

## THE EVOLUTION OF BEHAVIORAL PHARMACOLOGY JOE BRADY

**In 1956, when the Psychopharmacology Service Center organised the first Conference for the Evaluation of Psychotropic Drugs you were there as the lead person representing the potential input from or stake of behavioral pharmacology in this new world. How did you get into that position?**

I was working with Murray Sidman in the laboratories at Walter Reed at the time, when the first of the tranquillisers appeared which as I recall it was reserpine. Around 1950/1951 I had looked at an animal model for affective performances, emotional responses - the conditioned emotional response, in which reserpine had some effects. In these animals were taught to perform a lever pressing response for food or water. They were put on a schedule so that they got paid off intermittently for a performance. In the middle of the performance you would turn on an auditory stimulus, in those days we used a clicking noise, and this would continue for three minutes. Contiguous with the end of the clicking noise, the animal received a footshock through the grid floor. Initially the clicker has no effect upon the performance, the animal goes right on pressing the lever but depending upon the intensity of the shock, after a single trial many animals, the second time they heard that clicker, after they'd been shocked on its termination showed complete suppression. That's an unusual case, in most cases you see an early approximate response but as you continue to run trials with the pairing of clicker and shock you get complete suppression.

Now how did I come to this. Before I came back to the University of Chicago, I had been in Germany for three years, in the early part of which I was one of the people who made the world safe for democracy. I had been in the infantry and I stayed in the army of occupation for a year or two more but under rather strange conditions. There was a practice at the time to send people back home in relationship to the amount of time they had been there. You got points for each month. I had been a late arriver and therefore had relatively few points for repatriation. But I was picked up at the headquarters in Frankfurt at the time and sent to the 317th station hospital as the chief clinical psychologist of the European command. Now only the military can rationalise a move of that sort. They went through my record and found that I had taken a course in psychology once as an undergraduate and said oh well, obviously this is the chief clinical psychologist of the European command. I spent two years there with 4 psychiatrists, who knew about as much about psychiatry as I knew about psychology. Three of them had a medical degree and an internship and they had spent 3 months at Fort Sam Houston where they learnt all about hebephrenic and paranoid schizophrenia. The chief of psychiatry at that time on the other hand was a major who had had a one year residency. I remember him well. He was well known for telling his patients when they would tell him what their problems were that that was a sin and they should stop doing it.

I remember checking into this assignment with my infantry badge on. The military used to assign speciality numbers to you - I was a 2285. I checked in with the chief of the hospital, Colonel Boyle, who looked at my record and said "oh you're a 2285, I've always wanted one of those - what do you do?" He had

no idea. As an indication to the extent of the confusion, within 3 weeks I found myself on a roster one weekend for medical officer of the day. So I spent a weekend on call. I had one phone-call from a woman, a dependent, who was in pain because she had a tooth removed and she wanted to know if she should take an aspirin. I told her to take two and call somebody else in the morning.

The important thing about this was that when I went to see the chief of service he said "My God am I glad you're here, I've got a major general up on the 2nd floor who's just been brought in, I've got to get a Rorschach on him right away". Now I had this image of somebody holding up card 5 in an undergraduate course with a butterfly on it and telling me that that was the Rorschach - that was the extent of my knowledge. But when you have just come from the infantry and you're a first lieutenant and a major tells you something, there's only one answer - Yes Sir! So I rushed in the hospital library and as luck would have it I found a book by a man named Klopfer on the Rorschach and I read that book that night as though it was an army field manual. I memorised it and came back the next day and gave the first of approximately 500 Rorschachs over the next two years - I became the greatest living expert on the Rorschach in Wiesbaden, Germany.

This group of psychiatrists that I worked with and I, as I say, were out there all by ourselves, so we would give ourselves courses. We'd read something and then we'd meet on Tuesday and Thursday nights - the blind leading the blind. The relevance of this is that this was a German hospital, remember this was the mid-40s, where the availability of treatments was extremely limited. There was a big room full of tubs for hydrotherapy. You could put somebody in these tubs and run warm water over them which was not bad. We used to do this ourselves - it felt pretty good. We also had electroconvulsive shock. And when you were admitted to this service, along with your bathrobe and slippers came your electrodes because this was a very popular procedure.

I was impressed with one very effective procedure. In those days there were a large number of people diagnosed with what was called reactive depression, which was one of those disorders which was largely environmentally determined, I gather, as opposed to endogenous depression. If you let them sit quietly for 2-3 weeks, it goes away but if you plug them into the light circuit and give them electric shock it goes away in 2-3 days. Its very dramatic. There were lots of proposed theories as to why this occurs. I ultimately did a dissertation using electroconvulsive shock and in the process of writing the dissertation, of course, I was required to cover the literature and I found a paper in The Military Surgeon and the title was Seventy-Five Theories on Electro-convulsive Shock & Why it was Effective. The one I found most engagin theorized that "shock becomes the Mother"!

**That was in the late 40s, so it had only been introduced a few years before but even then they had 75 theories.**

Exactly. I only remember one which was shock becomes the "Mother" theory and indeed it was a mother in the current sense of that word. I think a perfectly plausible hypothesis is the reason that it worked so fast in these reactive

depression cases is that you can easily come to conclusion that if you don't get out of there these guys are going to electrocute you! Levity aside there is clearly an effective physiological process involved here.

I remained in the military but they sent me back to Chicago. What happened was that at the end of the war the surgeon general in Washington hired a consultant from the Meninger Clinic in Kansas, who was sent around to evaluate the facilities that the military was supporting. He came to Wiesbaden, Germany to the neuropsychiatric center of the European command and he couldn't believe what he found there. He told the surgeon general that he either had to get these people trained or get out of the business. So in typical military fashion, they picked this up and sent us back to school. They sent me back to graduate school in Chicago. One of the psychiatrists went back to there with me to do a residency at the medical school.

There were big things happening in Chicago at that time. They had just gotten a new departmental chairman, James G. Miller, who was an MD/PhD from Harvard University and he came in with fresh ideas on how to train graduate students in psychology and the behavioral sciences. One of the brightest of his ideas was that there would be a complete review of the field within your first 9 months. You came in in September and in May of the following year you took comprehensive exams over the whole field and those were the qualifying exams to get you into advanced training. This was quite a chore. For everyone of the faculty you would do something. Miller did medical psychology for which the textbook was Cecil's Textbook of Medicine - this was a large volume. Even in the early 50s it was a substantial body of knowledge. I still have that book in my library. I read Cecil's Textbook of Medicine in 2 weeks and memorised it. Subsequently I discovered that if I got myself a Merck Manual along with Cecil's Textbook I could practice medicine. I can't actually lay on hands but not many of these guys here can fool me.

In any event, there was another condition - in order to take the qualifying exam you had to have selected an experiment from the literature and replicated it. That sounds like a reasonable requirement but have you ever tried to replicate an experiment that's in the psychological literature, believe me its a formidable task. They're unreplicable. The experiment I selected was one by Estes and Skinner on conditioned anxiety which was published in 1942. This was the procedure I described earlier. The publication was in the Journal of Experimental Psychology and it was represented in cumulative records. The interesting thing about it is that in order to see what I have just described to you, the animals in the Estes Skinner experiment were trained on a fixed interval schedule rather than a variable interval schedule and in this case in order to see the "perturbation" that occurred as a result of this condition super-imposing a "Pavlovian" procedure on an operant baseline, you had to hold the reprint up and sight along the curve which tells you it wasn't a big change.

As I got to know Fred Skinner better, this was one of the eras in his life when he fell under the influence of someone by the name of Heron in the University of Minnesota. Heron was a big mechanical apparatus person and Heron and Skinner devised a device where a group of animals would run concurrently on a

lever-pressing procedure and all the responses would feed into a single stepping switch which drew a cumulative record for the group. When you do group statistics you get a group average which is not typical of any animal. He obviously became disenchanted with that but its an interesting note on his evolution into a single organism approach to biology. In this experiment what he published was average data which over the years no-one in the world would ever accuse him of.

That was the experiment I decided I could replicate. I was working with Howard Hunt and we had just built two rat boxes and we were learning how to get animals to press the levers - it was wonderful. I took these two boxes and I had four animals, I remember very well, and I trained them to press levers only we used a variable rather than a fixed interval which was close enough and then we super-imposed the clicker and the shock and got complete suppression. Actually to start with I got nothing and then I discovered you had to crank the shock level up a bit. Then the first thing you know everyone of those animals when they heard the clicker they didn't just slow down a little, they stopped cold, they defecated, they had piloerection - I had produced real anxiety in these animals. The name of the game was the shock level. Increase the shock level and you didn't have to worry about these "perturbations", you got complete suppression of behavior.

Anyway that satisfied the requirements for my exam which I passed in May. Now I had these 4 animals available who were completely trained and I had a summer when I was relatively free. I was in clinical psychology and I was enrolled the following Fall with Carl Rogers. I became a non-directive therapist and I spent a year learning how to out-non-direct people. But anyway during the summer I remembered my old days at Wiesbaden and I said to myself I wonder what would happen if we plugged these animals into the light circuit and gave them electro-convulsive shock.

There was a literature on ECS in small animals. I found a paper by someone who had developed an electroconvulsive shock machine for rats. This was late 40s. You used alligator clips wrapped in gauze soaked in saline on their ears and it was hooked up to a timer and a shocking device which delivered 50 mAmps of current for 2/10ths of a second. That was all it took. That produces a full-blown tonic-clonic convulsion in the laboratory rat and within 60 seconds the animal stands up, shakes its head and walks away and I would defy you or anyone else to tell the difference between an animal who has just had one of these convulsions and a normal or a control animal - which I also did. Two of the four animals were controls and I did everything with them including putting on the clips except that I didn't pass the current - I even threw the switch on the box except that there was no current.

I remember going through this. I took a week or two taking baselines to make sure we had good suppression. By that time we had other graduate students using the apparatus and since I was finished with my experiment the only time I had on the apparatus was from midnight to 2 am. I ran these 4 animals at midnight every night and I gave them ECS. The reason for selecting the values I used was completely fortuitous - there was no literature. But three times a

day for seven days I gave them a convulsion. I remember it was 2 am one morning when I ran the 4 animals in the box post-treatment and an experience like that is an experience that says you will never do anything else in your life. It was an incredible reinforcer. The two rats that had the control procedure continued to show complete suppression, piloerection and defecation but the two animals who had had the treatment, when the clicker came on they worked right through it without any piloerection or defecation. I had completely cured them.

### **You hadn't just caused them amnesia?**

It is amnesia but its a very selective amnesia. They went right back in there and went to work but when the clicker came on they paid no attention to it. Plus we did all sorts of other controls. We hadn't knocked out their hearing for instance. Anyway that was sufficient for my dissertation. Here I was 3 months after I finished my qualifying exam I had my dissertation done and I was ready to leave. But while I was working by day in the counselling center, I continued running experiments at night. One of the ones I did was a parametric study on the number of electric shocks. What would happen if you did this once a day for 7 days as opposed to 15 times a day for 7 days, what do you think turns out to be the optimal number?

### **The one you picked**

Three times a day for 7 days. You don't get it if you do one shock a day for 7 days and you don't get it if you do all 21 shocks in 1 days. There is this temporal distribution which is rather critical. At any rate that was the history that I came to Walter Reed with.

### **Can you tell me something about Howard Hunt?**

He and I were about the same age. He was in the Navy but he had gotten his degree before he went into the military whereas I had not. He and I arrived at the University of Chicago at the same time but he came as an assistant professor. He had gotten his degree at the University of Minnesota, where he trained with Stark Hathaway. Howard was big on the Minnesota Multiphasic Personality Inventory and he was trained in clinical psychology but he aspired to be an experimentalist and that was how we got into building the rat boxes together. I guess one of the important influences on his career was that he was a classmate of and shared an office with Bill Estes. Estes had been Skinner's first PhD in Minnesota.

### **Why did so much of this come out of Minnesota? The movie Fargo wouldn't suggest to you that a lot would come out of Minnesota.**

I think in large part Skinner is the responsible agent for the basic experimental part of that. Although it is a remarkable place. When I came to Washington at Walter Reed, I took an appointment at the University of Maryland and I started the first "psychopharmacology" lab there. My first post-doc there was Travis Thompson, who got his PhD at Minnesota with Gordon Heistad who was one of my contemporaries at Chicago and was also trained by Howard Hunt before going back to Minnesota. Travis Thompson's program after he returned to Minnesota of course became the focus of psychopharmacology training in the United States. Most of my lab at Hopkins is now staffed by Travis' students

from Minnesota. They come extremely well trained - George Bigelow, Roland Griffiths, Maxine Stitzer. I don't have any account of why this should be..

**Nothing to do with any German influence..**

No but they have a reputation for being highly inbred, they keep rehiring their best people, plus Paul Meehl and Ken McCorkadale are intellectual giants and they have only about one decent day of summer a year as far as I can make out. Whatever it is it is interesting. I attribute much of it to B F Skinner. His influence on Howard was second-hand but still potent.

When I was still a graduate student I remember I gave my first paper at the American Psychological Association meeting at Penn State. This was the late 40s/ early 50s when only about 250 people would come to an APA meeting. They met at universities at the end of the summer so they could use the student rooms. I was due to give this paper and I had taken a movie with 8 mm movie camera showing the conditioned emotional rats defecating, and freezing as well as their cure with electroconvulsive shock. The papers began at 8.00 am, so I came early to set up the movie camera. Leonard Carmichael was the session Chair and when he called the session to order for the first paper which was by a man named Bugelski, at Buffalo, there were 3 people in the room, Leonard Carmichael, Bugelski and me - and I was only there to set up my camera but I obviously was obligated to stay. And I heard a historic paper that everybody has completely forgotten by now. Bugelski discovered Sidman avoidance but nobody knows it. The moral of the story is try to avoid giving your paper at 8 in the morning.

Bugelski reported a study in the late 40s of a rat jumping back and forth over a barrier without an exteroceptive stimulus because he timed the shock. The animal had ten seconds to jump over to one side without being shocked and if he wasn't out of there in ten seconds he got a shock. This is Sidman avoidance, where the shocks are based every 20 seconds except a lever response resets the timer. This didn't appear in the literature until the early 50s. I've often told Murray about this but he had never heard of Bugelski's experiment because it was never published. But I swear that was the report he gave at this meeting and look how famous Sidman avoidance has become since then. Bugelski missed the boat. As I've said to my students repeatedly, if you don't write it up and publish you didn't do it. I heard it and pretty soon I'll be gone and nobody will remember Bugelski's experiment at all. He was chairman of the Department of Psychology at Buffalo and he wrote a textbook on psychology but to the best of my knowledge he never published this experiment whereas Murray of course published his paper in Science and it has become a classic.

At any event when my paper came on at 10 am, guess who was sitting in the front row - B Fred Skinner. Howard who knew him arranged for us to have lunch and I had lunch with Skinner, Howard Hunt and Skinner's wife Eva. That was the greatest moment of my life. This turned out to be true of Fred Skinner right to the end of his life. When he came to a meeting he was parked up front listening to papers, he wasn't out politicking. Fred and I developed a rather close relationship over the next 30 years. He and I were on the President's

Science Advisory Commission during the Kennedy administration. We were convinced we could save the world but nobody cared as usual.

**What about Bill Estes, did you know him then?**

No, not at that time. I knew him by his publications. I subsequently got to know him but not well - nobody knew Bill Estes well. He was a very quiet retiring individual. Howard on the other hand was a very articulate person, who expressed himself well and continuously. One root then of the behavioral pharmacology tree came from this group in Chicago and Minnesota.

I did another experiment there which had something of the beginnings of psychopharmacology in it. One of the controls we were interested in for the electroconvulsive shock study was the extent to which the electricity was the critical variable and the extent to which the convulsion was the critical variable. My somewhat less than successful entree into behavioral pharmacology came with an attempt to produce convulsions chemically which of course can be done if you know what you're doing but I had no idea what I was doing. I did read a lot and I discovered that both strychnine and metrazol would produce convulsions. Strychnine is a spinal cord convulsant whereas metrazol gives a more general CNS convulsion. I trained up all the animals but the problem was the lethal dose and the convulsant dose of both strychnine and metrazol are very close - I killed an awful lot of animals. I finally ended up doing the experiment with audiogenic seizures.

This was in the transition between Chicago and Walter Reed and we did a few collaborative things. We tried nitrous oxide and a few other things, which began the behavioral pharmacology emphasis at Chicago. Subsequently Howard developed a relationship with the pharmacology department. Len Seiden is still there in both the psychology and pharmacology departments. Over the years Bob Shuster and Lynda Dykstra, among others, staffed the laboratories there so the behavioral pharmacology tradition persisted at Chicago after these early experiments.

Given a normal distribution of laboratory rats, 50-60% of them are subject to audiogenic seizures. What I did was to get a garbage can and a set of keys and I put the rats in the can and shook the keys around the outside. They start with a running fit and then they have a full-blown tonic-clonic convulsion. This was very nice because it gave you a control group as well at the same time. It was very clear that the convulsion was the critical element. The animals who had the convulsion showed an attenuation of the conditioned suppression and the animals who had the keys jingled over them but had no convulsion showed no attenuation of the conditioned suppression. This was the setting into which the reserpine experiment came. When you have a hammer everything looks like a nail!

**The trick is then to find a few nail-like things. Where did reserpine actually come from. Did you approach Ciba or did they approach you?**

It had nothing to do with Ciba. It came from the clinical side of the house. There were all these reports about reserpine as an effective tranquilliser. This was in 1953 and 1954. So I decided let's see if it works in the laboratory and

that's when I did the experiment with reserpine and saline controls. I have no good rationale for saying why I did this experiment the way I did it except that when we gave reserpine its acute effect was a heavy-duty suppression of all behavior. You can't argue about differential effects if you wipe all behavior - its like curing mental disease with decapitation; it works like a charm. That was initially the way I looked at reserpine - you can hardly say that this is a cure if I'm knocking you cold.

That was when I decided that maybe the thing to do was to give the drug after the run each day and to do it the way I did the electroconvulsive shock study. This way they had a 23 hour period during which they "recovered" from the acute effects of the drug. I did this for 7 days for no good reason except that it seemed like a good idea. Sure enough gradually what happened was that although reserpine suppressed the overall rate of lever pressing, it clearly elevated the rate in the presence of the clicker and reduced the defecation and so on. On the other hand, with amphetamine, which was one of our controls, the overall baseline rate was elevated but in the presence of the clicker whatever residual behavior was there beforehand there was no behavior at all now - one could argue that there was an increase in their anxiety response if you will.

Murray Sidman and I were so enthralled with that clear effect, which we replicated several times, that we decided to give every animal in the lab reserpine, including for instance a bunch of animals Murray had on Sidman avoidance. This turned out not to be a smart move. We learned subsequently that reserpine does dramatic things to serotonin and we never recovered the baseline in many of those animals. Reserpine has certain shortcomings that we are now well aware of but in those days if you had something with such dramatic effects, there was the temptation to "see what it does.." What it did was to ruin the lab for all practical purposes. Having a good baseline and being able to recover it was critical to all the research we were doing at the time - A-B-A designs.

### **Did it have any effect on Sidman avoidance?**

Well we didn't do it the way we did the CER studies. We only looked at acute effects and we didn't go back and do it because Murray was a little discouraged - he wasn't going to have anymore of his animals ruined. And we moved on to chlorpromazine.

### **What can you tell me about Murray?**

I can tell you that Murray Sidman was the discoverer of Sidman avoidance! Like me he did this as a graduate student. Avoidance procedures were long-standing in our business. They are always done where you get a warning stimulus - a tone or a light - and you say if you don't press this lever you're going to get a shock or if you press the lever you can avoid the shock. What he showed was that it could be done without the need for the exteroceptive stimulus by just shocking the animal every 30 seconds - the animals learned that beautifully even as me and thee would learn it I suspect.



After I'd come to Walter Reed the division of neuropsychiatry was just starting. We had the advantage of being there first. This is a great advantage when you're establishing laboratories and doing things - you don't have to buy anyone else's problems. I had to go out and recruit people and the first thing I did was to call up my friends and relatives at Columbia - Nat Schoenfeld and Fred Kelleher. They lined up some people for me to talk to. I talked to 3 or 4, one of whom was Murray and it was clear I wanted him. This was in 51-52; we offered him the grand sum of \$6,000 a year and he jumped at it. A lot of money - it was a government job at the GS-9 level as I recall.

He came to Walter Reed. We developed our families together in Washington at that time. He wrote a classic text while he was with us - *Tactics of Scientific Research*, which I think of as the 20th century equivalent of Claude Bernard's *Treatise on Experimental Medicine*. When Claude Bernard wrote *Experimental Medicine* nobody paid any heed to it - it was a hundred years ahead of its time. The vital force was still alive and well in physiology. Murray's *Tactics of Scientific Research* in my view is to the behavioral sciences what Bernard's book was to the physiological sciences. I had read Claude Bernard and while Murray was writing his book I asked him if he was aware of Claude Bernard's work but he had never even seen the book. So it wasn't plagiarism which was something I might have done - you may know of Tom Lehrer from Harvard who wrote satirical songs such as *Shooting Pigeons in the Park* but there was also one about a Russian mathematician Lobatchevsky who plagiarised, which had the line "let nobody else's work evade your eyes". You end up plagiarising yourself after a while which is okay - that's when you become original.

While he was writing the book he had an inviolate period from 9.00 to 11.00 in the morning, when he was undisturbable. I remember our boss Dave Rioch came by one morning at 10.00 and Murray's door was closed. He opened the sliding door quietly and said "Murray". Murray didn't answer. This was his boss but he went right on writing and Dave stood there for a while. I was outside handling some rats and I could observe this whole thing. Dave Rioch was a psychiatrist and a very sophisticated man. Eventually he quietly turned around and tiptoed out and walked away. Murray never budged. He knew damn well who it was. That I regarded as a testimony to both of them. But that's Murray Sidman. He is still very much involved in the business, writing very creatively these days on second and third order derived phenomena of stimulus events and he's got a firm handle on the thinking problem.

**What relationship if any does the CER bear to learned helplessness.**

Well Howard and I did another experiment which bears on this. If you make a slight modification of our procedure - when the clicker comes on, instead of the shock occurring contiguously with the turning off of the clicker, the shock is contingent on a lever response, this is what you would characterise as a discriminative punishment procedure. If they make a response in the presence of the clicker they get a shock. Topographically those two performances look identical. On the cumulative record you see a 3-minute period during which the animal is not responding. However, reserpine has no effect on the punishment performance but it did on the conditioned anxiety. Subsequently Irv Geller, who was with me in the lab before he went to Wyeth, took that procedure which he

called a conflict procedure because you have a hungry animal who is constrained from pressing to get food, and he demonstrated that if you titrate the intensity of the shock they will work through that but at a lesser rate. But if you gave librium to that animal you could get an elevation of the rate and this became a screening procedure for minor tranquillisers.

In that sense you can characterise the CER as a form of learned helplessness. What differentiates it is that it does not seem to be generalisable. Its confined to that clicker. Learned helplessness, as I understand Seligman's work, generalises. And the procedures for generating these responses are different. In learned helplessness all behavior is punished. The CER is very discriminative - its clear what you are going to get hit for.

The one thing all these procedures, including conditioned avoidance, have in common is aversive control. What we are talking about here are various ways of attenuating the effects of aversive controls. The complexity of the matter is contributed to by the multiple procedural variables on the behavioral side as well as the multiple chemical variables on the pharmacological side and it is the dedication to sorting out all of that which defines behavioral pharmacology. I think it is a reasonable parcelling out to talk about those events that are under aversive control and those that are under appetitive control. The big rage these days is more away from the aversive side and its on to "cognitive enhancers". We even have people who call themselves cognitive behaviorists which is the oxymoron of the decade.

Anyway the fact that we were in there doing all this drug stuff in the early 50s came to light in a number of ways - one was the publication of the Science paper on reserpine. Science is a medium that is looked at across the pharmacological sciences - at least it was in those days. That experiment was the one that brought the drug houses to the door. I did not solicit them. The other thing was a visit by a neurophysiologist by the name of Irwin Slater who came from Eli Lilly where K.K. Chen was the director of research. Irwin Slater came to visit Bob Galambos, an electrophysiologist, in the lab with us at Walter Reed. He turned right when he should have turned left as he came down the hall. Murray and I, at the time, were working in a huge shielded room which made it look as though we must have been doing something like electrophysiology. Actually what we were doing was protecting Galambos who was across the hall. He had complained about our work because in those days we were not solid state - we were using stepping switches and relays and there were sparks flying around the place which were driving him crazy across the hall with his electronic recording equipment. So we ended up shielding him in and shielding us out.

Of course Slater ended up in our middle control room where we had all the relays and recorders and saw all this and asked what it was. I said it was an animal behavior lab and he asked where the hell the animals were - if you're in an animal behavior lab you expect to see animals behaving. They were in four smaller rooms on each side and I explained to him what we were doing, that we had some two-way mirrors, that we had a couple of monkeys and that we had done the reserpine studies but that they weren't quite published yet.

Anyway he asked me whether I'd be willing to come out to Indianapolis and tell them about some of the work we were doing. I thought it was one of those cocktail party type invitations, the next time you're in town why don't you give me a call. But within the week I had a call from K.K. Chen wanting to know whether I would come out to one of their weekly research seminars and give a talk on the things we had been doing on drugs and behavior and these new procedures. I'm talking about the early 50s, when if someone offered me a captive audience I would have crawled out there on my hands and knees but I hoped they were going to pay my way. I was making maybe \$6,500 - \$7,000 a year and I had 5 kids. He said well of course we'll pay your expenses and I breathed a deep sigh of relief and then he got very apologetic and said unfortunately they were coming toward the end of the fiscal year and they could only offer me a \$200 honorarium. Nobody had ever offered me a \$200 honorarium before that. When I picked myself up off the floor, I mumbled that that would be all right, as though I would get one of those everyday. He said of course you can answer questions at the end of your talk or not as you chose.

This was a man who knew what he was doing. They put me up at the Indianapolis Athletic Club. They invited me at the time of the Indianapolis Decoration day. They have this big car race out there and they took me to it. Drug companies knew how to treat you in those days. I gave my talk and answered a few questions. Then he invited me into his office and asked me what I thought it would cost for them to set up a laboratory of the type I had described. I assured him it was prohibitively expensive, probably \$40-50,000. He said "do you have any idea what it costs us to get a drug to the market, in terms of the preclinical work and clinical trials and so on - \$10 million. That was what it cost in the early 50s, so \$40-50,000 was a drop in the bucket. Ten million dollars is still a lot of money but in those days it was an incredible amount.

About a year ago I did a job for Pfizer in which I was invited to chair a workshop on a new compound which they had taken through the preclinical stages and they had to make a decision whether to go into clinical trials with it. They had gathered a large group of clinicians and scientists. The only issue had nothing to do with efficacy which was about the same as the comparator but it had fewer side-effects - a mild attenuation of side-effects was what had recommended it. They had already put \$20 million into the preclinical stages and they were facing a total expenditure of \$200 million if they went ahead. So the decision was do we stop here or do we put the other \$180 million to get this to the market.

The bottom line was that Eli Lilly and every other company in the country in the 1950s and 1960s had literally hundreds of compounds on the shelf without anyway to screen them for these unique "behavioral" effects that had appeared with reserpine and chlorpromazine. Chlorpromazine when it came on the market grossed \$75 million in its first year on the market. That's a drop in the bucket these days but in the 50s that set the stage for every other drug company in the business to pursue their "me too" programs.

**Frank Ayd was saying to me recently that in Maryland alone there were 3 state asylums each with a population of 8-9,000 patients and in 1955, perhaps a bit like you with reserpine and the rats, every single one of those patients just about was getting chlorpromazine - so in those terms this was clearly a substantial market.**

That's exactly right. The issue here was me-too drugs. SKF made \$75 million the first year on the market. Every other drug company had to have one of these compounds. They all had them on the shelf - but how do we know? This is where behavioral pharmacology in the drug houses came from. Of course when the word got out that Eli Lilly had gone this way... The other issue was staffing.

**Len Cook's lab would have been going at this stage.**

Yes but that was pharmacology. I also was invited to give a talk at Merck. Paul Beyer was the head of pharmacology at Merck and he invited me. They also decided they had to get into this.

Apropos the issue of where do you find the people, an interesting comment was made after my talk at Merck. Beyer asked why they couldn't send somebody, one of their pharmacologists, down to our lab to be trained and then have them come back to work in the Merck program. Ciba asked the same question. I said yes they could do that and it would certainly be better than not doing anything at all, but the problem was that while that pharmacologist was on the way back on the train a new development might come about on the behavioral side - in other words they wouldn't be able to keep up with the field. Actually Skinner also suggested this but I disagreed with him - I thought the field would get away from them very quickly - if in fact the critical parameter was the behavioral methodology. They didn't have to worry about the pharmacology but what they needed was someone who was professionally competent on the behavioral side and would keep in touch with that science community. So I ended up sending people to companies. Tom Verhave was the first one, he got the job at Eli Lilly. They weren't pharmacologists at all but they were good behavioral people and I figured they could learn pharmacology or they had enough pharmacological support and enough models to work out what would be appropriate for screening purposes, which is what they were wanted for - to screen drugs.

Many of these people came from Walter Reed because we had a recruiting system at Walter Reed you can't beat - the Korean War and there was the draft. We drafted in all these guys and had a whole lab full of PhDs at Walter Reed. Larry Stein was one of them, John Boren, George Heise, Irv Geller, Dick Herrnstein - guys who had to do military service. We would get calls from all over the country from medical schools about physicians for instance who hadn't even taken internship but had gone straight into research - Dave Whitlock, Ed Perl and folks like that who were MDs but they never had any clinical training. The army didn't bother making those fine distinctions. If you were an MD you were fair game for assignment to a battalion aid station putting on band-aids and giving aspirin. I used to get these calls and we would go out of our way through the surgeon general to get them assigned and we always felt we were doing a great service - not only for the scientific community but for the patients

who might have been at risk under the circumstances. So we got these guys assigned to Walter Reed and later sent them off to academic and industrial jobs.

An interesting background feature was that we had people from Harvard and Columbia, who were the better trained group. They had good academic training but at Walter Reed we were into all sorts of applications and they then went off to the drug-houses. Some never even came through Walter Reed because the demand became so great that I ended up dealing directly with the universities looking for someone who had a degree in this area.

**You mentioned reserpine but what about chlorpromazine which had also appeared at this point?**

Yes we were also moving from rats to monkeys at this stage. We did similar type studies with chlorpromazine in the monkey and we were able to demonstrate its effects on the CER and avoidance behavior in the monkey. The screening techniques we set up at Merck ended up capitalising on Sidman avoidance. I remember them training large numbers of small animals. The interesting thing about Sidman avoidance and the way we came to look at the behavioral effects of drugs, we made it possible for an organism to learn something that they never learned otherwise. If you have an animal on a 30 sec. RS interval in a Sidman avoidance, the rate at which he is pressing that lever to keep the shocks away is faster than one every 30 seconds. He is probably doing it once every 5-10 seconds. There is excess behavior, in other words, to make sure they don't get shocked. Now if you give them a drug like chlorpromazine what we discovered early on was that the rate got suppressed but not necessarily in a manner that produced an increase in shock. They may be pressing slower but still fast enough to avoid all the shocks and when you took the drug away they had "learnt" something and they would continue to press at a more moderate rate and still avoid the shocks.

**That's interesting. Is there a therapeutic application for that?**

Well the use of certain therapeutic drugs is based on the ability of the drug to bring the organism into contact with the contingencies in the environment, which for whatever other extraneous reason they haven't been very good at. Nonetheless the suppression of avoidance turned out to be a very effective way to screen certain tranquillising drugs and that was the standard procedure at Merck. Of course the other thing was that the influence of many behaviorists who went into the industry spread far beyond screening for drugs. Tom Verhave would be a classic case. In some instances this was not to their advantage. Tom developed a technique where he trained pigeons to do quality control over pills. The pill would normally come down a chute and women would stand there and pick out the defective ones. He trained pigeons to discriminate anything that was different and he had this working beautifully but he got into trouble with the unions.

The presence of behavioral pharmacologists in industry peaked and then dwindled off. But there are still people in there. The new breed are guys like Jim Barrett. The University of Maryland lab turned out to be a source of training for behavioral pharmacology and as a result when I left there to go to

Hopkins it was taken over by people like Jim Barrett and we in turn hired Nancy Atour who is a Jim Barrett product. Receptor dynamics had become a big thing. They are now very much concerned about the relationship between a specific receptor site and behavioral expression. These are now much more sophisticated, much more basic behavioral pharmacology than we were looking at when we were just taking hundreds of compounds off the shelf and seeing if they had an effect that might be interesting. Its a more rationale approach now to designing drugs for specific behavioral effects. Jim Barrett is a good example of the new look even though he came from the old school.

### **What was the influence of Peter Dews?**

He and I are exactly the same age. Peter had a history that goes back to Cambridge and the pharmacologic route. While in Cambridge, he was given a jar full of hashish and had to find out if it had any behavioral effects. He saw how limited the relevant procedures they were using were. Obviously these kind of beginnings were important because they alerted him to the fact that there is an important field here that has to do with establishing the effects of these compounds across a range of phenomena, including behavioral ones. When he came to the United States, he took the initiative of going over and hanging out in Skinner's pigeon lab. Its probably that kind of history that led Skinner to recommend to pharmaceutical industry people to send people who he could train and send back. Given someone like Peter Dews that would be obviously the right way to go but they weren't all going to be like Peter who would then take off and become a real devotee of the field. It was through Peter that the whole Harvard group, Charlie Catania, Charlie Ferster, Roger Kelleher, Larry Bird, Bill Moss and people like that, got into behavioral pharmacology. As near as I can tell, the group at Harvard, the pigeon lab had very little interest in pharmacology until Peter got there.

### **Even though Skinner himself had done some work with caffeine and things like that in the 1940s**

That was in the "Behavior of Organisms" that Skinner published 50 or 60 years ago. There was of course very little that Skinner hadn't done but in terms of a more sophisticated interest in the field, Peter was responsible for that. It wasn't the casual let me see what these guys have to offer, he really got himself into it. His appointment at the Harvard Medical School is as a Professor of Psychobiology in the Psychiatry Department. Bill Morris, Roger Kelleher and that whole crowd were clearly out of the Dews tradition. They had less of an immediate influence on the drug house development than the group that came out of Walter Reed and Columbia. There were also second generation influences. Len Cook had an assistant by the name of Bob Shuster, who I took as a graduate student. When Bob left that lab Len replaced him with Roger Kelleher and Charlie Catania, who came from the Harvard lab.

### **What about the drugs of abuse field. This is an area where it seems to me the behavioral pharmacology input has been very sophisticated.**

That's were all the money has been for the past two decades. I think that came out of the Maryland lab from the behavioral side. As often happens, there were two things that happened concurrently without the people who were doing them even knowing about one other. Weeks did a rat experiment at Upjohn in the

early 60s and at the same time Bob Shuster who was a graduate student with me and Travis Thompson who was my first post-doc started looking at whether or not monkeys would do drug self-administration. Their early work in that regard provided more impetus to the behavioral community to get into this area than the Weeks work - Weeks was a pharmacologist.

Bob's dissertation was the beginning of the drug discrimination field. An animal was trained to get food only if a certain substance was injected into a cannula and they learned to discriminate the difference between a drug and saline. In the paper, this was characterized as interoceptive conditioning, which was very big in the Soviet Union. Gregory Razran, who was a professor at City College in New York was fluent in Russian and very well connected in the Soviet Union, convinced Bob and I that we should submit that paper for publication to the Pavlovian Journal of Higher Nervous Activity. We did. Years went by without us hearing a word from them. About three years later we get a reprint in Russian of that paper. I still have it. Its completely unintelligible. Because of their different alphabet we couldn't even recognise our names. We found someone at Walter Reed at the time, a military-intelligence type, to translate it back but it was completely unintelligible. We didn't know whether the problem was in the translation from English to Russian or from Russian to English but the whole thing was a garbled mess.

Bob and Travis, when they had the cannula in and had done their interoceptive conditioning experiment, said what would happen if we gave the monkey a lever and let him inject the drug himself and that's where the primate drug self-administration study was first done. That was published in Science. I think the major conceptual influence the animal drug self-administration observations has had on the field of substance abuse is that it changed the way we looked at these performances from being controlled primarily by antecedent events. The prevailing view was that people are driven to be drunks or substance abusers by the environment, by having a mother-in-law that drives you crazy. Well the monkeys had no mothers-in-law. One of my favorite quotations is by W C Fields "it was a woman who drove me to drink and I never got a chance to thank her". That was how one presumably got to be an alcohol and or drug abuser but animal self-administration calls attention critically to the consequences of drug intake. The relationship between performance and its consequences, I think, is the critical one and that study opened up a whole new way of looking at drug abuse. It was the start of new therapies such as the contingency management field. What Steve Higgins is doing in New Hampshire with cocaine abusers is clearly part of this.

### **You've moved into therapy yourself - you have a mobile drug treatment program in Baltimore.**

I have a mobile drug abuse treatment program which came out of human work I had been doing for some years in controlled environments. We did get into looking at drug effects in a programmed environment and this was an extension into a larger unprogrammed environment.

### **Are any of the behavioral principles paying off in this?**

Well I can give you the classic example of approximation. This mobile drug abuse program clearly had its origins in a problem in the city of Baltimore. We have 50,000 I/V drug abusers in the city. The proportion who are positive for AIDS is larger in the City of Baltimore than in any other city in the United States. We have 5,000 treatment slots. By the same token there hasn't been a new drug abuse treatment program in the city for 25 years. Its the NIMBY problem; everyone wants to go to heaven but nobody wants to die, everybody wants drug abuse treated but not in their backyard even though all the abusers are in their backyard. The logic of this escapes me but its not a logical issue. Never was.

I got this idea about a mobile drug abuse program. It turns out that what the communities object to is fixed site programs because the drug abusers hang around there. So I said suppose we just come in for a few hours, provide the medication, do some counselling and then we're out of there. I talked to the Mayor of Baltimore, who is very progressive, and he said "its a great idea, now here's who you need to talk to". I talked to everyone of the city council members who all said "great idea, now here's who I want you to talk to". I spent a year talking to people and was making very slow progress. Baltimore is a very community oriented city - all sorts of ethnic groups who all have community associations and I had to go and talk to each one and they listened to me and said "its a great idea, why don't you park it over there". They didn't want the bus to stop on their corner.

Then I finally stumbled upon the answer which if I had thought of it a year earlier I'd have been in business a lot faster - the local clergy. In the city of Baltimore, when one of the Church pastors says this is how its going to be - that's how its going to be. I talked to a few clergymen and told them we were having trouble finding sites where we could park the vehicle but that we had a few dollars in the grant that could be put towards something if one or another of the parishioners could help us find us a place to park. The people who turned out to be the most helpful were the clergymen themselves, suggesting that we use the church parking lot but never on Sunday. A dynamite idea. We lined up 3 or 4 churches and started.

Carrying off this demonstration research project involved some logistics and this is where the behavioral principles come in. When you run a medication based drug abuse treatment program, you can't just go out and medicate people. The community is not delighted with this approach, sometimes seeing it as another trick to get folks on a drug that you control like methadone or another opiate. The FDA requires that you do counselling and so forth. So when I got a 5-year demonstration grant from NIDA, I had to get self-propelled medication vans to deliver the medication and trailers in which we did the counselling. The medication vans had to meet all sorts of requirements from the Drug Enforcement Agency. When I went to see the head of the DEA in Baltimore and told him about this great plan, he said - "you're going to do what? you mean like a Good Humor truck" (an ice-cream van). I said "no bells, we're just going to go out there quietly and do our thing and get out". He said that they required that each one of the medication vans have a bullet proof nurses station, with the very thick bullet-proof glass you have in banks, behind which



the medication was dispensed. We had to have an armed guard on board, a safe for the medication and an alarm system that alerted the whole East Coast of the United States, if anyone looked crooked at one of these vehicles.

We only did counselling once a week whereas we had to do the medication everyday so we had to work out a plan whereby the medication van tows the trailer and goes to site A on Monday, for example, where it drops the trailer all day for counselling, while the medication van went on and did the other sites. On Tuesday it drops the trailer at site B etc. Well one day while I was out there getting all this going right, I noticed that on the outside of one of the churches, close to the door was an external AC plug. Now remember when you run a mobile program everything has to be self-sufficient. Each one of these trailers has a generator on it, mobile phones etc. Anyway I asked the pastor of the Church, whether we could use the AC plug because in that way we could stop using the generator on the trailer and then maybe we could help out with the churches electric bills. A few days later, I noticed that just inside the door there was a modular telephone jack, I said these mobile phones are very expensive, if we could use the jack we could help out with the Church's phone bill. The bottom line is that for the past two years we haven't brought the trailers out at all. We've been doing the counselling in the churches and are near to consolidating the entire program in a Church.

We had been doing everything except the medication in the churches because of the requirements for the safe etc. A short while ago one of the pastors asked me why didn't we just leave the drugs there and I said well we need a security man with a gun and an 800 lb safe. He then showed me that in a corner of their church, which was split level on a whole block, they used to have a cheque cashing place, which had big thick cinderblock walls and big thick glass. Its a perfect place to put a medication site, so we're now working on rezoning a church as a drug abuse treatment program.

If you think that's an easy task you should try it sometime. There's a good reason why Baltimore hasn't had a new drug abuse treatment program in 25 years. First you have to have 3 members of the city council introduce a bill, which has to have 3 readings at the city council over a 3 month period. Between the readings you have to come up with approvals from the housing department, the planning commission, the medical department etc. - everybody has to sign off on this. You have to hold 3 public hearings, where anybody from the city of Baltimore can come and say why we don't want this. You have to advertise in 2 separate newspapers for a month at a time and then you have to post signs all over the city giving the address of where you're going to do the rezoning. Is it any wonder we haven't had a new program. No-one in his right mind would go to this trouble but the pastor of the Church said not to worry. He produced 3 council members who were part of his parish and we put the signs up and we got to the housing department etc. The day before I came here, we appeared before the planning commission, who had to ask why we want to do this and what the neighbours think etc. The pastor did the introduction and this was really inspired. He said he came there to talk to them about his substance abuse treatment and rehabilitation *ministry*. By the time he got done, the head of the commission stood up and said that he wanted to compliment him on this

great work. These are people who wouldn't normally let you rezone anything. That's approximation. It proved absolutely invaluable in this case.

However, this has not been fast, it has taken 3 years to move from a little outside AC plug. But this really is the answer to the drug abuse problem in a place like this. We have demonstrated that we can gain entry into a community and we have published data on the 3-4 years we have been running the program. We have compared our program to 6 other fixed site programs in Baltimore. The average length of stay in our program is 18 months. In fixed site methadone treatment programs normally the turnover is absolutely drastic. Within the first 30-60 days you have usually lost 40-60% of your patients. One of the reasons is that these are programs where they have to show up every day to get your medication. Now if you have to take 2 trolley-cars and a bus, which most of the people in this kind of a program have to because they can't afford automobiles or taxi-cabs, this gets onerous very quickly. The behavior gets weak and there's a man on the corner who will supply you a lot faster - that's where the mobile treatment program comes in. The rationale was a response-cost rationale. I thought that's the reason why you have such a large drop-out but if we bring the mountain to Mohammed, retention should be better. The single most important factor to success of treatment is retention. Now we have demonstrated that we can keep them in treatment and my plan is that we can now use this method to get a community that was completely against this approach to accept it and to be more effective in the treatment. This may not be the final step of behavioral pharmacology in the drug abuse business but I never expected to be participating in a ministry, when I undertook this initiative.

### **Apotheosis is hard to beat**

Its going to be about as far as I'm going to go. Its been an all-consuming business. The grant money ran out and we're hoping to run it as a private program. NIDA gave us 5 years of money to do this which was very generous but the whole point behind a demonstration program is to show that it works and then it should be taken over by the city or the state or somebody. The trouble is that drug abuse treatment is off the screen. Its not high on anybody's agenda. The state and the city are completely out of money and they're cutting down on the programs, so we have had no support from any of these people. I decided that we should see if we can't go on our own as a private program.

You might have serious questions as to whether the population I had been treating would have the money to pay. My view was that the new lick in this age is that those who profit most from a service should pay for it - sounds like a Republican I'm sure but its very popular in this country right now. So we told the clients we're out of planning here - we can't keep treating if we can't start charging and the charge is \$75 a week. I heard the counsellor with some of the first patients who were exclaiming "\$75 a week"! and she asked "well how much do you pay the 'man'". They pay the 'man' \$30-40 a day and to get that they have to steal or commit other acts of violence. So she was able to sell a deal for \$75 a week and they've been coming up with it. It reminds me of another Tom Lehrer song when he alluded to the fact that one of his relatives was selling what they used to give away! We've got 125 patients now paying for their own treatment and I have to tell you that they are different from the

group we used to treat for free. They get better a lot faster, they get their urines clean a lot more easily. When they ask to get off, we detox them. And it turns out there's a population out there willing to pay.

The behavioral pharmacology of substance abuse has really capitalised on the behavioral developments in a dramatic way - from drug discrimination and drug self-administration work and animal psychophysics. As regards psychophysics, my first assistant at Walter Reed in the early 1950s was a young man by the name of Bill Stebbins, who ultimately wrote the book on animal psychophysics. I now have one of his students running the shop for me at Hopkins. It's an extremely effective way to do behavioral toxicity - to look at not only the extent that a drug has reinforcing functions, or the extent to which it has discriminative functions but the price the organism is willing to pay and we ultimately pay for the toxic effects.

**Behavioral toxicity was something you talked about a lot in the 1956 meeting but it still hasn't taken off. It hasn't become an FDA requirement.**

Well drug self-administration is required by the FDA but in my view this is something that is not restricted to drugs of abuse. We've been running psychiatric drugs like the benzodiazepines for instance and there are clear effects on auditory and visual thresholds at therapeutic doses so there are people driving around in cars whose eyeballs and ears aren't working at full capacity. But you're right, it hasn't caught on as a critical part of the assessment. We continue to do it and I argue that it is critical because simply determining if a substance is discriminable and whether it is reinforcing is not a sufficient condition for making it abusable - if that was the case popcorn and Hershey bars would be schedule 1. Abuse liability is determined in large part by toxicity. Scott Lucas and I published a little book on screening drugs and I made the point in there that there are some drugs that are not very reinforcing but their toxicity is so great that they are regarded as highly abusable drugs. It's the behavioral consequences that make LSD what it is and this is so as well with the amphetamines and the opiates.

**Can you remember how you were asked to participate in the 1956 meeting - did the invite come from Jonathan Cole or Ralph Gerard or Seymour Kety? What can you remember of the flavour of the meeting or the process of putting it together?**

I think it was Seymour Kety, with whom we had most contact at Walter Reed, who invited my input, the flavour of which, as I recall, was very upbeat in considering the prospects for new pharmacological approaches to psychiatric and behavioral problems.

**You hinted that there has been a dwindling of behavioral pharmacology input to industry - is this because companies have gone down a molecular biology route and have lost interest in in-vivo pharmacology or is it that the "cognitive" revolution stemming from learned helplessness for instance has in part distracted the field and diverted attention to areas that are just not pharmacologically friendly ?**

I think behavioral pharmacology has had and continues to have relations with industry that are somewhat cyclical. The initial enthusiastic embrace of

behavioral pharmacology by industry lost some of its passion when new discoveries did not come fast enough or often enough to affect the “bottom line”. But I think that behavioral pharmacology may be coming into its own again in industry via the neuroscience route, drug discrimination, receptor dynamics, “designer drugs” and the like.

### **References**

Hunt HF, Brady JV (1951). Some effects of electroconvulsive shock on a conditioned emotional response (“anxiety”). *Journal of Comparative Physiological Psychology* 44, 88-98.

Brady JV, Hunt HF (1955). An experimental approach to the analysis of emotional behavior. *Journal of Psychology* 40, 313-324.

Brady JV (1956). Assessment of drug effects on emotional behavior. *Science* 123, 1033-1034.

Brady JV (1956). A comparative approach to the evaluation of drug effects upon affective behavior. *Annals of the New York Academy of Science* 64, 632-643.

Brady JV in Cole JO, Gerard RW (1959). Psychopharmacology. Problems in Evaluation. Nat Acad of Sciences, public no. 583, Washington DC.

Brady JV, Lucas SE (1984). Testing Drugs for Physical Dependence Potential and Abuse Liability. National Institute on Drug Abuse Research Monograph #52, DHHS Publication no (ADM) 84-1332. Washington D.C. US Government Printing Office.

Brady JV (1993). The origins and development of behavioral pharmacology. *European Behavioral Pharmacology Society Newsletter* 7, Sept 1993, pp 2-11.

Brady JV (1996). Drug policy and the enhancement of access to treatment. In WK Bickel, RJ DeGrandpre (eds) Drug Policy and Human Nature, Plenum Press, New York, pp 155-174.