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Dear Herb:

Please find enclosed a transcript of my interview with Len Cook, conducted in conjunction with the APA Centennial Oral History Project. Len finally got around to editing the raw transcript at the end of October, 1992. The typescript enclosed contains only those portions of the interview that Len consented to make public. As you will see when you read the material, we strayed a bit from the central purpose of documenting the history of Division 28; nevertheless, I think there is some valuable material here, especially the details regarding the discovery of chlorpromazine's therapeutic and laboratory effects. Len's description of drug discovery strategies is also quite informative, I believe.

As you select the portions to be included in your volume, or otherwise edit the typescripts feel free to call on me for assistance at any time. I can supply an ASCII file on diskette if you wish.

This was a very interesting experience, and I appreciate having this opportunity to look more closely into the history of psychopharmacology.

Have a happy and prosperous New Year!

Sincerely,
Steve Fowler

This is an edited transcript of an interview with Dr. Len Cook, Senior Research Fellow, Central Nervous System Diseases Research, DuPont-Merck Pharmaceutical Company, October 1, 1991. The interview, recording, and transcription were conducted by Stephen C. Fowler, Professor of Psychology and Pharmacology, University of Mississippi. Dr. Cook edited the transcript in the fall of 1992. The interview was carried out under the auspices of Division 28 (Psychopharmacology and Substance Abuse) of the American Psychological Association as part of its Centennial oral History Project. Thanks should be extended to Cynthia Shearer and to Elaine Cremaldi, who toiled long and skillfully in transcribing the audiotapes into a readable transcript.

Fowler: First I will ask you a few questions that Herb Barry recommended and this other Fellow, Popple-Stone, who is a historian of Psychology recommended, to get at the founding of the division and your role in it. And I guess that would be the first question. You were one of the early presidents of the division in Psychopharmacology- and you were probably nearby or present and knew all of the people involved in it. And the first president was Murray Jarvik. Do you have any recollections about how it was formed and whether it was mostly psychologists, mostly pharmacologists?

Cook: I'm not sure if I'm historically correct here, but in the APA Division 25 was the original group.

Fowler: Right.

Cook: It was 25. It was called...

Fowler: Experimental analysis of behavior.

Cook: And if I'm not mistaken, Charlie Ferster was involved with Division 25 and other operant psychologists. The pharmacological overlay grew.

Fowler: 1966 was the founding of the division.

Cook: By then there were at least ten years of history of the study of drugs interacting with behavior. In the early days the operant behavior techniques took an almost immediate role of prominence. And therefore there was a blend between such sophisticated behavior and some of these new drugs. It became clear that the drug was as important a variable as the technical manipulandum. And I think they decided to form this division because of the very special aspect of pharmacological interventions in regard to behavior and also the fact that there wasn't really a vehicle for the people who were doing drugs and behavior to get to4ether. I don't completely-recall who the movers and shakers were in forming that division. I would suspect it might have been Ferster. Certainly Murray Jarvik. I know I was involved to some extent. I think it was formed primarily to give a meeting forum for the people studying drugs. Interestingly, when it first started, some people in behavior really thought of drugs as some trivial factor of intervention.

Fowler: Well, they thought--some of the scientists, I think-- thought of it as "just an independent variable." That's the way a lot of operant people talked about it.

Cook: And what really began to happen is that they realized that the drugs were not so much another independent variable but that there was an interaction between drugs and behavior and it wasn't all one way. In one particular study I published it was very clear that the behavior itself was a predeterminant of the quality of the drug effect. What the animal was doing had an important influence on the quality of the pharmacological effect. That the drugs didn't act on the behavior like perhaps an antibiotic acts on a bacterium, but that something I've been very strong about is that the drugs don't affect behavior, they interact with behavior. What the animal is doing, how that animal is doing it, and why he is doing it--all affect the quality of the drug effect. I think that early recognition of this was one of the main reasons for forming the group.

Fowler: Well, do you recall who all might have been involved besides Ferster and Jarvik?

Cook: I think Joe Brady must have been involved. I wish I could remember now.

Fowler: Look at this list.

Cook: I think Larry Stein, myself, Bernie Weiss, the names you've got here: John Boren--these people were the movers and-- Peter Carlton with his cholinergic findings. These people were highly involved.

Fowler: Did you attend APA and a Division 25 function before Division 28 existed?

Cook: I did.

Fowler: So in a way...

Cook: I think there may have been political reasons as well for trying to break from 25 and I don't recall clearly what they were.

Fowler: Well, probably the circumspection of language that was required if you were there--

Cook: I remember I went to a meeting at the CIBA Foundation in London. Larry Stein was there and Peter Dews was there and, oh, a whole bunch of these guys--I forget what year. I was talking about chlorpromazine and meprobamate and I showed a slide that absolutely lifted Peter Dews off his seat. The next day he said, "I've got to have that slide." Essentially what that slide showed was a multiple FI-FR schedule. It showed clearly that when the animal is working for a similar reinforcement but on a different schedule of reinforcement at the very same time, that what he was doing and why he was doing it predetermined whether it was going to be an increase or a decrease in response rate.

Fowler: Yeah, it's a very powerful effect.

Cook: Then Charlie Catania and I several years later adjusted the rates of responding and it still happened. So it was not a baseline thing.

Fowler: That's right. It's a qualitative effect based on the kind of behavior--what's controlling the behavior--

Cook: Yes. Exactly. And that was really exciting. Drugs didn't act on behavior, they interacted with behavior. And to me, that's been an extremely important point to all kinds of applications--like antidepressants. Why does it take an antidepressant so very long to show its effect? There's a buildup of biochemical levels, but it may just be that it has to have a certain type of interaction--residual effects of the interaction between drug and behavior--that just takes a while to occur.

Fowler: And learning phenomena have a very long time course., if you think about it, for consolidation of very long term memories- -I guess that makes sense.

Cook: Yes. These are the kinds of the things I think stimulated the organization. There also might have been some political aspect as well. The people in drug not really able to voice much or have much impact in Division 25.

Fowler: Do you recall, at that time was there a restriction on how many papers could be presented at the annual meeting and was that part of the motivation—to have your own program time?

Cook: I think, yes, because we used to vote [on amount of time] according to the number of [Division] members.

Fowler: Yes, we still do that.

Cook: That was one of the things. It was a matter of not having a sufficient vehicle to present all the research--that stimulated the group to form.

Fowler: Do you recall who might have been the major kind of bureaucrat, not pejoratively, but the one that did all the paperwork that you have to do to do these things?

Cook: In 25?

Fowler: No, in 28. I mean in the founding of 28. Because you have to deal with the APA central office—

Cook: I really don't know.

Fowler: You have to correspond with people and stuff.

Cook: I think maybe Murray might have--I don't know.

Fowler: Okay. I'm just curious about that. A small group always has to have a few people who are willing to do that kind of work, and they often go unknown.

Cook: Yes, I know. I remember the beginning of the journal JEAB. Charlie Ferster and his wife ran it from their sun porch. I know this. Their office was a sun porch of their house. Because I was at Smith-Kline and I gave them the seminal amount of money to get that going. I really did. Talk about beginnings of these things!

Fowler: How long has the Hospitality Suite been a part of Division 28? Do you recall? Did it start with the Division?

Cook: I think so.

Fowler: And did they hit you up immediately to help pay for it? Cook: They've been hitting me up for years. Indeed, I'm happy to do it. I would try to kick in a little bit. They would always look to the drug companies. And every time they went to drug companies, they hit Len.

Fowler: Well, frankly, I think that's had a very beneficial effect on the organization. The interchanges that occur at the hospitality suite are as good as any that you get in the formal part of the meeting.

Cook: Oh, yes. And the other one was the Behavioral Pharmacology Society.

Fowler: Do you know the story of its founding?

Cook: Although I was there, I can't remember specifically how that ever got started. I know I was involved with it in the beginning.

Fowler: I think it started in 1960, according to Herb Barry's notes here. But that was sort of before my time. In the same context, how would you say Division 28 has, or has not been, influential in shaping psychopharmacology in general? In other words, providing that forum in 1966--how important was it, or was the really important stuff already done, in a sense?

Cook: A lot of important stuff was done in the 50's. Let's say the last six years of the 50's, and the 60's. I think a lot of the principles had already been laid out--if not clarified. I kind of think that the work that was done by

people like Brady and Don Finocchio (at CIBA). My lab was very influential. We had Bob Schuster and Roger (Kelleher]. Roger left me in 1960. So Catania was there even in the early 60's with me.

Fowler: And Ed Weidley?

Cook: Oh, Ed Weidley was with me through 1951 until I left (Smith-Kline] in 1969.

Fowler: Was he a pharmacologist or a psychologist?

Cook: He was a technician.

Fowler: Oh, he was a technician. That's interesting.

Cook: He was a high school kid.

Fowler: No kidding! He must have been a fast learner!

Cook: That guy had outstanding innate scientific qualities. I just picked him up when I interviewed high school kids. Did you ever know anybody who intuitively has all of the skills that you need? I couldn't think of a better fit. He eventually went to college at night. Got his degree and eventually moved up in the company to the equivalent of a group leader, which is like the middle level of PhD's. He's still there, I think. But he was a high school kid at the time.

Fowler: That's interesting, indeed.

Cook: And he was a true colleague. Don't forget--we wrote the book in this area, so he was involved with me in all the thought processes.

Fowler: It strikes me as the equivalent nowadays, or ten years ago, of the computer hacker. Some of these people that were just geniuses turned loose on computers. This guy Gates that founded Microsoft, that's the way he got started.

Cook: I've never seen anyone in all my years in the field to compare to Weidley in setting up a protocol with the appropriate controls. That protocol he wrote was absolutely perfect. I wish I had someone like him doing protocols today.

Fowler: Well, maybe he was so good because he didn't have any education.

Cook: (Laughter] No contamination!

Fowler: Right. That's what people say of great writers. Many, many great writers trained themselves and weren't influenced by academia so as to kind of calcify their thinking. I think there's some merit in that idea.

Cook: I wish I had a clone of him. But in any event, the work we did influenced the field. The work that was done by guys like Bob Schuster and me. We were deeply involved with the principles involved. Roger Kelleher and Keith Killam also were early members of my group. Many of the principles of psychopharmacology were formulated then in our group.

Now. I think the work we did influenced their thought processes in their careers. The influence they had in terms of the field was also important. It had to have an influence.

Fowler: How about Neal Miller? It strikes me that he did the work with amobarbital and conflict and the Miller-Dollard conflict theory. But that never really influenced psychopharmacology.

Cook: No, it did not.

Fowler: It's because the methods were too cumbersome, maybe.

Cook: Neal Miller was around, but just wasn't a great influence ..... As I recall.

Fowler: Yeah. I think that was it (the reason Miller's work did not affect psychopharmacology]. It was the lack of a stable baseline concept in the kind of experiments they did.

Cook: I guess the one thing I did--and people like me in the drug companies as well--was that in the evaluation of drugs, we needed precision, we needed accuracy, we needed quantification. We needed stability of baselines. And what we did--I know my lab focused on it more than anybody--was to attempt to have stable baselines. My focus was that there was no reason in the world, despite my arguments with Ferster, why behavior couldn't be as reliable a baseline as the heart or any other system. It follows all the same rules, and there's no reason you can't quantify it, demand stable baselines, run all the standards, run dose-response curves, run time-response curves. All of the things that had never really been done before. If I had one contribution, that certainly was one of them. Demanding that behavior be considered as any other substrate system to evaluate drug effects.

Fowler: Right.

Cook: It was to demand that the behavior be looked upon no less than any other baseline in terms of physiology.

Fowler: Right, right. The quantification is really the key. Because you know, academics spend so much time testing a hypothesis and accepting it or rejecting it, as opposed to quantifying the size of the phenomenon. That's something I've always had a peeve with.

Cook: Exactly.

Fowler: I've spent my work trying to quantify [behavioral drug effects] and I think that's the key.

Cook: But, Steve, that was so key, and I know that that's one thing my lab brought to Division 28.

Fowler: Right.

Cook: And as a matter of fact, it was such an impressive thing @hen Peter Dews saw this in a JPET paper, that's when he got Roger (Kelleher]. Because our paper presented quantification.
And I'm trying to think in what way Division 28 had an impact in terms of "drug discovery" in psychopharmacology. Well, I think they enriched it in a sense that

they described more drug- behavior interactions. I think it certainly did have an impact in terms of the discovery of new therapeutic agents. I would go to these meetings and get a lot of ideas and say "Gee that was an interesting thing; I think I want to come back and try it." So, these early meetings offered a rich source of ideas and interesting projects to follow.

Fowler: Right.

Cook: I guess that was the real beauty of those meetings. You heard people talk about some of the things that they were doing--even though they may not have fully appreciated what they were talking about in terms of the drug-behavioral studies. They may not have fully appreciated what that meant in a more pragmatic sense.

Fowler: Right.

Cook: I would often sit there and say, "Boy, that test is- just right for that series of compounds that I need to look at. So, it was an excellent learning forum. We used to visit each others' labs a lot. That crew reflected a very close fraternity. We knew everybody. God, I remember going down to visit Dick Herrnstein when he was in Washington at Walter Reed. He was a great guy.

Fowler: I don't recall that.

Cook: He was at NIH.

Fowler: For a couple of years. He's been at Harvard a long time.

Cook: I knew him when he was in Washington. I believe he was with Brady, because se I remember I used to visit Joe (Brady] a lot, and I was trying to learn his operant approach. I remember going there when Roger [Kelleher] first joined us in '56. We went down to see Joe [Brady] and Herrnstein.

There was a good healthy interaction within Division 28. All of the work they did behaviorally with drugs had good fallout in terms of discovery and applications. Guys like myself would say, "I think I could use that", or even just as important--there would be a lot of discussion about what's going on. And questions we didn't originally think of, e.g., "That's a baseline effect and not the FI schedule--you're talking about a low baseline." The meetings elicited a dialogue, that was very sophisticated and made us think about all the little nuances of what was going on. And we had great meetings. I have not seen in the last ten years anything that even approached the sophistication of drug behavior interactions. I think it's an enormous loss. I think about the concurrent schedules and secondary reinforcers, and issues like that. All the tremendous critically important experimental factors that were recognized then. But today we're all the way back to motor activity. We're all the way back to passive avoidance. We're all the way back to the most pedestrian behavioral work. When I hear people say, "oh, we did some behavioral work," and what they call "behavioral work," the rat is walking around. And I think we've lost a real distinction. I wonder where all the sophisticated behavioral approaches went. You mentioned before that perhaps the hard sell operant guys turned so many people off by their jargon that others just moved away from it. I saw that happen.

Fowler: And that those people, too, could not embrace some of the new concepts, yet, while keeping their old concepts. I see the sector of

pharmacology as kind of coming in and taking over in a way. And good and bad coming from that.

Cook: And now they're being replaced by the molecular biologists.

Fowler: Yes, right. This is your history, but it seems to me that one of the most serious problems here is the belief in deterministic systems that are not influenced by the environment. The molecular biologist has this idea that he can figure it all out from the genes and the way environment influences behavior is not even important. Clearly, in something that is as complex as we are...

Cook: They would laugh at our point of view.

Fowler: Yeah. Maybe it's just going through a cycle. The understanding of how important the environment is, in influencing behavior and individual history will come back, and a resurgence of some of these [behavioral] methods will also.

Cook: I feel that an enormous amount has been lost. For whatever reason. In terms of the entire field of psychotherapy, pharmacotherapy, or psychopharmacology. An enormous amount has been lost. I see such things happening even here, within a very sophisticated company. They said, "oh boy, the peak effect of this drug in blocking conditioned avoidance is three and a half hours, and yet the drug blood level peaked at a half hour--the half life was already gone. Isn't that weird; we can't explain it. "

I'm sitting there and thinking of all the things that I learned over the years, such as residual effects of the behavior- drug interaction. Even though the blood level has dropped, it is still contributing more and more to the block of behavior. How do we explain this? When one refers to such concepts, they look at you as if you were from the moon.

Fowler: Well maybe we're close to a threshold though, of being able to talk to them in both languages, like once we know more about how learning is laid down, say, through protein synthesis, and get an idea of some of the time course of those syntheses, maybe we'll be able to explain a little better how the environmental event is changing behavior in biochemical terms that then make these drug effects that seem residual a little more understandable to the chemist.

Cook: Right. But now, they correlate reasonably well the half-life and the blood levels with the effect in blocking a calcium channel in a heart, and they got these things set up, e.g., correlation coefficients. But they say, "... behavior's kind of weird, though, it doesn't correlate." I point out, "the blood level may not be nearly as important as the brain levels of drug."

Fowler: Indeed.

Cook: The drug could be building up in the brain and the blood levels could be gone, while the brain level of the drug is still going up.

Fowler: Right.

Cook: If you give chlorpromazine to a rat, you block conditioned avoidance. However, the maximum effect after any dose could be hours and hours later.

Fowler: This is an indication of what chlorpromazine's brain levels are, to some extent.

Cook: There was a very sophisticated period. A golden era in the 50's and 60's of experimental psychology/psychopharmacology. It has been replaced by the receptor theory. We lost very important tools that could be used.

Fowler: There's not many...

Cook: You have some very sharp guys on that list of early workers in this field. Each one had a school of disciples after him. That's gone. I think it will take a long time to ever build up. Today, we're doing delayed matching to sample, which is reasonably sophisticated. But we're not doing all that great stuff we did with Catania, on concurrent schedules, titrated working for food, working for shock, where we found the schedule of reinforcement is more important than reinforcer!

Fowler: Right.

Cook: I mean--who would have believed then some of the principles that evolved? That's what's not going on today.

Fowler: Well, maybe some of it's not going on partly because the funding for university research, or basic research in general, hasn't kept up with the military buildup. Our proportion of GNP spent on research and development by the government is low compared to many countries. Maybe that's had an influence. Another thing that strikes me, though, that had an influence, relates to this operant terminology--is that "memory" wasn't in their vocabulary. They had a communication problem there.

Cook: My colleagues would have shot me if I went before the society and talked about "memory." "Come on, Cook, it's supposed to be operational here." I remember a little story that almost changed the course of psychopharmacology in my company at that time [Smith-Kline-French].

I had put in a huge budget request to buy equipment and to get a set-up for operant psychology, e.g., Skinner boxes, etc. I tried to impress the research board committee with its value. I knew that Peter Dews had the golden tongue. This guy was good. So I said, "Peter, would you come down and talk to the research people and tell them why all this is important."

Peter was just elegant, so I invited him. Well, he came down with a pigeon in a pigeon box, and his young colleague named Bill Morse, and instead of speaking with his eloquent tongue, Peter turned our meeting over to Bill Morse. And Bill shows a slide. Do you remember when, years ago, workers would compress the cumulative records, and you got fifty cumulative records cut out? He said, "Well, you can see the post-reinforcement pause, etc." -- These directors were sitting there, they didn't know what he was talking about. It didn't mean beans to them.

Fowler: That's right. They want condensed language.

Cook: They want words like "memory". Bill was referring to overall rates, local rates, post reinforcement pause. I thought that was the end of my job. My lab was seminal and pivotal in the field in that period of time. We were leaders. And I thought, that's the end of this approach. But it wasn't, fortunately. That was a period of great tension, that day. In any event, I think

that was a period in which Division 28 brought to the world this elegant science. It was primarily operant, but it showed how to control behavior--maybe define behavior in many of its elements. The people working with the drugs then could define how drugs and behavior affected each other.

George Heise was one of the leaders in that group. To answer your question, I think the group did impact on the field with a degree of sophistication. But precise language and their insistence on describing it operationally made it difficult to be accepted.

Fowler: It [hard core operant language) just doesn't relate well enough to people's base of knowledge.

Cook: Right. And I see that the people who have succeeded in science don't hesitate. They say, "Well, I did this little snail . . . and it learned!"

Fowler: Kandel.

Cook: Kandel. He used the aplysia for his studies. He did his experiments and he talked about memory and learning, and it sells. He talks to the decision makers and the vice-presidents and the directors, and they are impressed with his style of communication. I think a great mistake the operant scientists made was not that they developed a very sophisticated science, but that they were hesitant to compromise in regard to their style of communication.

Fowler: Right.

Cook: Let me tell you what I tell all my young colleagues. I say, "Look, I'm hiring you because you're a good scientist, but there's something else you've got to know. You are a spokesman for your science. Every scientist, every artist in the world, always has had to have a patron. If Michelangelo didn't have a patron, he would have been be painting the outside of houses rather than the inside. You as a scientist have benefactors here--the Board of Directors, the stockholders, the boss. They are not there to support you because you're good-looking or because you're smart. They support you in terms of what you can do for them. Bottom line. We're here to make money for them, and they pay us for it. Now that means that they're relying on us to bring the very best science in here to do one job.

And we hire only the best scientists in the world. But the responsibility we have is to communicate to them why they need us. And why what we're doing is important for them. Nobody's going to support you unless they understand what you're doing. Understanding is the key. Once somebody understands what you're doing, you've got them. You've got 'em lock, stock and barrel when they understand. The minute they understand it, inevitably they'll say, "Isn't that great!"

So your job is to communicate, in language that they understand, what you're doing and why its important to them and where it'-s going in the future. That's your job, in addition to your technology. So don't take the attitude that this is prostituting yourself. Don't consider taking this job if you feel you're contaminating yourself by selling what you're doing and communicating in a language they understand. In my experience, the very best scientists are the ones that can describe their science to their eight-year-old child or to their grandmother.

Fowler: Yeah, I agree with you. I think it's extremely important.

Cook: You don't say "I'm using a concurrent schedule with an F15” when you're communicating with someone not in the field. In molecular biology you can get away with it. They do get away with it. We cannot. We never have been able to get away with it, and we never will. You know why? Everybody considers himself an expert in behavior. So, when you describe behavior, you've got to describe it in terms that explain your goals to them.

Fowler: Don't want to oversell.

Cook: You've got to be careful. I will say, "What we're talking about is a cognitive enhancer... 11 And I refer to "memory", and I talk about short-term memory and long-term memory. I talk about psychoses in terms with which they are familiar.

Fowler: Right.

Cook: I feel that I've got to prove that what I'm doing is valuable. And they deserve an explanation of what I'm doing in language they can understand. No other discipline that I know has the burden of a psychologist in asking for support from non- psychologists.

Fowler: Yeah, it's a problem. It's had a big effect on funding, in my opinion. The psychologists who have been unable to learn the language of the other people they'll be speaking to have had trouble getting funded for about the last ten years.

Cook: Now. one of the issues regarding Division 28 is that through all the years they have not come to grips with "selling" what they're doing for the support that they needed, and in language that is understood. They had to package that beautiful science into some communication style to tell people why it was so important.

Fowler: I think it's worked in drug abuse. Take drug self administration. It's easy enough for a person to see that.

Cook: Their approaches have face validity.

Fowler: And I think that's one of the reasons why most of the leaders now in Division 28 are related to drug abuse research in some manner.

Cook: When I talk about drug abuse and drug discrimination in the company, I refer to the animal's "perception" of how he feels or doesn't feel. That's my language, and non-psychologists seem to understand the study.

Fowler: Yeah.

Cook: They say, "Wow, that's great."

Fowler: I've had that same experience.

Cook: If they ask me further questions, then I can fine-tune it scientifically. But you don't fine-tune it up front.

Fowler: Right. You know it strikes me that B.F. Skinner was excellent at translating. Not in the context of drugs, but in the context of behavior

analysis, and he made a tremendous effort to say how this could be applied in a society, in the classroom.

Cook: I see.

Fowler: He was very effective at it, I think—

Cook: But his disciples—

Fowler: Did not--

Cook: Charlie (Ferster] didn't do it.

Fowler: No, no. Most of them did not.

Cook: Charlie, Catania, and Herrnstein were some of his disciples.

Fowler: Brady's been pretty good at translating findings of operant psychology into common parlance, I think.

Cook: Yes. Some of the real purists never would have done it, and that's what turned the vice presidents off. It's unfortunate, because the scientists did it to themselves.

Fowler: But do you think it might have been related to the breadth or narrowness of their training? I mean, as general scientists, like, to be trained as a general scientist first, then to pick up behavior--you can see how to put them together better.

Cook: Probably.

Fowler: That just a hypothesis I've had.

Cook: Probably.

Fowler: Let’s talk about being a successful scientist a little bit more here. I was going to put that question to you, and this really addresses it. Salesmanship we already talked about. I wrote out a list here: how much of it is raw intellect, how much of it is entrepreneurial spirit, how much of it is perseverance, how much of it is risk-taking, how much of it is luck? In addition to sales, what makes for a successful scientist?

Cook: "Successful," meaning what?

Fowler: In my opinion, meaning that you did something substantive, whether it was recognized or not. It's not necessarily achieving notoriety, or developing a new drug.

Cook: It's not giving this great institution a new recharger- -you don't mean that.

Fowler: No, no. I mean actually making a contribution that affects the way things go scientifically. Whether it's recognized or not.

Cook: Well, I think we should break success down into a couple of things. Success in terms of support, let's say. First, in any one of the things we talk

about, there has to be competence. That goes without saying. Success in getting support. I think it's the things we talked about. Communicating what you are doing in terms of its overall importance in this world. Its overall importance, for example, in terms of understanding a disease state or treating a disease state. And why what you're doing is particularly helpful. This doesn't demand as much salesmanship as really understanding where you are. The really top scientist understands what he's doing and its importance to the world. The good scientist knows it. I also know a lot of people that are so techo-proficient, and they themselves don't realize the overall picture. success requires technical competence, but also an understanding of what turns on the funding in order to build a useful science group.

Fowler: It strikes me--and I'd like your comment on this--that maybe universities have created an environment, in at least some top universities, that have gotten people away from an understanding of what it means in a broader sense. And this has actually inhibited this kind of understanding. It's only people who brought it in and resisted the kind of sophisticated minutiae that you often do in a Ph.D. program that have made the successful scientists. Do you think that's true? Like, the people you hired, you want to make sure they already understood the broader implications, but how many of them did you not hire because they didn't, and how much of that was university training?

Cook: I would say I hired or would have considered hiring maybe one out of ten that I have interviewed.

Fowler: Yeah.

Cook: All things being equal, of all the competent young people, about one of four I sensed intuitively could go for the jugular and would help me to find a drug for therapeutic ends. Where that goal would become his priority instead of concentrating only on his own technical career. I always weeded out people who I sensed had as their first priority building up their technical shtick. Those I hired, who were willing to adhere to my goals are the ones you know: Kelleher, Killam, Catania, Holz, Sepinwall, Davidson, Gamzu. I must have talked to dozens and dozens of interviewees--to find those who were not only technically good but were willing to work with me to satisfy our "patrons" and our primary goal. Our patrons are paying us to find new drugs. So I look for the best scientists who were willing to help satisfy those patrons so we would get more money to do better science. And those were the people that I sensed were willing to do it.

Fowler: You know, as you've been talking about the history of this, especially learning from people on the East Coast about behavioral pharmacology, it strikes me that one thing really characterizes your approach is the degree to which you will seek information from any quarter, whenever you sense you need it.

Cook: Yes, that's true.

Fowler: And I think that's one way of defining "problem-solving research" as opposed to "discipline-based research." It seems to me that really characterizes what you've been doing. It's only in academia in the last decade that people have begun to say "problem-oriented" research, as opposed to departmental research.

Cook: I'm an adjunct professor at Rutgers in psychiatry and at the University of Pennsylvania and at Temple in pharmacology. I know what's going on in the universities. I have friends from all over the country coming in and saying, "I have a grad student, and we can't get him a job. I need your help-"

I see the result of six to seven years of graduate studies, just killing themselves at the end of which they're a clone of their professor. They're the image of their professor. And this professor is trying to sell him to me. Unfortunately, the student wasn't trained for the job market but to reflect the professor's interest.

Fowler: Right, right. You've got to make it work.

Cook: It can be so much fun working in industry, Stephen. We get to write papers. We get to go to meetings and give our talks. We're colleagues with everybody. It's fun to do industrial pharmacology. It's the greatest secret in the world. The point I'm making is that these professors come asking, "Get my kid a job." What I see is a real failure of many of the faculty in the following way. They train the students in their image. I want someone who knows pharmacology, who knows the whole animal, who understands psychopharmacology. Today we may be in dopamine, tomorrow we may be in calcium blockers. I want these students to know what drugs do. And to know that if an animal's stopped responding, is it because its blood pressure is down 40 millimeters. I've gone to the pharmacology society, and I tell the people who are training the students, "How many of you have gone to the potential employers and asked 'Where do you see the future jobs ten years from now?"'

"How many of you chairmen have gone to the drug companies as potential employers for your students and said, 'What are the skills or what are the jobs you need ten years from now? How can I train my kids so that after six, seven years of hard work they can now get a job in an area where they can do the best of science, and also make a living?"' Isn't that what it's all about?

Fowler: Yeah, well, there's not many graduates in pharmacology that meet these criteria.

Cook: They don't. When the professors do come to me, I tell them the kinds of skills I need now and what we will need five years, six years down the line. And if they are interested in training the student to make a living--which in my book is the primary, responsibility of a professor, learn where the jobs are. For example, say, "We're going to train you for the pharmacology of age-associated memory impairment. We're going to train you for Alzheimer's. We're going to train you for drug abuse. We're going to train you for this, so that you can get a job in the pharmaceutical industry because they told us what kind of young scientists they want. We went down to ARC, spoke to Roy Pickens and said 'Okay, Roy, where do you see your needs are going to ten years from now?'

Fowler: Right, right.

Cook: This doesn't happen very often.

Fowler: Yeah, I know. The Professors are not nearly flexible enough. And in my opinion, the institutions aren't flexible enough either in terms of having liquid resources to change direction. You know, that's with respect to laboratory apparatus or whatever it happens to be.

Cook: I know, I know. I think they could do more. You know, I graduated from Yale in pharmacology. The chairman at that time, Salter, essentially trained pharmacologists for industry. He said industry had come to him over and over for appropriately trained pharmacologists--that was in '48. There was nobody trained to fill the jobs in the new, infant industry. So Salter said,

"Okay, what do we need? We need people that know animal models, who know the physiology, and know statistics."

Fowler: He was a rare one. Because a lot of pharmacology departments don't do that.

Cook: Did you ever hear of Bliss? Chester Bliss?

Fowler: Yeah, I think so.

Cook: Fisher's student (Fisher was the originator of analysis of variance. Three years I had with him (Bliss]. [Laughter] That's my training. We had three years of biometry. Salter also trained us in alkaloidal chemistry and steroidal chemistry. We did clinical pharmacology. He specifically trained us because he knew what the industry wanted. When I went into industry, I hit the ground running because I was prepared. And so did everyone else in that group. Salter, at Yale, was one of the rare chairmen that asked where are the job needs. Do you know that when I graduated, without leaving New Haven--this is the truth, Stephen--I had six job offers? I swear to you I had six job offers and never left New Haven. Because industry knew we were all being prepared. They said, "We want your guys, we want your students."

Fowler: They knew how to do the job.

Cook: We were trained to go--we knew pharmacology, we knew biology, we knew physiology, biochemistry, statistics, animal models.. That's what industry wanted. Today, this is being done at the Medical College of Virginia.

Fowler: Yes. And they've had a specific mission ever since Lou Harris got there, to be a top place.

Cook: He came from industry.

Fowler: I didn't know that.

Cook: Lou was an industrial pharmacologist in Sterling for a number of years.

Fowler: Oh, I see. And then he went to North Carolina, isn't that correct? Then he left North Carolina for Virginia Commonwealth University?

Cook: That I don't know. So. Success. Knowing how to sell young students. Knowing and having the skills and tools to do what is relevant. That's not all success is. But I look upon success as being able to gain support; because, without a patron, you’re a dead duck.

Fowler: Yeah. Unless you're wealthy.

Cook: I was just talking to somebody yesterday. He got a 1.3 or a 1.4 score for his grant. It wasn't funded.

Fowler: Indeed. But we're just talking six per cent in NIDA just now. Well, I know several stories like this, in the last ten years. It's been extremely difficult to get funded.

Cook: I've sat on several grant committees over the years. In particular, the psychopharmacology grant committees. I get grant proposals that are twenty-four

agonizing pages. Have to re-read them three and four times to understand them. Frequently, the message doesn't come across.

Fowler: The battle is lost.

Cook: The battle is lost for the grantee. If I have to go to Table I and Table 3 to figure out what the point is, he's making me work. Other proposals are very clear, I know just what he's doing. And I understand. Remember the secret word, that I understand what he's doing. That's success. Also, ingenuity, imagination, having that "x factor" which lets somebody go for the jugular--what is the word--"creativity?"

Fowler: Well, defining the x-factor has been tried by many people. Not satisfactorily, but--

Cook: Matter of fact, I went to a dinner party Saturday night. I was sitting at a table with a woman who is an artist and she was talking about creativity. How she walks for weeks around that blank canvas and all of a sudden she picks up that brush and it goes. Well, you know that's the magic moment. It happens with us, too.

Fowler: Yes, it comes to you in ways that you'd never predict. That you can just get an idea, but then say, "ah-HAH."

Cook: Yes. Writing papers. We look at that blank paper, sometimes for weeks, and you just can't get started. Then, all of a sudden you pick up that pencil and it goes.

Fowler: You're ready to go. That's right.

Cook: The same way as happens with an artist. I was telling the artist, I don't believe she just picked up the paintbrush and started painting. I said, "Unconsciously or whatever, you've been formulating the idea or concept for weeks and weeks, and you had the magic moment and it all poured out. It's the same way when I write a paper. I've been writing it in the back of my mind for weeks. And all of a sudden it comes out on paper.

Fowler: Right.

Cook: Well, that is what we call creativity. Some people read the literature avidly. And there's a class of people who keep up with the literature but are not overly influenced by the literature.

Fowler: Extract the main ideas from it, say.

Cook: Yes.

Fowler: And it's something to think with.

Cook: The creative scientist knows what's going on in a general sense. But they're not the followers. They somehow have that intuitive sense of digging into a problem. And these are the people who do great experiments but don't know all the literature. For them, the worst part is getting the background literature, but their data are outstanding! I'm not sure I'm touching that question of creativity.

Fowler: No, no. That was very good. That was very interesting. I was just going to say Catania could really write, and it was good. If you want to take a slight break for a few minutes and then we'll come back. I really want to ask you some detailed questions about the chlorpromazine story.

[Coffee break]

Cook: What are we going to talk about now?

Fowler: I want to ask you a few questions about the chlorpromazine story, before we try to beat the traffic rush. You outlined some of that in the ACNP historical narrative, but I'd like just a little more detail. That meeting in Philadelphia when Delay and Deniker came over, and—

Cook: It was Kochet. They were from Rhone-Poulenc in Paris.

Fowler: I just wan to know more about what you recall the meeting was like. I mean, here you were, a young pharmacologist who'd just hit the ground running with a pharmacology degree and you'd just got-into CNS pharmacology and tried some tests, and so on—

Cook: Yes, that story's interesting. It was in one of the papers I gave you. I have to go to the [illustration] board to tell you.

Fowler: That sounds fine. Did these guys speak English?

Cook: Oh, yes.

Fowler: And how did they get there--did they come on plane, in a ship?

Cook: They came by plane. These were the big wheels of Rhone-Poulenc. The story goes this way. I graduated and my thesis was on analgesics. When I got to Smith-Kline, even though my thesis was in analgesia--the spinal effects of analgesia--they indicated that they wanted me to get into a program of drugs that would be useful for stomach ulcers. Also, they wanted me to start another program looking for non-barbiturate sedatives. Because they knew that barbiturates had a bad reputation. So, I said okay. I liked the challenge and change--and what's "success" --can I refer this back to success? Flexibility, flexibility, flexibility. Industry or academic--the people who are successful are the ones that go where the action is. I have a scientist in my group who, after twelve years, is still doing what he did in his thesis. No more, no less. Same procedures, same concepts, same everything. And, frankly, he's marking time. Other people that come in with certain skills go where the action is, where the "money" is, where the need is. That’s success and flexibility.

The one or two people who will continue to do what they did in grad school, fifteen years later are going to end up as this guy did, with a little lab, maybe a technician, and they'll survive; but that's about all they're going to do. Maybe there are exceptions, but I don't believe there are many exceptions to that.

In regard to the chlorpromazine story, one of the tasks that I used was motor activity. All doses of the barbiturates below prostration, cause stimulation. Animals start getting semi- prostrated. You can't measure in rodents sedative effects of barbiturates. All of the sub-prostrating sub-severe ataxic doses,

cause stimulation. That was the limitation of motor activity with the available (1950s) sedatives. We couldn't measure their sedative properties in animals.

Fowler: As in an open field.

Cook: I used photocells, that's much better. It was always impossible to measure the sedative effects of barbiturates. They [animals] were excited. But the one thing that was used at that time, in 1951-52, was to put an animal into sleep with hexobarbital and the animal slept for twenty minutes. If you gave him a sedative, like chloral hydrate or methylparaphenol (Dormasol), they would then sleep for thirty-five, maybe forty minutes. That was a measure of sedation. Theoretically, the sedation added to something you can measure and you get a little more. It was kind of a sloppy thinking, but that's the way it was done. On this basis, I started the sedative program. I went ahead, and I found something- called SKF-525A. Have you heard of it?

Fowler: You refer to it in your writings, but that's the only place I've heard of it.

Cook: That compound started the field of drug metabolism. My findings with SKF-525A were seminal to the field of drug metabolism. Ed Weidley, my technician, said, "Len, those animals are still asleep. I said, "What animals? What are you talking about'?" He says, "Those animals that we did at nine o'clock. And it's twelve o'clock. They're still sleeping."

I said, "Are they dead, Ed?"

He said, "No, they're alive."

I said, "Look, Ed, there's no way you can give doses of that barbiturate alone without killing them and have them sleep more than forty-five minutes."

Fowler: Right.

Cook: A higher dose is going to kill them.

Fowler: Right.

Cook: But they were still sleeping. A hundred and sixty- eight minutes. I go: "No, no. Do it over again tomorrow."

He said, "Sure.

Well, what happened was that this compound inhibited the metabolism of barbiturates, and it just hung around without being broken down. But we didn't know any of this. It prolonged the effect of barbiturates. The company got very interested in it, and we started a program called "drug potentiators." The idea was--and I've published a little on this--that instead of giving more of a drug and getting the side effects, maybe we could keep with the therapeutic dose and give a potentiator. That is, use a low dose and enhance the therapeutic effect.

Fowler: Right.

Cook: And we started a program called "drug potentiators." There was a lot of excitement in the field. This was the biggest thing in 1952 or 53. SKF-525A. Then somebody came to us and said there was another drug potentiator.
I said, "What's that, a compound like SKF 525-A?"

"Oh, it's called Largactil or chlorpromazine. I said I'll compare that drug potentiator with my drug potentiator. That drug from Rhone-Poulenc was Largactil. RP 4560. I was just 26 years; old, and I was lucky! Chlorpromazine also enhanced the barbiturates. SKF-525A enhanced analgesics and also enhanced amphetamines. But chlorpromazine antagonized amphetamines! That was a surprising dissociation! SKF-525A had no side effects, but chlorpromazine was very sedative. We wrote to this company that we were interested in chlorpromazine. Also, this drug was being used in what they called a lytic cocktail. You never heard that, did you?

Fowler: No, only in writings.

Cook: Yes. That was a lytic cocktail, it was utilizing its drug potentiation enhancement of drugs for anesthesia. It also rendered the animal poikilothermic.

Fowler: Hypothermic.

Cook: Not hypothermic.

Fowler: Poikilothermic.

Cook: Poikilothermic. Chlorpromazine rendered the animal poikilothermic. You could increase or decrease the animal's body temperature with the environmental temperature. So there were some differences from SKF-525A. So, the people from Rhone- Poulenc were interested and came over to meet us. Oh, also, chlorpromazine was antihistaminic and SKF-525A was not.

Then we found out the whole story, that that drug was pretty old, chlorpromazine. At first it was not called chlorpromazine. And they approached seven companies in the United States trying to sell it as an antihistamine.

Fowler: Oh. I didn't know that part of it.

Cook: Interestingly, all the companies turned it down. Because of the sedation. The last thing in the world they wanted was another antihistamine with sedative properties.

Fowler: Well, they had Benadryl.

Cook: Yes. So. Seven United States companies turned it down. As they should have. Meanwhile, as part of my early program I developed a motor activity assay which I put aside because it was no good to test the sedative effects of the available sedatives.

Also, I remembered when I was in college there was something about Pavlov and conditioning. I'll never forget this--I went out---I bought a doorbell in a hardware store. I made a grid floor, which was four two-inch brass plates with a rheostat plugged into the wall. [Laughter] And I had a button to hold down for the bell. I gave the rats 120 volts. I thought, "Okay. I'm going to develop conditioned behavior." I didn't know much about: avoidance-escape or conditioned reflex. The conditioned reflex--I remember I read about that.

And I put this testing box together. At first it had a shelf. The rat climbed onto the shelf and then I pulled the shelf out so the rat would be exposed to the grid again. But it was not working well. So I looked around, and I saw a

broom handle in the corner. I took the broom handle and I used that to develop the pole climb test. Pretty crude.

And what happened is that when I put the animal in the box and I wanted to develop this reflex, I would ring the bell and a few seconds later I'd give him the shock. After a while, when I rang the bell, the rat climbed up the broom handle. But he would urinate while I'm training, and the brass plates would steam up. The whole thing was steamed-up with urine.

Of course, I'd ring the bell and all the other rats are sitting right here. They're hearing the bell and extinguishing. God knows what's going on--but--it's a good thing I didn't know psychology. But it worked. And what I found is the classical conditioned avoidance-escape behavior.
I trained the animals and 'nothing [the classical sedatives) worked. The conditioned avoidance didn't work because where I gave the available drugs--the barbiturates, the Dormasol, chloral hydrate--the avoidance was blocked. But, the escape was also blocked. You know. The classical sedative drug just zonked the animals. So, nothing very specific happened.
Actually, I took that test and I put it in the closet as not being very useful for the available compound. My conditioned reflex box. okay. I had in my test battery a couple of things, and it ended up that hexobarbital sleeping time was the only thing I really used. When I later tested chlorpromazine in the CAR test, the effects were very different. Also, the motor activity test.

The Rhone-Poulenc people came over. I said, "You know, my feeling is, quite candidly, that our drug is a pure potentiator, but your drug has got all these sedative effects, behavioral effects, and stuff like that." In the locomotor activity test, I administered one to four milligrams per kilogram of chlorpromazine, orally. The mouse's activity declined as a function of chlorpromazine dose, but the animal was still on all four legs! Until I got to, like, fifty-to a hundred milligrams (per kg]. Never happened before! They were immobilized--BUT STILL ON ALL FOURS!!

Fowler: Right.

Cook: You could lift: them up, you turn them oh their backs-- and they righted themselves. You touch and squeeze their foot-- they pull it away. You did a placing reflex, it was there. And yet, the mice were totally impassive to the environment. And I said, "Look at the amazing difference between chlorpromazine and barbiturates in this test." I went ahead with the CAR [conditioned active avoidance], and I blocked the conditioned avoidance with chlorpromazine. The rats are just sitting there and that bell is ringing. I gave them the shock and they jumped up. A hundred percent of the animals are blocked to the CS, and I give them the shock so they can climb. So why aren't they? I think they are really confused, you know, or they're totally indifferent to the environment.

Fowler: Now, this was rats--

Cook: Yes, rats. This is all a totally new approach. Nobody knows anything about drugs and conditioning. And I say, "Holy smoke--I'm able to make an animal totally immobile but he's on all four legs." Never before in history did anyone see that. This effect of barbiturates at "sedative" doses is the stimulation, running around.

Now with chlorpromazine I was able to make the animal indifferent to what's going on: "I'm threatening you--I'm going to kill you with shock--you don't

care." However, when you give him a shock, he jumps up--he can do it. He's indifferent to his environment. At first I thought, he lost all his hearing. Well, we found out it wasn't that. Then I thought, he doesn't care about the shock, even though there's no shock threshold change.

At this point the people from Rhone-Poulenc came over to us. We first discussed the comparative drug-potentiating aspects of SKF-525A and chlorpromazine. They said they were into surgery studies. They're able to do cardiovascular surgery because of the poikilothermia it produces. They packed the patients in ice, and they went from a limit of three minutes to twelve minutes. Major thing and it was drug-potentiation. A lytic cocktail in surgery. But then they mentioned that they also had a couple of psychiatrists named Delay and Deniker and they're finding and reporting all kinds of fascinating things in schizophrenia.

Fowler: Who were those two guys at the meeting? Delay and Deniker?

Cook: No, no. These were Dr. Kochet and other. They described what happens in schizophrenic people who are now tractable; they're not wild and climbing all over. They're not sleeping. I'm thinking, "Holy smoke, it fits with my data!" And after they leave I spoke to management. I said, "You know, I have a feeling that this unique indifference to aversive events, impending aversive events, may have clinical implications for what he's describing about schizophrenia.

Fowler: Right.

Cook: At first our company people were thinking in terms of the utility of chlorpromazine in surgery. Most importantly, the effects I reported about inhibition of avoidance behavior and indifference to explore in motor activity studies tied in somehow.

Fowler: Well, in that meeting, did anybody use the word "psychology, 11 or was the word, "psychopharmacology" ever mentioned?

Cook: No. I recall I used "psychopharmacology" in a seminar I gave at Emory University about 1953 or 1954 on this data. Because I remember thinking should I call it pharmacopsychology or psychopharmacology. I think I used it then for the first time.

Fowler: And in this meeting you didn't use the word "psychology". You used the word, "behavior," though?

Cook: I think I used the term "psychology" to describe these findings. However, I really don't know that. I wasn't a psychologist. I wouldn't have even had the repertoire at that time to talk in these terms about the importance of the differences. But, essentially, I thought operationally. Not that I knew enough to consciously do that. I thought, "He just doesn't want to do it. The rat doesn't care." That was my introspection at that time.

I don't recall talking in any psychological terms at all, nor did they. So, Smith-Kline got together with Rhone-Poulenc. They felt that my data tied in. This may, in fact, be something. They agreed to follow the psychotherapeutic--the psychiatric treatment aspect of this drug-, as well as its use as a lytic cocktail in surgery.

Fowler: I see. When did you and when did the management of Smith-Kline become aware that this might mean the end of, say, lobotomies, this might mean massive

change in mental hospitals? Or did they--how long did it take for people to understand that this is really important?

Cook: I think it became immediately important when they start-ed doing the clinical studies. Interestingly, I joined them in 1951--about 1952, late 151--I took a course in Boston on mental disease which included descriptions of frontal lobotomies. To my surprise, most of the things they spoke about were lobotomies.

Fowler: Right, I know. I teach a course--that's part of the course.

Cook: They mentioned that the family is unhappy, but [after the surgery] the patient is happy. They're not climbing the walls, they're not breaking the chairs.

Fowler: Right, right. They weren't close enough to--

Cook: Well, chlorpromazine appeared on the scene, and they did the first clinical studies. As you know, it's now history. They were literally evaluating the success of that drug by the decrease in chairs and tables and window's that were broken. And it really was true. Most psychiatric wards were violent. To deal with the patients, they knocked them out with drugs or they put a straitjacket on them. Suddenly, with chlorpromazine, they were bringing people out of the back wards into the front wards. And for some of the patients, the families would visit them for the first time in ten, fifteen years. The psychiatrists were able to at least have an interaction with them. And it was a miracle. It was literally a miracle at that time.

Now. In retrospect, my contribution, I think, was primarily getting my company--Smith, Kline, and French--giving them the opportunity to get the drug and start looking at it. I remember going to my vice-president and saying, "I think we're in a new era. This is more than just a routine pharmacological study leading to a new drug." His name was Capp Clark. I said "Capp, I really believe this is the beginning of a new era, and I think that we should prepare ourselves for the future."

He said, "What do you mean?"

I said, "I'd like to request the resources to build up a psychopharmacology unit in order to maintain our position in a new field." And he immediately said, "Len, I think you're right."

It was just me and Ed Weidley at that time. And I built up an extensive--what was probably the best psychopharmacology lab in the country. in the world. I hired Killam, and I hired Schuster and eventually Kelleher and all those wonderful colleagues.

Fowler: Well, how many pharmacologists at the time even had two such behavioral tests as an assay?

Cook: Few, if anybody. Capp asked what did I want to do with these resources. I said, "Well, Capp, as I see it, there is biochemistry measuring things like norepinephrine in the brain. There's people up at Harvard who are doing EEG work--" Mary Brazier. Do you know that name?

Fowler: Yeah, yeah I do.

Cook: And neurophysiology work being done in California.

This was Magoun. That's when I lost Keith Killam, because he married Eva Killam and went to California. Keith used to work for me. He worked at our place before his degree. He was getting married to Eva. It was a choice of hiring Eva at Smith-Kline-French or his going to California and working with Magoun where Eva was.

Fowler: Oh, yeah.

Cook: And he did all right for himself with that decision. He had a great career.

Fowler: Moruzzi and Magoun.

Cook: Yes. Well, in any event, I went on to describe to Capp that there's also an approach called psychology. I said, "Theoretically we should be doing all three." He said, "But what is it that you feel we should concentrate on?" This was the turning point--I remember it distinctly! He said, "If I can't fund everything, what would you choose?"

I said, "Well, my feeling is that I want to see what the whole animal does. In terms of clinical prediction, the behavioral approach would predict more relevantly. I think we ought: to go in a clinic with that kind of data." If all I knew was what it did to nor-epinephrine, or if all I knew was a certain EEG pattern, or 'cerebral (cerveau?) isole' that Keith Killam was studying, I wouldn't know the relevance. But I'd be willing to bet my salary on what I know now in the behavioral psychology." I said, "What I'd like to do is build my resources up here [effects of drugs on whole animal behavior], have something also going in biochemistry, and have something going in neurophysiology. But, the main effort should be in behavior.

And he said, "Okay. You build it the way your instinctive gut tells you to build it."

I said, "Okay. Now I'm going to have to learn as much as can about psychology." I said, "I'm going to have to travel--"

He said, "Len, you do whatever you want and you build the best unit you possibly can with the most relevant measures you can, and go where you have to go and do what you have to do." It's the true story. I've never told this part--since I made my commitments to the behavioral approach--at that time people in behavioral pharmacology were not there to hire. They just weren't there.

I'm going to need to learn psychology or experimental behavior. I recall thinking, "I better damn well learn what this is all about." All I knew was a course I took--psych 101--and I think I just about passed that. So that's when I got together with Karl Pribram who in turn introduced me to Ferster, who came on to me like a shock regarding his operational approach. I didn't know what hit me. I gave a couple of seminars to B. F. Skinner when Charley Ferster brought me up to Harvard. And I told them about this new drug, chlorpromazine. He was fascinated by the fact that a pharmacologist like myself was talking about all this behavioral data. I went around to others, as I told you before. To [A. J.] Riopelle and I went to Wisconsin--and I learned about operant behavior. I just told you the story about the pole climb avoidance behavior, the 120 volts, the urine sizzling, and steam on the grid. I'm almost embarrassed to tell you this story. Of how I really got into operant behavior.

I read a paper by Wikler and Hill, in which they described the animal pressing a lever and getting food. I forget the schedule he was using, but he was studying the opiates. I thought, "Well, that's interesting." The animal was working for food and he was testing the drugs. So, what I did was I got a box and I got a pencil--I swear it was a pencil--and I put a pin through it just like that (so the pencil would pivot), and--I knew a little about shaping behavior--and whenever the animal touched the pencil or pressed it, I took a piece of lab chow, broke it up, and I'd throw a piece of food in his cage.

I had a food cup in the box. Whenever the rat would hit the pencil, by chance or whatever, I'd throw a piece of pellet. And that's the way I did my first operant. And I got the rat to press. Then I would test the effect of drugs. I can't remember what schedule it was, I think it was an FR.

And the rats are responding and taking the food. But my technician, Weidley, was standing over the box; and whenever the rat hit the pencil, he'd throw a piece of food into the cup. He was the food dispenser. And we played with it. That's when I hired a guy named Bob Schuster, who at that time had a B.A. degree. We learned about winding our relays and we start getting very schmaltzy, very fancy with this thing. We had relays going. We had relays all around us and, again, it was 120 volt AC powered.

Fowler: Dangerous stuff [the 120 volt power).

Cook: We developed this very crude type of equipment. We did a lot of different schedules. One of the early studies he reported on, Joe Brady had published on CER. We tried to repeat that with the reserpine, but we never could. I did a dog conditioned leg-lift; conditioned avoidance. I also included conditioned heart rate studies. I visited Horsley Gantt and became familiar with his studies.

Fowler: Startle response? Orienting response?

Cook: Yes, orienting response. I went through a couple of years of seeing what might help me, what's important. We learned a number of things. Bob Schuster and I had a conflict schedule. But all we had were the phenothiazines, which didn't work in conflict behavior, so we put that aside.

Fowler: Yes, right.

Cook: We did have barbiturates, and we got some effects; but we know the barbiturates don't work well in this task. We didn't have meprobamate or Valium at that time.

Fowler: Right.

Cook: We went through a great-deal of different kinds of behavioral studies, and we learned a lot. We also had Ferster around, and he helped us enormously. Then we found Roger Kelleher, and he was a godsend. But the interesting thing was that Bob Schuster came to me. He was concerned. He said, "How can you make Roger head of a lab? How could you not also do this for me as well?"
I said, "Well, you're terrific, but he [Kelleher] came with a lot of experience and a Ph.D. And that makes a difference to the company. The company hires according to degrees, and they pay a bigger salary for him than you because he has a Ph. D.

He said, "But I know as much as him.

I said, "I know you do but he's got a degree and he gets two thousand bucks a year more than you do."

About a day or two later, Bob came to me and said I want to get a degree. He made all the arrangements. He went down to Maryland and, as you know, he did very well. Bob did okay!

Fowler: Indeed.

Cook: He did terrific. I'm very proud of him [C. R. Schuster]. Keith Killam went on and became chairman of pharmacology--president of the pharmacology - society ACNP.

Kelleher also did okay at Harvard. Catania did very well for himself. Most of those guys did okay. I hope my training them in pharmacology made some difference to their careers.

Fowler: I'm sure it did.

Cook: In any event, we built up the operation and eventually got people going. But I just decided at that time--that's what I mentioned before--that I better learn what behavior is all about and what makes it tick. So I went around, as best as I could, to learn behavior, what controls it, and in what sense behavior follows all of the rules that the heart or any other physiological system does. For example, does behavior respond to drugs in any way--as do other physiological systems?

Fowler: Guinea pig ileum.

Cook: Guinea pig ileum in vitro. Thank you. The effect of a drug on that ileum's activity depends on temperature, the ionic concentrations, the tension, et cetera. Any one of these environmental things, all of these can modify the pharmacological action. Behavior exists in an environment and is affected by nutrition, temperature, restrictions on behavior, tension, or whatever. Let's say "the contingencies." I listed all of the things that not only control the behavior but modify it and would be important in terms of the drug effect. You know very well that if the animal's body temperature is down, you get a different drug effect.

So that behavior is acting in a milieu very much the same as that guinea pig ileum; and, in the same way, you can modify the drug effect. I wanted to know what are the important contingencies and factors that maintain the behavior and maintain its sensitivity to the pharmacological intervention. And I analyzed that as a pharmacologist. I approached behavior as a substrate system like any other physiological system. And, to this day, I look at behavior as a substrate system for drug effects.

Fowler: Well, I think that's very astute and I think that's correct.

Cook: This is how I talk to students about it, in a sense, that I just look upon behavior--from my point of view--as an ileum in its environmental medium.

Fowler: Well now we can replace the ileum with a set of neurons in the brain. Knowing so much about them now--of course we don't know how they're all interacting with other neurons that produce the behavioral output but the tissue

slice preparation is an extension of the ileum preparation. And as we learn more about these sets of neurons we can even make more sense of this, although it's going to be frightfully complicated.

Cook: In any event--that's a little background, Stephen.

Fowler: Before we leave this I have--

Cook: I didn't realize it was getting so late, but—

Fowler: You were doing good, so I didn't stop you.

Cook: It's all right, we're in no rush.

Fowler: Egas Moniz received the Nobel Prize for lobotomies. This Portuguese psychiatrist. And yet it's clear now that that was a bogus thing, yet there was nothing else anybody could do at the time [for schizophrenia]. Do you think society--in particular, the Nobel Award Committee--will begin to recognize how important psychopharmacology is and will there be a Nobel Prize in psychopharmacology per se. And I don't mean the substrate science, like Axelrod, you could say...

Cook: Yeah.

Fowler: ...was a Nobel Prize in psychopharmacology. But that's not what they called it. Would you care to predict when and if that will occur?

Cook: That's interesting. I've never heard it said before.

Fowler: Well, it seems to me that it's a tremendously underappreciated medical discovery. And I often tried to grapple with that--why is it? It may be related to what you said earlier. That everybody thinks they know something about behavior already.

Cook: Yes, behavior is pretty tough to accept as a hard science by many scientists in other disciplines.

Fowler: Yes. I think it's being more and more accepted.

Cook: Right.

Fowler: I was thinking about some of our university administrators--trying to explain to them what psychology is. Many of our administrators have never had a psychology course. And yet for the next generation that will not be true.

Cook: Well, you know, I have found in my dealings in this field is that people really believe in "dualism."

Fowler: Yes.

Cook: The idea that there's relevance to an animal climbing a pole or learning a schedule for reinforcement and that a drug modifying that has any relation to their own psyche. They just don't buy it. Because they believe in a free will, and that they are in total control. When you bring them the idea that they're nothing but a factor of their environment, it's a little disquieting.

Fowler: It reduces their sense of dignity or that's the way they perceive it.

Cook: And when I first started presenting this data and concepts to non-psychologists, I used to talk about the experimental details: "and the animal was trained to do this, and then I do this and then I do that--" And I lost them! I realized the mistake. And every young person that came to work for me, or that was going to make a presentation of the work, I said, "Don't you dare get into the experimental details. You say: "The animal learned to press the lever under these conditions, and this is what we found." Don't you dare say we used this schedule, because they get into the details and they get to empathize how they would deal with this situation if they were a rat. Stay the hell out of the technical details!"

Fowler: Right.

Cook: You just don't get into describing the experiment, because they'll kill you. Everyone considers themselves an expert in behavior and will challenge everything you say and lose the important points.

Fowler: Yes.

Cook: They'll take over. They'll wipe you out. You just talk about the basic elements. If you want to use- God forbid-- the word "conditioned fear" it's okay. If it really adds to the credibility of what you're doing. Don't go ahead and say, ... ring the bell and six seconds later I did this and the animal did this. I say, "Deal with it in terms that you are the expert and you're giving them the conclusions. Don't give them the details and hope they're going to come to the same conclusions. Tell them what your conclusion is.

Fowler: Right, right.

Cook: You're the expert. You tell them: "That's what this all means."

Fowler: Well, I think you're right about the dualism. I think though--the drug abuse problem though--that people there are understanding that this is a behavioral problem. It is fundamentally behavioral.

Cook: That one. Yes.

Fowler: Yes. Well, maybe the understanding of that will eventually generalize to others things, like psychosis and so on.

Cook: The drug abuse people can get away with it. Because it has face validity. Such as the drug discrimination, I understand that. Self administration, the withdrawal work, substitution, for example.

Fowler: Right.

Cook: When I think back on the mistakes that we made over the years that we could have avoided. I mean, I should have done what they do with the aplysia: "Memory". Everybody buys it, no questions asked.

Fowler: Yeah.

Cook: And, now we also try to do it. You should see us at the research committee. Last week. We talked about the "anti-psychotic effects" of these drugs and we measure the "anti-hallucinatory behavior" and we measure the "conditioned fear" behavior. And, oh, boy, it's good stuff! If I gave a seminar

in an academic department in this manner, they would kill me. They'd say, "Whoa, wait a minute. You only measured the antagonism of a mescaline-induced behavior. How do you know it's an hallucination?”

Fowler: But memory, I think, is something that is accurately described, even in the rat in the Skinner box. It is what we ordinarily mean by "memory." It is clear that something is stored in that animal's head that makes him different by virtue of that learning experience. And memory is a reasonable way to speak of that. I think that's not offensive on either side any more.

Cook: You can get away with it. Memory. Learning and Memory. Learning and memory as two separate things. Right. I started using the terms learning and memory. Now just memory. And people buy "acquisition”, and will buy the consolidation of information. They buy it. You're right. It's been easier to deal with learning and memory. Much easier to deal with.

[After dinner at Dr. Cook's house]

Fowler: Let's talk about receptor pharmacology from your days as a graduate student up to right now, as a kind of recurring theme. The degree to which thinking about receptors influenced what you were doing as opposed to the pharmacology of it--namely what was the whole organism response as opposed to the receptor concepts, whether it was Clark's dose response concepts, or whether the new [receptor] binding concepts.

Cook: You mean what influence do they have?

Fowler: Yes--how important has that been in your thinking. And has Lt affected the pharmaceutical industry. Both of these things.

Cook: Yes. I remember when the whole concept of receptors and bindings started. Some people understood it and some people didn’t. Initially, not many people attended to it in terms of an important role in drug discovery. It was a very theoretical type of science, mostly at that time to explain possibly the mechanism of how drugs worked. Over the last ten to twenty years receptors have really found a very critical place. The role that they've had--I can only speak about this from a drug discovery point of view--has moved from a curiosity to an explanation of how drugs work. The receptors are not only a part of the pharmacological spectrum, receptor studies are the first some labs do in sizing up drugs in terms of what compounds are interesting to follow up and which ones are not.

So I, too, in my group, have receptor screens. in many of our projects--like right now we're running--and most drug companies are--we're running about 5,000 compounds a week through a receptor screen that may have twenty, thirty, thirty-five different screens, that include types from neurotensin receptor to a GABA to a serotonin 1-A to a dopamine 2, 3, 4. Like NOVA has this huge screen--all the companies have an entire spectrum of receptor screens. Well, that's okay to use as one of the ways to identify compounds that will go into your in vivo testing.

I look upon the receptors not as a go-no-go screen, although some people do, but to identify compounds of different pharmacological receptor profiles to pick up and add to, to enrich the input in your screen, not as necessarily a go-no-go criterion. Take some compounds which have effects on neurotensin and serotonin receptors or dopamine 3 or dopamine 2 and bring those into the screening tests.

Not as a go-no-go, yes or no. I know people do that, but I wouldn't limit the input into in vivo screens totally to receptor criteria.

Fowler: Some people talk about mechanism based discovery, and I think that's what they're talking about, first---

Cook: --and I believe that, because most companies do have the mechanism approach to drug discovery and we do as well! But what mechanism do we want? You can focus on neurotransmitter release, or you can take a mechanism of MAO inhibition like deprenyl in the area of cognitive improvement.

Fowler: Right.

Cook: Or you can say we want a mechanism of calcium channel block, so we'll have that input as well. Today we are well beyond just setting up a learning test in rats, as an example, and just blind screening of random compounds (get anything and just shove it in!). Nobody does that anymore. One chooses a reasonable mechanism or mechanisms to test and concentrates on that approach.

Fowler: Right.

Cook: So I look on a receptor screen as a way of identifying different compounds to put in through your most important decision screen, but not limited to this. Not a yes or no. Some people do that, but I don't.

Fowler: Because you don't know what you're missing if you don't test it in vivo. But what are the alternative ways for deciding what to try? In other words you have to have some hunch as to what to try.

Cook: Good question.

Fowler: Yes, is that part of the art?

Cook: I was just thinking how to explain the art. For example, instead of that receptor level you can go at it in another level. For example, I'm trying to think of things that we've actually done. To find some candidates to test you go to your computer, you know, for the last 20 years. Data have been in that computer, go into the computer and get some compounds that were antidepressant at doses below 10 mg per kilogram in the tetrabenazine model of depression. Operationally, I'll say see how many compounds you can find that were antitetrabenazine and yet did not produce overt effects below 70 mg/kg. Throw in two or three more search criteria and say we come up with seven compounds that are antitetrabenazine and meet our other criteria.

Fowler: I see, so you identify candidates that way?

Cook: So, I'll look at those in some second test, and it may work. Or none of them works. Okay, it was a shot in the dark. Let's say for one of the compounds there's something there, something positive in our test procedure. Then we might look at that structure and then we go digging for analogues of that structure in the computer. The chemists will find a match because they go into the computer and identify analogues, homologs of that particular chemical structure. Then they may do a structure activity and zero in. That happens. Very common. That's happened to me a couple of times. You can't just go ahead and grab things off the shelf and try them, that's not the way it's done.

Fowler: It gets too expensive.

Cook: You're right, it makes no logic to go at it haphazardly. You may be lucky in one out of a million. Some people do try with what they call a "random screen" and it's paid off occasionally; or you can do what I call "rational screening." Rational screening, one subsection of rational screening, is a mechanistic approach. That could be to find all compounds which have an affinity toward dopamine 2, serotonin 2, sigma or no sigma, or to see if we can find how many compounds are- DI and sigma or D1 and neurotensin. God knows what you would find. If you make a hit, you then go SAR, structure activity relationship, for a look at other compounds. First you have to decide whether to follow pharmacological profile or the structure. You play around, and you decide. But what you are essentially doing is selecting compounds on some basis to make it a rational screen, although not too rational. You can do it in terms of receptors. or you can say, let's see how many compounds are anticonvulsant as a start. Because that has a lot of analogies to anxiolytic activity or maybe if it is proconvulsant or anticonvulsant it has to do with the NMDA receptor or glutamate.

How many compounds produce seizures or convulsions in the Overt symptomatology screen? So what you do is go back and look at the computer search and you try to enrich input so that different kinds of profiles are going in, and you essentially do what we call. Rational screening/rational assessments. Receptors have a role to play. An important one. one of the things to help you evaluate things more rationally.

Fowler: Do you recall when you first became aware of the receptor having been identified as a specific molecular entity as opposed to just a concept? Because it has only been recently that they had been cloned and sequenced and seen in an electron micrograph representation and so on. Do you recall when that occurred? Did it have any impact on you?

Cook: No, it never really had any impact on me early on.
But, I have been more of an empiricist. I have discovered a lot of drugs. Chlorpromazine, Stelazine, Compazine, Parnate, at Smith-Kline-French. Then at Roche, there was midazolam. And I am working on some things here at Dupont-Merck. But to me, I am more of an empiricist. First of all, it has a better track record. However, the down side of that is increasing the probability you are going to find more of the same.

Fowler: Right.

Cook: For example, the conditioned avoidance test. My God, that thing is almost as old as I am. That test is the best predictor of clinical efficacy there is for antipsychotic activity, and I know that is true. Every known clinically effective antipsychotic works and a correlation of clinical potency and potency in the avoidance test is 0.95. Different chemical structures, different everything, it works. I have been very confident with that, but I do listen to critics and when they say, "Okay, Len, but you are increasing the probability that you are going to get similar things." And I can argue with that by saying well maybe that test reflects such a broad range of things that it predicts clinical utility but not necessarily the same. So we go back and forth there, but I must tell you they are right to a large extent. Where if they say, "Well, let's get something that has a different mechanism, say it acts at the sigma receptor, that doesn't block the CAR. Anything that doesn't touch the dopaminergic system directly, like Thorazine and Haldol do. Having a compound with only part of the profile of Haldol may be very valuable (e.g., no dopamine effect but has a sigma affinity). And if that slice of the pie's pharmacological

effect has clinical efficacy, good enough, as long as it does not produce side effects. That is why I predict that sigma drugs are not going to be typically antipsychotic. It is not going to quiet the wild man down. It is going to be adjunctive therapy in combination with Haldol-like drugs or to specifically decrease thought disorders.

Fowler: It is going to be an antihallucinatory, anti-thought disorder, but not calming and immobilizing.

Cook: It may be a supplement to Haldol. And that is about the best effect; but it is not going to replace Haldol or Mellaril, because those drugs have a breadth of clinical activity. What I am saying now is that drug discovery has this dilemma. If my boss came to me and said, "Len our marketing tells us that there's really good market potential and a lot of money to be made for new non-benzodiazepine anxiolytics," and it is true. You get a non-Valium anxiolytic and just the public relations aspect of it will make a fortune because you are not starting off with the classic addictive housewife with Valium. I know that the Cook-Davidson test, the conflict test, the Geller-Seifter test, conditioned suppression doesn't fail to identify anti-anxiety compounds.

Fowler: Especially if you use the right species for it, if you use a range-of species it is really positive.

Cook: I know it works in rats. I also did it in monkeys, and it works in humans. Peter Carlton and I did that human study.

Fowler: Also it works with pigeons and buspirone, whereas buspirone doesn't work well on rats.

Cook: Well that is another story, buspirone. I'll tell you about that. Buspirone is not a classic anxiolytic in my book. You see, when you study phenothiazines in pigeons, they are totally disinhibited. Chlorpromazine will do the same thing as buspirone in the pigeon.

Fowler: Well that is something that Jack Marr said to me once after a talk. He is an operant kind of guy at Georgia Tech. He wanted to make this point that chlorpromazine increases response rate in the pigeon. I wasn't aware of that, and that is interesting. So you think that Buspar, buspirone is a weak dopaminergic drug?

Cook: It has some therapeutic benefits, like a low dose of Stelazine or a low dose or Thorazine. These have some therapeutic benefit by quieting the patient, but it is not anxiolytic. It is clear it isn't. In order to identify anxiolytics, I would use a few tests that are very useful, and I would find the drug we are seeking. However, although it may be a different chemical structure, it might not be different enough. But if it is basically the same pharmacology, the chances are very high it is another Valium. On the other hand, it is an anxiolytic effect. Whether it would be sufficiently different to give them a market advantage, I do not know.

Fowler: You predicted buspirone in higher doses would produce extra-pyramidal symptoms. In high doses, can you get the CAR effect with buspirone?

Cook: I really do not know. I have been so unimpressed with that drug and its pharmacology, I never did a lot with it. It's a good question, but I'm not sure.

Fowler: The PDR says that it has risks of extra-pyramidal symptoms but it doesn't give you any details. It just says that, but I think that the PDR statement is based on the fact that buspirone binds to dopamine receptors to some extent.

Cook: A few years ago there was a buspirone presentation at the ACNP. I forget who it was said, "Well, that will be the first anxiolytic that produces extra-pyramidal symptoms."

Fowler: There is a clinician I know that is privy to what is going on out there in clinical practice. He says he thinks there is a narrow window of doses when it does something useful, perhaps like low doses of Thioridazine. It could be that is all there is to it.

Cook-: In the 1960's while I was at Smith Kline they came to me and said, "Len, we want to sell Stelazine, low dose Stelazine as an anxiolytic." And I said you are crazy. They said maybe you can get some animal data on Stelazine as an anxiolytic. And at that time I had the conflict test in rats, and it had a big capacity. So I ran the Stelazine over the whole wide dose range: from minute doses all the way up to incapacitating doses. We found that, indeed, low dose Stelazine had an anticonflict effect; but, as you just said, the therapeutic window was narrow. But we could pick a dose that did have a moderate anticonflict effect. When buspirone came along, I was at Roche, and Jerry Sepinwall and I did study it. We had the Cook-Davidson test running. Jerry did a fabulous job setting up the test with computers. We had it running better than we ever had it running at Smith Kline. He did a super job. When we ran buspirone, we didn't get the anticonflict effect. We ran different pretreatment times and we tested chronic doses. We did everything and we couldn't get anything other than a typical neuroleptic type of effect, which was essentially decreasing the nonpunished baseline without any increase in the punishment period. We gave up on it.

Fowler: I remember seeing two or three presentations by Jim Howard of Burroughs Welcome. He could just barely get the slightest anti-conflict effect with rats.

Cook: Yes.

Fowler: And he mentioned this, you know. He just said this is a very weak anxiolytic, if it's an anxiolytic.

Cook: That's right. Same thing I experienced. Jim's a very competent person.

Fowler: Yes, he is good. So, I've been thinking about using buspirone in one of my procedures.

Cook: We've got some more coffee, if you'd like.

Fowler: Thank you.

Cook: It's decaf; at least it was in the green can.

[Laughter]

Fowler: Well, but decaf means not as much as caffeine.

Cook: Is that right?

Fowler: Yes.

Cook: Is that right? I just always assumed that it was no caffeine.

Fowler: if you look carefully, the label says 95 percent caffeine-free. But what they don't tell you is that regular coffee is about 50 percent caffeine free.

Cook: Oh, really. Oh, great. No wonder I don't sleep.

Fowler: Yes. In a cup of really strong decaf you still get a sizeable dose of caffeine.

Cook: So, are you saying that two cups of decaf will be almost equivalent to one cup of regular coffee?

Fowler: Well, maybe three cups.

Cook: Maybe three.

Fowler: Yes. I don't know where I heard this, but I heard it somewhere. The way they listed the amount of caffeine is suspicious.

Cook: Ninety-five percent, right.

Fowler: Yes.

Cook: When the regular is 90 percent free.

Fowler: Fifty.

Cook: Oh, 50 percent free. I never knew that. Well, generally the only time I drink coffee at night with dinner is with guests. I usually have tea.

Fowler: At work that's what I drink most of the time.

Cook: Do you? You look like a coffee guy.

Fowler: Well, I used to, but it is too strong. You know, the only time I'd really drink a full strength coffee is when I want to stay awake and I know I need to.

Cook: Well, I'm such a bad sleeper, that I try to avoid coffee but I'm kind of, well, since my wife was ill ... I'd wake up 2 or 3 times a night, and I still do that.

Fowler: Well, from what I understand in terms of sleep dynamics, it's a normal thing.

Cook: Right.

Fowler: As you get past about age 55, your tendency to wake up in the middle of the night becomes greater, and greater, and greater. It just keeps increasing.

Cook: Great...

Fowler: And so it's something you shouldn't worry about. It turns out that a more natural sleep pattern is to sleep every once in awhile around the clock, rather than to sleep all at once.

Cook: Yes.

Fowler: Yes. So taking a nap in the afternoon is a good way to rest yourself.

COOK: I can't do that. I can never take a nap.

Fowler: Okay. Well, I haven't taken one for years except when I am just totally exhausted.

Cook: I just could never take a nap. I'd try it. My wife was the type that if we were going out for a big evening and she had finished at 4:30, she would say, "I think I'm going to go take a nap for about 20 minutes." I looked at her and said, "How can you decide when to sleep for 20 minutes?" She could, z-right out! Oh, I used to envy her.

Fowler: You know before we stop recording, I would like to ask you one more question.

Cook: Sure.

Fowler: This relates to your being in the drug business, thinking about pharmacological compounds that affect behavior and brain for 40 years. Do you think, and this is a question about cultures--our culture and others--do you think this culture will evolve to the point of accepting or even embracing a new recreational drug that is more benign than any that we have in the sense that it doesn't have, you know, hazardous effects.

Cook: A happy pill?

Fowler: Yes.

Cook: Or a tranquilizer?

Fowler: Yes, something --- or a stimulant--but...

Cook: Are you saying acceptance by whom?

Fowler: Well, by the legal system and the government.

Cook: The body of society as a whole?

Fowler: Yes. Because it seems to me that...

Cook: Well, not for a long time. Oh, gee, we've had so many conversations about this. We've talked about changing cultures, but they really didn't change. In 1956, in the middle 50's, there was the first meeting of the International College of Neuropsychopharmacology. It was the parent organization for the ACNP.

Fowler: That was 1957 according to Herb Barry's notes.

Cook: Nineteen fifty-seven, in Rome. Okay, '57. 1 think he was absolutely right. There was this meeting in Rome and I presented data on chlorpromazine and it was one of the major themes. Was Herb Barry at that meeting?

Fowler: He might have been. [*He was not*.]

Cook: Okay. Everybody was there. I remember Joe Brady was there, and he and I had an awful good time. This guy can break you up. Have you ever traveled with Joe?

Fowler: No, I've seen him at meetings and talked to him.

Cook: Well, he is a dear friend of mine and we've known each other for about 38 years. And we've been to a number of meetings and he just breaks me up. So we were in Rome. I remember we rented a car and we did some crazy things there. But I presented data on chlorpromazine.

And Pope Pius XII invited a contingent from the meeting to the summer palace, the Castle Gondolfo. He invited the chlorpromazine crowd. I forget how many were there. We had the audience, and he expressed his Papal concern about popping a happy pill to achieve nirvana, as opposed to agonizing introspection and disciplined life style. That was what we talked about. Many of the typical psychiatrist were Freudian, psychoanalytical types, who were absolutely aloof to this idea of the drug [chlorpromazine] working therapeutically. More than aloof, they were absolutely against it. But those were the very people who became the leaders in the fields of using these drugs. I remember talking to them. So they make this big turnaround [and came to endorse chlorpromazine's use].
But that's a whole other story of how we got chlorpromazine into the medical profession, and I was involved in that. The first reaction from psychiatrists, that was 1957, was a lot of skepticism and concern about how a drug could achieve nirvana, a tranquilizer, an ataractic, "a drug to create a sense of well being." There was some concern. Even among the public there were a lot of jokes about tranquilizers. Then the next drug that came along was Miltown [meprobamate]. Milton Berle and other comedians on TV used to make jokes out of it. There were literally whole patterns of jokes about Miltown. Also, a lot of people were concerned about that. But the greatest PR that made Miltown popular was Milton Berle. He went on week after week talking about this great pill. Wow, man, Miltown! He absolutely brought Miltown to the consciousness of the American public.

Fowler: That's amazing!

Cook: It's the truth. A lot of jokes about Miltown by him and others. Getting back to your question about society's acceptance of behavior altering drugs, Miltown was on the scene, and there was little negative reaction to Miltown. It was a big joke, and everybody was popping Miltowns. Then Valium came along, and although Valium is not a very addictive drug, it gained a reputation for addictive properties. When you consider the millions of people taking Valium, you would have half the population climbing telephone poles if it was as addictive as some thought.

Fowler: Right. It's really a safe drug.

Cook: But there was tremendous publicity on TV. They had a show about Valium, and there was an enormous public concern and reaction that developed about the harried housewife popping a Valium pill and becoming addicted.
In regard to the public concern about the impact of future drugs affecting behavior, the next thing we've got is a drug for Alzheimer's disease. They ask what do you mean by Alzheimer's, the "memory" of Alzheimer's. "Aha, memory!" And then it stampedes into the issue that you inevitably face from an audience when

you talk about drugs like that, "What happens if a college kid takes it?" That is an inevitable question that the audience asks, no matter where you are. What if a college kid takes it? They are very worried about it. So there's been and will be even a far greater growing concern than we have today about a "smart pill". The ethics and morals of the smart pill.

Fowler: What if the smart pill has no abuse liability in the usual sense of the term? That it's only abuse liability is like caffeine, in that it is instrumental to some end but is not necessarily fun.

Cook: Yes, well to hear the questions, "What about the abuse of that, the drug abuse?" What they really mean is not classically "drug abuse" but "misuse".

Fowler: Yes.

Cook: Misuse.

Fowler: Yes, well unless it damages the brain in the process of improving memory. Indeed until it is clear that it's going to reduce your function long term in some manner, then the logical conclusion is that everyone will take it to compete.

Cook: We didn't even get to your first question on recreational use. I'm referring to areas of acknowledged medical need!

Fowler: Exactly.

Cook: I remember one time I was invited to give a talk to a lay audience. They asked me to talk about drugs of the future. I started talking about the drugs of the future and got into drugs that we already use for psychotic behavior, depressed behavior, anxiety behavior, and pain. Now we're reversing the coin and instead of selectively inhibiting certain behaviors and certain emotional tendencies, we are enhancing functions such as cognitive enhancers. The first question, "What happens to the college kid who takes it?" I said that these agents are designed and put forth for recognized medical need. "But what about the college kid who...."

Now to answer your question, will there be an acceptable recreational drug? I don't know what you mean by that.

Fowler: Well, I mean beyond what we have. Certainly alcohol, it's regulated and all, but it's clearly recreational.

Cook: Okay, but you're saying, a social drug to feel better.

Fowler: To feel better. Maybe more than one. But one that is specifically given with the idea of, well, there's science fiction writers that have written about this like Aldous Huxley. It makes people feel better and that's why it's recreational. It's like walking around the block in the sunshine.

Cook: How about pot?

Fowler: Well, yes, I think it's one of them.

Cook: Honest and truly, I am almost embarrassed to say this: I have never experienced these drugs; I've never taken a recreational drug. My kids called me square. "God, Dad, you're square." I can think of better things to do to turn me

on. I haven't had that experience. But the point is there may be nothing wrong with it--if in fact it doesn't hurt, has no social implications or risks, and, downside, has no impact on the rights or well-being of others, and has no physiological costs. A person may say with a drug such as you describe, "I'm smarter, I'm better, I'm happier, I haven't felt this good-since I was 14 years old." Well, what is wrong with that?

Fowler: Actually nothing. It just occurred to me that something you said earlier today was similar to this. It's in the drug-behavior interaction that the drug will have altered behavior in a kind of irreparable way. In the sense that after you've experienced a kind of high in an artificial sense, it alters your ability to experience other highs that are non- artificial. Maybe that's the argument.

Cook: Like cocaine.

Fowler: Yes, cocaine is probably the drug that makes a person feel the best.
Cook: Cocaine "addiction" is not necessarily because of a physiological change but because "I like that so much that I'm willing to go to hell and back for it." And that's a danger, you know.

Fowler: Yes. It's like creating an artificial delusional state that a person would rather have than his normal state.

Cook: And if it's really that good, as I said, they'll go to hell and back for it. Apparently from what I understand about cocaine.

Fowler: Yes, but that's the danger, the state that it creates really is delusional.

Cook: That's why I asked for clarification. I wasn't sure what you meant by recreational.

Fowler: Well, you've got it.

Cook: I don't know. To me there are so many ways to get a high that you don't need drugs to feel great.

Fowler: But, in this context, I always think of alcohol, because alcohol is so well accepted. I mean there are certain segments of our society that won't accept it; but, by-and-large, it is accepted. It's legal, it's licensed, it's regulated, and it's so extremely dangerous when it comes to driving and that sort of thing. The fetal alcohol syndrome is extremely damaging.

Cook: Yes. The only time I drink is socially. I never drink unless I’m at a party, or if you come over and had a drink, I would have a drink.

Fowler: It seems perfectly all right.

Cook: I take a glass of Jack Daniels with a little soda, and I just relax, I feel terrific. And I rarely do it. Saturday night we were out at a party. My boss had a party over at his house. It was a lovely affair, there was about 40 people there, and I had a Jack Daniels and I just totally relaxed and felt great. I drink one, one is all I can handle; that is all I need and I feel great. So, to me that's the recreational drug. I think you're quite right.

Fowler: It may be the kind of thing that will require a long social evolution for its acceptance and properly regulated use, just like alcohol.

Cook: I don't think it will ever go because of our society. I don't think they could ever feel relaxed enough to accept somebody popping a Valium.

Fowler: Well, there are studies that show that alcohol use in moderation promotes health.

Cook: Oh, yes, no question about it. But really society can't buy that. Society took awhile for the first Thorazine to be accepted, and Valium still isn't. They never had the slightest hesitation about antidepressants. The feeling with something like Thorazine is lousy.

Fowler: That's one of its major problems.

Cook: I've taken a Thorazine once. When my second child was born, I took my wife to the hospital. The doctor said, "Go on home and get some sleep. It's going to be a long time, I'll call you, and you can come back in the morning. It'll take a couple of days. Or else I'll call you at night in plenty of time. Just go on, you're a wreck." So, I went home, and took a Thorazine; and that was the most unpleasant feeling I've ever had. People have told me that.

Fowler: Haldol is worse.

Cook: I don't know. I never took that one.

Fowler: I haven't taken either one.

Cook: But for a normal person taking it, it is just horrible. Okay, so no one is worried about that. But Valium is smooth. I mean, I've taken a Valium to go to sleep; and I must tell you I just glide into sleep. It doesn't produce sleep, it is a sleep inducer. You just gently fall asleep. It's not like a barbiturate which heavily puts you to sleep.

Fowler: Right, a barbiturate hammers you. It's an anesthetic type drug.

Cook: I see nothing wrong with that [Valium for sleep induction]. If it’s not abused and if it doesn't take over. But I can't believe this society, with its mores and ethics, will ever accept it. I don't believe it, not until there's enough generational change.

Fowler: Well, I think that will be required. Like a hundred years.

Cook: Not in my lifetime. And I don't think in your 1ifetime, no way. It's just not going to happen.

Fowler: I think you're right.

Cook: Why are people---

Fowler: I think it's the loss of control. I really think that--

Cook: You've said that a number of times. What do you mean loss, what loss of control?

Fowler: That instead of putting your faith in coping with reality, in so far as we can in a unfettered way, there's this other element that reduces functioning in some dimensions. Putting your faith in this artificial element frightens people because they are not coping at their maximum, so to speak.

Cook: You don't have to use certain coping mechanisms.

Fowler: Yeah, that's right. That's what I mean by that. I think it's a fundamental biological trait to try to optimize the sense of control over your body--

Cook: You know the amount of ulcers that are decreased because of drugs like Valium? I've seen the statistics in regard to anxiolytics in terms of what they would otherwise expect in ulcers and physiological disorders. How it's helped prevent that, and some in society still won't buy using Valium.

Fowler: I think that it will take time for these things to be accepted; I think the religious dimension is also important.
Cook: I'm thinking about drugs for Alzheimer's disease that found use among students, and it really worked. Suddenly kids are getting A's and A+'s. One would be accused of offering advantages to some people.

Fowler: You're saying that if we can't be in control, we don't want anybody being in control.

Cook: I don't know how it works.

Fowler: I think that's it.

Cook: But the thing is, a cognitive enhancer is fulfilling such a serious medical need [Alzheimer's disease]. Now in fact I doubt very much that these drugs will have any significant effect in normals. The studies that we've done show that when animals are doing well, there's not much room to improve. It's only when we have a deficient baseline or are doing a difficult almost unsolvable task that you see the effect of cognitive enhancers. You don't have that much elbow room left in normal behavior to see an effect. So, with a perfectly normally functioning individual, I don't believe you're going to really see a significant impact in their intellectual capacities or memory. I don't believe that.

Fowler: Right, with this [memory) drug.

Cook: Years ago we did studies of delayed matching to sample in monkeys, with strychnine. It's not a medically used drug, but it certainly enhances those systems that you want pushed for cognition. And what we found in delayed match tasks, by altering the time between signal and choice or by putting correct matches on what we call a fixed ratio, we could adjust the animals' performance It was one out of three choices for reinforcement. They had to hit it one out of three, three times in a row correctly. They had a triangle correct, box or dots. It's one out of nine for the choice baseline. So, 18 percent was chance performance. I equilibrated the animals, I think we had about ten animals, so all of them were doing about the same. We equilibrated the animals to 25 to 30 percent correct. Strychnine did not work at the low correct baseline. The monkeys didn't have the performance going, they didn't understand the task. This result told me that strychnine can only help something that's already well functioning. It can't put it together for the animal. By having that long delay where the very best that they can do was 25 percent correct, they couldn't

handle it. Strychnine couldn't improve performance. And that was true until we went to about 60 percent baseline correct. And strychnine enhanced these 60 percent animals, up to 80 percent.

Fowler: So it's a performance enhancer but not a learning enhancer?

Cook: But then we went up to 85 and 90 percent correct baselines. At 85 percent the drug did not improve performance significantly above the baseline. There wasn't that much room to show any significant effect. So, it told us that if the performance is really well functioning, you don't get much improvement. There is not enough elbow room to see improvement.

Fowler: Right.

Cook: Where the performance is so bad that there isn't any significance performance, the drug is not going to work on something that's not functioning enough, not working.

Fowler: Right.

Cook: They have got to have the concept, and once they have it going then a drug can help them. That taught me a lot about studies in the area of cognitive enhancers.

Fowler: That makes sense. It does.

Cook: That was a fabulous study. We published a little of it in a paper with Catania. It is one of the Federation Society papers. But, with the really functional normal, I don't think we will ever be able to show consistent, clear, significant improvement.

One of the major issues in the field of cognitive enhancers is we don't know how much effect preclinically we have to have in order to have a significant improvement clinically. Do we have to double it? Just make believe we are talking about IQ and in the normal animal it is 120. I tell you that I brought them up i5 percent, which is up to 138. Fifteen percent, don't tell me that doesn't have a significant implication. So it's only 15 percent or 10 percent (120 up to 132). Or 20 percent, let's say the drug helped the animal 20 percent. I say we are talking major changes. Suppose this drug improves 20 percent. God, you are -taking a normal IQ of 120 and adding 24 points. You went to an IQ of 144--what a genius, this guy is pretty good.

In this particular area the major question is how much improvement do we need in cognition for significant clinical benefit. Supposing the drug improved 15-20 percent; automatically most of us would say forget it. Think about it, if IQ can be used as a sample in our argument here. Even modest changes in animal pharmacological studies could have major implications clinically in areas of recognized medical need.

Fowler: It is not an antibiotic.

Cook: An antibiotic kills 100 percent of bacteria. Analgesic dose response curves can produce 120 percent, 150 percent change, or whatever. In most pharmacological areas you get big dose response curves. Zero to 100 in terms of the ordinate. In the case of cognitive enhancers, I can't do that and I can't tell you how much of a change is necessary. We don't know that. And another thing is a very important issue here. When you deal with psychology and

cognition, where it differs from all other areas of pharmacology is the inverted U-shaped curve. You have a real problem in clinical pharmacology from three points of view. One, we are dealing with an inverted U-shaped curve, and at very best from the lowest dose to the highest dose is a factor of ten. So you've got a window. This just happens to be true with all physiological systems where you are dealing with improvement of function. You can only go so far and then you are fighting it. It is not an antibiotic.

Second, and I just told you about that strychnine experiment, as in the strychnine experiment we were just talking about, if the baseline of performance is not working well enough you are not going to improve it. Or, if it is working too much you are not going to improve it. So, therefore, for example, in Alzheimer's disease there is a critical period when things are still functional. But if the patients are burned out the drug is not going to work; and if it is early in the disease, it's too close to normal and you are not going to see much drug-related improvement. So you have to superimpose the optimal dose with the optimal stage of Alzheimer's disease for treatment.
Third was the task. If the test task is really easy you are not going to see an improvement, and if the test task is really tough they can't improve it. So you have to superimpose the sensitive test, the correct stage of the illness and the right dose. Our animal pharmacology told us that you have to superimpose all these to show your effect, and you have to do the same thing clinically. And don't tell me that the drug doesn't work if you haven't set all the proper conditions to show it. I had such fun with that lecture [to the ACNP], it was a presidential symposium and I had a lot of fun with this. I said we do a lot of pharmacology. The drug goes to the clinic, we get an answer back: It worked or it didn't work. As if God from the Mount has given us the word! But let's face it, you are not Moses coming down from Mount Sinai with the tablets. When you say it works or doesn't work in patients, in this field of psychopharmacology you need to be more specific about defining your boundary conditions.