PHARMACOLOGY, BEHAVIOR & CHLORPROMAZINE
LEN COOK

How did you get started in the area?

I graduated from Rutgers in 1948, after being in the airforce in the 1940s. I was a celestial navigator in the Air Force. After I was discharged from the Service, I went on to college. After I finished college I was wondering what to do next. I was married less than a year. My wife was working in a lab for a pharmacologist, Dr Molinas, while I went to college at night. Dr Molinas had a picnic in his house one day and while we were sitting under a tree, eating salad, he said "what are you going to do?". I said "I don't know, I've finished college, I'm not sure what I'm going to do. I'd love to go to grad school in some sort of science but I just don't know". He said "have you ever heard of pharmacology?". I said "I didn't want to work in a drugstore and make ice-cream sodas". He said "no no, and he explained to me what pharmacology really was". I said "that sounds fascinating". Would you believe that I had never heard of it before and here I was a college graduate. I said "where do I go for training" and he indicated that one of the best training courses was in Yale. I said "I'm not going to be able to go to Yale, a poor kid from the inner city" and he said "Oh no, go and see so and so". I went and was interviewed by the Chairman, Bill Salter, and by the end of the interview he said "I'd love to have you here".

So I went to Yale. They provided a fascinating opportunity for me as it turned out because quite distinct from offering a conventional course in pharmacology, they were specially training pharmacologists to go into the pharmaceutical industry with specific training in drug discovery. It was the only department before or since, that I am aware of, training people for drug discovery rather than training in terms of certain scientific theories or specific interests. It was great and most of the 15 students who went there at the time became the leaders for drug discovery in the industry for the next 30 years - myself, Irv Tabachnick, Bill Grey and Bernie Rubin. We learned the strategy of drug discovery which few people learn in more classical departments.

Even then, there was hostility to working in the pharmaceutical industry. At Yale, I was with a Professor Desmond Bonneycastle, a Canadian, an MD PhD. I worked with him on certain aspects of analgesic research for my doctorate thesis. Finally, because the department was set up to train people for the industry, I had 6 offers without having to leave New Haven. All of the companies knew about this program and the pharmaceutical industry was getting rolling around then - 1950/1951. It was beginning to become a strong research and discovery business. But my professor thought it was wrong to go into industry when you could spend your career training others who could train others etc. At that stage I had a 4-month old baby.

SmithKline came up to interview me and after that I received an offer from them. This was in 1951. They offered to pay me $6,000 a year - at a time when my professor, Dr Bonneycastle, a full MD, PhD at Yale, was getting $5,000. Naively, I said "Professor Bonneycastle I received a job-offer" and I showed him the letter, which as I reflect on it now was a stupid thing to do. He was a brilliant scientist but he had his own ideas about "prostituting" oneself. I thought he was going to say "Len I'm so happy for you". He knew my wife, Rheva, worked upstairs in nutrition and that we had a baby but he was obviously very upset. Next morning he called me in and said "You know Len, I've been thinking that you really should spend another

year here for your own good". I said "But Dr Bonneycastle my thesis is just about ready, I've had my primary defence, I've accepted the job, I have a little baby, what do you mean another year. I've not only done every single thing in my proposal but I've done more. Nobody else around here in recent years has ever come close to doing more than 50% of what was in their proposal". He said " well this is for your own good". I looked at him. Maybe two years in the airforce helped but I said "Dr Bonneycastle, if you do this to me, I'm going to see the Dean of the grad school and have a hearing on this thing". He said "okay if you want to be whore, if you want to prostitute yourself, go ahead".

I still had the final defence of my thesis ahead. I went down the hall to a friend of mine, Professor Nick Giarman, who was the "defender" of grad students and said "Nick, I'm in trouble" and I told him what had happened. He said "don't worry, I'll be there at the defence". Everything turned out okay even though my own professor let me swing in the wind. Interestingly, I then had another letter from SmithKline saying that my salary was no longer $6,000, owing to adjustments it was $6,350, a $350 raise without even starting, which I went and showed to Professor Bonneycastle. Subsequently, everytime he would see me in Atlantic City at the annual pharmacology meetings, he would say "Hi moneybags, how are you doing?". Ironically about 7 years later Kapp Clark, the vice-president at SmithKline called me down and asked me if I knew a Dr Bonneycastle and said he had just applied to a job, even though as Kapp commented "he doesn't seem to very friendly to the pharmaceutical industry even though he wants a job here".

There was an enormous hostility among the academic community to young students going into the pharmaceutical industry. Do you know about KK Chen at Lilly? He was the one who brought over *Ma Huang*, ephedrine, and he was head of pharmacology at Lilly. He was thrown out of the Pharmacological Society because he worked in the drug industry. Ironically, he subsequently became president of the society years later. During that period of my career, for the first ten years or so, we were not considered very legitimate by many academicians, even though we were doing as good research as most people in university. I am very proud that I became a member of the Pharmacological Society after only 4 years out and years later one of the proudest moments of my life was to become a fellow of ACNP. I'm the only person from industry to hold an office in ACNP, first vice-president and then later in 1982 I was voted in as President. This was so exciting - it was on a par to my son being born. That legitimised me in my own mind but it also was a recognition of what was happening in industry. In fact, even in ACNP there was some hostility to industry at the time. I also got the Paul Hoch award which is one of the highest awards the ACNP hands out. Many people in industry told me that they considered that my experience in this society helped legitimise their own scientific role, which greatly pleased me.

Anyway, at SmithKline in Philadelphia my first job, my initial research project was on gastro-intestinal pharmacology. The head of research, Kapp Clark, later came to me and said "Len what we would like to do right now is to get into a non-barbiturate sedative program. The barbiturates have had a bad rap, they're not very safe and there is a real need out there for such sedatives". Now at that time sedatives were the main CNS modulators - sleep-inducers such as barbiturates along with methylparaphenol and chloral hydrate. That was essentially it. What was available

pharmacologically was not behavioral modification as much as behavioral knockout. I said “that sounds good to me and very interesting but I wonder how do you measure sedation in animals?”.

At that time, if you gave the available CNS depressants or sedatives to animals you didn’t see “sedation”, they got excited and then they’d fall on their backs. You don’t see in animals that sub-hypnotic sedative effect you see in humans. Essentially I set up a few laboratory tests. In college I took Psychology 101, which was a six-month course and I remembered something about conditioned reflexes - Pavlov and all that. One of the things I set up therefore was a conditioned reflex test which ended up being a conditioned avoidance response. The animals were essentially trained to avoid auditory stimuli associated with aversive stimuli such as electric footshock. I tested many of the then available drugs on this approach.

I also had an apparatus to monitor and quantitate spontaneous exploratory motor activity. I did neurologic exams on mice and rats, such as placing reflexes, cross-extensor and other neurologic reflexes - this was something I had learnt at Yale. But when I tested all these compounds, nothing very useful came up, so when Kapp Clark said “Len how’re you doing on the non-sedative research program ?”, I said “not very well. I think I’ve got effective test procedures but I don’t have any compounds that work the way I project that they should”.

One of the tests people were using in 1951 to identify sedatives was to administer a low-dose of a short-acting barbiturate, hexobarbital, and then combine it with the experimental compound. If, instead of sleeping for 20 minutes, the control condition, the mouse slept longer, this was used as an indirect way of measuring sedation. One day, my technician, a young man named Ed Weidley, said “Gee, Len, the mice are still asleep. I gave them hexobarbital and instead of sleeping for twenty minutes they’re still asleep and its almost an hour”. I said “they must be dead Ed”. I went over and sure enough the mice were still asleep. The next day I said “do it over again” and sure enough it was not only confirmed but there was a dose response to this phenomenon. They were sleeping longer than any single dose of a barbiturate could ever produce without killing them. Most importantly the drug itself was essentially pharmacologically inert - it produced no CNS effect. We subsequently found out that this compound, SKF 525A, interfered with the metabolism of the barbiturate and prolonged the plasma level and this was its mechanism of action.

That was a critical finding in the field of pharmacology. It opened up a new research program. I went to the president, Mook Boyer, it was a small company at the time, and said that “if we can get compounds that are innocuous in their own right but which prolong the effects of other drugs that might be a new research area - we could call it the “drug potentiator” program. He said “Go ahead”.

About six months later, I heard about a compound from France, made by Rhône-Poulenc, which they were primarily testing for its enhancing or potentiating effects on other primarily CNS drugs - you may have heard about Laborit’s lytic cocktail. I requested a sample and received a gram and tested it in my new “drug protentiating” program. Now, whereas my research compound SKF 525A prolonged sleeping time without any obvious overt pharmacology of its own, the French compound, RP4560, chlorpromazine, did the same but even on its own it also made the animals sluggish

and heavily sedated. By this time the non-barbiturate sedative program had significantly slowed down but I thought I'd test the French compound in the tests I had developed for that program. So we gave it to animals in doses from 1 mg/kg and higher. They became progressively quieter until they became totally immobile. For the first time in pharmacological history they were not moving around although they remained upright on all four feet. I turned them on their side but they righted themselves. I pinched their tail and they pulled it away. I clapped my hands but they didn't move. I tested corneal, pinna and placing reflexes, everything I could. These animals were alert, their motor system was intact, but they were totally impassive to their environment. I had never seen a pharmacologically induced syndrome like this.

In order to chase the CNS profile of this compound further, I set up the conditioned avoidance apparatus again. With the barbiturates in this procedure, whenever I reached a dose where conditioned rats did not respond to the conditioned stimulus - a doorbell - which preceded an electric foot-shock, I also blocked their ability to escape the effect of a shock. In other words the rats didn't respond to the conditioned stimulus because they couldn't move. Their failure to respond was a physical incapacitation. When I gave RP4560 and rang the bell they also didn't move. Now these were animals who were well trained and when you rang that bell they normally jumped onto the pole immediately. But after treatment they didn't move, unless I subsequently gave them a foot-shock, which they did escape. Therefore they could still feel the shock and they could still move but they didn't seem to care about the warning - the conditional stimulus - that was my first interpretation. Six months of a psychology course and I didn't even know what words to use in defining this phenomenon.

After that I carried out a full dose-response curve in the conditioned avoidance procedure and in almost every other task I was trained to do in grad school. I reran the barbiturates and everything I had in the CNS armamentarium and what I found was with most compounds, the dose that blocked the response to the conditioned stimulus also blocked the response to the shock, but with RP4560 you could totally block the response to the bell with no effect on the response to the shock. It was a unique effect. The question was what was the significance of this effect? Did it have any therapeutic applications?

How big was the company at the time?
Well, I was the first PhD in pharmacology they had ever hired. They did have some technicians and other scientists and a modern laboratory facility. I used to have lunch with the president and director of research at the time. Over lunch one day I said "this is really really strange, this new drug is making the animal totally impassive to the environment". The research director said "what good is that Len? Maybe if you give it to people, they might kill themselves. It may totally inhibit all life preserving reflexes and warnings". I pointed out that not all responses were obtunded - it was only an inhibition of responses associated with emotionality, at least that was my first interpretation of the effect.

You must remember that this compound, chlorpromazine, was originally made as an anti-helminthic and it had already been touted to 7 companies in the United States as an anti-histamine. Quite appropriately they had turned it down - it was a strong sedative and everybody wanted an anti-histamine that didn't have the strong

“benadryl-type” sedation. This one certainly had no less. Mook Boyer, the SKF president, said “these Rhone-Poulenc people were here about 6 months ago trying to sell this compound as an anti-histamine”.

Was this before the psychiatric indications had begun to come out?
Rhone-Poulenc were pushing it as an anti-histamine before Delay and Deniker had made their claims for its psychiatric utility. Mr Boyer asked me “Len on the basis of your findings what do you think?”. I said “I think this is a totally new aspect of pharmacology” so Mook Boyer said “let’s call these guys from Rhone-Poulenc over and talk to them”. We contacted them and a month or two later they sent over a scientist named Pierre Koetschet, who was their research director. At this time they were still interested in it as a drug potentiator in lytic cocktails. I explained the work I had done on its effects on behavior and he said “there are two doctors called Delay and Deniker in Paris who have contacted us and said that they have found very significant effects on abnormal mental states” - we didn’t have any better terms then. He went back to Paris and I was left thinking whether this correlated with my data on behavior in animals. Again the President said “what do you think Len?” and I said that it still seemed to me that this could be a whole new area of pharmacology. So we had the French back again and by this time Delay and Deniker had studied a few more patients and their effects and my work on conditioned avoidance and other tests seemed to fit...

Rhone-Poulenc had also done some behavioral work in this area
Yes Mme. Courvoisier had. I heard about her work after I had carried out mine. After M. Koetschet saw my work, he sent over the brochure of pharmacology but her behavioral work was not really conditioned avoidance behavior. Her animals were trained to climb up a rope to get food so it was a different thing but it essentially fitted in with what I had seen, which was a decrease in the tendency to respond. She never did many more studies after that. We formed an SK&F/Rhone-Poulenc collaboration and I ended up going over to Paris a great deal - I was only 28 years old at this time.

The companies then signed a deal for chlorpromazine. The rest as they say is history. I started our research on Compazine and Stelazine right after that. Mook Boyer and Kapp Clark called me down to their offices one day soon after the deal had been signed and they said “you know this looks like something interesting”. I said “I’m glad you said that because from my limited experience I think we’re into a whole new field. There’s renal pharmacology, there’s cardiovascular pharmacology etc but I think we’re into something totally new, I would call it psychopharmacology”.

Did you coin that word then?
As far as I know I did. I know I used it publicly at a seminar in Emory University in 1953 when I started to talk about some of the work.

You said Rhone-Poulenc pushed chlorpromazine first as an anti-histamine and then you guys asked them back - did they do a further tour of US companies trying to sell it as an anti-psychotic?
No. We at SK&F expressed a strong commitment to chlorpromazine and we were the only US company to get it. My research findings were then very influential with the SK& F people and also in Rhone-Poulenc regarding the use of the drug.

Paul Janssen also tells a story about you saying to SK&F that if chlorpromazine failed to work as an anti-psychotic it would be good for nausea?

Well one of the other things I did at that time was an anti-apomorphine vomiting test in dogs. We used dogs hanging in a sling from the ceiling and I had one technician, Ed Weidley, spending all day pushing the dogs back and forth until they vomited. I did all of the research with chlorpromazine initially with two technicians who were both high-school youngsters. One of the things we had noticed while doing the apomorphine induced vomiting work was that you would go into the room with a laboratory tray to give the experienced dogs their apomorphine injection and they would vomit. We were using this as a screening test for anti-emetic drugs, which one of the vice-presidents felt was a good market. Now one day one of the technicians said to me "Len its so funny, I give the dogs an injection twice a week and after 5 or 6 injections, when I walk in with the tray they start vomiting even before they are injected. I rattle the tray and they start vomiting their heads off" - you see this in humans too, cancer patients for instance. So I said "why don't you give them chlorpromazine before you come into the room and see what happens" and he came back to me and said "none of them are vomiting". I said "that's a conditioned reflex. Why don't you go further and give them the drug and see if blocks the actual apomorphine-induced vomiting" and he came back and said that none of them were vomiting. We made a new solution of apomorphine and repeated the studies and it really worked. We later did some work with the chemoreceptor trigger zone and the vomiting center and it was clear that chlorpromazine didn't block drugs which had their effect on the vomiting center. It specifically blocked agents which stimulated the chemoreceptor trigger zone.

I went to see the president and vice-president and told them about this and they said "Len you know it looks like we're off and running". We now had more and more information coming from Paris from Delay and Deniker". Laborit was still demonstrating chlorpromazine's effects in his lytic cocktails. I said to them "I'd really love to give up the other pharmacology I'm doing, the G.I. program etc and get into this full-time". They said "ok anything you want, we've got the money, you set up whatever you think you need. What do you need?". I said "Can I go home and think about it?". They said "sure, we'll see you Friday". I thought about it and I went in Friday and they were both there, very kindly guys who did everything so I wouldn't be intimidated. This was 1952 and I said "right now we can go into 3 things. What I'm doing is psychological research" - I didn't use the word behavior at the time, it was psychology as applied to pharmacology. "Or there's a new field opening up called biochemistry". They said what's that and I explained that its measuring epinephrine and other biochemicals in the brain. Also I'd been up to Harvard and MIT and spoken to a woman named Mary Brazier who was doing EEG - where I saw a room full of equipment for doing EEG analysis[1]. I had spent a week there learning about electrophysiological signals. When I was in Boston I also went and saw a person called B.F. Skinner who was doing some work with pigeons pecking and rats pressing levers. I learned something about operant psychology there. I also met Peter Dews and said that I was really interested in what they were doing and asked if they had anyone I could hire to do similar studies in my laboratory. That's where

[1]see Lasagna L (1997). Back to the Future. The Psychopharmacologists vol II, pp

contact with Roger Kelleher came from. He had worked with Charlie Ferster in Florida at Yerkes' lab. I learned most of my behavior from Kelleher. I later spent at least a month every year learning psychology in Wisconsin and other places looking at what people were doing in the line of experimental behavior with monkeys and rats etc.

Anyway I said "as far as I can see we can do these three things behavior, biochemistry and electrophysiology and I think they are all going to become relevant. However if I tested a drug - today it costs $100 million to put a drug on the market whereas then it ran about $2-3 million which was a lot of money - and I came to you and said I had biochemical, electrophysiological or behavioral data, which would you go with?" I said "I'd go with the behavior because we can see changes in something we want to change in people but we need to have some information on the other aspects as well". They said "why don't you hire whoever you have to?". I already had woking in my group a young man named Bob Shuster. Bob had both a B.A.and an M.A. I then hired Roger Kelleher from Ferster's department to run the behavioral studies. I hired Keith Killam who had just got out of Chicago with his PhD and he ran my neurophysiology lab. Harry Green ran the biochemistry. So essentially we had a little bit of all three areas. I used to go over to Rhone-Poulenc frequently and we had Laborit come to our laboratory to demonstrate the effects of chlorpromazine containing lytic cocktails.

Around 1953, as I understand both Laborit and Pierre Deniker came to the US and at that time Laborit and his anaesthetic indications were still the front-runner at least in Rhone-Poulenc's eyes.
Laborit's interests were still the lytic cocktail, whose primary objective was to achieve a state of hypothermia for cardiac surgery that would let the surgeons go beyond 2-3 minutes, which was the limit at the time, to 15 minutes. This was a big deal then. I started to do similar hypothermia work in dogs and rats in which we would wrap them in ice-cubes and bring them down to body temperatures that were impossible to sustain without chlorpromazine. Chlorpromazine and Laborit's contribution was twofold here. You could take advantage of its drug potentiation properties so that you only had to use a little bit of each of the various drugs in the lytic cocktail but it also rendered the animal poikilothermic. Essentially they lost body temperature control and you could bring them up or down to body temperature levels you couldn't possibly achieve any other way.

We subsequently went to Maimonides Hospital in Brooklyn to talk to a surgeon Dr Ribstein who carried out the first clinical trial with chlorpromazine in the United States - for surgical hypothermia. I used to go up to see him because at that time the preclinical pharmacologist used to personally deal with the clinician - we don't have this interaction very much today but it was so fruitful. We used to learn from each other. He'd say something and I'd go back and test it in the animals or I'd say something about the animals and he'd say "you know I saw this". Anyway he was doing cardiovascular surgery, where he would drop the body temperature to allow a longer surgical time. I went up frequently but at one session he said "Len something's really weird, when I'm giving this drug" - and it was not the lytic cocktail, we'd narrowed it down to just chlorpromazine - "when I give that drug people behave real funny". I said "what do you mean" and he said "it looks like they're amnesic". That was the only word he could think of. "They're not with it and I've noticed

something else - they don't seem to care". That was the first clinical observation in the United States, as far as I am aware. Of course I wondered if the conditioned avoidance data meant anything that was relevant to this. It ended up that it was very relevant. But along with the anti-emesis data, the hypothermia angle was another thing that helped drive this compound forward into clinical use.

Through all this I was supported with almost anything I needed. I was riding a crest and I could do no wrong. Support that would be incredible today. We developed many different laboratory test procedures which are still used today that seem to measure relevant and predictive aspects of the pharmacology. Conditioned avoidance is perhaps the most important test. I used to call it conditioned fear but later I realised that was irrelevant, its not conditioned fear. We looked at all of the CNS drugs that had been developed over the years for schizophrenia and found that their clinical potency correlated 0.99 with their effects on inhibiting the conditioned avoidance task, so its measuring a pharmacological property that is particularly relevant to therapeutic applications in severe emotional disorders.

The next step was that we had to get to the psychiatrists with chlorpromazine. Now this was a revelation to me. In the early 1950s, Freudian psychotherapy was popular and many people in the field were psychoanalysts. I remember one who later became very famous saying to me "Len, are you telling me what you've got in this little pill is going to modulate libido and other complex behaviors - how's a chemical going to do what I can do with 6 months of psychoanalysis?". Its hard to relate now, the skepticism that psychiatrists had then to the concept of an intervention with a drug - they had forgotten what Freud himself had said. Then we went to Paul Hoch in New York and I remember him saying "that's very interesting, if you want I'll try some". He tried it and said "its great". We went to Heinz Lehmann, Fritz Freyhan and others for clinical evaluation. We went to Kinross-Wright in Texas who did a conditioned avoidance response which he had developed using the thumb. It worked and confirmed in humans what I had seen in the rats.

We seemed to be developing the building blocks of a new area of pharmacology and I was very fortunate to be involved. In France everything seemed to stop after Mme Courvoisier did some of the early work. She dropped out of the scene - I think she was ill. So I was the leading scientist all through the 50s while Compazine, Stelazine and all of the follow-throughs came on line. We developed these on the basis of the pharmacological principles we had set up at SK&F. I began to get super people working for me during this time and I began to build up in SmithKline the best, most advanced lab in psychopharmacology in the world. I remember an advisory board meeting where I gave a presentation and Lou Goodman afterwards said "in all the research the government has funded, I have never seen a program as comprehensive, relevant and productive as what you have here".

My understanding is that SK&F when they applied to the FDA for a licence for chlorpromazine did so for an anti-emetic, is this true?
Yes. They were so smart. At that time I was somewhat naive and I didn't understand the marketing strategy. SK&F went to the FDA with chlorpromazine as an anti-emetic and they got the approval for something that was very conventional pharmacologically - no sweat, no raised eyebrows. They said here's the data we have on the anti-emesis, motion-sickness and on the anti-apomorphine test.

I was not privy to all of the business thinking but their strategy was to get it approved as a drug and if somebody wanted to write prescriptions for something else that would expand its therapeutic use that was okay. So they got the drug out there as an anti-emetic and then when it was out there they began to broaden the indications. I mean who in the world in 1955 was going to go to the FDA and say we have a drug that will modulate the symptomatology of schizophrenia or modify behavior or mood? As I recall it that was their strategy, there was no question about it.

On the basis of all this I personally started to learn more about experimental behavior. I said to the vice-president that the basic pre-clinical research is relatively easy but the clinical people don't seem to understand how to do clinical research in this field and I would love to go to medical school so that I could become a clinical psychopharmacologist. I was all set for SK&F to send me to medical school but in the end one administrator killed this plan.

One of things that was particularly at issue in those days was the relevance of what we had seen in animals to the clinic. Even though there were high correlations between what we saw and what happened clinically there was still this enormous reluctance based on the idea that people are unique - "they're not rats". There also was this concept of dualism - there's a body and a mind and "I'm in charge of my mind and drugs can't change my mind. They can change my heart and my kidney but they can't change my mind".

I decided to look further at correlations between animal and human behavior regarding responsivity to pharmacological agents. I did this by setting up in one of the prisons a conditioned avoidance procedure with prisoners. You could do it easily then. And I found that when a human being is put in the same experimental conditions as an animal, they will show the same pharmacological effect, e.g. specific inhibition of conditioned avoidance behavior. Chlorpromazine did this just as in the animals and the barbiturates and meprobamate didn't. We published that data - you couldn't tell by looking at the data if it came from a rat, a mouse or a human, when you controlled the contingencies in the environment in a similar way in each case. This doesn't necessarily prove therapeutic use but it proves that whatever drug-behavioral interaction is seen in animals is not something special that is seen only in animals.

At SmithKline, we also did some nice work with benzodiazepines and conflict behavior which has some interesting resemblances to anxiety in humans. What we found was that where the animal was trained in the conditioned avoidance procedure, if you gave a conditioned stimulus that encouraged overt behavior such as jumping, moving or pushing a lever in order to avoid an unpleasant consequence, chlorpromazine would inhibit that. But if you can arrange for the environment to inhibit a behavior rather than to produce it, chlorpromazine will never reverse that inhibition. However certain low-dose barbiturates, benzodiazepines or meprobamate will attenuate environmentally induced suppression, whereas they never selectively inhibit active conditioned avoidance. That's the work that shows that major and minor tranquillisers are not linear in their effects - they are qualitatively different. We published on this in 1960.

In the same way that we showed that human subjects would selectively press a telegraph key to avoid an electric tingle and this could be blocked with chlorpromazine. At Rutgers university medical school, several years later when I was with Roche, Peter Carlton and I did something similar with benzodiazepines. We got medical students as volunteers. They were selectively trained to make money by pressing a lever when a green light was on. Every once in a while a red warning light would come on and during this time they could make more money but they would also run a high risk of losing all the money they had earned. When the warning light came on they would show severe anxiety as the counter showing how much money they had earned began to sink. When that happened, they started sweating, their operant behavior slowed down and some of them used language a sailor wouldn't use. Their behavior was suppressed until the red light went off. When we gave them one 10mg dose of Valium they would work right through the red light period just like a rat would. Chlorpromazine didn't have this effect. This was exactly what you find in animals. Benzodiazepines inhibit conflict suppressed behavior but not active conditioned avoidance behavior.

I also began to realise that what we had were a series of compounds that selectively suppressed certain things in the brain and not just everything. I began wondering given that we could selectively inhibit certain brain functions whether we could enhance certain functions as well. At the time we had an advisory board and Lou Goodman, Al Gilman and a number of other very famous people were on it and they kept saying "Len, where do you think we're going to go in the next ten years?". I said "well I think the future may be in enhancing certain brain functions" and they said "what do you mean?". I showed them some slides that certain compounds made the animal learn more and learn it faster and I said "its not that the animal did it faster but he did it better and remembered longer". The drugs were nicotine and strychnine. Nicotine works in more different types of learning tests than any other drug I tested. I developed Skinnerian test procedures with monkeys where they had to remember over 10, 20 or 30 seconds what they had to remember for appropriate reinforcement and I gave strychnine. At very low doses the animals learnt better. I said these are not the specific drugs that will have a future but they prove the feasibility of enhancing learning and memory. We started a program for learning and memory drugs in the late 50s and early 60s and we found that drugs like imipramine, nicotine and strychnine, in the right dose, improved cognitive function.

Another research area which I felt was very important started one night when I was doing some paperwork in my office at home. I was nervous and I wondered what was I nervous about - everythings fine at work, the kids are okay, everything seems to be fine, why am I nervous? And I suddenly realised I'm nervous because my heart is going fast and because my stomach is a little queasy and because of noticing the tachycardia and queasiness I'm nervous - that is really interesting. So I went into the lab the next day and I set up a type of Pavlovian test procedure. I put very fine catheters into a dog's vein and I trained the animal to lift its paw to terminate an electric shock. Then I went ahead and injected a low dose of epinephrine and whenever the monitor showed that blood pressure began to rise, which was an indication that it was just beginning to have a physiological effect, a shock was presented to the dog's leg. It was just like an exteroceptive conditioned stimulus but I was now using an interoceptive conditioned stimulus. After a while I found that just as soon as a small dose of epinephrine was administered, the dog

would lift his leg and avoid the shock. The next step in another dog was to use two catheters in the same vein to give the lowest physiological dose of acetylcholine and the lowest dose of epinephrine and reinforce only one of the drugs. The dog learnt to discriminate the effects of one drug from the other and this could be reversed. Not only that but what I found was that once you trained an animal on a conditioned avoidance paradigm to an external stimulus you could extinguish this in about twenty trials. If you don't reinforce it they lose it. But once you develop a behavior that is controlled by an autonomic system response you never ever extinguish it. Then I began to realise that much of our behavior is interacting with our internal physiology and our internal physiology can essentially control some of our behavior. Chlorpromazine, incidentally, inhibited both exteroceptive and interoceptive controlled avoidance behavior.

I went to Kapp Clark and said "Kapp I got a big one to request. I want to go to Russia. All of Russia is very heavy into conditioned physiological responses and I want to learn what they know. The available literature is terrible". He said okay. It took me almost a year to set up. I went with an interpreter to Leningrad and visited Pavlov's old lab with a Dr Ariapetsyanse. I visited the biggest primate lab in the world on the Black Sea, Sukumi, and I went to Moscow. I gave several lectures. They referred to me as the American Pavlov which was a great title. I presented my findings on conditioned physiological responses and they said "oh yes, Dr Bikov did that 50 years ago" - and he did. That was very interesting. I went back and said to Kapp Clark that one of these days we would be testing for drugs that would have effects on psychophysiological disorders. Nothing much happened in this area, however.

Around then we heard about Milltown - meprobamate. This was put out by Frank Berger originally to compete with Thorazine. We tested it to see if it had effects in the conditioned avoidance test like chlorpromazine and it didn't have the specific chlorpromazine effect. Subsequently, Librium was put out by Roche and they also originally put that out as a competitor to Thorazine until they discovered that it had other unique effects of its own.

They were all seen as tranquillisers in those days weren't they?
Yes the word tranquilliser was an all-encompassing term. I don't know how it was coined.

There was a guy called Yonkman from Ciba who took some credit for it and there is some suggestion that Nate Kline may have coined it..
I don't know if Yonkman did but Nate Kline didn't.

Another thing I did at this time was that I went to Kapp Clark and said here I am a scientist looking for drugs to modify behavior and I don't know anything about psychiatric syndromes. If I were a kidney pharmacologist I would know the kidney like the back of my hand. On the basis of this I went to the University of Penn and saw Karl Rickels, who was young at the time, and made an arrangement that twice a month I would make the rounds with him. I did this for a few years and I saw depressed and schizophrenic patients. I may have been one of the few preclinical scientists that ever did that. What I saw was that a depressed patients is not somebody just hanging over the bed limply, these guys have a lot of anxiety.

They're depressed but they're not emotionally blank. I met schizophrenics and after a while I swear I could spot many schizophrenics - some by their odor.

This is not an uncommon claim.
I said this to Karl and he laughed at me but he also said that a lot of people say this. We would walk through the yard of the mental hospital and I would say "he's a schizophrenic, isn't he? - from his walk, from his body build etc". So I began to learn a little about what the diseases looked like, what the symptom complexes we were dealing with were and what actions a drug might have to modify the syndrome. It was clear that you didn't want to give a stimulant to a depressed person because he already is somewhat uptight.

Talking about stimulants to depressed people, wasn't tranylcypromine an SK&F drug?
Tranylcypromine didn't originally come out of a program looking for an antidepressant. We were not only looking for drugs which would be useful for schizophrenia, we were looking for sleep-inducers, we were looking for stimulants which would be different to amphetamine.

The concept of an antidepressant can't have been there at that time, stimulant yes ..
That's correct, it wasn't. You know the story - it was Nate Kline at the tuberculous hospital and they had the insight that these people weren't feeling better just because they got rid of their tuberculosis - that was a great contribution. So they and others began to work on the pharmacological treatment of depression and this made us aware of the possibility of drugs that might be antidepressant. We did a lot of work and eventually came up with tranylcypromine and went into the clinic with it. I have to tell you it worked very effectively. However the side-effects were more than we anticipated which, as you know, restricted its use.

Did you have much contact with Alfred Burger- he was the one who made it wasn't he?
Burger was a consultant to our medical chemistry department. He was located in the University of Virginia. A nice person and very capable. Whenever he came in to consult with medicinal chemistry he came into my lab because I was doing the testing of the compounds he advised them what to make. He made tranylcypromine. We had carried out some work on it and said "well this looks like a very different agent. We couldn't pick up much on it behaviorally. It was inert on the motor activity tests, on the Skinnerian tests - the fixed intervals, the DRLs etc. But what it did was it worked in the drug interaction tests that essentially identified enhanced biogenic amines. It wasn't until we went clinically and it was tried in depressed patients that we began to realise that it worked well as an antidepressant. We eventually got FDA approval for it but then the cheese and pickled herring interactions began to appear.

My impression is that when the interactions began to appear SK&F stuck with the drug in a way that Roche didn't stick with iproniazid.
Not entirely. When SK&F began to get these reports the reaction was we had to restrict its use. We were broken-hearted when management said we should stop work on this because when you work in a research lab and you find drugs, these are like your children. They pulled the drug off quickly instead of waiting to see how it

could be used more carefully. It was later re-introduced for very limited uses. It may have been used more widely but now when I look back I accept that if you have a drug out there you can't be assured that all physicians are going to use it properly. You are going to get problems and people may get injured or worse so I think they did right. Later on management felt it had been premature to pull it entirely off the market and to tell us to forget the antidepressant program which is what they did.

However, we were riding high at this point. We had done critical work with the phenothiazines, we were starting a new program in learning and memory, we had done work on meprobamate and shown it was different to the phenothiazines but then something strange happened in the company. The head of chemistry Glenn Ullyot who was a terrific guy said at one of the meetings "I think we've got all the drugs we're going to get in this field, I think we should drop the phenothiazine program". I said "what ! - we're just scratching the surface, we're on the edge of new frontier". "No", he said "we've got Thorazine, Compazine, Stelazine, who needs more?" I said "don't do this, there are other chemical classes besides the phenothiazines and besides there will always be a competitor in the field, why don't we come up with our own competitive drug, why let other people do it?". For the time they agreed to keep going but....

I had another interesting insight at the time. Looking through the range of drugs at the time, the only drug that blocked the conditioned avoidance test selectively the way the phenothiazines did was morphine. I got the group to run demerol, methadone etc and we found that all of the opiates and powerful analgesics worked like chlorpromazine. I started thinking about whether there was a drug that could do what demerol did but was not also a pain-threshold elevater. It would be out of the class of analgesics but maybe it maintained the behavioral effect of morphine, codeine and demerol even though it was not analgesic. I went to a meeting and spoke to Paul Janssen about this, who was very interested in the idea. Subsequently haloperidol appeared. I'm almost sure that haloperidol came out of that concept and conversation. Paul is brilliant. He was a happy combination - someone who owned a lab and was both the chief chemist and a brilliant biologist. He could move quickly and efficiently.

Much of the field, you know, came out of the enormous opportunity that industry provided to young people like myself and allowed them to follow their noses. But that era has changed in the pharmaceutical industry. All of the companies now have followed what the Harvard Business School say which is "focus, focus, focus". You can't have what I used to have which was maybe a dozen projects going at any one time never knowing what was going to pop up in any one of them. Now they say *a priori* you pick your best 2 or 3 projects and you put everything into it. Well as much as the advantage may be to maximising your effort, what you lose is all of the other happenstance, serendipity, the cross-fertilisation. You couldn't today easily follow a lead from a non-sedative barbiturate program to drug potentiators to chlorpromazine and anti-psychotics. Now there is very little room in the industry for the unexpected. I don't mean to imply for a minute that you should carry only out non-directive research hoping that something might happen but equally you shouldn't limit or overly restrict the imagination and latitude of young scientists.

SmithKline got into strategic planning very early. They had been ahead of the other companies by ten years in almost everything. The gist of strategic planning was to quantify and analyse and program the entire process of drug discovery to try to make it more efficient. But they lost in the process those special elements that are required for discovery - intuitiveness, and opportunities for serendipity. Most everything was prescribed and it had to be approved by scientific boards. Very often the essence of research boards that approve programs is that people are covering their backsides and playing safe. There are good elements to the idea of research planning but they tend to lose something. I recall people asking me how many compounds does it take to discover a muscle relaxant - "I don't know" - "guess" - "maybe 2, 000" - "okay and how long does that take" - "maybe 30 months". Then in 30 months or 2,000 compounds later they call you in and ask what have you found and you say we've got a couple of leads and they say well if you haven't found the breakthrough by now forget it - the program is terminated.

Were the people in charge in SmithKline in the early 50s still in charge in the late 60s when all of this began to come in?
No there had been a change at the top. The people who gave the scientists the opportunities to make discoveries were gone and those who came in had little feel for science themselves and they attempted to overly program the elements of the discovery process. It was an interesting phenomenon I must say but it wasn't for me and this is what made Roche's offer to be Director or Pharmacology attractive when it came in 1969.

There are two ways of doing strategic planning, one is that you let your own staff carry it out with guidance from someone. We did it this way first in Du Pont and we ended up with recommendations for the same programs we had beforehand. "What are you doing" they said "you're doing the same thing as you were doing before". I said we evaluated all the factors and we think what we are doing is good. It wasn't just my group that did this - all the groups did this and came up with recommendations to continue what they were doing. So then they called in an outside group to force change. I said change for what reason and they said we need change, change in itself is good, its the future. Then we realised management were doing it to cover their backsides. They could say whatever we're doing was carefully analysed, "we've called in hotshots from New York and Harvard and this is the program they suggest, so if it falls on its face its not our fault". It was a security blanket for management. They wouldn't have to put their own necks on the block and say "yes I was in charge and I let these guys do it because I believed in it". You cannot argue with the process but the process can run away with itself.

What about GLP Good Laboratory Practice and all the things the FDA imposed on the industry, how much impact did all of that have?
I don't think that Good Laboratory Practice or Good Manufacturing Practice had much inhibiting impact on our research. In fact in some ways it helped to improve many aspects of pharmaceutical businesses.

So its what the companies did to themselves?
Yes. I don't think this was a result of government intervention or pressure at all. There are two kinds of people in an organisation, lets say a drug-house. There are the risk takers and they are generally the scientists and then there are people who

are covering their backsides. They know that 9 out of 10 things you do in the lab are going to fail so if you say no 10 times you're going to be right 9 times.

Why did you leave SK&F in the end and move to Roche?
I had the golden era of the pharmaceutical business in the 1950s and 1960s. If I wanted to go to a meeting in Rome and drop off in Milan to see Silvio Garattini that was okay. It was a wonderful time. You could do any different studies you wanted to regarding drug development such as modifying learning and memory or modifying autonomic physiology. The strategic planners changed all this. Things began to get nasty and disruptive in research and decisions were not always made by the people who are the most knowledgeable in the field.

At that time I got a call from John Burns, vice-president for research at Roche, a giant in the field. The director of pharmacology was just about to retire and he said he had been talking to Lou Goodman and asked him who was the best person to take over the department when the former director retired and Lou said Len Cook. I talked to my wife and I thought about the changes at SK&F. However, even when you become a little bit unhappy or dissatisfied, you don't throw away something so quickly when you have invested 18 years of your life in it. Burns called me every Sunday night for a while and then gave me a written offer over a meal at a meeting in Pittsburgh. It was a more than satisfactory offer. It was the best job in pharmacology in the country but leaving a department I had built from nothing that was then over 100 people wasn't easy.

Had Roche begun to go in under a cloud at that stage - they came in for an awful lot of stick during the 70s because of the benzos..
The harried housewife syndrome. That didn't bother me. I knew that Valium and Librium were legitimate and effective drugs. I had published more on the benzodiazepines than the scientists at Roche had. No, head of pharmacology at Roche at the time was as good a job as there was in the industry but still leaving SmithKline was like breaking up a marriage. However, everything was changing and I felt I wanted a change and I went to Roche and we started a whole new CNS operation in Nutley and in Basel.

Did you meet Willy Haefely in Basel.
Yes, he was an outstanding guy. He was very aggressive but also a very sweet man. He should have been headed for greatness but he was not handled well by Basel. He began to lose ground. He was given a new boss who changed things around without knowing the field as well as Willy. Willy was an extraordinary man whom it was an honour to work with. Moise da Prada was the head of chemistry and Alfred Pletscher was also there but he became more academic. Pletscher had been to NIH and worked with Brodie on the reserpine research.

Did you guys do any of the work looking at the behavioral activation caused by the combination of iproniazid and reserpine which Pletscher and Brodie were involved with.
No, but I can tell you something about reserpine - this guy who brought reserpine over came to us at SK&F before he went to Ciba. He had a gunny-sack and said he had some roots. We were highly involved with chlorpromazine at the time, it was early in the 50s. I got a call "Len, there's some guy coming tomorrow with some roots

gathered from the foothills of the Himalayas or something like that, would you talk to him?". I said "do I have to?". Anyway this man came with his gunny sack and said "these are the roots". I said "what does it do?" and he said "its good for colic, its good for hypertension, its good for people with mental disease, its good to drop body temperature, its great for sleep" and I said "ah-ha, ah-ha!". One of the executives said "Len buy him a lunch and get him the hell out of here". So I bought him a lunch and he later went to Ciba and lo and behold it was reserpine. After that any guy who said he had roots was immediately offered $50,000 for the privilege of testing it. They put him up in a hotel and bought dinner not just lunch. I remember that because the claims sounded absurd. It was inconceivable that a compound could do all of those things but it did everything he said it would do. If you think about chlorpromazine though, if somebody had said to you it will drop blood pressure, it will drop body temperature, it will help schizophrenia, its good for nausea and vomiting, it enhances the effects of other drugs - you'd have said "Right!" and raised an eyebrow.

Roche in the 60s and 70s ended up being almost only into anxiolytics, why was that?

I went to Roche in 1969 and John Burns called me down to his office, where I asked him what plans he had in mind. He said "you know Len, we've been working with the benzodiazepines for a while and we're getting flak because of the drug dependency issue, so even though we're doing a billion a year, there's so much negative publicity that I'd like you to start a non-benzodiazepine program. Find a Valium that's not a benzodiazepine".

So we started a program in the non-benzodiazepine area but Hoffman-la-Roche was a strange organisation. Basel Switzerland never stopped trying to control Nutley. John Burns was a power in himself so they couldn't do it fully. But they had the most critical control of all, the head of chemistry was a Swiss, who even though he reported to John Burns kept primary contact with Switzerland. I could never get him or the medicinal chemistry people in Roche to make compounds that were not benzodiazepines. They kept flooding my department with benzodiazepines. Burns was getting frustrated and so was I.

You see medicinal chemists are a strange lot. One issue with them is that when they have an active chemical series they will never leave it. They get patents out of it every week and they aren't going to leave it because to find an active series may take a lifetime. They hate to let go. So I had to deal with them while their leader in chemistry was saying don't you listen to this guy Cook, I want more patents out of this series. Chemists you see were evaluated for their annual bonus in terms of their number of patents - so are they crazy? Are they going to leave this series, all the compounds of which are active? That led to a serious problem for the company. The medicinal chemists at many pharmaceutical companies control the research direction. They make the compounds, all I can do is test them. Even though I can identify active compounds, I'm not going to discover anything that they haven't made. So that was a very serious problem at Roche. I don't remember a week going by without some emergency clinical reaction reported to the company with the benzodiazepines and yet, even John Burns, as powerfull as he was, couldn't get the chemists to leave the benzos because of the Swiss control network.

Why did you move from Roche to Du Pont
When I first got to Roche it was a lot of fun but then after about 14 years they also called in the Harvard Business School types who said you can't have 20 projects going at the same time. You have to focus. Basel decided to move CNS research to Switzerland and I began to lose projects to the Swiss labs. Although Basel owned Nutley we had a very strong protector in John Burns. When he retired the Swiss moved in and that was when Roche started doing strategic planning and I increasingly saw what I felt were really good projects being pushed aside. Then a friend of mine, Bob Taber, moved from Schering to Du Pont as research director and he offered me a job taking over CNS research. They could afford me, it looked like fun and it was nearer to my family who were in the Philadelphia area. So I had 18 years at SmithKline, 15 at Roche and 12 at Du Pont.

Behavioral pharmacology of the type you have done has contributed a huge amount to the drug abuse field. Where has that got to?
At present, one of the things I do is to act as a scientific adviser for NIDA on drug abuse. They are looking for medications to intervene in cocaine and heroin abuse. There are two main directions at the moment. One is focussing on cocaine which is a big issue at present. One option here is to look for agonists, just like methadone for morphine, which will be synthetic, cheaper, produce less side effects and will hopefully get the person out of crime and give them more stability. There is also the antagonist approach like naloxone for morphine. But all of this presumes that the addict wants to get off. With some addicts you have some degree of coercion but unless the person is highly motivated to get off the drug staying off is tough and so the focus is now turning to the issue of craving, in the hope that drug induced craving can be reduced without decreasing craving for food or other life-sustaining cravings. You need to prevent relapse. You can get someone motivated to stop taking drugs but preventing relapse is the big one. Now relapse occurs in response to stimuli like a glass or syringe causing all kind of secondary things going on internally. Its almost like ..

Hypnosis almost or autopilot..
Yes the stimulus precipitates everything, the stimulus causes all the internal longings, cravings etc. If you could get a drug that would block this process and block whatever autonomic effects have been conditioned, that would be great. Behavioral research can best address these issues, so one of the things that have been recommended to NIDA is to focus their research in this area. I think its feasible to do but getting a good strong program going using different animal models isn't easy. Right now the problems are getting support to follow all the various approaches because many people still think of drug and alcohol abuse are a loss of will-power, a socially weak personality, when in fact its a disease, at times an uncontrollable disease.

The recent work on naltrexone and alcohol I think is very impressive and that seems to work on a process related to craving. I was at Du Pont, who sell naltrexone, when the first reports on this came through from Valpocelli and Chuck O'Brien of U of Penn and I can remember initially thinking this doesn't make sense. I was asked by the company if it made sense to me and I said that given what I knew, then, it didn't because naltrexone has nothing to do with what alcohol works on but the more I read about the work the more sense their ideas about the mechanism of action

made. One of the pieces of research that I came across was that alcoholics have a very low baseline level of beta-endorphins and when they drink alcohol they increase this. In alcoholics there is an even greater increase than occurs in normals so there is a greater contrast effect and this is what they may be getting their kick out of. There's a big literature on this and one of the things that has been shown is that the children of alcoholics who are not drinkers also have low beta-endorphin levels. When you look at the U of Penn data and the Yale data from O'Malley the results are almost identical - what you find is that people don't totally stop drinking and nobody went cold-turkey but the amount they drink and the frequency of their drinking is down by about 50%. Coming back to the point about the internal stimuli when they asked them about their drinking they said that they didn't get the buzz from drinking that they used to get.

I think there's a lot of pharmacology that can be done in this whole area of heroin, cocaine, alcohol and smoking. I used to be a heavy smoker years ago - when I would get a cocktail in my hand I had to have a cigarette in the other one. You develop these behavioral patterns. Everytime a knock would come to the door of the office I'd light a cigarette, everytime the phone would ring I'd light a cigarette, afterdinner etc. I realised that I probably enjoyed no more than 3 or 4 cigarettes a day and the rest were strictly conditioning - I wouldn't even remember lighting up. I wish now I had the opportunity and resources to look at some of these things. I don't think that molecular biology as valuable as it is is really going to answer these things.

Who've been the other behavioral pharmacologists who count?
Peter Dews, Roger Kelleher, Joe Brady, Bill Morse, Larry Stein, Jerry Sepinwall, Arnie Davidson, Ed Boff and Charles Shuster. Skinner's significant contribution was that he laid the basis of the field. I used to hire experimental psychologists and teach them pharmacology and I'm probably one of the few pharmacologists who learned the behavior. Joe Brady did a lot of important work with his executive monkeys, which was relevant to this whole area of the autonomic nervous system coming into play.

Behavior and drug-behavior interactions reached its peak in the 50s and 60s and maybe the 70s. Now you don't see that type of elegant drug-behaviour interaction studies. People have gone back to very simple, mundane behaviors. The work we did in the 50s, 60s and 70s offered the opportunity to study how drugs fine-tune or modulate behavior particularly in the area of anxiety. There's still a lot to be done but with the swing of the field to molecular biology, which is also needed, there's not nearly enough in-vivo behavioral pharmacology being done.

Who were the clinicians you think counted. You mentioned Paul Hoch earlier
He was a giant. He understood immediately, it seemed to me, what I was talking about when I first discussed chlorpromazine with him. He understood what a drug like that might be able to do and he accepted that this was an effective approach in psychiatry. He knew exactly what dependent variables to look at in terms of a patient population, what the most relevant criteria in drug evaluation clinically might be. There were others Heinz Lehmann, Fritz Freyhan, who was a friend of Heinz, Nate Kline who came in a little later, Joel Elkes, Jonathan Cole and Seymour Kety who was also a member of our scientific advisory board at SK&F.

Why don't we seem to make the same breakthroughs anymore?
I remember giving a talk here in the Caribe Hilton over twenty years ago and I told the audience, which was composed then mostly of psychiatrists, that the problem in the field and the greatest barrier to the development of drugs that will have applicability in mental disease is a lack of description of the patient population and symptomatology in terms that can be used in animal research. If we were in the cardiovascular area, I would go to a clinician and ask him "what is it you want a drug to do?" and he would say I want you to hit pulse pressure or reduce blood pressure etc. They would specify things they want the drug to do that I could take back to the lab and try to find. But if I tell psychiatrists, that I have a magic wand and I can produce a drug that will do anything that they tell me they want it to do provided they don't just say make the patient well. They must tell me specifically what they want the drug to do in order to make the patient well. They couldn't do it.

I said that at the end of 1960s and then a few years ago I gave a talk again to ACNP and told the audience about the earlier talk and asked them - have you guys settled it yet? Everybody laughed. But you see psychiatry is still a mostly descriptive science of symptomatology and the greatest barrier in psychopharmacology today is the lack of specification in terms that can be applied in the lab. It could be in terms of biochemistry or in terms of the EEG, whatever you want, but not in terms of simply getting the patient well.

In the 1950s, most of all the great discoveries were made by chance in the clinic but not because of any prior specification of what kind of drug was needed. We then used these drugs as standards to develop our test procedures to find similar but better and cleaner drugs. Now in the area of Alzheimer's for example if a clinician were to say I've found a truly effective drug, I'd say Thank God, we can now go ahead and develop animal models that are sensitive to the effects of this drug. But for now we have to develop tests that have face validity. Molecular biology has a long way to go in this field because many of its approaches are presumptive in terms of their relevance.

I personally believe we should have more pure clinical research. I have proposed to Du Pont and NIDA that we should be doing far more conceptual clinical testing. For example, take a sigma receptor blocker or other compounds which have any possibility of working for any rational reason, once they have been shown to be safe we should put them in the clinic for conceptual clinical testing using good experimentally minded clinicians to see just what they do. Then we could go back to basic research and work it up further and develop meaning and better preclinical studies.

Forget the impact on the illness, look for the impact on behavior.
Yes but its not happening. If a medical school would accept me today, I would try to get a program like that going, a program to carefully study behavioral and emotional changes produced by many different compounds with various kinds of mechanisms. There are so many things that are not being examined that would only take a short-term investment to realise. But today everything is molecular biology. This is the future but it should not happen at a cost to more conventional pharmacology.