On the other hand, the more I've thought about it, the more I've worked with it, I've decided that it's always going to be variable and that it's probably wrong, I think, if somebody is consistently a placebo reactor and somebody else is consistently not.

I also realize with the passage of time, that the placebo effect, whether you're talking about a desirable effect or an undesirable effect, like a reported side effect which isn't for real, as it were, but that there are two components to those reports. One is suggestibility, anticipation, whatever you want to call that part of it. And the other one is spontaneous change. If your pain is going to go away anyway, like in my case, headache, I rarely, if ever, have a headache that lasts for a whole day, let alone days on end, and if I don't take anything, the headache goes away anyway. And that isn't suggestibility; that's spontaneous change.

MELDRUM: Mm. Right.

LASAGNA: And the reason we, we don't know about that is that we hardly ever -- I've done it once in my life -- do a study where some patients get a placebo and some patients don't get anything.

MELDRUM: Not anything.

LASAGNA: And when we did that with the first sleep study I ever did –

MELDRUM: Mm. Right.

LASAGNA: We found out that about two-thirds of the patients fell asleep in less than an hour when they got placebo; two-thirds fell asleep in less than an hour when they got nothing.

MELDRUM: Right.

LASAGNA: Just interviewed the next day. And it's a pity that to this day people act like placebo is always suggestibility. I mean, this, when I talk to my students, I say "Now, for example, if you want to get this concept clearly in mind, think of the following. Suppose you were foolish enough to ask the question, 'Will a placebo keep people from dying from the common cold?' You do your study; you find out that a hundred percent of them are protected from death. But it isn't that the placebo has talked them out of dying, it's that they wouldn't have died in any case." [both laugh]

But when I did another study which I don't think I ever wrote up at the Baltimore City Hospital there -- again there was a feeling that placebo reactors were people who had more confidence in the system, who were more positive about drugs, were ardent churchgoers –

MELDRUM: Right. Right.

LASAGNA: And so forth. So I think that, you know, clearly, just as different people are not equally susceptible to the approaches of an insurance salesman and can be sort of talked into things, so people, I think, are going to differ with what they expect to have happen to them. But with the advent of informed consent and the leveling with people about what may happen to them, I think you tend to mitigate the anticipation, the phenomenon.

MELDRUM: Right.

LASAGNA: As a matter of fact, you -- we may be undercutting the therapeutic performance of treatments by implanting doubt –

MELDRUM: Right. Yes.

LASAGNA: In the mind of patients.

MELDRUM: People will be more wary.

LASAGNA: Yeah. Yeah.

MELDRUM: Okay. In terms of the different, the use of different scales for pain measurement -- you commented on that just a few minutes ago –

LASAGNA: Yeah.

MELDRUM: With quite -- that was quite interesting.

LASAGNA: Yeah.

MELDRUM: Beecher's original scale was, they asked the patients if fifty percent of their pain was relieved, and the patient said yes or no. And the results were reported as simply the percentage saying that their pain had been relieved versus the percentage [unrelieved]. And then, later, Houde and Wallenstein, and you yourself, did several studies in which the patients responded with severe, moderate –

LASAGNA: Yes.

MELDRUM: -- or whatever, and then numbers were assigned --

LASAGNA: Right. Right.

MELDRUM: -- to those. You felt that -- What -- [she laughs] -- So I'm just sort of interested in that why you decided to use this method and if you feel there are any advantages in -- if this quantification has some – does improve our knowledge about pain --

LASAGNA: Yeah. Well, I --

MELDRUM: And analgesia.

LASAGNA: I think I was attracted to it originally because I thought that there probably was a difference to fifty percent relieving pain, if you had very severe pain or moderate pain to begin with; and that was part of my reason for wanting to stratify pain in that way so that you could at least retrospectively look back and see, well, how did things look when you just looked at the patients that had mild pain or moderate pain or severe pain or very severe pain? And I think doing that, we began to realize that if you study patients with mild pain, it was hard to distinguish anything from anything else because of the placebo response and spontaneous experience, remission, and so forth.

So it's interesting that even for over-the-counter drugs that are labeled "to be used for mild to moderate pain," they would get on the market because of studies done in patients with moderate to severe pain the idea of being that, well, that's how you distinguish, you know, and if it works for moderate to severe pain, then it probably should work for mild –

MELDRUM: Mild pain as well.

LASAGNA: To moderate pain. So that was part of it. In retrospect, I think that it was a mistake in some ways, to move away from Beecher's approach, which was sort of a global approach. You may remember that you not only had [to have] a 50% drop in your pain, but it had to stay there for a period of time.

MELDRUM: That's what I -- Yeah.

LASAGNA: And that's not a crazy notion--

MELDRUM: No.

LASAGNA: It's even less crazy if you ask questions of a patient at the end like, "What did you think of this pain relief?" where they might be lumping together benefit and side effects, giving you a distillation of what, you know, and in the long run, that's what you'd like to know, is what do patients think of this, as they weigh the benefits against the harm of a medication? Is medication A better than medication B or not? And you do complicate things by asking them just in that way because it might be -- I'd find out in some of my sleep studies, that a patient might describe an experience as dreadful, despite the fact that they went to sleep promptly and stayed asleep all night long. Why? Because it seemed like sort of chemical rape.

MELDRUM: Hmm. Right.

LASAGNA: "I don't like a drug that overpowers me."

MELDRUM: Yeah.

LASAGNA: And I guess now I would say that what we ought to be doing is measuring pain relief, measuring side effects, but also asking sort of global questions about, "What did you think of this medication?" at the end. And that's tended not to be done over the years, but it's beginning to be a bit more--

MELDRUM: A bit more.

LASAGNA: -- in recent years.

MELDRUM: Right.

LASAGNA: Also, you know, the reason I did that study about asking people how grateful they would be for drops -- there's always been the assumption that a drop from severe to moderate was the same as the drop from moderate to mild.

MELDRUM: Yes. Yes.

LASAGNA: And that's why I did this study.

MELDRUM: Mosteller raised that question, too.

LASAGNA: Yeah.

MELDRUM: And we -- Do we know the answer to that --

LASAGNA: [he coughs] No, we don't. We don't. Yeah, in some ways, you might say, "You ought to ask patients before you do the trial about how they interpret these drops." Then finagle with the scores, weighting them differently for each individual patient, because nobody's ever done that. Maybe it's just too impractical to do.

MELDRUM: Yeah. It would be difficult.

LASAGNA: Yeah. I mean, you know, actually, you think about it, it isn't easy to answer that question. If I say to you, "What are you more grateful for -- a drop from severe to moderate, or moderate to slight, or slight to zero?" you know, you might say, "What the hell kind of a crazy, God-damned question is that?" [he laughs] I was consulting with a guy with regard to protocol the other day, and, and they had severe, moderate, and mild. Then they tried to transmute this into words. And the words were just gobbledygook, like "mild" was something that -- "that changes my disposition but doesn't make me want to do something urgent," or something.

I said, "Look." I can understand if the words were something like, "mild" is something where I don't feel badly enough that I want to take a medication. "Moderate" is something where I do want something, and "severe" is something where I do want it immediately, I'm not going to delay this. But it's hard to transmute these terms which seem so simple into words; what do you mean by that? And, as I say, if you give people a score, a scale, and say, "Where on the scale would you put severe? Or moderate?" people vary quite a bit in whether they pick 80 or 50 or

60. In a way, it's amazing that things work as well as they do, in view of this inherent individuality.

MELDRUM: It is interesting. Well, one of the things you did with Beecher, then, was to work on narcotic antagonists.

LASAGNA: Yeah. The -- what happened there was that nalorphine had come along, and that was acknowledged to be an antagonist, but nobody had any idea that it was also an agonist. And we did a study originally, because we were hoping that if you come out with some magical ratio of morphine to nalorphine, you might lose some of the bad effects. And we didn't care what bad effects we lost, whether it was the nausea or the vomiting or the dizziness just so long as we were moving in the right direction, or less likely to be abused and so forth. And when we set up the trial, we used a couple of ratios, and then I said, "Well, we've got to have the nalorphine by itself." I had no idea that it was going to be an analgesic, and it turned out, to my great surprise, to be an analgesic. And that was the start of the search for mixed agonist-antagonists. And when pentazocine and some of the other drugs came along, that was really attributable to this --

MELDRUM: Nalorphine.

LASAGNA: -- study, this sort of serendipitous stumbling on the fact that it wasn't a pure antagonist; it was an agonist type.

As a matter of fact, I think that naloxone, which is ordinarily thought to be really a pure antagonist, probably is also the same thing. I did a study with that some years ago where, as you went from one to two milligrams, and then we were always comparing it against morphine, it looked like you were moving toward morphine's effects. Then, when you went up to five and eight, things got worse. And eight was the highest dose I studied. Nobody got any pain relief, and actually people would talk about their pain being worse as if we'd given them an algesic compound, not an analgesic. And I interpreted that, due to the fact that that you were maybe under the stress of the post-operative situation, mobilizing your own endorphins, and if you had something that antagonized your own endorphins--

MELDRUM: Endorphins. Ah.

LASAGNA: It made things worse for yourself. [he laughs]

MELDRUM: Yeah.

LASAGNA: But, anyway, that's the story of the narcotic -- the agonist-antagonists. By the way, our work was mostly supported in Beecher's lab by, as I remember, grants from the National Research Council [NRC] Committee on Drug Addiction and Narcotics, as it was then called. And the candidates would come from industry and we'd pick whatever we wanted to study and we'd study it.

MELDRUM: And there was a search going on at this time to find an effective non-narcotic analgesic.

LASAGNA: Yes. It had started maybe back in the '20s with Nathan Eddy and I forget who else. And it had been, it had been a goal for a long time to come up with a nonaddicting substitution for morphine. That was really what drove us.

MELDRUM: Mm-hmm. Morphine, I'm always reading studies in which they say that basically morphine is still the best [drug] available for severe post-operative and cancer pain.

LASAGNA: Yeah.

MELDRUM: And so that search has never really been –

LASAGNA: [he sighs] The only, I think, the advances we've made are there are some nonsteroidal anti-inflammatory drugs [NSAIDs] which, when given by injection, look almost as good as morphine.

MELDRUM: Really?

LASAGNA: I haven't done the studies myself. But they look like close to achieving the goal and they certainly are devoid of many of the --

MELDRUM: Side effects.

LASAGNA: Adverse effects of morphine. And they're not abusable and so forth. And that came out of a search for not morphine substitutes, but aspirin substitutes.

MELDRUM: Mm-hmm. Yeah.

LASAGNA: So I think we -- That, I would say, was much more important than all the other stuff we did, because all the other drugs that we studied, and some of them made it to the market, were really not much different from either morphine or nalorphine. We learned a lot about our misconceptions.

For example, when I started out, there was this notion that the morphine molecule was sacrosanct, and if you nibbled away at this piece or that piece of the oxygen bridge, what have you, that then you would destroy the potency. And what happened was that as you studied little bits and pieces of the molecule, sometimes you actually had a more powerful drug, in terms of milligram per milligram potency. So the studies were good in the sense that they forced us to realize how wrong we'd been in our theoretical speculations. [he laughs] Shouldn't be a total loss!

MELDRUM: [she laughs] You did get some information.

LASAGNA: Right.

MELDRUM: Let me -- The main problem that you perceived, that you personally perceived with morphine, I mean, it does have side effects --

LASAGNA: Yeah.

MELDRUM: There's also a concern about addiction liability.

LASAGNA: Yeah. Yeah. Actually, to me, the major drawbacks were the –

[PAUSE TO CHECK MICROPHONE]

MELDRUM: Okay.

LASAGNA: Okay. Were the nausea and vomiting and dizziness and so forth that patients had. And my experience in the hospital world was that you rarely produced addicts from the legitimate use of morphine. So for me, the goal was always, or most of the time, anyway, not a nonaddicting drug, but a drug that was free of respiratory depression, free of nausea and vomiting, free of anorexia-producing effects, and so forth. I think that's what patients, even to this day, want.

MELDRUM: Yeah. Well, right.

LASAGNA: [he laughs]

MELDRUM: Okay. You were with Beecher for two years.

LASAGNA: Two years.

MELDRUM: And went back to Johns Hopkins.

LASAGNA: Right. He wanted me to stay on. He sort of hinted I could succeed him as the Henry Isaiah Dorr Professor [of Anesthesiology]-- that's a ridiculous notion that he could pick his own successor -- but I never wanted to be an anesthetist. That was the most boring way to take care of the sick. Beecher was a practicing anesthetist. Every day he was in Boston he would do at least one case. He wasn't an especially skillful anesthetist, but it -- partly he did it because his salary was determined in part by how many patients he saw.

MELDRUM: Yeah.

LASAGNA: So I went back to Hopkins to head up the Division of Clinical Pharmacology. I think that was while a man named Gordon Zubrod, who then went to the National Cancer Institute, had sort of started it. He never really got it rolling because he was required to work in a clinic for the indigent to earn his keep and so forth. So I really started in earnest the first Division of Clinical Pharmacology anywhere, and began training people, as well as doing research and moved into many other areas besides analgesics.

MELDRUM: Mm-hmm. Yeah, and I wanted you to comment, talk a little bit about your work during this period, because if you look at the published work, you were certainly involved in many different kinds of drugs.

LASAGNA: Right.

MELDRUM: And, presumably, some of these were studies with students –

LASAGNA: Mm-hmm.

MELDRUM: And people who were working with you. I just -- What -- Could you sort of categorize your work in that period? What was interesting you? What kind -- What was the uppermost goal of what you were doing, or -- ?

LASAGNA: Well, I think mostly I was trying to study drugs rationally and to train people to study drugs well. And exactly what I would do at any time was determined in part by who was working with me and what interests they had. Like if I had somebody who was interested in hypertension, so we would do an hypertensive study. But then also what compounds, investigation compounds came my way from the drug industry.

MELDRUM: Mm-hmm. So most of these were coming from the drug industry.

LASAGNA: Yes. Yes. So, if I had colleagues in psychiatry who wanted to study a new tranquilizer, or an old tranquilizer to modify its effects, we would move into that area. And in some ways, you're going to accuse me of having been a dilettante, but I thought it was more fun to just follow your nose and study whatever seemed interesting to study. I mean, I still remember when chlorpromazine came along. I went to meetings and they'd have all these descriptions of what it would do, different things, different effects, and I thought, "Jeez, this sounds crazy!" But with the passage of time, as we studied, we realized that, by God, you know, it wasn't a perfect drug for schizophrenia, but it did have an impact; and antidepressants, the stimulants for -- that help children with attention-deficit disorder and so forth -- Oh, and then the field of oncology; Zubrod, having gone to the NCI, wanted to start clinical trial groups, and we were the first group of what's now called the Eastern Cooperative Oncology Group. I don't remember what we called it back when we started. But the whole idea there was to develop a rigorous method for evaluating drugs.

MELDRUM: Right.

LASAGNA: So I think the sort of methodological aspects of it were always an attraction for me. And now that we are asked to study anxiety or schizophrenia or what have you, how do we do it?

MELDRUM: Yeah.

LASAGNA: What skills do we use? And what safeguards are required? And so forth.

MELDRUM: Mm. That is very interesting. What do you think is the major contribution of the Beecher group's work on analgesic trials?

LASAGNA: I think the major contribution was just convincing people that you could quantify subjective responses. You know the book that he wrote on the subjective response [*The Measurement of Subjective Response*, 1959]. He changed the world in the sense that here were things in the past that were deemed beyond science, you know, they were just too flaky, too ephemeral. Pain? I mean, pain, what is pain? You know. Can you measure it with a galvanic skin reflex or tachycardia? So the fact is, you can measure all those things, but they're --

MELDRUM: Right.

LASAGNA: No better -- [he laughs] they're not as good as asking people about how they feel.

MELDRUM: Right.

LASAGNA: So I would say his major, or it was putting the cloak of science on the subjective response, starting out with analgesics and then moving on into other areas. Plus, I might say, the plugging for controlled trials -- is better than giving a new drug to a bunch of doctors and saying, "Play around with it and tell us what you think."

MELDRUM: Mm. Okay. What about your own contribution?

LASAGNA: Well, I guess I'd say my main contribution was sort of picking up on what Harry Gold had started and helping to make respectable the discipline of clinical pharmacology. Because before I started that group at Hopkins, people weren't being trained for careers in this game.

MELDRUM: Right.

LASAGNA: And to this day, I keep saying that there's very little in one's training as a physician or a Ph.D. or a Pharm.D. [Doctor of Pharmacology], what have you, that prepares you for a life of drug development, drug regulations. So when people go to work for the FDA, they have to be trained -- they --

MELDRUM: They have to be shown how to pick it up.

LASAGNA: They don't know how to do it.

LOUIS LASAGNA INTERVIEW

TAPE ONE, SIDE TWO

LASAGNA: I remember, back probably in the '60s, going to Switzerland and Sweden, and visiting all the medical schools and trying to convince them that this discipline needed to be supported. And Switzerland -- God, I'd, I'd meet these professors of medicine, they'd say, "Oh, we really, we're doing that already." I knew they weren't doing things properly. And [in] Sweden, the seed fell on fertile ground, because they have done the best job of any country as far as supporting clinical pharmacology. They had chairs established at most, if not all, of the medical -- I imagine they only have four or five medical schools, but they're supported by the government, they can request additional grants and so forth -- but there's a real infrastructure there, which is acknowledged to be important. The Brits have, I'd say, done the second best job, because they also have chairs. And the United States has done a very poor job. To this day, there's one chair named after me at the University of Rochester [NY].

MELDRUM: Right.

LASAGNA: And there's a chair at Johns Hopkins. But very few formal commitments to the discipline. And so you have the discipline considered important in industry because they can't survive without it. And then the FDA, because they need to be in it.

MELDRUM: Right.

LASAGNA: But in academia, you look around and you see some of the original gurus of this field. They'd build up a big group and then they'd leave, and they wouldn't be replaced, you know, whereas if they lost their head cardiologist, they wouldn't think for a minute about the need to replace this person. But clinical pharmacology is sort of a luxury; and it's silly, because these days, you know, with cost containment, for example, pressures fighting against quality of care, the therapeutic conscience of a hospital might well be a clinical pharmacologist who was hired to, -- you know, who would know something about the ways of quantifying drugs and evaluating the work of the drug they had, but also making judgments about comparative performance and costs and so forth.

MELDRUM: Yeah. Mm. Okay. Now, at this period -- The FDA -- We haven't gotten to the Kefauver-Harris Amendments yet.

LASAGNA: No.

MELDRUM: The FDA was basically only evaluating drugs for toxicity.

LASAGNA: Yeah.

MELDRUM: And –

LASAGNA: Not really, though, because, as somebody told me who used to work for the FDA, even pre-1962 when they would look at a dossier, they would perforce look at what good it was supposed to do, because how could you evaluate this toxicity data without knowing –

MELDRUM: Yeah. Exactly.

LASAGNA: -- what it was going to be used for? You know, if there were serious side effects and the drug looked like it was trivially useful. So in a sort of illegal way [he laughs] or paralegal way, they were looking at it, but the formal commitment came with the testimony of Modell and me in 1960 to '62. See, I was a consultant to the Kefauver Committee.

MELDRUM: Right. Right.

LASAGNA: And so we plugged for this, and that's why in the final language you had that you must rely on experts who based their opinion on whatever, including controlled trials.

MELDRUM: Controlled trials.

LASAGNA: So the FDA's preoccupation with both efficacy data in general and the controlled trials in particular, I think, harked back to those hearings.

MELDRUM: Mm-hmm. And so you were at that time pushing the idea that ultimately drug evaluation should rest on controlled trial data.

LASAGNA: Yes. Yes.

MELDRUM: Was that common in the academic profession?

LASAGNA: No. No. It was not.

MELDRUM: When the amendments were actually passed, what was the reaction among physicians?

LASAGNA: Well, I think physicians didn't pay all that much attention to it because they -- their lives were so far away from that. It was the industry that -- where the impact was felt.

MELDRUM: Right.

LASAGNA: Yeah. And they had to learn to do things differently.

MELDRUM: Mm-hmm. When the FDA got this new authority, though, it did not immediately say, "Well, okay, now everybody has to do clinical trials." There was a period of time --

LASAGNA: Yeah. They had to learn, too, and you must remember [he laughs] that in '62, when the amendments passed, I think they had seven physicians working in the FDA.

MELDRUM: Oh. [she laughs]

LASAGNA: So –

MELDRUM: Yeah. Okay.

LASAGNA: They weren't loaded with talent or experience either, so there was a sort of process of working things out, both inside the agency and outside the agency. The drug companies began to realize that they had to hire better doctors than they'd had to in the past, because the industry used to be a place where you went if you failed as a practitioner, or developed tuberculosis and took the cure, or what have you. So there was a period of sort of working things out. I don't know when things really got into high gear, but it was certainly a couple of years after that.

MELDRUM: After that. Yeah.

LASAGNA: Mind you, there were other important things that happened such as having to check with the FDA before you started any human work.

MELDRUM: Right.

LASAGNA: Prior to that, the FDA only got into the act at the very end when you wanted to get approval. So that was a big change and that required both the sponsors and the FDA to pay attention to what was being proposed to be done.

MELDRUM: Right. Okay. Well, tell me a little bit about the NAS-NRC [National Academy of Sciences-National Research Council] study, then, the –

LASAGNA: Yeah.

MELDRUM: -- Drug Efficacy Study.

LASAGNA: Yeah. [FDA Commissioner] Jim Goddard had this genius of an idea which was that he wanted to do something about the drugs that had been approved between 1938 and 1962 -- and knew that it was a horrific task. So how to do it? "Let me get some outside experts." And I don't know who chose me -- I don't know, I think it must have been folks at the National Research Council. And then I think I was asked who I would like to have on the committee, because they were all friends of mine. So I must have played an important role.

And what we did was to look at both over-the-counter and prescription drugs that had been approved between '38 and '62, and look at what their labeling said, and make a judgment as to whether these claims were justified or not. And that involved subjectivity par excellence, because it was partly looking at controlled trials and partly looking at experience and one's personal experience and so forth. And we would sometimes say, for example, "Well, uh, here's this combination of drugs, and there's an adequate dose of aspirin in there, and we don't know what some of these other ingredients are doing -- whether they're adding to it or subtracting to it.

But, God damn it, it's likely that there's some pain relief." So rather than saying "ineffective as a fixed-ratio combination" we'd say, "effective, but dot, dot, dot."

This drove the National Research Council and the NPA folks crazy, because they wanted everything in a nice category and we found it sometimes hard to do that. So often what we'd say is that, "Well, this part of the labeling should go; that part's okay," and so forth, and it was an attempt to make the best judgment call we could, relying a lot on evidence that was convincing to us, but not ignoring something that had been around for a long time, and that we all were sure was an analgesic.

MELDRUM: Was a -- Yeah. Something that worked.

LASAGNA: Yeah. It took a long time for our recommendations to ever be implemented.

MELDRUM: They still working –

LASAGNA: They're still working on it, yeah.

MELDRUM: -- on implementation.

LASAGNA: But it was a good idea, I think, and, and I would hope that they would do something like that -- except more quickly, today, with regard to off-label uses. In the field of oncology, for example, the labels are dreadfully out of date for the older drugs, and even for the newer ones -- the fact that these days you rarely cure cancer unless you use three, four, five drugs simultaneously. It means that the label with regard to all those drugs, which are usually made by different manufacturers, are hopelessly out of date. And it has reimbursement considerations, you know, the HMOs may not pay for it that's not an approved use and the cancer guys will say, "But we all know that that works -- "

MELDRUM: It works.

LASAGNA: " -- because we do it all the time."

MELDRUM: Right.

LASAGNA: So a return to that DESI [Drug Efficacy Study Implementation] approach might be one way of quickly bringing these labels up to date. And mind you, you know, the legislative history of the '62 amendments, as well as the final language of the Act of the amendments, says that the judgment should be what experts, qualified by experience, judge to be the case, and even if a minority of experts believe this to be the case, then that should do it. And unfortunately the FDA has sort of lost sight of that original intent, which, because they had only seven doctors at the FDA, clearly was not meant to say "FDA experts" --

MELDRUM: Right. Right.

LASAGNA: It was outside experts.

MELDRUM: Yeah.

LASAGNA: The real experts – the professors and what have you. [he laughs]

MELDRUM: Okay. We're talking about two things here. On the one hand, we're talking about the quest to have more rational, unbiased evaluation of drugs, using the randomized controlled trial method.

LASAGNA: Mm-hmm.

MELDRUM: On the other hand, we're talking about, ultimately, in many cases, there was not that much trial evidence for some drugs; in that case, you really had to rely on the judgment of experts –

LASAGNA: Right.

MELDRUM: -- which, inevitably, is not perfectly objective –

LASAGNA: No.

MELDRUM: -- is it?

LASAGNA: No. Not at all.

MELDRUM: Yeah.

LASAGNA: Not at all. You know, as somebody once said, the only way to be completely free of bias is to not know anything about a subject or not care anything about a subject. And that wasn't the case with these experts and these drugs. They knew some -- they knew a lot about it, had personal experience, had cared about it. So you did have a judgment call.

MELDRUM: Right.

LASAGNA: And it was a mix of – The – I would say in the analgesic field, it was largely a reliance on controlled trials. But not completely.

MELDRUM: Okay.

LASAGNA: And we were not asked to justify our judgments, you know. We just were asked, "Come on; tell us, effective, ineffective?"

MELDRUM: Bop, bop, bop, bop, bop. [she laughs]

LASAGNA: Whatever. [he laughs]

MELDRUM: When the panel began, did the members understand what the FDA intended to do with the results?

LASAGNA: I think so. I think we realized that we were being asked to give guidance to the FDA about whether labeling was okay or needed to change. And I think we knew that, unless they were going to ignore us completely, that what we said would have some impact on labeling. I think that's why we did it, you know. I don't remember that we were paid to do it --

MELDRUM: [she laughs] I don't believe so.

LASAGNA: So we did it as a sort of public service venture. Plus I suppose the fact that our egos were flattered to be asked to pontificate.

MELDRUM: Some drugs were taken off the market.

LASAGNA: Yeah.

MELDRUM: And there was a lot of furor about that.

LASAGNA: Yeah.

MELDRUM: One or two of them had been -- had had at least a long clinical history of use.

LASAGNA: Yeah. Some drugs were taken off the market because they weren't selling anyway.

MELDRUM: Well, yeah, that's -- [she laughs]

LASAGNA: There were very few drugs where we would say "Hopeless," you know. "Nothing."

MELDRUM: "Nothing."

LASAGNA: "It doesn't deserve to be on the market."

MELDRUM: Right.

LASAGNA: It was mostly a matter of changing the labeling. Because, well, for example, some of the labels used to have long lists of procedures that had been studied. Like you did a post-operative study and you had a couple of cholecystectomies and a couple of herniotomies, so you would list, well, you weren't entitled to say it was good for all those conditions because all you'd done was show that, in general, patients post-operatively were better off if they were treated. And so we thought, "Well, let's stop that. Let's just say that it's a sort of general pain reliever and not specify –

MELDRUM: What it was.

LASAGNA: "-- conditions."

MELDRUM: Yeah.

LASAGNA: So a little of it was sort of tidying it up and holding people -– holding their feet to the fire and saying, "Come on. Some of these things you've got evidence for and some you don't." It was a useful exercise, I think. Yeah. Not perfect.

MELDRUM: Well –

LASAGNA: What is?

MELDRUM: What is? Yeah. Did you then agree with the FDA's decision to make randomized clinical trials the *sine qua non*, the ultimate –

LASAGNA: Yeah, I still feel that that's the way you've got to start out.

MELDRUM: Uh-huh.

LASAGNA: What I object to is ending with that. But, you know, if you want to get a drug on the market, it seems to me you should have shown beyond a reasonable doubt [he laughs] -- that the drug is better than nothing. And these days it's even tougher than that, because at the launching of a drug you really are going to be asked increasingly, by HMOs, or in other countries, pricing authorities, "Why should we use your drug at all?"

MELDRUM: Right. Right.

LASAGNA: "Why should we pay for it at all?"

MELDRUM: Yeah.

LASAGNA: And so on. So it's become more and more a comparative game. Not comparative over placebo, which is what it used to be, but now compared to what's already available, since very few drugs come along where they're the only drug in the therapeutic category and how does it perform then? And I think that's still important. I worry a little bit about the FDA if they become involved in economic judgements, because I don't think that's their forte. But they're certainly qualified to judge whether the statement that this drug will work better than that one or this drug has fewer side effects. That's science; that's not economics. So, as I say, it’s still important, still a fundamental part of the judgment process.

It's a pity that even after the drug is marketed, there is so little attempt to individualize to find out -- well, are forty-five-year-old left-handed Lithuanians more likely to benefit from this drug or to get sick? You know, I mean, if you take something like clozapine for treatment of refractory schizophrenia, if we have ever been able, and we still aren't, to predict who would get agranulocytosis, the drug would have been on the market a long time before it did, and without all the requirements for blood counts all the time and so forth. And, you know, that's just one

example of how, if we were to at least put our minds to individualization rather than homogenization, we could go, as Austin Bradford-Hill put it, beyond what satisfies regulatory authorities, and what the practicing doctor or the patient wants to know. "What's best for me, Doctor?" you know.

MELDRUM: Mm-hmm. Yeah.

LASAGNA: "Don't tell me you're going to try, you know, trial and error -- "

MELDRUM: Right. [she laughs]

LASAGNA: You know. Of course, if that's the best you can do, do it. And we do do that, take patients with the pain of rheumatoid arthritis, or the discomfort, you know, and you try this drug, and --

MELDRUM: Try another one.

LASAGNA: That doesn't seem to work, try another one –

MELDRUM: Right.

LASAGNA: -- and eventually you find one that seems to be best for that person. But wouldn't it be nicer to be able to do that in advance without trial and error?

MELDRUM: It would be.

LASAGNA: Yeah. So in a sense we've sort of oversold, and I'm partially responsible for that, because I was trying to get them to do it at all. And now, with the passage of time, I've also become more sophisticated. [he laughs]

MELDRUM: In some of the papers you wrote at this time, there was at least some suggestion that you really couldn't do that. I mean, it really wouldn't be possible to individualize treatment, that what the RCT would tell you was what's the drug that will give you the best average performance over all –

LASAGNA: Yeah. Yeah.

MELDRUM: -- and that's maybe the best we can do.

LASAGNA: And it still may be often the best we can do. But what I argue with the FDA about is, uh, "Well, look now, you will look retrospectively at the trial and say, 'Hey, the patients with renal disease seem to get more toxicity, so we ought to change the labeling for that, or give more warning' -- "

MELDRUM: Mm-hmm. Right.

LASAGNA: So, you know, if it's okay to look retrospectively at clues about individualization for side effects, what about for benefit? You know. If women seem to respond better than men, shouldn't you use that information. Or it looks like the elderly need smaller doses or what, or whatever. You know. So I'd say that the next big revolutionary step would be an attempt, as best we can, to move from the herd phenomenon, as I call it, to the individual members of the herd. Because I still think that that's the goal, ultimately -- is how do I treat this patient, this unique patient because everybody is unique, the best that I can instead of stumbling around.

MELDRUM: Well, that does sort of bring up another question, which is the relationship of the trial data to actual prescribing practices. I mean, I think the goal -- to treat this patient the best I can -- is --

LASAGNA: Yeah.

MELDRUM: -- every physician's goal.

LASAGNA: Yes.

MELDRUM: But there's a mass of information out there which is difficult to digest.

LASAGNA: Yeah.

MELDRUM: Is there any way that can be improved?

LASAGNA: Well, I think that one of the things that we could be doing is more what I call naturalistic studies. The drug is on the market. Okay. Now, just track how it's performing. Just how happy are doctors as they -– as the doctor compares personal experience with what the randomized control trial data said and what the labeling says. Are they synchronous or are there big discrepancies? And if there's a discrepancy, can you explain it? Now who should be doing those studies? Well, I suppose the sponsor ought to be at least interested –

MELDRUM: Somewhat, yeah.

LASAGNA: -- in the phenomenon. But they tend not to be, and up until now, companies have usually been blissfully happy if they have big sales.

MELDRUM: Sales, right.

LASAGNA: The FDA, for about half of the drugs, according to our data, that they approve, will have a sort of gentleman's agreement that you'll do these studies after the drug is on the market. Sometimes they're pediatric studies, whatever. But I don't know how often they're actually done or come up with useful information. I mean, if the FDA, being busy, tends to feel, well, you know, we've put the drug on the market and we'll track its toxicity -- and if some bad news surfaces, well, we may have to take the drug off the market.

MELDRUM: Right.

LASAGNA: But about two, three, four percent of the drugs that are marketed in Britain and the United States are taken off the market --

MELDRUM: Eventually, right.

MELDRUM: – for reasons of unpredictable, or unpredicted, anyway, toxicity.

MELDRUM: Right.

LASAGNA: But that's it. And the benefit side of the equation, the FDA tends to take -- to feel it's not their problem. Maybe it shouldn't be their problem; maybe it's the medical profession's problem or the drug companies' problem.

MELDRUM: Hmm. Yeah. Maybe it is. Okay. I want to go back to a question I asked a little bit earlier, because I do have the impression that [she sighs] there was concern, let's say, among the academic medical community during the '60s over what exactly the FDA was going to do -- whether they were going to impose restrictions on drug research that hadn't been there before. Am I wrong about this? Was there concern? Did the academic community as a whole seem to support the imposition of clinical trials?

LASAGNA: I think that those members of the community --

MELDRUM: After all, a lot of academic physicians did a lot of drug trials.

LASAGNA: Yeah. Yeah. I think that the ones who were doing controlled trials had no problem with it. Many others probably weren't all that concerned about it. I think the drug companies had problems because they weren't geared up to do the studies. They didn't have the personnel, or -- I can't remember whether there was a sort of clamor of concern and anxiety about what might happen. I mean, the hearings were mostly harpoon throwing at the industry for not doing things well. I mean, I got to testify under the weirdest circumstances. I would never do it again. I was, as I said, an advisor, and they were planning to have testify a man named Mark Nickerson, who was a distinguished pharmacologist, had moved from Michigan or somewhere to Canada. And he'd been a card-carrying Communist. And they had him scheduled to -- during a break one of them said to me, "Do you think Dr. Nickerson is going to be a good witness?" I said, "Yeah, I think he will be." I said, sort of jokingly, "He's had experience testifying at those House Un-American Affairs [Activities] Committee [HUAC]."

MELDRUM: House Un-American Activities Committee.

LASAGNA: Well, they whisked him out of the room so quickly, and they put me on the stand. And I, like a fool, go [he laughs] on the stand completely unprepared for anything. And, as I say, I would never do that again. But in those days, I had been trying -- I wrote a paper called "Gripesmanship: A Positive Approach", where I sort of warned them. You know, I said, "You know, if you don't clean your own house -- "

MELDRUM: Mm-hmm.

LASAGNA: "-- It'll be cleaned for you, and maybe in a way that you won't like." And I remember being approached by Arthur Sackler, the man after whom this building is named, at a meeting, and he came up to me and he said -- he was then running one of the big advertising agencies, he himself had been responsible for the multicolor, multipage spread in journals. And he said, "You're right. I've been telling them that for years, and they didn't listen to me; they're not going to listen to you, either." And it was absolutely true. Matter of fact, there was a lot of bitterness because here -- the Pharmaceutical Manufacturers Association was then called something else -- American Drug Manufacturers Association -- they'd given me the first fellowship for clinical pharmacology. And here I was, a traitor, you know coming –

MELDRUM: Deserting.

LASAGNA: -- and accusing them of this. The trouble is that those were halcyon days financially for the industry, and I used to say that you could be a CEO in a drug company and be either a crook or stupid or both and still make money, but there was a sort of public-be-damned attitude about it all.

MELDRUM: Yeah.

LASAGNA: Well, there was this feeling that these pettifogging academics, you know, they don't know what the hell they're talking about. "Aren't we selling these drugs like crazy? Why is everybody bitching about it?" So, you know, I went through a period where I was sort of a darling of the industry and then I was sort of reviled by them and they complained to the president of Johns Hopkins about how dreadful a person I was. Now I guess I'm their buddy again. [he laughs] And someone once referred to me as a switch hitter, you know -- both sides of the plate, and he meant that pejoratively, you know.

MELDRUM: Yeah. That's good.

LASAGNA: But, you know, in baseball it's good to be a switch hitter. [he laughs]

MELDRUM: Yeah. Yeah. Okay. Well, tell me a little bit about the NSAIDs, then. This has been a new development since the '70s, am I right about this?

LASAGNA: Yeah, something like that. What happened was that the industry was looking for better antiarthritic drugs, I think that's probably what they were looking for, better aspirins and so forth. And so they began to discover some of these drugs, and it turned out that they were all wonderful analgesics and, for some situations like dysmenorrhea, better than the traditional ones.

MELDRUM: Right.

LASAGNA: They also had a different spectrum of side effects. And they'd become very important, and as they'd gone over the counter and become even more important, both to the public and to manufacturers' profit ledgers.

MELDRUM: Well, yeah. No doubt.

LASAGNA: And I think they're a real advance. They -- I mean, there are many situations where aspirin or acetaminophen will work fine and there's no need for it. But there are other situations where the NSAIDs are a real step forward.

MELDRUM: And this was developed by industry –

LASAGNA: Yeah.

MELDRUM: -- looking for –

LASAGNA: Well –

MELDRUM: -- better aspirin?

LASAGNA: Yeah, actually –

MELDRUM: Something that wouldn't cause gastric problems, or -- ?

LASAGNA: Yeah, I think, both better performance, because, you know, the serious arthritics still have lots of problems even with the NSAID issue.

MELDRUM: Right.

LASAGNA: Part of it was a hope that they could change the course of rheumatoid arthritis, for example. Matter of fact, Lilly had a drug that they marketed as showing that you could actually change the life history. Turned out not to be the case and they had to stop their advertising [he laughs] and they took the drug off the market for unpredicted toxicity.

MELDRUM: Right.

LASAGNA: But there was a desire for better antiarthritics, and I think that was the original motivation. And I think a man named John Vane, in Britain, had theoretical speculations about prostaglandins and so forth. So I think there was a good scientific base for being interested in it.

MELDRUM: Right. Right. Okay. And so what has your own work been like since the '70s?

LASAGNA: I'm sorry?

MELDRUM: Your own work.

LASAGNA: Well, you know, during the time I was at Rochester, and I left there about 11 years ago, I continued to do analgesic trials. I say "I" -- I and my colleagues did, you know, and continued to look for improvements or quantification of proposed candidates. Did I do anything

really interesting? Well, we did do work on whether pre-operatively talking to patients about what was going to happen to them, and reassuring them about our ability to deal with their pain, whether that made life any easier for patients. And it looked like it did, in terms of anxiety levels, and also demand for analgesics post-operatively. I might say [he laughs] we never convinced a surgeon at the Strong Memorial Hospital [Rochester, NY] to do what we suggested was useful. And then we had this guy, [K.] Sriwatanakul, who published papers on what people were doing with the various approaches to moderate pain. I don't think -- I can't say that anything I did during the '70s was crucial for the field or provided any great insights.

MELDRUM: Was there a particular reason why you went to Rochester? It was a move up?

LASAGNA: Well, I'd been at Hopkins for two years and then I was at the [Massachusetts] General for two years, and then I went back for another sixteen. And I was pissed off that I had never been made a full professor, you know. One of my early fellows was a full professor; here I was not. I went up and I asked them, my chief in medicine, you know, I said, "What's going on here?" "Well, you don't understand. You know, it's sometimes difficult in the academic world." And I said, "You're telling me that you've suggested my promotion and it failed?" He said, "No." I said, "Well, that's what I want to hear." So I decided, well, I was sort of unappreciated there. And also I'd been doing the same thing for sixteen years; I wasn't ashamed of it, but it sort of plateaued.

MELDRUM: Right.

LASAGNA: And here was a chance at Rochester to be chairman of the department and to do some things about teaching that I couldn't. Because I lacked the power at Hopkins. It was mostly that. Sort of time for a change. I did that; I chaired the department for ten years, and at the end of that time decided I'd done as much good or harm as I was going to do to the department, and I was getting bored. So I stayed on for another four years, and then was succeeded by somebody who didn't see eye to eye with me on the importance of anything, including clinical pharmacology. And I realized that the old chief shouldn't hang around a department and split loyalties and so forth.

MELDRUM: It does make things difficult.

LASAGNA: And so I decided better to leave, and most of my children were living in New England, so I looked at two different universities up here and took this job [at the Sackler School]. And I've enjoyed it. And I continue to run the Center for the Study of Drug Development. Moved that up here with me. That's where I really get most of my fun these days.

MELDRUM: Mm. And what do you -- What exactly goes on there that it makes it --

LASAGNA: Well --

MELDRUM: -- so much fun? [she laughs]

LASAGNA: Yeah. We sort of study whatever the hell we want to study in the field of drug development and drug regulation. Exactly what we do at any given moment depends on who we have on board.

MELDRUM: Right.

LASAGNA: If I have an economist or a lawyer, we do things that we wouldn't do if we didn't have such people. But also what deserves to be studied at any given time. And, you know, I've gotten involved in the Lasagna Committee, which looked at drugs for cancer and AIDS, and is recently working with a group that's figuring out possible legislative changes to the Food and Drug Act. So I've become a sort of spokesman for what I hope is rational drug development and drug regulation. Sometimes going to bat for the Agency, for example, sometimes criticizing them.

MELDRUM: Right.

LASAGNA: Sometimes going to bat for industry and sometimes telling them that there's as much fault on their side as there is on the FDA's. So it's a way of kind of being superacademic in the sense of following your nose and doing what you want to do, and still that's very nice. Yeah. Yeah. And still tackling things that you feel are fundamentally important. And at this moment in history with cost containment pressures, you know, more than ever we need to, for example, make the drug development process more efficient and quicker. Fourteen to sixteen years is our guess from discovery to marketing. That's ridiculous.

MELDRUM: Yes. That is ridiculous.

LASAGNA: And it's very expensive and if industry isn't able to be profitable enough to keep plowing money into the search for the tough things that we haven't been able to tackle, as somebody put it recently," we've plucked the fruit from the lower branches of the tree and now it's the fruit up high." We may not even see the fruit up high, let alone being able to reach it. And, you know, in the field of cancer, we cure about twenty percent of our cases; that leaves most patients still not very well treated. With Huntington's Disease and muscular dystrophy and, you know, so many ailments for which we have sub-optimal therapy or no therapy at all, AIDS. Yeah. So I continue to feel that I have a role to play with regard to making the process as efficient and rational as possible. And that means working both with industry, to get them to shape up and working with the FDA to get them to shape up. And not requiring things which an academic might think were interesting, but are not crucial to getting a drug on the market.

MELDRUM: Getting a drug on the market. Yeah.

LASAGNA: Differentiating between what needs to be done before the drug gets on the market --

MELDRUM: Needs to be done.

LASAGNA: -- and what can be done after the drug gets on the market.

MELDRUM: Afterwards. Well, how do you think the FDA's doing these days?

LASAGNA: I think they're doing better, because the user fee legislation made them set some goals, which by and large they seem to be reaching. I say "seem to be" because we hear stories about how they'll tell a manufacturer, "Don't submit it yet," you know. Or, "If you submit it, we'll refuse to file." Because what they promised was action. Action could be approval; it could be only an approvable letter, which means you're not quite ready; or it could be a rejection. Those are all actions.

MELDRUM: Right.

LASAGNA: So they can meet their quotas in ways that the Congress didn't have in mind. But I think they are doing better. They've got better people than they used to have. What's needed now is, I think, mainly sort of an effective ombudsmanlike deal where, when there's disagreement between a sponsor and the FDA about what has to be done, you have an appeal mechanism where at least occasionally the FDA would be told by the ombudsman, "You're wrong -- "

MELDRUM: [she laughs]

LASAGNA: "You're asking for too much." Or, "You're -- " That -- And I think what's also needed is early and continuing interaction between the regulators and the regulated. Because while you could argue that the FDA only gives it to the sponsor when the NDA is filed, and in fact that isn't true because all through you're looking ahead to, "What are we going to have to have?"

MELDRUM: Have to have. Right.

LASAGNA: So if there was early and continuing collegial discussion between the regulators and the regulated, in theory, the NDA would be self-reviewing, because you would have settled all the issues before you file. And that's my goal, and --

MELDRUM: Yes. That would be --

LASAGNA: Yeah. And now there is a pressure to have the reviews done outside the agency.

MELDRUM: Right.

LASAGNA: And that could work. I don't think it's likely to work, but the FDA did an experiment with supplements and it worked fine. So I don't doubt that it could be that. Whether it will be, I don't know. I think the reason legislative action may occur, not in this Congress, but in the next one, is that there've been so many reports critical of the FDA over the decades that I've been watching the agency, with repeated suggestions for change which -- a few of which were made and many which were not made --

MELDRUM: Not made. Right.

LASAGNA: A lot of people are thinking, "If we don't do this legislatively -- "

MELDRUM: Right.

LASAGNA: "These bastards are not going to shape up." So it's an interesting time. I testified recently before one of the House subcommittees and I was appalled at how ignorant the congressmen are about this whole process. The chairman, for example, said to me, he's an engineer, he said, "Why couldn't you say, you only need 84 patients to be studied?" You know. So I tried to explain to him that, "Well, it depends on the disease, and -- "

MELDRUM: Right.

LASAGNA: -- you know, all the caveats. I'm thinking, "Holy Jesus; if this is their level of sophistication, what's the hope of anything rational coming out of [he laughs] their deliberations?" But I --

MELDRUM: It doesn't sound too promising.

LASAGNA: -- I don't think any -- I mean, I don't think they're going to throw the FDA out of existence, you know --

MELDRUM: No way.

LASAGNA: So, and they are trying to do better, and I think they are, in some ways, doing better. But they still need to be watched, because, you know, they -- Dave Barry, the humorist, had a column last Sunday [he laughs] in which he said, "The motto of the FDA is, 'We haven't figured out what our motto is yet.'"

MELDRUM: I didn't see that. I'll have to look it up.

LASAGNA: When I was on the committee that [Health and Human Services Secretary] Lou Sullivan put together to look at the FDA, I remember asking the woman who was general counsel of the FDA, I said, "What would you think of the mission of the FDA being not just to protect the public health, but to protect and promote the public health?" She said no. And I thought, "Jesus, that's what's wrong," because, yes, the public does need to be protected from harm and from fraud and chicanery, but they're harmed if good drugs are delayed from getting on the market. And that ought to be a legitimate goal for the agency.

MELDRUM: Yeah. Yeah. But it's [she sighs] -- Well, there's a lot of historic baggage there, too.

LASAGNA: Yeah.

MELDRUM: A few years back there was a considerable minor furor over the fact that women had not been included in drug trials as subjects, whereas men frequently --

LASAGNA: Yeah.

MELDRUM: Some trials used only men, even though the disease in question affected both sexes. Would you care to comment on that?

LASAGNA: Yeah. Well, when I started out with Beecher, he was against using women as volunteer subjects in some of the research we were doing because -- And it had nothing to do with protecting women who might be pregnant and didn't know and so on and so forth -- it had to do with the stereotype that women, because of the menstrual cycles, have more ups and downs than men do.

MELDRUM: Really? [she laughs]

LASAGNA: And therefore, there's less noise, if you – so that was originally. And then with thalidomide, it became this worry that we've got to protect --

MELDRUM: Mm-hmm. The fetus.

LASAGNA: -- the possible fetus.

MELDRUM: Right.

[PAUSE TO CHECK TAPE]

LASAGNA: And now we have certain groups saying, "You're not doing us a favor by not studying us before you approve the drug." So in the old days [he laughs], I remember being criticized that at Hopkins we used black patients more than white patients, because they were available. And now we're moving towards -- well, if black patients are different in their responses from white, by God, you ought to study them before [approval]. So I think what we're seeing is a move towards realizing that if you don't study patients before a drug is put on the market, you're in a sense experimenting with them after the drug is on the market, because you don't know how to treat them. And I think that's good. What's bad is if we end up saying, "You didn't study enough Pakistanis," you know --

MELDRUM: Yeah. Yeah. Exactly.

LASAGNA: "You didn't study enough --" you can make it so crazy --

MELDRUM: So compartmentalized.

LASAGNA: -- so Jonathan Swiftian-like --

MELDRUM: Right. Right.

LASAGNA: -- that you'd never get done. And, as I say, some of this stuff can be done after the drug is marketed, but I think that some of the things they're doing, like suggesting that, well, you can get a certain amount of pediatric experience and, on the basis of adult studies plus some of this, that's enough for a label. You don't have to do randomized controlled trials and so forth. And I think that kind of approach probably would be in the public interest. But there is this trend or change going on where groups that used to object to being studied now object to not being studied.

MELDRUM: Now everybody wants to be studied, because --

LASAGNA: Yeah. Yeah.

MELDRUM: Yeah. Yeah. A friend of mine asked me to ask you a little bit about LSD. I know there was a lot of LSD experimentation and that you did some of that --

LASAGNA: We did. Yeah.

MELDRUM: -- on paid volunteers, am I right about that?

LASAGNA: Yes. Yes. Yes. Yes. We [he laughs] – it was interesting, because we'd have these sometimes weird volunteers come in and one of them said to me, "Gee, my roommate had LSD in this local psychiatric hospital in Boston. He went crazy in the middle of the night, was discovered in his nightgown or pajamas eating grass on the Boston Commons – "

MELDRUM: [she laughs] Oh, gee.

LASAGNA: "And I hope that happens to me!" And I realized that there could be this interesting interaction between personality and motivation and the drug and subject, which is so more the nondrug factors than the drug. We studied LSD because it was part of Beecher's Army contract to study hallucinogens.

MELDRUM: Right.

LASAGNA: And that's all I did with it was, I didn't study its therapeutic benefits, just studied its hallucinogenic effects. And felt that there was a relationship between personality and response to the drug. And that's about it.

MELDRUM: Mm. Okay.

LASAGNA: We studied other hallucinogen, or other putative hallucinogens as well, as part of the Army contract.

MELDRUM: Right. Right. Yeah, those were the studies where you then tried to see if the man would tell you his mother's maiden name.

LASAGNA: Right. Right.

MELDRUM: Did they tell you their mother's maiden name at all?

LASAGNA: No.

MELDRUM: Oh, they didn't! [she laughs]

LASAGNA: No! [he laughs]

MELDRUM: Ah, I see! Not so successful!

LASAGNA: No, no. It was a crazy project. As I say, I was grateful for the fact that my psychologist colleague, Jack von Felsinger, was doing all that. I didn't have [he laughs] because I knew it was crazy. I tried taking a couple of the things myself because I thought, "Well, maybe I ought to see what these things are like." And I remember taking one thing, and then being busy and even forgetting that I'd taken it. I didn't know whether that was the effect of the drug or whether it had such limited impact on me. [both laugh]

MELDRUM: Well, that's interesting. Certainly there were some physicians who did engage in self-experimentation.

LASAGNA: Yeah.

MELDRUM: And I guess that was another question I kind of wanted to ask you. I mean, was there an ethical aspect to that, "We'd better try this on ourselves before we try it on anybody else"?

LASAGNA: Yeah. The -- there was an ancient tradition along those lines.

MELDRUM: Right.

LASAGNA: A limited tradition, not much. I remember Chauncey Leake telling me one time about how he almost killed himself by taking some medication and it precipitated out in his bladder and caused terrible urinary symptoms and so forth. But the --

LOUIS LASAGNA INTERVIEW

TAPE TWO, SIDE ONE

MELDRUM: Resuming our conversation with Dr. Lasagna, this is tape two on Friday, September 8. Dr. Lasagna is talking about Dr. Beecher and his ideas on informed consent and where they came from.

[tape off]

LASAGNA: -- about how Beecher got interested in this informed consent thing.

MELDRUM: Yeah. yeah.

LASAGNA: I've been told -- I didn't know this at the time -- but have been told in recent years that he had, or he left, a big file on the Nuremberg [war crimes] trials. And I just wanted to say that I really have no insight into what made him become interested all of a sudden in informed consent. It, I'm sure, was attractive to him because of the drama in it. But I'm not aware of any particular incident that -- I know that the Mass[achusetts] General [Hospital] did have a committee in existence, and -- I've only found this out by serving on the committee recently for them that looked back at what they used to do -- that he probably had to get some sort of high-level permission for whatever research he did, but I know we weren't getting informed consent. So that sort of ethical sensitivity must have come later in life to him and it's just curious as to why he suddenly became interested in that.

MELDRUM: That's, I think, an interesting question. And I've looked at the Beecher papers, which are at the Countway [Medical Library]. They hadn't been processed at the time I looked at them. They have now been processed.

LASAGNA: Uh-huh.

MELDRUM: I mean, they haven't-- As far as I know, they haven't yet been processed. [she laughs] [as of March, 1997, they had been processed.] And I could not find this -- At one point he writes a letter, saying, "You know, I've been thinking about this, you know, I think I should, you know, do an article about it" to -- It wasn't, I think, to the editor of the *New England Journal* [*of Medicine*] originally; it was to someone else. And then, from then on, his letters begin to get more and more detailed and he begins talking more and more about informed consent, and instances in which he's observed that it's not being used and instances in which he thinks things are not being done correctly. And it seems like a sudden conversion. Something must have triggered that.

LASAGNA: Yeah.

MELDRUM: And it may be, you know, in those unprocessed papers in some other file --

LASAGNA: Yeah.

MELDRUM: There are masses of papers --

LASAGNA: Yeah. Yeah.

MELDRUM: -- which I just haven't looked at. So it's an interesting question.

LASAGNA: I recently served on the task force looking at the old radiation experiments that were done in, some of them at least, in retarded people. And looking back, in fact, it looks like no great physical harm was done to anybody and actually some of those people were getting consent, maybe not quite the way we would do it today -- but in retrospect, what they did was upset an awful lot of people who began to have worries about, "Oh, my God, I'm going to get cancer!" or what have you, without any particular purpose. Also I'm interested in the fact that there is a lot of talk recurring these days about Tuskegee [the Tuskegee syphilis experiments], and I'm not quite sure why but I remember Leonard Goldwater, who taught at Columbia, in the School of Public Health, and wrote a book about mercury, telling me one time that at the time that the Tuskegee trial was started, its purpose wasn't unethical because there was evidence that, if you got treated with heavy metals, which was the only thing they had, you actually lived a shorter period of time than if you weren't treated, because they weren't very effective and they were clearly toxic.

MELDRUM: Mm-hmm. They were toxic.

LASAGNA: Now, that doesn't make the way they did the study desirable, nor does it excuse them not treating with penicillin --

MELDRUM: Penicillin not at all, right.

LASAGNA: -- when that came along, but it isn't quite as bad as it looks at first blush. The second thing that came up when we were looking over the Mass General traditions and their current practices, that we now have come to the point where some of the bioethicists are saying that informed consent is a sham and it's fake. How can you get consent? Now, I would admit that it's imperfect, what we're doing these days, but it's so much better than what I did that I can't understand why they don't keep trying to improve the process. There are ways that it could be improved. For example, in the IRB that I sit on here, we have nobody sitting around that table who reads only at an eighth-grade level, for example. So we don't know whether the language we come up with is understandable by some of the folks we approach. So I think we can do it better, but I consider it such a desirable revolution that has occurred, as a consequence of Beecher and others, that going back to the old days has no appeal to me at all.

MELDRUM: Do you remember your initial reaction to all this? I mean, were you -- [she laughs] how did you feel when people started talking about informed consent given that you'd been doing trials all along without doing informed consent?

LASAGNA: Yeah, I think my first reaction was one of dismay that it hadn't occurred to me ever that we weren't leveling with people.

MELDRUM: Right.

LASAGNA: But you know, I'd seen other things going on, too, that I also knew were wrong. For example, at Hopkins when I first went there, there were black wards and white wards. And what made that change was not ethics but economics because patients didn't come in neatly and tidily half white and half black and so --

MELDRUM: Yeah. What could you do?

LASAGNA: -- you couldn't fill your beds if you did that. And the black technician who helped Blalock with the blue baby operations, he deserved an awful lot of the credit because he actually did the dog surgery --

MELDRUM: Wow.

LASAGNA: -- but never even -- [He] had it acknowledged late in his life by being given an honorary title of some sort from the Department of Surgery. So I think it was good that it happened; I think I was ashamed when it finally got to my level of consciousness. I probably wondered why we hadn't thought about it a long time before.

MELDRUM: Yeah. And do -- You don't recall any general conversation or consciousness of the Nuremberg trials among --

LASAGNA: No.

MELDRUM: Certainly I haven't noticed that, either.

LASAGNA: No.

MELDRUM: One thing that, I don't know exactly what it reflects -- I guess I'll ask you -- was that in that period, in the '50s, subjects for trials were frequently chosen from disadvantaged groups -- from retarded individuals, or from poor or minority populations. There are different ways that you can interpret that. That was the material that was available, or was there some -- It -- There was not -- There was some sort of tacit feeling that you couldn't approach white, middle-class patients and suggest that they participate in trials?

LASAGNA: Yeah, well, at the General we certainly never did any studies on private patients, except this kind of documenting of how much drugs they got that Beecher did, just tracking how they were treated. And I think it may have had to do with the need to get permission from individuals' doctors; I never heard it discussed. I never heard anybody say, "Hey, Harry, why don't we study some of the Phillips Building patients?" We studied people without any knowledge of their income or their educational level or what have you, just that if they were on the ward service, they were sort of --

MELDRUM: They were fair game.

LASAGNA: -- fair game.

MELDRUM: Yeah.

LASAGNA: It wasn't so much sort of a conscious ruling in or ruling out as kind of doing what everybody did.

MELDRUM: Everybody did, right.

LASAGNA: [he laughs] And it never occurred to me to question my boss with regard to whether what we were doing was right or not. He was a Harvard professor --

MELDRUM: Yeah. Well, yeah, he was the Isaiah, what --

LASAGNA: He had the Isaiah Dorr --

MELDRUM: Isaiah Dorr professor. [she laughs]

LASAGNA: Yeah.

MELDRUM: First one. Who did you train with before Beecher? We sort of leaped over that.

LASAGNA: Well, I worked with E. K. Marshall, Jr. who was the second pharmacology chair at Hopkins. The first one was John Jacob Abel, who was sort of the father of American pharmacology --

MELDRUM: Of American pharmacology, right.

LASAGNA: -- and Marshall was the second chairman. So I went there to work as a post-doc with him and that was where I learned about pharmacological research in general, but that was mostly animal stuff. And then I didn't really get into the clinical trial game until I went to work with Beecher.

MELDRUM: Okay. Well, we sort of cut short what we were saying about self-experimentation.

LASAGNA: Oh, yeah.

MELDRUM: Yeah.

LASAGNA: I don't know that I have anything more to say about that.

MELDRUM: Okay.

LASAGNA: I've done it to myself on a couple of occasions.

MELDRUM: Right.

LASAGNA: I remember one time doing a respiratory study with morphine to see whether aspirin could counteract the respiratory-depressant effects of morphine and the subject didn't show up, so I said, "Well, do me." And I was so sick. I was nauseated for many hours. I remember I had my wife come with the station wagon and me lying down in the back of the station wagon taking me home. [both laugh] Oh, and that reminds me of one time when I was doing studies with morphine in healthy volunteers and, of course, we never told them what was happening to them. And I got a call from somebody at the Harvard infirmary, telling me that this student was having a lot of nausea and vomiting and I knew that he'd gotten a fair dose of morphine and he asked me what he'd gotten and I said, "Well, he got morphine." He said, "Oh, well, it can't be that." And I knew it was that, you know, but it had lasted a long time and he thought, well it can't be this long; it must be something he ate.

MELDRUM: Ate! [both laugh]

LASAGNA: So I did a little bit of it myself, didn't look on it as something that you should do or shouldn't do. I was never in an environment where it was sort of traditional for you to do it yourself, to yourself.

MELDRUM: But there were some environments like that?

LASAGNA: Well, I mentioned this Chauncey Leake experience out in California. So, I heard of them occasionally, but they were not prominent.

MELDRUM: I do have the sense it sort of belonged to an earlier era.

LASAGNA: Yeah.

MELDRUM: Mm. Okay. Let me clarify one thing. I mean, when I think of randomized clinical trials, nowadays we always tend to think of blinding. Were the analgesic trials the first trials to use blinding as sort of a standard tenet?

LASAGNA: Well, certainly the old streptomycin trials didn't, in Britain. So at the very beginning they didn't. Blinding, I think, we owed to Harry Gold. I think that he did some studies, as I remember, with ether; there were questions whether something bad happened to it after you opened the container, and so they engaged in blinding to sort of keep people honest. And over the years it's been attacked on occasions, as being a sham because if the patient experiences side effects from the drug, then they can guess accurately if they've ever been on placebo. I don't have any great answer to that except that it seems to me that a partial attempt at concealment is better than no attempt.

And furthermore, it's not that uncommon to have adverse effects reported by patients who were on placebo, and also I don't think it's necessarily the case that you attribute beneficial effects to

something that is making you sick, you know, that you're sort of talked into the benefit as a result of being made to feel badly. So I -- there are people who think that when you get through, you should ask the patients, the observers, "What do you think the patient was on?" And somehow take account of this. I don't know what to do with data of that sort because, for example, if a placebo never helped you, and the drug that you're studying always helped people, at the end of that time you might well get an overwhelming vote, for the active drug which was based on benefit, not guessing because you were made sick or something like that.

MELDRUM: Yeah. Yeah.

LASAGNA: So there are problems occasionally. For example, when you're wanting to compare your drug with something that's already on the market if you, for example, take a marketed tablet and put it inside a capsule, you might be interfering with its bioavailability and so you have a case where they might say, "You didn't study my drug; you studied my drug hidden in a capsule."
You sort of have --

MELDRUM: That's very problematic.

LASAGNA: -- fine points which are okay to talk about, except that I don't know that there are great solutions to--

MELDRUM: What do they contribute?

LASAGNA: Yeah.

MELDRUM: Yeah. [she coughs] Do you think patients maybe become sensitive to drugs, though? A population of chronic-pain patients, with malignancy, with arthritis, with any kind of chronic pain, who have had different kinds of medication. You put them in a trial, I mean, they're familiar with the effects of morphine when they take it. They're familiar with what different drugs feel like. Aren't they going to be able to distinguish between them in some sense automatically? Have you ever encountered that, or is that ever considered?

LASAGNA: I encountered it in patients. Years ago, Beecher and I went down to the Public Health Service facility in Lexington, Kentucky, to where they would use recidivist addicts --

MELDRUM: Right. Post-addicts.

LASAGNA: -- and some of them were very good. You could inject them and they'd say, "That's 15 milligrams of morphine." Or, "That's five milligrams of heroin."

MELDRUM: Wow.

LASAGNA: So with the sophisticated drug user, they certainly can do it, some of them. With patients, I guess I've had more troubles with people who are on chronic medication who are quite happy with it --

MELDRUM: Really!

LASAGNA: -- and don't want to participate in a trial. You know they've been taking something to help them sleep at night for years; it's not clear whether in fact they're still getting pharmacotherapeutic benefit or it's placebo or they don't need to take anything.

MELDRUM: Right. But they're used to it.

LASAGNA: We had a disastrous trial years ago with some very elderly people who were unhappy about agreeing to participate in the first place and quickly dropped out of the study even though it was a crossover design because they were unhappy about not getting what they'd been used to getting for years.

MELDRUM: Wow.

LASAGNA: So that I have had trouble with. Maybe the answer to that is, don't study people who are happy with what they have.

MELDRUM: Look for unhappy people! [both laugh]

LASAGNA: Right! Right!

MELDRUM: Okay. We know that you're -- maybe I'm making a wrong assumption about this -- you haven't been deeply involved in the field of pain studies, the IASP. Do you, have you been observing them? Do you have any sense of the -- what's going on in the interdisciplinary field of pain studies that you want to comment about?

LASAGNA: Well --

MELDRUM: Do you see it as a useful approach --

LASAGNA: Yeah --

MELDRUM: -- to this problem?

LASAGNA: I mean, periodically, I will read that somebody rediscovered something that we rediscovered a long time ago [he laughs] --namely, that patients aren't treated well. You know, that doctors and nurses still, many of them, are too fearful about narcotics, for example. They're going to make addicts out of everybody, or we're going to kill people by depressing their respiration. And so whenever somebody does a study on post-operative pain, for example, they find out that the patients are not treated optimally. And that seems to be a recurring phenomenon that we don't make much progress on. And so I've kept up with -- I read a lot of literature, so --

MELDRUM: Right. Sure.

LASAGNA: -- I'm not unaware of things. But as far as the sort of formalistic society approach to pain, I haven't played a role ever in that. In the old days, I might say, because of this NRC Committee on Drug Addiction and Narcotics -- we would meet regularly, once or twice a year, and everybody who was doing analgesic studies would talk there. Houde and Wallenstein, for example, never published anything, but they would --

MELDRUM: I know.

LASAGNA: -- appear in the minutes of that committee.

MELDRUM: Right.

LASAGNA: And so you sort of knew what everybody was doing. I lost interest in that particular group because they moved away after a while from analgesic methodology to social concerns about drug abuse and addiction and so forth, so they had sociologists come and so forth, and it wasn't that it was unimportant, but it wasn't my bag and so I don't go to those meetings any more. I'm still on the mailing list; I get announcements about the meeting and the, whatever it's called these days -- the Society for Drug Addiction and Research.

MELDRUM: Yeah, I guess it's changed names several times over the years.

LASAGNA: Yeah.

MELDRUM: Okay. Well, are there any -- What would you like -- Anything you'd like to see changed in the way that doctors, for instance, are trained to deal with pain or how the pain is treated nowadays?

LASAGNA: I don't think doctors get trained to deal with pain. It's the sort of thing that gets short shrift in the curriculum, by and large. And I think there ought to be some attention paid to that. Probably, ideally, they should learn something about the drugs in the second year, but then in the third and fourth years, they get on the wards or in the clinics. That's when they should be given some advice. I mean -- For example, the hospice movement in this country is still fairly primitive compared to Britain. And you know, those folks have shown us that the way to treat people with chronic pain is to give them enough to keep them pain free, that if you wait for the pain to come back, you end up using more drug and having people more uncomfortable than if you don't do that. And so we've learned that oral morphine does work.

We used to think that there wasn't any point, you know, it was so ineffective to give oral morphine, you've got to give six or seven times as much. But you don't have to give six or seven times as much, and there are things that happen when you take morphine chronically. And there are little insights like that that could easily be taught to doctors; it just requires giving time in the curriculum somewhere, preferably, I think, later in the career rather than early. From people who know what they're talking about.

MELDRUM: Know what they're talking about.

LASAGNA: I don't think we do a great job of it.

MELDRUM: You don't think the pain clinics have improved the situation?

LASAGNA: [draws breath] I think they've improved the lot of patients who get to the pain clinic, but not as far as having impact on the great unwashed medical [both laugh] profession.

MELDRUM: Certainly there are still some patients with pain that seems to refuse to be treated, chronic, intractable pain.

LASAGNA: Yeah. Yeah.

MELDRUM: Have you dealt with any such patients, or --?

LASAGNA: We got interested at one point in using anti-depressant drugs in patients with phantom-limb pain or more often, post-herpetic pain. They'd get shingles and the shingles would dry up, but they'd be left with all sorts of weird pain, often terribly distressing, not responsive to traditional medications, but sometimes wonderfully responsive to anti-depressants. And it's got nothing to do with them being depressed, which they sometimes are; it's not a matter of undepressing them, and that's why they don't have pain; it has somehow an effect on the pain itself. And that's something that isn't appreciated as much as it should be.

Sometimes, just the anti-depressant alone works; sometimes we used to use something called Triavil. Anyway, it's a combination of a phenothiazine tranquilizer and an anti-depressant drug and sometimes that seemed to work better. But these are sort of tricks of the trade; there's a little bit about it in the literature, but it's very easy never to know that. [he laughs]

MELDRUM: Yes. I sometimes think that you can get buried, I guess. Well, anything else you want to comment on?

LASAGNA: No, maybe just a word about-- some words about 1974, my experiences with acupuncture --

MELDRUM: Oh, yes! I'd love to hear about that.

LASAGNA: -- in China. We went over there and found out that, after we saw some surgery being done, and major surgery, with acupuncture, always, as far as my experience went, in conjunction with a little spritz of Demerol they'd inject, and then twirl the needles or whatever. And at times it seemed to be working fine. We saw one young woman who had a fracture of the wrist, and she had this grim look on her face, and it looked like it was not politically acceptable to say that it wasn't working! [he laughs] I was struck by the fact that they didn't use acupuncture on children, by and large.

MELDRUM: Mm! That's interesting.

LASAGNA: And they had found by trial and error that there were certain procedures, like abdominoperineal resection where you do major surgery on, on the gut, where apparently acupuncture didn't, didn't work, so they would -- And it was interesting because unlike old acupuncture, which had been around for a long time, where you treated liver disease or what have you, acupuncture analgesia or anesthesia was really a post-Mao phenomenon.

MELDRUM: Oh, really?

LASAGNA: Yeah.

MELDRUM: I didn't know that.

LASAGNA: And so I ended up thinking, well, it does seem to work at least some of the time. Was it Melzack's gating, I mean, was it that if you have enough impulses going in that are not painful, they sort of make it hard for the painful ones to get through? We did do a trial once at Rochester, where we tried to treat arthritis with acupuncture, and the question there was, what's the control? How do you blind it? And the placebo control was sticking the needles in the wrong places. You had the right places for arthritis and you had --

MELDRUM: The wrong places.

[interruption to check recording]

LASAGNA: And we didn't see much difference between them. But you can argue that, well, we weren't skilled acupuncturists; maybe the right spots weren't being hit quite as neatly. So I ended up feeling that there was something to it. There were some experiments in animals or horses that suggested that it might work.

MELDRUM: Now, what prompted this trip?

LASAGNA: Oh --

MELDRUM: Or who else was involved?

LASAGNA: I was chairing a delegation -- this was shortly after Nixon opened up China --

MELDRUM: In '74, yeah.

LASAGNA: -- to go over there to see whether there were any hidden treasures in the traditional medicines of China. And we came back feeling, God, they've been doing this for centuries by trial and error; they probably have figured out some things that really do work. But you can't tell because their records were terrible -- they would admit a patient to the hospital and on Day One, they'd get three or four herbs; Day Two, they'd drop one and add two, you know. It was not Western research.

MELDRUM: Right.

LASAGNA: Since then there has been a lot more interest in whether they have any goodies over there. Not a lot has happened so far, but --I wanted somebody to give us a grant to study populations in different parts of the world, because I'm told by botanists that the kind of plants that grow in a given latitude are the same wherever you are in that latitude. So, my idea was, let's go to populations that are geographically separated and if they're using the same thing for the same ailment, then maybe that's prima facie evidence.

MELDRUM: That that's correct. [both laugh]

LASAGNA: Never could do that. But that's why we went, was to see whether there were any traditional herbs, or whatever, that we should follow up on. It was a funny time to be in there because they were just coming out of the Cultural Revolution.

MELDRUM: Right. Right.

LASAGNA: And a lot of scientists had been sent to the countryside to pick radishes, as the expression went.

MELDRUM: Yeah. Be janitors.

LASAGNA: And they'd put on displays for us showing us stuff that we knew had been done ten years earlier because they didn't want to admit that things had ground to a halt. And Mao was dying, and nobody knew what was going to happen. My own feeling was that unlike the sentiments of some of the members of my delegation who thought, oh, he's had such a wonderful impact and his spirit will triumph forever. And I said, "Look, we're meeting some awfully tough cookies here." I said, "I think there's going to be a fantastic struggle for power when Mao dies, and we're going to see--" I went back in 1980 or '81, and some of the ins were out; some of the outs were in; and things were better but still not great. And today I'm depressed to read about what must be close to --

MELDRUM: Ghastly.

LASAGNA: -- the most repressive society in the world.

MELDRUM: Uh-huh. Interesting. I'm not supposed to talk about myself but we have time. I have a close friend who, in fact, was trained as a physician in China and came here. The Chinese government funded her to study history here. She decided she wanted to stay; she went to nursing school [she laughs] because it was the quickest way she could get a needed skill so she could stay in this country. And she said to me, you know, "You don't know how it is there. You just can't -- you can't imagine how horrible it is and how you're not able to think for yourself." So --

LASAGNA: Well, when we were there, we'd meet people who were 65 and retired, and they'd talk about how wonderful things were, and I ended up feeling, yes, things are better than they used to be.

MELDRUM: Really?

LASAGNA: But things are bad! [he laughs] And I thought, maybe for the old people who remember the dreadful old days, this is a step forward.

MELDRUM: Oh, sure.

LASAGNA: But if you're a young person and don't remember the bad old days -- after a while, especially with contact --

MELDRUM: With the outside.

LASAGNA: -- with the outside world, you're going to feel, there's a better life than this somewhere.

MELDRUM: Yeah. And I'd certainly, a lot of young Chinese people who have managed to come to the United States and have done everything they could to stay here --

LASAGNA: Absolutely.

MELDRUM: -- or to other countries.

LASAGNA: Yeah. We get an enormous number of applicants to our graduate school here every year, and a lot of them are, just as you say, determined [he laughs] not to go back.

MELDRUM: Not to go back. And it is sad because there is a rich tradition there.

LASAGNA: Yeah.

MELDRUM: Um --

LASAGNA: Have we done it?

MELDRUM: I think so.

LASAGNA: Okay.

MELDRUM: I think so. Well, thank you very much!

LASAGNA: You're welcome!

END OF INTERVIEW